Screening mammography for early detection of breast cancer

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Summary

From numerous studies on breast cancer it can be concluded that no single measure can lessen the burden of this frequent cancer in women in all developed countries. Complex strategies including primary prevention by identification of risk factors and their modification, secondary prevention by earlier detection and tertiary prevention by improving treatment outcome are needed to control the disease.

Besides age, the established breast cancer risk factors include certain benign breast diseases, family history, ionising radiation, some reproductive factors and obesity. Primary prevention includes general recommendation for healthy lifestyle, e.g., avoidance of obesity, proper diet, physical activity and moderate alcohol consumption.

Randomised controlled trials conducted in the USA, Canada, Scotland and Sweden have shown that regular mammography, alone or in combination with clinical examination, is effective in reducing mortality for about 30% in women over the age of 50, and much less in younger population. However, mammography screening has several drawbacks, the major being its tendency towards false positive and false negative results with all their potential psychosocial consequences. High quality assurance and control, as well as effective and readily available treatment, all of which demand high investments, are indispensable for good results. Even in the absence of organised screening, the availability of effective treatment may contribute to reduction in breast cancer mortality.

Key words: breast cancer, mammography, prevention, screening

Introduction

Breast cancer is among the most common cancers affecting women in the developed western world. It is second in North- ern Africa, the Caribbean, South America, Western Asia, and Micronesia/Polynesia [1]. The number of new breast cancer cases worldwide was estimated to be 719,000 in 1985 (422,000 in developed countries and 297,000 in developing countries). It is estimated that the total number of new breast cancer cases per year worldwide will increase from 794,000 in 1990 to close to 1 million in the year 2000. This represents an increase of 23.9% for the period 1990 to 2000, over 2% per year. The increase in the total number of cases is due to population increase and ageing, changes in data sources and methods and/or a true increase in risk [1]. It is estimated that breast cancer caused 339,000 deaths worldwide in 1990: 6% of all cancer deaths and 13.3% of all female cancer deaths. It is expected that the number of deaths will increase to 420,000 by the year 2000 [2].

Wide geographical variation is observed for both incidence and mortality rates. In the period from 1988 to 1992 the highest age standardised incidence rates around the world were found among white females in USA; in certain parts of Canada and France (80–100 per 100,000), intermediate rates in Canada, in Western and some countries in Central Europe (30–80 per 100,000) and the lowest rates in Asia and Africa (7–30 per 100,000). The highest risk is more than 12-fold greater than the lowest [3].

Compared with other cancers the impact of breast cancer is magnified because women are at risk beginning in their middle years rather than at more advanced ages. As a consequence, the average years of life lost by those with breast cancer (20 years) is higher than the average for all cancers combined (16 years) [4].

From numerous studies on breast cancer it can be concluded that no single measure can lessen the burden of this disease. Complex strategies including primary prevention by identification of risk factors and their modification, secondary prevention by earlier detection and tertiary prevention by improving treatment outcome are needed to control the disease.

Breast cancer risk factors and primary prevention of breast cancer

The identification of factors associated with an increased risk of breast cancer may provide information regarding the etiology and progression of breast cancer. In addition to providing clues for effective preventive interventions, this information can be used to identify individuals at high risk of developing breast cancer, so that prevention and screening interventions can be provided to the individuals most likely to benefit.

Large variation in the rates of breast cancer among countries and over time within countries, and increase in the rates
of breast cancer among populations migrating from low risk to high risk countries indicate that a large proportion of breast cancer is related to environmental or lifestyle factors [5].

Established breast risk factors, consistently found in the majority of studies, include previous breast cancer in one breast, family history of breast cancer, fibrocystic disease and ionising radiation. The reported range of relative risk estimates of breast cancer in relation to these factors is 2.1 to more than 4 [6]. For others, the reported range of relative risk estimates is 1.1 to 2.0. These include hormonal and reproductive factors, such as early age at menarche, late age at menopause, late age at first full-term pregnancy and nulliparity [6].

Numerous epidemiologic studies have investigated the role of oral contraceptives in breast cancer risk [7]. The pooled analysis of the individual data from the majority of studies showed a small increase in risk (relative risk in current users 1.24, 95% CI 1.15–1.33) in the time while women are taking oral contraceptives that is gradually approaching 1 after 10 years after stopping [8]. The results of the same data set on the association of hormone replacement therapy and breast cancer showed that among current users of hormone replacement therapy or those who ceased use 1 to 4 years previously, the relative risk of breast cancer is increased by 1.023 for each year of use [9]. Five or more years after cessation there was no significant excess of breast cancer.

Lifestyle related factors include body mass index, physical activity, diet and alcohol consumption. The risk of breast cancer appears to increase with increasing body mass index among post-menopausal women [10]. Even though there is no evidence from prospective studies that adult fat intake is associated with breast cancer risk [11], some studies point to the possible protective effect of olive oil [12, 13]. There is evidence of a modest increase in risk of breast cancer with increased alcohol consumption [14]. A recent pooled analysis of six prospective cohort studies indicates, that for alcohol intakes of less than 60 g daily (about two to five alcoholic drinks), breast cancer risk increases linearly with intake. Women drinking at least 30 g alcohol daily have a 30%–40% higher breast cancer risk than non-drinkers, a risk similar to or greater than that associated with several reproductive factors [15].

Some factors have not consistently been associated with breast cancer in all studies or are still under investigation, such as the protective effect of breast feeding in premenopausal women [16], the role of spontaneous or induced abortion [17] as well as certain chemicals in the environment [18] or breast implants [19].

Despite years of studies and identification of several established and possible breast cancer risk factors, many of them are not readily modifiable through either behavioural or environmental changes. According to the current knowledge, general recommendations for healthy lifestyle, included in the European Code Against Cancer, apply also to primary prevention of breast cancer [20]. The expert panel of the Diet and Cancer Project of the American Institute for Cancer Research concluded in 1997, that the most effective dietary means of preventing breast cancer are the consumption of diets high in vegetables and fruits, avoidance of alcohol, and the maintenance of body weight within recommended levels by consumption of appropriate food and by regular physical activity throughout life [21]. It was estimated that following these recommendations breast cancer incidence may be reduced by about 33%–50% [21]. The panel also judged that the greatest benefit could be achieved if such diets and related factors were established before puberty and continued throughout life. The potential for prevention starting in adult life may be limited largely to that conferred by maintenance of a recommended body weight and avoidance of alcohol; this may account for 10%–20% of cases of this cancer.

Chemoprevention by the use of tamoxifen, retinoids or gonadotropin-releasing factors is being evaluated in large randomised trials in several countries [22, 23]. Although the study on the preventive role of tamoxifen in high risk women in the USA was stopped earlier than planned because of the benefit found [24], there are still too many uncertainties to recommend the use of the drug generally [25].

Secondary breast cancer prevention: Screening

The goal of screening is to detect and treat cancer in its earliest stages to prevent death from the disease. As a disease control strategy and policy, the goal of breast cancer screening is to reduce mortality from breast cancer by distinguishing those individuals in an asymptomatic population who are likely and not likely to have breast cancer. A woman identified by screening tests as likely to have the disease is then referred for further diagnostic testing to determine whether she in fact has the disease and therefore needs treatment [26].

Screening modalities for breast cancer include mammography, clinical breast examination and breast self examination. The efficacy of screening modalities is judged by a reduction in the disease-specific mortality, with randomised clinical trials providing the highest quality of evidence.

Breast cancer screening with mammography alone or in combination with clinical breast examination has been evaluated in several such studies as well as with other study designs.

Screening with mammography: Overall results from randomised controlled trials and results in women aged 50 and over

The first randomised controlled trial that demonstrated the effectiveness of mammography and clinical breast examination in preventing death from breast cancer was the Health Insurance Plan (HIP) Breast Cancer Screening Project that started in 1963 [27]. Women aged 40 to 64 were randomly allocated to either the intervention or control groups, each consisting of 3,100 women. The women in the intervention group were offered four annual screening examinations consisting of two-view mammography and clinical breast examination. Women in the control group received usual care that at that time did not include routine mammography. In the
first 5 years of follow-up, a 37% reduction in breast cancer mortality was observed in the intervention compared to the control group. Nine years from the date of entry, the mortality reduction was 29% [28].

Since then, seven randomised controlled trials have been performed in Sweden, Scotland and Canada [29-35]. The studies differ in the age range of women, screening modality, e.g., the number of views used for mammography and whether clinical examination was included, the interscreening interval and the number of rounds (Table 1).

In the meta-analysis published in 1995 [36], the summary relative risk estimate for breast cancer mortality for women aged 40–74 years undergoing screening mammography in randomised controlled trials compared with those who did not was 0.79 (95% CI 0.71–0.87). In women aged 50–74 the relative risk was 0.77 (95% CI 0.69–0.87). The magnitude of the benefit in this age group was similar regardless of the number of mammographic views, screening interval or duration of follow-up. In women aged 40–49 the relative risk estimate was 0.92 (95% CI 0.75–1.13). It was reduced to 0.83 (0.65–1.06) after 10 to 12 years of follow-up.

From this study and from other reviews of breast cancer screening [37, 38] it can be concluded that screening with mammography reduces breast cancer mortality by around 30% in women aged over 50. The European Society for Mastology Breast Cancer Screening Evaluation Committee concluded in 1993, that screening women aged 50 and over should be part of public health programmes organised on an invitation basis with full quality control and monitoring. It was estimated that when applied to a population it could be expected that a well-organised programme with good compliance could lead to a reduction in breast cancer mortality of the order of 20% [38].

Screening with mammography: Women aged 40–49

The current controversy surrounding screening for women aged 40 to 49 years emanated from the results of subgroup analysis of screening studies. Based on the results of randomised controlled trials there appears to be a delayed reduction in breast cancer mortality 10 years after the initiation of screening [36]. The latest meta-analysis combining the data from eight randomised controlled trials at 10.5 to 18 years of follow-up of women aged 40 to 49 at entry showed a statistically significant 18% mortality reduction among women invited to screening (relative risk: 0.82; 95% CI 0.71–0.95) [39]. Combining all data from the five Swedish trials yielded a statistically significant 29% mortality reduction among women invited to screening (relative risk: 0.71; 95% CI 0.57–0.89) [39].

There is no general agreement to what extent the delayed appearance of this benefit comes from the original screening or from other factors, such as different tumour biology or mammography offered to the women after age 50 [40, 41, 42].

Breast cancer among women 40–49 represents an important public health problem. It has been estimated that almost 20% of cancer deaths and 34% of all years of life expectancy lost because of breast cancer among women of all ages result from cancers found among women younger than 50 years [27]. It is not surprising that in the last few years several expert groups and professional organisations tried to find the most appropriate recommendations on regular screening of women in this age group. Examining the available data on mammography screening in women aged 40 to 49 they have reached different conclusions [38, 43–45].

At the collaborative meeting in Falun, Sweden, in 1996 [44], combined data on population based trials (without the Canadian trial) that included women aged 40–49 were presented showing a relative mortality of 0.76 (95% CI 0.62–0.93). The relative mortality from all randomised trials was 0.85 (95% CI 0.71–1.01). It was concluded that it is likely that mammographic screening of women in the age group 40–49 could reduce subsequent mortality from breast cancer. As detailed analysis suggested that tumour progression in this age group is faster than in the groups aged 50 or more, it is probably necessary to screen the younger group every 12–18 months, with two-view mammography and double reading of films, to obtain substantial benefit.

The same conclusion was not reached at the National Institute of Health Consensus Meeting in January 1997, that ended in two different reports [45]. The majority concluded that the data available did not warrant a universal recommendation for mammography for all women in their forties, while two panel members writing a minority report concluded that

Table 1: Characteristics of the breast cancer screening randomized controlled trials.*

<table>
<thead>
<tr>
<th>Start (y)</th>
<th>Study name</th>
<th>Age</th>
<th>Clinical breast exam</th>
<th>Number of views</th>
<th>Screening interval (mo)</th>
<th>Number of rounds</th>
<th>Participants</th>
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<tr>
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<td></td>
<td></td>
<td></td>
<td>Study</td>
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<td>HIP</td>
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<tr>
<td>1976</td>
<td>Malmö</td>
<td>45–69</td>
<td>no</td>
<td>2</td>
<td>18–24</td>
<td>6</td>
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<tr>
<td>1977</td>
<td>Sweden: two-county</td>
<td>40–74</td>
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<td>24 for aged &lt;50</td>
<td>5–6</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td>33 for aged &gt;50</td>
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<tr>
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<td>12</td>
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<tr>
<td>1982</td>
<td>Göteborg</td>
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<td>5</td>
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</tr>
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</table>

* Adapted from reference 37.
the data did support a recommendation for screening for all women in this age group and that the survival benefit and diagnosis at an earlier stage would outweigh the potential risks [45]. Despite this controversy the American Cancer Society changed its guidelines and started to recommend annual mammograms for women aged 40 to 49 [46].

**Absolute benefit of breast cancer screening in different age groups**

Reporting relative risk reduction between screened and nonscreened population as percentage obscures the differences in the incidence of breast cancer among populations. This is especially important when the incidence is low as is in women aged 40 to 49 years. The absolute risk reduction or risk difference takes into account the underlying incidence and tells us how much the risk of death is reduced by screening [42]. The number needed to screen (the reciprocal of the absolute risk) is the measure of clinical significance and quantifies the effort required by patient and physician in order to prevent one death from breast cancer.

By mathematical modelling it has been estimated that under the assumption that among women who start screening at age 50 the mortality reduction is 27% and starts 5 years from initiation of screening, 270 50-year women would need to be screened for 20 years biannually to prevent one death, e.g., 2700 screening examinations are needed to prevent one death [47]. For women who initiate screening at age 40 (assuming 16% reduction in mortality starting 10 years after initiation of screening) it was estimated that 2500 would have to be screened every 1 to 2 years for 10 years to prevent one death. This means between 12,500 and 25,000 screening examinations to prevent one death [47]. The 10-fold difference between younger and older women in the number needed to screen in order to prevent one death is due to the lower incidence among younger women, the lower relative risk reduction and the delay in benefit. If the risk reduction would be the same in younger and in older women it would still mean performing between 7150 and 14,300 screening examinations in order to prevent one death [47].

When balancing benefits, risks and costs of screening programmes, such analyses are an important startpoint for public health recommendations and decisions.

**Risks of breast cancer screening**

The benefits of screening must be weighed against the risks and costs before instituting large-scale screening programmes or counselling individual women. Breast cancer screening with mammography introduces a risk from radiation exposure and psychosocial consequences following false positive and false negative results.

**Radiation exposure**

Although no women have ever been shown to have developed breast cancer as a result of mammography, not even from multiple examinations received over many years at mean glandular dose considerably higher than the current average mammographic doses of 3–4 mGy, the possibility of such risk exists because excess breast cancers have been observed among populations receiving much higher doses [48]. Using a risk estimate provided by the Biological Effects of Ionising Radiation (BEIR) V Report of the National Academy of Sciences and a mean glandular dose of 4 mGy from a two-view per breast bilateral mammogram, it has been estimated that annual mammography of 100,000 women for 10 consecutive years beginning at age 40 will result in at most eight breast cancer deaths during their lifetime [48]. As the estimate is based on statistical models from epidemiological studies of high-dose exposures, the actual risk could range from a much higher estimate to non-existent. Women with inherited or acquired defects in DNA repair mechanisms may have a different susceptibility to the effects of radiation [45].

**False positive screening examinations**

False positive screening examinations are another potential risk that lead to unnecessary anxiety and the risks of further diagnostic evaluation, including invasive procedures. Approximately 10% of all screening mammograms are read as abnormal in the USA, while the number is much lower in Europe, e.g., 2%-5% in Sweden [49]. Each of these will prompt the performance of an average of two additional diagnostic tests, such as diagnostic mammography, ultrasound, needle aspiration, core biopsy or surgical biopsy [45].

The cumulative risk of a false positive result of a breast cancer screening test has recently been estimated in a 10-year retrospective cohort study of breast cancer screening and diagnostic evaluations among 2400 women, members of Harvard Pilgrim Health Centre, a health maintenance organisation in New England, who were aged 40–69 years at study entry [50]. Of the women who were screened, 23.8% had at least 1 false positive mammogram, 13.4% had at least 1 false positive breast examination, and 51.7% had at least 1 false positive result for either test. The estimated cumulative risk of a false positive result was 49.1% (95% CI 40.3–64.1) after 10 mammograms and 22.3% (95% CI 19.2–27.5) after 10 clinical breast examinations. The cumulative risk of a false positive result was higher for women aged 40–49 at the time of the test than for those aged 50–79. For women aged 40–49 the cumulative risk of a false result after 10 mammograms was 56.2% and for those aged 50–79 it was 47.3%. The costs of working up patients with a false positive result was approximately one-third the cost of performing screening. The corresponding costs in the Stockholm trial were about one-fourth of the costs of the initial screening [51].

**False negative screening mammograms**

False negative examinations are associated with the risk of false reassurances to women who may then delay evaluation if symptoms occur. Up to one-fourth of all invasive breast cancers are not detected by mammography in women aged...
Breast cancer screening guidelines

Recommendations regarding screening depend on whether counselling individual women, making recommendations to population groups or considering implementation of organised screening programmes.

Many organisations and countries have issued guidelines for routine breast cancer screening [53]. Considerable differences in the guidelines exist for age limits for routine screening, the inclusion of clinical breast exam or breast self-examination instructions and periodicity of screening. The variation reflects differences in methodology and criteria used to develop the guidelines, international differences in the purpose of guidelines, and differences in the type and periodicity of screening evaluated in studies. Depending on the country, the guidelines have different implications for medical practice. Where the guidelines are developed as a part of the health service, they denote what will be covered, so cost considerations may enter the decision process more heavily than where recommendations do not determine medical practice and coverage of the services [52].

Age and periodicity of screening are areas of uncertainty in the guidelines. All guidelines are consistent in recommending routine screening to women starting at age 50 and this recommendation is included also in the European Code Against Cancer [20]. The inconsistency of guidelines concerning screening women aged 40-49 reflects the smaller benefit compared with risks and costs for this age group demonstrated in the randomised controlled trials and other screening studies [43].

No uniform recommendation can be given to all countries regarding introduction of breast cancer screening. Health policy recommendations require careful evaluation of scientific evidence of the benefits and adverse effects of screening, evaluation of cost and cost effectiveness and careful consideration of medicolegal, ethical and economic implications. Recommendations that affect large numbers of people should not be made without regard to other health policies that must also be implemented with finite resources [54]. Screening is cost effective and can result in mortality reduction in the countries where breast cancer incidence is high and at least 70% of the target age group is screened [55]. The provision of adequate resources, equipment, facilities, technologies and interpreting radiologists is a necessary condition and high quality is the key for a successful breast cancer screening programme. In the frame of the Europe Against Cancer Programme the guidelines for quality assurance in mammography screening have been developed [56] together with a European protocol on dosimetry in mammography [57].

Even where organised screening in not implemented and screening is introduced on an individual basis, quality assurance and control is indispensable for benefits to outweigh the risks. Women, especially younger women, need objective information on benefit and harms of screening. It has been shown that women tend to overestimate their risk of breast cancer and also the benefit of screening [58] and that older women who are at greater risk of breast cancer are less worried about this disease than younger [59].

Breast self-examination

Breast self-examination is a simple method available to all women. Even though the recent large trial did not show mortality reduction among women who had been trained in breast self-examination [60], in the absence of better alternatives, breast self-examination should be recommended to women when organised screening programmes are not available, and between routine mammographic screens [20].

Conclusions

Breast cancer control could be achieved only by combined efforts directed into primary prevention and early detection, as well as improving availability of effective treatment.

The outcome of treatment of breast cancer is gradually improving. The EUROCare study [61] revealed variations in survival of breast cancer patients in 12 European countries. The quality of treatment may partially explain the differences. The study of survival outcome of care by specialist surgeons in breast cancer in Scotland [62] found a 9% better survival of breast cancer patients at 5 years and 8% better survival at 10 years when cared for by specialist surgeons. A reduction of 16% (95% CI 6%-25%) in risk of dying was found after adjustment for the prognostic factors of age, tumour size, socio-economic status and nodal involvement. These results stress that in reducing mortality from breast cancer, equity in the treatment of breast cancer is also important.

References


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