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EDITORIAL/EDİTÖRDEN

BREAST CANCER SCREENING: CURRENT CONTROVERSIES

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Among women, breast cancer is the most common cause of cancer-related death worldwide, and case fatality rates are highest in low-resource countries. Over 457,000 deaths result from breast cancer annually, accounting for >1.6% of female deaths from all causes (1). Projecting to 2010, the annual global burden of new breast cancer cases will be 1.5 million, and an ever-increasing majority will be from Low Middle Income Countries(LIMC). Globally, breast cancer is the most common cancer among women, comprising 23% of the 1.1 million female cancers that are newly diagnosed each year (1,2). Approximately 4.4 million women who were diagnosed with breast cancer in the last 5 year currently are alive, making breast cancer the single most prevalent cancer in the world. Despite the common misconception that breast cancer is predominantly a problem of wealthy countries, the majority of breast cancer deaths in fact occur each year in developing rather than developed countries.

Breast cancer is an urgent public health problem in high-resource regions and is becoming an increasingly urgent problem in low-resource regions, in which incidence rates have been increasing by up to 5% per year. Although global breast cancer incidence rates have increased by approximately 0.5% annually since 1990, breast cancer rates in Turkey, Japan, Singapore, and Korea have doubled or tripled in the past 40 years (2). Despite the younger age structure of most developing countries, breast cancer already accounts for approximately 45% of the incident cases and 54% of the annual deaths (2).

The breast cancer burden in LMICs predictably will continue to increase in coming years on the basis of 1) increasing life expectancy and 2) shifting reproductive and behavioral patterns associated with heightened breast cancer risk(Westernizing Life). Even assuming conservatively that there will be no change in underlying age-specific rates, there could be a nearly 50% increase in global incidence and mortality between 2002 and 2020 due to demographic changes alone (1,2). These increases will be disproportionately high in the developing world.

Favorable breast cancer survival rates in developed countries have been attributed to early detection by screening and timely and effective treatment. But, poorer survival in LMICs is largely due to the late presentation of the disease(lack of awareness, low education, lack of screening programms), which, when coupled with limited resources for diagnosis and treatment, leads to particularly poor outcomes(2).

Breast cancer screening modalities include breast self-examination (BSE), clinical breast examination (CBE), and screening mammography.

Final results from trials of BSE in Russia and Shanghai have been published (3,4,5). The effect of BSE on all-cause mortality in St. Petersburg, Russia, a community without routine mammography screening, was evaluated in a trial that met criteria for fair quality. Despite a significant increase in the number of cases of breast cancer detected when BSE instruction was provided, there was no reduction in all-cause mortality (3). A good-quality randomized trial conducted in Shanghai, China, indicated breast cancer rates of 6.5 per 1000 for women instructed in BSE and 6.7 per 1000 for control participants after 11 years of follow-up (6). The number of women who died of breast cancer was the same in both groups. Published meta-analyses of randomized trials and nonrandomized studies of BSE also indicate no significant differences in breast cancer mortality between BSE and control groups (7,8,9).

Few trials have evaluated the effectiveness or harms of CBE in decreasing breast cancer mortality. In countries with widely practiced mammography screening, the use of CBE rests on its additional contribution to mortality reduction. The Canadian National Breast Screening Study-2 trial (CNBSS-2 trial), which compares mammography with CBE versus CBE alone, showed no difference in mortality between these 2 approaches (10).

Breast cancer is known to have an asymptomatic phase that can be detected with mammography. Mammography screening is sensitive (77% to 95%), specific (94% to 97%), and acceptable to most women (11). Screening mammography is the single modality that has been shown to improve breast cancer mortality in prospective randomized trials, but its cost is prohibitive in many settings. When screening mammography is employed in LMICs, target populations and screening intervals need to be selected in a way that is judged to be optimal for the overall population and within the scope of available resources. Breast cancer carries poorer prognosis in young patients and its frequency in women below 40 years of age is 20%

in Turkey and up to 30% in developing Asian countries (12,13). Thus, screening younger women in LMICs requires more attention and resources to implement.

In LMICs, the average age of women with breast cancer is 10 to 20 years younger than in the western world. In our Turkish Breast Cancer Registry Program, 45% of patients are premenopausal, but in developed countries, this rate is 25%. The rate of women under 40 years old is 53% in US, but it changes from 58% to 83% in different regions of Turkey(68%) (12,13). That means, Turkey and other developing countries have a younger women population and this causes relatively high rate of breast cancer in women under 40 years old. However, this observation does not suggest that the incidence of breast cancer is higher in younger women in LMICs than in more developed countries. This age difference is primarily because of the differences in the age structures of the different populations, with relatively fewer older women in LMC populations. Therefore, recommendations that early detection begin at a younger age in LMICs than in developed countries should be studied. Results of our study with a title of "Breast cancer screening for women aged between 40 to 69, in Bahcesehir, Istanbul will help to understand the place of screening mammography and screening age period in a developing country, Turkey (14). This study also evealuates the value of mammographic screening in women aged between 40 to 49 (14).

U.S. Preventive Services Task Force (USPSTF) reviewed eight important randomized prospective clinical trials in 2009 to determine the effectiveness of mammography screening in decreasing breast cancer mortality among average-risk women aged 40 to 49 years and 70 years or older, the effectiveness of clinical breast examination and breast self-examination, and the harms of screening (15). The conclusions of this survey show that mammography screening reduces breast cancer mortality for women aged 39 to 69 years; data are insufficient for older women, false-positive mammography results and additional imaging are common. No benefit has been shown for clinical breast examination or breast self-examination.

According to results of review, the USPSTF has recommended against routine screening mammography in women aged 40 to 49 years (15). The decision to start regular, biennial screening mammography before the age of 50 years should be an individual one and take into account patient context, including the patient's values regarding specific benefits and harms. The USPSTF recommends biennial screening mammography for women between the ages of 50 and 74 years. It concludes that the current evidence is insufficient to assess the additional benefits and harms of screening mammography in women 75 years or older. The USPSTF also concludes that the current evidence is insufficient to assess the additional benefits and harms of clinical breast examination beyond screening mammography in women 40 years or older. The USPSTF recommends against clinicians teaching women how to perform breast self-examination.

The most controversial recommendation of the Task Force is to delay the onset of routine screening mammography from 40 to 50 years of age. Many observers were concerned that this move away from intensive screening might signal a shift away from the war on cancer, posing a threat to advocacy organizations such as the American Cancer Society. But at a deeper level, the recommendations raise concerns about access to potentially lifesaving care.

Examination of the available data, however, suggests otherwise. The Task Force concluded that among women between 39 and 49 years of age, screening mammography results in a 15% reduction in the risk of death from breast cancer, with the prevention of a single death from breast cancer requiring the screening of 1904 women. Clearly, screening mammography does offer an identifiable survival benefit to women in this age group (16).

What about the harm of screening? The harm of mammography includes radiation risk, short- and long-term anxiety associated with false-positive results, biopsy for benign lesions, and the possibility that some breast neoplasms detected on mammography are nonprogressive and thus overtreated. The risk of a radiation-induced cancer from low-dose mammography(7cGy) is so low that although theoretically possible, it would be impossible to measure empirically (16,17). The possibility that some breast cancers are nonprogressive has been a source of considerable interest, but the weight of evidence from long-term studies suggests that it is a small problem and mostly confined to ductal carcinoma in situ (18,19,20). Studies that have concluded that the magnitude of overdiagnosis is large have commonly examined population data over a period of limited duration and confused overdiagnosis with background increases in incidence and increased incidence associated with the lead time gained from screening (20). The more common and more directly measurable harm associated with mammography includes the inconvenience from additional imaging resulting from false positives, benign biopsy for abnormal findings, and short- and longterm anxiety resulting from false-positive results.

Despite of the USPSTF recommendations, the ACS still recommends that average-risk women should begin annual mammography at the age of 40 years. Women also should be informed about the scientific evidence demonstrating the value of detecting breast cancer before symptoms develop, and that the balance of benefits to possible harm strongly supports the value of screening and the importance of adhering to a schedule of regular mammograms (21). The benefits of mammography include a reduction in the risk of dying from breast cancer, and if breast cancer is detected early, less aggressive surgery (ie, lumpectomy vs mastectomy, sentinel lymph node biopsy vs axillary lymph node dissection), less aggressive adjuvant therapy (ie, hormonal therapy alone), and a greater range of treatment options. Women should also be told about the limitations of mammography, specifically that mammography will not detect all breast cancers, and that some breast cancers detected with mammography may still have poor prognosis. Furthermore, women should be informed

about the potential for false positives, some of which may not be resolved with additional imaging, and that if not, a biopsy will be required to rule out the possibility of breast cancer.

These changes in the recommendations were unanticipated. Based on prior evidence reviews, the only new data that the USPSTF was likely to consider was from the results of the UK Age Trial, which randomized women aged 40 to 41 years to a group invited to screening versus usual care to measure the effect of mammography in a group of women in their 40s without any age migration past age 50 years (22). The Age Trial observed a 17% reduction in breast cancer mortality in the group invited to screening compared with the control group (relative risk [RR], 0.83; 95% confidence interval [CI], 0.66-1.04.11), a result that was consistent with results from earlier trials, and also consistent with the less sensitive screening protocol applied in this study,33 ie, double-view mammography on the first exam and single-view mammography on subsequent exams. The USPSTF updated the meta-analysis of all trials excluding the Edinburgh trial, and concluded that an invitation to mammography was associated with a 15% reduction in the risk of dying from breast cancer among women screened in their 40s, and a 14% reduction in risk for women screened in their 50s (23).

As the case can be made that breast cancer is an important health problem for women in their 40s, is the evidence of benefit so small and the magnitude of harm so great that their previous recommendation for screening women in their 40s should be rescinded? With respect to benefit, the randomized trials provided convincing evidence that mammography screening saves lives principally by advancing the lead time and reducing the incidence of advanced disease (21). However, the summary RR from metaanalysis of all the trials is not a good measure of effectiveness for several reasons. First, the trials measured the effectiveness of an invitation to screening, not actually being screened. Second, in a meta-analysis, trials with ineffective protocols are combined with trials that had effective protocols. It is well established that in some of the early trials, women were screened with protocols that were especially limited for women under age 50 years (24). These ineffective protocols are characterized by long screening intervals (>24 months) and single-view mammography. It is also evident from examining the RR of being diagnosed with an advanced breast cancer in the different trials why some trials showed significant mortality reductions and some did not, because there is a strong association between the magnitude of the risk reduction of being diagnosed with an advanced breast cancer and the eventual observed mortality reduction (25). This was especially the case with 2 second-generation trials, the Gothenburg Trial and the Malmo trial, which screened women at a shorter interval (12 to 18 months) with double-view mammography and observed 44% and 36% mortality reduction, respectively (26,27).

There are a few organized population based screening programs in Turkey. Mostly, opportunistic screening has been performed in different centers. For this reason, we have started "Bahcesehir Breast Cancer Screening Program" in 2008 in Istanbul Turkey. Aims of the study are to detect possibility of implementation of an organized population based breast cancer screening program in Turkey, as a developing country. This trial will also help to find the age (40 or 50 years) to start screening and cost effectiveness of screening mammography. This long term (ten years, 2010-2018) program will include 4.500 asymptomatic women between the aged 40 to 69. Physical examination and, two views of mammogram have been performed to invited women. Additional views and/or ultrasound are performed in patients with BIRADS 0 mammograms. 3.650 women screened in two years, and recall rates for additional views were 15% in 2009, and 20% in 2010, respectively. 1855 women (57.5%) aged 40-49 years, and 1370 women(43.5%) aged 50-69 years were screened. 13 breast cancer were diagnosed. Seven of them were the aged 40 to 49, and six of them were over 50 years old. Four patients had ductal carcinoma in situ (DCIS), and eight patients had stage I breast cancer. Only one patient with stage II breast cancer and required systemic chemotherapy. Preliminary results of the trial showed that screening mammography is feasible and should be started at age 40 years old.

As a conclusion, screening mammography for women in their 40s is clearly effective. The problem is that the benefit is tiny and expensive. BSE and CBE have advantages to increase breast cancer awareness in women.

As we move forward, we must remember that mammography may be our best tool for breast-cancer screening, but we urgently need more accurate and cost-effective screening methods to decrease the burden and mortality rate of breast cancer. Our understanding of the molecular basis of breast cancer continues to evolve, and we now view it as a family of distinct disease subtypes which may well require their own screening tools. Moreover, the evolution of breast-cancer treatment is likely to have a profound effect on the way we conceptualize screening. There may be room for debate about the optimal age at which to begin screening and the optimal frequency of screening, but there is no debate that technical advances will make these controversies fade. Although we must optimize what is available today, we must also promote far better approaches for tomorrow.

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