Chapter 2
Breast Cancer Screening

Breast cancers account for about 30% of cancer deaths in women in developed countries, and about 15% in developing countries, this is therefore an important public health problem. Primary prevention should be given highest priority in the fight against cancer; however, the reduction in breast cancer incidence, which can be achieved by primary prevention, based on present knowledge of risk factors, is limited.The early detection of cancer encompasses the detection of cancer in individuals who exhibit signs and symptoms in the evolution of the disease, as well as the detection of cancer (or precancerous lesions) in apparently healthy populations.

Early detection programs for cancer have two components:

1) early diagnosis, based on awareness (by the public or health professionals) of the signs and symptoms of cancer which can result in substantial improvement in the outcome of persons destined to develop cancer if they are adequately treated,

2) screening, based on the presumptive identification in an apparently asymptomatic population of either precancerous lesions or very early stage cancers by means of tests, followed by effective treatment for the lesions detected Both approaches involve costs to the individual (in terms of time spent, distance traveled possible cash payments for detection/diagnosis) and the health services (manpower, subsidies for detection/diagnosis, treatment, follow-up), and may be associated with undesired harm. It is important to establish that the benefits of early detection outweigh complications and harmful effects before implementation of one or the other type of early detection as a cancer control policy.

Thus a decision to implement early detection of cancer should be evidence-based, depending on the burden of the disease, efficacy and cost-effectiveness of each early detection solution and the level of development of health services in a given setting. The latter is particularly important in low resource settings, as the whole process may involve substantial costs and risk diversion of resources from other health-care activities. It is important to bear in mind that interventions for the early detection of cancer can help reduce mortality from cancer only if they are part of a wider cancer control strategy that offers individuals appropriate diagnostic procedures and effective treatment and follow-up.

These activities need to be integrated at appropriate levels of health services and specific additional investments in health service infrastructure are required to cater for the additional cases resulting from early detection.

Systematic mammographic screening (any radiographic examination of the breasts of asymptomatic women) to detect breast cancer is a public health measure, which has aroused increasing interest in many countries of the world. Apart from mammography, physical examination by a physician or nurse, breast self-examination, ultrasound, thermography, diaphanography, computed tomography and magnetic resonance imaging have been used to detect breast cancer.

Evidence of the efficacy of breast cancer screening by mammography for post-menopausal women has been provided by several randomized trials, but the effectiveness of screening on the reduction of deaths from breast cancer in pre-menopausal women is still controversial.

Furthermore the question remains as to whether the benefit of screening, when applied in routine to large asymptomatic populations, justifies the risks and the costs. Most of these women would not in their lifetime have developed breast cancer and therefore, would not benefit individually from reduction of breast cancer mortality but may well experience adverse effects. The numerous pilot programs undertaken throughout the world will undoubtedly provide the experience indispensable for the implementation of routine wide spread programs.Policy recommendations should be established after a three dimensional evaluation: epidemiologic, medical and economic.

Epidemiology: Potential Efficiency

The first requirement for the justification of a population based screening program is the importance of the public health problem caused by the disease, i.e. the disease should be relatively frequent and have serious consequences.

Before implementation of a breast cancer screening program, national morbidity and mortality rates should be considered. Cost-effectiveness of screening clearly depends on the prevalence of the disease (number of undiagnosed cases in the population at the time of screening). The higher the prevalence, the higher the detection rate at the same cost. A low incidence rate will give a low prevalence and then, the cost for the whole population could become unacceptable. Many countries, would exclude breast cancer screening programs with mammography from their priorities on the simple grounds of efficiency, due to the epidemiological

situation. Society should not use resources for cancer screening programs unless there is strong evidence showing that there is a clear benefit for the population. Another important indicator to consider is the stage at diagnosis: if the majority of breast cancers are advanced cases (stage 3 or 4) at first presentation it is not appropriate to undertake a screening program, but to promote measures for earlier diagnosis, referral and access to care.

Medical: Effectiveness

The aims of mammographic screening are to detect cancer at "stage 0" (before symptoms) where more effective and less aggressive treatment can be offered. Any medical evaluation should cover, reduction of the number of cases of late-stage disease, deaths from breast cancer, side-effects such as unnecessary check-ups or treatments, and potential impact of the program on the general health of the target population, such as potential years of life saved weighed by quality of life.

The evaluated screening tests for breast cancer include mammography, physical examination of the breasts (Breast Clinical Examination: BCE), and Breast Self Examination (BSE). These 3 types of test for Breast cancer screening have been evaluated by randomized control trials and case-control studies. The 2002 IARC review concluded that there was *sufficient evidence* that mammography alone in women age 50-69 reduced mortality from breast cancer. The expert also concluded that the evidence in women age 40-49 is *limited* . In fact the cut off point is the menopause witch influences the sensitivity and specificity of the mammography due to change in the density of the breasts.

The magnitude of the reduction using mammography alone in risk of breast cancer death ranges from 6%, to 48%, with an overall estimate of +25% (95% CI: +33% to +15%), for women aged 50 to 69 years. The overall estimate of reduction in risk for women aged 40 to 49 years is +19% (95% CI: +35% to -1%), and ranges, in the different studies, from +42% to -48%. The results in women aged 50-69 years were statistically significant regardless of, the number of views per screen (one or two), the screening interval (18 to 33 months), the duration of follow up, or the addition of a clinical breast examination. For women aged 40 to 49 years followed for 7 to 9 years, there was no significant risk reduction in breast cancer mortality as well as for women followed for more than 10 years.

Thus, it appears that no benefit is observed for younger women until 10 to 12 years of follow-up, by which time women who were 40 to 49 years when entering the

study are 50 to 61 years of age and mostly in a post-menopausal phase when a mammography becomes more sensitive.

These findings suggest that it might be possible to begin mammographic screening of menopausal women only of women aged 50 or more. This is a major problem for many developed countries where, because of their populations pyramids, breast cancer is relatively more frequent in women age 40-49.

Detection by Clinical Breast Examination tends to diagnose breast cancer at an earlier stage than those not detected by screening. Some epidemiological studies (in Japan) suggested that CBE reduces mortality from breast cancer. In the Canadian breast screening trial (CNBSS2) mortality from breast cancer was similar among women who received combined screening (mammography + CBE) and those who had only CBE. The CNBSS2 trial demonstrated that mammography results in the diagnosis of in situ carcinomas and good prognosis small invasive carcinomas that do not impact upon breast cancer mortality, providing a woman is having regular good breast physical examination. This result was re-enforced by a model-base evaluation, that suggested that CBE resulted in a 20% reduction in breast cancer mortality. Such screening with CBE is now being evaluated in India and Egypt. There is preliminary indication from the Egyptian trial that stage shift towards more limited disease is being achieved by such screening (A.Miller).

Breast self examination (BSE) has intuitive appeal since it should result in earlier diagnosis if practiced regularly. However, it has proved to be difficult to adequately perform it and 2 large randomized trials using BSE have yield disappointing results.

Apart from the impact on breast cancer mortality, another potential benefit of breast cancer early detection is the increased use of conservative surgery such as partial mastectomy, segmental excision or lumpectomy. The results of the prospective studies showed, in the screened group, an increased proportion of women undergoing conservative surgery.

Adverse Effects

Adverse effects of screening for breast cancer have also to be considered. In the first place a screening program could create an over “medicalisation of healthy people”: by being confronted with too many preventive and diagnostic procedures, women belonging to the target population could be over concerned with health and medical issues. In the second place, participation in screening programs might

cause undue anxiety: the confrontation with the possibility of having breast cancer is frightening; anxiety is particularly increased in women presenting with a false-positive result, i.e. when abnormalities detected by mammography are subsequently found to be benign. However, documentation on these aspects is scarce. The few studies dealing with worry and anxiety show that such reactions seem relatively infrequent and tend to regress rapidly. The prevalence of anxiety has been reported to be significantly greater in women with false-positive results (29%) than in those with negative results (13%).

Furthermore, mammography involves compression of the breasts, which can cause physical discomfort: 10% to 20% of women reported moderate or severe discomfort. Surgical biopsy, when necessary, involves a risk of infection, scaring, hematoma, pain and breast abnormalities are also possible:

Firstly, some screen-detected cancers would never have become clinically apparent during the woman's lifetime. The possible magnitude of this effect is uncertain but predictions give as many as 70% of breast cancers remaining clinically unapparent. Secondly, it is certainly possible that not all in situ cancers become invasive. Thirdly, false-positives based on histology have been reported for small lesions.

The difficulty to classify minimal or borderline lesions as benign or malignant is now recognized and should result in the review of pathological procedures. It has been suggested that women with a false-negative result, might subsequently delay seeking treatment if symptoms develop, because of a false sense of security. This could ultimately result in greater morbidity and poorer prognosis.

The increase of life time risk of radiation-induced breast cancer from mammography (if the dose is 0.12 rad per two-view film-screen examination), has been estimated to be less than 1%. Finally, screening can result in a large burden of unnecessary investigations and treatments when the quality of such interventions is not assured.

Economical Cost

Effects on health should be considered in relation with the resources allocated for establishing those effects. The main aim of an economic assessment is to assist the relevant decision makers for an optimal use of the available health care resources.

The analysis of the costs components should take into account, the size of the target population, the investments (equipment), the operating costs (mammography,

diagnostic examinations, quality control, call-recall system, data collection and analysis, information and training, evaluation ...). Generally, in developed countries, organized screening would replace current "spontaneous" practices. Considering the problem from this angle totally modifies the approach of costs and their evaluation. In France, the estimate of the yearly cost of screening considering a population of 860,000 women aged 50-69 a 50% participation rate , a 3-year periodicity and a 10% recall rate reached Francs 33.4 million Euro, i.e. 35 Euro per woman screened. In comparison, an estimate of the cost of spontaneous screening made in the late eighties and based on an observed annual activity of 1.12 million mammographic examinations (40% of such mammographies presently concern French women less than 50 years of age) reached 45.9 millions Euro, i.e. 41 Euro per woman screened. The possible decrease in cost with the organized program should be due to the targeting of the program to a limited population for whom breast cancer screening has proved effective on one hand; and on the second hand a better use of quality controlled health structures, thus reducing false positive and unnecessary examinations to the minimum.

Furthermore, the cost of breast cancer screening could be partly compensated, by the subsequent decrease in the costs of management of late-stage diagnosed breast cancers.

These estimations for France, should have been correct if the individual spontaneous screening had been strongly reduced, which is not the case presently in France where the participation rate to the organize screening is far too low (45%) and the spontaneous mammographic screening still high (35-40%). An important item, which does not facilitate the problem, is that costs occur long before favorable effects and savings are observed.

Benefits and Risks: Efficiency

The decision to screen part of the population on a routine basis must be taken only after careful assessment of the risks and benefits. Several factors play an important role and contribute to the success of a programme. The reduction of mortality rates obtained with clinical trials will be difficult to reach with population-based routine programmes; that is mainly due to lower participation rates and difficulties in obtaining high quality level of procedures: mammography (technique and reading), follow-up of women with abnormalities, biopsies, pathological interpretation and adequate treatments.

The rate of participation depends mainly on the woman's age, the place of residence, the socioeconomic status and modalities of screening (call-recall system, facilities and access to mammography). The rates of 65% to 93% observed in the trials will be impossible to reach and this will result in a lower level of detection in the target population. Compliance is also of crucial importance in women with mammographic abnormalities, if there are women lost to follow-up after the mammographic test, then the benefit of the program will be null and the intervention in itself will become unethical. All the women with an abnormality have to be recalled, diagnosed and treated if necessary..

Quality control of all steps of the screening process is, thus, mandatory; high quality mammographical testing requires not only modern equipment but also trained radiologists who need to acquire equilibrium between sensitivity and specificity, i.e. to balance the need to find all cancers with that of keeping the number of unnecessary biopsies as low as possible. Pathology, including cytopathology and histopathology, are basic to achieve screening objectives. Pathologists should be able to make accurate diagnoses when assessing clinically occult lesions revealed by mammography. Any screening program should include experts (radiologist and pathologist) in charge of maintaining high quality standards of diagnosis, teaching of colleagues, and organization of quality control. Quality-assurance requirements and objectives have already been assessed and well documented.

Effectiveness of treatment of women with screen-detected cancer is of major influence on the results and, inadequacy, may drastically reduce the expected benefit.
Therefore, the efficiency of a program strongly depends on the organization of the program, which should include the improvement of the participation rate, the quality control of each step of the process, and data collection for evaluation.

Evaluation

Two levels of evaluation have to be checked: the first one will assess the general procedures in terms of participation rate, compliance (lost follow up), and quality. Such an evaluation will allow the identification and correction of the dysfunctions in the course of the program if any; the second will estimate the results in terms of health benefits and costs. The benefits can be expressed as the number of prevented breast cancer deaths or potential years of life saved; the change in the distribution of advanced stages of the disease can also be used as a surrogate indicator (table 3.1).

Indicator	**Acceptable** Level	**Desirable** level
Participation rate	>70%	>75%
Inadequate mammography	<3%	<1%
Recall rate		
Initial (1st round)	7%	5%
Subsequent	5%	3%
Lost of follow up with mammographic abnormality	<3%	0%
Cancer detection rate		
Initial	3xIncidence	>3xIncidence
Subsequent	1.5xI	>1.5xI
In situ ductal carcinoma	10%	10-20%
% of node negative		
Initial	70%	>70%
Subsequent	75%	<75%
% of invasive cancer≤10mm in size		
Initial	≥20%	≥25%
Subsequent	≥25%	≥30%
Benign to malignant open surgical biopsy ratio		
Initial	≤1/1	≤0.5/1
Subsequent	≤1/1	≤0.2/1

Table 2.1 Major European key performance indicators

Quantitative assessment of the comparative risks and benefit of screening is difficult due to the diversity of screening effects. The benefit-risk balance can be calculated as the number of breast cancer deaths prevented per women-years (number of women x number of years of follow-up), per number of mammographic examinations, per number of biopsy, and per number of cancers detected. For example, the Swedish two-country study investigators calculated that for women aged 50-69 years at entry, one breast cancer death was prevented per 4000 woman-years, per 1460 mammographies, per 13.5 biopsies, and per 7.4 breast cancers detected. This type of evaluation incorporates the reduction from the baseline risk of breast cancer death, and the increase in risk of undesirable investigations. It

could be extended to include adverse effects such as pain, false reassurance, over-treatment, psychological morbidity and economical costs.
A second way of measuring the risk-benefit balance is to calculate the cost per quality-adjusted life-years saved. This measure weighs the increase in life expectancy according to quality of life and years. Such a calculation implies to estimate the weight of the various types of undesirable events. The results of these calculations vary considerably according to studies. This is due to the variations in the health care systems of each country, the screening programs designs, the compliance of the target population, the weighing of adverse effects, and finally in the cost analysis methodology.

The decision in terms of public health to implement a breast cancer screening program should be based on country specific assessments taking into account the epidemiology of the disease, the current practice (average stage of breast cancer at diagnosis, mammographic equipment and practice, training of professionals, treatments possibilities...) and the available resources (table3.2). Once the decision has been taken, all efforts have to be implemented to ensure high quality at each level of the program in order to minimize the risks and maximize the benefits.

Table 3.2 Questions to be answered before deciding what type of detection program for breast cancer to implement in a country

- What is the breast cancer burden in the country?
- Are accurate diagnosis and effective treatment available and accessible to the whole targeted population?
- What proportion of cancer cases presents with potentially curable disease?
- Are there already programs for early detection running and evaluated?
- What are the resources needed and available (humans, structures, economic…)?

Update

More is probably known about breast cancer screening than about screening for any other malignancy. WHO did not recommend that developing countries implement screening for breast cancer, because it believes that, the focus for any screening efforts should be on screening for cervical cancer. Other resources should be devoted to palliative care or diagnosis and treatment.

Similarly, the Global Summit Early Detection Panel concluded that mammographic screening is not currently a realistic goal for most countries with limited resources and recommended that early detection efforts first be focused on the education of patients and physicians and increasing general social awareness about breast cancer.

The Summit Panel suggested the following sequential approach: 1) promote the empowerment of women to obtain health care, 2) develop the infrastructure to diagnose and treat breast cancer, 3) begin early detection efforts through breast cancer education and awareness, and 4) when resources permit, expand early detection efforts to include mammographic screening if breast cancer treatment is available for all detected cancer.

The Panel argued that although such programs will first provide care to a portion of the population and could serve as pilot programs for more extensive programs covering larger populations, and ultimately the entire population, as resources becomes available.

As completely new technologies emerge, such as the ability to identify genetic risk factors, new challenges also emerge. We cannot be satisfied with simply identifying women at particularly high risk. We must be prepared to counsel them about the risk and to propose them some solution.

Within the past 10 years, work defining the basis of genetic susceptibility to breast cancer in general and the identification of *BRCA1 and BRCA2* specifically has enhanced the accuracy of breast cancer risk prediction. The subsequent diffusion of risk prediction tools, such as genetic susceptibility testing and the National Cancer Institute's "Risk Disk" have resulted in the identification of many women at increased risk of breast cancer. Although this information has implications for many areas of medical care, its potential impact is particularly great in the area of cancer screening. In theory, the ability to stratify breast cancer risk allows intensive screening regimens to be targeted to women at high risk who are most likely to benefit, with more limited screening for women at lower risk. This approach both reduces complications associated with low-risk biopsies and saves health care resources. The challenges now are translating this approach into practice.

In a recent study by Brekelmans et al., the effectiveness of breast cancer surveillance in *BRCA1/2* gene mutation carriers and women with high familial risk was demonstrated.

These results provide a rationale for tailoring screening recommendations to breast cancer risk, as rates of cancer detection were 10-fold higher among *BRCA1* and *BRCA2* mutation carriers than among women at moderately increased risk of breast cancer. Moreover, Brekelmans et al., observed a substantial risk of interval cancers in *BRCA1* and *BRCA2* mutation carriers undergoing annual screening beginning some time between the ages of 25-35, suggesting that current approaches may be insufficient in this very high-risk group. Moreover it has not been proven that screening of this predisposed group reduces their mortality from breast cancer and because the BRCA1 and BRCA2 genes participate in the repair of radiation-induced DNA breaks, it has been suggested that women who carry these mutations are at greater risk for radiation-induced breast cancer than are women in the general population. The sensitivity of magnetic resonance imaging has been reported to be greater than that of mammography for women at high risk because of CRCA mutation or a family history. Prospective studies of alternative screening regimens are clearly needed.