

# **Breast cancer screening by mammography: International evidence and the situation in Switzerland**

A joint publication of the Swiss Cancer League and Oncosuisse



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## Preface

In February 1997 a request was submitted by the Swiss Cancer League (Schweizerische Krebsliga) to the Federal Office of Social Insurance (Bundesamt für Sozialversicherungen, BSV) to include screening mammography in the basic health insurance coverage. This request was accepted and screening mammography was introduced in the health insurance regulation (Krankenleistungsverordnung, KLV) as of December 1997 for a limited period of ten years. In 2000, the Federal government decided furthermore to exempt screening mammography from the *franchise*.

In July 2007 Oncosuisse and the Swiss Cancer league submitted a new request asking for a continued inclusion of mammography screening in the basic health insurance coverage, under the same conditions as previously and without time limit. This report is a slightly shortened version of the request submitted to the Federal Office of Public Health (BAG / OFSP). It summarizes the current evidence and should allow decision makers, health authorities, public health professionals and others to determine whether and how organized breast cancer screening should be continued and expanded in Switzerland.

The document starts with a **summary of the evidence**. The evidence is then presented in detail in seven chapters. **Chapter 1** sets the scene by describing mammography screening. **Chapter 2** reviews the epidemiological situation with particular reference to Switzerland and what we know today about the biology of breast cancer and its treatment. **Chapters 3 and 4** present the international experience. Evidence on the efficacy and effectiveness of mammography screening in reducing breast cancer mortality is reviewed in chapter 3. It also includes a section on the hazards of screening. The international overview is completed in Chapter 4 by a brief description of the current status of breast cancer screening programmes in Europe. Chapters 5, 6 and 7 are devoted to the experience with breast cancer screening in Switzerland and what it may mean for the future. **Chapter 5** describes the experience of existing mammography screening programmes in the French speaking cantons, comparing it to the European recommendations. **Chapter 6** presents summary results of a cost-effectiveness analysis of breast cancer screening. The costs and potential impact on breast cancer mortality of various combinations of organised and opportunistic mammography screening are explored. **Chapter 7** then discusses important issues to consider if mammography screening is to be made available to more women in Switzerland. This includes resources required, financing options, information of women, quality control, and the estimated uptake of breast cancer screening.

We hope that the wealth of information provided in this document will not discourage the reader by its volume, but rather allow each person to focus on those aspects of mammography screening least familiar to them. This is the first time to our knowledge that an overview of the current situation in Switzerland based on all available data is presented. Supported by additional evidence on the effectiveness of longer standing programmes in other countries, we trust that this report provides a solid base for discussion of the future of mammography screening in Switzerland.

## The evidence presented in this report in brief

### Chapter 2

In Switzerland about one woman in ten will suffer from breast cancer in her life-time. Over 1'350 women die of breast cancer every year. It is the most common cause of cancer death for women, and accounts for the highest number of potential years of life lost from any disease. In the age group 50-70, where the incidence is highest, about 10% of all deaths are due to breast cancer leading to 8'000 potential life years lost every year.

A number of risk factors for breast cancer are known. Few of them relate to life style, but most are not under the direct control of women (age, sex, genetic predisposition, hormone and reproductive factors). Therefore, the role of primary prevention is limited in reducing breast cancer incidence and mortality. New therapeutic approaches have improved survival of breast cancer patients in the past decades, in particular if the cancer is detected at an early stage. But even with improvements in therapy, breast cancer remains a potentially deadly condition. Early detection is currently the best option to reduce the impact of the disease.

### Chapter 3

It is uncontested that population-based breast cancer screening reduces breast cancer mortality in women over age 50. The first evidence came from randomised controlled trials carried out between the 1960s and 80s, showing a trend of reduction in breast cancer mortality among women over age fifty. Various meta-analyses showed that this reduction lies in a range of 15% to 30%. Randomized controlled trials of breast cancer screening have shortcomings, many of which are inherent in the conduct of large population-based studies with long-term intervention and follow-up. The shortcomings could have led to an over- as well as an underestimation of the effect on breast cancer mortality. Fortunately we now have evidence of the impact of long-standing breast cancer screening programmes (Australia, Canada, Denmark, Finland, the Netherlands, Sweden and the United Kingdom) on breast cancer mortality. The decrease observed is similar to the reduction measured in the randomized controlled trials. Its magnitude depends on the evaluation design; the length of the intervention; participation rates achieved; and, estimated contribution of adjuvant therapy to prolonged survival. This, however, does not yet represent the maximum cumulative effect that occurs 25 years after onset of a screening programme. Beyond a decrease in breast cancer mortality, early detection also leads to an increase of quality of life due to less invasive treatments (tumorectomy versus mastectomy, less aggressive adjuvant therapy).

False-positive screening results and overdiagnosis of breast cancer are harmful and inevitable consequences of screening. At the population level these harms should be largely outweighed by the benefits of screening. Findings from the randomized controlled trials as well as longstanding screening programmes indicate that this is the case. Further studies have shown that the risk of overdiagnosis is modest, considering that it is not possible at the moment to distinguish which cancer will progress to invasive and metastatic disease and which will not do so. The potential risk of radiation-induced breast cancer due to screening exists, but is minimal.

### Chapter 4

Eighteen western European countries have meanwhile established nationally or regionally organized breast cancer screening programmes, reaching overall more than 75% of the target group. Most programmes focus on screening women aged 50-69. All programmes invite women in this age group to have a mammography every second year, with the exception of the UK (invitation every third year). The proportion of eligible women being effectively screened in organized breast cancer screening programmes varies. Most programmes have intermediate to high participation rates (50% to more than 80%). In a majority of countries the costs of the screening are totally covered by health insurance, with no extra funding needed and no co-payment by women.

Access to screening mammography is currently highly variable within Switzerland. In the five existing mammography screening programmes (FR, GE, JU/NE, VD and VS) women aged 50 to 70 are invited every second year for a screening mammography. In the other cantons, women may be referred by their general practitioner or gynaecologist for a screening mammography that will often be labelled “diagnostic” to ensure reimbursement by the basic health insurance. This leads to inequitable access across cantons and within cantons.

The implementation of organized screening programmes in several Swiss cantons has shown that it is possible to reach European standards in terms of performance. Stage shifting has occurred thus providing a first indication of the impact these programmes may have on breast cancer mortality in the long run. The main constraints identified are a relatively low participation rate in some cantons, mostly linked to persistent opportunistic screening; a relatively low reading volume of second reader radiologists; the absence of a unified tariff and reimbursement scheme; and, the total lack of national guidance.

Opportunistic screening is more expensive than organized screening, its quality is not controlled (no double reading of the mammography, no evaluation of the impact) and it leads to more additional examinations (ultrasound, biopsies) than organised screening. It also requires a higher financial contribution by women, as it is not exempted from the franchise and always subjected to a 10% co-payment.

To assess the potential effects and costs of organised and opportunistic mammography screening, several hypothetical scenarios that may represent breast cancer screening in Switzerland were examined with the micro-simulation programme ‘MISCAN’. The analysis showed that mammography screening is an effective way to reduce breast cancer mortality. A mortality reduction of around 20% was achieved in the 50-79 years old age group by an 80% participation in either biennial organized mammography screening, biennial opportunistic screening or a mix of both.

However, the lowest cost per life year gained is obtained with organised biennial mammography screening only (21'833 CHF), which is twice as cost-effective as opportunistic screening (46'611 CHF). By far the most costly scenario is 40% of women undergoing biennial organised screening and a further 40% having annual opportunistic screening (50'059 CHF per life year gained), which may actually be the situation in some Swiss cantons. The relatively high costs of opportunistic screening and associated diagnostics thus result in a substantially less favourable cost-effectiveness ratio of opportunistic screening compared with organised mammography screening.

Based on this evidence, the following is recommended:

- All women age 50 and above living in Switzerland should have access to organised, quality-controlled screening mammography.
- All breast cancer screening programmes should fulfil the same quality criteria.
- Funding for breast cancer screening programmes should be secured and be similar across cantons.

Furthermore, to implement high quality organised breast cancer screening in Switzerland, it is necessary to ensure appropriate information of women; to address existing organisational and structural constraints; to devise mechanisms to reduce opportunistic screening; and, to designate a national coordinating and supervising body.

# Chapter 1: Setting the scene

## 1.1. What is breast cancer screening by mammography?

Breast cancer screening is the systematic application of a mammography to a defined age group (50 years and above) of women in a defined population. It is based on the principle that detection of early disease, followed by effective treatment, will lead to a better prognosis and improved chances of survival. Currently mammography is the only accepted screening technique for the early detection of breast cancer. Screening with mammography does not prevent the occurrence of breast cancer, but is the best technique currently available to detect breast cancer at a very early stage in an average risk population.

### SOME DEFINITIONS

**Screening mammography** is a public health service proposed to all women from age 50. It is a standardised service with two main components:

- a standard questionnaire collecting socio-demographic, epidemiological and medical information about the woman;
- a two-view radiography of the breasts done according to predefined criteria

A dedicated X-ray machine is used for breast cancer screening. The same device is used for diagnostic mammography. These mammography devices are either analogue using photographic films, or digital capturing the image with an electronic device. These devices are generally installed in radiological institutes/services. The interpretation of the mammography is done according to a predefined protocol, including an independent blind reading by two radiologists. In case of disagreement, a third radiologist examines the mammography and takes a final decision, considering the first two interpretations. A screening mammography does never allow making a diagnosis. Its aim is to divide a population of asymptomatic women into two groups: those who have no suspect lesions and those who have lesions that may be malignant and need further investigation.

**Diagnostic mammography** is a medical service for women consulting with symptoms related to their breasts. This implies a medical consultation (history and clinical examination), a mammography, an ultrasound and frequently a biopsy. The procedure is not standardised and there is no defined quality control.

Diagnostic mammography is often used for screening purposes. This is called **opportunistic screening**. The percentage of additional tests is significantly higher in the case of opportunistic screening than if screening is done within an organized programme (with double-blind readings). A study in the canton of Vaud showed that in 8.8% of mammographies that were read once, complementary examinations were required. In case of double (and if necessary, triple) reading, this percentage decreased to 5.0%.<sup>i</sup>

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<sup>i</sup> Jean-Pierre de Landstheer. Evaluation de l'impact financier d'un programme organisé de dépistage du cancer du sein par mammographie. Programme vaudois de dépistage du cancer du sein. Octobre 2003.

## **1.2. What is the expected benefit of breast cancer screening by mammography?**

The main benefit is an earlier detection of malignant breast tumours, which means detecting cancers at an earlier stage and of smaller size (stage shifting). Breast cancers are classified in four stages (I-IV) depending on invasion, size, lymph node involvement and metastases. The change in distribution of these four stages is called stage shifting.

Detecting and treating breast cancers at an early stage have several benefits. The surgical treatment will be less mutilating, the medical treatment less drastic. The probability that metastases will occur is reduced. This leads to better prognosis and longer survival. The secondary benefits thus are a significant reduction of breast cancer mortality and enhanced quality of life for women diagnosed with breast cancer.

The relationship between early detection, tumour size and treatment outcomes is described in Chapter 2.4. The impact of earlier detection on breast cancer mortality and the effectiveness of mammography screening programmes are reviewed in Chapter 3.

## **1.3. Who should be offered a screening mammography?**

All women from age 50 should be offered a screening mammography every second year. These women should not be considered “patients”, but healthy persons using a test to detect cancer.

**Why from age 50?** The most convincing evidence from randomized controlled trials on the benefit of screening was for women aged 50-69 at entry to the trial (see chapter 3). Fewer results are available for women age 70 and above. With further results and increased follow-up benefit for elderly women becomes apparent. However, after age 75 other competitive mortality causes like cardiovascular disease are also more frequent, thus off-setting the potential benefits of breast cancer screening. For this reason, most screening programmes now target women 50-69, allowing women beyond this age range to continue screening if desired and if no major co-morbidity exists. This is current practice in the screening programmes in Switzerland.

**What about women aged 40 to 49?** In addition to the initial randomized controlled trials, there is more recent evidence that breast cancer screening in this age group reduces breast cancer mortality.<sup>1</sup> However, screening in this age group is less cost-effective as the incidence of breast cancer is lower. In addition, the screening interval needs to be shorter (12-18 months) as higher breast density, which is common in pre-menopausal women, reduces mammographic sensitivity.

**Why every two years?** Most of the randomized controlled trials involved a 1- or 2-year screening interval. Most countries have opted for a 2-yearly screening interval as this seemed the most cost-effective approach.<sup>2</sup> This was corroborated by a cost-effectiveness analysis carried out in the Netherlands in 1990. Four alternatives in the age group 50-70 were examined (interval of 4, 2, 1½ and 1 years corresponding respectively to 5, 10, 15 or 20 invitations). Extending the screening period up to age 75 and starting screening at age 40 were also explored.<sup>3</sup> Two important conclusions of the analysis are that extending screening from 69 to 75 years of age is more cost-effective than extending the programme

to younger age groups; and that the marginal cost of preventing more life-years with a shorter screening interval than 2 years is very high (see table 1.1).

**Table 1.1 Predicted mortality effects and cost-effectiveness indices for breast cancer screening in the Netherlands, 1988-2015**

	Screening interval			
	4 year	2 year	1½ year	1 year
Deaths prevented	2'700	4'100	4'800	5'400
Life-years gained	28'400	43'800	51'500	57'500
Cost per death prevented (US \$)	42'050	50'300	58'100	73'140
Marginal cost per life-year gained (US \$)	4'050	6'050	12'900	14'800

N.B. Study carried out in 1990 for the Dutch breast cancer screening programme.

The effectiveness of a 2-year screening interval was compared to the effectiveness of a 1-year interval in a more recent study in the United States using the proportion of women diagnosed with late-stage breast cancer as a reverse measure of effectiveness.<sup>4</sup> No increase in late stage disease was found for women more than 50 years old with a 2-year versus a 1-year screening interval.

**Should women with special conditions be excluded from organised screening?** In Switzerland, gynaecologists and radiologists have agreed that women with the following conditions may need closer medical follow-up outside a mammography screening programme.

- first-degree family history of breast cancer (mother, sister or daughter with breast cancer before age 50)<sup>ii</sup>
- previous breast cancer
- breast implant
- previous breast biopsy indicating lesions with malignant potential

This may concern 5-10% of the target population. In some countries with regional or national breast cancer screening programmes, similar criteria are applied to exclude women from the programme. In other countries all women in the relevant age group are invited for a screening mammography regardless of particular risk factors.

Long-term hormone replacement therapy is a known risk factor for breast cancer and may also increase breast density. It is well known that dense breasts reduce the sensitivity of screening mammography. This effect is increased when combined with hormone replacement therapy.<sup>5</sup> Information on hormone use should thus be collected at the time of screening, but is no reason for exclusion.

<sup>ii</sup> **Art.12 o.1.** of the health insurance law gives the right to women who have a first degree relative who suffered from breast cancer before age 50 (mother, daughter or sister) to have a yearly diagnostic mammography without lower or upper age limit.

#### **1.4. How is a mammography screening programme organised?**

The main elements of a screening programme are the fact that all eligible women are invited to participate at no or minimal cost, that the quality of the procedure is controlled and that the programme's effectiveness is regularly evaluated.

##### **Accessibility**

The screening programme invites all eligible women to participate in the screening service. The invitation list may be based on cantonal population registers or a specially established screening register encompassing all communes in the canton.

The invitation letter informs the women of the voluntary nature of the screening. There is no obligation to participate.

The women also receive an information booklet explaining the pros and cons of mammography screening. This booklet contains the state of the art information following the latest edition of the EU guidelines on how women should be informed. All five existing screening programmes use the same booklet. Reference is made in the booklet to the extensive brochure on mammography issued by the Swiss cancer league.<sup>iii</sup>

There are no social economic exclusions as all eligible women are invited and the service is exempted from the franchise and free except for the 10% co-payment.

The mammography images are taken in existing radiological practices which are geographically spread.

##### **Quality assurance and control**

The quality of the mammography screening is ensured and controlled according to the European Guidelines. These requirements are laid down in the „Verordnung über die Qualitätssicherung bei Programmen zur Früherkennung von Brustkrebs durch Mammographie (SR 832.102.4)“.

All participating radiologists and radiology institutes commit themselves to comply with the programme quality requirements.

The service process is fully transparent. Its public health nature allows a monitoring of the service delivered.

The quality of the final result is a team responsibility. In this respect, screening provides incentives for a multidisciplinary team approach.

##### **Evaluation**

The screening programme will systematically collect the data on screening outcome and follow up of screened women.

The programme must collaborate with population and cancer registries for programme evaluation. There is a feedback loop to the population register if data are incorrect.

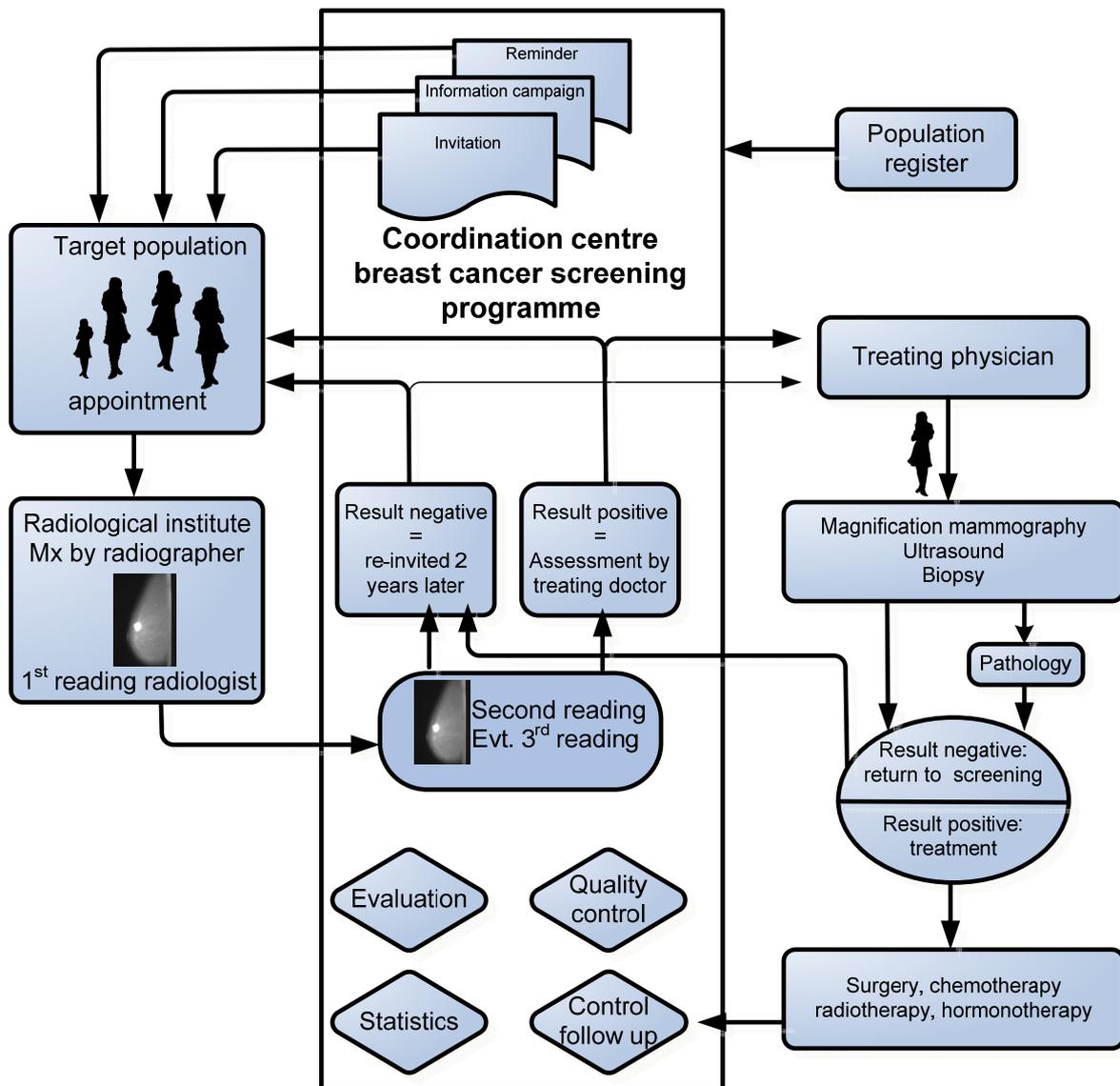
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<sup>iii</sup> The brochure can be found under the following link:

[http://www.swisscancer.ch/fileadmin/swisscancer/praevention/files/Brochure\\_Le\\_d\\_pistage\\_du\\_cancer\\_du\\_sein.pdf](http://www.swisscancer.ch/fileadmin/swisscancer/praevention/files/Brochure_Le_d_pistage_du_cancer_du_sein.pdf)

The evaluation reference and endpoint parameters are specified according to the European guidelines.

**Figure 1.1** The components of the screening pathway and their relationship



## 1.5. Who is responsible for the programme?

Mammography screening is a public health strategy for the early detection of breast cancer. The responsibility for such a public health programme has ultimately to be born by the political decision makers. The **Cantonal Directors of Public Health** thus have to take the initiative to launch and support breast cancer screening programmes. In general, they place the realization of these programmes in the hands of private institutions within the framework of a public mandate (breast cancer screening centres). The direction of public health<sup>iv</sup> also has to ensure the screening program's evaluation. In order to allow less populated cantons to set up such programs, intercantonal cooperation is necessary.

The **breast cancer screening centres** are responsible for inviting eligible women, a good day-to-day functioning of the screening procedure, for 2<sup>nd</sup> and 3<sup>rd</sup> reading of mammographies, and for quality assurance of the programme. **Radiologists** are responsible for implementing the screening tests with the best possible quality.

Primary care **physicians**, as well as many physician specialists are called upon to provide complete, objective and easily accessible information on breast cancer screening to their patients and help them in making the best possible decision. Physicians should also cooperate with breast cancer screening centres in providing information about the follow-up of screen-positive cases.

The **professional associations of physicians** (and of other professionals involved in screening programmes such as radiology technicians, medical secretaries etc.) are responsible for the continued education and the ongoing training of their members in matters of cancer screening.

The **Swiss Cancer League** and the cantonal cancer leagues contribute to informing the population by publishing and distributing booklets or by their participation in the development of booklets which are made available to patients, for example, at their physician's office.

Finally, the effectiveness of breast cancer screening also depends on investigations and treatment for those women whose mammography detects a suspicious lesion. Many **medical specialists** are involved in the follow-up: pathology, gynaecology, surgery, oncology, radiotherapy, internal medicine, family medicine. It is the responsibility of the specialities concerned to provide guidelines and training. It is the joint responsibility of the specialists in each canton to organise the follow-up of women suspected to have breast cancer and treatment of patients in the most efficient way.

In a screening programme, some activities must be assured at the cantonal or intercantonal level (invitation of targeted groups, integration of physician specialists, evaluation, population information, etc.). Other activities are more efficiently carried out at the regional or national levels. A **national institution** should coordinate these activities and assume a part of them (see also chapter 7.6).

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<sup>iv</sup> In German : Gesundheitsdirektion. In French : Département de la Santé

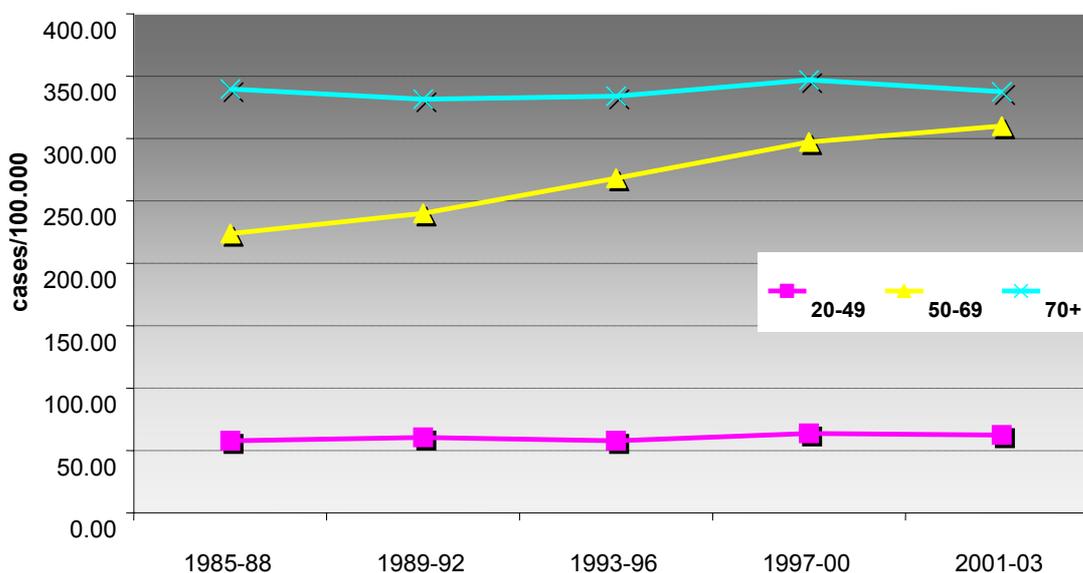
## Chapter 2: Breast cancer in Switzerland

Breast cancer is the most frequent malignant neoplasm in women accounting for more than a quarter of all female cancers in high-income countries.<sup>6</sup> For European women the life-time risk of developing breast cancer is 1 in 10<sup>v</sup>.

### 2.1. Incidence of breast cancer in Switzerland

In Switzerland about 5300 new cases were diagnosed each year (estimated incidence) in the period 2001-2004.<sup>vi</sup> Incidence has increased steadily since 1985 particularly in women age 50-69 (Figure 2.1).

**Figure 2.1 Time trends in breast cancer incidence by age group, 1985-2004**

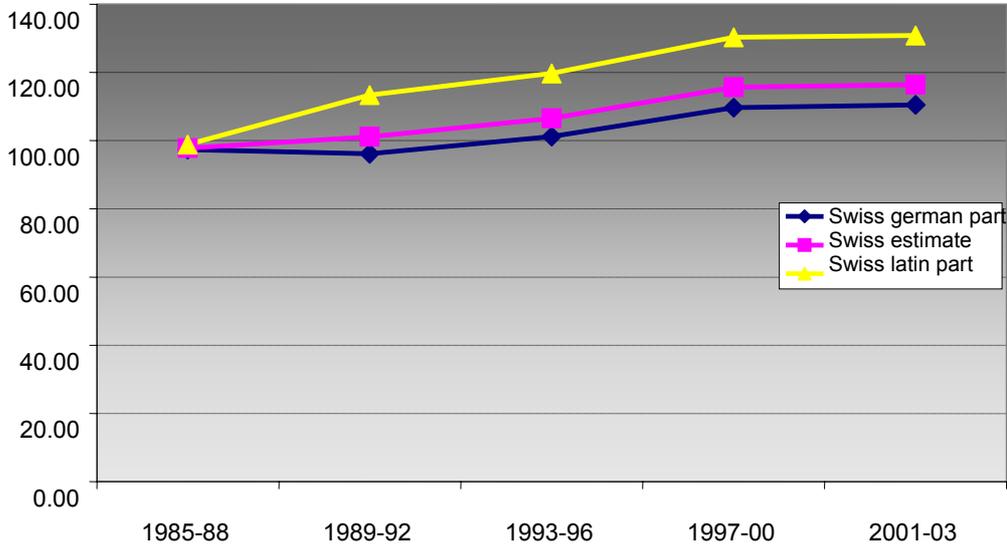


The increase has been found in all regions of Switzerland with a steeper increase in the Latin part of the country (Figure 2.2). The overall increase in age group 50-69 may be at least partly attributed to hormone replacement therapy. The steeper increase in the Latin part is most probably due to the wider availability and use of mammography screening.

<sup>v</sup> From "Breast cancer facts. The European parliamentary group on breast cancer", [www.epgbc.org/BreastCancerFact.asp](http://www.epgbc.org/BreastCancerFact.asp) (accessed October 2006)

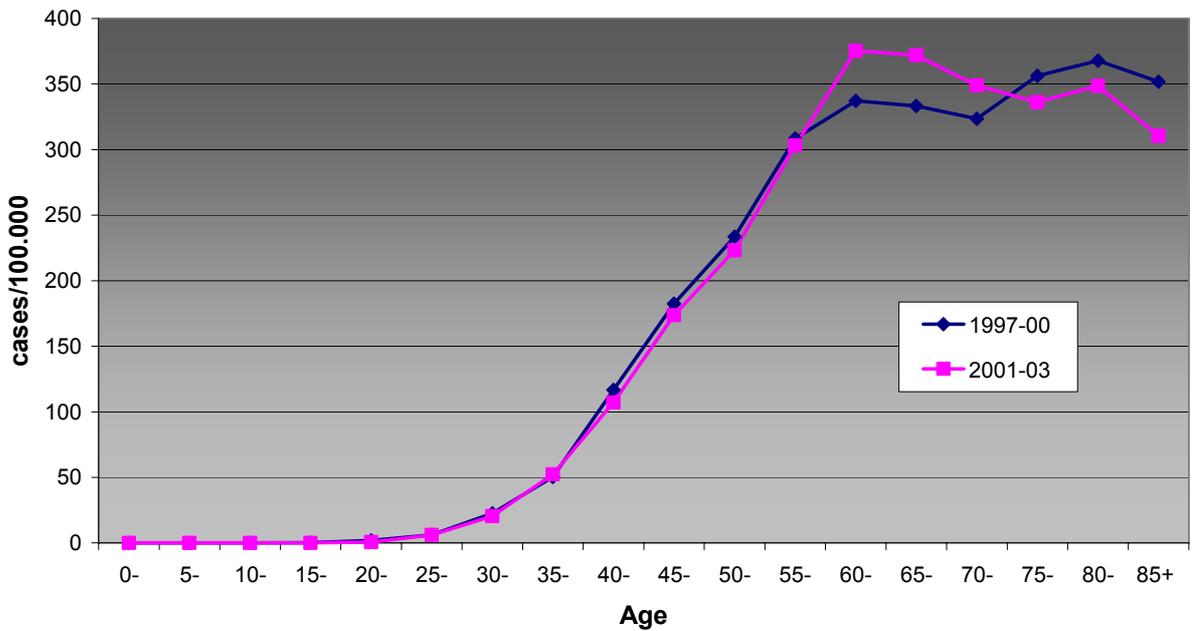
<sup>vi</sup> If not otherwise indicated, data on breast cancer in Switzerland are based on the statistics of the Swiss Association of Cancer Registries (ASRT/VSKR) [www.asrt.ch](http://www.asrt.ch) In 2005, Swiss cancer registries covered about 56% of the population.

**Figure 2.2 Trends in breast cancer incidence by language region, 1985-2004**



As can be seen in Figure 2.3 the highest incidence is around age 60 with the most pronounced recent increase in incidence in the age group 55-65.

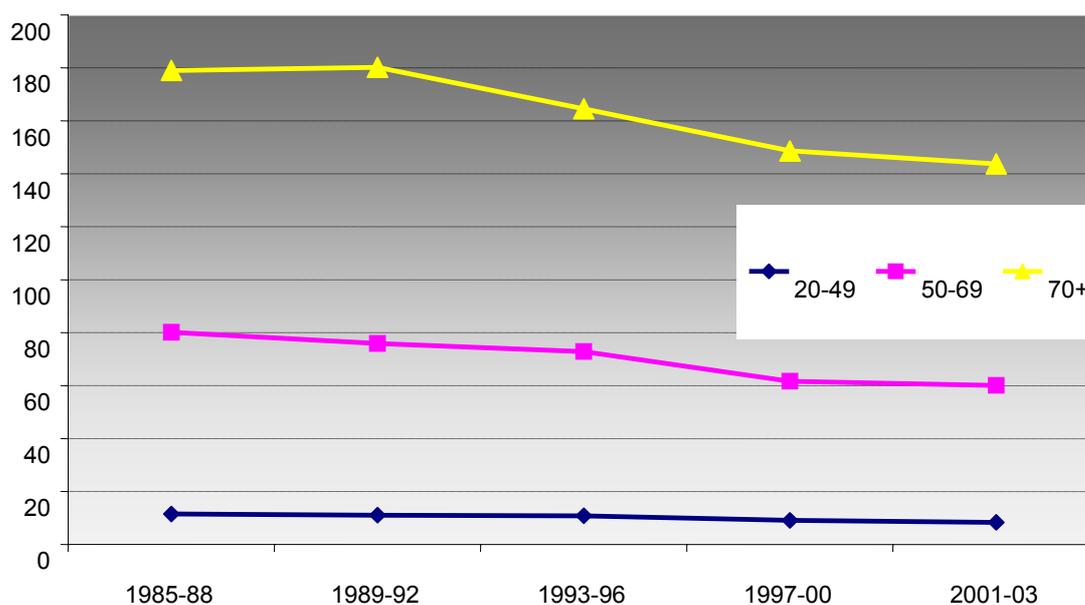
**Figure 2.3 Age-specific breast cancer incidence 1997-2000 and 2001-2003**



## 2.2. Breast cancer mortality in Switzerland

Breast cancer is the most common cause of cancer death for women in Switzerland. 1'379 women died of breast cancer in 2004, accounting for 7'913 potential lost life years. No other single disease comes close to this number except if suicide is called a disease. As shown in Figure 2.4, mortality rates have been decreasing between 1985 and 2004 in all age groups with a stronger decline in elder women.

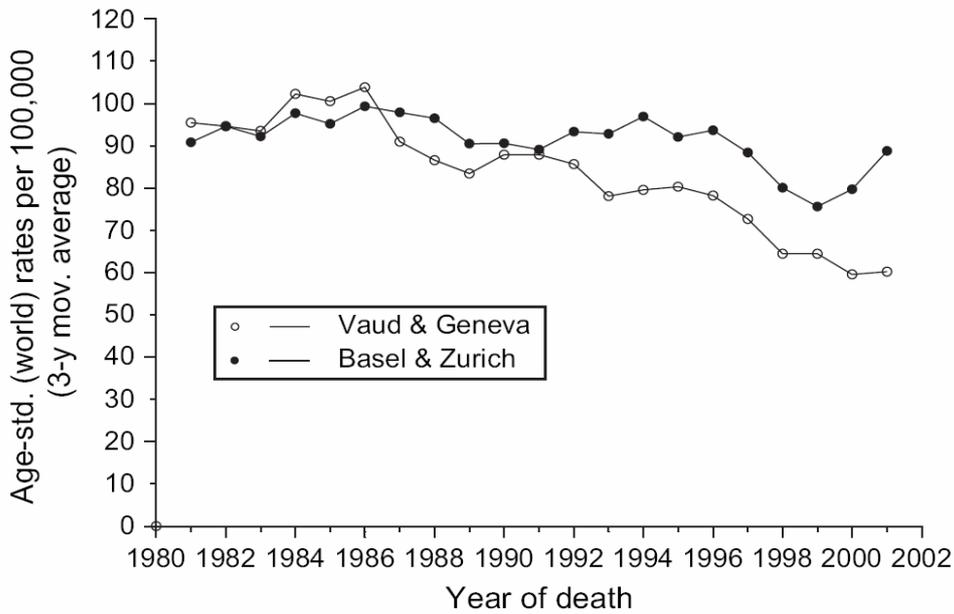
**Figure 2.4 Time trends in breast cancer mortality by age group, 1985-2004**



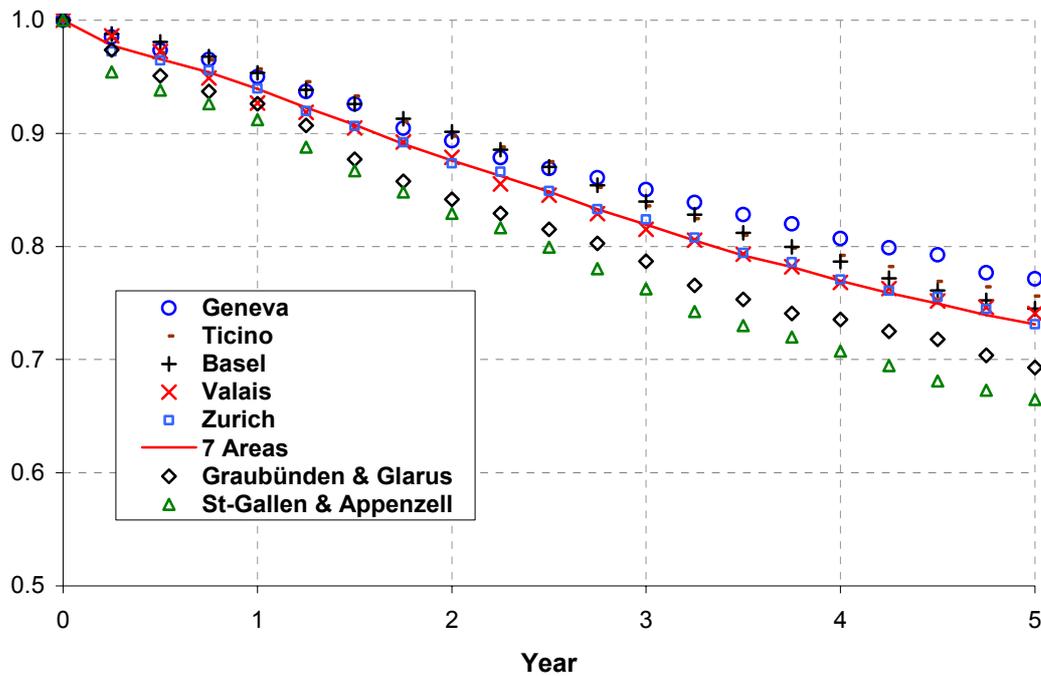
A similar trend has been observed more generally in Europe with a decrease in breast cancer mortality in most European countries in the decade 1990-2000.<sup>7</sup> However, in Switzerland, this decline is not uniform. A comparison of breast cancer mortality trends between 1980 and 2002 in two French- and two German-speaking cantons shows considerable differences (figure 2.5).<sup>8</sup> Expressed in numbers of death, this difference amounts to an excess of about 350 deaths in women aged 55-74 in the two cantons of Basel and Zurich between 1991 and 2002 (about 30 deaths per year) as compared to Vaud and Geneva.

A previous study examined 5-year breast cancer survival rates across seven cancer registries comparing the two periods 1988-1992 and 1993-1997.<sup>9</sup> Survival was lowest in rural parts of German-speaking Switzerland and highest in urbanised regions of the Latin- and German-speaking north-western parts of the country (Figure 2.6). This predates widespread use of mammography screening and may point more to differences in access to and quality of care, than early detection.

**Figure 2.5 Comparison of breast cancer mortality trend among women aged 55-74 in the combined Vaud and Geneva cantons and Basel and Zurich cantons, 1980-2002**



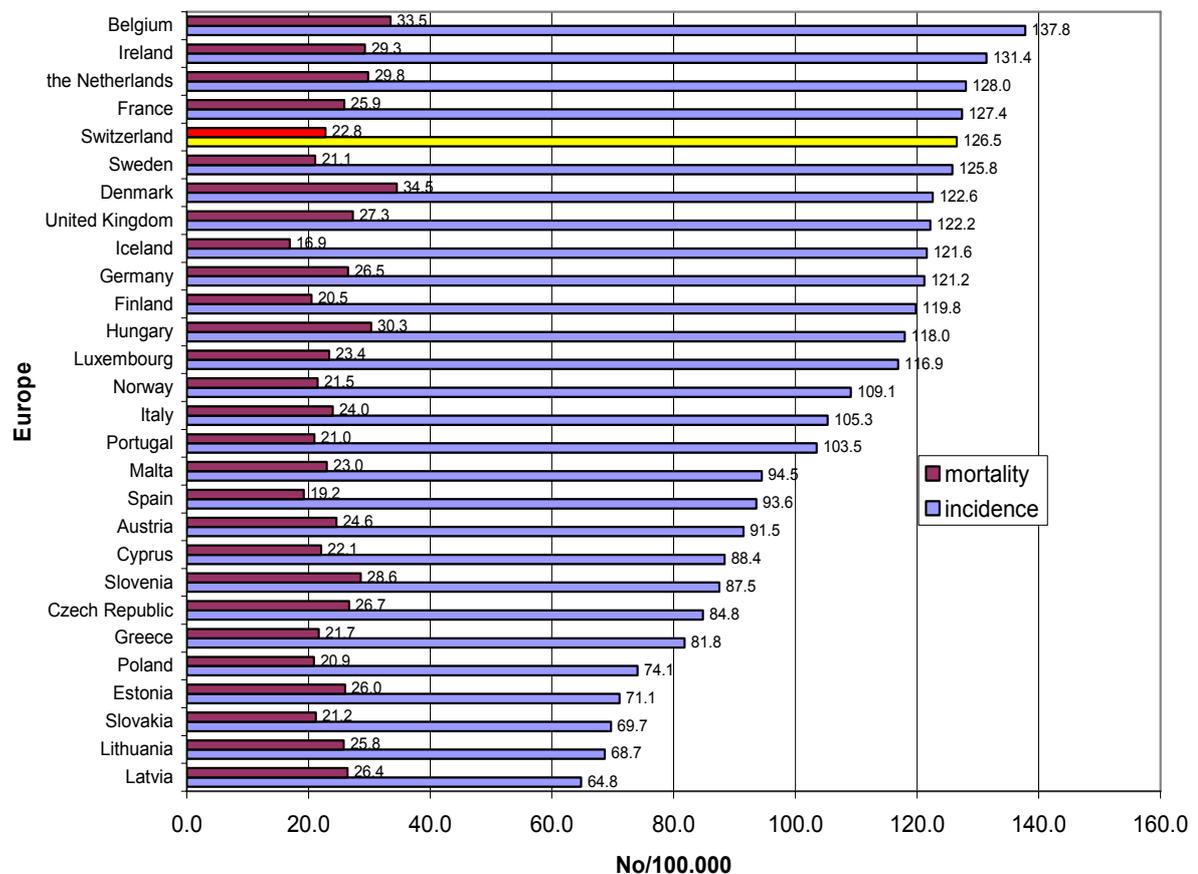
**Figure 2.6 Observed survival after breast cancer in women all ages in different cantons (incident cases 1993-1997/8)**



In addition to these geographical disparities, a further study found social class to be an important prognostic factor of breast cancer mortality in the canton of Geneva.<sup>10</sup> Among women diagnosed with invasive breast cancer before the age of 70 years between 1980 and 2000, those of low social class had a significantly higher risk of dying from their cancer than those of a high social class.

Comparing the situation in Switzerland to other countries incidence as well as death rates are in the middle range (figure 2.7)<sup>11</sup>.

**Figure 2.7 Estimated age standardised incidence & mortality breast cancer rates 2006**  
(Source IARC 2007)



### 2.3. Causes of breast cancer

The exact causes of breast cancer are not known. Certain known risk factors are outside the control of the woman, such as age (nearly 8 out of 10 breast cancers are found in women over age 50), early menarche and late menopause, genetic factors (about 5% to 10% of breast cancers are linked to mutations in certain genes, e.g. BRCA1 and BRCA2 genes), family history (having a mother, sister, or daughter with breast cancer about doubles risk), a previous breast cancer, and earlier radiation treatment to the chest area for another cancer. Other known risk factors on which women have some influence are not having children or having the first child after age 30, longstanding postmenopausal

hormone therapy, alcohol consumption, lack of exercise, obesity and high-fat diets. Some risk factors remain controversial such as smoking and environmental pollutants (pesticides, PCBs)<sup>vii</sup>. This long list of known and potential risk factors mainly shows that the role of primary prevention in reducing breast cancer incidence and mortality is limited. Secondary prevention is thus all the more important.

## 2.4. Biology and pathology of breast cancer

Breast cancer is a heterogeneous group of diseases with more than one natural history. It may not be true that all cancers progress from atypia to carcinoma in situ, to invasive cancer and metastasis. As screening mammography detects early abnormalities, it has become increasingly important to know more about the risk of progression of the various types of lesions identified. A good summary of the biology of breast cancer and prognostic factors can be found in the IARC Handbook.<sup>6</sup> A very brief overview is provided below to ease the understanding of terms used further on in this report.

### THE DIFFERENT TYPES OF BREAST CANCER

Very broadly speaking there are **three categories of breast abnormalities**: benign conditions, in-situ cancers and invasive cancers. *Benign conditions* increase breast cancer risk 1-5 times depending on the degree of epithelial proliferation and atypia. *In-situ lesions* are lobular or ductal. *Lobular carcinoma in-situ* is associated with an increased risk for breast cancer but is usually an incidental finding and is not generally detected by mammography. The natural history of *ductal carcinoma in situ* is not well known. However high-grade lesions (poorly differentiated cytonuclear lesions) appear to be more aggressive with a higher rate of recurrence after breast-conserving surgery. Low-grade ductal carcinoma (well-differentiated) is associated with low-grade invasive cancer, usually with a good prognosis. *Invasive cancers* penetrate the basement membrane of the epithelial site of origin (duct or lobule) and are mostly adenocarcinomas. The morphological appearance of these tumours varies widely, determining prognosis and treatment approaches.

**Ductal carcinoma in situ** (DCIS) plays an important role in the debate on effectiveness of organised breast cancer screening by mammography because it is encountered much more frequently (up to 20%) in breast cancers detected by screening than in clinically detected breast cancers (3-5%). These high percentages of DCIS among screen-detected breast cancers have led to various interpretations. Some authors are of the opinion that this mainly represents overdiagnosis as DCIS does not progress to invasive cancer and thus causes harm (unnecessary treatment). For other experts, DCIS represents a large number of invasive cancers avoided and thus is the ideal target for early detection. A recent review of data on the frequency and rate of progression of DCIS comes to the conclusion that DCIS of all grades has the potential to progress, though high-grade lesions progress more rapidly than lower grade lesions and are more likely to lead to metastatic disease and death.<sup>12</sup> The challenge thus is to accurately identify which low-grade lesions are likely to progress and to provide the most appropriate treatment avoiding over-treatment.

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<sup>vii</sup> American Cancer Society (accessed 24 January 2007).

[http://www.cancer.org/docroot/CRI/content/CRI\\_2\\_2\\_2X\\_What\\_causes\\_breast\\_cancer\\_5.asp?sitearea](http://www.cancer.org/docroot/CRI/content/CRI_2_2_2X_What_causes_breast_cancer_5.asp?sitearea)

## **PROGNOSTIC FACTORS**

Prognosis depends on many factors, including histological type, tumour size, loco-regional lymph node involvement and metastasis in other organs (liver, bone marrow, lungs, brain), as well as molecular markers. Tumor size is one of the most powerful prognostic factors for overall as well as recurrence free survival. Tumor size shows a positive relationship to frequency of axillary lymph node metastasis. In some studies axillary lymph nodes were tumor free in all patients with tumors  $\leq 0.5$  cm. This correlation between size and axillary lymph node status suggests some additive prognostic effect of the two parameters.

Presence or absence of axillary lymph node involvement is the most powerful single and independent prognostic factor in breast cancer patients. Only 20 to 30 % of lymph node negative patients will develop recurrences within ten years compared to about 70% of patients with positive axillary lymph nodes. Number and level of axillary lymph node metastasis predict overall survival and disease free survival. Regarding the number of involved lymph nodes, patients with more than four involved lymph nodes are demonstrated to be of significantly high risk of recurrences.

## **TREATMENT OF BREAST CANCER**

Treatment approaches have changed in many ways since the introduction of breast cancer screening in the 1960s. Whereas radical mastectomy was then the predominant form of therapy irrespective of tumour characteristics, at present breast conserving techniques with radiation therapy, adjuvant chemotherapy and hormonal treatments are combined in various ways and tailored to the patient and tumour characteristics.

### **Surgery**

Breast conserving surgery (followed by radiation therapy of the breast) has become the routine procedure for the initial treatment of breast cancer. In general only patients with small tumours ( $< 3$ cm) are candidates for this type of approach, for patients with larger cancers pre-operative systemic therapy is generally the option of choice in order to reduce the tumour size and allow breast conservation thereafter. In addition, patients with clinically node-negative (N0) disease are candidates for the sentinel lymph node procedure which avoids axillary clearance and related morbidity such as lymphoedema of the arm, reduction of the mobility of the arm and chronic pain.

### **Systemic treatments**

Systemic therapies have experienced an evolution during the last years with the change from “the maximal therapy for all” to more targeted approaches which allow avoiding unnecessary short and long-term toxicities to patients. In general one can say that for more advanced cases the initial treatment is more extensive (surgery), carries more toxic effects (chemotherapy) and is generally much more expensive than for patients with less advanced disease at diagnosis. For example patients with smaller tumours ( $< T2$ ), without axillary node involvement are candidates for endocrine therapies alone, avoiding the burden of toxic side effects and the costs of chemotherapy.

Patients treated with chemotherapy have in general a longer time to resumption of work than patients treated with endocrine therapy alone. The short term side effects of chemotherapy are, for example, alopecia, with the need of wigs; nausea and vomiting with the need of corresponding anti-emetic therapies; haematological disturbances with the need of medication with growth-factors and the danger of infections (with all related

complications from the need for antibiotics up to the need for hospitalization); stomatitis with the need for medication or intravenous nutrition. In the long-term chemotherapy may induce heart failure, secondary tumours, impairment of fertility and other complications.

### **Radiation therapy**

Radiation therapy applied to the whole breast area is generally used after breast conserving surgery. There are experimental attempts aiming at reducing the extent of radiation therapy first with the application of a single course during the operation of the primary tumour and secondly reducing the extent of radiation therapy to the affected breast. This new approach reducing length of therapy and costs is obviously only possible in early stages.

### **Treatment of early breast cancer**

Since 1978 the St Gallen conferences have focused on developing consensus opinions for the management of early breast cancer and these are now recognised as the leading European treatment guidelines for the disease. The most recent guidelines were adopted at the 9th Conference on Primary Therapy of Early Breast Cancer in St Gallen, Switzerland in January 2005. Despite the consensus conferences taking place in Switzerland, there probably is wide variation in treatment approaches across the country. As there is no national and very little cantonal data collection on breast cancer treatment and outcomes, regional differences cannot be documented.

### **IN CONCLUSION**

Breast cancer remains the most common cause of cancer death for women in Switzerland, despite decreasing mortality rates since 1985. During the same period the incidence of breast cancer has increased, probably partly due to the introduction of mammography screening. Breast cancer mortality trends and survival rates differ by canton, pointing to differences in access to and quality of care.

Some of the risk factors for breast cancer are known. Few of them relate to life style and are under the direct control of women. Overall the role of primary prevention is limited in reducing breast cancer incidence and mortality.

Tumour size and the presence or absence of axillary lymph node involvement are the two most powerful prognostic factors. Not only will treatment be more effective if the cancer is detected at an early stage, but it will also be less mutilating.

New therapeutic approaches have improved survival of breast cancer patients in the past decades, in particular if the cancer is detected at an early stage. But even with improvements in therapy, breast cancer remains a potentially deadly condition. Early detection thus remains paramount.

## **Chapter 3: What is the evidence on the efficacy and effectiveness of breast cancer screening by mammography?**

This chapter will briefly recapitulate the evidence on efficacy of mammography screening based on the initial randomised controlled trials. The details of this evidence are presented in the annex. The focus will then be on the effectiveness of breast cancer screening in reality, examining evidence from longstanding programmes. Finally, the hazards of screening will be considered.

### **3.1. The efficacy of screening for breast cancer**

The fact that most cancers respond well to treatment if detected early is not in itself sufficient evidence to support population-based screening. A screening test needs to be sufficiently sensitive to advance the time of diagnosis to a more successfully treatable phase. However, even an earlier diagnosis may not prevent death. Rather than extend life, screening may simply extend the length of life with the disease by advancing the time of diagnosis (lead time bias). Screening may selectively detect only the less aggressive cases, the majority of which survive regardless of the mode of detection (length bias), or screening may detect cases that would never have been diagnosed without screening (over diagnosis). For these reasons, evaluation of the efficacy of screening is best carried out by a prospective randomized trial in which mortality from the target disease is the primary endpoint.<sup>viii</sup> The term “efficacy” will thus generally be used to refer to the relative reduction of breast cancer mortality rates in the screened group with respect to the control group.

Eight randomized screening mammography trials were implemented between the 1960s and 90s.<sup>ix</sup> Based on the results of these trials and numerous meta-analyses, showing a 25 to 30% decrease in breast cancer deaths, several industrialised countries started implementing national mammography screening programmes in the 1980s and 90s.

In 2000 two Danish members of the Cochrane Collaboration, Peter Gotzsche and Ole Olsen, published a review of the data on breast cancer screening.<sup>13-15</sup> They deemed that five of the seven eligible randomized controlled trials were not performed properly, and discarded the results from those trials (which happen to show a benefit of mammographic screening). They only included two trials (Malmö trial and National Breast Screening Study of Canada I) arguing that they were fairly well performed and that only their results were valid. They interpreted those two trials as showing that mammographic screening

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<sup>viii</sup> As survival is subjected to all the biases mentioned above, it is not recommended as a valid endpoint measure.

<sup>ix</sup> A ninth trial, involving women aged 40-49 only (UK Age Trial), begun in 1991 in the United Kingdom. Results have been recently published<sup>1</sup> showing a 17% reduction in breast cancer mortality, which did not reach statistical significance (RR 0.83; CI 0.66-1.04). This trial will not be discussed as it does not concern the relevant age group (women 50 and above).

had no benefit, and concluded that there was no benefit from mammographic screening for women at any age.

In the months following the publication of the Cochrane review, a very extensive review of the randomized controlled trials of mammographic screening was published by the United States Preventive Services Task Force.<sup>16,17</sup> The task force concluded that the data support recommending screening, beginning at the age of 40 years. The International Agency for Research on Cancer convened a panel of 24 experts to review the data. The panel concluded that the issues raised by Gotzsche and Olsen were either misinterpretations of the facts or were inconsequential.<sup>18</sup> The National Health Council of The Netherlands published a point-by-point review of the concerns raised by Gotzsche and Olsen and concluded that many of those concerns were a result of misunderstanding the trials and the data or were of no consequence.<sup>19</sup> Furthermore many papers were published in 2002 and 2003 that countered specific issues raised in the Cochrane review<sup>20-27</sup>. In addition, an overview based on individual data of the Swedish trials was published.<sup>28</sup>

In 2006, the Advisory Committee on Breast Cancer Screening in England considered efficacy of mammography screening to be underestimated in the randomized controlled trials.<sup>29</sup> The same year a health technology assessment requested by the Quebec Ministry of Health (Canada) re-examined the scientific evidence on which screening mammography programs are based.<sup>30</sup> This extensive review concluded that modern breast cancer screening programs may achieve greater reduction of breast cancer mortality than was found in the screening trials. Finally, an update of the Cochrane review that initially triggered much debate was published online on 18 October 2006.<sup>31</sup> One of the two authors had participated in the initial review. The trials included in the analysis are identical to the initial review, but the conclusions are different.

*“Screening likely reduces breast cancer mortality. Based on all trials, the reduction is 20%, but as the effect is lower in the highest quality trials, a more reasonable estimate is a 15% relative risk reduction.”*

Much attention was paid in Switzerland to the debate that followed the publication of the initial Cochrane review. This triggered a rejection of mammography screening by many Swiss cantons, particularly in the German and Italian-speaking parts and effectively stopped the development of a national screening programme. To lay this debate to rest a summary of judgements made about the eight trials and conclusions reached by each review are provided as annex.

It is now uncontested that the randomised controlled trials have shown that population-based breast cancer screening reduces breast cancer mortality in women over age 50. The question, however, is if this effect persists outside the controlled trial environment. To answer this question the impact of breast cancer screening programmes on breast cancer mortality.

### **3.2. Are mammography screening programmes effective in reducing breast cancer mortality?**

This question will be addressed focusing on long-standing programmes as the impact of breast cancer screening programmes only becomes fully apparent 10 to 15 years after implementation. Breast cancer screening programmes by mammography have been operating for more than 10 years in Australia, Canada, Denmark, Finland, the Netherlands, Sweden and the United Kingdom. The history of the national or regional screening programme is briefly summarized for each country followed by current evidence on their possible role in reducing breast cancer mortality.

#### **How was the scientific evidence gathered?**

A first review at an international level was done by IARC in 2002. The findings of the IARC review were revised and updated with materials published between 2000 and 2006.

The types of materials used are published peer-reviewed papers; published reports from countries; handbooks, monographs, books; and, annual reports of mammography screening programmes. This includes reports from Australia, Belgium, Canada, France, Ireland, Italy, Luxemburg, The Netherlands, New Zealand, Norway, Portugal, Spain, United Kingdom. No reports were found from Greece and Denmark. Reports from Sweden and Finland could not be used due to language difficulties.

Evaluation reports of long-standing national programmes done by accredited national institutes were searched: Australia, Canada, France, The Netherlands, United Kingdom. Information on mammography screening was retrieved from national websites for Germany, Ireland, France, Italy, Spain and the United Kingdom. Information presented in abstracts, poster presentations and meeting reports (European Breast Cancer Network) was used as relevant.

A Medline search on effectiveness, mortality reduction and overdiagnosis linked to mammography screening (programmes) was carried out and complemented by a search of references in relevant articles identified.

Information retrieved through this wide search strategy is presented in chapters 4 and 5.

#### **AUSTRALIA**

The National Program for the Early Detection of Breast Cancer, now known as BreastScreen Australia, was established by the Commonwealth and the States and Territories in 1991. It is targeted at women without symptoms aged 50-69, although women aged 40-49 and 70 years and older are able to attend for screening. BreastScreen Australia operates in over 500 locations nationwide, via fixed, semi-mobile and mobile screening units. The Program's aim is to achieve a participation rate of 70% among women aged 50-69 years. In 2002-2003, the programme screened 56.1% of women in the target group. The highest priority of the programme is to increase uptake.

The 2006 progress report of Australia<sup>36</sup> shows that the five-year relative breast cancer survival has increased from 70.9% in the period 1982-1986 to 86.6% in 1998-2002. There was no change in breast cancer survival in men during the same period. The age-standardised breast cancer mortality rate for women age 40 to 85 was fairly steady until the early 1990s, but since then has fallen from 31.0 deaths per 100,000 women in 1990 to 23.4 deaths per 100,000 in 2004 corresponding with a 24.5% mortality reduction. Furthermore the median age of death due to breast cancer for women increased from 64 years in 1983 to 67 years in 2004.

## **CANADA**

Organized breast cancer screening began in British Columbia in 1988 and has since expanded to include all 10 provinces plus the Yukon, Nunavot and Northwest Territories. The last province, Prince Edward Island, started screening in 1999. The average national participation was 33.9% in 2002. Breast cancer screening includes a bilateral, two-view screening mammography. Nationally the target population is defined as asymptomatic women between the ages of 50 and 69 years with no prior diagnosis of breast cancer. However, each province may in addition propose screening to women outside this target age group. In addition to mammography screening, some programmes offer clinical breast examination performed by a trained health professional. The remaining programmes encourage women to obtain regular clinical breast examination outside the programme from their family physicians.

British Columbia has the longest standing screening programme, and by 2003 more than 50% of women aged over 40 had received at least one screening mammography through the programme. Women aged 40-79 are offered screening mammography free of charge through community clinics with interpretation by radiologists affiliated to the program. Women under the age of 50 are screened annually and those over 50 every 2 years. The impact of this screening programme on breast cancer mortality was recently assessed.<sup>37</sup> A cohort of women aged 40 to 79 having had their first screen in the period 1988-2003 was identified. Observed breast cancer deaths were compared to those that would have been expected in the same cohort without screening. The calculation of expected deaths was derived from incidence and survival rates of non-participants during the same time period. It was assumed that those women participating in screening had the same risk of developing breast cancer as those who did not. The breast cancer mortality ratio was calculated by dividing observed by expected breast cancer deaths. It was estimated at 0.60 (95% CI 0.55-0.65) for all ages combined. There were no significant differences between age groups. Corrected for self-selection bias using estimates from the literature the mortality ratio was 0.76 corresponding to a 24% decrease in breast cancer mortality in women over age 40 undergoing screening.

## **Denmark**

Denmark has one of the oldest national cervical cancer screening programmes in the world, but does not offer country wide mammography screening to its female population. Mammography screening was introduced between 1991 and 1994 in three out of 16 administrative regions.

In Copenhagen the screening programme started in 1991 with two view mammography in the initial round and one view in subsequent rounds. Participation rate in the initial round was 71%. In 2005 a study was carried out to compare breast cancer mortality in women invited for screening in Copenhagen between 1991 and 2001 (five rounds) and a national control group (regions without a mammography screening programme) as well as a historical control group (1981 to 1991).<sup>38</sup> It should be noted that opportunistic mammography screening has remained very limited in Denmark. The study showed a significant reduction in breast cancer mortality during the 10 year screening period of 25% (RR 0.75, 95% CI 0.63-0.89) compared with what would be expected in the absence of screening. For women actually participating in screening, breast cancer mortality was reduced by 37%.

## Finland

In Finland, nationwide population based breast cancer screening was introduced in 1987. The programme covers women aged 50-59 years and can be continued up to age 64. Women are screened every two years. From 1987 until 1990 a randomly chosen birth cohorts of women aged 50-59 were invited for their first screen. These birth cohorts were considered to be study cohorts, and could be compared to cohorts invited for the first time after 1990. Participation rates are very high at 88.5%.<sup>39</sup> The centralised screening registry for identification, invitation, and follow up of the women is part of the Finnish Cancer Registry, which operates nationwide and is population based. The National Population Registry, national registration of deaths, and cancer registrations are linked to the screening registry.

In an early study 89 893 women invited to join the screening programme in 1987-89 were followed up until 1992. These were matched by 68 862 “control” women not invited to the service screening. The rate ratio of death was 0.76 (95% CI 0.53 to 1.09). The effect was larger and significant (0.56; 0.33 to 0.95) among women aged under 56 years at entry.<sup>40</sup>

A similar study with a longer follow-up period was carried out in Helsinki, where breast cancer screening started from 1986 onwards progressively including birth cohorts of women aged 50 to 59. Breast cancer mortality among women who had already been invited for screening and those not yet included in the screening programme were compared in the period 1986 to 1997. A 19% decrease in refined mortality was found, but was not statistically significant (RR 0.81, 95% CI 0.62-1.05).<sup>41</sup> One should consider that only women aged 50-59 were included, and that one would thus expect a lower impact on breast cancer mortality than if the full age range 50-69 was invited.

A recent study analysed time trends in breast cancer incidence and mortality in three cities with different screening histories: screening offered to women 55-69 since 1987 in Turku, screening offered to women 55-59 since 1987 in Tampere, no screening in these age groups in Helsinki.<sup>42</sup> The incidence of breast cancer during the 11-year screening period 1987-97 in women born in 1918-32 was compared with incidence during the pre-screening period 1976-86 in women born in 1907-21 in each city. The follow-up for breast cancer mortality was four years longer. The incidence of breast cancer increased by 31-38% in all study cities irrespective of screening. No statistically significant changes in breast cancer mortality were seen in Tampere (non-significant 14% mortality reduction) or Helsinki (non significant 11% mortality increase). In Turku, a significant 36% mortality reduction (RR 0.64; CI 0.47-0.88) was found in the whole study population. Although a consistent mortality reduction was found in all age groups screened, it was statistically significant only in women aged 65-69 at entry (RR 0.53; CI 0.28-0.99).

## Sweden

Mammography screening was introduced in Sweden in 1986 by the National Board of Health and Welfare. The screening targets women aged 50 to 69 and is implemented at the county level. The first counties started screening in 1986 followed progressively by other counties. National coverage was achieved in 1997. Opportunistic screening exists in the large cities but is rare elsewhere. The attendance rate has been around 70-75%.

A recent study examined the time trend in incidence-based breast cancer mortality among women screened in 13 large areas within nine counties over a period of follow-up of 20 to

44 years.<sup>43,44</sup> Only counties with at least 10 years of follow-up after the initiation of screening were included. This represents approximately 45% of Swedish women and includes information about age at diagnosis, age at death, and screening history for 542,187 women in the prescreening and 566,423 women in the screening epochs. The prescreening epoch examined varies by county from 1958-1979 to 1979-1989. The screening epochs vary in length from 8 (1 county) to 15 years covering the period 1980-2001. Each screening epoch had an additional follow-up of 5 years for mortality. Attendance of screening was uniformly high, averaging 75%. Detection rates averaged five breast cancers per 1,000 women screened in the first round, and four breast cancers per 1,000 women screened in subsequent rounds. After adjusting for self-selection bias, there was a significant 43% reduction in incidence-based breast cancer mortality associated with screening (RR 0.57; 95% CI 0.53-0.62). The number needed to screen to save one life was estimated as 472.

The breast cancer mortality decline associated with mammography screening was examined in the two Swedish counties where one of the randomized controlled trials had taken place.<sup>45</sup> Comparing the period when no screening was available (1968-1977) to the period when screening was made widely available (after the trials; 1988-1996), a reduction in mortality corrected for selection bias of 48% was found in women 40-69 undergoing screening (RR 0.52, 95% CI 0.43-0.63). No significant change in breast cancer mortality was found in these time periods for women who did not undergo screening. However, in this latter category, women 20-39 years were included.

Another analysis compared counties which started offering mammography screening in 1986-87 (intervention group) to those which started in 1993 or later (control group).<sup>46</sup> After a mean follow-up of 10.6 years, a statistically non-significant 16% reduction in mortality from breast cancer was found (RR 0.84; CI 0.76-1.05). After adjustment for inclusion and lead time biases the reduction was 20%.

In a further analysis, deaths from breast cancer diagnosed in the 20 years before screening was introduced (1958-77) were compared to those diagnosed in the 20 years after the introduction of screening (1978-97, thus including the period of the randomized controlled trial) in women aged 40-69 years. It appeared that adjusted breast cancer mortality declined in women who were screened (RR 0.56, CI 0.49-0.64) as well as for those who were not screened (0.84, CI 0.71-0.99). This mortality reduction of 16% is estimated to be caused by improved management of breast cancer and higher awareness (earlier response to self-detected breast symptoms), while the additional 28% mortality reduction in screened women is attributed to the impact of screening.<sup>47</sup>

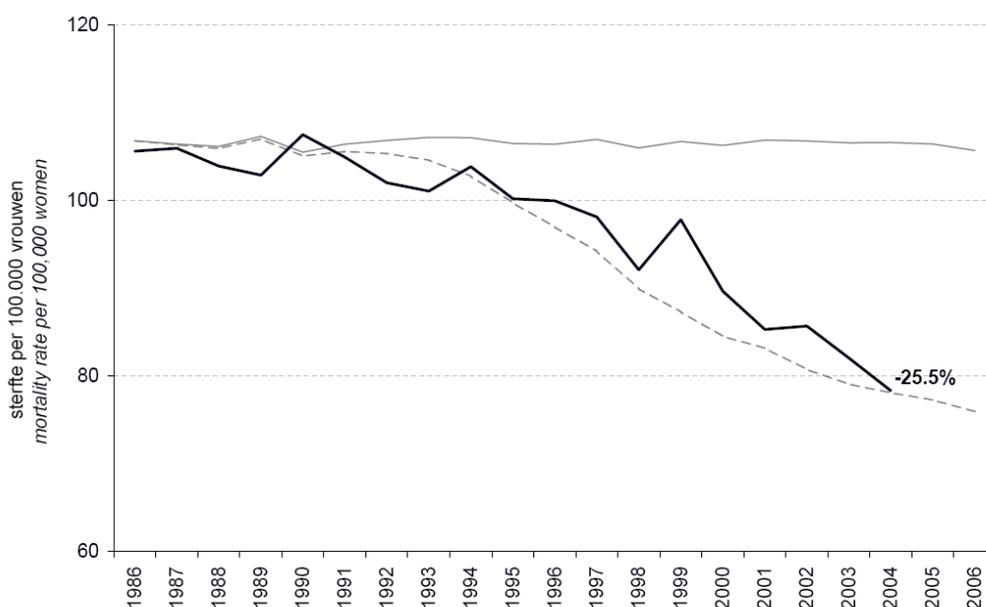
### **The Netherlands**

The Dutch national breast screening programme started in 1990 and invites women aged 50-69 years. National coverage was reached in 1997. In 1998, it was extended to include women aged 70-75 years old. Screening is organized regionally. There are nine screening regions, which coincide with the regions covered by the Comprehensive Cancer Centres. Each of these centres cooperates with the Municipal Health Services in its region to implement the programme. A total of 64 mainly mobile units are used for screening. Between 1990 and 1999, 5.7 million invitations were issued and 4.5 million examinations performed. This corresponds to a participation rate of 79%.

In 2001 the national breast screening evaluation team (LETB) reported a 19.9% statistically significant breast cancer mortality reduction in the age group 55-74 as compared to death rates in 1986-88.<sup>48</sup> Adjuvant systemic therapy seemed unlikely to explain this reduction, as mortality rates continued to rise up to one year after implementation in municipalities where screening began after 1995. The decline in mortality was mirrored by a decrease of the incidence of advanced breast cancers (stage shifting). In women aged 50-69 advanced cancer incidence declined by 12.1% between 1989 and 1997.<sup>49</sup>

This trend in mortality decline continued and reached 25.5% in 2004, 14 years after the start of the national programme.<sup>50</sup> This reduction has also been achieved through the high average participation rate of 78.8% over 15 years. The observed decline in breast cancer mortality is very similar to the decrease that had been predicted by a microsimulation model as shown in Figure 3.1.

**Figure 3.1** Age-standardised breast cancer mortality rates as observed (bold line) in the Netherlands and predicted by the MISCAN model<sup>x</sup> for the situation with (dotted line) and without screening (thin solid line) programme in women aged 55-74 years in the period 1986-2004



### Spain

A breast cancer screening programme was set up in the province of Navarra in 1990, achieving a participation rate of more than 85%. Based on breast cancer incidence trends 1975-1990, breast cancer deaths without screening were estimated for the period 1990-

<sup>x</sup> The Department of Public Health of the Erasmus Medical Centre has developed the microsimulation computer model 'MISCAN' to enable evaluation of screening programme to examine the cost-effectiveness of different scenarios of opportunistic and organized breast cancer screening in Switzerland (see chapter 10).

2004 and compared to observed breast cancer mortality after the introduction of screening.<sup>51</sup> Overall breast cancer mortality declined by 20% (RR 0.8; CI 0.69-0.93) with the largest reduction in the age group 50-69 (RR 0.65; CI 0.51-0.82). Excluding prevalent cancers, mortality decreased by a further 7% among women included in the screening programme. Comparing observed to expected deaths (extrapolating the pre-screening trend), the estimated decrease in mortality was 62% in the screened age group, but only 22% in unscreened age groups (30-44 and ≥75 years). Breast cancer mortality rates have been declining since 1993-95 in the whole of Spain. However, the decline has been more pronounced in Navarre.

Thus this programme with a very high participation and retention rate (about 95%), achieved major reductions in breast cancer mortality.

### United Kingdom

In 1986 an expert committee recommended the introduction of a national breast screening programme which started in 1989. National coverage was reached in 1994. Since April 2001 the screening programme was expanded to routinely include women aged 65-70. Until today over 19 million women have been screened by the NHS Breast Screening Programme (NHSBSP), participation rates being fairly constant around 75%.

Death rates from breast cancer in England and Wales were fairly constant, or increased slightly, during the 1980s, but since about 1990 they have fallen in all age groups by about 25%.<sup>29</sup> Recent statistics from the National Cancer Intelligence Centre show a decline of 27.3% in women aged 50-64 over the ten-year period 1995-2004 (Table 3.1).

**Table 3.1 Decline in breast cancer mortality in the United Kingdom, 1995 to 2004<sup>(\*)</sup>**

Breast cancer deaths	units	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004
women 50-64	thousands	3	2.8	2.8	2.9	2.8	2.8	2.7	2.7	2.6	2.6
Women all ages	thousands	11.8	11.4	11.2	11	10.9	10.6	10.8	10.8	10.5	10.3
per 100'000 women (50-64)	rate	77	71	70	69	66	65	62	60	58	56
	% decrease		7.8%	9.1%	10.4%	14.3%	15.6%	19.5%	22.1%	24.7%	27.3%
per 100'000 women (all ages)	rate	36	34	33	33	32	31	31	30	29	28
	% decrease		5.6%	8.3%	8.3%	11.1%	13.9%	13.9%	16.7%	19.4%	22.2%

(\*) Summary statistics on breast cancer and the NHS breast screening programme, National Cancer Intelligence Centre

It is not easy to ascertain the direct contribution of the NHSBSP to the reduction in mortality from breast cancer. The rapid decline in mortality is believed to be partly the result of earlier diagnosis of breast cancer, which is associated with screening and increased breast awareness, and partly the result of increased use of hormonal and other effective therapies. Several methods have been used to estimate the contribution of the NHSBSP to the reduction in mortality. Estimates of the decrease in breast cancer mortality attributable to screening vary between 6-15% depending on the number of screening rounds, and the use of one- or two-view mammography.<sup>52;53</sup>

### Screening mammography and adjuvant therapy

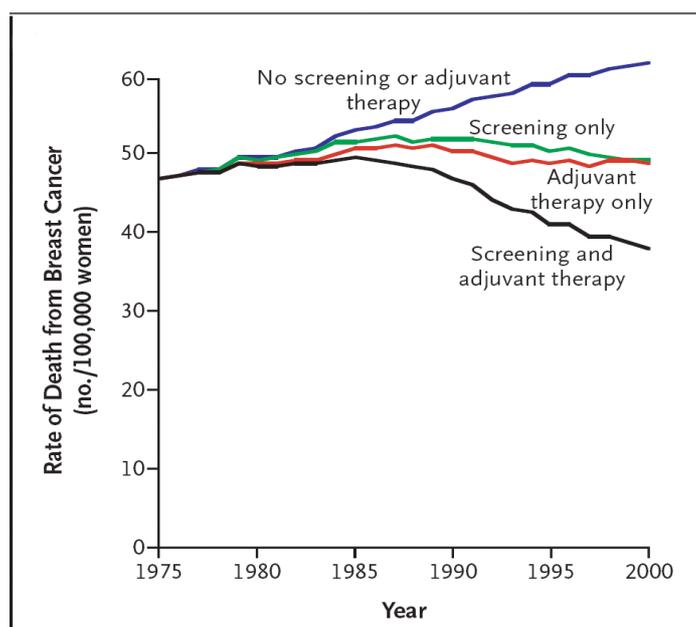
The decline in breast cancer mortality seems to be undisputed, but the major question already alluded to above is: To what extent are mortality reductions due to screening mammography or to adjuvant treatment?

In 2005, a study of a consortium of investigators was published estimating the relative and absolute contributions of screening mammography and adjuvant treatment to the reduction in breast-cancer mortality in the United States from 1975 to 2000. It showed that both screening mammography and treatment have helped reduce the rate of death from breast cancer in the United States.<sup>54</sup> Figure 3.2 shows estimated age-adjusted rates of death from breast cancer among women aged 30 to 79 for four scenarios: no screening and no adjuvant treatment; screening, but no adjuvant treatment; no screening, but adjuvant treatment; screening and adjuvant treatment.

In the absence of screening and adjuvant therapy breast cancer mortality was expected to increase by 30% between 1975 and 2000. The reduction of breast cancer mortality due to screening was estimated at 7 to 23% across seven models used, with a median of 15%. Adjuvant therapy was estimated to reduce mortality by 12 to 21 %, with a median of 19%.

A similar model study was carried out in the Netherlands in 2004.<sup>55</sup> The reduction in breast cancer mortality due to adjuvant therapy was estimated at 7% in women aged 55-74 years, while the reduction due to screening (implemented in women aged 50-69 years since 1990-97) would be 28-30% in 2007. The contribution of adjuvant systemic therapy was thus anticipated to be less than the mortality reduction caused by mammography screening. The divergence between conclusions reached in these two studies and the lesser relative impact of mammography screening in the US may reflect differences in assumptions made about the use of adjuvant therapy and its effectiveness in different tumour types, as well as differences in the implementation of mammography screening (no national programme in the US).

**Figure 3.2** Estimated impact of mammography screening and adjuvant therapy on breast cancer mortality (age 30-79) in the United States, 1975-2000



### **3.3. Further benefits of breast cancer screening programmes**

The main claim of breast cancer screening is that the detection of breast cancer at an earlier stage and of smaller size (stage shifting) leads to less invasive treatment, better prognosis and thus longer survival. Having reviewed the evidence on decreased breast cancer mortality, one may also want to examine what mammography screening programmes have achieved in terms of less invasive treatments. Some of the recently published evidence is presented without claiming completeness.

#### **More breast conserving surgery**

All breast cancers diagnosed between 1997 and 2001 in women aged 40-79 years resident in 17 areas of Northern and Central Italy were classified by size, nodal status and method of detection (screen-detected at 1<sup>st</sup> screen, at subsequent screens, not screen-detected).<sup>56</sup> The type of surgical treatment performed was classified in two categories: breast conserving surgery and mastectomy. 21'148 invasive breast cancers and 2'162 *in situ* breast cancers were analysed. Among women 50-69 years the rate of early cancer (*in situ* or < 30mm) increased by 13.7% in the screened group during the study period, while the advanced cancer rate decreased by 19.4%. In the screened population, breast conserving surgery rates increased by 24.6% and mastectomy rates decreased by 24.2%. Breast conserving surgery was carried out in more than 75% of screen-detected cases in the first round and in 83% of cases detected in subsequent rounds as compared to 54.4% and 52.5 % in cases not yet-invited and never-respondent. The reduction of mastectomy rates over time was due to a decreased proportion of mastectomies in early cases (from 31% to 21%,  $p < 0.001$ ).

A study in Australia found similar difference in surgical treatment between screen-detected and not screen-detected cases.<sup>57</sup> 59.5% of women undergoing surgery in the screen-detected group had breast conserving surgery as compared to 42.3% in the not screened-detected group.

A further study in Australia, focusing solely on breast cancers detected with or without screening in 1999, found that screen-detected cases received significantly less mastectomies (30.6% vs. 48.9%), less chemotherapy (18.4% vs. 33.9%) and more radiotherapy (60.8% vs. 47.5%) than not screen- detected cases.<sup>58</sup>

#### **Shorter (and less expensive) hospital treatment**

In Turku, Finland, all women diagnosed with primary invasive breast cancer during the period 1987-1993 were categorised by method of detection: screen-detected, interval and clinical cancer.<sup>59</sup> The number of days of hospitalisation (14 vs. 21) and the number of outpatient visits (22 vs. 28) were significantly lower for screen-detected versus clinical cancers. This translated into lower treatment costs per patient (7'359 vs. 10'353 Euro, adjusted for age) and per survival day (5.2 vs. 17.8 Euro).

Having reviewed evidence on the positive impact of breast cancer screening, the potential harms need to be examined.

### **3.4. Hazards of screening: false positive results, false negative results, overdiagnosis and radiation-induced breast cancer**

The benefits of screening clearly need to outweigh potential harms. The two most important and debated harms are false positive results and overdiagnosis. A further, although minor risk inherent to mammography screening is breast cancer induced by ionizing radiation. Relevant data from the randomized controlled trials will be presented first, followed by evidence from breast cancer screening programmes.

Interval cancers, sometimes referred to as “false-negatives”, may also be perceived as a hazard of screening and will be briefly discussed at the end of this sub-chapter.

#### **False positive results**

Like all medical tests, mammography is not perfectly accurate and can lead to false positive results. The term “false-positive” refers to a benign lesion found at mammography in an asymptomatic woman ultimately found to have no evidence of cancer. False positive results will lead to additional testing (diagnostic mammography, ultrasound, MRI), invasive procedures (needle biopsy) and unnecessary anxiety for these women. The probability that a woman will require further assessment after a screening mammography will depend on the quality of the screening test and the usual practice in a given health care system (different thresholds for recommending further investigations). The risk for false positives also depends on the woman’s profile: younger age, previous biopsy and hormone replacement therapy increase the risk. In addition, false-positives are more frequent at first screening rounds than in subsequent rounds when previous films are available for comparison.

In the Stockholm trial the false positive rate was 1% after 2 screens.<sup>18</sup> In the Finnish national programme the risk of being re-called for further investigations without a cancer being detected was 2.9%.<sup>39</sup> Although a recall for further investigation causes anxiety and discomfort, the main harm caused by mammography screening was considered to be surgical biopsy. Less than 0.3% of the women screened (1 in 372 screens) had a benign surgical biopsy.

In the United Kingdom the false positive rate was 7% in the first screening round, and 3% in further rounds.<sup>60</sup> In the Netherlands the rates are much lower: 2.5% and 1.2% respectively.<sup>50</sup> On the other hand, in the United States recall rates are much higher between 6.4 and 13.3% (all rounds combined).<sup>61</sup>

A comparison between two screening programmes in the United States and the national programme in the United Kingdom showed that recall rates in the US are much higher than in the UK for the first screen (11.2-13.1% versus 7.4%) as well as subsequent screens (6.8-8% versus 3.6%).<sup>62</sup> But cancer detection rates are similar. The much higher rate of false-positives in the US are due to several factors: fear of malpractice lawsuits in the US; lower standards for the volume of mammographies to be read by the 1<sup>st</sup> reader (480 per year in the US versus 5000 in UK); no standard 2<sup>nd</sup> reading in the US; and better access to previous mammographies in the UK; a centralised programme in the UK and a less mobile population.

## THE PSYCHOLOGICAL IMPACT OF FALSE-POSITIVES

A systematic review of the psychological impact of mammography screening of all publications between 1982 and 2003 identified 54 papers in 13 countries.<sup>63</sup> The results indicate that women who have further investigations following a screening mammography experience significant anxiety in the short term, and possibly in the long term. The nature and extent of the further investigations determines the intensity of the negative psychological impact in the short term. Evidence regarding the long term consequences of false positive results and their impact on subsequent attendance of screening is conflicting. It is difficult to compare study outcomes because the measures of psychological impact differ, they are not applied in a uniform way, and different time intervals were used. Lack of baseline data and difficulty in following up the comparison groups further confounds results.

The U.S. preventive services task force also reviewed evidence on the impact of false positives on women.<sup>17</sup> It concluded that the proportion of women suffering from anxiety after an abnormal mammography and the persistence of this anxiety vary. However, anxiety does not seem to dissuade women from further screening and may even be associated with improved adherence. Most women are willing to accept the risk for false-positive results.

A study carried out in the canton Vaud (Switzerland) in 1995 during the pilot phase of the screening programme compared levels of anxiety between women having received negative results and those with false positive results.<sup>64</sup> The overall mean level of anxiety was low, but women screened positive had a sustained higher anxiety at 8 weeks follow-up than women screened negative. The predictors of anxiety were mainly educational level and the initial level of anxiety before screening.

### Overdiagnosis

Overdiagnosis refers to the detection of cancers that may never cause symptoms or death during a woman's life because she dies of another cause before the breast cancer becomes symptomatic. These breast cancers would not have been found if there was no screening test. Women in whom such cancers are detected do not benefit, but experience harm such as unnecessary worries and unnecessary treatment with its complications. Overdiagnosis is inherent in any screening programme, as it is not possible to accurately predict the future behaviour of a detected cancer based on histopathology. However, increased detection of one particular type of breast cancer, ductal carcinoma in situ (DCIS), in breast cancer screening programmes has been considered as an indication of overdiagnosis.

Data from randomised controlled trials of mammographic screening can be used to determine the extent of any overdiagnosis, as soon as either a time equivalent to the lead-time has elapsed after the final screen, or the control arm has been offered screening.<sup>xi</sup>

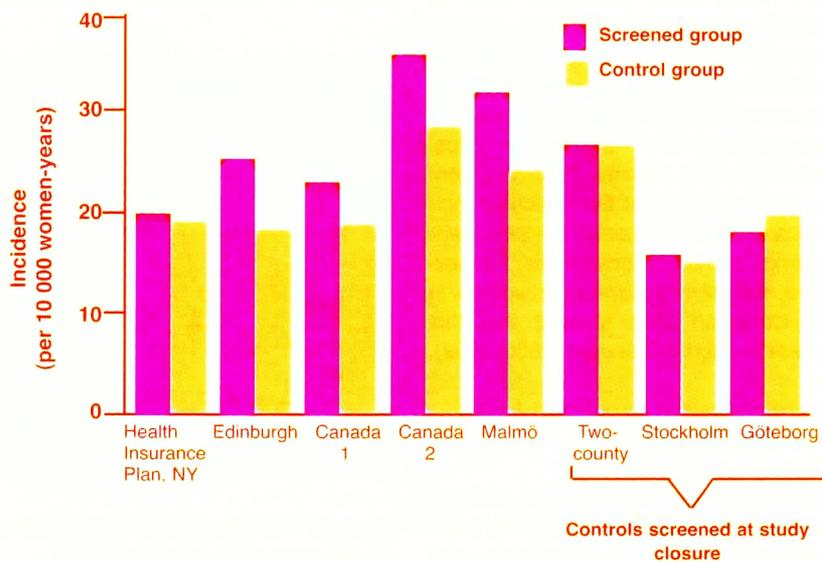
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<sup>xi</sup> "While screening is continuing in the intervention arm of a trial, incidence in that arm will be increased because of the advancement of diagnosis by the lead-time in screen-detected cancers, as well as by any overdiagnosis. This 'prevalence peak' will be followed by a corresponding decrease once screening ceases. Overdiagnosis can therefore be estimated only after a time equivalent to the lead-time has elapsed following the final screen. In several trials, women in the control arm have subsequently been offered screening. Once this has occurred, only overdiagnosis due to incident, not prevalent, screens would be observable, because women in both arms of the trial would be subject to any overdiagnosis occurring at prevalent screens." (from <sup>65</sup>)

The extent of any overdiagnosis in trials of breast screening may be affected by the ‘intensity’ of screening (one or two views, modalities employed, screening frequency and recall policy), and by the uptake of screening in the intervention arm. It may also depend on the age range of women included in the trial, both because of variation in the natural history of the disease with age and because of increased mortality from other causes in older women during the ‘lead-time’ before a screen-detected cancer would have presented clinically. The extent to which overdiagnosis is observed will also depend on the extent of ‘contamination’ in the control arm by opportunistic screening. Due to different combinations of these factors in the eight randomized controlled trials, comparison of the incidence of breast cancer between the screened and the control group varies as shown in Figure 3.3.

Data from three of the Swedish trials suggest that if there was overdiagnosis it was confined to the prevalent cases detected at initial screening. However, data from the other trials indicate that mammography screening initially increases the observed incidence of breast cancer by 24 to 38%, suggesting potential overdiagnosis.<sup>18</sup>

**Figure 3.3 Breast cancer incidence among women invited to screening versus those who were not (controls) in eight randomized controlled trials of screening mammography (from IARC handbook, p.145)**



A more recent re-analysis of the differences in breast cancer incidence between intervention and controls arms in the follow-up period of each of the randomized controlled trials (from 5 to 13 years) came to similar conclusions.<sup>65</sup> In this case overall incidence, as well as incidence of invasive breast cancers and DCIS was presented. In the Canadians trials which have the longest follow-up and did not propose screening to the control group at the end of the trial, an excess of 11-13% of all breast cancers is found in the intervention group after 13 years of follow-up, mainly due to DCIS. In the trials in which the control group was invited to screening (Two-County trial, Stockholm, Göteborg) there was a possible shift from invasive cancer to DCIS, but no evidence of overdiagnosis was found.

In another study the incidence data from the Two-County trial and the Gothenburg trial were used to estimate the timing and magnitude of an excess incidence of invasive breast cancer and DCIS in women invited to screening.<sup>66</sup> The study also ascertained whether excess incidence of DCIS was balanced by a later deficit in invasive cancers, taking into account lead time. In the Two-County trial, 15% of DCIS cases, corresponding to 1% of all breast cancers detected were considered to be overdiagnosed. In the Gothenburg trial, the corresponding rates are 18% and 2%. Applying the overdiagnosis model to the number of women screened and of cancers detected at the first three screens, the overdiagnosis rates are considerably lower at second and third screen than at the prevalence screen (decreasing from 3.1% to 0.3% in TCS, and from 3% to 0.2% in Gothenburg). The authors conclude that overdiagnosis is probably a minor phenomenon, but that further studies with much larger numbers are needed.

Beyond evidence from the randomized controlled trials the issue of overdiagnosis has been investigated in mammography screening programmes.

In Florence, Italy the incidence of breast cancer 1990-1999 following introduction of mammography screening in 1990, was compared to the incidence 1985-1989 before screening started.<sup>67</sup> When corrected for lead time, an apparent excess of 11% of invasive cancer decreased to 2%. When *in situ* cancers were included the excess incidence due to true overdiagnosis was estimated at 5%. A sensitivity analysis using different sojourn times indicated estimates of overdiagnosis for all breast cancers from 3% to 7%.

A similar, more recent analysis included six breast cancer screening programmes in Northern and Central Italy, covering in each case a ten-year study period starting as early as 1986 or as late as 1991.<sup>68</sup> Only programmes with at least five years of screening data were included. Excess incidence was estimated based on breast cancers diagnosed in the pre-screening and screening years. In total, the excess ratio of observed to predicted *in situ* and invasive cancers was 36.2% in women age 50 to 74. After correction for lead time the excess ratio was 4.6% (95% CI 2%-7%), mostly attributed to ductal carcinoma *in situ*.

Incidence of invasive breast cancer in women aged 40 to 74 before and after the start of a mammography screening programme was analysed in 11 Swedish counties.<sup>69</sup> Screening started between 1986 and 1990. The average follow-up after screening started was 12.8 (8-15) years. Data on breast cancer incidence were obtained for all counties from 15 years before screening started until 2000. Comparing expected incidence, based on the incidence before screening started, to the observed stabilised incidence 7-14 years after screening started and adjusting for lead time a relative risk of 1.54 (95% CI 1.33-1.79) was found for the age group 50-59 and of 1.21 (95% CI 1.04-1.41) in the age group 60-69. The excess incidence due to overdiagnosis was thus much higher in this study. The authors did attribute the increased incidence mainly to small sub-clinical breast cancers that would never have been diagnosed without mammography.

Using data from the first and second round of the Copenhagen mammography screening programme, a multistate model was fitted estimating the mean sojourn time as 2.7 years and screening sensitivity as 100%.<sup>70</sup> Overdiagnosis was estimated to be 7.8% (95% CI 0.3-26.5) at first screen and 0.5% at second screen (95% CI 0.02-2.1). The confidence intervals are broad due to the relatively small data set (35'123 women screened at least once).

Another study recently examined a longer period in Copenhagen and Fyn county (1979-2001). Incidence data of invasive breast cancer from the screening regions (five rounds)

were compared to time-equivalent data for the rest of Denmark and to pre-screening data.<sup>71</sup> Incidence of breast cancer was found to have increased regardless of screening. After a marked prevalence peak in the screening regions (1991 and 1993), the incidence rates were found to be similar to what would have been expected without screening taking into account lead time and newcomers.

In the Netherlands the natural history of breast cancer as well as the effect of screening were modelled (MISCAN model).<sup>72</sup> Incidence of breast cancer observed after screening was introduced was compared to incidence predicted with and without screening. Overdiagnosis of screen-detected breast cancers was estimated at 8%.

To estimate the proportion of ductal carcinoma *in situ* which is overdiagnosed a mover (progressive DCIS moving to invasive cancer) – stayer (non-progressive DCIS) model was fitted to screening data from the Swedish Two-County trial and from service screening programmes in the UK, the USA, the Netherlands and Australia.<sup>73</sup> It was estimated that 37% of DCIS are overdiagnosed at first screen, and about 4% at second and third screen. Considering that DCIS constitute a minority of cancer detected at screening, these results imply that one woman in 3'300 has a chance of overdiagnosis at first screen and one in 50'000 at subsequent screens.

### **Radiation-induced breast cancer**

The risk of inducing breast cancer through the repeated exposure of the breasts to ionizing radiation during mammography cannot be measured directly. Indirect evidence comes from atom bomb survivors in Japan, cohorts of women which were irradiated repeatedly for diagnostic or therapeutic reasons (tuberculosis patients, patients with benign or malignant breast disease), and women with professional exposure.<sup>74</sup> Depending on assumptions made in applying data from these cohorts to women 50-69 in Western Europe, the additional risk of a breast cancer after a 20 year screening period (one screen every 2 years) is estimated to be between 0.01 and 0.1%. This should be compared to the “spontaneous” risk to develop a breast cancer after age 50 of about 8%.<sup>75</sup> In the United States the risk of radiation-induced breast cancer for women undergoing mammography for 10 years beginning at age 40 was estimated to be only one in 12'500.<sup>76</sup> The risk thus is real, but minimal. The harms of ionizing radiation should be reduced as much as possible. However, they are not a determining factor in deciding for or against mammography screening.

## INTERVAL CANCERS

Interval breast cancers are cancers that present clinically in the time period between a normal screening result (regardless of it having needed further assessment or not) and the next routine screening examination. Interval cancers are an inevitable part of any breast cancer screening programme and their frequency is one indicator of the effectiveness of the programme. They can be separated into three categories based on the previous screening mammography<sup>77</sup>:

1. The previous screening mammography had normal or benign features;
2. With hindsight a feature is seen on the previous screening mammography that is subtle and does not clearly have malignant features (minimal cancer signs);
3. Retrospectively an abnormality suspicious of malignancy is seen on the previous mammography.

Only this last category should be referred to as “false-negatives”. The other two categories were not detectable at the time of the screening mammography and are called “true interval cancers”. Interval cancers during the first year after a normal mammography are the most significant as they reflect cancers missed by screening. Second year interval cancers are more likely to be cancers which could not have been detected at the previous screen. Interval cancers have worse prognostic features than screen-detected cancers, and are similar to non-screen detected cancers<sup>78</sup>. There is no conclusive evidence to show that true interval cancers have a worse prognosis than false-negative interval cancers<sup>77</sup>.

Interval cancers can only be identified if a good functioning cancer registry is in place with feedback to the screening programme and an efficient matching procedure between the two databases. An assessment in four European breast cancer screening centres showed rates around 2 per 1000 women screened, with the exception of one centre having a much lower rate.<sup>79</sup> Differences, among others, in defining interval cancer, completeness of cancer registration and the prevalence of opportunistic screening were shown to affect the comparability of interval cancer rates in 19 international screening programmes<sup>80</sup>.

It is very important to inform women before entering the screening programme that a breast cancer can appear between two screening rounds. True interval cancers are not a hazard of screening as these cancers would appear regardless of screening or not. However, if women think that they are “protected” against the appearance of a breast cancer in between screening intervals, interval cancers become a hazard of screening.

## **IN CONCLUSION**

It is now uncontested (even in the latest Cochrane review) that population-based breast cancer screening reduces breast cancer mortality in women over age 50. All randomised controlled trials have shown a trend of reduction in breast cancer mortality among women over age fifty, which was usually statistically significant. Various meta-analyses show that this reduction lies in a range of 15% to 30%.

Evidence from long-standing breast cancer screening programmes indicates an impact on breast cancer mortality similar to the decrease observed in the randomized controlled trials. The magnitude of the impact varies with the evaluation design; the length of the intervention; participation rates achieved; and, estimated contribution of adjuvant therapy to prolonged survival. All programmes included in the review started offering breast screening services between 1987 -1995.

The first statistically significant results can be expected 10-15 years after the introduction of the screening and the maximum cumulative effect arrives 25 years after onset of the screening programme. This is due to the fact that a screening programme covers a period of 20 years, involving 10 screens between age 50 and 69, and a 5 year follow-up thereafter to assess survival after diagnosis. It may thus take some more years before the full impact of these mammography screening programmes can be assessed.

Further benefits of breast cancer screening are a decrease in mastectomy, less invasive treatments and reduced hospital stay.

False-positive screening results and overdiagnosis of breast cancer are harmful and inevitable consequences of screening. These harms should be largely outweighed by the benefits of screening. Findings from the randomized controlled trials as well as longstanding screening programmes indicate that this is the case. Further studies have shown that the risk of overdiagnosis is modest, considering that it is not possible at the moment to distinguish on an individual basis which cancer will progress to invasive and metastatic disease and which will not do so. The risk of radiation-induced breast cancer due to screening is minimal. Interval cancers are an inevitable part of screening programmes. False-negative interval cancers should be reduced as much as possible.

## **Chapter 4: Status of breast cancer screening programmes in other European countries**

Chapter 3 has provided some information on breast cancer screening programmes that started at least ten years ago focusing on measures of effectiveness in terms of breast cancer mortality reduction. To allow comparison with the Swiss situation, some more data on the functioning of European mammography screening programmes regardless of the duration of implementation will be presented in this chapter. Currently 18 screening programmes exist in western, northern and southern Europe (“old” EU and EFTA countries). The new EU member states are not included as information is difficult to access and most programmes are very recent.

### **4.1. Access to and uptake of breast cancer screening in Europe**

More than 20 years after the first breast cancer screening programmes started in Sweden, Finland, United Kingdom and the Netherlands, the situation in Europe has significantly changed. As described in the previous chapter, these pioneer countries have achieved significant mortality reductions and the quality of their programmes has seen a continuous improvement. Many breast cancer screening programmes have started in Europe in the last decade. A great incentive for implementing organised programmes has been the Europe against cancer programme of the European Commission. From 1989 to 2002 it actively supported the establishment of screening programmes following the best practice of the United Kingdom, the Netherlands and Sweden, the first countries with a national programme.

Table 4.1 shows the coverage achieved in 2006 by 18 programmes in western, northern and southern Europe. Coverage is defined as the proportion of women eligible for screening who have had a test with a recorded result at least once in the previous screening period. The national target populations are based on data from EUROSTAT. The number of women invited per screening round in 2006 is drawn from annual reports or was provided by the evaluation offices of the programmes.

The number of regions offering screening indicates the extent to which the screening programme is aiming at national coverage. For example, in Denmark only 2 of the 13 districts offer screening compared to France where 99 out of 99 regions have introduced screening. In Germany three pilot regions started screening programmes in 2005, and 57 additional regions started in 2006<sup>xiii</sup>. It is planned that all 92 regions will offer screening by the end of 2007.

By far the lowest national coverage rates are found in Austria, Denmark, Greece and Switzerland. In Austria, two pilot regions implemented screening from 1999 to 2004. No screening was offered in 2005. In 2006, five new regions started pilot programmes, each testing different screening modalities. Based on the results from these programmes a national policy should be developed. In Greece, there is no national screening policy and

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<sup>xiii</sup> Germany was divided into 92 mammography screening regions each covering about 1 million inhabitants.

no political will to implement a screening programme. Existing efforts are entirely supported by volunteer organisations.

**Table 4.1 Status of breast cancer screening programmes in Europe**

	Year first programme started	Number of regions offering screening in 2006	Age of screened population	National target population	Women invited per screening round	% of national target population invited (2006)
<b>Austria</b>	1999	2/9	50-69	953'897	70'000	7.3%
<b>Belgium</b>	1990	2/2	50-69	1'122'388	1002161	89.3%
<b>Denmark</b>	1991	2/13	50-69	667'065	73'500	11.0%
<b>Finland</b>	1986	11/11	50-59/69 <sup>xiii</sup>	397'302	395'459	99.5%
<b>France</b>	1989	99/99	50-74	8'452'650	8452650	100.0%
<b>Germany</b>	1999	6/16	50-69	10'418'081	6'459'200	62.0%
<b>Greece</b>	1989	5/52	40/50-64	1'002'583	42'411	4.2%
<b>Iceland</b>	1987	1	40-69	48'813	48'813	100.0%
<b>Ireland</b>	1989	2/4	50-65	293'600	158'524	54.0%
<b>Italy</b>	1985	18/21	50-69	7'242'800	3'530'000	48.7%
<b>Luxembourg</b>	1992	1	50-69	46'723	44'974	96.3%
<b>Netherlands</b>	1989	9/9	50-74	2'193'157	2'129'220	97.1%
<b>Norway</b>	1996	19/19	50-69	507'795	482'397	95.0%
<b>Portugal</b>	1990	15/18	45-69	1'634'866	1'144'406	70.0%
<b>Spain</b>	1990	17/17	45/50-64/69	4'244'500	4'190'570	98.7%
<b>Sweden</b>	1986	21/21	40/50 -69/74	1'688'373	1'688'373	100.0%
<b>Switzerland<sup>xiv</sup></b>	1999	6/26	50-70	908'398	223'391	24.6%
<b>UK</b>	1988	4/4	50-70	6'838'000	6'223'716	91.0%
				<b>48'660'991</b>	<b>36'759'626</b>	<b>75.5%</b>

In most programmes the age group invited for screening are women 50-69/70. Only Iceland and some regions in Sweden and Greece recommend beginning breast cancer screening at the age of 40. Two programmes start at the age of 45 (Spain, Portugal) and 13 at the age of 50. With respect to the upper age limit, 12 programmes have set this limit at 69/70 years. In France and the Netherlands all women are invited up to age 74, while in Sweden only some regions have extended the upper age limit.

<sup>xiii</sup> 59/69 means that in some regions the upper age range for inviting women is 59, while in other regions women are invited until age 69. Similarly 40/50 means that some programmes invite women from age 40, while others do so from age 50.

<sup>xiv</sup> A pilot programme started in Switzerland in 1993 in canton Vaud.

More than 36 million women are invited to screening enabling over 75% of the female target population of these 18 countries to participate in mammography screening. Table 4.1 does not show participation rates but the total number of women having access to an organised breast cancer screening programme. Participation rates will be shown in Table 4.3.

Figure 4.1 illustrates the geographical repartition of three distinct categories of national coverage by invitation of women 50-69 by organised mammography screening. In Western Europe, Switzerland is joined by Denmark, Austria and Greece in the lowest category.

**Figure 4.1 Percentage of women age 50-69 invited to organised breast cancer screening in Europe by the end of 2006**

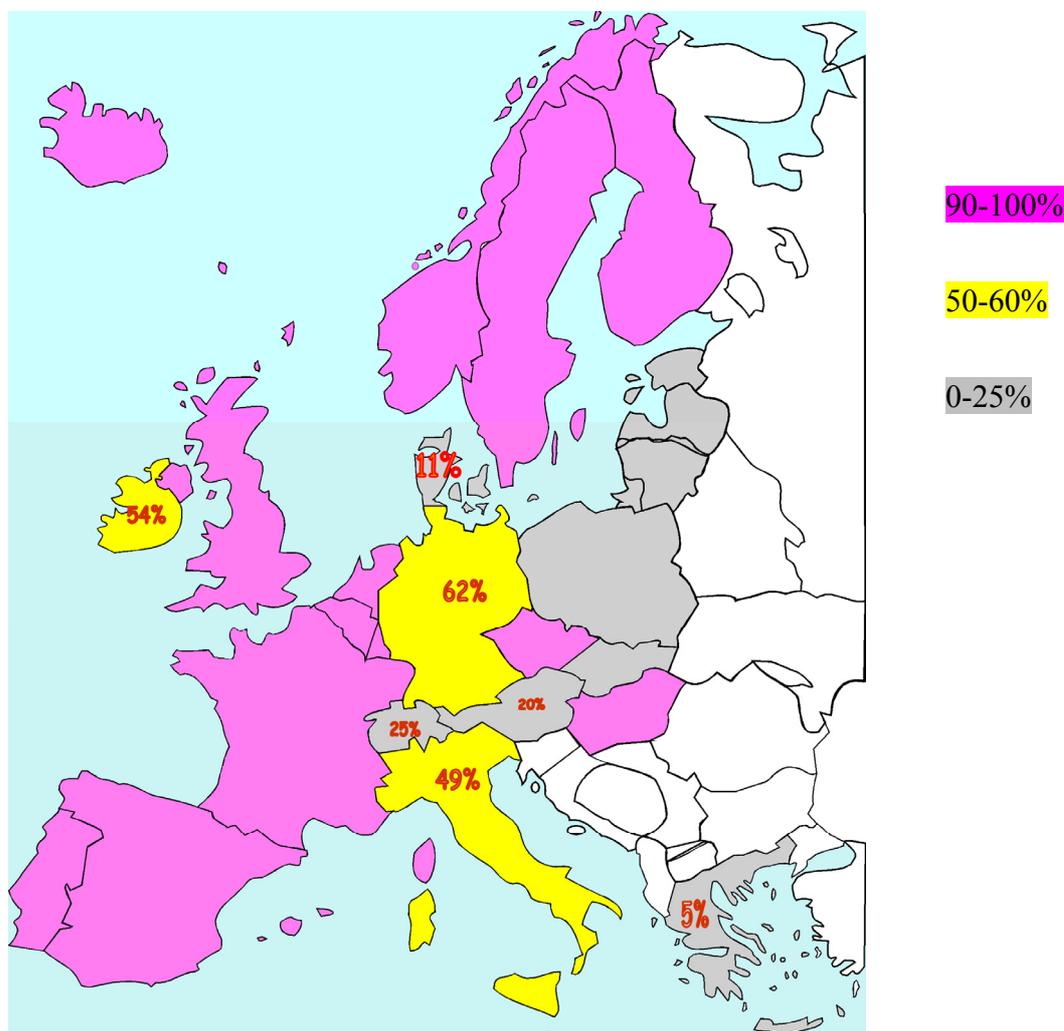


Table 4.2 shows how breast cancer screening programmes are organized. Most programmes are organized in a centralised manner. This means that the screening programme is distinct from the delivery of general medical care and that the screening tests are provided in distinct, fixed or mobile specialized units. In centralised programmes opportunistic screening is relatively rare. A centralised programme can be administered at either national or local level and is supported by the government.

In decentralised programmes screening is done in the context of general medical care, screening tests being provided either in specialized structures or in private radiological units. The role of the national government extends from no plan to strictly regulated programmes that follow guidelines, professional and structured certification, regulations, laws and continuous evaluation.

**Table 4.2 Organizational characteristics of European breast cancer screening programmes**

Country	Invitation specifies date and time	Screening organisation	Detection method	Cancer registry in screened area	Interval (years)	No. of views (first/ subsequent)
Austria	no	D	M			
Belgium	no	C	M	partial	2	2 / 2
Denmark	yes	C	M	Yes	2	2 / 1
Finland	yes	C	M	Yes	2	2 / 2
France	no	D	M + CE	partial	2	2 / 2
Germany	yes	D/c <sup>xv</sup>	M	partial	2	2 / 2
Greece	no	C	M + CE +BSE	No	2	2 / 2
Iceland	yes	C	M + CE	Yes	2	2 / 1
Ireland	yes	C	M	No	2	2 / 1
Italy	yes	D	M	Yes	2	2 / 1
Luxembourg	no	D	M	Yes	2	2 / 2
Netherlands	yes	C	M	Yes	2	2 / 1
Norway	yes	C	M	Yes	2	2 / 2
Portugal	yes	C	M	Yes	2	2 / 1
Spain	yes	C	M	Yes	2	1 / 1
Sweden	yes	C	M	Yes	1.5 / 2	2 / 1
Switzerland	no	D	M	Yes	2	2 / 2
UK	yes	C	M	Yes	3	2 / 2

C=centralised; D=decentralised; M=mammography; CE=clinical breast examination; BSE=breast self-examination

<sup>xv</sup> The programme in Germany is organized in a decentralised manner, but is centrally coordinated.

In organized programmes, whatever the type of organization, direct mail invitations are generally sent to women in previously defined age groups, offering them free screening. Publicity campaigns through media advertising, pamphlets, newspapers, radio and television and referrals from general practitioners are frequently used with the mailings. A date and a time for the appointment are always offered to the women in centralised programmes. In Greece, given the particular geographical situation, women living in small villages in the mountains are collected by minibus and arrive at the screening unit or mobile screening bus. Once all of them are served, they return to their village.

The primary detection method in all programmes is mammography. Some programmes add clinical breast examination (France, Greece, Iceland) and only in Greece they also teach the women to do breast self examination. With the exception of Spain, all programmes apply a two-view mammography of each breast at the first screen. In about half of the programmes only one view is done at subsequent screens. Some countries recently modified their policy from one view to two views in the subsequent rounds to increase the sensitivity of the test. In Switzerland two views are used at each screen. The screening interval for women over 50 years of age is 2 years in almost all programmes and once a year for women under the age of 50 and for those with a family history of breast cancer. In the United Kingdom, women aged 50 to 70 are offered screening every 3 years. In Sweden women 40 to 49 are screened every 18 months.

Table 4.3 shows the participation rates achieved in 2005. While the coverage rate presented in table 4.1 refers to the entire eligible population, the participation rate is the proportion of women invited to screening for whom a test result is recorded.<sup>xvi</sup> Overall 13.3 million women were invited and 8.2 million participated, corresponding to a 62% participation rate. In longstanding programmes such as in the Nordic countries, in The Netherlands and in the UK, the coverage by mammography is well over 70%. In some countries with lower participation rates such as Belgium, France, Germany, Italy and Switzerland, a considerable volume of opportunistic mammographies exists outside the screening programmes. There is an obvious variation in participation between centralised programmes and decentralised programmes.

The European guidelines recommend double reading of mammograms to improve the quality of the interpretation, as this increases sensibility and specificity. This is the standard in all European programmes. However, in France double reading is only done for women with a negative result after the first reading. Women found positive on the first reading are immediately followed-up for further investigation. Each programme using double reading has an established policy for arbitration of discordant interpretations. The results, whether positive or negative, are always sent to the woman, except in Luxembourg where a notice is sent only to the referring physician. In about half the countries, the results are not sent to the physician.

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<sup>xvi</sup> The invited population is smaller than the eligible population because it excludes women who are eligible for screening but are not invited because either they have made their own informed choice that they no longer wish to be invited for breast screening, or they are not on the health service register (e.g. diplomats), or they are not invited within the two year screening round because of slippage in a programme.

**Table 4.3 Participation rates achieved in European programmes in 2005**

	<b>Women invited annually (2005)</b>	<b>Annual number screened</b>	<b>Participation rate in 2005</b>	<b>Screening organisation</b>
<b>Austria</b>	(no screening in 2005)			
<b>Belgium</b>	501'081	130'841	26.1%	C
<b>Denmark</b>	36'750	28'151	76.6%	C
<b>Finland</b>	200'248	175'014	87.4%	C
<b>France</b>	4'226'325	2'083'185	49.3%	D
<b>Germany</b>	76'185	41'448	54.4%	C
<b>Greece</b>	21'206	11'129	52.5%	C
<b>Iceland</b>	22'400	15'000	67.0%	C
<b>Ireland</b>	79'262	59'600	75.2%	C
<b>Italy</b>	1'480'000	843'000	57.0%	D
<b>Luxembourg</b>	22'983	14'657	63.8%	D
<b>Netherlands</b>	1'070'700	865'260	80.8%	C
<b>Norway</b>	243'997	186'046	76.2%	C
<b>Portugal</b>	226'472	140'039	61.8%	C
<b>Spain</b>	2'095'285	1'354'601	64.6%	C
<b>Sweden</b>	844'187	675'342	80.0%	C
<b>Switzerland</b>	91'256	39'779	43.6%	D
<b>UK</b>	2'074'572	1'584'695	76.4%	C
	<b>13'312'909</b>	<b>8'247'787</b>	<b>62.0%</b>	

In order for women to obtain the maximum benefit from a breast cancer screening programme, an accurate recall system must be in place to avoid losing women to follow-up after an abnormal result. All programmes except the Danish one are responsible for ensuring the follow-up of women with a positive result. The follow-up includes full assessment for diagnosis, biopsy and treatment when necessary. In all programmes, there is reporting on the collection of data, computerized or not, and on the results of additional diagnostic procedures and cancers detected at screening.

## 4.2. Regulatory, reimbursement and legal status in other European countries

Table 4.4 summarizes who pays for screening in the European programmes: health insurance, tax monies and women themselves. With two exceptions the mammography itself is paid by health insurance. In Sweden local taxes are used and in Greece two volunteer organisations cover the costs.

**Table 4.4 Regulatory and reimbursement status of European breast cancer screening programmes**

	Screening programme	Screening paid by	External sources necessary	Contribution of women
<b>Austria</b>	Regional projects scheduled	National pilot project		none
<b>Belgium</b>	National	Health insurance	Yes for organisation and evaluation	none if insured
<b>Denmark</b>	Regional	State health insurance	Yes, county contribution	none
<b>Finland</b>	National	State health insurance	No	none
<b>France</b>	National	Health insurance	No	none if in programme
<b>Germany</b>	National	Health insurance	No	none
<b>Greece</b>	Regional	Hellenic Cancer Society / Church	Yes	none
<b>Ireland</b>	National incomplete /	State health insurance	No	none
<b>Iceland</b>	National	State health insurance	No	none
<b>Italy</b>	Regional	State health insurance	Yes, Regional Health System pays for the organisation	none
<b>Luxembourg</b>	National	State health insurance	Yes for organisation and evaluation	none
<b>Norway</b>	National	State health insurance	No	200 NOK ( $\cong$ 40CHF)
<b>Portugal</b>	Regional	Health insurance	Yes, Cancer League	none
<b>Spain</b>	National	Health insurance	Yes for organisation and evaluation	none
<b>Sweden</b>	County level	County taxation	No	0 - 150 SEK ( $\cong$ 27CHF)
<b>Switzerland</b>	Regional	Health insurance	Yes, cantonal contribution for organisation and evaluation	10% $\cong$ 15 CHF
<b>The Netherlands</b>	National	Health insurance	No	none
<b>UK</b>	National	National taxation	No	none

In about half the countries additional funding sources are needed to pay for costs related to the organisation and the evaluation of the programme, as is the case in Switzerland. Only three countries, including Switzerland, also ask for a co-payment from the women. In Norway this amounts to about 40 CHF per screen, and in Sweden can go from no co-payment up to 27 CHF.

How a screening programme will be set up and how it is going to be regulated depends to a large extent on the existing health system. In most instances a formal document specifies who is responsible for the management, organisation, quality assurance, evaluation and financial reimbursement. It is beyond the scope of this report to describe in detail which regulatory and legal instruments have been used or instituted as a basis for breast cancer screening programmes in other European countries. It is noteworthy that the Netherlands are the only European country to have adopted a formal law on population screening. The original texts regulating breast cancer screening of 11 European countries and 2 Belgian regions (Austria, Belgium Flemisch, Belgium Wallone, France, Germany, Ireland, Italy, Luxembourg, Netherlands, Norway, Portugal, Spain, United Kingdom) can be obtained on request from the Swiss Cancer League.

#### **IN CONCLUSION**

Most European countries have established nationally or regionally organized breast cancer screening programmes. In many countries the screening facilities are administered regionally.

Most programmes focus on screening women aged 50-69. With the exception of the UK, all programmes invite women in this age group to have a mammography every second year. Three programmes include clinical breast examination of the participants.

The number of screening views per breast is reduced from two to one after the initial screening in half the programmes. Some national policies are currently changing to two views at all screens.

The proportion of eligible women being effectively screened in organized breast cancer screening programmes varies. Most programmes have intermediate to high participation rates (50% to more than 80%).

In a majority of countries the costs of the screening are totally covered by health insurance, with no extra funding needed and no payment by women.

## **Chapter 5: The experience of breast cancer screening programmes in Switzerland**

In this chapter the latest data from the five Swiss mammography screening programmes will be presented. The cantons Geneva, Vaud and Valais have been operating a mammography screening programme since 1999<sup>xvii</sup>. A screening programme was introduced in the canton Fribourg in 2004 and in the canton Jura in 2005. The canton Neuchâtel has formally joined the Jura programme in July 2006 and has started inviting women in May 2007.

Data related to the functioning of the programme are available for all five programmes. In addition, the three longstanding programmes in Geneva, Valais and Vaud have recently undertaken a complete epidemiological evaluation. Data on their performance and effectiveness will be summarised and compared with the European standards. The complete evaluation report of canton Valais is available on request.<sup>81</sup>

Finally, lessons learned, as well as constraints and limitations in the Swiss context will be discussed.

### **5.1. How well are existing screening programmes functioning?**

Indicators of performance can be used as a basis for corrective action early on in a mammography screening programme. They also allow predicting whether a reduction in mortality is likely to happen in the long term. In this section the indicators related to the functioning of the programmes, such as participation rates, timeliness of follow-up after mammography and of re-invitation, and recall rates will be described. In the next section indicators of effectiveness such as rates of detection of cancer, of advanced disease and of interval cancers will be presented.

#### **PARTICIPATION RATE**

As shown in table 5.1 the participation rate is variable across the five programmes and does not reach the 70% proposed for decentralised programmes in the European Guidelines. This may be due in part to the fact that opportunistic screening was (widely) available before the programmes were set up. The programmes in Fribourg and Jura are very recent and have not yet reached their full potential. However, it should be noted that Jura achieved a remarkable participation rate in the first round. As was shown in table 4.3 participation rates in other European programmes vary between 26 and 87%.

The evaluation of a six-year period in Valais showed that there are three groups of women: those who participate regularly (55% of eligible women), those who never responded to an invitation (36.5%) and those who participate occasionally (about 10%). It is also interesting to note that about half of the women presented a previous mammography at their first screen indicating a considerable use of mammography screening prior to entering the programme.

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<sup>xvii</sup> The pilot phase of the screening programme in Vaud started in 1993.

**Table 5.1 Participation rates in the mammography screening programme in five cantons (latest round for which data were available)**

	Period	Women Invited	Eligible	Screened	Participation rate
VD	04/2003 - 03/2004	33'528	32'887	15'479	47.07%
	04/2004 - 03/2005	35'058	34'299	17'206	50.16%
		68'586	67'186	32'685	<b>48.65%</b>
VS	01/2004 - 12/2004	15'323	13'869	9'119	65.75%
	01/2005 - 12/2005	16'450	15'317	10'111	66.01%
		31'773	29'186	19'230	<b>65.89%</b>
GE	01/2003 - 12/2003	19'007	17'096	5'123	30.0%
	01/2004 - 12/2004	25'946	24'177	5'555	23'0%
		44'953	41'273	10'679	<b>25.9%</b>
FR	03/2004 - 02/2005	13'181	11'699	1'874	16.02%
	03/2005 - 02/2006	14'740	13'073	6'652	50.88%
		27'921	24'772	8'526	<b>34.42%</b>
JU	01-12/2005	1'969	1'817	785	43.2%
	01-12/2006	4'653	4'390	2'264	51.57%
		6'622	6'207	3'049	<b>49.12%</b>

In some programmes the participation rate is calculated per screening round, in others per calendar year. The figures are thus not exactly comparable, but provide an overall estimate of participation and differences across programmes.

#### **TIMELINESS OF THE SCREENING PROCESS**

In a well-functioning programme, women should get the results of their screening mammography quickly. The further assessment of those found to have a suspicious radiological image should not be delayed. Finally, re-inviting a high percentage of eligible women within the screening interval indicates if a programme is able to function efficiently. This indicator only applies to the longer standing programmes in GE, VD and VS.

As shown in Table 5.2, the three long-standing breast cancer screening programmes are within or close to the European norms, with one exception in the Geneva programme. In 2005 this programme came to a complete halt because the health insurances refused to

continue to reimburse the screening mammography. Due to this funding crisis the invitation of women was delayed for six months. This explains the unusual difference between re-invitation at 24 and 30 months.

**Table 5.2 Indicators to assess the timeliness of the screening process**

	GE	VD	VS	European norms
<b>Time between screening and result (% 15 working days)</b>				
Initial screen	95.2	99.6	98.6	>=90%
Subsequent screen	96.3	99.8	99.1	>=90%
<b>Delay between screening and further assessment (% 20 working days)</b>				
Initial screen	n.a.	91.1	87.0	>=90%
Subsequent screen	n.a.	90.8	90.1	>=90%
<b>Re-invitation within screening interval (% within 24 months)</b>	76	91.8	83.2	>95
<b>Re-invitation within screening interval (% within 30 months)</b>	96	98.0	94.6	>98

n.a. = not available

The time between screening and transmitting the result to the woman and her physician, if applicable, is well within the European standard in all three programmes. It is also remarkable, that the delay between screening and further assessment is within 20 working days for about 90% of women found to have a suspicious lesion in Vaud and Valais. The European norms have been established in countries with assessment centres linked to the breast screening centres, which is not the case in Switzerland. It thus indicates a good collaboration between the screening programmes, the women and their physicians.

#### **QUALITY OF THE SCREENING PROCEDURE**

The recall rate indicates the proportion of women screened for breast cancer which will undergo further investigations. These can either be a diagnostic mammography and/or a biopsy for cytologic or histologic examination. A low recall rate may spare women unnecessary anxiety and the hassle and pain of medical procedures, but at the same time it could reduce the sensitivity of the screening test. There is thus a fine balance to find between reducing the number of false-positive results, while at the same time avoiding false-negative results. As can be seen in table 5.3 the Swiss programmes are at the upper end of or slightly above the European norm. As should be expected the recall rate is lower in subsequent screens, as the initial mammography serves as comparator.

The benign to malignant biopsy rate is a further indication of the quality of the programme. Among women recalled for additional investigations, a certain percentage

will undergo biopsy. The majority of the biopsies should allow the detection of malignancy. Otherwise many women would be uselessly submitted to an invasive procedure. The European norm is that there should not be more than one negative biopsy for one positive biopsy at the initial screen, and not more than one negative for three positive biopsies in subsequent screens. As with the recall rate, the Swiss programmes are at the upper end of the European norms.

**Table 5.3 Quality indicators of the breast cancer screening programmes**

	<b>GE</b>	<b>VD</b>	<b>VS</b>	<b>FR</b>	<b>JU</b>	<b>European norms</b>
<b>Recall rate (%)</b>						
Initial screen	7.9	6.4	7.1	7.7	6.0	< 7
Subsequent screen	4.8	3.9	3.3	6.1	n.a.	< 5
<b>Benign:malignant biopsy ratio</b>						
Initial screen	n.a.	0.47	0.55	0.49	n.a.	≤ 0.5
Subsequent screen	n.a.	0.28	0.24	0.24	n.a.	≤ 0.25

n.a. = not available / not applicable

*N.B. Regarding data from the FR programme, these should be considered with caution as the programme started recently and epidemiological data have not yet been validated. The same is true for the JU/NE programme, only the recall rate being available.*

When comparing the results of the Swiss programmes to the European norm, one should keep in mind that these are high standards that are not achieved at any rate outside screening programmes. This was corroborated by an analysis of the use of breast pathology examinations (cytology or histology) carried out in Valais for the same period as covered by the screening programme (1999 to 2005).<sup>82</sup> Pathology examinations were found to be twice as frequent for women who did not participate in the screening programme than for participants (RR 1.96). Benign or negative results of pathology examination were more frequent for non-participants than for participants (RR 2.38). Participating in the screening programme thus has a favourable and measurable impact on the use of pathology examinations. For women participating in the screening programme, the probability to have a tissue examination is halved. In case of a histologic or cytologic test, the probability of a negative or benign result is also reduced.

## 5.2. How effective are the screening programmes?

All Swiss screening programmes are still quite young and below 10 years of age. It is thus too early to expect a reduction of breast cancer mortality. However, cancer detection rates, the stage at which cancers are detected and the rate of interval cancers are valuable surrogate markers for assessing the effectiveness of a breast cancer screening programme. These indicators are presented in table 5.4 for four cantonal programmes. Figures for Fribourg only pertain to the initial (prevalent) screen and have not yet been epidemiologically validated.

**Table 5.4 Surrogate indicators for assessing the effectiveness of the breast cancer screening programmes in Switzerland**

	GE	VD	VS	FR	European norms
<b>Breast cancer detection rate (‰)</b>					
Initial screen	6.1	7.6	6.2	8.8	(3x I.R.)
Subsequent screen	5.9	5.9	4.8	n.a.*	(1.5xI.R.)
<b>In situ cancers (%)</b>					
Initial screen	17.7	18.2	12.2	29	10-20
Subsequent screen	15.8	17.1	12.5	n.a.	10-20
<b>Invasive cancers ≤ 10 mm (%)</b>					
Initial screen	31.8	39.6	25.2	32	≥ 25
Subsequent screen	50.0	44.7	21.2	n.a.	≥ 25
<b>Stage ≥ II (%)**</b>					
Initial screen	38.5	29.7	35.4	11	< 30
Subsequent screen	29.2	28.9	39.3	n.a.	≤ 25
<b>Node-negative cancers (%)</b>					
Initial screen	76.9	72.3	74.3	74	≥ 70
Subsequent screen	79.2	73.8	75.9	n.a.	≥ 75
<b>Interval cancers (initial screen)</b>					
0-11 months after screening	22.7	24.0	27.3	n.a.	≤ 30
12-23 months after screening	51.3	41.9	53.2	n.a.	≤ 50

\* n.a. = not available / not applicable

\*\* Stage II is divided into Stage IIA (T 2-5 cm, N negative, or T <2 cm and N positive) and Stage IIB (T > 5 cm and N negative, or T 2-5 cm and N positive (< 4 axillary nodes)).

Given the fact that opportunistic screening existed before starting the screening programmes, the European norm to detect three times the baseline incidence rate at the prevalent (first) screening round and 1.5 times at the subsequent screen is not applicable in the Swiss context.

In the three long-standing programmes the proportion of advanced cancers ( $\geq$  II) is above the European norms. However, the detection rates of in-situ cancers, of node-negative cancers and of small invasive cancers are well within European norms, indicating that the programmes are effective in detecting breast cancer at an early stage (stage shifting).

The interval cancer rate in a defined period after screening is expressed as a proportion of the background (expected) breast cancer incidence rate in the absence of screening. The proportions for the first and second year after screening should not be considered cumulative. These data are currently only available for Valais and Vaud and indicate that occurrence of interval cancers meet the European norms.

In the cantons Valais and Vaud breast cancers detected in participants to the screening programme could be compared to those detected in non-participants (Tables 5.5 and 5.6).

**Table 5.5 Distribution of prognostic indicators for breast cancer by detection and screening modalities in the canton of Vaud, 2000-2005, (women age 50-69 at cancer diagnosis)**

Prognostic Indicators** (%)	Participants		Non participants*	
	Screen-detected cancers (n=488)	Interval detected cancers (n=133)	Screened (n=241)	Unscreened (n=560)
In situ	18.9	9.0	22.4	3.6
Invasive $\leq$ 1 cm	43.3	25.0	39.7	17.7
Invasive $\leq$ 2 cm**	83.2	71.6	84.4	54.6
Stage $\geq$ II	28.8	44.8	27.5	43.7
Node-negative	72.0	58.6	73.0	58.5

\* Includes former participants for which the cancer was diagnosed more than 2 years after the last mammography test.

\*\* Except for the % of *in situ* cases, indicators are based on invasive cancers only.

The prognostic profile differs between screen and non-screen detected cancers, each indicator being systematically more favourable for screened-detected cancers. The profile of interval cancers is overall similar to that of cancers detected in unscreened subjects as one would expect. In Vaud, however, interval cancers have a smaller size at diagnosis than unscreened cancers.

Opportunistic screening and organized screening afford a similar prognostic profile in Vaud. In Valais, opportunistic screening was associated with a slightly more favourable prognostic profile. This is due to the fact that opportunistic screening often implies annual screening and mostly includes three views per breast and an ultrasound. One should also

consider that cancers detected by organised screening and opportunistic screening are compared in two cantons that have implemented a mammography screening programme. As the same radiologists perform opportunistic and organised screening mammographies, the quality-controlled organised procedure also benefits to some extent quality of opportunistic screening.

**Table 5.6 Distribution of prognostic indicators for breast cancer by detection and screening modalities in the canton Valais, 2000-2005 (women age 50-69 at cancer diagnosis)**

Prognostic Indicators* (%)	Participants		Non participants	
	Screen-detected cancers (n=259)	Interval detected cancers (n=89)	Screened (n=137)	Unscreened (n=256)
In situ	10.8	5.6	13.1	5.5
Invasive $\leq 2$ cm**	75.8	54.7	79.7	51.2
Stage $\geq$ II	40.5	58.5	31.6	64.7
Node-negative	69.6	58.5	81.0	54.0

\* Except for the % of *in situ* cases, indicators are based on malignant cancers only.

\*\* pT stage was not directly available from the Valais Cancer Registry. Construction of this information on the basis of clinical and pathological data did not allow to reliably estimate the % of malignant cases  $\leq 1$  cm (pT1a or pT1b).

In addition to breast cancers detected in the screening programme, overall prognostic indicators for breast cancer were compared in Swiss cantons with and without a screening programme (Table 5.7). These data are based on all breast cancers detected in the period 2000 to 2005 in women aged 50 to 69, regardless of the mode of detection. In cantons with screening programmes this includes cancers detected within the screening programme as well as cancers detected either by opportunistic mammography screening or clinically.

The proportion of cancers detected at an early stage (less than 1 or 2 cm and/or node negative) is higher in VD, VS and GE than in TI and SG. Breast cancer prognostic indicators are systematically more favourable in cantons with an organised screening programme than in cantons without such a public health programme. Among cantons without a screening programme, those with a high prevalence of opportunistic screening (Ticino), seem to have more favourable prognostic indicators in breast cancers than cantons with a low prevalence of opportunistic screening (St Gallen).

**Table 5.7 Prognostic indicators for breast cancer in Swiss cantons with and without a screening programme and according to prevalence of opportunistic screening (SG: low, TI: high); 2000-2005 (women 50-69)**

Prognostic indicators * (%)	Cantons with screening programmes			Cantons without screening programmes	
	VS	VD	GE	SG	TI
In situ	8.5	12.5	12.3	9.3	5.8
Invasive ≤1 cm	n.a.**	30.1	26.1	10.9	18.2
Invasive ≤2 cm	64.2	70.1	70.4	49.6	63.5
Stage ≥II	46.4	36.4	51.5	65.5	56.5
Node negative	67.2	65.2	64.5	56.0	55.4

\* Except for the % of *in situ* cases, indicators are based on malignant cancers only.

\*\* pT stage was not directly available from the Valais Cancer Registry. Construction of this information on the basis of clinical and pathological data did not allow to reliably estimate the % of malignant cases ≤1 cm (pT1a or pT1b).

The evidence presented in section 5.1 and 5.2 indicates that the five existing breast cancer screening programmes are able to reach European standards in terms of performance. Stage shifting has occurred thus providing a first indication of the impact these programmes may have on breast cancer mortality in the long run. Before further elaborating the lessons learned from these experiences in section 5.4, the economic issues faced by these programmes will be described.

### 5.3. The economics of breast cancer screening in Switzerland

The potential cost-effectiveness of various screening scenarios will be analysed in chapter 6. Before doing so, it is useful to examine current costs of the existing screening programmes and how these are shared among the different actors.

Currently each canton negotiates the rate and mode of reimbursement of mammography screening separately with the health insurance or its representative, santésuisse. This leads to different reimbursement schemes as illustrated in table 5.8.

**Table 5.8 Variations in item costs (in CHF) of a screening mammography in six programmes**

	GE		VD	VS		FR	JU	NE
	public	private		public	private			
	01.05.07		01.05.07	1999		01.04.07	01.04.07	01.04.07
Convention in place since	01.05.07		01.05.07	1999		01.04.07	01.04.07	01.04.07
<b>Sum received</b> by screening programme from health insurance +10% co-payment (paid either by participant or by external contribution, e.g. canton, cancer league)	161.33	221.78	168.46	104.00	132.00	158.15	139.00	165.15
<b>Sum disbursed</b> by screening programme for:								
Mammography + 1 <sup>st</sup> reading paid to radiology institute	145.33	205.78	123.46	84.00	112.00	119.23	92.00	100.00
2 <sup>nd</sup> reading radiologist	(paid by canton)		19.00	20.00	20.00	20.30	20.00	20.00
3 <sup>rd</sup> reading radiologist**	(paid by canton)		20.00	(paid by canton)		20.30	20.00	20.00
3rd reading is x% of second reading			10%			10%	15%	15%
<b>Remaining income</b> for screening centre	16.00	16.00	24.00	0.00	0.00	16.59	24.00	42.15

As of 1<sup>st</sup> April 2007 Tarmed 1.04 has come into force and changed the situation for almost all programmes. In Valais (and Vaud before the new convention) the conventional tariffs are lower than the Tarmed reimbursement, whereas in Geneva they are considerably higher.

The reimbursement of the cost of the **third reading** of the mammography at the screening centre has been negotiated differently by each programme. In Vaud and Fribourg 10% and in Jura/Neuchâtel 15% of the mammographies are estimated to need a third reading. In Valais, the cost of the third reading is included in the cantonal subsidy.

In Valais and Jura the cantonal subsidy includes the **10% copayment** of each woman screened, in Geneva this is paid by the Cantonal cancer league, as will be the case in Neuchâtel. The service is thus provided for free in these four cantons.

In Vaud, the screening programme negotiated 24 CHF per mammography for the **administrative workload** (appointments, sheets, invoice and payment to the institutes). In Geneva the amount negotiated is 16 CHF, in Fribourg 16.58 CHF, in JU 24.40 CHF and NE 42.15 CHF.

#### **Why is mammography screening not exempted from the 10% copayment?**

In a message on 21 September 1998 the Federal Council asked the Parliament to exempt preventive services from the franchise as well as from the co-payment. The National Council was favourable to this proposition, but the Council of States was opposed. In 2000 (March session) the Parliament examined an amendment of the Health Insurance Law providing for free breast cancer screening examination, when carried out under a cantonal or regional screening program. The National Council approved the amended regulation. The Council of States, on the contrary, required a full financial cost-sharing (deductible and copayment), arguing that this principle should be strictly applied also to preventive measures. Advocates for the exemption stressed the necessity of high participation rates in the screening program. In the final vote, Council of States' members reached equality (13 – 13). The President gave the casting vote against the exemption. In the conciliation procedure, the proposal of a compromise (10% copayment) was finally approved by the two Councils.

In Valais, a convention was passed in 1999 between health insurers and GEHVAL (Groupement des établissements hospitaliers valaisans) foreseeing a reimbursement of SFr 104.- per mammography with two readings. The third reading is not reimbursed. A separate convention with private radiologists agreed to pay them SFr 132.- for the same service. This difference is due to the fact that investment costs for technical installations in the hospitals are partially paid by the canton.

In Geneva, a convention signed in 1998 was based on reimbursement of ambulatory care services and agreed to a reimbursement of SFr 200.- for each screening mammography. Higher costs in Geneva are due to the following factors: only private radiologists carry out the mammography whereas in other cantons public, subsidized institutions (hospitals) participate; digital mammography was introduced early on; being a “city” canton living costs and salaries are higher than in cantons with a large rural population. A new convention has recently been signed with a transitory period of 8 months where an extra payment is negotiated for the private radiology practice of 60.45 CHF.

Based on the annual reports of existing mammography screening programmes, the **costs per woman screened** were calculated for the 3<sup>rd</sup> screening round for Vaud, Valais, and Geneva, and the first screening round in Fribourg (participation up to December 2005) and in the Jura-Neuchâtel programme. These data are presented in Table 5.9. The data from the JU-NE programme are not included in the calculation of the average as the programme only started in June 2005 in Jura. In Neuchâtel no women have yet been screened, thus leading to an overall low number of participants and a proportionally high cantonal contribution. However, these data are interesting as they depict the financial situation in the initial phase of a programme.

The variations in cost per woman screened are due to different reimbursement conventions as described above. In addition, **overhead costs** including organisation, administration, invitation, quality assurance, training and salaries become proportionally less as the number of mammographies performed rises. Overhead costs appear to be quite variable between the programmes. However, if the administrative costs born by the health insurance in Fribourg and Vaud are taken into account, the overhead costs are 41.4% in Vaud and 43.7% in Fribourg.

**Table 5.9 Cost per woman screened and total costs in mammography screening programmes in Switzerland (over the period 2003-2006; based on TARMED 1.03 before September 2006)**

Period	Women Screened	Participation rate	Reimbursed by health insurance (Fr.)	Share of total cost Health insurance	Canton	Other	Total cost	Percent overhead costs	Cost per woman screened
04/2003 - 03/2004	15'479	47.07%	140.00	2'167'060	814'800	111'839	3'093'699	29.95%	
VD 04/2004 - 03/2005	17'206	50.16%		2'408'840	819'400	110'740	3'338'980	27.86%	
	32'685	48.65%		4'575'900	1'634'200	222'579	6'432'679	28.86%	SFr. 196.81
01/2004 - 12/2004	9'119	65.75%	104.99	957'398	537'914	321'435	1'816'747	47.30%	
VS 01/2005 - 12/2005	10'111	66.01%	106.49	1'076'713	485'144	279'875	1'841'732	41.54%	
	19'230	65.89%		2'034'111	1'023'058	601'310	3'658'479	44.40%	SFr. 190.25
03/2004 - 02/2005	1'874	16.02%	143.45	268'825	380'000	300	649'125	58.59%	
FR 03/2005 - 02/2006	6'652	50.88%		954'229	380'000	40'000	1'374'229	30.56%	
	8'526	34.42%		1'223'055	760'000	40'300	2'023'355	39.55%	SFr. 237.32
01/2003 - 12/2003	5'123	29.96%	200.00	1'071'800	1'000'000	79'735	2'151'535	50.18%	
GE 01/2004 - 12/2004	5'552	22.96%		1'344'800	1'000'000	16'678	2'361'478	43.05%	
	10'679	25.87%		2'416'600	2'000'000	96'413	4'513'013	46.45%	SFr. 373.50
<b>CH-R 4 cantons</b>	<b>72'524</b>	<b>44.96%</b>		<b>10'249'666</b>			<b>16'627'526</b>		<b>SFr. 229.27</b>
JU 01-12/2005	785	43.2%	139.00	98'204	251'374	8'417	357'995	72.57%	
JU-NE 01-12/2006	2'264	51.57%		283'101	262'581	11'710	557'393	49.21%	
	3'049	49.12%		381'305	513'955	20'128	915'388	58.34%	SFr. 300.23

For Valais the amount reimbursed by health insurance is an average of public and private costs. The cost figures presented in Table 5.9 have changed with the introduction of Tarmed 1.04 in April 2007.

These wide variations in item costs and reimbursement schemes clearly show the need for a common agreement with health insurances. Fees should be based on standard tariffs in all cantons with some room for variation due to local differences (e.g. only private providers, mix of public and private providers). The third reading should be reimbursed in all programmes as this is part of a quality service to the screened woman. The administrative costs linked to the invitation and follow-up of women should be covered by the health insurance fee as currently in Vaud. And finally, the service should be provided without copayment in all programmes.

#### **5.4. Lessons learned from implementing breast cancer screening programmes in Switzerland: the experience of Valais, Vaud, Geneva, Fribourg and Jura**

The first important lesson learned is that it is feasible to implement organized screening for breast cancer by mammography in Switzerland. Strong political support and in some cantons a good synergy with the cantonal cancer league have been essential in the development of the programmes.

In some cantons a high level of pre-existing opportunistic screening burdened the introduction of the screening programme. This has been most prominently the case in Geneva.

The creation of a regional coordinating body has shown that a **supracantonal organization** is useful to harmonize the screening process, to have a uniform message and to have common trainings. Today, **uniform messages** are spread by all programmes. The same logo is used for the screening organisations, all information brochures have the same content and there is a uniform poster exhibit for each programme. There is still room for improvement in unifying the medical questionnaire for women and doctors.

**Women** seem to appreciate the screening service because it is convenient, cheaper and with a guaranteed quality. The extra time necessary for the results does not seem to be a major problem. In most cantons a large proportion of eligible women for breast cancer screening are interested in the organised program. The screening programme stimulates empowerment of women by providing information about breast disease, importance of early diagnosis and self examination.

One downside of the Swiss set-up is that women cannot be invited to the breast cancer screening centre for the mammography itself (as is the case in many European countries), as they are entitled to a free choice of doctor. There is thus the additional step for each woman to make an appointment with a private radiology institute, a public hospital with mammography facilities or via the screening programme (e.g. in the Vaud programme).

The most efficient way to sensitise women to the screening is through their **gynaecologist** (more than 90% of screened women ask to send the result to their gynaecologist). Most gynaecologists are convinced about the usefulness of mammography for early detection of breast cancer. A proportion of gynaecologists (and sometimes internists) do not refer to

the existing screening programme, but prescribe an opportunistic screening mammography.

It is possible in the Swiss context to reach or come close to the **European standards** in terms of performances of the programme. The surrogate effectiveness indicators allow a precise evaluation of the screening programme after a few years, before the effect of mammography screening on breast cancer mortality can be measured. One has to take into account the decentralized set-up in Switzerland which does not allow the same efficiency as a centralised programme. One major constraint in Switzerland is the difficulty to assess the overall impact of mammography screening (organised and opportunistic) on breast cancer mortality since data about opportunistic screening are limited and sketchy.

It has been shown that the **prognostic profile** is considerably better for screen detected cancers than for interval cancers or cancers diagnosed due to symptoms.<sup>81</sup>

Through the **evaluation process**, the programmes promote a constructive relationship with pathologists, the tumour registry, epidemiologists and public health managers. This is a stimulus for quality assurance as the evaluation identifies means to improve the screening process, and discusses those with the management in order to introduce them. The management also refers to the evaluation team prior to introducing a modification in the screening process (e.g. in canton Vaud to decide which delay would be the most efficient between invitation and reminder letters).

The programmes **promote quality** in many ways. The quality assurance process applied for mammographic equipment, radiographers and radiologists improves radiological standards within the screening programme. The reading statistics for radiologists, a quantitative assessment of the quality of a sample of mammographies performed in each radiological unit, providing information about readings of all positive mammograms and organising periodic readings workshops, all these measures control and improve the quality of reading (learning curve, lowering of false positive results). In addition, the outcome of positive mammographies is monitored to ensure optimal diagnostic and therapeutic management. In some instances, the screening programme has contributed to a better and more efficient use of existing radiological equipment.

The **role of the pathologist** in the screening programme is variable and still too restricted in some cantons. In others, the pathologist takes part in seminars for radiologists and presents radio-pathologic correlations. Overall, the role of the pathologist in the screening programme is important, as a direct feedback of the results of biopsies to the radiologists reading the mammographies, and in particular to first readers, improves the reading quality.

Overall the dynamic relationships of the programme with radiologists, gynaecologists and general practitioners (follow-up and diagnostic work-up of patients) are very fruitful. The programme promotes continued education through seminars for the radiographers, meetings with the radiologists for mammography readings, “quality meetings” (cercle de qualité gynécologues-radiologues), and discussion of radio-pathological correlations.

#### **ROOM FOR IMPROVEMENT**

The **participation rate** is below the EU recommendation of 70%. However, it must be taken into consideration that a considerable fraction of the eligible population is covered

by opportunistic screening. The ability of the breast cancer screening centres to intervene in case of low uptake of the service by invited women is limited.

Due to the decentralized nature of the cantonal screening programmes and depending on numbers of women screened, the **volume of mammographies done and read** (1<sup>st</sup> reading) in the radiological units are often low and do not reach European quality standards. In addition, there are limited sanctions if the delivered product (quality of mammography, interpretation by first reader) does not meet the required quality norms.

Depending on the cantonal health care set-up, the procedure of **diagnostic work up** could be improved. A breast centre would ensure a more structured and efficient follow-up to the patients. This is also a matter of centralization of technical tools and closer team work. In canton Valais, the medical council has edited guidelines for the diagnostic work-up of the various anomalies discovered by screening mammography.

A **unified tariff** and reimbursement scheme is absolutely essential to avoid duplicate efforts, inequitable conventions favouring one canton over another, and at worst, the stalemate of a programme as happened in Geneva in 2006. Future negotiations should take into account the rising cost of equipment related to the transition from film to digital mammography. Currently the cost of running the programme itself is not incorporated into the cost of the screening mammography. Additional financial sources are thus needed. The running costs of the programmes are relatively high.

Implementation of the cantonal screening programmes has not always led to the desired **reduction of opportunistic screening** mammography. This might be due to cultural and historical elements in the Swiss health system and personal preferences of the women concerned, determining which service is chosen.

**National** guidance would be very desirable to negotiate tariffs, define quality assurance procedure, establish quality control and performance criteria, certify screening units, etc. If a national institution cannot take responsibility, at least a regional coordinating structure should take on these tasks and thus also enable smaller cantons to jointly reach a sufficiently large volume to be more cost effective.

## Chapter 6: Potential cost-effectiveness of breast cancer screening in Switzerland

As organised and opportunistic mammography screening coexist to varying degrees in Switzerland, the potential effects and costs of several hypothetical screening scenarios were studied. A computer simulation model was used to determine which screening scenario would be most cost-effective to decrease breast cancer mortality and increase survival in Switzerland.<sup>xviii</sup>

### 6.1. Methods

The best way to predict benefits and costs of screening is by using computer simulation.<sup>54</sup> The Department of Public Health of the Erasmus Medical Centre in Rotterdam has developed the microsimulation computer model 'MISCAN' to enable evaluation of breast cancer screening programmes.

#### THE MISCAN MODEL

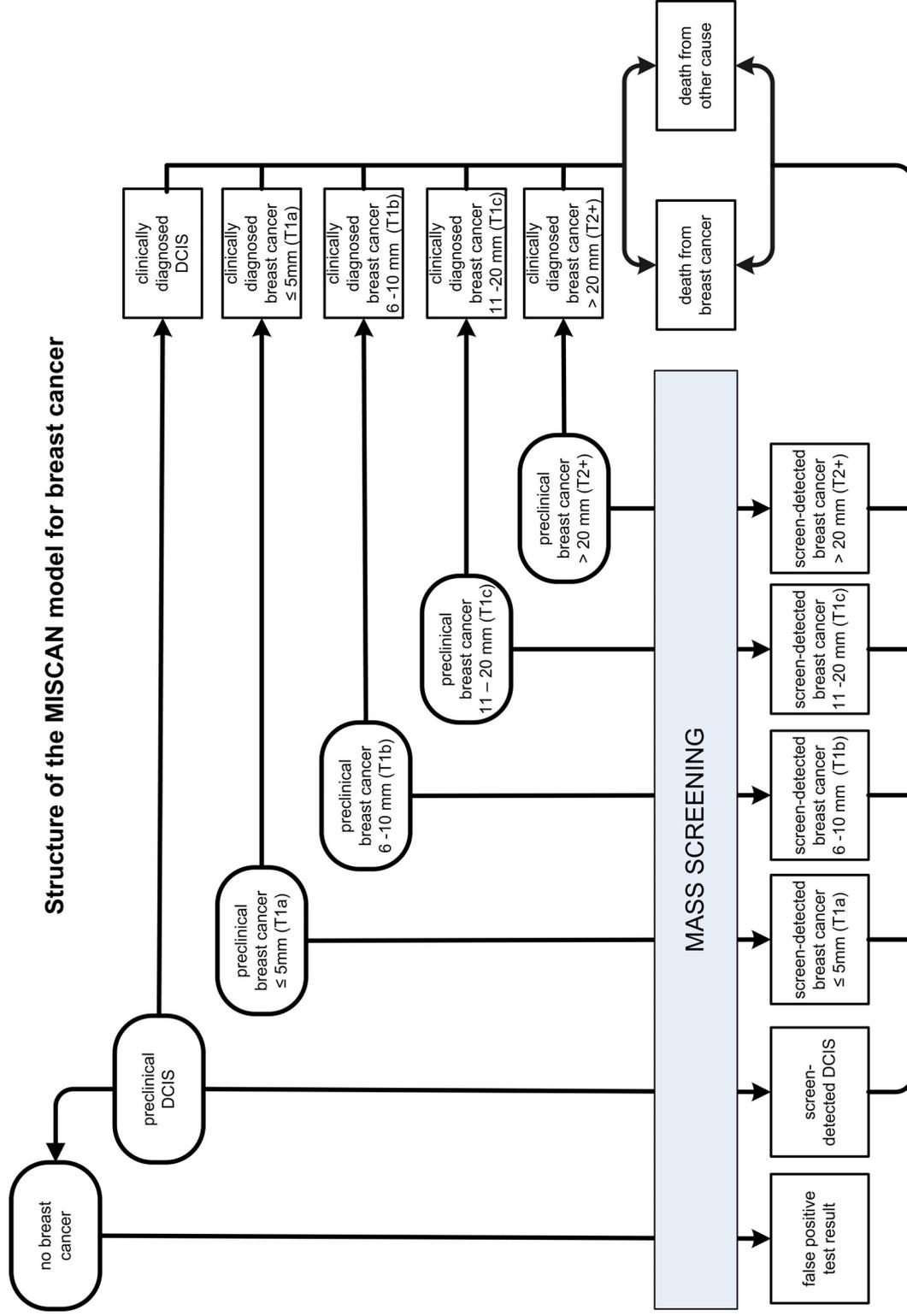
In MISCAN, breast cancer is modelled in such a way that it replicates the Swiss female population, and then determines which percentage of the Swiss population will develop breast cancer during lifetime, and if and how such tumours progress from one stage into the other. The structure of the model is graphically represented on the next page. It determines if the tumour is detected in clinical practice or by screening, depending on the programme scenario. The parameters that are incorporated in the current MISCAN breast cancer model were based on the outcomes of the Swedish mammography screening trials, the two Dutch pilot projects in Nijmegen and Utrecht, as well as the results of the Dutch nation-wide screening programme that started in 1989.<sup>28;83;84</sup> Although susceptible to some degree of uncertainty, the MISCAN model has proven to be capable to reproduce breast cancer in various situations fairly accurately.<sup>85-88</sup>

As a first step, clinically diagnosed tumours, screen-detected tumours and interval cancers that were observed in Vaud were used to calibrate the MISCAN model. The canton of Vaud was used as a starting point for validation, because it has a long-standing cancer registry (clinical data available from 1974, when no screening took place) and a centrally organised mammography screening programme. After some minor adjustments in MISCAN with regard to tumour stage duration and test sensitivity, a breast cancer model was obtained that correctly reproduced observed breast cancer incidence and mortality in pre-screening years, as well as the observed incidence of screen-detected tumours and interval cancers in Vaud. Based on this calibrated model, the long-term effects and costs of various screening scenarios in Switzerland could be further estimated.

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<sup>xviii</sup> The authors of this study are Rianne de Gelder, Gerrit Draisma, Jacques Fracheboud, and Harry J. de Koning from the Department of Public Health, Erasmus University Medical Center. The full report of this study can be obtained from the Swiss Cancer League.

### Structure of the MISCAN model for breast cancer



## THE SCENARIOS

The costs and effects of a hypothetical 20-years screening period, during which women aged 50-69 years were screened annually or biennially within an organised mammography-screening programme (MSP) and/or on their own initiative (“opportunistic screening”, OS), were assessed. Effects were calculated by comparing seven scenarios with a hypothetical situation in which no screening took place. Screening was assumed to have started in 1999 and continued up to and including 2019. The percentage of women who were screened was varied to account for hypothetical Swiss scenarios as follows:

- Sc1** 30% biennial OS: probable situation in some central Swiss cantons
- Sc2** 60% biennial OS: close to the situation in Ticino and Basel
- Sc3** 80% biennial OS: possible evolution if no organised screening is offered
- Sc4** 80% biennial MSP: ideal participation rate in an organised screening programme
- Sc5** 60% biennial MSP and 20% biennial OS: close to current situation in Valais
- Sc6** 40% biennial MSP and 40% biennial OS: close to current situation in Vaud
- Sc7** 40% biennial MSP and 40% annual OS: other possible scenario for Vaud

Probably neither 80% biennial opportunistic, nor 80% biennial organised screening (scenarios 3 and 4) are the most realistic predictions of the future of mammography screening in Switzerland, but these scenarios are useful to directly compare OS with MSP. In scenario 5 to 7, it was assumed that an individual woman who participated in an organised mammography screening programme was not screened opportunistically, and vice versa. The interval between two opportunistic screening examinations was assumed to be broader than between two organised mammographies: a range of 1.75-2.25 years was defined for biennial OS, a range of 0.75-1.25 years was used for annual OS, and an exact interval of 2 years was defined for MSP. The effects of screening were then rescaled to a population of 1'000'000 women (Swiss female population: approx. 3.5 million) and were measured over a period that was long enough to allow maximum benefits of screening to occur.

Costs and effects were calculated with no discounting and with a 3% discount rate (starting in 1999). MISCAN calculates the effects of screening for the whole female population. To measure the direct impact of the different screening strategies on the subpopulation that is targeted for screening, the main outcome parameters – breast cancer mortality reduction and costs per (quality-adjusted) life-year gained – were also estimated for women aged 50-79 years. Although women actually are targeted in the age of 50-69 years, significant breast cancer mortality reduction can first be observed ten years after the start of screening.

## 6.2. Assumptions

### OPPORTUNISTIC SCREENING

Little is known about the performance of opportunistic screening in Switzerland. To model OS, three assumptions about the test sensitivity of opportunistic screening were therefore tested in MISCAN.

- A 6% higher test sensitivity of OS compared to MSP, which might be related to additional imaging diagnostics that are frequently used along with a mammography, and which may reflect the slightly better tumour stage profile that was observed after OS in Valais (chapter 6, table 6.6).
- A test sensitivity of OS similar to MSP, which might reflect the situation in Vaud where a comparable stage shifting was observed (chapter 6, table 6.5). This may be the situation in a canton that has implemented an organised screening programme, thus improving the performance of radiologists and positively affecting the quality of opportunistic screening.
- A 6% lower test sensitivity of OS compared to MSP, which might be related to the lack of comparison with a previous screening mammography, the absence of double-blind second reading, no specific mammography training for radiologists, low mammography reading volumes of radiologists, less quality control of equipment. Such lower sensitivity was seen in a pilot project in Germany.<sup>89</sup> Although no data to support this assumption exist in Switzerland, this may reflect the situation in cantons with no quality-controlled organised screening programme.

### DIAGNOSTICS

The health insurance company CSS provided data on the remunerated Tarmed-codes claimed by women aged 50-69 years, who had a diagnostic mammography in the period 2004-2006. Although diagnostic mammography also includes a small fraction of examinations in symptomatic women, these data give an estimate of the number of imaging diagnostics that follow opportunistic screening. Santé Suisse data were used to estimate the number of clinical breast examinations and biopsies performed with each OS mammography.

According to information provided by santésuisse, in 2006 the following breast examinations in women aged 50-69 were reimbursed:

- 166'994 clinical breast examinations
- 56'853 diagnostic mammographies<sup>xix</sup>, and
- 35'552 ultrasound examinations.

The following should be kept in mind: santésuisse statistics only cover about 60% of women living in Switzerland with wide variation in cantonal coverage (i.e. the coverage rate is much lower in the French speaking cantons). Actual numbers are thus not very meaningful, as one does not know if the 40% of women not covered by santésuisse

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<sup>xix</sup> Opportunistic mammography screening is declared as “diagnostic mammography” for reimbursement purposes.

statistics behave in a similar way than those represented here, and as an unspecified number of women will not have asked for reimbursement because of the *franchise*. However, the relationships between the three types of examinations are of interest. About one in every three CBE is followed by a mammography, and about 60% of the mammographies are followed by an ultrasound<sup>xx</sup>. Unfortunately, *santésuisse* only has aggregate data. It is thus impossible to know what combinations of tests a woman has had and in which sequence.<sup>xxi</sup>

The number of diagnostics that is involved with the detection of one breast cancer in an organised screening programme was directly derived from the Vaud screening database. An estimate of the diagnostics that are needed to detect one cancer case among symptomatic women based on Swiss data was not available; Dutch data were used instead. This may be a rather conservative estimate as the Dutch health system is probably more restrictive in the use of diagnostics than the Swiss health system.

### **TREATMENT PROBABILITIES**

Treatment probabilities that were associated with screen-detected cancer were derived from the Vaud screening database, but Swiss data for opportunistically and clinically diagnosed cancers were unavailable. The ratio of screen-detected versus clinically diagnosed cancer from the Dutch COBRA study was therefore used to assess treatment probabilities.<sup>89</sup> A tumour that was detected by screening was treated less aggressively than a clinically diagnosed case.

### **COSTS**

The costs of diagnostic mammography were assumed to be higher than that of organised mammography screening (Tarmed 1.03). One mammography in a screening programme costs on average 230 CHF, while a mammography made on the woman's own initiative approximately costs 290 CHF. This does not include the costs of clinical breast examinations and additional imaging diagnostics, which were used in approximately 53% of the women who had an opportunistic mammography [CSS].

Since no data were available on the costs of treatment in Switzerland, data from the Netherlands<sup>90</sup> were used and multiplied by 1.21 to account for the relatively higher health care costs in Switzerland.<sup>91</sup>

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<sup>xx</sup> It is very unlikely that a woman would have an ultrasound of the breast without also having a mammography.

<sup>xxi</sup> Individual data were made available by the CSS health insurance, but coverage was too incomplete and their records did not include hospital-based investigations (limited to outpatient investigations).

### 6.3. Predicted effects of screening on breast cancer mortality

The MISCAN analysis shows that mammography screening is an effective way to reduce breast cancer mortality in each analysed scenario. Biennial screening of 80% of the female population aged 50-69 in an organised programme resulted in a breast cancer mortality reduction in all age groups of 15.0%, while biennial OS resulted in a mortality reduction of 14.5%. Opportunistic screening of 60% of the 50-69 years old female population would result in a reduction of 10.9%, and opportunistic screening of 30% of the population leads to a mortality reduction of 5.5% (Table 6.2). These expected mortality reductions were based on the total female population of all ages. The mortality reduction analysed for the 50-79 years old age group separately was considerably higher, up to a mortality reduction of 20.0% (80% biennial MSP) (Table 6.1).

**Table 6.1 Breast cancer mortality reduction in women age 50-79 by 7 different mammography screening scenarios, each of them assuming a 6% lower, a similar or a 6% higher test sensitivity of opportunistic screening (OS) compared with the organised screening (MSP)**

	Scenario			Mortality reduction		
	MSP (all biennial)		OS	6% lower sensitivity OS	similar sensitivity OS - MSP	6% higher sensitivity OS
<b>Sc 1</b>	-		30%	7.1%	7.3%	7.4%
<b>Sc 2</b>	-		60%	13.9%	14.3%	14.7%
<b>Sc 3</b>	-		80%	18.5%	19.0%	19.5%
<b>Sc 4</b>	80%		-	20.0%	20.0%	20.0%
<b>Sc 5</b>	60%	and	20%	19.6%	19.7%	19.9%
<b>Sc 6</b>	40%	and	40%	19.2%	19.5%	19.7%
<b>Sc 7</b>	40%	and	40% annual	21.5%	21.7%	21.9%

When confined to the 55-74 age group, the mortality reduction would be expected to reach 22.4%, a benefit in line with international screening programmes.

For all scenarios with an 80% coverage rate, regardless of the mix of organised and opportunistic screening (scenarios 3 to 7), the mortality reduction is very similar and close to 20% in the 50-79 year age group. However, the benefits of screening decrease considerably as coverage decreases (scenarios 1 and 2). Most benefits were obtained if 40% of the 50-69 years old population were annually opportunistically screened, combined with biennial MSP of another 40% of the population. This scenario resulted in a total reduction of 4'567 breast cancer deaths and a gain of 77'900 life years (women of all ages and assuming a 6% higher test sensitivity of OS compared to MSP). As a comparison, biennial organised screening of 80% of the 50-69 year old population would result in 4'190 prevented deaths and 70'600 life years gained. When the mortality effects are calculated for women aged 50-79 only, a 21.9% mortality reduction could be expected after 40% annual OS combined with 40% biennial MSP (test sensitivity similar or 6% higher than MSP), while the expected mortality reduction of 80% biennial MSP is 20.0%.

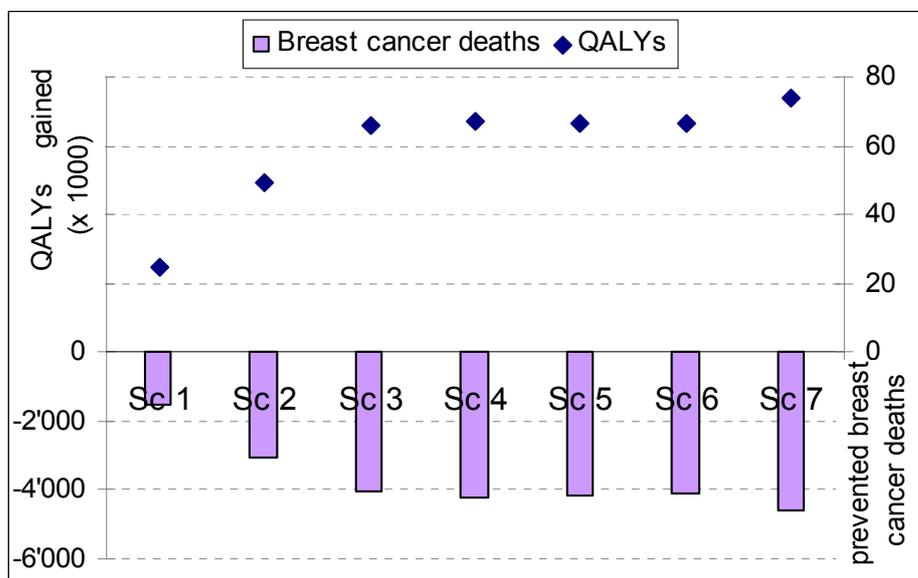
**Table 6.2** Cost-effectiveness of different screening scenarios  
(per 1 million Swiss female population, all ages) \*

	Sc 0	Sc 1	Sc 2	Sc 3	Sc 4	Sc 5	Sc 6	Sc 7
	No screening	30% OS	60% OS	80% OS	80% MSP	60% MSP 20% OS	40% MSP 40% OS	40% MSP ann. OS
	No screening	Difference with no screening						
	Sc 0	Sc 1	Sc 2	Sc 3	Sc 4	Sc 5	Sc 6	Sc 7
<b>Effectiveness (all ages)</b>								
Breast cancer deaths	27,941	-1,536	-3,045	-4,063	-4,190	-4,158	-4,126	-4,567
% reduction	-	-5.5%	-10.9%	-14.5%	-15.0%	-14.9%	-14.8%	-16.3%
Life years	37,325,400	+26,300	+52,100	+69,300	+70,600	+70,275	+69,950	+77,900
QALYs	37,225,821	+24,962	+49,439	+65,766	+66,949	+66,653	+66,357	+73,904
<b>Costs in CHF (x 10<sup>6</sup>)</b>								
Screening	0	+435	+869	+1,159	+918	+978	+1,039	+1,559
Diagnostics	626	+251	+502	+669	-51	+129	+309	+648
Primary treatment	1,272	+17	+34	+45	+48	+47	+46	+49
Adjuvant treatment	126	-2	-4	-6	-6	-6	-6	-7
Follow-up	405	+15	+29	+39	+40	+40	+40	+43
Palliative care	993	-55	-108	-144	-149	-148	-147	-162
Sentinel node procedure	78	+2	+4	+5	+6	+5	+5	+6
<i>Total costs (x 10<sup>6</sup>)</i>	<i>3,501</i>	<i>+663</i>	<i>+1,326</i>	<i>+1,768</i>	<i>+806</i>	<i>+1,046</i>	<i>+1,289</i>	<i>+2,136</i>
	Sc 0	Sc 1	Sc 2	Sc 3	Sc 4	Sc 5	Sc 6	Sc 7
Discount rate	3%	3%	3%	3%	3%	3%	3%	3%
<b>Effectiveness</b>								
Breast cancer deaths	13,885	-852	-1,688	-2,251	-2,298	-2,286	-2,274	-2,518
Life years	21,583,800	+11,100	+22,000	+29,300	+29,600	+29,525	+29,450	+32,750
QALYs	21,534,815	+10,245	+20,300	+27,039	+27,271	+27,213	+27,155	+30,195
<b>Costs in CHF (x 10<sup>6</sup>)</b>								
<i>Total costs (x 10<sup>6</sup>)</i>	<i>1,783</i>	<i>+512</i>	<i>+1,024</i>	<i>+1,366</i>	<i>+646</i>	<i>+826</i>	<i>+1,006</i>	<i>+1,639</i>
<b>Cost-effectiveness (CHF)</b>								
Costs per life year gained	-	46,151	46,551	46,611	21,833	27,980	34,159	50,059
Costs per QALY gained	-	50,002	50,450	50,509	23,697	30,357	37,046	54,295

\* To calculate effects and costs for scenario 1-7, the difference in costs and effects between a scenario without screening (scenario 0, 2nd column) and scenarios with screening were calculated. This means that effectiveness of scenarios 1-7 is expressed in relative terms and the numbers of prevented deaths and gained (quality-adjusted) life years are shown. The cost-effectiveness is calculated by dividing the difference in costs by the difference in effects.

Figure 6.1 shows the number of breast cancer deaths prevented and the amount of quality adjusted life years gained for each screening scenario.

**Figure 6.1 Breast cancer deaths avoided and quality adjusted life years gained by seven mammography screening scenarios**



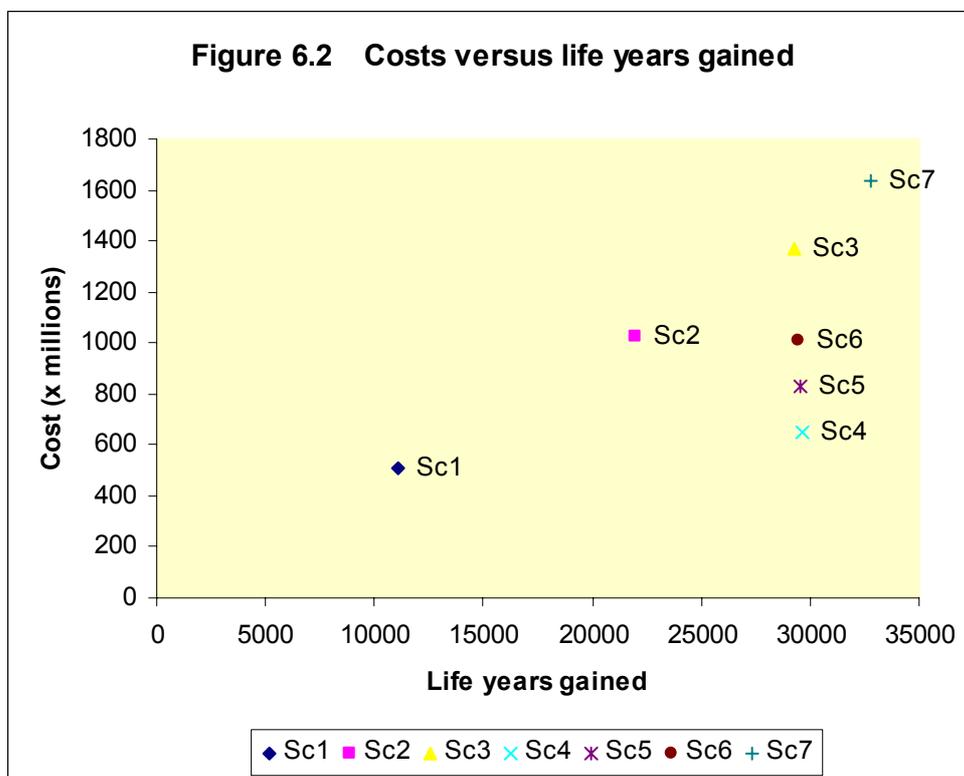
Organised biennial mammography screening (scenario 4) was slightly more effective than biennial opportunistic screening (scenario 3), even if the test sensitivity of an opportunistic mammography was assumed to be 6% higher than that of a programme mammography. This may be due partly to the larger variations in the screening intervals in opportunistic screening as compared to organised screening that were assumed in the model.

#### 6.4. Predicted cost-effectiveness of breast cancer screening

Table 6.2 shows the cost-effectiveness of the different screening scenarios per 1 million Swiss women of all ages. The upper part of the table shows non-discounted effects and costs and the lower part cost-effectiveness with a 3% discount rate. Although annual OS in combination with MSP was the most effective screening method, the relatively high costs associated with it decreased the cost-effectiveness of this strategy substantially.

In a scenario with 80% biennial OS, the additional imaging interventions and clinical breast exams will increase the costs of diagnostics by 669 million Swiss Francs (non-discounted). As less diagnostic interventions were associated with screen-detected cancers compared to clinically diagnosed tumours, the costs of diagnostics in a scenario of 80% MSP were 51 million Swiss Francs lower than in a scenario of no screening (non-discounted). The costs of palliative care decrease after screening: the higher the breast cancer mortality reduction, the lower the costs of palliative care. The estimates of costs, however, are imprecise, and may be underestimated.

As shown in Figure 6.2 the most cost-effective approach is organised screening covering 80% of eligible women (scenario 4). The other scenarios achieving 80% coverage with a mix of opportunistic and organised screening or with only opportunistic screening (scenario 3) are as effective, but much more costly.



N.B. Costs are calculated using a 3 % discount rate

For the scenarios in which a part of the population is screened opportunistically, and another part on a programme-base, the relative costs for each QALY gained increases with the higher proportions of OS (Table 6.2). The cost-effectiveness of OS in a scenario with less intensive screening (scenario 1) is comparable to the cost-effectiveness of OS with a higher intensity (scenario 2 or 3). The effects are highest with a high participation rate of 80%. The cost-effectiveness of the most beneficial scenario of 40% annual OS and 40% biennial MSP (scenario 7) is comparable to that of OS only (scenario 3), but the scenario of 80% MSP is more than 2 times more cost-effective (Figure 6.2).

If 80% of the 50-69 years old female population is biennially screened in an organised screening programme, the costs for each life year gained at 3% discounting are 21'833 CHF (13'161 euro) (Table 6.2). This is considerably higher than the estimated cost-effectiveness of national or regional breast cancer screening programmes in Europe (range between 2650 and 9600 euro per life year gained)<sup>92</sup> or the estimate of approximately 2'200 euro for each life year gained, for the Dutch nation-wide breast cancer-screening programme.<sup>90</sup> There may be several reasons for the important difference in cost-effectiveness of organised screening between the Netherlands and Switzerland. Firstly, the costs of mammography screening are approximately three times higher in Switzerland

than in the Netherlands (€ 155 vs. 50). Secondly, Swiss living costs are about 20% higher (purchasing parity 1.21). Thirdly, the Dutch figure is based on a broader target population range (50-75 years) than in Switzerland (50-69 years). In addition, estimates in other European programmes date from the early 1990's. Considering inflation rates, the 9'600 euro per life year saved estimated for organised breast cancer screening in Germany in 1994<sup>93</sup> are quite comparable to the 13'161 euro estimated for the Swiss setting in 2007.

## **IN CONCLUSION**

The MISCAN analysis showed that mammography screening is an effective way to reduce breast cancer mortality in Switzerland. A mortality reduction of around 20% was achieved in the 50-79 years old age group with an 80% biennial participation in organized mammography screening, opportunistic screening or a mix of both.

However, the lowest cost per life year gained is obtained with organised biennial mammography screening only (21'833 CHF), which is twice as cost-effective as opportunistic screening (46'611 CHF). By far the most costly scenario is 40% of women undergoing biennial organised screening and a further 40% having annual opportunistic screening (50'059 CHF per life year gained).

The relatively high costs of opportunistic screening and associated diagnostics thus result in a substantially less favourable cost-effectiveness ratio of opportunistic screening compared with organised mammography screening in Switzerland.

## **Chapter 7: Expanding mammography screening in Switzerland – Important issues to consider**

Based on the evidence presented in the previous chapters showing that mammography screening is effective in reducing breast cancer mortality and that organised screening is more cost-effective than opportunistic screening, the final question to be answered is how breast cancer screening could be made available to all women above age 50 in Switzerland. Some issues that need to be considered are discussed in this last chapter.

### **7.1. Addressing the access gap for women age 50 and above to organised, quality-controlled screening mammography**

Access to screening mammography is highly variable within Switzerland. Mammography screening programmes that ensure access to organised, quality-controlled mammographies either free of charge or against a modest co-payment exist in all six French speaking cantons as of May 2007. Only women resident in these cantons have access to mammography screening programmes. No such programmes currently exist in the German and Italian speaking cantons of Switzerland.

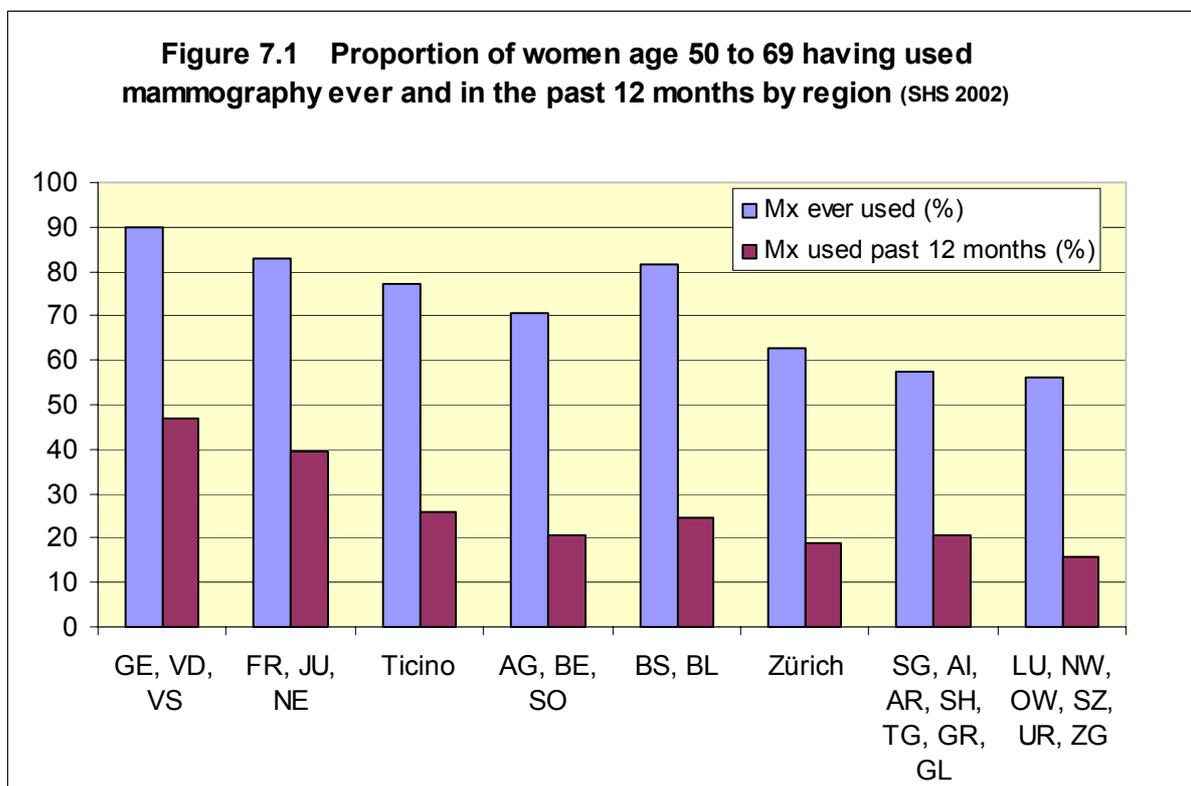
In the latter cantons, women may be referred by their general practitioner or gynaecologist for a screening mammography that will be labelled “diagnostic” to ensure reimbursement by the basic health insurance. These screening tests will, however, only be reimbursed if the “franchise” has been reached, are more expensive than mammographies carried out in a screening programme and always entail a 10% co-payment by the woman. There is anecdotal evidence that women who do not have access to screening in their canton of residence (eg. Bern) have tried to gain access to a breast cancer screening programme in the neighbouring canton (eg. Fribourg and Jura).

Data from the last Swiss Health Survey in 2002 (SHS 2002) illustrate **inequalities between cantons**.<sup>94</sup> Figure 7.1 shows that the proportion of women who ever had a mammography varies between less than 60 percent in Central and Eastern Switzerland to more than 80% in the French speaking cantons and in the cantons of Basel, rural and urban combined. The odds for a woman to have had a mammography are seven times higher in Geneva, Vaud and Valais than in the Eastern and Central regions. The trend is similar for use of mammography during the past 12 months. Usage rates in the French speaking cantons with long-standing screening programmes are about three times higher than in Central Switzerland (47% vs. 15.7%).

These cantonal differences may be due to the awareness of women about the potential benefits of mammography screening as well as the availability and accessibility of a mammography screening, including the cost of mammography. According to the SHS 2002, the probability of having used a mammography ever or in the past year is significantly higher among women who have a semi-private or private health insurance than those who have only basic health insurance.

To reduce this gap in access to breast cancer screening it would be necessary to establish new mammography screening programmes. Some efforts are already underway. The Public health department of the canton Bern announced in March 2007 that women living

in the Jura bernois will have access to organised mammography screening as of January 2009 through collaboration with the JU/NE programme. Other cantons are interested to start organised mammography screening programmes, but are awaiting decision on future reimbursement of the service. For example, St.Gallen is currently planning to start a breast cancer screening programme in 2008, if reimbursement of screening mammography is continued.



## 7.2. Can high-quality organised screening programmes be implemented across Switzerland?

### ARE THERE ENOUGH RADIOLOGISTS AND MAMMOGRAPHY DEVICES?

According to the membership statistics of the Swiss medical federation (FMH) 540 radiologists (191 in the French speaking part) were practicing in 2006, of which 248 have a private practice (radiology institute)<sup>xxii</sup>. There were 239 mammography devices in Switzerland in 2006. It is reasonable to assume that not all radiologists would be interested in performing mammographic radiology. This would actually be desirable in order to increase the volume of mammographies interpreted per radiologist per year.

As shown in table 7.3 (p.81) with a maximum participation rate of 70% of eligible women about 580'000 mammographies would be performed in two years, corresponding to 290'000 mammographies per year. If 290 radiologists participated in a national

<sup>xxii</sup> FMH-Aerzte- und Mitgliederstatistik / Statistique médicale et des membres de la FMH (31.12.2006). Schweizerische Aerztezeitung 2007 ;88 :Nr 12

programme, meaning about half of all practicing radiologists, this would mean 1000 mammographies per 1<sup>st</sup> reading radiologist per year. If a volume of 2000 mammographies per year per 2<sup>nd</sup> reader was deemed adequate, not more than 145 radiologists should participate in a country-wide screening programme. However, it is very likely that the participation rate would be considerably lower than 70%, and would be variable between regions and cantons. The volume per 1<sup>st</sup> reader would thus be most probably considerably lower, and much less radiologist should participate as 2<sup>nd</sup> and 3<sup>rd</sup> readers (see below).

With approximately 240 mammographic devices in Switzerland, a 70% participation rate will result in an average volume of 1200 mammographies per year per device. In high volume screening programmes such as the centralised programmes in Europe, average volumes of 10'000 to 12'000 mammographies per year are standard (UK, NL, Sweden).

The implementation of a nation-wide breast cancer screening programme is thus restricted neither by the number of mammography devices nor by available human resources. Of course, additional training will be needed. As it is not likely that all cantons will introduce this screening service at the same time the training capacity available in Switzerland and in the surrounding countries should be sufficient.

#### HOW TO IMPROVE THE QUALITY OF RADIOLOGICAL EXAMINATION AND READING

Several radiologists participate as second and third readers in each canton. Depending on the number of radiologists involved, participation rate and the size of the canton this can lead to relatively low volumes by international standards as shown in Table 7.1.

**Table 7.1 Reading volume in Swiss breast cancer screening programmes**

	<b>Number of mammographies read per 2<sup>nd</sup>/3<sup>rd</sup> reading radiologist per year</b>	
<b>FR</b>	Average	1600
	Min/max	1100 / 2500
<b>GE</b>	Average	1298
	Min/max	1043/1513
<b>VD<sup>xxiii</sup></b>	Average	6120
	Min/max	4434 / 7435
<b>VS</b>	Average	1050
	Min/max	594 / 2749

The numbers in table 7.1 only take into consideration screening mammographies within these programmes. Most radiologists will in addition read opportunistic and diagnostic mammographies.

<sup>xxiii</sup> Second and third readings of mammographies carried out in the JU/NE programme are done by the radiologists of the Vaud screening programme. The readings performed by the radiologists of Vaud are computed by the JU/NE programme.

In the Vaud screening programme, the team of second and third readers is composed of few radiologists reading a large number of mammographies. The benefit brought by this method of multiple readings was clearly demonstrated. Indeed, the proportion of positive mammographies which is nearly 8% after the first reading decreases to 5% after the multiple reading process (prevalent and incident screens combined). Some cancers are detected by only one of the reading radiologists. The amount of such cancers detected by the second readers is larger than the amount detected by the first reader.

### **Reading volume is related to reader performance**

Given the decentralised nature of the screening programmes in Switzerland and the high number of available radiologists the issue of rather low reading volumes is important. To inform the debate on desirable reading volumes available evidence is briefly summarized.

The European recommendation is 5000 mammographies for all radiologists in centralised programmes and for 2<sup>nd</sup> and 3<sup>rd</sup> reader in a decentralised mammography screening programme. This number is based on expert opinion without support of peer reviewed literature. A study in British Columbia, Canada, demonstrated that a minimum annual reading of 2'500 screening mammographies per radiologist is associated with lower abnormal interpretation rates and average or higher cancer detection rates than a reading volume of less than 2'000.<sup>95</sup> Another study in New South Wales, Australia, investigated the relationship between reader volume and cancer detection rate in incident screens. It found that there is no significant increase in cancer detection after approximately 1000 mammographies read per radiologist per year, with an optimal volume around 1375.<sup>96</sup> The performance of low- (less than 1200 mammographies per year), medium- (1200-3600) and high-volume (>3600) US radiologists was compared to the performance of high-volume UK radiologists.<sup>97</sup> The average sensitivity varied from 70.3% for low-volume to 77% for high volume US radiologists, and remained below the 79.3% sensitivity of UK radiologists. Average specificity varied between 83.6% and 88%. The average percentage of cancers detected ranged from 71.5% to 83.5%. In this study higher volume continuously improved diagnostic performance. These three studies thus don't come to the same conclusions regarding the relationship between reader volume and performance. In France and Luxembourg, a minimum of 2000 mammograms are required for the second reader.<sup>xxiv</sup> Recent data from the screening programme in Valais also seem to indicate that the rate of false positive readings decreases as the annual volume increases (from <1500 to >5000). However, cancer detection rates are not clearly related to reading volumes.<sup>98</sup>

When starting a program, it can be difficult to build a reduced team of experienced radiologists, as nobody is experienced enough in mass screening and as most radiologists want to participate. Reducing the number of second readers in a second phase to increase yearly numbers of readings is felt to be a difficult task in Geneva and Valais, as the performances of the readers are similar and as there are no clear cut criteria for exclusion (specific reading volume, recall rate etc.). Nationally defined criteria would be very useful.

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<sup>xxiv</sup> [http://www.senologie.com/site/pdf/24-05-06-cdc\\_radiologues.pdf](http://www.senologie.com/site/pdf/24-05-06-cdc_radiologues.pdf) page 24

When starting a new programme, stricter selection criteria should be applied to limit the number of sites participating. For example, not more than one mammographic device per 5000 eligible women should be included at the start of the programme. Depending on the participation rates this could be extended in a second phase.

## **HOW TO ENSURE QUALITY ASSURANCE AND EVALUATION**

Cancer registries are the prerequisite for a complete evaluation of a mammography screening programme, as this is the only means to notify interval cancers in screening participants and cancers in non-participants. The national centre for cancer epidemiology, one of the objectives of the National Cancer Control Programme 2005-2010, will hopefully be instituted soon. In the meanwhile, existing cancer registries should cover the needs of new screening programmes.

Currently quality assurance and evaluation of the mammography screening programmes are the responsibility of the cantonal breast cancer screening centres and Directions of Health. However, to avoid divergent quality and evaluation criteria the existing screening programmes use the same evaluation criteria and share a common data base. Furthermore, three (JU/NE, VD, VS) of the five existing programmes are assessed by the same evaluation team. The « Coordination romande des programmes de dépistage du cancer du sein » is a useful platform to ensure coherence.

A national institution should be responsible for establishing quality assurance criteria based on the European guidelines; ensuring that cantonal or regional programmes are implemented according to these criteria; granting and periodically renewing certification of screening centres/programmes; requesting and supporting regular evaluation of the certified programmes based on a pre-defined set of indicators. The national institution can delegate certain tasks to other organizations, such as university departments of preventive medicine or cancer registries.

### **7.3. Financing options**

Screening mammography including double (and if necessary triple) reading should continue to be reimbursed *hors franchise* by the basic health insurance.

The appropriateness of the currently requested 10% co-payment should be examined. The reason for a contribution by the patient for medical services is to avoid over-use. However, in the case of an organised screening programme for the early detection of cancer over-use is inherently impossible and adequate use is highly desirable. As women are invited, they cannot come more frequently than foreseen by the screening programme. This being a public health programme to reduce breast cancer mortality, one would want to entice women to use the service as often as useful (every two years) and remove any barriers to access.<sup>xxv</sup> It may not be so much the 15 CHF that prevent women from attending than the administrative hassle linked to it. One could also wonder if it is worth the administrative effort on part of the screening programme and the health insurers.

The major question is how the administrative expenses linked to each mammography (invitation, follow-up) as well as costs of the programme itself will be financed. This

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<sup>xxv</sup> A study in Finland showed that women who had to pay a fee (17 Euro) for mammography attended less often than women who were entitled to free screening.<sup>99</sup>

question has been a major stumbling block for implementing breast cancer screening programmes beyond the French speaking part of Switzerland.

One option is to entirely devolve financial responsibility for breast cancer screening programmes to each canton. This makes it difficult for small cantons to establish such programmes and hampers the emergence of intercantonal programmes. Another option is that health insurance covers part of the administrative costs of such programmes. There may be good reasons to consider this option. Screening mammography is considerably less expensive than opportunistic screening for health insurers at currently agreed rates of reimbursement (see box). If health insurances have a real interest in organised screening as a means to reduce cost, they should consider supporting such programmes. This is the only effective instrument to control the number of mammographies, due to the limits imposed by the programme (one mammography every two years, beginning at age 50). If screening is done on an individual basis, there will be numerous women who will go for a mammography before they are 50 years old and/or who will go once every year instead of once every two years.

#### **Diagnostic mammography is more expensive than screening mammography**

According to Tarmed 1.03, a screening mammography is reimbursed 147.91 points. A diagnostic mammography similar to a screening mammography (two views) and including a gynaecological consultation is reimbursed 236.46 points. The gynaecological consultation is obligatory as diagnostic mammography can only be obtained by prescription. If an ultrasound of the breast is added 441.99 points will be reimbursed. Screening mammography thus costs about 33% of the complete diagnostic intervention and about two-thirds of a diagnostic mammography.

Sharing the costs of the programme between public health services and insurers could be done along the following lines.

- The screening mammography is covered by health insurance based on a common tariff agreement with health insurances and santésuisse that is valid for the whole of Switzerland. In due time the tariff for screening mammography should be adapted simultaneously with the tariff for diagnostic mammography in order to consider the rising cost of equipment related to the transition from film to digital mammographies.
- The third reading should be reimbursed in all programmes as this is part of a quality service to the screened woman.
- The administrative costs linked to the provision of a screening mammography (communication of result, archiving, payment procedures, follow-up) should be covered by the health insurance fee.
- All costs related to the public health aspects of the programmes should be financed by cantonal and/or federal public health authorities (e.g. invitation of target population, communication activities, quality assurance procedures, professional training and accreditation, evaluation)

## 7.4. Information of women

Users of health services should receive accurate information on the benefits, risks and limitations of any medical intervention proposed in order to make an informed decision. This is particularly important in screening programmes, as these are targeted at people who perceive themselves as free from the disease being screened. In addition, screening programmes have the objective of improving public health, rather than providing an individual service. The need to achieve a high coverage rate could lead to overstating the benefits of screening, while minimizing risks.

It has been shown that women's understanding of the likely benefits and harms of screening are variable depending on age, educational level and setting. A telephone survey carried out in 1999 in three European countries (Italy, Switzerland, UK) and the US showed that misconceptions are widespread and that benefits that can realistically be expected from mammography screening are overstated.<sup>100</sup> At that time misconceptions were more prevalent in the two countries with organized screening programmes (UK, Italy) than in Switzerland and the US.

The question then is what type of information should be provided to women, in which form and by whom. Given the complexity of the issue, a major focus has been on providing well-balanced print information. Based on a review of articles (1966-2004) related to mammography screening, informed decision-making and risk communication, the content elements of written information were defined. Existing materials from 16 breast cancer screening programmes were then assessed based on these elements.<sup>101</sup> There was considerable variability in detail and comprehensiveness of the information provided and in framing the risk information (reducing the risk of breast cancer, as well as hazards of the screening). The authors conclude by pointing to the challenges in deciding what information is important for women to know and how it should be framed and delivered:

- Balancing the goals of a national screening programme – maximizing participation vs. maximizing individual consent and autonomy;
- Making decisions among expert disagreements about numerical values for benefits and adverse effects;
- Understanding how women process complex information;
- Relaying complex information to women of varied educational and cultural backgrounds and with variable preferences to learn detailed scientific information.

Recognizing these challenges, the breast cancer screening programmes in Switzerland have put much emphasis on improving information provision. In 2003, a working group developed recommendations for oral and written information and quality criteria.<sup>102</sup> Furthermore, an information booklet explaining the pros and cons of mammography screening was produced, following the latest edition of the EU guidelines on how women should be informed. Currently all women invited to breast cancer screening in any of the cantonal screening programmes receive the same booklet. Reference is made in the booklet to the extensive brochure on mammography issued by the Swiss cancer league.<sup>xxvi</sup>

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<sup>xxvi</sup> The brochure can be found under the following link:

[http://www.swisscancer.ch/fileadmin/swisscancer/praevention/files/Brochure\\_Le\\_d\\_pistage\\_du\\_cancer\\_du\\_sein.pdf](http://www.swisscancer.ch/fileadmin/swisscancer/praevention/files/Brochure_Le_d_pistage_du_cancer_du_sein.pdf)

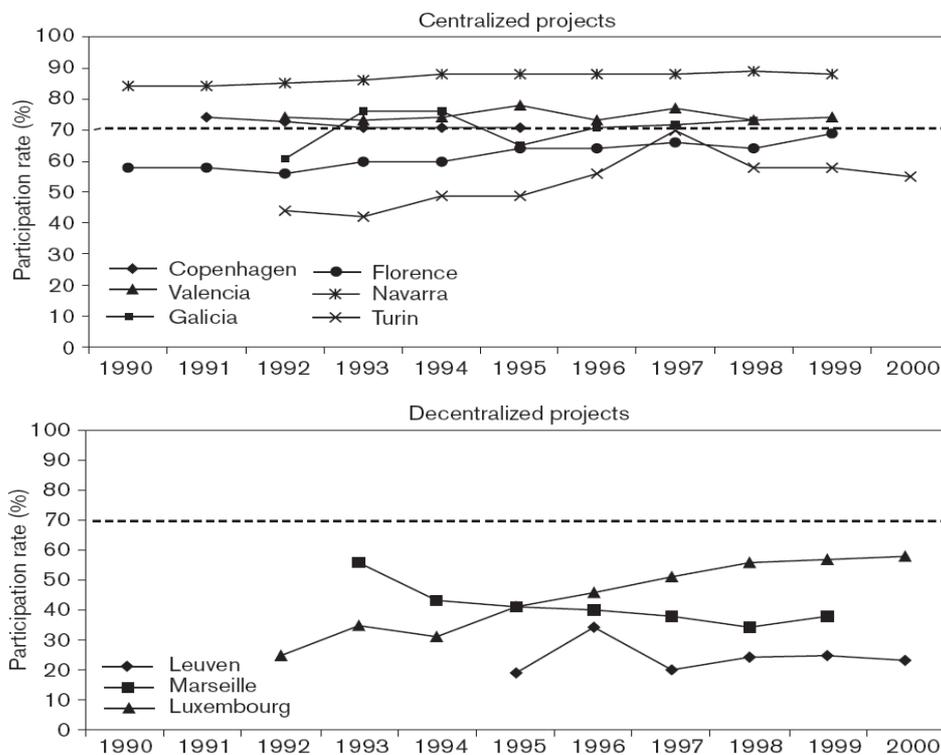
In the future, written communication tools in cantonal and/or regional mammography screening programmes should convey the same information, with some room for adaptation to the local setting (e.g. practical information). Various stakeholders, including women of different social and educational backgrounds and consumer groups, should be involved in designing, pre-testing and periodically evaluating the materials. The communications guide for breast cancer screening<sup>103</sup> recently published by the International Cancer Screening Network will be very helpful in (re-)designing and developing print materials.

Coherent and well-designed written information is central in a high-quality mammography screening programme. Women should take a well informed decision to undergo mammography. However, it should be clear that the choice is between having a mammography or none and not between participating in an organised screening or undergoing opportunistic screening. In this regard, the crucial role played by family doctors, gynaecologists and other information sources such as the internet should not be overlooked.

### 7.5. Estimated uptake of breast cancer screening

It is very difficult to make projections on the potential uptake of screening mammography across Switzerland. International evidence shows that participation rates in screening mammography vary greatly due to cultural differences and to the programme being centralised or decentralised. Figure 7.2 shows time trends in participation rates in various regions or cities by type of programme.

**Figure 7.2 Participation rates in centralized and decentralized breast cancer screening programmes**



In general participation rates are higher in centralised than in decentralised screening programmes. Luxembourg has a set-up that can best be compared to the Swiss situation. After eight years a coverage rate of about 60% was achieved. During the first three years of the programme it was around 30 %.

Table 7.2 shows the evolution of participation rates since the start of the cantonal programmes in Switzerland. Data on uptake in the three programmes of longest duration should be applied with caution to cantons without screening programme in 2007 as the environment has considerably changed in the past years. In particular, the awareness about the usefulness of mammography and the use of individual mammography screening has increased in many cantons. The evolving participation rate in the canton Fribourg may provide some indication on the potential uptake in German-speaking cantons, particularly in those with low background screening. Participation increased from 16.2% in the first year to 50.9% in the second year giving an average coverage rate of 34.4% in the first round. Achieving 30% coverage in the first two years of the programme may thus be a realistic goal.

**Table 7.2 Uptake of mammography screening over time in five cantons**

	1999	2000	2001	2002	2003	2004	2005	2006
	Participation rate in %							
<b>VD</b>	20.1	28.3	40.1	40.9	64.3	40.5	64.1	49.1
<b>VS</b>		26.5	48.4	54.4	57.7	65.7	66.0	62.1*
<b>GE</b>			28.0	24.7	31.3	29.2		
<b>FR</b>						16.0	50.1	43.4
<b>JU</b>							43.2	51.6

\* Interruption of screening programme in one radiology unit during 3 months

The only data currently available in Switzerland to analyse the time trend in use of mammography are the results of the Swiss Health Survey in 1997 and 2002. The next survey is planned for 2007, and results should be expected by 2008. As shown in figure 7.3 the proportion of women age 50 to 69 having used a mammography in the past 12 months has increased in all regions, with the exception of Ticino. The use of mammography has also increased in those cantons that do not have a mammography screening programme in place from 7% to 16% in Central Switzerland and from 6 to 21% in the North-eastern part. This is paralleled by an increase of women reporting having ever used a mammography.

**Figure 7.3 Time trend in use of mammography ever and in past 12 months by canton comparing data from the SHS 1997 and 2002**

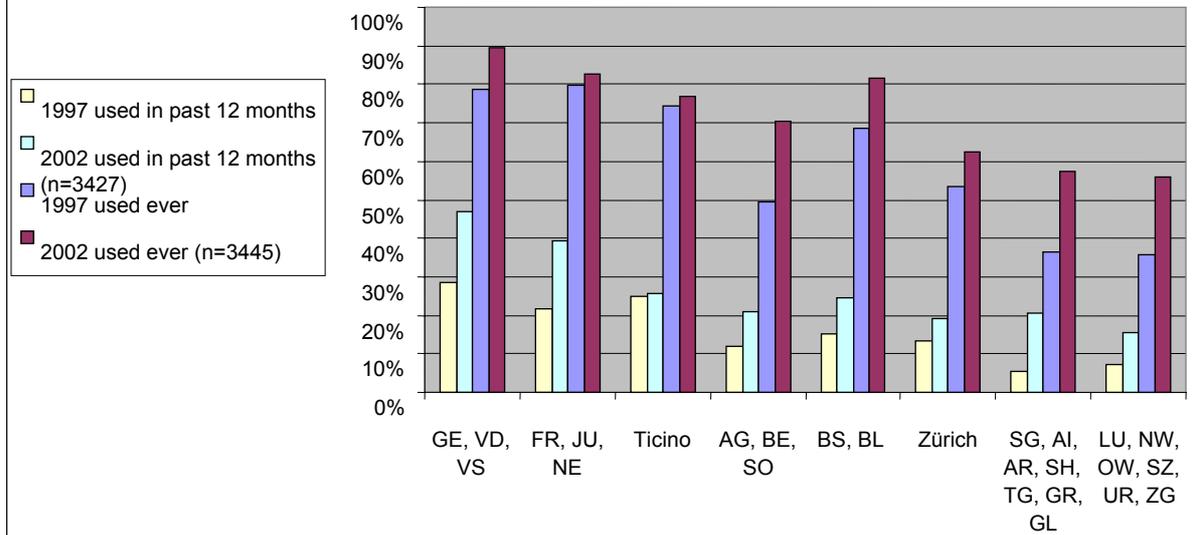


Table 7.3 shows the number of women 50-70 living in each canton and the number that would be eligible for mammography screening. Experience from the existing programmes shows that approximately 10% of the target group are not eligible due to pre-existing conditions (see chapter 1.3). Depending on the coverage rate achieved the table indicates how many women would do a screening mammography over a two year period (one screening round). Annual numbers are thus half of these. The last column provides numbers screened and coverage rate in the existing programmes.

**Table 7.3 Estimated number of women screened by canton and coverage rate**

Based on: Ständige Wohnbevölkerung am Jahresende nach Kanton, Statistisches Lexikon der Schweiz Bundesamt für Statistik, ESPOP, 2005. (Elisabeth Aebischer, [info.dem@bfs.admin.ch](mailto:info.dem@bfs.admin.ch) )

	Target population	Eligible women	Estimated number screened per 2 years by coverage rate			Number screened in latest round (coverage rate)
	age 50-70	(- 10%)	30%	50%	70%	
ZH	157'827	142'044	42'613	71'022	99'431	
BE	122'416	110'174	33'052	55'087	77'122	
LU	40'030	36'027	10'808	18'014	25'219	
UR	4'038	3'634	1'090	1'817	2'544	
SZ	14'972	13'475	4'042	6'737	9'432	
OW	3'566	3'209	963	1'605	2'247	
NW	4'634	4'171	1'251	2'085	2'919	
GL	4'375	3'938	1'181	1'969	2'756	
ZG	12'280	11'052	3'316	5'526	7'736	
SO	30'263	27'237	8'171	13'618	19'066	
BS	23'813	21'432	6'430	10'716	15'002	
BL	36'255	32'630	9'789	16'315	22'841	
SH	9'533	8'580	2'574	4'290	6'006	
AR	6'393	5'754	1'726	2'877	4'028	
AI	1'520	1'368	410	684	958	
SG	52'831	47'548	14'264	23'774	33'284	
GR	22'782	20'504	6'151	10'252	14'353	
AG	67'843	61'059	18'318	30'529	42'741	
TG	26'244	23'620	7'086	11'810	16'534	
TI	43'383	39'045	11'713	19'522	27'331	
VD	78'335	70'502	21'150	35'251	49'351	32'685 (48.7%)
VS	35'531	31'978	9'593	15'989	22'385	19'230 (65.9%)
NE	20'599	18'539	5'562	9'270	12'977	n.a.
GE	53'095	47'786	14'336	23'893	33'450	12'083 (30.1%)
JU	8'319	7'487	2'246	3'744	5'241	3'049 (49.1%)
FR	27'512	24'761	7'428	12'380	17'333	8'526 (34.4%)
<b>Switzerland</b>	<b>908'389</b>	<b>817'552</b>	<b>245'266</b>	<b>408'776</b>	<b>572'286</b>	

## **CAN OPPORTUNISTIC MAMMOGRAPHY SCREENING BE REDUCED?**

As discussed previously the uptake of organised mammography screening is influenced by the pre-existing background level of opportunistic screening. In a number of cantons the question will thus be how to reduce opportunistic screening while offering quality-ensured organised screening. To address this issue, the interests of the various stakeholders must be taken into account. In this regard, one needs to acknowledge that it may not be in the interest of the private physicians (gynaecologists and radiologists) to reduce opportunistic “diagnostic” mammography screening, as reimbursement is higher than for mammographies done within a screening programme. In addition clinical examination and an ultrasound can be charged to the health insurance.

However, health insurances should have an interest in decreasing opportunistic screening as it costs them more than organised screening. However, in most cantons without a programme the level of screening is still quite low. This means that overall health insurance pays less for mammographies in cantons without programmes than in cantons with programmes. These reflections are solely driven by economic considerations and do not aim at improving the health of women.

Women in the relevant age group could have an interest in using organised screening rather than opportunistic screening: easy access, regular recall, no or fewer costs, and better quality of radiological reading. This may be offset by the wish to have an individualised service.

Public regulatory authorities will have to provide incentives and exert some pressure to reduce opportunistic screening. At the national level the Federal Office of Public Health would need to provide clear guidance to health insurance as well as professional associations.

### **Reducing opportunistic screening in Luxembourg**

One possible approach to reducing the use of “diagnostic” mammography has been tested in Luxembourg. As an incentive the health insurance company provides each eligible woman every second year with a voucher for a mammography free-of-charge. This voucher can only be used within the breast cancer screening programme. In addition, gynaecologists are encouraged to decrease the prescription of “diagnostic” mammographies for the purpose of screening.

It is also important to acknowledge that the introduction of organised screening has induced new behaviours in women as well as physicians. For example:

- a tendency of the gynaecologist to prescribe a breast ultrasound in the days following the screening mammography even if the result of the mammography is negative;
- a tendency to perform a screening mammography every year, once in the screening programme and, the second year, as an opportunistic screening;
- a growing proportion of women age 40 to 50, doing screening mammography because they are reached by the information campaigns addressed to women aged fifty and over.

These behaviours of women and physicians should be taken into consideration when discussing how to reduce opportunistic screening.

## 7.6. A national coordinating and supervising body is needed

In a screening programme, some activities must be assured at the cantonal or intercantonal level (invitation of targeted groups, integration of physician specialists, evaluation, population information, etc.). Other activities are more efficiently carried out at the regional or national levels. A national coordinating and supervising body is essential to:

- Ensure a uniform mammography screening practice throughout Switzerland;
- Negotiate unified tariffs with health insurances;
- Define quality assurance criteria for the entire mammography procedure (invitation, screening, referral, assessment, treatment, feedback) based on the European guidelines;
- Certify breast cancer screening centres based on these criteria;
- Define requirements for special training of radiographers and radiologists;
- Ensure that the quality control of equipment used to execute mammographies in radiology units is performed by certified services having no conflict of interest with equipment suppliers according to a standard protocol;
- Guarantee the production of well-balanced information materials about the benefits and hazards of breast cancer screening (e.g. brochures in all national and frequently used languages);
- Provide unified management tools for breast cancer screening centres;
- Ensure epidemiological support and a unified evaluation procedure.

It would be the responsibility of the Federal Office of Health either to take on this national coordination, to delegate it to an existing organisation or to revive the Swiss Foundation for Cancer Screening.

### IN CONCLUSION

Access to screening mammography is currently highly variable within Switzerland. Existing mammography screening programmes in the French speaking cantons offer all women aged 50 to 70 a screening mammography every second year. In the other cantons, women may be referred by their general practitioner or gynaecologist for a screening mammography that will often be labelled “diagnostic” to ensure reimbursement by the basic health insurance. This leads to inequitable access across cantons and within cantons.

The implementation of organized breast cancer screening in several Swiss cantons has shown that it is possible to implement such programmes and to reach European standards in terms of performance. Available resources such as radiologists, mammography devices, cancer registries suffice to offer organized quality-controlled mammography screening to all women above age 50 in Switzerland. However, to achieve this national coordination and guidance is paramount. In addition, uniform funding mechanisms, binding quality criteria and common information tools for women must be devised and implemented.

## **Annex. Efficacy of breast cancer screening by mammography: scientific evidence**

Eight randomized screening mammography trials were implemented between the 1960s and 90s to examine the impact of organised mammography screening on breast cancer mortality.<sup>xxvii</sup> The eight trials are in order of their initial years:

- Health Insurance Plan Trial (HIP), New York (1963)
- Malmö Mammographic Screening Trial (1 and 2), Sweden (1976)
- Two-County Trial (TCS; Kopparberg and Oestergötland), Sweden (1977)
- Edinburgh Randomised Trial of Screening for Breast Cancer, Scotland (1979)
- National Breast Screening Study #1: women 40 to 49 years old (NBSS-1), Canada (1980)
- National Breast Screening Study #2: women 50 to 59 years old (NBSS-2), Canada (1980)
- Stockholm Mammographic Screening Trial (Stockholm), Sweden (1981)
- Gothenburg Breast Screening Trial (Gothenburg), Sweden (1982)

With the exception of the two Canadian trials, all trials compare mammography screening to no screening. In the Canadian trials mammography screening with clinical breast examination is compared to clinical breast examination alone.

The results of these trials and numerous meta-analyses showed a 25 to 30% decrease in breast cancer deaths. While these results lead several industrialised countries to implement national mammography screening programmes in the 1980s and 90s, a Cochrane review published in 2000 contested the validity of the trials. Since the publication of the Cochrane review several further reviews have thoroughly re-examined evidence on the efficacy of mammographic screening from these trials. Each major review published since 2000 is briefly presented. A table at the end of this annex summarizes judgements made about the eight trials and conclusions reached by each review.

### **Cochrane review, 2001**

The objective of this review<sup>32</sup> was to assess the effect of screening for breast cancer with mammography on mortality and morbidity. Nine trials were identified, of which two (UK age trial, Singapore) had not yet published results. Seven trials were included in the analysis (the two Canadian trials were considered as one). The quality of these seven trials was judged based mainly on the quality of randomisation and cause of death assessments. Data were classified in four groups: high-quality, medium-quality, poor-quality and flawed. The two authors of the review extracted data independently and resolved disagreements by discussion. Intention-to-treat analyses were conducted, using a fixed effects model.

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<sup>xxvii</sup> A ninth trial, involving women aged 40-49 only (UK Age Trial), begun in 1991 in the United Kingdom. Results have been recently published<sup>1</sup> showing a 17% reduction in breast cancer mortality, which did not reach statistical significance (RR 0.83; CI 0.66-1.04). This trial will not be discussed as it does not concern the age group (women 50 and above) relevant to this request.

The judgements made are summarised in Table 6.1 (page xx). No trial is judged of high quality. Only two trials are defined as medium quality (Malmö and Canadian trials). Two trials are totally excluded from analysis being considered as flawed (Health Insurance Plan New York and Edinburgh). Using the two medium-quality trials in the meta-analysis no significant reduction in breast cancer mortality can be found: relative risk of 0.97 (95% CI 0.82–1.14). If data from all eligible trials (excluding flawed studies) are considered then the relative risk for breast cancer mortality after 13 years is found to be 0.80 (95% CI 0.71–0.89).

Beyond the quality of the trials and results regarding breast cancer mortality, the authors assert that breast cancer mortality is an unreliable outcome measure that is biased in favour of screening. In their view only an impact on overall mortality would be sufficient evidence to support mammography screening, as the assessment of cause of death may be biased and as screening may lead to an increased mortality due to other causes (in particular cardiovascular disease due to radiotherapy for breast cancer).

The authors *Conclusion* is:

*The currently available reliable evidence has not shown a survival benefit of mass screening for breast cancer. However, the trials and this review are still underpowered for all-cause mortality; the confidence intervals include both a plausible worthwhile and a possible detrimental effect. Women, clinicians and policy makers should consider these findings carefully when they decide whether or not to attend or support screening programs.*

### **Rebuttals of the 2001 Cochrane review**

As briefly mentioned in the introduction to this section, the initial Cochrane review led to several publications countering in much detail its criticisms and conclusions. Some of the very thorough and extensive rebuttals are briefly presented here.

In 2002, the Dutch Minister of Health requested the Health Council of the Netherlands to re-examine the arguments, criticisms and conclusions of the Cochrane review and to indicate if there is scientific evidence to discontinue the breast cancer screening programme. The report answers the Cochrane review criticisms in detail on the following points: methodological quality of the studies; breast cancer mortality as an endpoint; overall mortality as an endpoint; overdiagnosis and overtreatment.<sup>19</sup> The main conclusions are:

*In the committee's view, the currently available reliable evidence does show a survival benefit of breast-cancer screening for women over the age of fifty. The arguments presented in the Cochrane review are not considered convincing to refute this evidence. However, the committee does not discount the possibility that new evaluations will ultimately lead to the conclusion that the effect of screening is not as great as anticipated in 1990.*

In Switzerland, a group of scientists published a critical review of the 2001 Lancet article by Gotzsche and Olsen (GO).<sup>24</sup> This review had been requested by the Swiss Cancer League. The impartiality and objectivity of the methods used by GO to judge the validity of the randomized controlled trials are contested. The paper mainly focuses on scientific criteria to assess the quality of the trials, and in particular randomization. The authors conclude that the statistical analysis presented by GO is methodologically flawed and that

there is no reason to question the efficacy of mammography screening based on their analysis.

An in-depth methodological appraisal of the assessment made by GO concerning in particular three studies (Health Insurance Plan, New York; Two-county trial, Sweden; both parts of the Canadian trial) was published in 2003.<sup>26</sup> The authors counter the criticisms levelled at the New York and the Swedish study. At the same time, they raise a number of critical issues in the Canadian trials. They conclude:

*GO's critique of the positive studies (HIP and Two-County), like their defence of CNBSS, is careless at best. Rather than clarifying the issues, their papers have instead generated much confusion. Clinical trials of mammography have led to substantial advances in understanding breast cancer, and a substantial reduction in mortality from this disease. It is time to move on, although some questions may remain.*

Further papers either countered specific aspects of the Cochrane review or provided a more global view on the flaws of the criticisms raised by the Cochrane reviewers.<sup>20-22;25;33</sup>

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It is interesting, for example, that the principal investigators of the Malmö study (included by the Cochrane review as one of the best-quality studies) published a paper showing that after 10 to 11 years of follow-up during which screening continued, they estimate that screening -- at intervals of 18–24 months, with incomplete (about 70%) adherence -- resulted in a 55% reduction in case-fatality rate and thereby, after the requisite delay, in cause-specific mortality in the older women.<sup>21</sup>

A paper published in 2003 to provide recommendations about mammography screening for breast cancer screening for the United States reviewed responses to the criticisms of Gotzsche and Olsen.<sup>35</sup> It concludes that criticisms of all but one of the trials (Edinburgh) excluded from the meta-analysis in the Cochrane review, have been answered and that the effectiveness of mammography, especially for women older than 50 years, can not be negated.

## **Evidence for the U.S. Preventive Services Task Force, 2002**

The objective of this review<sup>17</sup> was to update recommendations on breast cancer screening and in particular to examine the effectiveness of mammographic screening in women younger than 50 years of age. The focus was on information that had become available after 1996. This led to the inclusion of eight randomized, controlled trials of mammography and two trials evaluating breast self-examination. One hundred fifty-four publications of the results of these trials, as well as selected articles about the test characteristics and harms associated with screening, were examined.

Predefined criteria developed by the U.S. Preventive Services Task Force were used to assess the internal validity of the trials. Quality ratings were based on the entire set of publications from a trial. A detailed description of this approach is provided. In addition, new meta-analyses were conducted to incorporate new information about the quality of the trials and longer follow-up results. A two-level Bayesian random-effects model was used to provide summary relative risk estimates and credible intervals for the effectiveness of screening with mammography, either alone or with clinical breast examination, in reducing breast cancer mortality by age group.

All trials with the exception of the Edinburgh trial were judged to be of fair quality and were included in the meta-analysis. The summary relative risk for all age groups was estimated at 0.85 (95% CI, 0.73-0.99). The number needed to invite for screening to prevent one breast cancer death after approximately 14 years of observation is 1224 among women in all age groups, and 838 among women aged 50 to 74.

Excerpts from the *Discussion*:

*Fair-quality, relatively consistent evidence suggests that mammography screening reduces breast cancer mortality among women aged 40 to 74. We found no evidence that including clinical breast examination conferred greater benefit than mammography alone. We also found no evidence supporting the role of breast self-examination in reducing breast cancer mortality. [...]*

*We identified many of the same design problems highlighted in the Cochrane review, but reached different conclusions about their bearing on the validity of the findings. With the exception of the Edinburgh trial, we found inadequate evidence to conclude that the specific flaws identified introduced biases of sufficient magnitude or direction to invalidate the findings or to reject the inference that screening mammography reduces breast cancer mortality. [...]*

*In summary, when judged as population-based trials of cancer screening, most of the mammography trials are of fair quality. Their flaws reflect tradeoffs made in the planning of the trial that make the trials widely generalisable with potentially some cost in internal validity. In absolute terms, the mortality benefit shown with mammography screening is small enough that biases in the trials could erase or create the observed mortality reduction. However, in our review, while there are flaws in the design or execution of the trials, there is insufficient evidence to conclude that the majority were seriously biased and consequently invalid.*

This is the most complete and thorough review identified.

## **IARC review 2002**

In March 2002, The International Agency for Research on Cancer (IARC) convened a working group of 24 experts from 11 countries to review evidence on breast cancer screening.<sup>18</sup> Efficacy of screening was one of several aspects examined. The same randomised controlled trials were included as in the Cochrane and US Preventive Task Force review. However, reasons for including certain trials and excluding others in the final summary analysis of the efficacy of mammography screening were diverging from other reviews. In particular, the Canadian trials were excluded because screening in both trials included clinical breast examination and the design of NBSS 2 was different from those of all other trial. The review thus mainly relies on the Swedish trials. In addition, evidence from the Finnish national programme was included, comparing breast cancer mortality between women invited for screening before 1990 and those invited after 1990. Methodological issues of each trial are discussed, including randomization, inclusion and exclusion criteria and outcome measures, and validity of each trial examined. The method used to assess the trials is not described. Most probably conclusions are based on majority or consensus expert opinion.

Aggregating findings from the five trials of mammography alone in women aged 50-69 and including evidence from the Finnish programme, a combined breast cancer mortality rate ratio of 0.75 (CI 0.67-0.85) was calculated. The reduction in mortality from breast cancer over a ten-year period after first invitation to screening was estimated to be 0.5 per 1000 women aged 40-49 and 0.9 per 1000 women aged 50-59. In addition, based on follow-up data from the Swedish trials, it was estimated that the breast cancer mortality

reduction for women aged 50-59 who are actually screened (taking account of lack of compliance in the intervention arm and dilution in the control arm) would be 35%.

### **AETMIS Quebec review, 2006**

This review was carried out by the *Agence d'évaluation des technologies et des modes d'intervention en santé* (AETMIS) to re-examine the quality of the scientific evidence on which the mammography screening programme of Quebec is based.<sup>30</sup> In particular the pertinence of extending screening to women less than 50 years old and the relevance of earlier trial results for modern screening programmes was to be assessed.

The eight published randomized controlled trials were examined regarding their validity as well as the strength of contrast between the study and the control interventions. A strength of contrast scale was constructed based on five elements: technical contrast (opposition of study and control intervention); era in which mammography was conducted (modern mammography is qualitatively superior); technical quality of the mammography performed (norms of mammography practice, quality control measures, interval between screening rounds); participation and contamination; timing of mortality effects (early and late timing dilution). In addition to the strength of contrast scale, a validity scale and scoring system was developed based on four elements: randomization, baseline equality, equal exclusion and follow-up (assessment of death).

For each of the trials all published articles were reviewed and the rating was assigned independently by two researchers. Ratings were then compared and discrepancies resolved by consensus with reference to the original research reports. Scores and ratings are presented in detail in the review. The summary rating of validity and strength of contrast for each trial is provided in table 1.

The reduction of breast cancer mortality obtained in the various trials is then presented in declining order of validity. A progressive combination of trial results shows the cumulative mortality reduction for women of all ages, ranging from 9% (medium-quality studies), to 15% (medium and poor-quality studies), to 23% (all studies). The more valid studies tend to show lesser reductions and confidence intervals sometimes include the null value. A sub-group analysis of data pertaining to women at least 50 years old at enrolment (55 years in the Malmö trial) show breast cancer mortality reductions between 24 and 29%, depending on studies included.

Excerpts from *Discussion and Conclusions*:

*There are serious concerns regarding the validity of most of the trials supporting mammography screening, based on methodological weaknesses in the screening trials. Studies are highly heterogeneous with regard to the strength of the contrast that they studied, with numerous weaknesses identified in all the major studies, meaning that the potential of screening mammography has perhaps not been thoroughly explored. Using the best available data, one can conclude that there is fair evidence of moderate reduction of breast cancer mortality, of the order of 9 to 15%; data restricted to women over the age of about 50 show greater reductions, of the order of 24 to 29%. Furthermore, our analysis has demonstrated that modern mammography, carried out under quality conditions that maximize its performance, has the potential to identify cancerous lesions earlier in their progression, and this may allow for some further reduction in mortality.*

*Conclusion: Existing scientific trials, despite their flaws, support mammography screening programs. In addition, there are good reasons to believe that modern, well conducted screening programs may achieve earlier detection and diagnosis of breast cancer and, perhaps, greater reductions in breast cancer mortality than what has been found in screening trials.*

## **Cochrane review 2006**

The Cochrane review published in 2001 was recently updated (18 October 2006)<sup>31</sup> One of the two authors of this update participated in the initial review. The randomized controlled trials included are the same than in the review published in 2001, as well as methods used to assess their quality. Reference is made to the meta-analysis of the Swedish trials published in 2002<sup>28</sup>. The Edinburgh trial is considered as flawed and excluded from analysis. However, the Health Insurance Plan Trial, New York is this time included in the review. The summary impact on breast cancer mortality of screening with mammography is examined for adequately randomised trials first. Then trials considered to be suboptimally randomised are added. The authors estimate that a 15% relative reduction in breast cancer mortality is realistic, and that this agrees with the review done for the U.S. Preventive Services Task Force and the meta-analysis of the Swedish trials. As in the initial Cochrane review the authors also focus on the detrimental effects of screening (psychological distress from false-positive findings, overdiagnosis and over treatment, time needed to attend screening sessions, costs to the health care system).

## **Conclusion**

It is now uncontested (even in the latest Cochrane review) that population-based breast cancer screening reduces breast cancer mortality in women over age 50. All randomised controlled trials have shown a trend of reduction in breast cancer mortality among women over age fifty, which was usually statistically significant. Various meta-analyses show that this reduction lies in a range of 15% to 30%. This evidence is supported by results from cohort and case-control studies.

Randomized controlled trials of breast cancer screening have shortcomings, many of which are inherent to the conduct of large population-based studies with long-term intervention and follow-up. The diverging views on the impact of screening on breast cancer mortality are due to different quality assessments and interpretations of the eight existing randomized controlled trials by different reviewers. There is general agreement that one of the trials, the Edinburgh trial, is flawed and should not be used in meta-analyses.

The evidence from the eight population-based randomized controlled trials is the best we have, as it is no longer possible to initiate a new randomized controlled trial to study the efficacy of breast cancer screening in women over 50 years of age for ethical and practical reasons. In virtually all industrialised countries some proportion of women over age 50 is undergoing mammography screening, either opportunistic or organised. Control groups thus no longer exist.

The randomized controlled trials have examined differences in breast cancer mortality between groups of women invited to mammography screening and not invited to screening. These trials may not be effective in estimating the true magnitude of the screening benefit because of non-adherence in the group invited to screening as well as contamination (i.e., participation in screening) among the "not invited," or usual care group, thus underestimating the true magnitude of benefit among screened individuals.

In addition, technical quality of screening has improved since the randomized controlled trials were implemented, thus most probably enhancing the efficacy of screening.

These conclusions are very well summarised in the AETMIS review:

*“Many of the conditions of screening trials resulted in significantly weaker contrasts than those of modern programs. In particular, all studies are from earlier eras when mammographic equipment and techniques were less refined. Many have used a single view of each breast, as opposed to modern standards using double views. Some studies have used intervals longer than two years (28 months in Stockholm, 33 months in Two-County). Participation rates have been as low as 53% (Edinburgh) and 54% (HIP) and as high as 87% (TCS) and 88% (NBSS), but in all studies the effective contrast has been reduced because women in the control group also received mammography, ranging from about 5% (HIP) to as high as 15% (Gothenburg) and 20% (Stockholm). The timing of the relationship between the screening period and mortality results has caused significant dilution in all studies, compared to the steady-state reduction that a programme could achieve after a suitable delay. In particular, the durations of all studies have been much shorter than the twenty years of screening that most programs propose (from age 50 to 69); some studies had only two rounds (Stockholm), three rounds (Two-County) or four rounds (HIP, Edinburgh, NBSS).”<sup>30</sup>*

**Table 6.1 Assessments of the quality of randomized controlled trials on the efficacy of mammography screening since 2000**

<i>Methods for analysis</i>	<b>Cochrane review 2001</b>	<b>U.S preventive services task force 2002</b>	<b>IARC review 2002</b>	<b>Quebec AETMIS review 2006</b>	<b>Cochrane review 2006</b>
<b>1. Health Insurance Plan, New York (1963)</b>	Fixed effects Adequate randomisation; data flawed	154 published articles; predefined quality criteria; Bayesian random-effects model Fair quality	Expert group (24)  Valid Not included as screening= mammo+CBE	Strength of contrast index (SCI; 5 criteria) + validity scale (4 criteria) SCI 12% Validity 1.5/4	Fixed effects  Suboptimally randomised
<b>2. Edinburgh, Scotland (1979)</b>	Randomisation procedure doubtful; trial flawed	Poor quality; serious imbalance between screened and control groups; severely flawed	Results confounded by diff. in SES and other variables. Not included	SCI 26% Validity 0.5/4	Not adequately randomised; very biased; no reliable data
<b>3. NBSS I, Canada (1980)</b>		Good quality, but inadequate concealment of allocation	Valid, but not included as screening= mammo+CBE (for NBSS II design too different)	SCI 45% Validity 4/4	Randomisation adequate
<b>4. NBSS II, Canada (1980)</b>	Adequate randomisation; data medium quality	Fair; Allocation concealed?	Latest published data from each of these trials are valid; included in analysis	SCI 31% Validity 4/4 (not included because design too different)	Randomisation adequate (Malmö I) / suboptimal (Malmö II)
<b>5. Malmö, Sweden (1976)</b>	Adequate randomisation; data medium quality (Malmö I) and poor quality (Malmö II)	Fair; Allocation concealed?		SCI 27% Validity 3/4	
<b>6. Two-County, Sweden (1977)</b>	Randomisation questioned; data poor quality and probably flawed	Fair;		SCI 42% Validity 0.5/4	Suboptimal randomisation probably biased
<b>7. Stockholm, Sweden (1981)</b>	Inadequate random. in 2 <sup>nd</sup> round; data poor quality	Fair; Allocation concealed? Fair;		SCI 28% Validity 2/4	Suboptimal randomisation
<b>8. Göteborg, Sweden (1982)</b>	Irregular randomis.; data poor quality	Fair; Allocation concealed? Fair;		SCI 37% Validity 1.5/4	Suboptimal randomisation
<b>Conclusions on survival benefit / relative risk: all age groups, if not noted otherwise; (studies included in italics)</b>	No survival benefit RR=1.03 (0.77-1.38) <i>(only 3,4,5)</i> Women > 50y (all studies except 1 and 2) RR=0.75 (0.62-0.89)	Survival benefit RR=0.84 (0.77-0.91) <i>(all except 2)</i>	RR=0.75 (0.67-0.85) for women 50-69 RR=0.81 (0.65-1.01) for women 40-49 <i>(only 5,6,7,8)</i>	Survival benefit estimate 9-23% RR=0.77 (0.7-0.84) <i>(all studies)</i>	Survival benefit RR=0.80 (0.73-0.88) <i>(all except 2)</i> Women > 50y RR=0.72 (0.62-0.85)

## Reference List

- (1) Moss SM, Cuckle H, Evans A, Johns L, Waller M, Bobrow L et al. Effect of mammographic screening from age 40 years on breast cancer mortality at 10 years' follow-up: a randomised controlled trial. *Lancet* 2006; 368:2053-2060.
- (2) International Agency for Cancer research. Effectiveness of screening. In: Vainio H, Bianchini F, editors. *Breast Cancer Screening*. Lyon, France: IARCPress; 2002. 119-156.
- (3) van der Maas, de Koning HJ, et al. Breast cancer screening and cost-effectiveness; policy alternatives, quality of life considerations and the possible impact of uncertain factors. *Int J Cancer* 1991; 49(4):531-537.
- (4) White E, Miglioretti DL, Yankaskas BC, et al. Biennial versus annual mammography and the risk of late-stage breast cancer. *J Natl Cancer Inst* 2004; 96:1832-1839.
- (5) Rosenberg RD, Hunt WC, Williamson MR, et al. Effects of age, breast density, ethnicity, and estrogen replacement therapy on screening mammographic sensitivity and cancer stage at diagnosis: review of 183'134 screening mammograms in Albuquerque, New Mexico. *Radiology* 1998; 209:511-518.
- (6) International Agency for Cancer research. Breast cancer and screening. In: Vainio H, Bianchini F, editors. *Breast Cancer Screening*. Lyon, France: IARCPress; 2002.
- (7) Levi F, Bosetti C, Lucchini F, Negri E, La Vecchia C. Monitoring the decrease in breast cancer mortality in Europe. *Eur J Cancer Prev* 2005; 14:497-502.
- (8) Bulliard J-L, La Vecchia C, Levi F. Diverging trends in breast cancer mortality within Switzerland. *Ann Oncol* 2006; 17:57-59.
- (9) Fisch T, Pury P, Probst N, et al. Variation in survival after diagnosis of breast cancer in Switzerland. *Ann Oncol* 2005; 16:1882-1888.
- (10) Bouchardy C, Verkooijen HM, Fioretta G. Social class is an important and independent prognostic factor of breast cancer mortality. *Int J Cancer* 2006; 119:1145-1151.
- (11) Ferlay J, Autier P, Boniol M, Heanue M, Colombet M, Boyle P. Estimates of the cancer incidence and mortality in Europe in 2006. *Ann Oncol* 2007; 18:581-592.
- (12) Jones LJ. Overdiagnosis and overtreatment of breast cancer: Progression of ductal carcinoma in situ: the pathological perspective. *Breast Cancer Research* 2006; 8(2):204.

- (13) Gotzsche PC, Olsen O. Is screening for breast cancer with mammography justifiable? *Lancet* 2000; 355:129-134.
- (14) Olsen O, Gotzsche PC. Cochrane review on screening for breast cancer with mammography. *Lancet* 2001; 358:1340-1342.
- (15) Olsen O, Gotzsche PC. Systematic review of screening for breast cancer with mammography. <http://image.thelancet.com/lancet/extra/fullreport.pdf> 2001.
- (16) U.S.Preventive Task Force. Screening for Breast Cancer: Recommendations and Rationale. *Ann Intern Med* 2002; 137(5):344-346.
- (17) Humphrey LL, Helfand M, Chan BKS, Woolf SH. Breast cancer screening: a summary of the evidence for the U.S. preventive services task force. *Ann Intern Med* 2002; 137(5):347-360.
- (18) International Agency for Cancer research. Efficacy of screening. In: Vainio H, Bianchini F, editors. *Breast Cancer Screening*. Lyon, France: IARCPress; 2002. 87-118.
- (19) van Veer WA, Health Council of the Netherlands. The benefit of population screening for breast cancer with mammography. publication no. 2002/03E. 7-3-2002. The Hague, Health Council of the Netherlands.  
Ref Type: Report
- (20) Boyle P. Mammographic breast cancer screening: after the dust has settled. *The Breast* 2003; 12:351-356.
- (21) Miettinen OS, Henschke CI, Pasmantier MW, Smith JP, Libby DM, Yankelevitz DF. Mammographic screening: no reliable supporting evidence? *Lancet* 2002; 359:404-405.
- (22) Duffy SW, Tabar L, Smith RA. The mammographic screening trials: commentary on the recent work by Olsen and Gotzsche. *CA Cancer J Clin* 2002; 52:68-71.
- (23) Green BB, Taplin SH. Breast Cancer Screening Controversies. *J Am Board Fam Pract* 2003; 16(3):233-241.
- (24) Bouchardy C, Raymond L LFP-HNTM, de Wolf C. L'efficacité du dépistage mammographique est-elle vraiment contestable? Une revue critique de l'article de Gøtzsche et Olsen. *Schweizerische Aerztezeitung* 2001; 82(12):588-594.
- (25) de Koning HJ. Mammographic screening: evidence from randomised controlled trials. *Ann Oncol* 2003; 14(8):1185-1189.
- (26) Freedman DA, Petitti DB, Robins JM. On the efficacy of screening for breast cancer. *Int J Epidemiology* 2004; 33:43-55.
- (27) Agence Nationale d'Accréditation et d'Evaluation en Santé (AENES). Dépistage du cancer du sein par mammographie: évaluation de la méta-analyse de Gotzsche et

- Olsen. 1-17. 2002. Paris, Agence Nationale d'Accréditation et d'Evaluation en Santé. Evaluation des technologies.  
Ref Type: Report
- (28) Nyström L, Andersson I, Bjurstam N, Nordensköld B, Rutqvist LE. Long-term effects of mammography screening: updated review of the Swedish randomised trials. *Lancet* 2002; 359:909-919.
- (29) Advisory Committee on Breast Cancer Screening. Screening for breast cancer in England: past and future. No 61, i-22. 2006. NHS Cancer Screening Programmes. NHSBSP Publication.  
Ref Type: Report
- (30) Deck W KR. Screening mammography: a reassessment. AETMIS 05-03, xii-77. 2006. Montréal, Canada, Agence d'évaluation des technologies et des modes d'interventions en santé (AETMIS).  
Ref Type: Report
- (31) Gotzsche PC, Nielsen M. Screening for breast cancer with mammography (Review). *Cochrane Database of Systematic Reviews* art.No.: CD001877[Issue 4], 1-61. 2006. John Wiley & Sons.  
Ref Type: Report
- (32) Olsen O, Gotzsche PC. Screening for breast cancer with mammography (Cochrane Review). *The Cochrane Library* 2001;(Issue 4):1-100.
- (33) Kopans DB. The Most Recent Breast Cancer Screening Controversy About Whether Mammographic Screening Benefits Women at Any Age: Nonsense and Nonsense. *Am J Roentgenol* 2003; 180(1):21-26.
- (34) Smith RA, Duffy SW, Tabar L, Gaber RL. Screening and early detection. In: Singletary ES, Robb GL, Hortobagyi GN, editors. *Advanced Therapy of Breast Disease*. 2nd edition ed. B.C.Decker; 2004.
- (35) Fletcher SW, Elmore JG. Clinical practice: mammographic screening for breast cancer. *N Engl J Med* 2003; 348:1672-1680.
- (36) Australian Institute of Health and Welfare and National Breast Cancer Centre. Breast cancer in Australia: an overview, 2006. Number 34. 2006. Canberra, AIHW cat. no. CAN 29, Australian Institute of Health and Welfare. Cancer Series.  
Ref Type: Report
- (37) Coldman A, Phillips N, Warren L, Kan L. Breast cancer mortality after screening mammography in British Columbia women. *Int J Cancer* 2006.
- (38) Olsen AH, Njor SH, Vejborg I, Schwartz W, Dalgaard P, Jensen MB et al. Breast cancer mortality in Copenhagen after introduction of mammography screening: cohort study. *BMJ* 2005; 330(7485):220.

- (39) Dean PB, Pamilo M, for the Mammography Working Group RSoF. Screening mammography in Finland - 1.5 million examinations with 97 percent specificity. *Acta Oncologica* 1999; Suppl.13:47-54.
- (40) Hakama M, Pukkala E, Heikkila M, Kallio M. Effectiveness of the public health policy for breast cancer screening in Finland: population based cohort study. *BMJ* 1997; 314(7084):864.
- (41) Anttila A, Koskela J, Hakama M. Programme sensitivity and effectiveness of mammography service screening in Helsinki, Finland. *J Med Screen* 2002; 9:153-158.
- (42) Parvinen I, Helenius H, Pylkkanen L, Anttila A, Immonen-Raiha P, Kauhava L et al. Service screening mammography reduces breast cancer mortality among elderly women in Turku. *J Med Screen* 2006; 13(1):34-40.
- (43) Swedish Organised Service Screening Evaluation Group. Reduction in breast cancer mortality from organized service screening with mammography: 1. Further confirmation with extended data. *Cancer Epidemiol Biomarkers Prev* 2006; 15(1):45-51.
- (44) Swedish Organised Service Screening Evaluation Group. Reduction in breast cancer mortality from organized service screening with mammography: 2. Validation with alternative analytic methods. *Cancer Epidemiol Biomarkers Prev* 2006; 15(1):52-56.
- (45) Tabar L, Vitak B, Tony HH, Yen MF, Duffy SW, Smith RA. Beyond randomized controlled trials: organized mammographic screening substantially reduces breast carcinoma mortality. *Cancer* 2001; 91:1724-1731.
- (46) Jonsson H, Nyström L, Törnberg S, Lenner P. Service screening with mammography of women aged 50-69 years in Sweden: effects on mortality from breast cancer. *J Med Screen* 2001; 8:152-160.
- (47) Tabar L, Ming-Fang Y, Vitak B, Chen HH, Smith RA, Duffy SW. Mammography service screening and mortality in breast cancer patients: 20-year follow-up before and after introduction of screening. *Lancet* 2003; 361:1405-1410.
- (48) Otto SJ, Fracheboud J, Looman CWN, Broeders M, Boer R, Hendriks JHCL et al. Initiation of population-based mammography screening in Dutch municipalities and effect on breast-cancer mortality: a systematic review. *Lancet* 2003; 361:1411-1417.
- (49) Fracheboud J, Otto SJ, van Dijck JAAM, Broeders M, Verbeek ALM, de Koning HJ et al. Decreased rates of advanced breast cancer due to mammography screening in The Netherlands. *Br J Cancer* 2004; 91:861-867.
- (50) Fracheboud J, Otto SJ, Groenewoud JH, et al. Landelijke evaluatie van bevolkingsonderzoek naarborstkanker in Nederland. Het elfde evaluatierapport. 2006. Rotterdam, Instituut MaatschappelijkeGezondheidszorg, Erasmus

Universiteit Rotterdam.  
Ref Type: Report

- (51) Ascunce EN, Moreno-Iribas C, Barcos Urtiaga A, et al. Changes in breast cancer mortality in Navarre (Spain) after introduction of a screening programme. *J Med Screen* 2007; 14:14-20.
- (52) McCann J, Duffy S, Day N. Predicted long-term mortality reduction associated with the second round of breast screening in East Anglia. *Br J Cancer* 2001; 84(3):423-428.
- (53) Blanks RG, Moss SM, McGahan CE, Quinn MJ, Babb PJ. Effect of NHS breast screening programme on mortality from breast cancer in England and Wales, 1990-8: comparison of observed with predicted mortality. *BMJ* 2000; 321(7262):665-669.
- (54) Berry DA, Cronin KA, Plevritis SK, Fryback DG, Clarke L, Zelen M et al. Effect of screening and adjuvant therapy on mortality from breast cancer. *N Engl J Med* 2005; 353(17):1784-1792.
- (55) Vervoort MM, Draisma G, Fracheboud J, van de Poll-Franse LV, de Koning HJ. Trends in the usage of adjuvant systemic therapy for breast cancer in the Netherlands and its effect on mortality. *British Journal of Cancer* 2004; 91:242-247.
- (56) Zorzi M, Puliti D, Vettorazzi M, et al for the IMPACT working group. Mastectomy rates are decreasing in the era of service screening: a population-based study in Italy (1997-2001). *British Journal of Cancer* 2006; 95:1265-1268.
- (57) Samnakay N, Tinning J, Yves A, et al. Rates for mastectomy are lower in women attending a breast-screening programme. *ANZ J Surg* 2005; 75:936-939.
- (58) Clayforth C, Fritschi L, McEvoy S, et al. Assessing the effectiveness of mammography screening service. *ANZ J Surg* 2005; 75:631-636.
- (59) Kauhava L, Immonen-Raiha P, Parvinen I, et al. Lower costs of hospital treatment of breast cancer through a population-based mammography screening programme. *European Journal of Public Health* 2004; 14:128-133.
- (60) Blanks RG, Moss SM, Patnick J. Results from the UK NHS breast screening programme 1994-1999. *J Med Screen* 2000; 7(4):195-198.
- (61) Rosenberg RD, Yankaskas BC, Abraham LA, et al. Performance benchmarks for screening mammography. *Radiology* 2006; 241(1):55-66.
- (62) Smith-Bindman R, Chu PW, Miglioretti DL, et al. Comparison of screening mammography in the United States and the United Kingdom. *JAMA* 2003; 290(16):2129-2137.

- (63) Brett J, Bankhead C, Henderson B, Watson E, Austoker J. The psychological impact of mammographic screening. A systematic review. *Psycho-Oncology* 2005; 14:917-938.
- (64) Meystre-Agustoni G, Paccaud F, Jeannin A, Dubois-Arber F. Anxiety in a cohort of Swiss women participating in a mammographic screening programme. *J Med Screen* 2001; 8:213-219.
- (65) Moss S. Overdiagnosis and overtreatment of breast cancer: Overdiagnosis in randomised controlled trials of breast cancer screening. *Breast Cancer Research* 2005; 7(5):230-234.
- (66) Duffy S, Agbaje O, Tabar L, Vitak B, Bjurstam N, Bjorneld L et al. Overdiagnosis and overtreatment of breast cancer: Estimates of overdiagnosis from two trials of mammographic screening for breast cancer. *Breast Cancer Research* 2005; 7(6):258-265.
- (67) Paci E, Warwick J, Falini P, Duffy SW. Overdiagnosis in screening: is the increase in breast cancer incidence rates a cause for concern? *J Med Screen* 2004; 11:23-27.
- (68) Paci E, Miccinesi G, Puliti D, et al. Estimate of overdiagnosis of breast cancer due to mammography after adjustment for lead time. A service screening study in Italy. *Breast Cancer Research* 2006; 8:R68 (doi:10.1186/bcr1625).
- (69) Jonsson H, Johansson R, Lenner P. Increased incidence of invasive breast cancer after introduction of service screening with mammography in Sweden. *Int J Cancer* 2005; 117:842-847.
- (70) Olsen AH, Agbaje OF, Myles JP, Lynge E, Duffy SW. Overdiagnosis, sojourn time, and sensitivity in the Copenhagen mammography screening program. *The Breast Journal* 2006; 12(4):338-342.
- (71) Svendsen AL, Olsen AH, von Euler-Chelpin M, Lynge E. Breast cancer incidence after introduction of mammography screening. *Cancer* 2006; 106(9):1883-1890.
- (72) de Koning H, Draisma G, Fracheboud J, de Bruijn A. Overdiagnosis and overtreatment of breast cancer: Microsimulation modelling estimates based on observed screen and clinical data. *Breast Cancer Research* 2006; 8(1):202.
- (73) Yen MF, Tabar L, Vitak B, Smith RA, Chen HH, Duffy SW. Quantifying the potential problem of overdiagnosis of ductal carcinoma *in situ* in breast cancer screening. *Eur J Cancer* 2003; 39(12):1746-1754.
- (74) Preston DL, Mattsson A, Holmberg E, Shore R, Hildreth NG, Boice JD. Radiation effects on breast cancer risk: a pooled analysis of eight cohorts. *Radiation Research* 2002; 158:220-235.

- (75) Nekolla EA, Griebel J, Brix G. Einführung eines Mammographiescreeningprogramms in Deutschland. Erwägungen zu Nutzen und Risiko. *Radiologie* 2005; 45:245-254.
- (76) Feig SA, Hendrick RE. Radiation risk from screening mammography of women aged 40-49 years. *J Natl Cancer Inst Monogr* , 119-124. 1997.  
Ref Type: Serial (Book,Monograph)
- (77) Porter GJR, Evans AJ, Burrell HC, Lee AHS, Ellis IO, Chakrabarti J. Interval breast cancers: prognostic features and survival by subtype and time since screening. *J Med Screen* 2006; 13:115-122.
- (78) Collins S, Woodman CBJ, Threfall A, Prior P. Survival rates from interval cancer in NHS breast screening programme. *BMJ* 1998; 316:832-833.
- (79) Törnberg S, Codd M, Rodrigues V, Segnan N, Ponti A. Ascertainment and evaluation of interval cancers in population-based mammography screening programmes: a collaborative study in four European centres. *J Med Screen* 2005; 12:43-49.
- (80) Bulliard J-L, Sasieni P, Klabunde C, De Landtsheer JP, Yankaskas BC, Fracheboud J. Methodological issues in international comparison of interval breast cancers. *Int J Cancer* 2006; 119:1158-1163.
- (81) Bulliard J-L, Levi F. Evaluation épidémiologique du programme valaisan de dépistage du cancer du sein, 1999-2006. 125, 1-39. 2006. Lausanne, Institut universitaire de médecine sociale et préventive. raisons de santé.  
Ref Type: Report
- (82) Luthi J-C, Duc C, de Weck D, Levi F, Bulliard J-L. Impact du programme valaisan de dépistage du cancer du sein sur le recours aux examens de pathologie. 1-21. 2007. Sion, Valais, Observatoire Valaisan de la Santé.  
Ref Type: Report
- (83) Verbeek ALM, Hendriks JH, Holland R, Mravunac M, Sturmans F, Day NE. Reduction of breast cancer mortality through mass screening with modern mammography. First results of the Nijmegen project, 1975-1981. *Lancet* 1984; 1(8388):1222-1224.
- (84) Fracheboud J, Otto SJ, van Dijck JAAM, Broeders M, Verbeek ALM, de Koning HJ et al. Decreased rates of advanced breast cancer due to mammography screening in The Netherlands. *Br J Cancer* 2004; 91(5):861-867.
- (85) Rijnsburger AJ, van Oortmarssen GJ, Boer R, Draisma G, Miller AB, de Koning HJ. Mammography benefit in the Canadian National Breast Screening Study-2: a model evaluation. *Int J Cancer* 2004; 110(5):756-762.
- (86) van den Akker-Van Marle ME, Reep-van den Bergh CM, Boer R, Del Moral A, Ascunce EN, de Koning HJ. Breast cancer screening in Navarra: interpretation of

- a high detection rate at the first screening round and a low rate at the second round. *Int J Cancer* 1997; 73(4):464-469.
- (87) Paci, Boer R, Zappa M, et al. A model-based prediction of the impact on reduction in mortality by a breast cancer screening programme in the city of Florence, Italy. *Eur J Cancer* 1995; 31A(3):348-353.
- (88) Rijnsburger AJ, Essink-Bot ML, van Dooren S, et al. Impact of screening for breast cancer in high-risk women on health-related quality of life. *Br J Cancer* 2004; 91(1):69-76.
- (89) Groenewoud JH, Pijnappel RM, van den Akker-Van Marle ME, et al. Cost-effectiveness of stereotactic large-core needle biopsy for nonpalpable breast lesions compared to open-breast biopsy. *Br J Cancer* 2004; 90(2):383-392.
- (90) de Koning HJ, van Ineveld BM, van Oortmarssen GJ, de Haes JC, Collette HJ, Hendriks JH et al. Breast cancer screening and cost-effectiveness; policy alternatives, quality of life considerations and the possible impact of uncertain factors. *Int J Cancer* 1991; 49(4):531-537.
- (91) Organisation for Economic Co-operation and Development (OECD). Purchasing Power Parities Data. OECD [ 2007 Available from:  
URL:[http://www.oecd.org/document/47/0,3343,en\\_2649\\_34357\\_36202863\\_1\\_1\\_1\\_1,00.html](http://www.oecd.org/document/47/0,3343,en_2649_34357_36202863_1_1_1_1,00.html)
- (92) de Koning HJ. Breast cancer screening: cost-effective in practice? *Eur J Radiol* 2000; 33:32-37.
- (93) Beemsterboer PMM, de Koning HJ, Warmerdam PG, Boer R, Swart E, Dierks ML et al. Prediction of the effects and costs of breast-cancer screening in Germany. *Int J Cancer* 1994; 58:623-628.
- (94) Schmidlin Kurt. Wie häufig und wie unterschiedlich werden Krebsvorsorgeuntersuchungen von der Schweizer Bevölkerung verwendet? Eine Auswertung der Schweizerischen Gesundheitsbefragung 2002. 1-59. 2006. Bern, Institut für Sozial- und Präventivmedizin der Universität Bern. Master-Thesis.  
Ref Type: Report
- (95) Kan L, Olivotto IA, Warren BURhenne LJ, Sickles EA, Coldman AJ. Standardized abnormal interpretation and cancer detection ratios to assess reading volume and reader performance in a breast screening program. *Radiology* 2000; 215:563-567.
- (96) Rickard M, Taylor R, Page A, Estoesta J. Cancer detection and mammogram volume of radiologists in a population-based screening programme. *The Breast* 2006; 15:39-43.
- (97) Esserman L, Cowley H, EberleC, et al. Improving the accuracy of mammography: volume and outcome relationships. *J Natl Cancer Inst* 2002; 94(5):369-375.

- (98) Bulliard J-L, Levi F. Performance des lectures radiologiques dans le programme valaisan de dépistage du cancer du sein. 2006. Lausanne, Institut universitaire de médecine sociale et préventive.  
Ref Type: Report
- (99) Immonen-Räihä P, Kauhava L, Parvinen I, Helenius H, Klemi PJ. Customer fee and participation in breast-cancer screening. *Lancet* 2001; 358:1425.
- (100) Domenighetti G, D'Avanzo B, Egger M, et al. Women's perception of the benefits of mammography screening: population-based survey in four countries. *Int J Epidemiology* 2003; 32:816-821.
- (101) Zapka JG, Geller BM, Bulliard J-L, Fracheboud J, Sancho-Garnier H, Ballard-Barbash R. Print information to inform decisions about mammography screening participation in 16 countries with population-based programs. *Patient Education and Counselling* 2006; 63:126-137.
- (102) Bressoud D, Casabianca A, de Wolf C, Jemelin C. Recommendations pour une meilleure information sur le cancer du sein. *Med Hyg* 2003; 61:677-679.
- (103) International Cancer Screening Network. Designing print materials: a communication guide for breast cancer screening. No. 07-6100. 2007. Bethesda (MD), NIH, National Cancer Institute (NCI). NIH Publication.  
Ref Type: Report

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