RESEARCH ARTICLE

Successful First Round Results of a Turkish Breast Cancer Screening Program with Mammography in Bahcesehir, Istanbul

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Abstract

Background: The Bahcesehir Breast Cancer Screening Project is the first organized population based breast cancer mammographic screening project in Turkey. The objective of this prospective observational study was to demonstrate the feasibility of a screening program in a developing country and to determine the appropriate age (40 or 50 years old) to start with screening in Turkish women. Materials and Methods: Between January 2009 to December 2010, a total of 3,758 women aged 40-69 years were recruited in this prospective study. Screening was conducted biannually, and five rounds were planned. After clinical breast examination (CBE), two-view mammograms were obtained. True positivity, false positivity, positive predictive values (PPV) according to ACR, cancer detection rate, minimal cancer detection rate, axillary node positivity and recall rate were calculated. Breast ultrasound and biopsy were performed in suspicious cases. Results: Breast biopsy was performed in 55 patients, and 18 cancers were detected in the first round. The overall cancer detection rate was 4.8 per 1,000 women. Most of the screened women (54%) and detected cancers (56%) were in women aged 40-49. Ductal carcinoma in situ (DCIS) and stage I cancer and axillary node positivity rates were 22%, 61%, and 16.6%, respectively. The positive predictivity for biopsy was 32.7%, whereas the overall recall rate was 18.4 %. Conclusions: Preliminary results of the study suggest that population based organized screening are feasible and age of onset of mammographic screening should be 40 years in Turkey.

Keywords: Breast cancer - mammography screening - detection rate - age - Turkish women

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Introduction

Breast cancer is the second most frequent cancer in women with 1.38 million new cases estimated in 2008. It has been the most common cancer both in developed and developing countries with 690,000 new cases estimated in each region. Breast cancer incidence in Turkey is 35.8/100,000 according to the data of Ministry of Health (Ferlay et al., 2008; Ozmen, 2008; http://www.ketem.org/istatistik.php). In 2008, 10065 new breast cancer case and 4311 breast cancer associated death were stated (http://globocan.iarc.fr/). Breast cancer incidence has increased more than twice in the last two decades in Turkey (from 24/100,000 in 1993 to 50/100,000 in 2010) due to westernizing life style and aging (http://www.ketem.org/istatistik.php). Randomized trials of breast cancer screening through mammography among women ages 40-69 years have shown a decreasing mortality rate from breast cancer by 25-35% (Andersson and Janzon, 1997; Larsson et al., 1997; Alexander et al., 1999; Bjurstam et al., 2003; Moss et al., 2006). In addition, detection of smaller cancers have the ability to benefit many women by permitting breast preservation. However, breast cancer mortality rates are still high in Eastern Europe, and especially in low-middle income countries due to lack of awareness and organized population based mammographic screening programs. Screening mammography is the only single modality that has improved breast cancer mortality in many prospective randomized trials, but its cost is prohibitive in many settings (Nyström et al., 1993; 2002; Anderson and Distelhorst, 2008; Ozmen and Anderson, 2008). Regular organized population based mammographic screening for breast cancer has been widely recommended by most preventive service organizations for the past several decades.

In Turkey, the national population-based breast cancer screening guideline was published by the Cancer Control Department of Health Ministry in 2004 recommending biannual mammographic screening for women aged 50-69 years similar to European Union countries (RSHMB, 2004). However, there are differences in age distribution and health expenditure between Turkey and western

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countries. The population is younger in Turkey than other western countries, and 68% of women are less than 40 years old. The statistical analysis of Turkish breast cancer registry program also showed that almost 50% of women with breast cancer were premenopausal and less than 50 years old (Ozmen, 2008). Therefore, the feasibility of an organized mammographic screening program including women aged between 40-50 years should be studied in Turkey.

The aims of the current trial are to demonstrate the feasibility of a population-based organized mammographic screening program in a developing country, to determine the efficacy of a screening program to detect breast cancer at an earlier stage and to find out the appropriate starting age of breast cancer screening in Turkish women.

Materials and Methods

Study population

A total of 4257 women living in Bahcesehir county were invited to Bahcesehir Breast Center (MEMEDER) for breast cancer screening between January 2009-December 2010. Women who responded to invitations if they were diagnosed with breast cancer by any physician, or had mammograms within the past year or a biopsy within 6 months, or were pregnant were not included in the study. An approval by Institutional Review Board of Istanbul University was obtained. Each eligible woman was informed and signed the consent.

Screening procedure

Data of first invitation to screening was defined as the start point. Two views, (mediolateral oblique (MLO), and craniocaudal (CC)), of each breast were obtained. All examinations were double read by two independent radiologists who were blinded to each other's interpretations. Mammographic findings were classified according to Breast Imaging Reporting and Data System (BI-RADS) of the American College of Radiology (ACR) (Reston, 2003), and management recommendations were based on the assessment categories. Mammograms reported as BI-RADS 1 and 2 in the initial reading were considered as "final mammography". The final BI-RADS categorization for BI-RADS 0 mammograms was however considered as "final report" following some additional work-up. Both radiologists made their decision in consensus whether the participant would be discharged or recalled for further evaluation. Women with negative mammograms, benign or probably benign mammographic findings (BI-RADS 1, 2 and 3) were not referred for further diagnostic workup. Women with mammograms categorized as BI-RADS 0 (incomplete, need additional imaging assessment) were recalled for additional workup including additional mammographic views such as spot compression and magnification mammogram, or ultrasonography (US). The recommendations for recalls which were due to technical reasons, such as image artifacts were excluded.

In case of suspicious abnormality or highly suggestive of malignancy (BI-RADS 4 or 5 cases) in the final report, the radiologists decided on whether to proceed to an additional workup such as core needle aspiration biopsy (CNB) guided by ultrasonography (14-16 gauge), or a vacuum assisted large core (11 gauge) stereotactic (VALCS) biopsy. The diagnostic process was completed within 4 weeks to minimize the period of uncertainty. The outcome data was collected prospectively, and entered into a computer database for practice audit purposes and to satisfy American College of Radiology (ACR) requirements.

Outcome measurements

The following parameters were used to evaluate the performance of screening mammography: True positivity, false positivity, positive predictive values (PPV) according to ACR, cancer detection rate, minimal cancer detection rate, axillary node positivity and recall rate. The PPV was calculated by dividing the number of true-positive examinations by the sum of true-positive and false-positive examinations (PPV: TP/(TP+FP). Three seperate PPV calculations were performed by using BI-RADS methods: PPV1 (probability of cancer following a positive mammographic interpretation), PPV2 (probability of cancer following a BI-RADS assessment of 4 or 5), and PPV3 (probability of cancer among patients undergoing biopsy following a BI-RADS 4 or 5 assessment).

Minimal cancer detection was defined by dividing the sum of DCIS cases and small invasive cancers <1cm by all TP cases (number of DCIS+number of <1cm invasive cancers/all TP)×100. Axillary node positivity was calculated as: ***(number of positive axilla/all cancers)×100***.

Results

Of 4257 women invited to participate in this study, a total of 3758 women between 40 and 69 years were eligible for screening (88.3%). The number of women aged between 40-49 years were 2024 (53.9%), whereas there were 1734 women (46.1%) between 50-69 years. Of 3758 women, 1193 (31.7%) were screened in 2009, and 2565 (68.3%) were screened in 2010, respectively.

A total of 2853 mammogram was categorized as BI-RADS 1 and 2 (mammograms finalized as BI-RADS 1 and 2 at the initial reading). There were 193 (7.3%) mammograms categorized as BI-RADS 3 with a 6 month short term follow-up. Twenty mammograms were categorized as BI-RADS 4 or 5. There were 692 BI-RADS 0 mammograms according to final mammographies. The overall recall rate for spot/ magnification mammography

Table 1. Number of Women Classified According to BI-RADS Categorization

BI-RADS 1 and 2 (Final mammogram=MMG)	2853 (75.9%)
BI-RADS 1 and 2 (Final report)	365 (9.7%)
BI-RADS 3 (Final MMG)	193 (5.1%)
BI-RADS 3 (Final report)	278 (7.4%)
BI-RADS 4, 5 (final MMG)	20 (0.5%)
BI-RADS 4, 5 (final report)	55 (1.4%)
BI-RADS 0	692

*Of 3764 screened women, 6 women with BI-RADS 0 haven't returned back for additional work-up and were excluded from the analysis and US was 18.4%. BI-RADS categorization of the patients were shown in Table 1.

Of 55 biopsies, 18 cancers were detected (%32.7). Of 18 cancers, 10 (55.6%) were detected in women aged between 40-49, whereas 8 (44.4%) were detected in 50-69 years. The overall cancer detection rate was 4.8 per 1000 women. The number of DCIS and invasive carcinoma were 4 (22%) and 14 (77.8%), respectively (Table 2). The rate of stage I cancers was 61%. Of 14 invasive cancers, 11 was invasive ductal cancers, whereas 2 were tubular cancers, and one was lobular cancer. The percentage of invasive breast cancer <1 cm was 27.8%. Axillary node positivity rate was 16.6%. The number of TP and FP cases, PPV, cancer detection rate, minimal cancer detection rate and axillary node positivity and the comparison of other values with previous reports are shown in Table 2.

Discussion

Early detection and effective treatment of breast cancer result in dramatic improvement in the outcome of patients. Data from the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) program stated that breast cancer mortality rate declined by 2.3% each year between 1990 and 2003 after effective breast screening in USA (SEER, 2005). Breast cancers detected by screening mammography are smaller and have a more favorable prognosis compared to tumors detected outside the screening (Gilliland et al., 2000; Groenendijk et al., 2000; Joensuu et al., 2004). Therefore, screening mammography has been claimed as the most valuable tool for detection of early breast cancer. The reports of randomized controlled trials demonstrated a reduction in breast cancer mortality rate by mammography screening among women 40-74 years of age (Tabar et al., 1985; Andersson et al., 1988; UK Trial of Early Detection of Breast Cancer Group, 1988; Frisell et al., 1991. Although the early detection has gained importance in developed countries, with increased awareness and organized screening programs, the situation is vice-versa in developing countries where screening is not common.

The population based screening mammography has been introduced in 2006 but a high attendance to the screening programs has not been achieved yet in Turkey. Bahcesehir Breast Cancer Screening Project, is a 10 year-organized population-based screening program (between 2008 to 2018) carried out in women aged 40-69 years living in Bahcesehir, which is one of the recent largest residencial aera in the European side of Istanbul, Turkey. Bahcesehir has been selected to carry out the current study because the address based population registration system is well organized in this county, and the population has a high level of education with a higher income compared to other regions of Turkey (Ozmen et al., 2011). We believe that by increasing the sociodemographic determinants, the awareness of breast cancer is increased and a higher attendance to screening programs may be achieved.

Due to nation-wide organized screening programs and increased awareness, ductal carcinoma in situ (DCIS), and stage I breast cancer rates were 20% and 62% in USA, respectively (Gnerlich et al., 2009). According to Turkish National Breast Cancer Registry Program Data, only 5% and 27% of patients had DCIS and Stage I breast cancer at diagnosis, respectively (Ozmen, 2012). The current prospective study showed higher rates of DCIS (22%) and Stage I (61%), respectively, and these results similar to results in developed countries with organized screening. Our findings strongly suggest that an efficient screening program can result in a significant stage shift towards lower stages, and saves lives. Especially in Eastern Turkey, breast cancer is diagnosed at advanced stages, and modified radical mastectomy is the standart treatment due to lack of awareness and screening programs. In many areas in Turkey, women presenting with a breast lump are diagnosed with surgical biopsies, and are treated without following a radiological work-up. It is very well known that most of the screening detected breast cancers are nonpalpable, and non-metastatic to axilla, and convenient for breast conserving surgery.

According to Surveillance, Epidemiology and End Results (SEER) Program Data; the average age of breast cancer in the years 2003-2007 is 61. The incidence of breast cancer in age 35-44, 45-54, 55-64 are 10.5%, 22.6% and 24.1% respectively. The recommendations of

Table 2. Outcome Values: TP, FP, PPV Cancer Detection Rate, Minimal Cancer Detection rate and Axillary Lymph Node Positivity

Age	40-49	50-69	Total
TP	10	8	18
FP	23	14	37
PPV1	2.4%		
PPV2	32.7%		
PPV3	32.7%		
Benign/Malignant Biopsies (n)	23/10	14/8	37/18
Cancer detection rate/1000	4.9%	4.6%	4.8%
Minimal cancer detection rate (%)	40%	62%	50%
DCIS (n)	3	1	4
invasive cancer (n)	7	7	14
invasive breast cancer <10mm (n)	1	4	5
Axillary node positivity (%)	30%	0%	16.6%

Table 3. Comparison of Outcome Recommendations with Our Findings

Outcome measurements (%)	Agency for Health Care Policy and Research (AHCPR) Guidelines (1994) (16)	European and United Kingdom Guidelines (2001 and 2005) (17)	British Columbia Study Results (18)	The Breast Cancer Surveillance Consortium (BCSC) (1996-2002) (15)	ACR Require ments (14)	Current Study
Recall rate (%)	≤10	<7 (min) ≤5 (desirable)	9.8	9.7 (4.4-16.8)	<10%	18.4
Cancer detection rate (%)	6-10	3	5	4.4 (2.4-7.0)	2-10%	4.5
PPV1 (%)	5-10	N/A	-	4.5 (2.6-8.6)	5-10%	2.3
PPV2 (%)	25-40	-	-	25.0 (14.1-38.8)	25-40%	26.9

mammographic screening are determined by international organizations and differ in every country according to their own standards dependent on screening policies. The randomized controlled trials and observational studies of screening programs have shown the efficacy of mammographic screening in women aged 50-69 years (Glasziou and Houssami, 2011). In almost all countries outside the USA, screening programs start at 50 years of age. In years between 2002-2009, United States Preventive Services Task Force (USPSTF) guidelines recommended routine mammographic screening at least every two years for women aged 40-49 and annual screening for women aged 50 and older (US Preventive Services Task Force, 2002; Woolf, 2010). In 2009, the recommendation was against routine screening for women 40-49 and it was stated that for each women the decision to start regular, biennial screening mammography before the age of 50 years should be an individual one (US Preventive Services Task Force, 2009).

In Turkey, the recommendation of Cancer Control Department of the Ministry of Health was a biennial mammography for women aged between 50-69 years up to 2012. However, according to the recent Turkish national database, the incidence of breast cancers detected 40-49 years is 30.4% (Olivotto, 2000), and the Turkish Ministry of Health has implemented a new recommendation of starting mammographic screening at the age of 40. In the current study, more than half of the cancers (55.6%) were detected between 40-49 years which was a considerable high rate among screening detected cancers.

For a high quality breast cancer screening program, a high cancer detection rate along with an earlier stage and also a low recall rate is required. It is well known that mammographic outcomes and accuracy measurements can be variable. In the first round, our overall cancer detection rate was 4.8 per 1000 women which is comparable with those published by other programs (Bassett, 1994; Olivotto, 2000; Liston and Wilson, 2005). The results of this study showed a quite high rate of minimal cancer detection (50%) and a very low rate of axillary involvement (16.6%). These are two important indicators of an effective screening. The positive predictive value (PPV) rates were also consistent with ACR recommendations (PPV2&PPV3=32.7%) (RSHMB, 2004). The PPV1 rate was lower than the recommended (2.4% vs 5-10%). This might be due to our higher recall rate which was 18.4%.

The recommended recall rates are less than 10%, 5% and 7% in United States, European guidelines and United Kingdom guidelines, respectively (Perry et al., 2001; Liston and Wilson, 2005) (Table 3). In the current study, the recall rates were 20% and 16.2 % in women aged 40-49 and 50-69 years, respectively, which is almost twice of these recommendations. This high recall rate can be explained by three factors. First; this study is the first organized screening program held in Turkey. The radiologists generally practice in diagnostic breast imaging units whereas screening is solely opportunistic. Therefore, they are not used to evaluate a high number of screening mammograms. Second; the rate of screened women aged 40-49 was 59% and this high rate caused a high number of dense mammograms leading to difficulty in interpretation. Third; the new malpractice law on medical practices in Turkey brought more responsibilities and penalties to the doctors that could cause an insecurity feeling in decision making. We believe that with increasing experience in screening program, these problems can be overcome, and recall rates can be decreased to acceptable lower rates (Sickles et al., 2002; Beam et al., 2003).

In conclusion, the preliminary findings of current study suggest that mammographic screening is possible and feasible in Turkey, but requires patients, continuous efforts, and experienced team. It increases in situ and stage I breast cancer rates. The prevailing view that mammographic screening increases early stage breast cancer detection rate. The starting age of breast cancer screening may be decreased to 40 years of age due to young age structure of the country and most of the patients detected are younger than 50 years old.

References

Alexander FE, Anderson TJ, Brown HK, et al (1999). 14 years of follow-up from the Edinburgh randomized trial of breast cancer screening. *Lancet,* **353**, 1903-8.

Altekruse SF, Kosary CL, Krapcho M, et al (2007). SEER Cancer Statistics Review, 1975-2007, National Cancer Institude. Bethesda, MD.

Anderson BO, Distelhorst SR (2008). Guidelines for international breast health and cancer-control implementation. Introduction. *Cancer*, **15**, 2215-6.

Andersson I, Aspegren K, Janzon L, et al (1988). Mammographic screening and mortality from breast cancer: the Malmö mammographic screening- trial. *BMJ*, **297**, 943-8.

Andersson I, Janzon L (1997). Reduced breast cancer mortality in women under age 50:updated results from the Malmo Mammographic Screening program. *J Natl Cancer Inst Monogr*, **22**, 63-7.

Bassett LW, Hendrick RE, Bassford TL (1994). Quality determinants of mammography. In: Clinical practice guideline no. 13: AHCPR publication no. 95-0632. Rockville, Md: Agency for Health Care Policy and Research, Public Health Service, U.S. Department of Health and Human Services.

Beam CA, Conant EF, Sickles EA (2003). Association of volume and volume independent factors with accuracy in screening mammogram interpretation. *J Natl Cancer Inst*, **95**, 282-90.

Bjurstam N, Björneld L, Warwick J, et al (2003). The gothenburg breast cancer screening trial. *Cancer*, **97**, 2387-96.

Ferlay J, Shin HR, Bray F, et al (2010). Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer*, **10**, 1002.

Frisell J, Eklund G, Hellstrom L, et al (1991). Randomisedstudy of mammographic screening: preliminary report on mortality in the Stockholmtrial. *Breast Cancer Res Treat*, **18**, 49-56.

Gilliland FD, Joste N, Stauber PM, et al (2000). Biologic characteristics of interval and screen-detected breast cancers. *J Natl Cancer Inst*, **92**, 743-9.

Glasziou P, Houssami N (2011). The evidence base for breast cancer screening. *Prev Med*, **53**, 100-2.

Gnerlich JL, Deshpande AD, Jeffe DB, et al (2009). Elevated breast cancer mortality in women younger than age 40 years compared with older women is attributed to poorer survival in early-stage disease. *J Am Coll Surg*, **208**, 341-7.

Groenendijk RP, Bult P, Tewarie L, et al (2000). Screen- detected breast cancers have a lower mitotic activity index. *Br J*

Cancer, **82**, 381-4.

Harris R, Yeatts J, Kinsinger L (2011). Breast cancer screening for women ages 50 to 69 years a systematic review of observational evidence. *Prev Med,* **53**, 108-14.

Joensuu H, Lehtimäki T, Holli K, et al (2004). Risk for distant recurrence of breast cancerdetected by mammography screening or other methods. *JAMA*, **292**, 1064-73.

Larsson LG, Andersson I, Bjurstam N, et al (1997). Updated overview of the Swedish randomized trials on breast cancer screening with mammography: age group 40-49 at randomization. *J Natl Cancer Inst Monogr*, **22**, 57-61.

Liston J, Wilson R (2005). Quality assurance guidelines for breast cancer screeningradiology. NHS Breast Screening Programmes publication no. 59. Sheffield, England:NHS Cancer Screening Programmes, January 2005.

Moss SM, Cuckle H, Evans A, et al (2006). Trial Management Group. Effect of mammographic screening from age 40 years on breast cancermortality at 10 years' follow-up: a randomised controlled trial. *Lancet*, **368**, 2053-60.

Nyström L, Rutqvist L, Wall S, et al (1993). Breast cancer screening with mammography: overview of Swedish randomised trials. *Lancet*, **341**, 973-8.

Nyström L, Andersson I, Bjurstam N, et al (2002). Long-term effects of mammography screening: upated overview of the Swedish randomized trials. *Lancet*, **359**, 909-19.

Olivotto IA, Kan L, d'Yachkova Y, et al (2000). Ten years of breast screening in the Screening Mammography Program of British Columbia, 1988-97. *J Med Screen*, **7**, 152-9.

Ozmen V (2008). Breast cancer in the world and Turkey. *J Breast Hlth*, **4**, 7-12.

Ozmen V (2012). Türkiye'de Meme Kanseri, Türkiye Meme Hastaliklari Federasyonu, Ulusal Meme Kanseri Veri Tabani Verilerinin Analizi. 2012, İstanbul.

Ozmen V, Anderson BO (2008). The challenge of breast cancer in low and middle income countries implementing the Breast Health Global Initiative Guidelines. *Asia Pac Oncol and Haematol*, **1**, 31-4.

Ozmen V, Ozaydin AN, Cabioglu N, et al (2011). Survey on pilot mammographic screening program in Istanbul, Turkey. *Breast J*, **17**, 260-7.

Perry N, Broeders M, deWolf C, Tornberg S (2001). European guidelines for quality assurance in mammography screening. 3rd ed. Luxembourg: European Commission.

RSHMB (2004). www.tusak.saglik.gov.tr/pdf 2004.

Reston VA (2003). Illustrated breast imaging reporting and data system (BI-RADS). In:American College of Radiology (ACR), 4th edn 2003:234.

Schopper D, de Wolf, C (2009). How effective are breast cancer screening programmes by mammography? Review of the current evidence. *Eur J Cancer*, **45**, 1916-23.

Sickles EA, Wolverton DE, Dee KE (2002). Performance parameters for screening and diagnostic mammography: specialist and general radiologists. *Radiology,* **224**, 861-9.

Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov): SEER* Stat Database: Incidence-SEER 9 Regs Public Use, Nov 2005 Sub (1973-2003), National Cancer Institute, Division of Cancer Control and Population Sciences, Surveillance Research Program, Cancer Statistics Branch.

Tabar L, Fagerberg CJ, Gad A, et al (1985). Reduction in mortality from breast cancer after mass screening with mammography: randomised trial from the Cancer Screening Working Group of the Swedish National Board of Health and Welfare. *Lancet*, **1**, 829-32.

UK Trial of Early Detection of Breast Cancer Group (1988). First results on mortalityreduction in the UK Trial of Early Detection of Breast Cancer Group. *Lancet*, **2**, 411-6.

US Preventive Services Task Force (2002). Screening for Breast Cancer: Recommendations and Rationale. *Ann Intern Med*, **137**, 344-6.

US Preventive Services Task Force (2009). Screening for Breast Cancer: U.S. PreventiveServices Task Force Recommendation Statement. *Ann Intern Med*, **151**, 716-26.

Woolf SH (2010). The 2009 breast cancer screening recommendations of the US Preventive Services Task Force. *Jama*, **303**, 162-3.