Current Status and Problems of Breast Cancer Screening

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Abstract

In cancer screening, it is essential to undertake effective screening with appropriate methodology. Effective screening should be supported by evidence of a reduced mortality rate. At present, mammography is the only method for breast cancer screening that has such evidence. However, mammography does not achieve sufficient screening accuracy in breasts with high mammary gland density. Dense breasts are common at ages below 50 and are more common in Japanese populations than in Western populations.

As ultrasonography achieves better accuracy in breast cancer detection even in dense breasts, attempts to use it in screening have started. However, the specifications for ultrasound equipment and the procedures for examination and image reading have not been standardized, and the effectiveness has not been verified.

The government therefore started the Japan Strategic Anti-cancer Randomized Trial (J-START) (http://www.j-start.org/), which is a controlled study to evaluate the effectiveness of ultrasound breast cancer screening conducted as a project in the Third-term Comprehensive Strategy for Cancer Control under the Basic Act for Anti-cancer Measures. This study makes a randomized comparison between 2 groups of women aged 40–49, 50,000 persons in each arm, who are screened using either combined screening with mammography and ultrasonography (intervention group) or mammography alone (control group), and evaluates the sensitivity and specificity as the primary endpoint and the accumulated incidence rate of advanced breast cancer as the secondary endpoint. J-START has been registered on the University Hospital Medical Information Network, ID: UMIN000000757. Although the outcome of cancer screening is reduction of the mortality rate, the planned study period (April 2006 to March 2011) is too short to confirm the results in this aspect, and we are investigating how to make evaluation possible in the future.

This study is particularly important because breast cancer screening at ages 40–49 is challenging not only in Asia but also in Western countries.

Key words Breast cancer screening, Mammography, Ultrasonography, Randomized controlled trial, Effectiveness evaluation

Introduction

Japan's fight against cancer under the Third-term Comprehensive Strategy for Cancer Control aims at a dramatic reduction in cancer morbidity and mortality rates. To succeed, the Comprehensive Strategy requires the establishment of measures to halt and reverse the steady increase in breast cancer. The Basic Plan for the Promotion of Anti-cancer Measures under the Cancer Control Act, implemented in April 2007, has set a target of achieving a 10% decrease in the cancer mortality rate within 10 years. The Cancer Control Act also provides for the promotion of studies that may contribute to the reduction of mortality rate.[1]

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Table 1 Recommendations concerning breast cancer screening

Breast Cancer Screening
(1) Screening Method • Mammography should be the standard method. Inspection and palpation may be used in parallel for the time being, considering the age-related variation in mammary gland density and the development of the system to support mammography screening.
(2) Target Age • Screening should cover individuals aged 40 years or more. • Further survey and study should be continued regarding inspection and palpation screening and ultrasound screening at ages 30–39.
(3) Screening Intervals • Screening intervals should be once in every 2 years.

(On the Revision of Breast Cancer Screening and Cervical Cancer Screening Based on the Elderly Health Program. The Interim Report of the Cancer Screening Study Group, MHLW, March 2004.)

Effective Screening with Appropriate Methodology

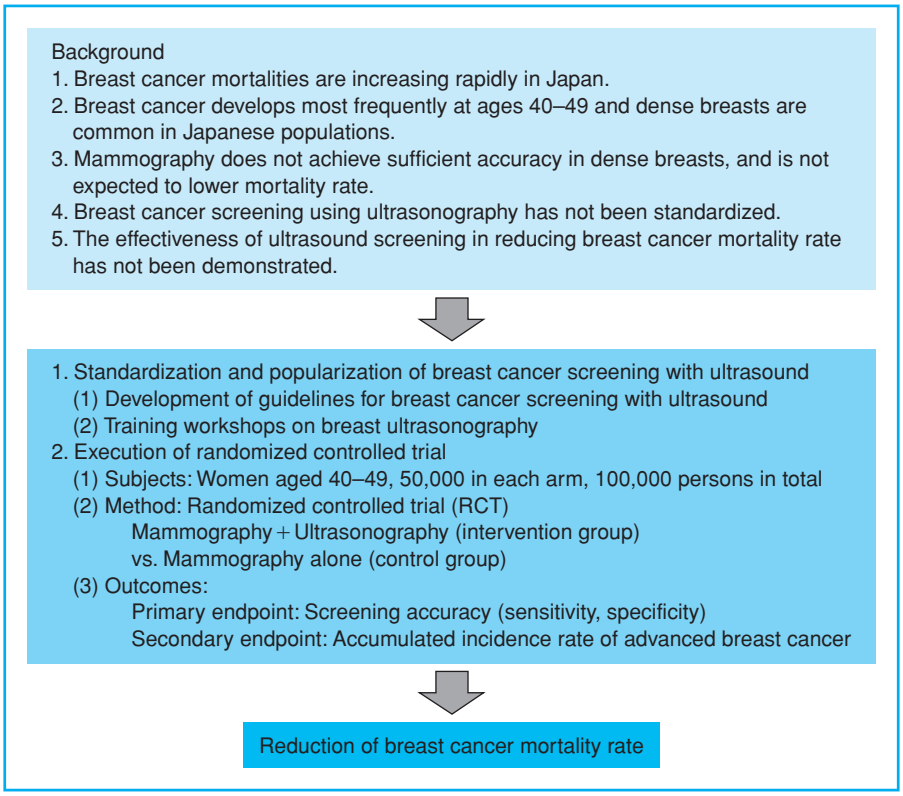
As mentioned in the WHO guidelines, "population-based cancer screening" conducted as a public health program should be undertaken only when there is evidence of the effectiveness in reducing the mortality rate.[2,3] In the case of breast cancer screening, mammography is the only method supported by evidence, which is based on randomized controlled trials (RCTs) conducted in Western countries.[4–9] However, the effectiveness of mammography is limited to individuals aged 50 or more, and opinions vary regarding its value for individuals at ages up to 49.[9–12]

To reduce cancer mortality rate, it is essential to undertake effective screening with appropriate methodology. The appropriate methodology means the complete implementation of quality control (cancer screening program evaluation). The Study Group on Cancer Screening Program Evaluation in the Ministry of Health, Labour and Welfare (MHLW) has discussed the evaluation indices from the aspect of technology and mechanisms, those regarding the program implementation process, and the outcome index. (http://www.mhlw.go.jp/shingi/2008/03/s0301-4.html, http://www.mhlw.go.jp/shingi/2008/03/dl/s0301-4a.pdf) (in Japanese)

For evidence of the effectiveness of mammography in reducing the mortality rate, we need to depend on the results of RCTs conducted in Western countries. However, mammography is less effective at ages 40–49 than at ages over 50,[10] and the results of RCTs in Western countries may not be directly applicable to Japanese populations. While mammography is suitable to detect tumors in relatively fatty or atrophied mammary glands, it is the low sensitivity to breast cancer in dense breasts at ages 40–49,[13] when the rate among Japanese women peaks.[14] Dense breasts are common at ages below 50, and are more common in Japanese populations than in Western populations.[15] The incidence rate of breast cancer peaks at ages 40–49 in Japan, in contrast to 70–79 in Western countries, and hence screening using mammography alone is not expected to be sufficiently effective.[16,17] There is an urgent need to develop a screening method other than mammography and evaluate its effectiveness in women ages 40–49.

Mammography Is the Only Evidence-based Method for Breast Cancer Screening

Mammography is the standard method for breast cancer screening at the present. Based on the interim report (Table 1) of the MHLW Study Group on Cancer Screening, the government revised part of the Guidelines for Health Education Focusing on Cancer Prevention and the Implementation of Cancer Screening (Notification No. 0427001 of the Division of the Health for the Elderly, Health and Welfare Bureau for the Elderly, April 2004). In essence, this revision provides that (1) mammography screening should be the standard practice, (2) screening should cover persons aged 40 or more, (3) screening intervals should be 2 years, and (4) further research and study on ultrasound screening should be promoted.



[Randomized Controlled Trial on Effectiveness of Ultrasonography in Breast Cancer Screening (J-START), a study project in the MHLW scientific research grant program and the Third-term Comprehensive Strategy for Cancer Control]

Fig. 1 Promotion of large-scale clinical trial (randomized controlled trial; RCT) for the founding of evidence-based medicine (EBM)

The government is promoting evidence-based cancer control measures. In this approach, "population-based" cancer screening conducted by municipalities must satisfy the important requirements that (1) the screening method is effective (there is evidence of effectiveness in reducing the mortality rate) and (2) quality control (cancer screening program evaluation) is practiced appropriately.[19] Effective cancer screening is defined primarily based on whether there is the evidence of effectiveness in reducing the cancer mortality rate, considering not only the data in Japan but also the evaluation and practice in other countries.

Is Ultrasound for Breast Cancer Screening Effective?

The screening accuracy of mammography is poor for breasts with high mammary gland density. Dense breasts are common at ages below 50 and are more common in Japanese populations than in Western populations. On the other hand, ultrasonography achieves better accuracy in breast cancer detection in dense breasts. Attempts to use it in breast cancer screening have started, and the combined use of mammography and ultrasonography at ages 40–49 has been reported to improve the breast cancer detection rate.[20–21] However, the specifications for equipment and the procedures for examination and image reading have not been standardized, and the accuracy of ultrasound screening and its effectiveness in reducing the mortality rate have not been proven. The government therefore started the Japan Strategic Anti-cancer Randomized Trial (J-START) as a strategic outcome study (a project in the Third-term Comprehensive Strategy for

Cancer Control). This study evaluates the accuracy and effectiveness of breast cancer screening targeted at women aged 40–49, comparing the combined screening with mammography and ultrasonography (intervention group) and mammography alone (control group). With the target number of study subjects being 100,000 persons in total, 50,000 persons in each arm, it is an unprecedentedly large-scale clinical trial in Japan (Fig. 1) (http://www.j-start.org/) (in Japanese).

Regarding ultrasound for breast cancer screening, the interim report of the MHLW Study Group on Cancer Screening recognized the usefulness of ultrasonography as a test method for the clinical diagnosis of breast cancer, but it pointed out the lack of documented evidence supporting the effectiveness of ultrasound screening in reducing the breast cancer mortality rate, and therefore made the following 2 recommendations: (1) It is necessary to verify the effectiveness of ultrasound for breast cancer screening, to standardize equipment and image capturing/reading procedures, and to establish diagnostic criteria as the basis for screening; and (2) the possibility of ultrasonography should be pursued for use in the screening of women with dense breasts, where mammography is not effective in visualizing lesions.[18]

In this context, implementation of the Randomized Controlled Trial on Breast Cancer Screening with ultrasound was proposed in the 2005 report of the Study Concerning the Planning of the Strategic Outcome (Principal Researcher: Kiyoshi Kurokawa).[23] This report pronounced the stance of strongly promoting strategic outcome study for cancer control in Japan, stating that "Japan should not remain in a state where randomized controlled trials are impossible."

The Need for Study to Demonstrate Evidence

The Basic Plan for Promotion of Anti-cancer Measures defined by the national government spelled out the goal of improving the effectiveness of cancer screening based on the latest scientific achievements for the purpose of promoting cancer research and expanding the availability of high-quality cancer therapies across the country. The only method for breast cancer screening supported by evidence at present is mammography, and this method is expected to have sufficient effectiveness only in women aged 50 and older.[13] Furthermore, it was 30 years ago when the RCTs demonstrating the effectiveness of mammography screening in reducing mortality rate were conducted, the era of 1970s. Breast cancer screening with ultrasound is a method that was first attempted in Japan. The evidence of its effectiveness should be developed in Japan and shared with the rest of the world.

Why is a controlled trial needed in the process of confirming the effectiveness of cancer screening? There are merits and demerits to cancer screening. Potential demerits include the unnecessary mental anxiety due to the increased percentage of persons referred for detailed examinations, the risk of malpractice resulting from excessive diagnosis and excessive treatment, and the increase in medical expenditure. On the other hand, if we consider that a merit is measured by a screening outcome index, the only merit is the effect to reduce the mortality rate. We may even consider that everything other than the effect to reduce the mortality rate is a demerit of cancer screening. Non-controlled trials are affected by many confounding factors and it is impossible to interpret accurately the test results from such trials. Conducting an RCT is the most appropriate way to make scientific analysis and verification of the effectiveness of ultrasound for breast cancer screening.

However, Japan lacks experience in conducting large-scale RCTs in this field, and there will be many challenges in the process of executing the study. To be able to provide appropriate medical care based on scientific knowledge, as required by the Basic Act for Anti-cancer Measures, we first need to verify the scientific foundation of screening methods.

In J-START, the primary endpoint is the inter-group comparison of the sensitivity/specificity and detection rate, and the secondary endpoint is the inter-group comparison of the accumulated incidence rate of advanced breast cancer during the follow-up period. The most important index in the evaluation of the effectiveness of cancer screening is the mortality rate from the cancer in question in the target population. However, in view of the natural history of breast cancer, the 4-year period scheduled in the strategic study is too short to observe a significant inter-group difference. It is necessary to have a system in which the long-term follow-up of the survival status of

individuals in both arms may be continued after the completion of the strategic study.

Future Directions of Breast Cancer Screening

The research and development of effective methods for breast cancer screening make important contribution to society, leading to the reduction of the cancer mortality rate in future generations. Breast cancer is rapidly increasing also in Asian countries, and the characteristics of this disease in these countries are similar to those in Japanese populations. Therefore, the effort of Japan to establish evidence of ultrasound screening is important in the context of international contribution focusing on Asia. Western countries are also looking for better ways to conduct breast cancer screening at ages 40–49, and this also emphasizes the importance of J-START, which is a large-scale RCT to evaluate the effectiveness of ultrasound for breast cancer screening.

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