Controversies on Mammography Screening in the World and Bahçeşehir Population-Based Organized Mammography Screening Project in Turkey

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Screening is one of the most important parts of preventive public health, which enables cancer detection while the disease is still asymptomatic. Diagnosis of cancer at asymptomatic and/or in situ stage increases survival, and preserves effected organs and quality of life. Screening can be successful if the method is adopted by the target population, is easy to implement, has few adverse effects, and reduces cancer-related morbidity and mortality. Additionally, the screening method should be feasible to the economic, social and cultural structure of the country in which it is implemented. In this editorial, I give my perspective on recent debates about breast cancer screening, based on our own experience from “Bahçeşehir Breast Cancer Population-Based Screening Program” and knowledge of the research literature.

Mammography screening has all the features listed above, and has been applied as a screening method for more than 50 years with proven efficacy in reducing mortality (1). With this test, the rates of ductal carcinoma in situ (DCIS) and Stage I invasive breast cancer have reached 20-25% and 50-60%, respectively (1-3). Randomized clinical trials showed that by using screening mammography; the rate of early-stage breast cancer (stages 0 and I) and the chance of breast conservation increased, whereas the mortality rate decreased (1-10).

An ongoing debate has continued for the last 20-25 years on the harms of screening mammography such as false positive findings, over-diagnosis and unnecessary treatment rather than its benefits (1-2, 5, 8, 10). These publications lack fundamental scientific support, which has lead to confusion in women and health care providers, particularly in developing countries such as Turkey. Mammography screening is not nationwide, and there are very limited organized population-based screening programs (such as Bahçeşehir Mammography Screening Project) in Turkey due to low awareness on breast cancer in healthcare providers and the targeted population, inadequate and incomplete screening centers, and low compliance with regular mammography screening. Negative talk on the television and negative articles and columns in newspapers on screening mammography by non-expert physicians and health reports cause adverse effects on mammographic screening and decrease opportunistic and organized screening. Unfortunately, these have achieved a high profile in the mass media and stimulated further debate.

One of the suggested harms of screening mammography is over-diagnosis. Over-diagnosis refers to the diagnosis of in situ or invasive breast cancer through screening mammography that would not have become clinically evident in the absence of screening, and would not change a patient's life expectancy (2, 5, 8, 10). Unnecessary spot and magnification mammography, ultrasonography, MR imaging, biopsy and surgical procedures are performed in these patients for diagnosis of cancer, and some of them require radiotherapy, chemotherapy, and hormonal therapy in addition to surgery. However, to make a conclusion on overdiagnosis and overtreatment, women with either in situ or invasive breast cancer detected by screening mammography should be randomized into two groups (study group with treatment; control group without treatment), and long-term follow-up is necessary to compare the groups. In this way, the value of early diagnosis and treatment in screen detected breast cancer patients can be demonstrated. However, this kind of clinical study cannot be performed due to ethical issues.

The reasons for the high over-diagnosis rate in published randomized clinical trials on mammographic screening may include poor quality of conventional mammography, inexperience of the mammographer or radiologist who interpreted mammography, and short follow-up of women who participated in these studies. All this causes have led to excessive use of both diagnostic methods and biopsy.

In a Canadian study published last year (Pan-Canadian Study of Screening Mammography and Breast Cancer Mortality from Breast Cancer), the results of 7 different Canadian screening programs were evaluated (4). Breast Screening Programs in Canada were invited to participate in this study, and seven out of 12 programs accepted the invitation. These seven programs represented 85% of Canada's popu-

lation within the screening age interval. Data were obtained from the screening programs and corresponding cancer centers and breast cancer diagnoses and details for the period between 1990 and 2009. The number of women in the screening program was 2 796 472. The average breast cancer mortality among participants was 40% (95% confidence interval [CI]=33% to 48%), lower than expected with a range across provinces of 27% to 59%. Age at participation in screening had no significant impact on reduction in mortality. It was concluded that breast cancer mortality was significantly reduced in participants of screening programs in Canada.

Different methods were used in observational studies on screening mammography to detect a reduction in mortality (6-8). The characteristics of the target population that were and were not screened should be similar, and observational studies should be designed in a modern way. Only deaths due to breast cancer should be taken into account during these studies. Broeders et al. (6) evaluated 17 studies on mammography screening in Europe and reported that the decrease in mortality rates among women who regularly attended screening varied between 38% and 48%. The higher mortality rates in observational studies as compared to randomized clinical trials may be explained by; bias, more effective treatment in early stage breast cancer, innovations in scanning technology, and increased participation in screening by invitation. In another Canadian study for the period between 1990 and 2000, there was an increase in overall survival among women who participated in screening, while the survival rate remained unchanged in those who were not screened during the same period (9).

The debate on the continuum and benefits of mammographic screening are linked to not using appropriate methods in the evaluation of these results (10). In order to further reduce deaths from breast cancer, we should emphasize the importance of screening for women and ensure that women start annual mammography screening from the age of 40 years. We should invite women to better quality screening programs, and need to support such programs. We need to create individual screening and diagnostic methods by increasing basic research and clinical studies, and by developing newer and better technologies.

Bahçeşehir Population-Based Organized Mammography Screening Project

Organized population-based mammography screening programs have been implemented in the United States of America and Western Europe for 50 and 30 years, respectively. Unfortunately, there is no organized nationwide mammography screening program in Turkey. The Cancer Early-Diagnosis, Screening and Training Centers (KETEM) founded by the Cancer Control Department have been providing opportunistic screening free-of-charge. In a study conducted in Bahçeşehir on 1200 women aged between 40-69 years, we found that only 49% had had a mammogram within the last 2 years (11). In the same area in which we implemented the screening program, the number of women who regularly attended the screening program was over 80%. In the Mus provinces in Eastern Anatolia, a study of 2400 women aged 40-69 years revealed that only 35% of these women had undergone a mammography within the last 2 years (12). The most important reasons for the relatively low participation in screening mammography are; failure to establish the necessary infrastructure, lack of sufficient trained health workers and breast imaging specialists, and the low level of awareness and knowledge on breast cancer in both society and health care providers. In fact, the lack of scientific studies from our country on this issue, not knowing how often and what age group

should be screened, and lack of cost-effective analysis are other significant shortcomings. Mammographic screening in our country is generally conducted by invitation of women through the media, family physicians, friends, and sometimes by the system. Unfortunately, there are no regular invitations or registration system based on addresses in Turkey. Women in the 40-69 years age group, and who present to the Ministry of Health Cancer Early-Diagnosis, Screening and Training Centers (KETEM), university medical faculty and state hospitals breast clinics, private hospitals and oncology institutes are encouraged to undergo mammography. With a regulation made by the Ministry of Health, mammography can be obtained free-of-charge.

The “Bahçeşehir Breast Cancer Population-Based Screening Program”, which will last for 10 years in Bahçeşehir, which was launched in 2008 in order to verify the feasibility of a population-based screening program, is organized, continuous, and based on invitation within our country's social, cultural, educational, and economic structure (13, 14). Other objectives of this study conducted by the Breast Health Society (Meme Sağlığı Derneği-MEMEDER), which may serve as an example for low- to middle-income countries, were to determine the age for starting screening (40 or 50 years), to show positive effect of mammography screening on DCIS, early stage breast cancer, breast conserving surgery and breast cancer mortality rates. Another important aim of the study was to determine the cost-effectiveness of screening in Turkey. The rate of participation in screening was relatively high (85%) among invited women.

To date, 7,500 women completed their fourth round of screening in our program. Some 59% of the screened women were in the 40-49 years age group, and 41% were aged 50-69 years. Thirty-eight out of 83 women who were diagnosed as having breast cancer (46%) were in the 40-49 years age group. Nineteen percent of patients had ductal carcinoma in situ (DCIS), and two thirds of these patients were in the 40-49 years age group. Of the patients with invasive breast cancer, 55% had stage I breast cancer. The rates of DCIS and stage I breast cancers detected in this program were similar to the rates in western societies where screening is performed regularly, which suggests that population-based screening could be implemented in our country. A comparison of patients who were diagnosed as having breast cancer in the Bahçeşehir program with those in the Turkish Federation of Breast Diseases Societies (TFBDS) Breast Cancer Registry Program revealed that mammography screening increased life expectancy to a mean of 5.84 years in each patient diagnosed in this program (15). The Cancer Control Department of Turkish Ministry of Health decided to lower the age for initiating screening for breast cancer from 50 years to 40 years because half of the women with breast cancer both in our screening program and breast cancer registry program were aged under 50 years.

An analysis of the Bahçeşehir Breast Cancer Population-Based Screening Program data revealed that 81% of patients underwent breast-conserving surgery (BCS). BCS was performed in 73% of women aged between 40-49 years, and in 88% aged 50-69 years. Some 93% of patients who were diagnosed as having invasive breast cancer were positive for estrogen receptor (ER), 87% for progesterone receptor (PR), and 13% for HER-2 receptor. HER-2 receptor positivity was 23% in the 40-49 years age group, and 7% in the 50-69 years age group. Among all patients, triple negative breast cancer rate was very low (6%).

The cost-effectiveness analysis of the Bahçeşehir Screening Program was performed at the end of the third screening period (14). In this analysis, the expenses on screening and treatment of patients who were

diagnosed as having breast cancer using screening (asymptomatic patients) were compared with the treatment expenses of patients in the TFBDS Breast Cancer Registry Program (symptomatic patients) (15). The number of women who participated in the third screening period was 7167, and the number of asymptomatic patients who were diagnosed as having breast cancer was 67. The pathologic stages of these patients from Stage 0 to Stage IV were 19.4%, 50.7%, 20.9%, 7.5% and 1.5%, respectively. Therefore, 1/5th of patients in the Bahçeşehir Screening Program had stage 0, and one half had stage II disease, which is parallel to the pathologic stage distribution of patients with screening in developed countries. Stages of breast cancer patients in TFBDS Breast Cancer Registry Program from stage 0 to stage IV were 4.9%, 26.6%, 44.9%, 20.8%, 2.8%, respectively. As such, the rate of in situ cancer among asymptomatic patients who participated in the screening program was 4 times higher, and the rate of stage I breast cancer was twice as high.

The Incremental Cost-Effectiveness Ratio (ICER) in the Bahçeşehir Screening Program (BSP) was calculated as money spent on extra survival for 1 additional year saved according to the TFBDS Breast Cancer Registry Program (ICER=cost BSP – cost FRP / lifetime BSP - lifetime FRP). The average national income in Turkey was accepted as 10,650 dollars per person for 2014 (Gross Domestic Product = GDP \$ 10,650 for 2014). According to the World Health Organization, an ICER value below GDP is considered as cost effective. In our study, the ICER value was calculated as \$ 1,897/year, and this value is equivalent to 15% of the annual national income. In other words, the Bahçeşehir screening program is very cost-effective, economical, and should be implemented.

In our country, where the period from the occurrence of breast cancer symptoms until the beginning of treatment is 14 months, the significance of improving awareness and implementation of population-based mammography screening programs is apparent (16). The 7-year results of Bahçeşehir Population-Based Mammographic Screening Program showed that screening can be performed in our country; the participation rate was 80% even in the 4th screening period; the rate of patients diagnosed with Stage 0 and I breast cancer was over 70%; and was in accordance with the rates in developed countries. Screening mammography has significantly increased the rate of breast conserving surgery (39% in the registry program and 81% in our screening program). As well as saving lives, mammographic screening would seriously contribute to our country's economy.

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