Meeting Report

Recent Progress in Carcinogenesis, Progression and Therapy of Breast Cancer: The 20th Hiroshima Cancer Seminar—the 4th Three Universities' Consortium International Symposium, October 2010

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The 20th Hiroshima Cancer seminar focused upon breast cancer research and treatment particularly on the mechanism of tumorigenesis and drug resistance and development of novel therapeutics. Several molecules such as retinoblastoma and p16 were raised as key factors in tumorigenesis and invasiveness. Estrogen-related pathways seem to be closely involved in the process. For the tumor lacking hormone receptor and human epidermal growth factor 2, some other mechanisms could be responsible. It seems that MicroRNA 22 directing some putative targets such as SIRT1, Sp1 and CDK6 plays a crucial role in breast tumor growth and metastasis. In addition, ribophorin and the associated molecules might be engaged in breast cancer stemness. Obviously, these molecules provide potential for therapeutic targets. It was also discussed about new drug development such as anti-human epidermal growth factor 2 therapy, anti-angiogenesis, pro-tumor aspects of anti-cancer therapy and application of circulating markers for monitoring, imaging and health-care system. Furthermore, we discussed risk factors, prevention and screening to reduce invasive cancers as well. Throughout the conference, panelists and attendee indicated the importance of translational research and biomarker exploration in order to realize efficient and individualized therapy for breast cancer.

Key words: breast medicine − carcinogenesis − chemo-breast

The 20th International Symposium of Hiroshima Cancer Seminar (HCS) in conjunction with the 4th Universities' Consortium (the Cancer Professional Training Plan, Tottori University, Shimane University and Hiroshima University) was held on 31 October 2010 at International Conference Center Hiroshima. The symposium consisted of 11 special lectures and 21 free papers for a poster session. Approximately 178 investigators and students were present and made discussions on recent progress in the research of carcinogenesis, mechanism of disease progression, novel diagnostics and therapeutics of breast cancer. Invites speakers included Dr Thea D. Tlsty (University of California, San Francisco, CA, USA), Dr Edison T. Liu (Genome Institute of Singapore, Singapore), Dr Hidetoshi Tahara (Hiroshima University, Hiroshima), Dr Mark D. Pegram (University of Miami, FL, USA), Dr Takahiro Ochiya (National Cancer Center Research Institute, Tokyo), M.T. (Kyoto University, Kyoto), Dr Seiichiro Yamamoto (National Cancer Center Research Center for Cancer), Dr Yasuhiro Fujiwara

Table 1. Author and titles for discussion

Author	Title and topics
Thea D. Tlsty	Molecular alterations that predict malignancy: Focused on the mechanism of early development of breast cancer
Edison T. Liu	Systems genomics in breast cancer: Presented on comprehensive analysis of human breast cancer with genomic, epigenomic and proteome
Hidetoshi Tahara	microRNAs act as tumor suppressor in breast cancer: Addressed on the significance of miR-22 in breast cancer
Mark D. Pegram	Molecular targeting therapy in breast cancer, recent progress and future perspective: Especially focused on new anti-HER2 therapy and antiangiogenesis therapy
Takahiro Ochiya	Ribophorin (RPN2) as a novel therapeutic target for breast cancer stem cell: Presented on the significance of RPN2 in the drug resistance and stemness of breast cancer
M.T.	Pro-tumor actions to anti-tumor therapy: Focused on the pro-tumor signals induced by anti-cancer treatments
Seiichiro Yamamoto	Risk factors for breast cancer in Japan: Summarized the results on risk factors from recent studies mainly conducted in Japan
Yasuhiro Fujiwara	Introduction of new drugs in health care system: Indicated the issues and future perspectives on new drug development and health system in Japan
Masahiro Ohara	Prognostic impact of 18F FDG-PET in operable breast cancer: Reported on the clinical significance, such as prognostic value, of FDG-PET in breast cancer
Masayuki Itakura	Current treatment of breast cancer and usefulness of measuring serum anti-p53 antibody and HER-2/neu ECD for the management of breast cancer patients: Focused on the importance of anti-P53 antibody and HER2-ECD measurement
Kiyosuke Ishiguro	Breast cancer screening in Tottori, Japan: current status and problems: reported recent outcomes of mass-screening program conducted in Tottori

FDG-PET, fluorodeoxyglucose-positron emission tomography.

(National Cancer Center Hospital, Tokyo), Dr Masahiro Ohara (Hiroshima University Hospital, Hiroshima), Dr Masayuki Itakura (Shimane University Hospital, Shimane) and Dr Kiyosuke Ishiguro (Tottori University of Faculty of Medicine, Tottori) spoke to more than 350 people about an evolutional progress in understanding of breast cancer development and novel therapeutics including chemotherapy, hormone therapy and molecular targeting therapy.

OPENING ADDRESS

E.T. (HCS Foundation), Chairman of the Organizing Committee of this symposium, gave an opening address. Tahara introduced a brief background and the purpose of this series of symposia annually organized for 20 years since the establishment of the HCS Foundation in 1992. This year, the organizing committee focused upon breast cancer research and treatment, in which the biology is engaged fully in clinical practice. The participants profited by exchanging and learning a great deal of information on understanding molecular mechanisms of disease development, molecular targeting, personalized therapy and prevention of breast cancer.

SPECIAL LECTURES ON CARCINOGENESIS, PROGRESSION AND TREATMENT OF BREAST CANCER

The main purpose of the symposium was to understand breast cancer biology deeply and to consider novel approaches for breast cancer treatment and prevention (Table 1).

Dr Thea D. Tlsty addressed on molecular alterations that predict breast cancer. Only a minority of women diagnosed with a pre-malignancy such as ductal carcinoma *in situ* (DCIS) develops a subsequent invasive tumor within 10 years after surgical lumpectomy. Still little is known about the molecular pathways that confer this differential risk for developing subsequent disease. Actually, many women diagnosed with DCIS who opt for surgery, with or without adjuvant treatment, are being over-treated. Dr Tlsty's group found that biologic markers within the epithelial cells of the early lesion predict women with a better or worse prognosis. It was demonstrated that differences in the retinoblastoma (Rb) pathway determine the conditionality of these biologic processes. Lesions that have maintained intact p16/Rb checkpoint regulation, reflecting an initiated senescent program, are less likely to result in a subsequent tumor event. DCIS lesions that exhibit a bypass of this barrier may predict an increased risk of developing invasive carcinoma. The finding that specific molecular characteristics of premalignant lesions along with their surrounding microenvironment have an increased risk of developing invasive carcinoma would suggest that these phenotypes could be assayed far in advance to the development of invasive disease and present clinical opportunities. These findings and knowledge will be beneficial for understanding and managing early breast cancers such as DCIS (1–3).

Dr Edison T. Liu introduced about the systemic approach for understanding breast cancer carcinogenesis and

progression with genomics in his institute. It is known that genomic medicine involves the provision of medical care that uses the power of genomic knowledge and technologies to resolve complex problems. The fundamental difference between this and older strategies in medicine research should be the comprehensiveness and the precision of the analyses afforded by new genomic technologies such as in sequencing, cloning and genotyping. The new challenge that he is trying to achieve would be the assembly and management of this high volume of data with dimensional complexity. He said that the systems biology, as a discipline, seeks to explain biologic phenomenon through the net interactions of all cellular and biochemical components within a cell or organism. Operationally, systems biology requires the digitalization of biologic output, the computational power to analyze comprehensive and massive datasets, and the capacity to integrate heterogeneous data into a usable knowledge format. It was highlighted that how genomic approaches change the understanding of breast cancer. His work, at the Genome Institute of Singapore, in transcriptional profiling seems to lead to transcription factor binding site dynamics, and human variations in those binding sites. These integrative approaches seem to permit modeling of complex interactions and allow covering complex mechanisms of drug action quickly. Lastly, he emphasized that an individualized approach with the sequence cancer genomes allowing the identification of unique and private mutations for each cancer is possible in breast cancer treatment (4–6).

Dr Hidetoshi Tahara focused on the role of microRNAs (miRNAs) in breast cancer progression and regression.

miRNAs, small non-coding RNAs, regulate the stability and translation of target protein-coding mRNAs at the 3′-untranslated region negatively. They are known to play crucial roles in the pathologic development and tumorigenesis. It is also underlined that miRNAs are potential regulators in cellular senescence, which is an important mechanism of tumor suppression. Therefore, it is hypothesized that senescence-associated miRNAs (SA-miRNAs) might attribute to tumorigenesis. Dr Tahara and his group have screened SA-miRNAs from up-regulated miRNAs in human senescent fibroblasts using miRNA array and identified several SA-miRNAs involved in cellular senescence. He talked about miR-22, which is up-regulated in senescent human fibroblasts and human mammary epithelial cell strains 184 (HMEC184). Interestingly, miR-22 expression was expressed at lower level in various cancer cells including MCF-7, MDA-MB-231 and SiHa cells. Overexpression of miR-22 caused senescence-like growth suppression, characteristic senescent morphologic alterations and significantly increased SA-β-gal activity, but did not induce apoptosis in these cancer cells. *In silico* analysis combined with prediction algorithm indicated some putative targets such as SIRT1, Sp1 and CDK6, which are implicated in cell growth and cell cycle regulation. Dr Tahara addressed that these genes are regulated directly by miR-22, using luciferase reporter assay. It was also indicated that the miR-22 down-regulated SIRT1, Sp1 and CDK6 and siRNAs against these genes suppressed cell growth and induced senescence phenotypes in cancer cells, suggesting that the down-regulation of SIRT1, Sp1 and CDK6 by miR-22 was involved in cellular senescence. In addition, therapeutic miR-22 delivery significantly suppressed tumor growth and metastasis *in vivo* in a murine breast metastasis cancer model using MDA-MB-231-luc cells. Dr Tahara summarized that miR-22, a novel SA-miRNA, can induce cellular senescence in human fibroblasts and cancer cells and acts as tumor suppressor to play an important role in breast cancer development (7,8).

Dr Mark D. Pegram talked on molecular targeting therapy in breast cancer, particularly on recent progress and the future perspectives. He addressed upon anti-human epidermal growth factor 2 (HER2) therapy and anti-angiogenesis therapy for breast cancer, which have progressed dynamically these days. It is evident that anti-HER2 monoclonal antibody therapy brings a dramatic survival advantage for the patients having HER2 overexpressed breast cancer. Recently, in addition, tyrosine kinase inhibitors of HER family, including HER1, HER2 and HER4, have been developed clinically. An HER1/Her2 inhibitor lapatinib has shown its efficacy in the combination use of anticancer agents such as capecitabine and taxane, and of trastuzumab. Intriguingly, a dual blockade of HER2 signals with trastuzumab and lapatinib may induce a paradigm shift in breast cancer treatment not only in metastatic situation but also in primary breast cancer therapy. Further clinical development with other novel anti-HER2 agents, such as neratinib, pertuzumab and TDM-1 is under clinical investigation. Neratinib can inhibit HER family entirely. Obviously, the toxicity such as diarrhea is an issue to deal with. Pertuzumab is able to block a dimerization of HER2 with other family proteins. TDM-1 is a trastuzumab conjugated with a toxic chemical DM-1, where the trastuzumab functions not only a neutralizing antibody but also a drug-delivery system. Dr Pegram explained about its mechanisms and introduced ongoing clinical trials. Anti-vascular endothelial growth factor therapy has been also touched upon. A combined analysis of three clinical trials using bevacizumab for metastatic breast cancer patients has clarified the significance of bevacizumab for prolonging disease progression, but it was also indicated that the prolongation of overall survival is limited. The therapeutic individualization would be indispensable for improving bevacizumab therapy. Dr Pegram touched on his recent translational research outcomes for individualization of molecular targeting therapy (9–11).

Dr Takahiro Ochiya elucidated the importance of ribophorin II (RPN2) as a novel therapeutic target for breast cancer stem cells (CSCs). Dr Ochiya recently discovered that RPN2 is a crucial molecule in drug resistance. He characterized the regulatory network responsible for docetaxel resistance in breast cancer with gene expression profiling and, using siRNA transfection array, he and his group have tried to identify the genes responsible for drug resistance. Of the

genes whose expression was elevated in patients who did not respond to docetaxel, the inhibition of the RPN2, a part of oligosaccharyltransferase complex, gene promoted docetaxel-dependent apoptosis and inhibited cell growth in a docetaxel-resistant human breast cancer cell line (MCF7-ADR). Silencing of RPN2 resulted in decreased glycosylation and membrane localization of the P-glycoprotein efflux pump, which caused increased sensitization of MCF7-ADR cells to docetaxel. *In vivo* validation study, it was demonstrated that the atelocollagen delivery system markedly enhanced the efficiency of siRNA for the inhibition of RPN2 in mouse tumor models of human breast cancer. Because siRNA shows low efficiency in gene silencing *in vivo*, various delivery methods, such as the use of plasmids and viral vectors encoding siRNA and the use of lipids, have been investigated. Dr Ochiya has previously shown that the atelocollagen-mediated systemic delivery of siRNA might be a unique strategy for the inhibition of bone metastatic prostate tumor growth. The siRNA−atelocollagen complex is a nano-sized particle and is stable *in vitro* and *in vivo*. Furthermore, his group has confirmed that the atelocollagen complex shows low toxicity and low immunogenicity *in vivo*. The atelocollagen-mediated local or systemic delivery system may hold a great potential for the practical application of gene suppression using siRNAs for cancer therapies. In drug-resistant models of mice given docetaxel, *in vivo* delivery of RPN2-specific siRNA substantially reduced tumor growth. It is noteworthy that these findings using docetaxel-resistant human breast cancer cells are found commonly in other types of cancers. Cisplatin-resistant human non-small cell lung carcinoma cells recover their sensitivity to cisplatin by knockdown of RPN2 expression and die by apoptosis. In addition, mouse mammary tumor cells resistant to docetaxel express mouse RPN2, and the inhibition of RPN2 results in apoptotic cell death in the presence of docetaxel. Therefore, RPN2 status is responsible for the drug-resistant nature of multiple cancer cell lines both in humans and in mice, and RPN2 expression may confer cross-resistance to a variety of anticancer drugs.

Dr Ochiya also found that RPN2 is highly expressed in breast CSCs or cancer-initiating cells. Biologically, these cells are distinct from the other cells that form the bulk of a tumor, in that they can self-renewal and produce differentiated progenitor cells. RPN2 is highly expressed in CD44+/CD24− breast cancer cells named MDA-MB-231 with highly metastasis ability. Knockdown of RN2 in breast CSCs expressing CD44+/CD24− by shRPN2 vector system allowed a significant inhibition of cancer growth and lymph node metastasis *in vivo* (unpublished observation). He also found that small non-coding RNA tightly regulates RPN2 gene expression (12−14).

M.T. talked about importance of pro-tumor actions to anti-tumor therapy. It is evident that anticancer therapy brings enormous benefits for cancer patients to survive longer. However, it is also indicated that anticancer therapy drives not only anti-tumor events but also pro-tumor ones. For instance, various types of chemotherapy could induce the activation of nuclear factor-κB (NF-κB), involved in inflammation, angiogenesis, anti-apoptosis and cell survival, through multiple mechanisms. In addition, recent clinical studies clarified that the pro-tumor effects are induced by anticancer therapy at systemic level. According to Dr Toi's recent investigations, the administration of cytotoxic chemotherapy could mobilize circulating endothelial progenitors (CEPs) in a considerable level of magnitude, which was compatible with the previous data reported in the experimental system. In mice, it is known that the mobilization of CEPs occurs regardless of the existence of tumor. The mobilized CEPs are recruited to the sites having the activity of neovascularization. Based upon these results, it is hypothesized that the pro-tumor reaction should be taken into consideration for cancer therapy strategy in a personalized manner. Currently, anti-angiogenesis treatment is examined in various situations, which might be relating to this issue because angiogenic response is the important part of this issue. Theoretically, it would be possible to suppress the pro-tumor storms, induced by anticancer therapy, by anti-angiogenesis therapy if it is used properly. For minimizing the therapy-induced pro-tumor events, metronomic style treatment schedule might be effective. It would be essentially important to pay more attention to the pro-tumor events elicited by anticancer treatment in order to enhance the efficacy of anti-cancer therapy (15−17).

Dr Seiichiro Yamamoto addressed on the risk factors and prevention of breast cancer in Japan. It is indicated that breast cancer incidence has been increasing over several decades in Japan. There are many systematic reviews concerning its risk factors. Among these, the one published by the World Cancer Research Fund/American Institute for Cancer Research and the other conducted by the Japanese epidemiologist group granted by the Ministry of Health, Labour, and Welfare were considered as most useful for Japanese women. According to these two, convincing and probable breast cancer risk factors for Japanese women are earlier age at menarche, late natural menopause, no experience of childbirth and late first birth. As for modifiable risk factors, probable or possible risk/preventive factors for breast cancer are body mass index, physical activity, alcohol intake, fat intake, soy/isoflavone intake, smoking and so on. The change of distribution of these risk factors, such as westernization of diet, earlier age at menarche and smaller number of children, definitely contributed to the increase in breast cancer. Unfortunately, however, the distribution of these factors and its change were not investigated comprehensively. Dr Yamamoto is keen on investigating these issues and he is trying to clarify the factors involved in the increment of breast cancer and to develop new prevention program particularly for ladies in Asian-life style (18,19).

Dr Yasuhiro Fujiwara raised three points upon the new drug development system and health-care system. First he indicated that we should always keep in mind these points when we criticize 'drug lag' issue in Japan. As previously

reported (20,21), new drug discovery and development cost much with high risk (low success rate), and with long time. Furthermore, it should be noted that the critical reason for drug lag in Japan is not because the reviewing time by Pharmaceuticals and Medical Devices Agency (PMDA) or Ministry of Health, Labour and Welfare (MHLW) is slow, but because the timing of starting clinical development or the period of clinical development is late/slow due to poor infrastructure for clinical development (JPMA OPIR news, February 2008). As for breast cancer, bevacizumab, fulvestrant and eribulin (E7389) are now under PMDA/MHLW approval review. In addition, several poly ADP-ribose polymerase inhibitors, HER2-targeted drugs and many molecularly targeted agents (mTOR inhibitors, etc.) are under development in Japan. Secondly, he indicated the cost for expensive drugs with modest benefits. Recently, many new expensive oncology drugs with modest benefit have appeared in the market. In Japan, the high-cost medical care benefit system ('Kougaku-ryouyou-hi seido') prevents placing excessive burdens of health-care costs on individuals. On the other hand, in western countries where no such benefit system is available, some people cannot take advantage of front-line standard treatments if they cannot afford to pay for high-cost drugs or diagnostic kits even if they are approved as medical products and there is no drug (approval) lag; this is called 'insurance lag' (22–24). Considering the budget deficit problems, we, Japanese, have to decide whether we will introduce value-based medicine, as typified by the UK-NHS health-care system guided by the National Institute for Health and Clinical Excellence (NICE), or not soon. Thirdly, the issue of Regulatory Approval in Japan, USA and EU was discussed. As reviewed drug approval processes and criteria/requirement for approval of oncology drugs in Japan (PMDA), USA (Food and Drug Administration, FDA) and EU (European Medicines Agency, EMA), criteria/requirement for approval seems to be almost identical in these regions. Nevertheless, according to a survey of these three regions' approval outcomes in recent years (from January 2006 to 2010), there exist divergent outcomes between FDA and EMA oncology drugs approval review results; there are eight discrepancies. For example, ixabepilone was approved for breast cancer in the USA on 17 October 2007, but EU refused to approve it in 2008. Availability of review documents in all these regions should be noted and it should also be noted that EMA is now providing 'withdrawal/refusal assessment report' on their website. We, physician scientist, had better check these documents regularly for smooth clinical development. Lastly, in the process of preparing new frameworks of health care in Japan, it is important to establish systems to systematically coordinate clinical trials, compassionate use (CU) programs and medical care using off-label drugs while maintaining the universal health insurance coverage under the current tight national financial conditions. An option similar to the system in the UK can be considered. Organizations like NICE, which do not control drug approval, judge the availability of health insurance reimbursement based on cost-effectiveness analyses by taking the results of clinical trials into account. These groups analyze the status of clinical trials to see whether clinical significance that meets the expensive drug costs is supported by the results of clinical trials. Then, national funds [e.g. the Cancer Drugs Fund, the UK: 200 million pounds (26 billion Japanese yen)] financially supports oncology drugs whose reimbursements are rejected by NICE-like organization. In addition, it might be a time to consider the following options: (i) raising the consumption tax rate in Japan to a level similar to the rate currently enforced in western countries and making the consumption tax a social security tax to ensure availability of health-care resources, and (ii) supporting the cost of drugs used in medical care conducted under programs similar to the expanded access program (EAP) or CU program, and in clinical trials and investigator-initiated registration-directed clinical trials, as well as the investigative medical care costs (such as diagnostic imaging costs), with development funds that will be supplemented with donations from companies and individuals.

In conclusion, a number of concepts are becoming commonly understood throughout the world: evidence of medical care should gradually and continuously mature from the stage of clinical research through that of health insurance-covered treatment. In Japan, these two stages are separated from each other with the drug approval process. However, it is desirable to support the development of medical care based on the concept of AEG (access with evidence generation) or AED (access with evidence development), in which the insurance- and self-pay ratios are gradually increasing, to help support clinical trials conducted only with research funds (25–27).

Dr Masahiro Ohara introduced his experience on 18F fluorodeoxyglucose-positron emission tomography (FDG-PET) for operable breast cancer particularly on the prognostic value. FDG-PET provides physiologic information on the uptake of glucose and its metabolism. Accumulation of FDG, which is regarded as SUV_{max} value, is reported to be associated with high grade or poor differentiation in various types of malignancies. According to the Glut-1 immunohistochemistry in lung cancer, he said that the phosphorylated FDG was trapped intracellularly and accumulated at a rate proportional to glucose utilization. However, in contrast to lung and other malignancy, clinical significance of FDG-PET in early-stage breast cancer is still controversial. A recent National Comprehensive Cancer Network taskforce report concluded that PET was not indicated for the diagnosis or screening of breast cancer; staging of the primary tumor, axilla or metastatic disease in patients with clinically early-stage disease or post-treatment surveillance. In his research, therefore, he focused on the prognostic value of a maximum standardized uptake of FDG-PET in operable breast cancer patients. He examined 520 consecutive operable breast cancer patients, between 2005 and 2010, retrospectively. Three hundred sixty-two patients performed

FDG-PET/computed tomographic imaging before initial therapy and 320 invasive breast cancer cases were carefully evaluated for SUV_{max} and the association with clinico-pathologic factors and disease-free survival (DFS). SUV_{max} varied from 0.6 to 22.1 and the mean value was 2.65. The receiver operating characteristic curves identified an optimal SUV_{max} cut-off value of 4.25 for predicting the recurrence. Area under the curve was 0.823, and the sensitivity and specificity were 0.778 and 0.761, respectively. A significant difference in DFS was observed in favor of the patients having SUV_{max} less than 4.25. A high SUV_{max} correlated significantly with tumor size, negative hormone receptor status, high grade and high Ki67 labeling index. In a multivariate analysis, SUV_{max} with a cut-off value of 4.25 and hormone receptor negativity showed a significant and independent prognostic value. In an exploratory subgroup analysis looking at the appropriate cut-off levels, a SUV_{max} cut-off value of 7.3 looked beneficial for triple-negative subtype, maybe because of different baseline values among the subtypes.

Dr Masayuki Itakura introduced his recent works on the serum anti-p53 antibody and on the HER2 extracellular domain (ECD). In the treatment of breast cancer, multiple modalities such as surgery, radiation therapy, chemotherapy, hormone therapy and molecular targeting therapy are used in a multidisciplinary manner. In addition, a variety of new diagnostics and therapeutics are currently under development. Therefore, treatment options are spreading widely and standardized, which result in the improvement of prognosis of breast cancer patients. Based on these aspects, Dr Itakura introduced his own experiences about anti-p53 antibody and HER2-ECD measurements using serum samples from breast cancer patients. It seems useful to monitor disease status and to predict therapeutic response.

Since current treatment strategies for breast cancer have become more individualized, these diagnostic tools would be applicable for tailoring the treatment, especially combination therapies in each individual.

In his presentation, clinical significance of the measurement of serum anti-p53 antibody and HER2 ECD for the management of breast cancer patients was highlighted.

Dr Kiyosuke Ishiguro talked on breast cancer screening program in Tottori. Until 2004 in Tottori, Japan, publicly organized screening consisted of clinical breast examinations for more than 30 years old, once every year, and the screening rate was about 25%. A mammogram screening once every 2 years began in 2005 in Tottori for women older than 40 years old. Population of subject of breast cancer screening is 118 674 in Tottori. He said that the screening rate increased slightly with 28% when they added the 2-year system. In Japan, the national average was 14.2% in 2007, but it is remarkably lower than the mean participation rate in Europe and the USA. After mammography screening began, the 3% positive rate by clinical breast examination increased to 10%. And the detection rate tripled. This creates an increased risk of false positives, which require follow-up exams and biopsies, which may cause unnecessary anxiety in the patient. The positive predictive value [PPV = true positive (TP)/ TP + false positive (FP)] for mammography screening was only 3.8% in 2005 and 2006. Dr Ishiguro's group classified mammogram findings into five categories. The most frequent in abnormal findings is Category 3. But a PPV of Category 3 was only 1.0% in Tottori. There are a lot of useless additional work-up examinations. The reasons for the high false-positive rate are not only the characteristics of mammography, but also the increased fear of misdiagnosis. But recently, work-up examination rates are decreasing. Every year, 50–70 patients were detected by publicly organized screening in Tottori, but half were detected at the first screening. Mammotome biopsies seem to be useful for the lesion with calcifications; however, 80% biopsy results were benign. We should be selective with regard to which cases should undergo biopsy, and we may follow-up such a calcification until the phase detected by ultrasound. It is important to evaluate screening program systematically. The mortality rate of breast cancer will decrease by screening, but the number of death will not decrease yet in Japan.

POSTER SESSION

Twenty-one papers concerning the pathology, biology and systemic therapy of breast cancer were presented in the poster session. The paper entitled 'A novel senescence-associated miRNA miR-22: implications for tumorigenesis' by Dr Xu and 'HOXB9 promotes the aggressive phenotypes through altering both tumor-specific cell fates and microenvironment' by Dr Hayashida were awarded the best poster prize.

CLOSING REMARK

M.T. made a closing remark on current aspects in the research of breast cancer, such as the mechanism of tumorigenesis, resistance to treatment and new therapy development. It would be essential to investigate early breast cancers in further depth and to conduct clinical trials with highly qualified translational researches. The integrated knowledge between basic science and clinical science would enable to realize individualized medicine based on the biology.

Conflict of interest statement

None declared.

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