



# Breast Cancer in Egypt: Preliminary Situation Analysis with a Focus on Early Detection

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Report by

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## EXECUTIVE SUMMARY

### *Incidence and mortality*

In Egypt, as in all developing countries, the incidence of breast cancer is rising. The incidence, recently estimated at 33 new cases per 100,000 women per year, is comparable to the incidence observed in neighboring countries (although still lower than that observed in Western countries such as the U.S., where incidence is 161 per 100,000 among Caucasian women). This estimate corresponds to 12,240 new cases per year in Egypt. It is estimated that more than 70% of the affected individuals will die from their disease, compared to 20-25% in Western countries. Late diagnosis and sub-optimal treatments are the most likely explanation for this gap.

### *Risk factors*

The most important risk factors of breast cancer (BC) are those related to the reproductive history of the woman and are therefore not preventable. To have few or no children or to have them late in life significantly increases the risk of BC; additionally, not breastfeeding slightly increases the risk of BC. Due to societal changes, the prevalence of these three factors is increasing in Egypt. Early menarche and late menopause also significantly increase the risk of BC. The prevalence of these two factors is known to increase with social development and improved diet and thus is expected to be on the rise in Egypt.

Preventable risk factors of BC include high body weight, low physical activity, and consumption of alcohol, but their effect on risk of disease is moderate. Current use of contraceptives and current use of hormone replacement therapy increase slightly the risk (by a factor of 1.4 and 1.6, respectively), but this increase of risk disappears when consumption stops.

Familial history of BC is commonly considered a major risk factor of BC; however, only a strong familial history of BC in very close relatives substantially increases the risk of BC. Having one sister or a mother affected multiplies the risk of BC by only 1.8, while having two sisters affected multiplies the risk by 2.9.

Some studies have suggested that having blood-related parents (consanguinity), a frequent condition in Egypt, could be an important risk factor for pre-menopausal BC. As consanguinity is rare in Western countries, its association with BC has hardly been studied; more research is needed, some of which could be conducted in Egypt.

### *Late diagnosis*

As in most developing countries, BC is diagnosed late in Egypt – in most cases, at a stage at which cure becomes impossible even with the best treatments. Data from the population-based cancer registry of Gharbiah shows that only 25% of BC patients are diagnosed at a localized stage (before the cancer spreads to lymph nodes), compared to 63% in the U.S. In 88% of the cases, tumor sizes are above 2 cm, a size easily detectable by clinical breast exam.

Low breast-cancer awareness in the public is usually invoked as the primary reason for late diagnosis. However other causes may be important, such as socio-cultural barriers that make women delay seeking diagnosis or treatment, logistical and economic issues (accessibility and affordability of health services), and suboptimal organization of health services. The Breast Cancer Foundation of Egypt study of barriers to early diagnosis of BC in Cairo (BED-BC-Cairo) revealed that up to 37% of the first doctors consulted by women for breast complaints advised them wrongly (inadequate treatment or inadequate referral) suggesting that it was an important cause of delayed diagnosis. Among the 204 BC patients included in the BED-BC-Cairo study, the mean delay between first visit to a doctor and effective diagnosis of cancer was 1.7 months among women who were advised correctly by the first doctor visited, and 9.1 months among

women who were not correctly advised ( $p < 0.0001$ ). The study also suggests that breast cancer awareness (prior to the disease) was low in this urban population and that the low awareness was a major reason for delaying a first consultation.

### *Methods for early detection*

The World Health Organization (WHO) distinguishes two programmatic approaches to early detection of cancer: screening and clinical down-staging. Screening consists of applying a test to the asymptomatic population at risk. To screen for BC, either mammography or a clinical breast exam (CBE) can be considered. Breast self-exam (BSE) is no longer considered because its sensitivity has proven to be too low and because there is evidence that its regular practice does not prevent mortality from BC.

Mammography is the most sensitive tool; however, scientific studies show that its superiority on well-performed CBE is not as important as commonly presumed. A recent study suggests that annual CBE screening can save almost as many lives as biennial mammography screening and with a cost-effectiveness ratio that is 2.5 times lower.

The efficacy of mammography in saving lives is overestimated even within the medical community. Recent reviews of scientific evidence on mammography screening conclude that it has a limited power to prevent BC deaths; that the overall impact on mortality is small; and that false positive tests, overdiagnosis and overtreatment are not negligible issues.

Whether based on mammography or CBE, screening programs as a health intervention are demanding of resources and complex to implement. As an alternative to screening, clinical down-staging is a cheaper and easier-to-implement alternative. This is relevant for countries with limited resources where the majority of cancers are diagnosed at stages III and IV. Clinical down-staging is intended to make use of the available health care resources: It consists of 1., education of the first-line health staff and the public about early symptoms of cancer and benefits of early detection; and 2., improvements in referral procedures and patient flow. It has the potential to reduce stage III and IV diagnosis to 30%. According to WHO recommendations, "A cancer-screening programme is a far more costly and complex undertaking than a clinical down-staging programme. Therefore, where resources are limited, and where the majority of cases are diagnosed in late stages, clinical down-staging of the most frequent cancers, linked to appropriate treatment, is likely to be the best option to reduce premature deaths and suffering due to cancer."

### *Main conclusions and recommendations*

In Egypt, where still a vast majority of tumors are above 2 cm by the time of diagnosis, there is room for improvement via a clinical down-staging approach. Screening with CBE would be relevant to regions and groups where stage distribution is sufficient that down-staging has no potential for major improvement. Early detection can result from both down-staging in some parts of the country and screening in other parts. This first-phase Breast Cancer Situation Analysis reveals a number of behaviors that motivate or restrain women in relation to receiving early diagnosis and treatment of breast cancer. This analysis also clearly identifies the need for further examination of Egyptian women's behaviors that may stand as barriers for early detection and treatment of breast cancer. A clear understanding of these obstacles to early diagnosis and treatment will allow the building of a successful breast cancer strategy for early detection and clinical down-staging. Indeed, because formal analysis is lacking on the benefit of screening and down-staging programs in developing countries, guidelines of the WHO and Breast Health Global Initiative call for countries to conduct research and pilot projects prior to establishing such programs on a national level.

## ABBREVIATIONS

AJCC	American Joint Committee on Cancer
ASR	"Age-standardized Rate" i.e., age-standardized incidence of disease
BC	Breast Cancer
BCFE	Breast Cancer Foundation of Egypt
BSE	breast self-exam
CBE	clinical breast exam
EDHS	Egypt Demographic and Health Survey
IARC	International Agency for Research on Cancer (WHO agency)
LMC	low and middle-income countries
MoHP	Egypt Ministry of Health and Population of Egypt
NCI-Cairo	National Cancer Institute of Cairo (cancer hospital)
NCI-US	National Cancer Institute (the national cancer research body of U.S.)
OR	odd ratio (measure of risk increase)
SEER	Surveillance Epidemiology and End Results (the national cancer registry of U.S.)
SES	socio-economic status
TFR	total fertility rate
TNM	TNM (Tumor, Nodes, and Metastases) staging system
WHO	World Health Organization

## INTRODUCTION

The report presented is a situation analysis of breast cancer (BC) in Egypt for 2008 with a special focus on prevention and early detection.

The main objectives of the report are as follows:

1. Provide an estimate of the disease burden, incidence, mortality, age groups at risk and other epidemiological aspect of BC in Egypt
2. Provide a picture of BC risk factors in Egypt
3. Evaluate the magnitude of late presentation/late diagnosis problems in Egypt
4. Identify modifiable barriers for early detection existent in Egypt
5. Review the best practices available for early detection of breast cancer in the world
6. Suggest strategic directions for early detection of breast cancer in Egypt
7. Review the ongoing actions for prevention and early detection existent in Egypt
8. Make recommendations for further action

To achieve these objectives, extensive information and data collection were undertaken, including:

- Interviews with Egyptian professionals
- Interviews with international experts
- A thorough review of the Egyptian literature including grey literature (reports, theses, etc.)
- An extensive review of the international literature
- Statistical analysis of raw data provided by Egyptian cancer centers

In addition, an original survey was conducted to understand the barriers to early detection/diagnosis existent in Egypt.

Objectives 1, 2 and 3 are addressed in Chapter 1 of this report. Objective 4 is addressed in the Chapter 2, which includes results of the original survey. Objectives 5 and 6 are addressed in Chapter 3, which includes an extensive review of BC early detection methods. Objective 7 is addressed in Chapter 4, and objective 8 in Chapter 5 of the report.

1 EPIDEMIOLOGY

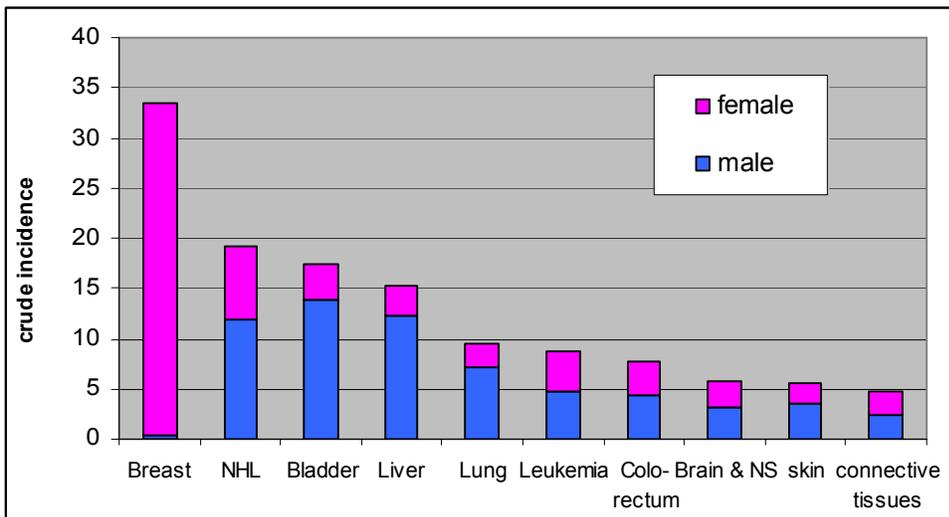
1.1 Incidence of breast cancer in Egypt, geographical variations, time trends

1.1.1 Incidence

Only population-based cancer registries can provide accurate incidence and age-specific incidence; hospital-based registries provide data that are usually not representative of the whole population (for more information, see IARC publication no. 95, 1996 or IARC publication no. 66, 1985). The Gharbiah Cancer Registry based in Tanta (see appendix 1 "The Gharbiah population-based registry" for more details) is the cancer registry of reference for Egypt. The incidence and age-specific incidence reported in this section are those of the 2007 Gharbiah Cancer Registry Report, which covers the years 2000-2002 and includes 10,440 cancer cases, 1,810 of which are female breast cancer. Data from comparable population-based registries in neighboring countries are also reviewed and reported. Contrary to widespread belief, cancer incidence does not vary tremendously across regions or neighboring countries: consequently, regional registries data are usually assumed to be an acceptable reflection of the situation in the whole country.

The Gharbiah data reveal that breast cancer (BC) is the most common cancer in Egypt, even when considering men and women combined (see Figure 1). BC in the Gharbiah data represents 17.5% of all incident cancer and accounts for 35.7% of all newly diagnosed female cancers. As everywhere in the world, male breast cancer is rare, representing only 1.1 % of all incident breast cancer.

Figure 1. The ten most common cancers in Egypt in both sexes 2000-2002 [Gharbiah population-based registry 2007]



The crude incidence rate of breast cancer among Egyptian women is 33.1 new cases per 100,000 inhabitants per year, and the age-standardized incidence rate (ASR)<sup>1</sup> is 41.9/100,000 per year. The age-standardized incidence is the rate corrected for country age pyramid structure and is the rate used usually for epidemiologic cross-country comparison. The ASR of breast cancer in Egypt is more than 2 times lower than that of the United States (U.S.) (see Table 1). Such a difference is not surprising.

It is well established that BC is more frequent in Western countries than in developing countries, due to major differences in the prevalence of risk factors (number of children, age at first child, breastfeeding, age at menarche, socio-economic status, etc.) [Parkin & Fernández 2006]. When considering strategies for early detection, it is important to keep in mind that the proportion of BC cases in Egypt is approximately 4 times lower than that in Western countries.

On average, there are 603 new cases of BC per year in the Gharbiah district. If one assumes that the Gharbiah incidence rate can be generalized to the whole country, one can estimate 12,240 new cases of BC per year in Egypt (Gharbiah Governorate, with a population of 3.7 million inhabitants, represents 4.9% of the Egyptian population). The real number may be a somewhat lower because the BC incidence in Gharbiah may be a little higher than the average in Egypt: The human development index rating of Gharbiah Governorate is slightly higher than the national figure for Egypt. Given that socio-economic status and level of development are associated with higher BC incidence (see Section 1.6 about risk factors for detailed information), this suggests that BC incidence in Gharbiah could be slightly higher than the mean incidence of Egypt [Gharbiah Registry Report 2007].

### 1.1.2 Geographical variations

With the exception of Morocco, the incidence of breast cancer in Egypt is higher than in neighboring countries (see Table 1). There are various possible explanations for this pattern:

1. Some of the incidence reported in table 1 may be underestimated due to variations in registry practices and coverage.
2. Some genuine variations may exist between countries due to different patterns of the risk factors in the population covered:
  - § For example, the Tunisian and Libyan registries cover more rural populations than do the Moroccan and Egyptian ones. As BC incidence is known to be lower in rural populations (see Section 1.6), this can explain a part of the variation.
  - § Obesity, a risk factor for post-menopausal BC, is more prevalent in Egypt than in the neighboring countries listed here [WHO SURF-2 report]. This might account for a small part of the variation; however, no conclusion can be drawn on this matter without an adequate scientific study.

Table 1. Incidence of breast cancer among women in Egypt, neighbor countries and U.S.

	Egypt	Morocco	Tunisia	Libya	Jordan	U.S. (white)	U.S. (all)
Years covered	2000-2002	2004	1995-1998	2003	1996-2001	1998-2002	1998-2002
Crude incidence	33.1	36.1	21.8	14.4	.	161.0	126.2
ASR	41.9	-	25.6	22.9	38.0	98.5	90.9
Source	Gharbiah registry	Casablanca registry	North Tunisia registry	Benghazi registry	Freedman <i>et al.</i> 2006	Curado <i>et al.</i> 2007	Curado <i>et al.</i> 2007

<sup>1</sup> See Appendix 2, "Definitions" for the definition of crude rate and age-standardized rate

No adequate data are available to assess geographical variation of BC incidence inside Egypt, however some slight variations may exist due to geographical variations in prevalence of the major risk factors, i.e., reproductive factors (number of children , age at first child, breastfeeding) and socio-economic status (which correlate to reproductive factors). These variations are detailed in Section 1.6. The trend to keep in mind is that BC is expected to be lower in rural and in low socio-economic level populations. No environmental factors such as pollution, pesticides, or chemical exposure are expected to have a noticeable effect on BC, as these factors have very little effect on risk of BC [Boffetta 2004].

### 1.1.3 Time trends

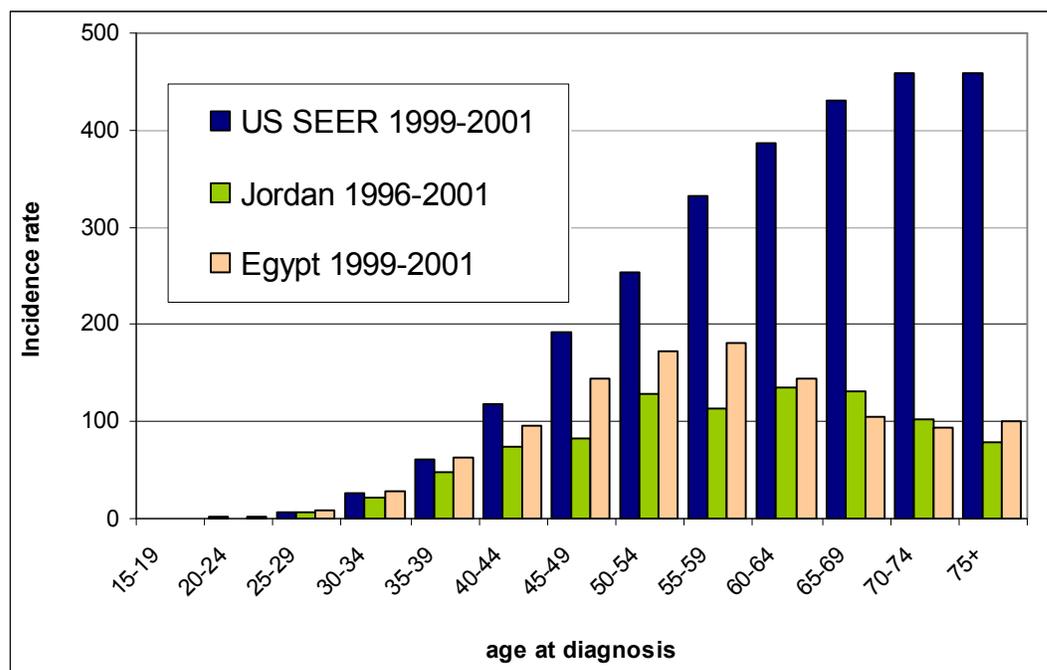
Although no solid data are available to assess time trends in BC incidence in Egypt, BC incidence is expected to rise in line with the general trend in all developing countries. BC incidence is known to increase with the woman's education, socio-economic status and with the country's level of development. The rapidity of the increase is usually correlated to the rapidity with which the country develops [Parkin & Fernández 2006]. Similarly, BC incidence is increasing in Western countries as a result of development: For example, in the United Kingdom (UK), the incidence of BC has risen by 50% over the last 25 years.

## 1.2 Age-specific incidence

The peculiar age distribution of BC cases has drawn significant interest and raised many questions in the Egyptian cancer professional community: Indeed, the onset of BC appears to be much earlier than in Western countries. The reasons for this are explained in detail below.

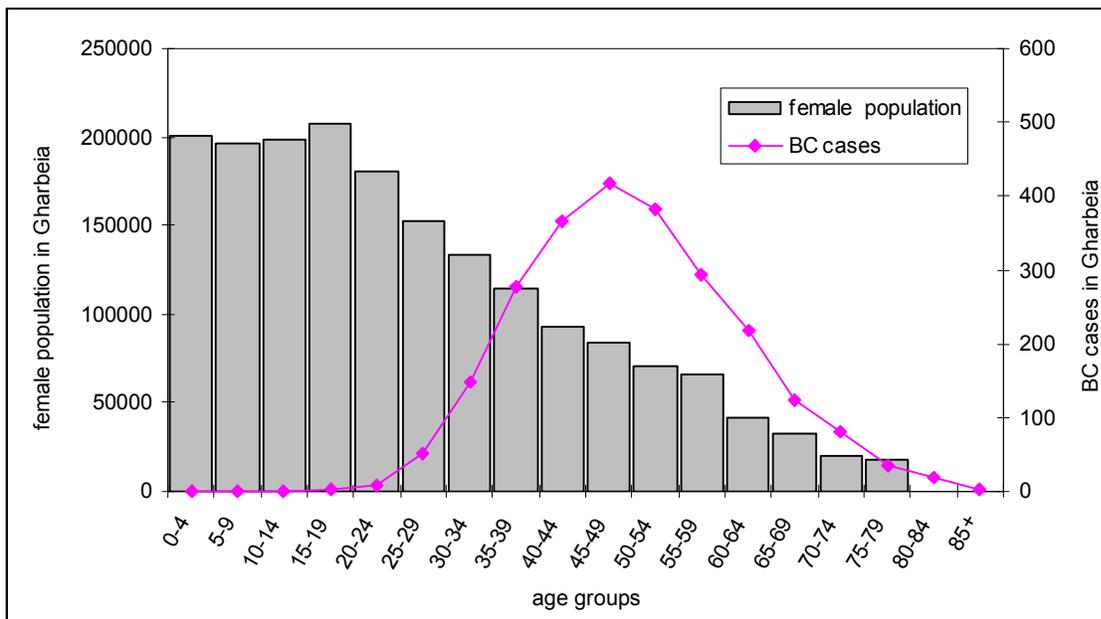
Contrary to what is observed in Western countries, where incidence of breast cancer increases with age, in most developing countries breast cancer appears to be a disease of the young generations, with incidence rates higher in women below 60 than in older women [Parkin & Fernández 2006]. Egypt displays this same pattern found in most developing countries: The incidence of BC peaks at 55-59 and decreases afterwards (see Figure 2). Figure 2, which displays the age-specific incidence rate for 3 countries including Egypt, shows that women most at risk to develop BC in Egypt are women in the 55-59 age group, followed by women 50-54, followed by women 60-64 and then women 45-49. The pattern is similar in Jordan, a neighboring country, while the pattern in U.S. is typical of Western countries with incidence rising proportionally to age.

Figure 2. Age-specific incidence rates for breast cancer from Tanta population registry, Amman population registry and US SEER [derived from Freedman *et al.* 2006]



Age distributions in *cases series*, such as those reported by cancer centers and oncology units, do not provide an accurate idea of the risk of BC at a specific age. Age distributions in cases series are not corrected for the age pyramid of the population. By contrast, *age-specific incidence*, which can only be reported by population-based cancer registries, do provide an accurate idea of the risk of BC by age. Age distributions in age-specific incidence are corrected for the age pyramid of the population. To illustrate this point, the case distribution in Gharbiah Governorate corresponding to the age-specific incidence reported in Figure 2 is displayed in Figure 3 together with the age pyramid of females in Gharbiah Governorate. The cases-series distribution shows a peak at age 45-49. But the general female population at 45-49 is more numerous than the female population 55-59: This obscures that there is a higher BC risk of women 55-59 (the "age pyramid confusing effect"). The age-specific incidence distribution accurately shows a peak at 55-59.

Figure 3. Age distribution in the cases from Gharbiah Governorate diagnosed in 1999-2002.



Thus, to compare age distributions from *cases series* between Egypt and Western countries, as is generally done, is misleading, since the age pyramids are very different. A case-series comparison gives the false impression that BC happens at a younger age in Egypt. This is not the case, as shown in Figure 2: Early onset cases are not more frequent in Egypt than in U.S.; however, late onset cases are much more rare.

This relatively low incidence of BC observed in old generations in Egypt, as in other developing countries, does not need to be attributed to some biological, ethnic or clinical feature of BC specific to these countries. It is most likely the result of the important societal and dietary changes which have taken place in the last three decades: Breast cancer risk factors were low and have rapidly increased (age at first pregnancy, age at menopause, obesity), while protective factors have decreased (number of children per women, breastfeeding durations, physical exercises, age at menarche). Women who are 45 years of age today have many more risk factors for breast cancer than those who are 70 because of the epoch in which they spent their life, so as a result, they have more breast cancer. This is called by epidemiologists

a "cohort effect." This implies that the age incidence curve of BC in countries such as Egypt and the position of its peak may evolve in the coming decades to reach the shape, and slowly the amplitude, of Western countries' curves (see Figure 2).

### 1.3 Mortality

Breast cancer mortality has not been surveyed in Egypt, so data are lacking, and only relatively old estimates are available. Two estimates have been produced, both by WHO entities, WHOSIS and the GLOBOCAN. Both estimates were produced in 2002-2003 and are referred to as "2002 estimates": The general population estimate is that of mid-2002; however, the disease rates are not those measured in 2002 but the most recent available data at the time, from 2-5 years earlier. The first data from a cancer-based registry became available in Egypt in the year 2004, so these data were not available for the GLOBOCAN or the WHOSIS exercises.

#### WHOSIS estimates

The WHOSIS database provides WHO estimates of mortality for all diseases based on version 3 of the Global Burden of Disease (GBD) study, published in the World Health Report 2004 [WHO 2004]; These mortality estimates are based on analysis of latest available national information on levels of mortality and etiology as of late 2003 (For details, see WHO 2004 and Mathers *et al.* 2003).

For BC among Egyptian men and women, 4,300 deaths per year were estimated, which corresponds to a mortality rate of 6.1 in the whole population, i.e., 12.2 if only the female population is considered.

#### GLOBOCAN estimates

The GLOBOCAN database created by IARC in 2002 provides estimates of cancer incidence and mortality for all countries in the world. These estimates are derived from multiple sources, including data from population-based registries (For more details about GLOBOCAN estimates, see Pisani *et al.* 2002, Ferlay *et al.* 2004). GLOBOCAN provides estimates for the year 2002.

For BC among Egyptian women, 4,911 deaths per year were estimated in GLOBOCAN. This corresponds to a crude mortality rate of 14.2, an estimate higher than that provided by WHOSIS (12.2, as reported above).

GLOBOCAN (but not WHOSIS) also provide estimates of the number of cases in 2002. For BC among Egyptian women, there were 6,945 new cases per year. This estimate is much lower than the number of cases derived from the Gharbiah data from the period 2000-2002 (12,240 new cases per year, as reported above). This suggests that the mortality rates provided by GLOBOCAN may be underestimated, as along with the WHOSIS mortality rate, which is even lower than that provided by GLOBOCAN.

If the mortality/incidence ratio provided by GLOBOCAN, which is derived from survival data from neighboring countries, is assumed to be reliable, it can be used to calculate a new mortality burden. The GLOBOCAN mortality/incidence ratio was estimated to be 70.7% for BC among Egyptian women: Applied to the previously stated estimate of 12,240 new cases per year, it corresponds to an estimate of 8,653 deaths by BC per year in Egypt. This estimate is based on Gharbiah data and the GLOBOCAN ratio: The true value may be somewhat different.

#### 1.4 Stage at diagnosis and tumor size

Stage and tumor size at diagnosis are vital when planning early detection programs, as they are the major criteria to assess the efficacy of such a program. Stage and tumor size at diagnosis are a function of both the public's awareness about BC and of the medical services' efficacy in early detection and diagnosis. Stage distribution may vary greatly within the same country because of variations in these two factors.

The population-based stage and tumor-size data for the entire population of cases diagnosed from 2003 to 2006 in Gharbiah Governorate were courteously made available by the Tanta Cancer Registry for the purpose of this report. Data were collected and organized by Dr. Ibrahim Seifeldin and Dr. Mohamed Ramadan and analyzed by Dr. Marilyns Corbex.

The other data presented in this section are based on cases series; they are not population-based. Thus, they cannot be considered perfectly representative of the governorate/locality where they were collected. Variations among these distributions can be due to true geographic variations as well as to a number of uncontrolled variables such as socio-economic status, education, etc. Case series from one hospital department cannot be assumed to be representative of the cases among residents of the area where the hospital is located: For example, very advanced cases may not be included in series from surgery or oncology departments. However, these distributions can provide an approximation of the situation.

The following data come from various sources (publications and internal reports) and include unpublished data courteously provided by investigators Prof. Nadia Mokhtar for NCI-Cairo and Prof. Alaa Kandil for the Alexandria School of Medicine.

There are different ways to measure stage. The SEER summary staging system and the AJCC staging system are the ones used in U.S. and Egypt. As the two systems cannot be merged, data are reported separately in the two following sections. The TNM classification is an intermediate tool in the AJCC staging system, the "T" corresponding to tumor size (see Appendix 3, "Stage & TNM").

When it comes to information related to tumor size, special attention has to be given to missing data. Indeed, patients for whom tumor size is missing are generally very advanced patients (i.e., with metastases) who mostly present with large tumors. In the tables below, the percentage of missing data has been reported whenever possible.

##### *1.4.1 SEER summary stage from Gharbiah cancer registry, comparison with U.S.*

Table 2 gives the stage distribution from the 1,810 BC cases which occurred in Gharbiah Governorate during the period 2000-2002 and from the 2,363 BC cases very recently collected by the registry for the period 2003-2006. The percentage of cases detected at the distant stage (i.e., with metastases) has significantly decreased, from 16.5% in 2000-2002 to 13.9% in 2003-2006 ( $p < 0.04$ ); however, the percentage of cases detected while still at a localized stage has not increased.

The stage distributions observed among white and black women in the U.S. are given for the sake of comparison. The proportion detected at the distant stage (i.e., with metastases) and the regional stage (i.e., spread to lymph nodes and/or direct extension) is high in Egypt compared to the U.S. The distributions among white and black are given to illustrate how socio-economic status and education impact stage at diagnosis. It is well established that black women in the U.S. have a worse stage distribution than white women because of lower socio-economic status and education [NCI fact sheet].

Table 2. Stage distribution of BC in Gharbiah and in U.S., according to the SEER summary staging system

	Gharbiah registry		US-SEER 2000-2005	
	2000-2002 (N=1810)	2003-2006 (N=2363)	whites	Black
SEER staging system				
Localized	25.5%	25.2%	63%	53%
Regional	58.0%	60.9%	31%	37%
Distant	16.5%	13.9%	6%	10%
(Missing)	(15.7%)	(15.2%)	(2%)	(3%)

#### 1.4.2 AJCC stage at diagnosis

Table 3 compiles AJCC stage distribution from the following sources:

- § Raw data about the 2,363 breast cancer cases diagnosed in Gharbiah Governorate from year 2003 to 2006 were graciously provided by Dr. M. Ramadan and Dr. I. Seifeldein for the purpose of this report. These data are the only population-based data presented here, and thus should be considered as the most informative and representative of Egypt. Gharbiah Governorate hosts a mixed urban-rural population. In this population, 57% of cases were diagnosed at a late stage (stage III or IV).
- § An article on "Profile of Familial Breast Cancer in Alexandria, Egypt" published in 2001 by Bedwani *et al.* contained data about stage. In this urban population, up to 55% of cases were diagnosed at a late stage [Bedwani *et al.* 2001].
- § Stage distribution and TNM distribution from 1,013 cases treated at the Medical Research Institute Clinical Oncology Unit in Alexandria were graciously provided by Dr. A. Kandil for the purpose of this report. In this series, 47% of cases were diagnosed at a late stage.
- § A report of the CARE project headed by Dr. Salah E.S. Labib at the MoHP and submitted to the WHO-EMRO office in 2006 described the stage distribution of a large series of BC patients, 31% coming from Greater Cairo, 14% from Upper Egypt and 43% coming from Lower Egypt (Nile Delta and Suez). 30,288 new BC cases were registered between June 2003 and May 2006. However only 18.7% met the criteria for full registration (ID, pathological report, stage, grade, TNM); thus, the number of cases for which stage data were reported are only 5,681. During the period 2003-2006, up to 69% of cases were diagnosed at a late stage.

Table 3. Stage distribution from various cases series.

Reference Location	Ramadan <i>et al.</i> * Gharbiah Gov. Pop-based data	CARE project All Egypt	Bedwani <i>et al.</i> 2001 Alexandria	Kandil <i>et al.</i> * Alexandria
Sample	2363 cases	30288 cases	3250 cases	1013 cases
Year	2003-2006	2003-2006	1989-1998	1990-2004
Stage I	5.5%	2%	3.5%	5%
Stage II	37.1%	29%	42%	48%
Stage III	44.1%	24%	44%	47%
Stage IV	13.3%	45%	10%	0%
(Missing)	(18.2%)	(81%)	(no information)	(no information)
Late stage	57%	69%	54%	47%

\* Personal communication

The proportion of late stage cases varies from 47% to almost 70%. To give a reference, in Canada where a screening program is implemented, 15% of cases were diagnosed at stage III or IV in 2006.

### 1.4.3 Tumor sizes

Table 4 compiles tumor-size distribution retrieved from published articles or from sources mentioned above. The data from the Gharbiah cancer registry are population-based and, as such, can be considered as the most representative of the situation in Egypt. In Gharbiah Governorate the mean tumor size is 4.2 cm, and the proportion of tumors equal to or below 2 cm is 12%. The range of tumor varies from 0.2 to 24 cm.

It must be noted that the mean tumor size detected by a woman who regularly examines her breast is 2 cm, and the mean tumor size found by a doctor or nurse giving a clinical breast exam is 1.5 cm.

Table 4. Tumor sizes from various sources

Reference	Ramadan <i>et al.</i> * 2009	Nouh <i>et al.</i> 2004	Mokhtar <i>et al.</i> 2007	Kandil <i>et al.</i> * 2008	Elzawawi <i>et al.</i> 2008
Location	Gharbiah Gov. Pop-based data	Cairo	Cairo	Alexandria	Port Said
Sample	2,363 BC cases	3,747 BC mastectomies	1,721 BC cases (pathology dept.)	1,013 BC cases	348 BC cases
Year	2003-2006	1993-2003	2003-2004	1990-2004	2004-2006
Tumor size					
≤2 cm	12%	8%	-	10%	20%
2-5 cm	47%	33%	-	62%	66%
>5 cm	15%	17%	-	26%	9%
Missing	27%	41%	-	2%	5%
mean	4.2 cm	2.8 cm	3.2 cm	-	-
range	0.2 cm-24 cm	0.5 cm-20 cm			
median	4 cm	3 cm			

\* Personal communication

### 1.4.4 Conclusion on stage and tumor size

The present data shows that BC is still diagnosed very late in Egypt, and that the proportion of cases diagnosed at a localized stage, when the disease is still easily treatable, is low. Even in the best situation, 80% of the tumors diagnosed are above 2 cm, a tumor size which a woman can detect easily by herself. This suggests that there is room for improvement by simply raising awareness about breast cancer in the population.

It is well established in developing countries, as well as in western countries, that late stage at presentation is positively correlated to low SES and rural residence [Aziz *et al.* 2008; Jemal *et al.* 2004]. This correlation seems to exist in Egypt also: Case series from urban areas (Alexandria, Port Said) display better stage and tumor size than mixed urban / rural areas (Gharbiah). Because they are population-based and because they cover urban and rural areas, the data from Gharbiah are expected to be the most representative of the country situation.

Stages and tumor sizes are the most important indicators for early detection of BC. They are the best indicators of the efficacy of any early detection program. As such, they need to be measured carefully before the implementation of the program and thereafter thoroughly monitored.

1.5 Survival and treatment

Survival data are crucial for assessing the efficacy of care and treatment received by cancer patients. Very little has been published about breast cancer survival in Egypt, with most information stemming from clinical trials, i.e., testing of new medications/treatment modalities. These data are not expected to represent the actual survival rates. Not only are clinical trial participants treated according to new/experimental treatment modalities, but also likely to receive much better than average follow-up and medical care. Moreover, no publications provide data on survival according to the stage at diagnosis in Egypt, although this is a primary determinant of survival. For example, U.S. data (Table 5) show that nearly all of breast cancer cases survive to 5 years if the cancer is detected at a localized stage versus only one-fourth of cases if detected with metastases (Distant stage).

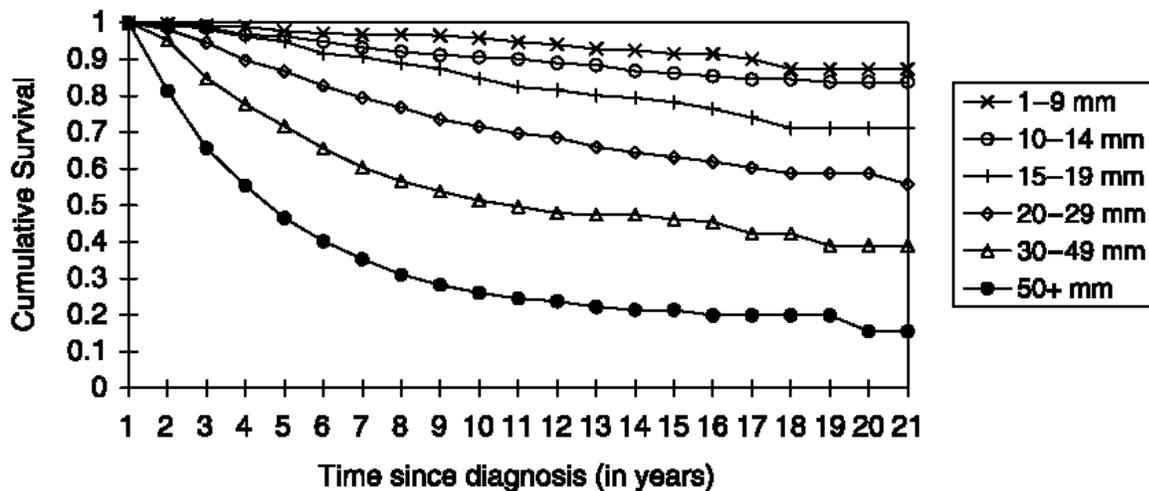
Table 5. Five-year relative survival rates according to stage in the U.S. (SEER data)

SEER staging	5-year relative survival (2000-2005)
Localized	98.1%
Regional	83.8%
Distant	27.1%

When planning an early detection program, it is important to also track survival according to tumor size, as tumor size is the most important determinant of detection. The 20-year survival rates according to tumor size observed in Sweden from 1980 to 2001 are displayed on Figure 4 [from Duffy *et al.* 2006].

Interestingly, the 20-year fatality rates for women with tumor sizes of 1-9 mm and 1-1.4 cm do not differ substantially (13% and 16%, respectively). While mammography is required to detect lumps of 1 mm to 9 mm, many lumps 1-1.4 cm can be detected by clinical breast exam, depending on the size and texture of the breast [IARC 2002].

Figure 4. 20-year survival in a cohort of 2,294 Swedish BC patients followed up between 1980 and 2001



Egyptian survival data reported below derive from a thorough review of the international scientific literature, Internet-registered local literature, and all postgraduate theses defended at NCI-Cairo since 1985.

- § A study done at NCI-Cairo on 400 patients treated between 1994 and 1998 reported an observed 5-year survival of 60% in the whole sample, with the tumor size distribution of these 400 patients being as follows: 13% below 2 cm, 54% between 2 and 4 cm, and 33% above 4 cm. No survival by tumor size was provided [Omar *et al.* 2003].
- § A study done at NCI-Cairo on 60 patients with T1-T2, N0-N1, M0 stages (i.e., stage I and early stage II) displayed a disease-free survival of 83% at 5 years and 78% at 10 years [El Naggar *et al.* 1999].
- § A study done at NCI-Cairo on 408 patients treated between 1983 and 1987 reported a 4-year survival of 61% for T1 (0-2 cm tumors) patients and 20% for T4 (large, ulcerated or attached tumors) patients [Omar *et al.* 2003].

The above data can not be generalized at the national level, because the cases studied may not be representative and because these data are limited to only one hospital. On the other hand, they suggest that there could be room to increase breast cancer survival in Egypt by improving treatment. The interviews of Egyptian cancer clinicians and international clinicians conducted for the purpose of this report support this view: Some economic barriers to optimum treatment exist (for example: expensive chemotherapy drugs replaced by cheaper but not so efficient ones because the patient cannot afford more), and sometime the available resources are not used in an optimum way, creating an opportunity for improvement without increasing resources.

However, data are lacking and a survey that appropriately categorizes survival by stage is needed in order to identify the main gaps and where improvement can be obtained within the existing economic constraints.

## 1.6 Risk factors of BC

The majority of the risk factors of BC are not modifiable, meaning that prevention strategies have a very limited potential to reduce BC incidence [IARC 2002]. Modifiable risk factors include diet and other environmental factors; non-modifiable risk factors include reproductive factors, familial history and few other factors. A review of these factors is presented below based on studies performed in Western countries. However the magnitude of the increase in risk associated to a factor is an inner characteristic of this factor and is not assumed to vary widely across populations. This magnitude is measured by the Odd Ratio (OR): an OR of 2.5 means, for example, that having the factor multiplies one's risk of BC by 2.5 compared to someone who does not have the factor. What varies from one population or country to the other is the prevalence of risk factors. Prevalence estimates for each risk factor in Egypt are reported when available.

Various sources for prevalence of risk factors in Egypt were reviewed including scientific articles, reports and WHO estimates. Data on fertility/parity, age at first birth, breastfeeding and consanguinity are based on the 2005 Egypt Demographic and Health Survey (EDHS 2005) which was conducted on a sample of 106,600 subjects representative of the general population [EDHS 2005 report]. Data on physical activity and overweight/obesity prevalence are based on the WHO Surveillance of Chronic disease Risk Factors Second Survey [WHO SURF-2 report]

### 1.6.1 Reproductive factors

#### Parity

The effect of parity on reducing the risk of BC has long been recognized. Meta-analyses show that nulliparity is associated with a 30% increase in risk (OR=1.30) compared with parous women [Ewertz *et al.* 1990]. The higher the number of full-term pregnancies, the greater the protection. For each birth after the first, BC risk is reduced by 7% in the absence of breastfeeding [Collaborative group, Lancet 2002].

#### In Egypt

Parity can be captured by the country's total fertility rate (TFR). The TFR corresponds to the number of children a woman would have by the end of her childbearing years if she were to pass through those years bearing children at the currently observed rates. The TFR of Egypt as measured by the EDHS 2005 is relatively high at 3.1. For comparison, the 2008 TFR reported by the CIA World Factbook for U.S., Tunisia and Italy were 2.1, 1.93 and 1.38, respectively.

TFR varies substantially between social groups in Egypt (Table 6). As in most parts of the world, fertility is lower among urban, educated and wealthy social groups.

Table 6. Total fertility rate in various social groups in Egypt (EDHS 2005)

Groups	Residence		Education		Wealth quintile	
	urban	rural	none	secondary complete/higher	lowest	highest
TFR	2.7	3.4	3.8	3.0	3.6	2.6

Geographic variations in the TFR observed in Egypt reflect the social composition of the governorates (see Table 7). Thus, TFR is highest in Upper Egypt and lowest in urban governorates.

Table 7. Total fertility rate across Egypt (EDHS 2005).

Place of residence	Urban governorates	Lower Egypt	Upper Egypt	Frontier governorates
TFR	2.5	2.9	3.7	3.3

Fertility has continually declined in Egypt, with TFR reported by the EDHS surveys declining from 4.4 in 1988 to 3.6 in 1995 and to 3.1 in 2005. This explains some of the increase in BC incidence that takes place in Egypt.

#### Age at first birth

The younger the woman is when she begins childbearing, the lower her risk of BC. Women who have their first child at age 35 years versus age 20 years have approximately twice the risk of developing BC. The relative risk of developing BC increases by 3% for each year of delay [Clavel-Chapelon 2002].

*In Egypt*

The median age at first birth in Egypt as measured by the EDHS 2005 is 22.4. As with the TFR, age at first birth varies according to social variables; thus, geographic variations reflect the social composition of the governorates (tables 8 and 9). In Egypt, as in most parts of the world, age at first birth increases with education and wealth.

Table 8. Median age at first birth in various social groups in Egypt (EDHS 2005)

groups	Residence		Education		Wealth quintile	
	urban	rural	none	secondary complete/higher	lowest	highest
Median age at first birth	23.7	21.3	20.3	24.6	20.3	24.8

Table 9. Median age at first birth across Egypt (EDHS 2005)

Place of residence	Urban governorates	Lower Egypt	Upper Egypt	Frontier governorates
Median age at first birth	24.3	22.3	21.3	23.0

The median age at first birth has slowly increased throughout generations. Women who were 30-35 in 2005 and women who were 55-59 displayed a median age at first birth of 22.8 and 20.3, respectively.

**Breastfeeding**

Women who breastfeed reduce their risk of BC compared with women who do not breastfeed. The longer a woman breastfeeds, the greater the protection: Risk is reduced by 4.3% for each year a woman breastfeeds. It is recognized that the lack of or short lifetime duration of breastfeeding typical of women in developed countries makes a major contribution to the high incidence of BC in these countries [Collaborative group, Lancet 2002].

*In Egypt*

Breastfeeding is much more prevalent in Egypt than in Western countries. The proportion of children ever breastfed in Egypt has remained stable at approximately 95% over the last decade. There is little variation across social groups and governorates [EDHS 2005]. A detailed study conducted in 1995 (EDHS 1995) showed that 79% of children were still breastfed at age 12-13 months, and 51% were still breastfed at 18-19 months. Thereafter, weaning took place rapidly, with less than 17% still breastfed at 25 months.

**Age at menarche**

Early age at menarche has been consistently shown to be associated with an increased risk of BC. Average age of menarche in Western countries fell from around 16-17 years in the mid 19th century to 12-13 in the seventies [Tanner 1973]. Relative risk for premenopausal BC is reduced by an estimated 7% for each year that menarche is delayed after age 12 years and postmenopausal BC is reduced by 3% [Clavel-Chapelon 2002]. Nutrition in early life strongly influences age of menarche. Low-income countries such as Bangladesh, Senegal, and Nigeria have a later mean age at menarche (15.8, 16.1 and 15,

respectively) than high-income countries such as U.S., France, and Italy (12.8, 13 and 12.2, respectively) [Thomas *et al.* 2001].

#### *In Egypt*

Mean age at menarche in Egypt varies between 12 and 13 according to studies [Attallah 1978, Ismail *et al.* 1998, Torres-Mejía *et al.* 2005, Mounir *et al.* 2007]. As in many countries, age at menarche may be higher in low socio-economic groups: A study performed in 1978 among 1365 Egyptian girls, showed that the mean age at menarche was 12.6 +/- 0.3 for upper-class girls in Cairo; 13.1 +/- 0.2 for the middle-class girls in Cairo; 13.9 +/- 0.2 for rural agricultural areas [Attallah 1978]. Earlier age at menarche is also associated with being overweight/obese and with urban habitat [Torres-Mejía *et al.* 2005].

#### Age at menopause

Late menopause increases the risk of BC [Kelsey *et al.* 1993]. For each year menopause is delayed, there is an approximate 3% increase in BC risk [Collaborative group, Lancet 1997]. Postmenopausal women have a lower risk of BC compared to premenopausal women of the same age. This is true for both natural menopause and menopause induced through surgery [Collaborative group, Lancet 1997]. Age at menopause varies among countries, being on average lower in less developed countries. For example, the average age at menopause reported for U.S., France, Sweden are 51.3, 52 and 50.9 years, respectively, while age at menopause reported for U.A.E., Philippines and Ghana are 47.3, 48 and 48.5, respectively [Thomas *et al.* 2001]. It is suspected that age at menopause is influenced by number of children and other reproductive-life variables like age at first and last pregnancy [Thomas *et al.* 2001].

#### *In Egypt*

Mean age of menopause in Egypt ranges between 43 years and 51 years according to the studies retrieved, this large variability being attributable to the populations studied (various governorates, various socio-economic level). Gadalla *et al.* reported a mean age of 45.2 years for Sharkia Governorate [Gadalla *et al.* 1986]. Eshra *et al.* reported a mean age of 43.1 years for Menoufia [Eshra *et al.* 1989]. In Alexandria, Nasr reported a mean age of 45.8 years in 1988 [Nasr 1988] and Kandil *et al.*, a mean age of 49.0 +/- 4.4 years in 1999 [Kandil *et al.* 1999]. Sayed *et al.* reported a mean age of 50.8 for Upper Egypt in 2000 [Sayed *et al.* 2000]

Furthermore, data suggest that age of menopause may be substantially increased among rural versus urban and lower versus higher educated populations. A study of 289 women in Alexandria, for example, found that semi-urban women reached menopause on average 6 years earlier than urban women (41.2 ± 5.6 years and 47.2 ± 5.1 years, respectively). In this study, age at menopause was significantly higher among highly educated women (49.5 ± 4.1 years) compared with those who were less educated (46.2 ± 4.4) or illiterate (46.3 ± 5.6 years).

### 1.6.2 Modifiable factors

#### Diet and body weight

A diet high in fat has been positively associated with BC in international correlation studies [Rose *et al.* 1986], animal studies [Welsch *et al.* 1992], and case control studies [Howe *et al.* 1990]. The evidence suggests that increased intake of fat, particularly animal fat, may cause a modest increased risk of BC. Overweight and obesity, as measured by high body mass index (BMI), moderately increase the risk of postmenopausal BC and are among the few modifiable risk factors for BC [Van den Brandt *et al.* 2000]. BMI is calculated by dividing weight in kg by the square of the height in meters: A BMI of less than 20 is classified as underweight, 26-30 as overweight, and greater than 30 as obese. In one pooled analysis, the

risk of developing BC was increased by around 30% in postmenopausal women with a BMI >28kg/m<sup>2</sup> compared to a BMI of less than 21kg/m<sup>2</sup> [Van den Brandt *et al.* 2000].

In premenopausal women, some but not all studies have observed that a higher BMI is associated with a slightly lower risk of BC – possibly because it results in decreased exposure to endogenous estrogens through increased anovulatory cycles [Bergstrom *et al.* 2001, IARC 2002].

#### *In Egypt*

Obesity is a major public health concern in Egypt. The results of the WHO SURF-2 study show that 69.7% of women above 15 years are overweight (BMI>25) in Egypt, a percentage comparable to of the rate in the U.S. (69.8%) but higher than those of European countries (France, 33.4%; Italy, 37.8%; Sweden, 43.3%) or other neighboring countries (Morocco, 53.0%; Tunisia, 65.4%; Libya: 56.0%) [WHO SURF-2 report]. The prevalence of being overweight seems to increase with age among Egyptian women, for example, a study performed in 1999 in Alexandria among 289 menopausal women revealed that the large majority (97%) of the women were overweight, with 8% being moderately overweight (BMI 25 to 29.9), 57% being obese (BMI 30 to 39.9) and 32% being morbidly obese (BMI>40) [Hidayet 1999].

#### Physical activity

A report from the International Agency for Research on Cancer concluded that physical activity has a preventive effect on BC [IARC 2002]. This may be an indirect effect with exercise lowering BMI, or a direct effect on hormonal and growth factor levels. The magnitude of this effect varies between studies; a typical result would be a 30-40% reduction in the risk of BC for a few hours of vigorous activity per week compared to no exercise at all [Key *et al.* 2001].

#### *In Egypt*

The majority of women in Egypt live a sedentary lifestyle. For example, a study of 6,052 households in Cairo and three rural villages in the Delta region revealed that the prevalence of sedentary lifestyle was 48% among women aged 22-45 years and 70% among women aged 45 years and older. The proportion of sedentary people (men and women) was lower in rural areas (52%) compared to urban areas, and lower in low-socio-economic status (SES) urban areas (73%) compared to high-SES urban areas (89%) [Herman *et al.* 1995]. These rates are higher than those observed in the U.S. and Europe (where about 20% of women have sedentary lifestyles) [WHO SURF-2 report]

#### Contraceptives

The use of oral contraceptives (OC) slightly increases the risk of BC in current (42% increase in risk) and recent users (16% increase in risk), but there is no significant excess risk ten or more years after stopping use [Collaborative group, Lancet 1996]. These estimates are based on a collaborative analysis of 54 studies in 25 countries, with data on more than 50,000 women with BC. Cancers diagnosed in women who have used OC tend to be less clinically advanced than those detected in never-users. The formulation of OCs has changed considerably since use became widespread in the 1960s, but current evidence suggests these changes have not affected risk [Collaborative group, Lancet 1996]. The risk of oral contraceptive use in women is similar regardless of family history, ethnic origin, years of education, age at menarche, height, weight, menopausal status or alcohol consumption [Collaborative group, Lancet 1996].

#### *In Egypt*

According to the EDHS 2005 report, the proportion of married women who currently use hormonal contraceptives in Egypt is 16.8% (9% oral contraception, 7% injectables and 0.8% implants). The prevalence of oral contraception (9%) is lower than the mean prevalence reported for North Africa (17%) or the U.S. and Canada (15%) and much lower than that observed in Europe (48%) [IARC 2007]. In Egypt, the prevalence of the use of hormonal contraceptives varies mainly according to residence (19%

among rural women and 16% among urban women) and according to wealth (22% in women of the lowest quintile and 13% in women of the highest) [EDHS 2005].

#### Hormone replacement therapy (HRT)

HRT use increases the risk of BC and reduces the sensitivity of mammography [IARC 2007]. The risk of BC for current users of HRT is 66% higher than for never-users [Beral 2003]. Risk increases with duration of use and decreases with cessation of use; past users have a similar risk to never-users. HRT is used by more than 20 million women in Western countries to counteract menopausal symptoms and protect against osteoporosis and possible consequent fractures. HRT may also protect from colorectal cancer [Beral 2002]. Risks and benefits of using HRT for the treatment of menopausal symptoms should be assessed on an individual basis.

#### *In Egypt*

HRT is rarely used in Egypt. A study conducted in Sohag Governorate among 500 menopausal women, of whom 69% were rural residents, showed that only 4.2% of the women had received HRT, mainly for relief of hot flashes and only for short periods. A community-based survey of 302 women in Upper Egypt in 2000 revealed that prevalence of HRT was very low and that most women were not willing to use it and described it as "unnecessary" [Sayed *et al.* 2000].

#### Alcohol

A significant association between alcohol intake and BC has been found, with an increase of risk of 7% for each alcoholic drink consumed on a daily basis [Hamajima *et al.* 2002]. Around 4% of breast cancers among women in developed countries may be attributed to alcohol. Although alcohol and tobacco smoking are closely related social habits, there is no direct association between tobacco and BC.

#### *In Egypt*

No study reporting prevalence of alcohol consumption among Egyptian women has been retrieved. However, it is assumed to be low, and therefore the fraction of breast cancer attributable to alcohol consumption in Egypt is likely to be insignificant.

#### Ionizing radiation

Ionizing radiation is an established risk factor for BC and excessive exposure to radiation should be avoided. The effect of radiation on the breast is strongly related to age at exposure (i.e., the younger the woman is exposed, the greater the risk). A study estimated that exposure to diagnostic x-rays may be responsible for 0.6% to 1.8% of all BC in the 13 developed countries studied, whereas in Japan, which had the highest estimated annual exposure frequency in the world, it was more than 3%. [Berrington & Darby 2004]

#### *In Egypt*

No study reporting level of exposure to ionizing radiation in Egyptian women has been conducted to date. However this level is assumed to be low, and the fraction of BC attributable to x-ray exposure in Egypt may be insignificant.

### 1.6.3 Familial history, gene and consanguinity

#### Familial history

Research has shown that women with a family history of BC have a higher risk of developing the disease. This occurs regardless of whether the family history is on the mother's or father's side, and is stronger if female patients are diagnosed before the age of 50. A collaborative reanalysis of individual data from 52 epidemiological studies showed that a woman with one, two, and three or more affected first-degree relatives (mother or sister) have a risk of BC multiplied by 1.8, 2.9 and 3.9, respectively [Collaborative group, Lancet 2001].

However, more than 85% of women who have a close relative with BC will never develop the disease, and more than 90% of women with BC have no family history [Collaborative group, Lancet 2001]. In developed countries, it is estimated that hereditary factors contribute around a quarter of inter-individual differences in susceptibility to BC, while environmental and lifestyle factors contribute the remaining three-quarters [Key 2001].

#### *In Egypt*

The fraction of BC attributable to familial history may be a little higher in Egypt than in Western countries because of the lower fraction attributable to reproductive factors. As a result, Egyptian BC patient may have familial history more often than Western patients. This assumption is supported by a study done by the Alexandria Cancer Registry in 2001 on 3,250 cases of BC. The prevalence of familial history among these cases was 12%. Familial history was significantly higher among young BC patients (<40) reaching 20%. The proportion of patients with familial history was lower in urban women (9%) compared to rural women (21%). Furthermore, it was lower in women with professional/managerial occupation (10%) than among unskilled workers (16%) [Bedwani *et al.* 2001].

#### BRCA1 and BRCA2

A small proportion of women have a particularly strong family history of BC, with four or more affected members. Mutations in the BC susceptibility genes BRCA1 and BRCA2 account for the majority of these families and for 2-4% of all breast cancers [Ford *et al.* 1998]. BRCA1/2 mutations are rare, with a worldwide frequency of BRCA1/2 mutations estimated as 0.10% to 0.25% of women [Chompret, 2004]. The risk to develop breast cancer is 50% to 80% for BRCA1 carriers and 40% to 70% for BRCA2 carriers [Goldberg & Borgen 2006].

#### *In Egypt*

##### BRCA1 and BRCA2:

No study to date has documented the frequencies of BRCA 1 and 2 genes in the Egyptian population; however these frequencies are not expected to be different than in the rest of the world, i.e., 0.10% to 0.25%.

#### Consanguinity

The offspring of a marriage between relatives is said to be consanguineous. Consanguinity is a risk factor for many diseases. Consanguinity as a risk factor of breast cancer has only been examined in one study of 341 BC patients and 200 controls from Pakistan. In this study, the risk of early onset BC (before age 40) was multiplied by 2.7 in consanguineous women, while the risk of post-menopausal BC was not significantly increased [Liede *et al.* 2002]. In a study of effect of consanguinity on adult diseases performed on 825 outpatients from Islamabad Hospital (Pakistan), the authors observed an increased consanguinity in their series of 58 cancer patients. In this study, 15 BC patients out of 20 (75%) were consanguineous, while consanguinity in Pakistan is 50-60% [Shami & Bittles 1991].

### *In Egypt*

Consanguineous marriages are common in Egypt, representing one-third of all marriages according to EDHS 2005. Marriages among first cousins are the most frequent type of consanguineous marriages and represent 9% of all marriages. Consanguineous marriages are more common in rural (38%) than in urban areas (24%). They are also more common for less educated women (41% for women with no education versus 24% for women who complete secondary or higher education) and among the poorer classes (43% for the lowest wealth quintile versus 20% for the highest). Proportion of consanguineous marriages has slightly decreased with time: 30% of the married women aged 45-49 years in 2005 were married inside the family versus 25% of the married women aged 20-25 years (EDHS 2005). However, the high increase of risk (OR=2.7) observed in the Pakistan study suggests that women with blood-related parents should be considered at higher risk than women with familial histories of BC. This question surely deserves further research, some of which could be conducted in Egypt.

#### *1.6.4 Other factors*

##### Socio-economic status

BC is one of the few cancers to have a higher incidence in the more affluent social classes. SES captures a substantial part of the intra-population variability of BC risk factors, including reproductive history and nutrition [Bigby & Holmes 2005]. Differences in SES and urbanization appear to largely explain differences in incidence rates at regional level within Western countries. For example, the variation of BC incidence within California is almost entirely captured by SES variation [Reynolds *et al.* 2005], with women from the San Francisco Bay Area, a highly urbanized and wealthy area, experiencing an incidence of BC 20% higher than the rest of California.

Furthermore, it has been widely documented in Western countries that women of lower SES present with more advanced disease stages than women of upper SES. SES is also related to BC mortality and survival rates, mortality being higher in women of lower SES [Baquet & Commiskey 2000].

### *In Egypt*

No study has been performed correlating SES with BC incidence, stage at presentation and survival. However, such a study would be of high interest given the very large disparities in SES that exist in Egypt.

##### Mammographic density of the breast

High mammographic density is associated with higher risk of BC. (Density relates to the relative amounts of fat, connective tissue and epithelial tissue in the breast. Breasts with a higher proportion of fatty tissue are less dense. Cancer is less easily detected in denser breasts.) Women with denser breasts have 2-6 times the risk of BC compared to women with less dense breasts [Boyd *et al.* 1995]. It is estimated that 20-30% of the variation in breast density is accounted for by menopausal status, weight and parity [Boyd *et al.* 2002] and there is growing evidence that the more important determinant of breast density is inherited [Boyd *et al.* 2002; Ziv *et al.* 2003].

### *In Egypt*

No study describing breast density among Egyptian women has been published to date. Some data are available but have not yet been fully analyzed [Dr. Gewefel, personal communication].

##### Benign breast disease and BC risk

Benign breast disease is a generic term describing all non-malignant breast conditions. As such it encompasses diseases associated with an increased risk of BC and others that do not have a raised risk.

The most common breast lump in young women is a fibroadenoma which is not associated with an increased risk of BC. Women in their 30s and 40s may develop cysts and those that suffer multiple cysts are at slightly increased risk of BC. Women who have had biopsies that showed proliferative breast disease without atypia have a twofold increased risk, while the risk for women with atypical hyperplasia is increased two- to fivefold [Byrne *et al.* 2000, Dupont & Page 1985].

#### *In Egypt*

No study describing prevalence of the various benign breast diseases in the Egyptian population has been published to date.

#### *1.6.5 Factors which do not increase risk of BC*

There are a number of misconceptions about what can cause BC. These include, but are not limited to, having a miscarriage or induced abortion, using deodorants or antiperspirants, using mobile phones, wearing a bra, drinking a large amount of coffee, drinking beverages in plastic bottles (exposed to heat or not), and bumping or bruising breast tissue. None of these factors have been shown to increase the risk of BC [NCI Fact Sheets & NCI summary report 2008].

Air and water pollution, pesticides and fertilizers have been studied quite extensively and have not been shown to increase significantly the risk of BC, either [Boffetta 2004].

The effects of tobacco smoking and passive smoking on the risk of BC have been controversial. The most recent authoritative reviews conclude that an increase in risk has not been demonstrated but cannot be totally ruled out. However, any increase in risk associated with tobacco is likely to be very small [Pirie *et al.* 2008]. Last but not least, cancer is not contagious: No one can "catch" cancer from another person.

#### *In Egypt*

Misconceptions about BC have not been formally evaluated in Egypt, neither in the general populations nor among health staff. However, misconceptions about risk factors may be common, as is the case in many countries.

### *1.7 Conclusion about epidemiology of BC in Egypt*

The most important determinants of risk of BC, besides age, are reproductive factors (number of children, age at first child, breastfeeding duration, age at menarche and age at menopause). However, it should not be concluded that family planning may have some negative impact on women's health because of its potential to increase BC risk factors. Family planning has been proven to decrease the risk of many diseases (including cervical cancer) and to improve women's health and quality of life.

The important geographical variations of BC incidence observed across the world are mainly due to variation in the reproductive factors [Parkin & Fernández 2006]. For example, it is estimated that the incidence of breast cancer in developed countries would be reduced by more than half if they shared the same average number of births and lifetime duration of breastfeeding that were prevalent in developing countries in the 1990s [Collaborative group, Lancet 2002].

Geographical variation due to variation in reproductive factors may also exist within Egypt. Actually more than geographical variations per se, they correspond to socio-economic level variations since reproductive factors involved in BC risks are foremost dependent on socio-economic and education levels. Rural and low-SES women are expected to have lower risk of BC, however, if less at risk for BC, rural and low-SES women are, in Egypt as everywhere in the world, more at risk of being diagnosed late and to die from the

disease. Thus the lower incidence expected in rural areas, for example, should not result in lower effort in early detection for these populations.

Finally, the serious increase in BC risk associated with consanguinity that has been reported in Pakistan is highly relevant to Egypt, where one-third of all marriages are consanguineous. Because consanguinity is very rare in Western countries, it has been little studied; its effect on BC clearly deserves more research, some of which research should be conducted in Egypt.

## 2 BARRIERS TO EARLY DETECTION AND DIAGNOSIS IN EGYPT (BED-BC-Cairo study with BCFE)

### 2.1 Objective and methods of the BED-BC-Cairo study

The purpose of the BED-BC-Cairo study was to assess which obstacles to early diagnosis of breast cancer (BC) are more significant for women in Egypt, be they socio-cultural, economic, or logistical or whether they are health-system related. The detailed objectives were:

- § To identify and measure women's barriers due to lack of knowledge and awareness (knowledge of BC symptoms, reduced perceived risk, etc.)
- § To identify women's psycho-cultural barriers (fatalism, anxiety, denial, wishful thinking, etc.)
- § To identify women's socio-cultural barriers (husband's attitude, traditional healer, stigma, etc.)
- § To identify and measure structural and logistical barriers (accessibility and affordability of health services)
- § To identify barriers due to health-system shortages (efficiency of health services)

To answer these questions, 204 breast cancer female patients were recruited at the National Cancer Institute and the BCFE office in Cairo. Women were recruited as soon as possible after diagnosis and not more than one year after diagnosis. They were interviewed by one sociologist according to a peer-reviewed questionnaire including 70 questions regarding:

1. medical journey
2. personal journey and socio-cultural aspects

All the questions related to knowledge and awareness of BC aimed at measuring patients' understanding before the disease. Therefore, before each question, patients were clearly reminded "before being concerned with BC" or "before your first symptoms."

Up to 302 variables were collected and entered into EpiData. Statistical analyses were performed with SAS software. Explained variables included 1., delays between first symptoms and first visit to a doctor; 2., delay between first visit to a doctor and effective diagnosis; 3., delay between effective diagnosis and beginning of treatment; and 4., patients' awareness about the cancerous nature of their disease. Explanatory variables included socio-economic status (education level and economic capacity), demographic variables (age, marital status, residence, household, etc.), awareness and beliefs (knowledge about BC, stigma, modesty issues, etc.), and behaviors and attitudes (what women do, what they share about their disease and with who, etc.). Associations between explained and explanatory variables were analyzed using univariate and multivariate logistic and linear regressions, including stepwise selection of variables.

The study was designed by Dr. Corbex for BCFE. Mrs. Joanne Mc Ewan of BCFE participated in the design of the questionnaire, conducted the interviews, extracted information from medical records and performed the data entry. Dr. Corbex designed the protocol and questionnaire, ensured the data management, and performed the statistical analyses.

### 2.2 Characteristics of the sample

The stage distribution and the mean tumor size in the sample are presented in Table 10. They were comparable to the those observed in other Egyptian series (see Section 1.4)

Table 10. Stage distribution and the mean tumor size in the sample

	BED-BC-Cairo Sample	National figures*
Late stage (III & IV)	58%	47% to 90%
Tumor size > 2 cm	85%	80% to 96%

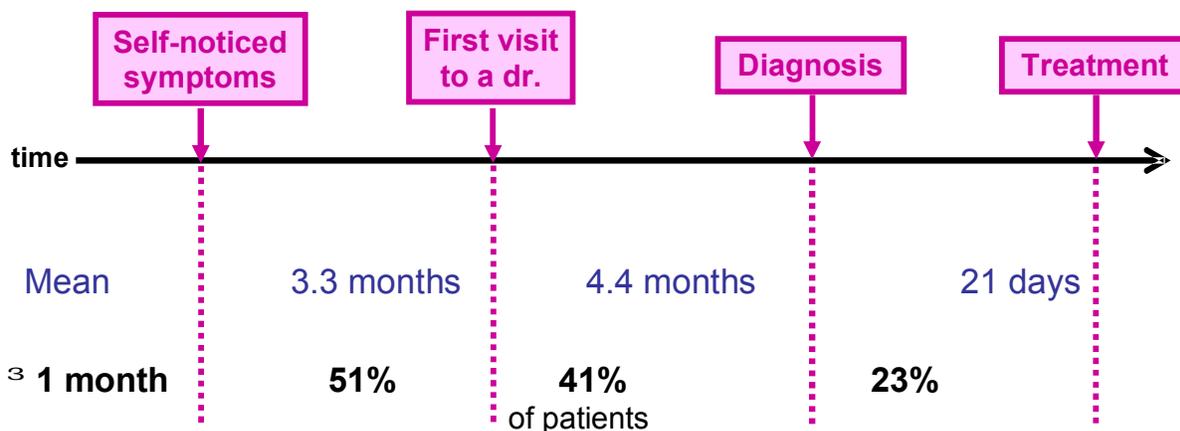
\*See tables 3 and 4 in Chapter 1.4.

As expected, patients in the sample were relatively young, with 57% of them below 50, a proportion comparable to what was observed in other cases series in Egypt (see Section 1.4). The proportion of illiterate women in the sample was 40%, which is below the national figure in the same age group, 57% [EDHS 2005]. Patients were from low/middle-income, with 70% of the households living on less than 500 LE per month, and only half of them owning an automatic washing machine. All households in the sample lived on less than 3,000 LE per month.

### 2.3 Results about delays

Patient journey through the disease was divided according to four milestones: 1., self-noticed symptoms; 2., first visit to a doctor; 3., pathological diagnosis of cancer; and 4., beginning of treatment. These milestones defined three key delays which are represented in Figure 5. The delay between discovering symptom and consulting a doctor was relatively long (mean=3.3 months, median=31 days). The delay between the first visit to a doctor and effective diagnosis was comparable (mean=4.4 months, median=19 days), and surprisingly long for some women, reaching more than three months for 26% of them and even more than a year for 12% of them. The delay between diagnosis and treatment was less than two weeks in 50% of patients. However, up to 23% of women waited more than one month before being treated.

Figure 5. Mean duration of delays



The duration of delays between first symptom and diagnosis were correlated with tumor size and stage at diagnosis. The determinants of the three types of delays were investigated in a systematic ways, the results are detailed thereafter.

### 2.3.1 Determinants of delay between symptoms and consultation with a doctor

The univariate analyses revealed that the most important reason for delay between first symptoms and first consultation with a doctor was low breast cancer awareness and knowledge. All the variables measuring knowledge and awareness about BC were strongly associated to delayed consultation (see Table 11). Delays were a little less than doubled in women with poor BC awareness compare to the other women. The women's education level was not significantly associated to delayed consultation but was significantly associated to variables measuring BC knowledge.

Table 11. Knowledge about BC and delay between first symptoms and first consultation with a doctor

	N	Mean delay in months	patients with delay $\geq 31$ days	p-value*
<i>All women</i>	202	3.3	50%	
1. Before being concerned, did you know that a lump is a symptom of BC?				
Yes	93	2.4	39%	p<0.004
No	95	4.1	60%	
2. After discovering your breast change, did you think it could have been BC?				
Yes	56	1.8	30%	p<0.002
Not really	85	2.5	54%	
I did not know about BC	49	4.1	64%	
3. Before meeting any doctor did you know the importance of being treated as soon as possible?				
Yes	122	2.8	41%	p<0.002
No	66	4.2	65%	
4. Before discovering your breast change, had you ever read an advertisement or pamphlet on BC or watched or heard a TV/radio program?				
Yes	98	2.9	42%	p<0.03
No	90	3.7	58%	
5. Before being concerned, did you ever receive any personal education on BC ?				
Yes	21	2.1	29%	p<0.05
No	167	3.4	52%	

\*p-value corresponds to percentages comparisons (patients with delay  $\geq 31$  days)

While consulting a non-medical doctor as a first step was quite unusual action (3.5% of women visited a pharmacist, and 2% visited an herbalist or traditional therapist), it was significantly associated with delayed consultation (see Table 12). Ten out of the 12 women who visited a non-medical therapist delayed medical consultation more than two months after symptoms.

Table 12. Determinants of delay between first symptoms and first consultation with a doctor.

	N	Mean delay in months	patients with delay $\geq 31$ days	p-value
After discovering the symptoms, did you speak about your breast to a non-medical doctor/therapist?				
Yes	12	3.2	83%	p<0.02
No	188	7.6	48%	

In the multivariate analysis, only one of the variables related to BC knowledge remained significant ( $p < 0.03$ ), which is expected as these variables were highly correlated. Non-medical doctor consultation remained significant ( $p < 0.05$ ) as did marital status ( $p < 0.05$ ), suggesting that married women have less delay for consultation than women without husbands. No significant effect was observed for women's level of education ( $p > 0.47$ ) or economic capacity ( $p > 0.27$ ).

The small size of the sample limited the ability to identify barriers among women who did have basic knowledge of BC. In this sub-group, delay did not appear to be any more strongly associated with marital status ( $p > 0.73$ ), or with women's level of education ( $p > 0.90$ ) or economic capacity ( $p > 0.85$ ). Screening of all the possible explanatory variables resulted in only one significant association: Women who have personal income have a longer delay than those with no personal income ( $p < 0.05$ ). This may suggest that women who are employed may have less opportunity to attend medical consultations, but this needs to be confirmed by further studies.

Denial, fears and psycho-social barriers regarding BC were not quantified per se in the study; as a result, they are not explored in the present analyses. However when asking the patients the main reasons for the delay in visiting a doctor, denial about the seriousness of the symptoms and fear of treatment were important reasons (13% of all reasons expressed), but far after lack of knowledge of the disease or poor symptom appraisal (68% of all reasons expressed). The other causes expressed by the patients were:

1. Competing priorities, causing patient to consider her breast health less important than other matters (6%),
2. Lack of money or fear of lack of money (6%),
3. Lack of trust in the medical system (4%).

Many women stated also that a cause for minor delay (1 to 3 weeks) was due to the search of the right doctor where to go.

It must be noted that modesty and travel to health facilities, two determinants presented as important causes of delayed presentation in other settings, had no significant effect in the present study.

Travel to health facilities was not considered by patients as an issue, nor a cause of delayed consultation. This observation was corroborated by the fact that there was no prolonged delay among women not living in Cairo compared to women living in Cairo ( $p > 0.47$ ). However most of the women not living in Cairo in our sample (35%) were from the peri-urban areas around Cairo where medical facilities and consultations are accessible.

Modesty was not an important issue with 5% of the women unwilling to show their breasts to a male practitioner and 2.5% unwilling to show their breasts to a male or female practitioner. No significant increase in delay of visit to the first doctor, nor delay in diagnosis, was observed for these women.

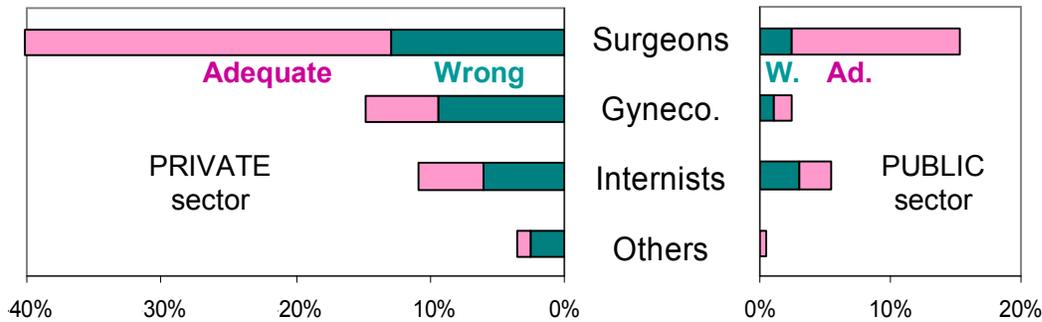
### *2.3.2 Determinants of delay between first visit to a doctor and diagnosis*

The univariate analyses revealed that surprisingly, the major determinant of late diagnosis was incorrect advice from the first doctors visited, its impact exceeding by far any other determinants. More than one-third (37%) of the first doctor consulted advised their patients wrongly, telling them either to "go home and not to bother," or to start ineffective or harmful treatments (injections in the breast, topical treatments, antibiotic therapies, etc.). As a result, the mean delay before diagnosis among the 37% women who experienced incorrect advice from the first doctor consulted was significantly higher (9.1 months) than among the rest of the women (1.7 months); and only 19% of the wrongly advised women were diagnosed within one month after their first visit to the physicians, compared to 67% for the rest of the women ( $p < 0.0001$ )

The first-line doctors consulted were all specialists according to patients (62% surgeons, 18% gynecologists, 16% internist, 4% others), general practitioners in primary health care seems not trusted in urban Egypt. It appeared that patients preferred to attend charity consultations by private specialists offered at mosques or to go directly to large public hospitals than to consult at PHC centers. Doctors who provided incorrect advice represented 60% of the first gynecologists consulted, 55% of the first internists and 25% of the first surgeons (see Figure 6).

Incorrect advice was significantly more frequent among private specialists (44%) than among specialists working at public facilities (27%,  $p < 0.03$ ). Such results are quite disturbing, but call for confirmation as no definitive conclusions should be drawn from only one study.

Figure 6. Wrong and adequate advices according to doctor's specialty and sector



Knowledge about BC appeared to be suboptimal at all health service levels. Some patients' statements are reported in box 1 which illustrates this problem.

Box 1. Patients' statements about health services

- § "I went to the hospital and had a mammogram. They told me there was nothing to worry about. Two months later I was told I needed chemotherapy."
- § "After removal of the tumor, each time (N=3) the surgeons said it was benign."
- § "My arm became swollen so I went to an orthopedic doctor. He put my arm in plaster. It was a woman in the street who saw my swollen arm and told me to go to the cancer hospital."
- § "I went saw two doctors, one was a surgeon and the other a radiographer, and they assured me that if it was cancer it would not be painful. It was a university hospital. Then the hospital lost my case notes. It took 40 days to find them. They kept telling me it was benign but I knew it wasn't. I went to four different surgeons until I was diagnosed and even the fourth doctor initially said it was benign"
- § "I went to an internalist due to pain, a lump and swelling in my breast. He told me that it was not serious but if the symptoms persisted I should see a surgeon. One month later I found a surgeon. Over a period of six weeks he gave me 25 injections into my breast. I don't know what kind of injections they were, but the tumor got bigger. The doctor told me to expel the discharge daily by squeezing it and putting corn flour on the ulceration to dry it up."

Among women who benefited from correct advice from the first doctor consulted, the analyses revealed that husbands' attitudes may have had a significant impact on delay. Women who spoke about their symptoms first to their husband experienced shorter delays between first visit to a doctor and diagnosis

(mean=0.9 months) than women who spoke first to somebody else (mean=1.9 months) or unmarried women (mean=3.2 months) ( $p<0.09$ ). Comparable, results, were observed for women accompanied through treatment procedures by their husband than by other family members ( $p<0.03$ ). Socio-economic, educational or demographic variable which could explain these associations were systematically tested, but no variable was identified which could explain these associations. Our hypothesis is that the above two variables may reflect the degree of closeness and supportiveness between spouses, a supporting husband being an asset.

Travel to health facilities was not considered by patients as an important cause of delayed diagnosis and surprisingly, among women correctly advised by first doctor, the delay was longer for women living in Cairo (mean=2.4months) than for women not living in Cairo (mean=0.4months) ( $p<0.007$ ). This association is unexpected and could be due to sample variations; a larger study is required to test its validity.

What patients perceived to be the main reasons of delay between 1<sup>st</sup> visit to a doctor and diagnosis corroborate our analysis, these reasons were:

- 1- wrong advice from first-line physicians (28% of all reasons expressed),
- 2- lack of trust in the medical system and looking for a second opinion (17%),
- 3- denial or fear (15%)
- 4- waiting list for diagnostic tests (12%),
- 5- fear of financial incapacity (11%),
- 6- patients' limited understanding of urgency of disease (8%),
- 7- competing priorities (4%),
- 8- travel to health facilities (1%).

### *2.3.3 Delay between diagnosis and beginning of treatment*

The analyses revealed that the most important determinants of delay between diagnosis and treatment were economic aspects. Women benefiting from health insurance were treated twice as fast as women without health insurance: only ten days on average instead of 22 days for women without insurance (see Table 13). Independently from health insurance status, socio-economic capacity was significantly associated with delayed treatment (Table 13). Woman's education was not associated to delay. The correlation between economic capacity/health insurance and delay in treatment could be explained by the fact that patients with health insurance or high economic capacity can afford having diagnostic examinations and analysis required prior to treatment in private laboratories, sidelining slower publicly-funded laboratories.

The analyses revealed also that married women (72% of the sample) were treated faster, particularly if the husband was educated. Up to 63% of the women not married waited more than two weeks between diagnosis and treatment, compared to 39% of the women married to an educated husband and 55% of women married to a less educated husband. When stratifying on health insurance status, this association remained significant only in the group of women without health insurance (see Table 13), being married having no effect when health insurance was present. No variable other than marital status and husband's education was a significant determinant of delay among women without health insurance. These results as well as qualitative data suggest that an educated husband may help to avoid waiting lists.

Table 13. Determinants of delay between diagnosis and treatment

		N	patients with delay $\geq$ 14 days	p-value
<i>All women who have begun treatment</i>		172	50%	
Women with health insurance	no	137	55%	p<0.008
	yes	36	31%	
Socio-economic capacity	low	96	58%	p<0.05
	high	74	40%	
<i>Sub-group of women without health insurance</i>		136	55%	
Husband education	no husband	40	73%	p<0.02
	high school or more	50	56%	
	preparatory school or less	46	41%	

When asked what their first intention was regarding treatment (within one week of receiving diagnosis), 86% of women declared they wanted to go for treatment (stating commonly that it was God's will), while 6% were not sure and 8% wanted to refuse treatment. The main reason was fear of treatment (71% of the reluctant patients) and not economic considerations (0%). The women who hesitated for treatment, begun it significantly later (mean delay= 28.1 days) than women not hesitating (mean delay=17.4 days,  $p<0.02$ ). First intention regarding treatment was not significantly correlated to economic capacity neither to education and remained a significant predictor of delay between diagnosis and treatment, when adjusted on those variables.

What patients perceived to be the main reasons of delay between diagnosis and treatment corroborate our analysis, these reasons were:

- 1- waiting lists (65% of all reasons expressed),
- 2- fear of financial incapacity (10%),
- 3- lack of trust in the medical system and looking for a second opinion (9%),
- 4- psychological aspects (fear of treatment, belief that treatment is futile) (3%).

#### 2.4 Results about patient information

It is worth mentioning that at the time of interview which took place after diagnosis and, for 87% of patients, after beginning of treatment, many women were not fully aware they had breast cancer. Among the 174 patient who had begun treatment, 8.6% were not fully aware they had cancer. This proportion increased to 50% among the 28 women who had not begun treatment (the interview took place on average 34 days after the pathological diagnosis had been made).

The analyses suggested that women were more informed of the malignant nature of their disease if they were educated, had high economic capacity, were married and if husband was educated. All these determinants displayed significant effects in the whole sample as well as in the sub-group of women who

had begun treatment. However such determinants being inter-correlated, the multivariate analysis kept only the most significant i.e. husbands' education ( $p<0.002$ ) in the whole sample and women's education in the sub-group who had begun treatment ( $p<0.003$ ) (see table 14). These results raise the hypothesis that once treatment has begun, a husband's role in getting information may be less decisive. Such a hypothesis may be worth testing in further studies.

Table 14. Determinants of patient information about the real nature of her disease

		N	patients not informed they have cancer	p-value
<i>All women</i>		202	14.4%	
Treatment status	not begun	28	50%	$p<0.0001$
	begun	174	8.6%	
Husbands' education	no husband	57	24.6%	$p<0.002$
	preparatory school or less	66	18.2%	
	high school or more	78	3.8%	
<i>Subgroup of women who begun treatment</i>		174	8.6%	
Women's education	preparatory school or less	98	14%	$p<0.003$
	high school or more	76	1.3%	

The small size of the sample limits the study of patients' information determinants in the sub-group of patients who had not begun treatment. However marital status appeared as a potentially determinant since before beginning of treatment, 60% of married women knew the real nature of their disease compared to 25% of un-married women ( $p<0.10$ ).

## 2.5 Results about education, media messages and awareness of BC

The above results show that awareness and knowledge about BC is the first determinant of delayed consultation. Awareness and knowledge of BC were low in our sample: before they were concerned by the disease, only 49% of the women knew that a lump in the breast could be cancer, only 15% to 21% knew the other symptoms of breast cancer (pain, swelling, etc.), 34% did not know anything about breast cancer. Most of the women found their lump accidentally and only 7% by examining themselves. Two thirds of the women declared that they never examined their breasts in a mirror. These results suggest that awareness and education campaigns could be highly beneficial to reduce late presentation of BC in Egypt.

Half of the sample (52%) reported that they had been exposed to messages on BC through pamphlets, radio or TV before being concerned by the disease. However among these women exposed to BC information, only 48% thought about breast cancer when they found their breast change (lump or other symptoms) and 77% knew that a lump could be BC, compared to 8% and 20%, respectively, among women not exposed. This result reveals that information programs improved women's knowledge but were not fully effective. The patients who did not think about BC when discovering symptoms, while they

had been exposed to pamphlets, radio or TV, appeared to be more frequent among married women than un-married women ( $p < 0.05$ ) and tended to have lower economic capacity than patients who thought about BC ( $p < 0.13$ ). No association was found with education level ( $p > 0.63$ ). Patients who were not exposed to pamphlets, radio or TV education programs appeared to be of lower education level than patients exposed ( $p < 0.02$ ) suggesting that special effort are required to ensure that programs reach un-educated women.

Among the women of our sample, 21 had received in-person education, and of these 90% thought about BC when they discovered their breast change, suggesting that in-person education, even by a friend (nine of the women), is more effective than pamphlets, radio or TV.

Among the 21 women who received in-person education, nine women (4.8% of the sample) had benefited in-person education on BC by a health professional, but only one third of them were shown how to perform BSE. This suggests that BSE is not considered as part of breast awareness by health professionals. The three remaining women benefited from a public lecture about BC with BSE demonstration and thought about BC when discovering their first symptoms.

## 2.6 Results about stigma and cultural issues

### 2.6.1 Behavior and beliefs toward husband

Our results show that husband's presence and level of education have important impacts on delays. However women's answers reveal that relationships with husbands in the context of the disease are not optimal. Indeed, among the married women:

- § 67% chose to speak about their symptoms to their husband first and 33% to another person of their entourage (usually a woman).
- § 2% declared that they wanted to hide their disease from their husband, and 9% wanted to hide it from their husband's family.
- § 51% had their husband accompany them during treatment procedure, the others having a child (24%), another family member/friend (20%) or just nobody (6%).
- § 92% declared they were making decisions for treatment themselves, while for the others, it was the husband's decision in 6% of the cases and a joint decision in 2% of the cases.
- § Among women who got surgery, 43% hidden their scar from their husband.

These results suggest that many stigma associated with breast cancer persists among couples which could, at least partly, be tackled through men's education. Our results suggest that husband supportiveness is an important asset to be diagnosed and treated early. Thus it seems important to enroll men in awareness programs. However, in our sample 28% of the patients did not have a husband (widows and divorced women); special services may be required to ensure equity for these women.

### 2.6.2 Behavior and beliefs toward entourage

Our results confirmed that social stigma toward BC is still important in Egypt. Among the patients who were informed they had BC, a relatively large proportion wished to hide their disease from their friends (21% of patients) and extended family (16% of patients).

When the patients were asked if they would agree to speak about their disease to a small group of women to inform them about BC, 65% of the patients accepted without restriction, but 19% stated that their disease was their secret and that they didn't want to share it with other people. The remaining patients were reluctant to speak to women who do not have BC (8% of patients), or were reluctant to speak to groups preferring face to face meetings (8% of patients). Text in box 3 illustrates the feelings of stigma experienced by some patients. Further investigations to define reasons why women don't want to share about their illness and consequent decisions would be beneficial.

Box 3. Patient's statements about stigma

- § "I live in a poor area where everyone knows everyone's business. They look at me differently. People fix their eyes on my breast. They ask me strange and nosey questions about my cancer. So I stopped going out. "
- § "I don't want to tell any outsiders that I have breast cancer until I get my daughter married. People will think it is genetic and it will ruin her chances of finding a husband"

## 2.7 Conclusion of the BED-BC-Cairo study

The results of the BED-BC-Cairo study suggest that delay between the onset of BC signs and symptoms and the first visit to a doctor is primarily due to women's lack of awareness while the delay between first visit to a doctor and effective diagnosis and treatment appear to be primarily linked to first line doctor's awareness.

The fact that 44% of private/charity practitioners suggested inadequate referral or treatments raises questions. It implies that a first and probably quite cost effective step to tackle late diagnosis of breast cancer in the region of Cairo would be to train doctors about BC. A second step would be to educate patients to 1- be aware of the first symptoms of breast cancer 2- be aware of the right path to go to get diagnosed and treated effectively.

Barriers out of Cairo may differ significantly: awareness and knowledge among women may be lower, stigma and cultural issues may differ in nature and magnitude, logistic barriers such as travel to health facilities may be more important than in the Cairo area. It would be beneficial to conduct the study in few other locations in Egypt.

### 3 BREAST CANCER EARLY DETECTION APPROACHES

If there is much published evidence about breast cancer early detection in high-income countries, there are only a few studies about early detection in low- and middle-income countries. However, the subject of BC detection in low- and middle-income countries has gained more attention in the last 5 years and, some relatively recent studies have been published which are reviewed in the following sections together with relevant data from Western countries. Various tools exist to detect BC at an early stage, the most widely used are mammography, clinical breast exam (CBE) and breast self-exam (BSE). Scientific evidences supporting their efficacy are reviewed below, followed by a discussion of the programmatic aspects of early detection.

#### 3.1 Screening by mammography, clinical breast exam or breast self-exam.

##### 3.1.1 *Breast self-exam*

###### DEFINITION

Breast self-exam (BSE) refers to a woman using her hands to systematically inspect her breasts and the surrounding areas for unusual lumps and shape changes. BSE is more than simply touching the breasts and "getting to know" them. It is a method developed for the specific purpose of searching for cancer. Women have to perform the BSE seated and lying down, use their finger pads and their three middle fingers for palpation; they also have to examine their breasts visually.

###### SCIENTIFIC EVIDENCE OF EFFICACY

In Western countries, people began to promote and teach BSE long before it had been adequately studied. Over the last few decades, many organizations have strongly recommended that woman perform BSE each month. Many of these organizations have spent considerable resources on shower cards, educational programs, videos, etc. that instruct women to use proper BSE technique [Gehrke 2000]. Some companies have even begun to produce and sell models of the breast for the purpose of teaching women how to perform BSE. In addition, many physicians and nurses have been involved in promoting BSE and teaching the technique to their patients [Tessaro *et al.* 2000; Warner *et al.* 1989]. Due to these efforts, women have come to believe that BSE is a life-saving intervention, even though there was no evidence showing this to be true. Indeed, it has not been demonstrated that promoting and teaching a monthly regimen of BSE really helps women catch breast cancers earlier than they would without the instruction. More importantly, these types of intervention carry a risk of negative consequences and thus far, scientific studies have failed to show that the benefits of BSE outweigh the risks.

Several observational studies, including cohort and case-control studies, have examined the effects of BSE in specific populations of women [Holmberg *et al.* 1997; Harvey *et al.* 1997; Muscat & Huncharek 1991; Newcomb *et al.* 1991; Gastrin *et al.* 1994]. In these studies, it was assessed whether women who chose to practice BSE detected earlier stages of breast cancer and/or survived longer than women who did not choose to practice BSE. These studies revealed conflicting results, but most have failed to show that BSE benefits women. However the results of these studies may be unreliable because observational studies have several limitations when they are used to examine a screening technique such as BSE. Only randomized trial can bring definitive conclusion regarding screening techniques.

Two randomized trials have attempted to measure the benefit of BSE. The Russian trial conducted in the late eighties involved 193 000 women aged 40 to 64. After 9 years of follow up, more BC deaths were observed in the group performing BSE than in the control group [Semiglazov *et al.* 2003]. The Shanghai trial conducted in the nineties involved 267 040 women aged 31 to 66. After 10 years of follow up, no difference in BC mortality was observed between the BSE group and the control group. Moreover, the number of cancers that had spread to the lymph nodes was similar in each group [Thomas *et al.* 2002]. These negative results, highly debated in the scientific community, discarded BSE as a potential screening tool.

A systematic review that analyzed the Russian and the Chinese trials together – greatly expanding the statistical power - confirmed that there was no beneficial effect of BSE screening on deaths from breast cancer. On the downside the analysis showed that twice as many biopsies with benign results were performed in the screened groups compared to the control groups [Kosters & Gotszsche 2008].

This result together with results from several other studies suggests that BSE screening greatly increases the number of benign lumps detected. This negative aspect of BSE is currently debated. The negative consequences of benign lumps over-detection include anxiety for women, unnecessary physician visits and unnecessary biopsies and other exams. Although breast biopsies are relatively simple surgeries, they can cause distress, scarring and disfigurement. Unnecessary physician visits and exams are a major concern in countries of limited resources where health facilities are scarce and where women have to pay for health care out of their pocket.

## CONCLUSIONS ON BSE

Today, the official position of health authorities like the U.S. Preventive Services Task Force, the Canadian Task Force on Preventive Health Care or the World Health Organization is that there is no scientific evidence that BSE saves lives or enables women to detect breast cancer at earlier stages and that, therefore, BSE should not be promoted or taught on a population-wide level all the more since there is evidence suggesting that such a public health interventions may cause harm, [WHO 2007; Baxter 2001; UPSTF 2002].

But because BSE has been aggressively promoted for so many years, these recommendations have appeared to be difficult to accept. However in the last few years, some changes have taken place: The National Cancer Institute (NCI) no longer prints a BSE guide in its breast cancer booklet, "Understanding Breast Changes," the American Cancer Society is phasing out materials that focus only on breast self-exam and the National Breast Cancer Coalition (U.S.) is even discouraging efforts to promote and teach BSE.

However, in countries with limited resources, to promote BSE at the individual level may help to raise awareness about breast cancer and overall breast health. But this promotion should not convey the false message to women that they can be in full control of their breast health and that they can rely on BSE to detect BC early enough to save their life. BSE promotion should also be careful not to create anxiety that may lead to increased consumption of unnecessary mammograms or other types of exams.

### 3.1.2 Mammography

#### DEFINITION

A mammogram is an x-ray of the breast that can reveal abnormalities, such as a tumor, inside the breast. Mammography can be used for screening and for diagnosis.

- Diagnostic Mammography-is performed if a woman has symptoms of breast cancer, such as a lump that can be felt in her breast.
- Screening Mammography-is performed in an attempt to detect breast cancer before symptoms occur in women without symptoms of breast cancer. It can identify breast cancers too small to palpate on physical examination and detect also ductal carcinoma in situ (DCIS), a noninvasive condition.

## SCIENTIFIC EVIDENCE OF EFFICACY

If mammography screening is perceived as highly beneficial health intervention by the public, it is not the case among the scientific community. A few years ago, a Cochrane review [Gotzsche & Nielsen 2006] reopened the debate on the benefit of mammography screening in Western countries.

The authors had no conflict of interest and were unbiased at the start of the review. They reviewed and evaluated the evidence on benefits and harms of mammography screening based on the 7 randomized trials of mammography screening ever conducted (all in Western countries). Using standard criteria, they rated the quality of each trial's randomization methods as either adequate or suboptimal. They concluded that only two of the trials [Miller *et al.* 1992, Miller *et al.* 2000; Andersson *et al.* 1997] were adequately randomized and these trials did not show that mammography screening decreased mortality from breast cancer. In these trials, the women who were offered mammography screening had the same breast cancer mortality (death rate) as the women who were not offered mammography screening. In contrast, the other trials, which had suboptimal randomization according to the authors, found that mammography did benefit women and reduced breast cancer mortality by about 25%, on average, after 13 years. The authors then calculated an overall effect on mortality by taking into account the quality of all the 7 trials minus one which was deemed biased according to them. This study concluded that mammography decreases the risk of death from breast cancer by about 15% in relative terms, or 0.05% in absolute terms. This means that throughout a ten-year period, 2000 women would need to be screened in order to prevent one death from breast cancer.

Finally, the authors calculated that mammography screening increased the relative risk of over-diagnosis and over-treatment by 30%. This translates to an absolute risk increase of 0.5%; which means that throughout a ten-year period, for every 2000 women screened, ten healthy women will become breast cancer patients and will be treated unnecessarily, many undergoing surgery, radiotherapy, and chemotherapy. Besides About 200 healthy women will experience a false alarm. In fact, this balance between risk and benefit has changed so much in recent years that nationwide programs of breast screening would be unacceptable, authors said in a subsequent interview. "We believe that if policy makers had had the knowledge we now have when they decided to introduce screening about 20 years ago... we probably would not have had mammography screening." [Chustecka 2009]

Prior to this Cochrane reviews, Humphrey *et al.* [2002] had produced a summary review of the same seven mammography screening trials for the U.S. Preventive Services Task Force. In their review, they conclude that screening mammography significantly reduced the risk of breast cancer mortality in screened women compared with unscreened women by 16%, a number very similar to the 15% reached by Gotzsche and Nielsen in the Cochrane review.

For women between the ages of 40-49 years, they found a 15% relative reduction in risk associated with screening mammography. However, this finding had a large confidence interval and only borderline statistical significance. Humphrey *et al.* concluded that "the absolute benefit of mammography screening on mortality is very small, and that biases in the trials could either erase or create it." Furthermore, the study underlined that "even in the best screening settings, most deaths from breast cancer are not currently prevented" and that "future research should be directed toward developing new screening methods as well as methods of improving the sensitivity and specificity of mammography."

In parallel in 2006, a review for the American College of Physicians was also published which focused on screening mammography in women 40-49 years of age [Armstrong *et al.* 2007]. It included publications from the 7 mammography trials as well as 117 other studies. The reviewers concluded to a 7% to 23% reduction in BC mortality thanks to screening mammography in women 40-49 years of age. They also pointed to rates of false-positive results as high as 20% to 56% after 10 mammograms with consequent increases in unnecessary procedures and breast cancer-related anxiety; as well as discomfort at the time of screening and exposure to low-dose radiation. They conclude that the evidence suggests that women 40-49 years have risks that outweigh the benefits of screening mammography. Subsequently, the American College of Physicians issued detailed guidelines for screening mammography among younger women that encourage doctors to carefully assess an individual woman's risks for breast cancer, and to

discuss with them the potential benefits and harms of screening mammography in order to make informed individual decisions about screening [Quasem *et al.* 2007]

#### FALSE NEGATIVE AND QUALITY ISSUES

If at the radiology cabinet, mammography is presented to women as a very sensitive tool, the sensitivity estimated by independent scientific studies go rarely beyond 90% and generally average around 75%. A sensitivity of 75% means that 1 out of 4 women (25%) diagnosed with BC had a normal mammogram within one year before her BC diagnosis (e.g., false-negative result). In the 7 randomized trials mentioned above, the sensitivity of screening mammography ranged from 68% to 88% [Elmore *et al.* 2005]. Out of these highly controlled trials, sensitivity levels reported for screening programs are generally lower. A review of the largest screening programs performed in Europe reveal sensitivity levels as low as 53% [IARC 2002]. A review from 7 population-based community screening programs in the United States on 463 372 screening mammograms revealed an overall sensitivity of 75 % with false-negative mammography examinations occurring in 20% to 40% of women according to location [Carney *et al.* 2003]. Breast density and age are important predictors of accuracy. In Carney *et al.* review, adjusted sensitivity ranged from 63% in women with extremely dense breasts to 87% in women with almost entirely fatty breasts; adjusted sensitivity increased with age from 69% in women aged 40 - 49 years to 83% in women aged 80 - 89 years [Carney *et al.* 2003]. However, it is well established that the most critical factor determining mammographic sensitivity is the radiologists' interpretation. Studies have shown substantial variability in interpretation and reading accuracy among radiologists [Kerlikowske *et al.* 1998; Barlow *et al.* 2004; Smith-Bindman *et al.* 2005].

Interestingly, the failure of mammography to detect certain BC is relatively independent of the tumor size. A retrospective study of 1131 BC patients diagnosed in US and Sweden revealed that the proportion of BC not seen on mammograms varied from 36% for tumor <1.5 cm to 22% for tumor 2-3 cm and 16% for tumor >5 cm [Kaplan *et al.* 2005]. The authors conclude that "reliance on mammography for breast cancer detection is not warranted and manual methods should be retained as an integral part of breast health programs."

#### DIGITAL MAMMOGRAPHY AND COMPUTER AIDED MAMMOGRAPHY

While digital mammography constructors spread the belief that this new tool is much more sensitive and specific for screening than screen-film mammography, scientific evidence produced by independent scientists have failed to support this view. Until the publication of the Oslo II (2004) and Digital Mammographic Imaging Screening Trial (2005) studies, the studies presented were small which made it impossible to assess accurately differences in diagnostic accuracy between the two techniques. Furthermore, these studies did not include follow-up [Dershaw 2006]. In the Oslo II trial, which included 23929 mammograms of women between the ages of 45 and 69, neither sensitivity nor specificity differed significantly between digital and non-digital mammography. The proportion of cancers with discordant double readings was also comparable between digital and non-digital mammography [Skaane & Skjennald 2004; Skaane *et al.* 2007]. In the DMIS trial which included 49528 mammograms, the diagnostic accuracy of digital and non-digital mammography was also similar. However in one sub group, the pre- or perimenopausal women younger than 50 years who had dense breasts, digital mammography was significantly better than film, while film tended non-significantly to perform better for women aged 65 years or older with fatty breasts [Pisano *et al.* 2008; Pisano *et al.* 2005]

Computer-aided mammography is another tool which is rapidly gaining acceptance, however data have not demonstrated its benefit for mammography screening. Computer aid detection in screening mammography has been evaluated in only 3 large studies. In the first and largest study taking place in the U.S., the results showed that computer-aided detection was not associated with statistically significant

changes in recall and BC detection rates, both for the entire group of radiologists (N=24) and for the subset of radiologists (N=7) who interpreted high volumes of mammograms [Gur *et al.* 2004]. In the 2 subsequent studies, taking place in the UK and reported by Taylor *et al.* [2005], no significant improvement in film readers' sensitivity or specificity or gain in cost-effectiveness was established (N=50 readers). New Computer aid detection tools, currently under development, may provide better results [Taylor *et al.* 2005]

## CONCLUSIONS ON MAMMOGRAPHY

All the recent reviews indicate that, overall, mammography screening has a limited power to prevent BC deaths. The two most recent and comprehensive reviews concluded that the overall impact in mortality is small and that false positive tests, over-diagnosis and over-treatment are non negligible issues. As summarized nicely in the Cochrane review "for every 2000 women invited for screening throughout 10 years, one will have her life prolonged. In addition, 10 healthy women, who would not have been diagnosed if there had not been screening, will be diagnosed as breast cancer patients and will be treated unnecessarily. It is thus not clear whether screening does more good than harm." [Gotzsche & Nielsen 2006]. Considering the incidence of BC in Egypt (much lower than in the west) the yields may be lower, i.e., One life would be prolonged for every 4200 to 4700 women screened. The proportion of healthy women over-diagnosed and over-treated is not dependent on BC incidence and may depend, at least partly, on the standards and quality of health services. It is thus unclear what the proportion of over-diagnosed and over-treated women would be in Egypt.

Finally, scientific evidence do not support that digital mammography perform better than traditional film mammography for screening. However, among young women, digital mammography has been reported to be a little more sensitive than film mammography. But it should be kept in mind that, in women younger than 50, the harm of mammography screening may outweighs the benefit.

### 3.1.3 Clinical Breast Exam

#### DEFINITION

Clinical Breast Exam (CBE) is a hands-on examination of both breasts performed by a doctor or healthcare professional. To be effective, CBE has to be performed in a very careful way, by specially trained personnel, taking 7 to 10 minutes to perform the full exam. It has to have a visual component and women have to be examined sitting up and lying down [IARC 2002]. Studies performed in developed countries and developing countries have demonstrated that CBE can be performed adequately by non-medical staff (nurses or health workers) [WHO 2007, Baines *et al.* 1989].

#### EVIDENCE OF EFFICACY

Evidence about efficacy of CBE is somewhat indirect. Two randomized trials, one in Canada and one in US, evaluated the combination of mammography and CBE. The Canadian trial conducted in the nineteen eighties, showed that there was no benefit in adding mammography to CBE: Mortality was similar in the 2 groups of women although yearly mammography in addition to clinical examination detected more small and lymph node–negative breast cancers than did screening with clinical examination alone [Miller *et al.* 2000]. The US trial, initiated in the seventies, indicated that the achieved reduction in mortality was for 70% attributable to CBE and the remaining 30% to mammography [Shapiro *et al.* 1988]. The sensitivity of CBE was published only for the Canadian trial and varied from 71% to 83% between the rounds. This has to be compared to the sensitivity of 68% to 88% reported for mammography trials (see preceding chapter).

Three trials have been initiated in low and middle-income countries to evaluate the efficacy of screening by CBE alone, but none of the trials are advanced enough to provide definitive conclusions. One of the trials is currently being conducted in Cairo on women aged 40-69 years; to date 14,807 women are enrolled. Early results show that stage distribution among women screened by CBE is significantly better than in the control group with 74% of early stage compared to only 27% in the control [Miller *et al.* 2008]. Unfortunately, the number of women enrolled is much too low to provide statistically valid results about mortality.

Another trial had been initiated in Manila (the Philippines) on women aged 35-64 years; 151,168 women were enrolled [Pisani *et al.* 2006]. After the first round of screening, screen-detected cases were less advanced than the others, but the difference did not reach statistical significance. However, the trial was stopped because of the refractory attitude of the population to clinical follow-up: of the 3479 women detected positive for a lump and referred for diagnosis only 35% completed diagnostic follow up whereas 42.4% actively refused further investigation even with home visits, and 22.5% were not traced. This behavior was not attributable to logistic or economic barriers. This unexpected result raised strong concerns in the scientific community regarding the feasibility of screening in low- and middle-income countries.

The third trial is currently conducted in Mumbai India on 150,000 women aged 35-64 years. This study has now entered its 9<sup>th</sup> year and more than 3 rounds of screening have taken place. Early results show that the stage distribution is significantly better in the screening group than in the control groups. The principal objectives of the trial, i.e., demonstration of a reduction in mortality, will however become evident only after 5 to 8 years [Dinshaw *et al.* 2003, Dinshaw *et al.* 2005].

However this trial, as the Philippines one, has raised several important issues regarding the degree of persuasion required to induce women to participate in the screening and to perform diagnostic procedures. Nearly 100 full-time personnel are engaged to screen the 75,000 women every 18 months and to maintain yearly surveillance on the control group. Door to door visits, usually more than one, were required not only to persuade women to attend screening tests but also to induce them to comply with other steps related to diagnosis and treatment. The manpower cost involved was formidable [Mittra 2008].

Some modelization studies have been conducted to assess the potential benefit of screening by CBE in developing countries. Using the data from the Swedish two country trial of mammographic screening, Duffy *et al.* [2006] calculated that if screening by mammography has the potential to reduce mortality by 21% in a typical Western population, screening by CBE has the potential to reduce it by 11% (approximately 42 deaths prevented per 1,000 BC cases, i.e., 52% of what mammography screening would achieve). When assuming a population with a tumor size distribution typical of a limited-resource setting (70% of tumors  $\geq 3$  cm at presentation), the same modelization shows that using CBE screening can approximately prevent up to 72 deaths per 1,000 BC cases. This shows that CBE can achieve a mortality reduction of about half of what is observed with mammography and that its benefit would be more visible in countries where women present late.

Okonkwo *et al.* recently published a very interesting cost effectiveness analysis of screening strategies for India [Okonkwo *et al.* 2008]. Using micro-simulation methods, they estimated the number of deaths averted and life years prevented by various modalities of CBE and mammography screenings and calculated the corresponding cost effectiveness ratios. The authors assumed stage-specific sensitivity and specificity to be as high as the ones observed in the Dutch and Canadian randomized trials of mammography and CBE [Miller 2000; Fracheboud 2004]. The stage-specific survival rates used were the ones observed in Western countries. Authors also assumed a participation rate of 100%, which is not realistic but makes their results easier to interpret. The screening programs modeled were all assumed to be run for 25 years in a virtual population of one million women.

The authors calculated that in India, the overall cost of one mammography test is 3.34 time higher than the overall cost of one CBE test. Their main results are summarized in table 15. These results show that:

- One lifetime CBE screening at 50 is the most cost effective program modality but do not avert a large number of deaths. If performed in younger women, even less lives are saved. If performed by mammography instead of CBE, the cost effectiveness ratio is not appealing anymore and 5 years interval screening by CBE has to be envisioned since it saves more lives for comparable cost (see Table 15).
- As soon as multiple screening rounds are envisioned, to target women 40-60 year old is more cost effective than to target women 50-70, not in terms of death averted but in terms of life year gained (see Table 15), which makes sense since young women have more to live than older women.
- Mammography programs are dominated by more intensive programs with CBE. For example, annual CBE screening achieves almost the same number of life year gained (88%) as biennial mammography screening but for half the net cost (see Table 15).
- Among programs of "reasonable cost," biennial CBE in women 40-60 is the one which achieved the greatest mortality reduction (see Table 15).

Table 15. Comparison of screening modalities (*Costs are in international \$*)

Type of program	One lifetime CBE age 40	One lifetime CBE age 50	One lifetime MMG age 50	5 yr interval CBE age 50-70	5 yr interval CBE age 40-60	Biennial CBE age 40-60	Biennial MMG age 40-60	Annual CBE age 40-60
Screen tests performed	275,735	212,018	212,018	740,227	1,056,544	2,319,839	2,318,641	4,426,854
BC deaths averted	21	45	105	172	184	358	599	528
Life year gained	359	625	1,422	1,913	2,462	4,896	7,955	7,242
Net cost of screening*	\$0.6 M	\$0.5 M	\$2.3	\$2.3 M	\$2.8	\$6.6	\$27.6	\$13.9
Cost / death prevented	\$28,878	\$1,154	\$22,220	\$13,532	\$15,152	\$18,312	\$46,021	\$26,241
Cost / life year gained	\$1,657	\$793	\$1,634	\$1,218	\$1,135	\$1,341	\$3,468	\$1,913

\*Net cost refer to the cost difference between the situation with and without screening and include cost of screening, diagnosis, primary therapy, adjuvant therapy, follow up and palliative care.

The authors recognized that there was considerable uncertainty in their estimation of costs as these varied from 1 to 3 according to the method and base prices used. However this uncertainty does not affect the comparison among the screening program modalities as costs varies proportionally among modalities.

Using the most optimistic method for calculation (cheapest estimates), the authors calculated that a biennial CBE screening program targeting 1 million women and taking place for 25 years would cost \$13.23 millions in India, while using mammography would raise the cost to \$44.21 million. This latest number corresponds to a cost effectiveness ratio of Int \$3,468 per life year gained (as indicated in table 1). In Europe cost effectiveness estimates for comparable mammography programs have ranged from Int \$2,889 to Int \$10,464.

Finally the authors assessed the sensitivity of their result to some key parameter variations:

- Variation in incidence (from 19/100 000 to 30/100 000) did not affect the results except that cost effectiveness ratios became more favorable. For comparison, the corresponding incidence in Egypt is around 42 /100 000.
- Screening attendance lowered from 100% to a more realistic 70% had minor effect on cost effectiveness.
- Stage-specific sensitivity for CBE lowered by 25% resulted in a 35% higher cost effectiveness ratio for screening modalities using CBE. However this keeps CBE more cost effective than mammography in all screening modalities.

## CONCLUSION ON CBE

Scientific studies suggest that CBE could be a valid tool for BC screening. Its effectiveness at reducing stage at presentation has already been demonstrated, its effectiveness at decreasing mortality has been suggested by simulation studies but this needs to be confirmed in reality. Studies show that if CBE screening is a little less sensitive than mammography, it is also less resources demanding and much more cost effective, thus an appealing option for a limited resources country like Egypt. However, a population-based screening intervention remains a very resource-demanding health program regardless of which tool is used. The pros and cons of screening programs are discussed in the following section.

### 3.2 Limitations and potential harms of screening

#### 3.2.1 *Clinical considerations*

It is important to understand that BC screening, contrary to cervical cancer screening, does not have the potential to prevent all BC deaths because of the inner characteristic of the disease. By the time mammography detects cancer it has been growing in the breast for an average of 6 to 10 years, which is plenty of time for the tumor's cells to spread to a vital organ and start to grow. As it could be years before the woman knows that her breast cancer has spread, women with breast cancer may die many years later, even though their cancer was detected by a mammogram and removed. That is one of the main reasons why mammography screening has not demonstrated more than 15% reduction in BC mortality in Western countries (the other reasons being not-100% sensitivity and not-100% participation rates).

#### 3.2.2 *Hazard of screening*

Two major categories of possible harm are relevant to any screening program: false positive results and over-diagnosis/over-treatment. Harm from false positive mammograms relates to the additional testing, invasive procedures and anxiety that would never have happened in the absence of screening and harm from over-diagnosis related to unnecessary anxiety and unnecessary treatment, both of which are inevitable if a screening program is to be effective [IARC 2002].

As already mentioned, mammography screening is associated with a high rate of false positive. Approximately 95% of women with abnormalities on screening mammograms do not have BC [IARC 2002]. The expertise of the radiologist is critical in assessing if these abnormalities warrant further investigation [Elmore *et al.* 2005]. It has been shown that the largest risk factor for having a false-positive mammogram is the individual radiologist's tendency to read mammograms as abnormal [Christiansen *et al.* 2000]. False positive rate between 0.5% and 11% have been reported in Western countries for mammography [IARC 2002]. These large variations can be explained by different thresholds for

recommending further evaluations of specific mammography abnormalities, such as calcification and well-circumscribed nodules. For CBE, false positive rates reported are usually lower than for mammography [IARC 2002], the Philippines randomized trials displayed a false positive rate of virtually 0% [Pisani *et al.* 2006].

As women repeatedly undergo screening tests, their risk of ever having a false positive result increases. In the United States, it has been estimated that a woman's cumulative risk for a false-positive result after ten mammograms is almost 50% and the risk for undergoing an unnecessary biopsy is almost 20% [Elmore *et al.* 1998].

False positive results are associated with increased number of medical visits, diagnostic mammograms, ultrasound and breast biopsies. Lidbrink *et al.* calculated that the cost of evaluating the positive result was 26.5% that of screening by mammography [Lidbrink *et al.* 1996]. In another study, Elmore *et al.* evaluated that about US \$33 would be spent on follow up procedure to evaluate false positive results for every US \$100 spent on screening mammography [Elmore *et al.* 1998].

Tumors exist that fulfill the histological criteria of cancer but would neither progress nor become clinically apparent in a patient's lifetime. Detection and treatment of these lesions constitute over-diagnosis and do not confer any benefit to the patient. It is currently impossible to distinguish with certainty the cancers that will progress from those that will not. Therefore, one of the consequences of screening a population of women is the detection, in some women, of cancers that are destined to remain occult during their lifetimes. When these clinically insignificant cancers are detected, there is no benefit, yet these women will undergo treatments such as surgery, radiation therapy, hormonal therapy, and chemotherapy. It is difficult to determine the proportion of screen-detected cancers that fall into this category, approximations of the magnitude of the problem range from 10% to 30% of mammography detected breast cancer cases, depending on utilization and intensity of screening [Gotzsche *et al.* 2006; Zackrisson *et al.* 2006]. There is some evidence that more over-diagnoses occur among women aged 40–49 years than among older women [Kerlikowske *et al.* 1993]. On the basis of the results of their meta-analysis, Humphrey *et al.* calculated that over 10 years of biennial screening among 40-year-old women invited to be screened, for each death from breast cancer prevented, approximately 400 women would have false-positive results on mammography and 100 women would undergo biopsy or fine-needle aspiration [Humphrey *et al.* 2002].

### 3.2.3 Resources required for screening

Screening programs are heavy public health interventions requiring the mobilization of important resources. Human resources required are important and constitute a bottle neck in low resources settings. We calculated that to screen on a biannual basis the 9 million women of Egypt who are in the 40-60 year range, an absolute minimum of 350 health staff full time dedicated only to the screening test would be required : 350 radiologists + 350 radio-technicians if the screening is done by mammography, 350 CBE specialists otherwise). This does not include the health staff dedicated to receiving the women, communicating the test result and counseling the women, nor the health staff required for the follow-up of positive women (true and false positives). This follow up requires important medical human resources as it includes additional investigations, biopsies, cytopathology and potentially unnecessary surgery, chemotherapy and radiotherapy. In addition, as observed by Mitra [2008], in low resource settings the human resources required to persuade women to attend screening tests and to induce them to comply with the others steps related to diagnosis and treatment can be formidable. To invite the target women and advise them to come again for re-screening as necessary requires a strong organization plus the involvement of community leaders, NGOs and all public health services.

The facilities and equipment required for a screening program can be substantial especially if mammography screening is envisioned. Pathology laboratory also must be prepared for the supplementary work load. Registration and coordination systems are essential to ensure adequate screening and follow up of all the women in the target group. They are also important for quality control monitoring and evaluation purposes. Quality assurance is of particular importance in screening programs

as too many false negative (low sensitivity) and false positive (low specificity) results of the test can cause unnecessary harm and costs. Both the development and the implementation of the program need to be monitored and evaluated periodically to ensure that the objectives of the program are achieved [WHO 2007].

### 3.2.4 Conclusions about screening

Screening programs are resource demanding and complex to implement health intervention. Cost and benefit of initiating BC screening programs should be weighted against competing health needs in each country. In addition, BC screening programs have the potential to highly increase the demand of health care since false positives and over-diagnosis/over-treatment are important. False positives and over-diagnosis/over-treatment result in increased and unnecessary use of health facilities and health human resources, as well as unnecessary costs for the patient and the health system.

The conclusions drawn here and in previous sections about pros and cons of screening are based on public health research and Health Authorities' positions. They are somewhat different than the positions commonly adopted by the clinical community which is the primary source for public information. In all countries, the clinical community generally overweighs the need to detect or report anomalies and symptoms and underweight the cost and harm of screening including the negative consequences of false positives and over-diagnosis/over-treatment. Cost and harm are of major concern in countries where resources are scarce and public health facilities are overloaded.

### 3.3 The clinical down-staging alternative

The WHO guidelines on early detection of cancer [WHO 2007] distinguish two programmatic approaches: screening which focus on detecting cancer in asymptomatic at-risk populations and "clinical down-staging" (or "early diagnosis") which focus on detecting cancer early in symptomatic patients. Clinical down-staging is a cheaper and easier-to-implement alternative to screening which is relevant to countries with limited resources where the majority of cancers are diagnosed at stage III and IV. It has been experimented with success in some low- to middle-income regions [Devi *et al.* 2007; Luthar 1994]. Clinical down-staging is intended to make use of the available health care resources in an area to improve the stage distribution of diagnosed cases. It consists of: 1) education of the first-line health staff and the public about early symptoms of cancer and benefit of early detection and 2) improved referral procedures and patient flow. It is a relatively simple and inexpensive method that can be integrated into already existing health care programs. The phases of a clinical down-staging program are detailed in Box 1.

Box 4: The methodology of clinical down-staging (*modified from the WHO-EMRO regional strategy for cancer control. 2008.*)

Phase I: Develop a strategic plan at the level of the NCCP committee, health authorities or cancer centers

- Amass relevant data regarding the target population and the existing first-line health care facilities and personnel.
- Develop a training curriculum and educational approach for primary health care personnel (training courses or workshops in appropriate locations).
- Determine how the program will be monitored (e.g., knowledge of trainees, monitoring the stage of cancer at the time of diagnosis before and after training)

*expected result:* written strategic plan

Phase II: Educate the first-line health professionals

- 1 to 4 days training sessions about the early sign of cancer,
- Training in low cost screening techniques (e.g., clinical breast exam)
- Training in education of the target population

*expected result:* integration of cancer early detection into primary and secondary health care level

Phase III: Education of the target populations

- education by first-line clinician and health staff through community outreach program
- education through media campaigns

*expected result:* groups at risk aware of early signs and symptoms and empowered to consult at appropriate health care facilities.

Phase IV: Improved patient referral and navigation across the health continuum, with more rapid diagnosis and treatment.

*expected result:* improved stage distributions after program enacted

A clinical down-staging program conducted in Malaysia and covering a 2.2 million population managed to reduce BC late presentation from 60% to 35% in less than 5 years. The program consisted of training by a teaching team (3 medical staff and 6 nurses) of about 400 first-line health staff throughout the state and cost < US\$34,000 [Devi *et al.* 2007].

Clinical down-staging programs would be unlikely to make a difference for BC outcome in countries where already large numbers of tumors are detected in stage I or II. It's objective is to confer benefit in regions where more than 50% of BC cases present in late stage or with lumps above 2 cm and where a substantial part of the difficulties are due to sub-optimal organization and quality of the health services.

Potential obstacles to down-staging include a paucity of access points to the health care system, stigmata pertaining to BC and socio-economic problems that may prevent symptomatic patients from seeking help. A plan to tackle these obstacles has to be part of any down-staging program [WHO-EMRO 2008]. The potential hazard of down-staging is an overload of primary and secondary health care facilities with women having breast complaints given that up to 95% of breast symptoms reported by women are not breast cancer. In this regard, the content and the quality of the breast awareness message delivered to the public are critical.

Although the benefit of down-staging programs has barely been studied and their effect on BC mortality never assessed, the WHO and the Breast Health Global Initiative recommend this approach as the minimal breast cancer early detection intervention in low resources settings [WHO 2007, Yip *et al.* 2008]. The WHO guidelines state that "A cancer screening program is a far more costly and complex undertaking than a down-staging program. Therefore, where resources are limited, and where the majority of cases are diagnosed in late stages, down-staging of the most frequent cancers, linked to appropriate treatment, is likely to be the best option to reduce premature deaths and suffering due to cancer." [WHO 2007]

### 3.4 Conclusions on methods for early detection and strategic directions for Egypt

Although screening by mammography has been accepted as the gold-standard to ensure early detection of BC, its cost-benefit ratio is still debated in the scientific community. It is important to keep in mind that even in the best screening settings; most deaths from breast cancer are not currently prevented by mammography screening. The latest reviews indicate a reduction of no more than 15% in BC mortality rate after introduction of mammography screening in Western countries. Recent studies suggest that screening by CBE could achieve a reduction of 52% to 88% of this magnitude with a better cost effectiveness ratio.

Whatever screening tool is used, screening programs are resource-demanding and heavy-to-implement health interventions. Down-staging programs are an appealing alternative when resources are scarce, and should be considered as the first option in regions where a majority of BC is diagnosed at late stage.

In Egypt, where still a vast majority of tumors diagnosed are above 2 cm, there is room for improvement by a down-staging approach. Screening by CBE would be relevant to regions/groups where stage distribution is good enough that down-staging has no potential for major improvement. Early detection can result from both down-staging in some part of the country and screening in other parts. However, Egypt should follow the WHO and BHGI guidelines which call for countries to conduct research and pilot projects prior to establishment of national programs, as neither benefit of screening, nor benefit of down-staging programs have been formally demonstrated to date in any developing country.

## 4 ORGANIZATIONS AND PEOPLE ACTIVE IN BC EARLY DETECTION IN EGYPT

### 4.1 The Ministry of Health and Population pilot screening program

The Ministry of Health and Population (MoHP) of Egypt has launched a pilot screening program in October 2007. This program is coordinated by Dr. Dorria Salem, Prof. of Radiology Cairo University and Head of Women's imaging unit and is under the patronage of her Excellency Mrs. Suzanne Mubarak. The purpose of this program is to screen women from 45 years old for:

1. Breast cancer (digital mammography exam)
2. Diabetes (Blood sugar test)
3. Hypertension (Blood pressure test)
4. Obesity (weight and height measurement)

The women recruitment process is based on the presence of mobile vans where all the above exams take place. Few weeks before a van is moved to a district, the population is informed about the importance of screening thanks to posters and pamphlets distributed in mosques, churches and streets. Women eligible for screening (i.e., 45 years old or more) are contacted by phone or visited by health workers of the Red Crescent to encourage them to come to the vans. Only women without breast complaints are admitted for breast cancer screening. The complaining patients can go to the women's imaging unit at Kasr Al-Aini Teaching Hospital, and also in a very near future to any of the static units that were installed at the different MoHP hospitals.

Four mobile vans are currently working, 10 additional static digital mammography machines have been purchased for the program and installed in the different governorates. The long term objective of the MoHP is to have at least 1 digital mammography machine in each governorate, and it is plan to train the radiologists present at these places.

For the reading of mammograms a center of excellence has been set up, where digital mammograms are sent as soon as taken. A team of 25 radiologists are dedicated to these mammograms reading.

The pilot phase of the project has begun in October 2007. By February 2009, 25 different locations in Cairo, Giza and Alexandria governorates were visited; up to 22,000 women had been screened, 406 were referred for further diagnosis, 75 (18%) turned out to be false positive. Out of the real positive, 59 (18%) were operated, 73 (22%) refused diagnosis or treatment, 35 (11%) were not reachable and the 50% remaining were into the diagnosis or treatment process.

One of the main problems encountered is to convince women who have a suspicious mammogram, to go for diagnosis and treatment as some refuse or disappear. Health workers from the NGO "Hope" are dedicated to this task. This kind of problem is frequently observed in developing countries when screening for breast cancer [see for example Pisani *et al.* 2006 & Mitra 2008]

A TV media campaign about screening has taken place during autumn 2008 to raise awareness about breast cancer and facilitate acceptance of screening, as well as a campaign on the local radio station Negoum FM; a new TV campaign should start soon.

*Source:* Information provided by Dr. Dorria Salem, head of the digital mammography screening project.

MoHP Women Health Outreach Program web site: [www.whop.gov.eg](http://www.whop.gov.eg)

## 4.2 The Breast Cancer Cairo Trial

The BC Cairo Trial is a research project designed to evaluate the efficacy of screening by clinical breast examination (CBE) in the context of primary health care (PHC). The project has been designed by Pr. Tony Miller, Epidemiologist at the Public health Science Dept. of Toronto University (Canada) and is headed in Cairo by Dr. Salwa Boulos, radiologist in charge of the mammography unit at the Italian hospital until recently and now at Al-Galaa Hospital. The project has been financially supported by the Italian embassy in Cairo and the European School of Oncology (Milan). The project is under the patronage of her Excellency Mrs. Suzanne Mubarak.

The study has been launched in other countries of the region (Yemen, Iran, and Sudan) but Cairo was the first and is thus the more advanced center of the study. The study was launched in May 2000 and has begun by a pilot phase (phase I) followed by a classical randomized trial (phase II and III). These phases are described below:

### Phase I (pilot study).

The initial target group was women 35-64 living in a geographically defined area (8 blocks) around the Italian Hospital (Abassiya district). In this pilot phase, 4116 women were contacted by social health worker (door to door visit) to attend designated PHC centers for Clinical Breast Exam at pre-determined date and time.

Of the women targeted, 60% (N=2481) attended, of those who attended 12% (N=291) were found to have abnormalities, of these 82% (N=236) attended the Italian hospital for diagnosis, and of these 3.4% (20 women) were diagnosed with BC. This latest number corresponds to a quite high prevalence of BC: 8/1000. Only one BC patient was less than 40.

### Phase II and III

The target group was restricted to women 40-64 and divided in 2 groups based on residential blocks (4 blocks each). The group A was offered active screening as in the pilot phase, the group B received only health education. Two additional areas were identified each with 5000 women aged 50-65 who were cluster randomized. The reputation of the trial preceded subject recruitment and there was higher acceptance than in the pilot phase, with 85-91% of women accepting to go for screening.

Although follow up of all groups is yet to be completed, preliminary results are encouraging. Stage distribution in both screened and control groups are given in table 16.

Table 16. Preliminary comparison of the stage distribution in the Cairo Trial

	Screened group	Control groups
Stage I	30%	8%
Stage II	43%	18%
Stage III	20%	44%
Stage IV	7%	30%

This trial is testing an approach to early detection which is promising for Egypt, it would be beneficial to extend this trial to other centers/towns of Egypt. However this requires important resources, especially human resources i.e., dynamic and highly dedicated local PIs, not mentioning international specialists, Dr. Miller being retired and having not much time to dedicate to such a trial.

It must be noted that the idea of screening by clinical breast exam usually receives very little support from the medical community in low- and middle-income countries; CBE is erroneously perceived as ineffective because of its low-tech nature. This is a misconception that could be tackled by an increased publicity about the BC Cairo Trial and Mumbai trial results.

*Source:* Information provided by Dr. Tony Miller, designer of the trial, and Dr. Salwa Boulos, PI of the trail in Cairo. Information retrieved in the following scientific publications:

Boulos S, Gadallah M, Neguib S, Essam E, Youssef A, Costa A, Mittra I, Miller AB. Breast screening in the emerging world: high prevalence of BC in Cairo. *Breast*. 2005 Oct;14(5):340-6.

Miller AB. Practical Applications for Clinical Breast Examination (CBE) and Breast Self-Examination (BSE) in Screening and Early Detection of BC. *Breast Care* 2008;3:17-20.

#### 4.3 The Fakous down-staging program

The Fakous down-staging program is a community-based pilot project aiming at improving the stage distribution of Breast Cancer in the Fakous district, a rural district located in Sharkia Governorate, in the Nile delta region. The project has been initiated by the Fakous Cancer center headed by Prof. Sherif Omar and Dr. Ayman Omar. The design of the program has been established by the Fakous Cancer Center with input of the NCI-Cairo (Dr. Nelly Hassan), the WHO regional office (Dr. M. Corbex) and the NCI-US Office of International Affairs (Dr. Joe Harford).

The project incorporates both public awareness raising and primary health care education. It has begun in January 2007 and has 5 components:

1. Education of primary health staff of the Fakous district in early detection techniques.
2. Door to door visit to women of the general population to raise awareness about breast cancer.
3. Women information and awareness meetings about breast cancer.
4. Information and awareness sessions for local religious authorities.
5. Free breast clinic open at Fakous Cancer Center twice a week

Between Jan. 25, 2007 and Feb. 16, 2007, 98 primary health care staff (44 doctors and 54 nurses) from all over the Fakous district were trained in breast disease and early symptoms of breast cancer. Besides, 33 young women (aged 23-28 yrs) recently graduated with bachelor degree were trained as "pioneers," i.e., person in charge of door to door visit to raise awareness among the women of the villages. Pioneers were resident from the villages, according to village size, 1 to 10 pioneers per village were hired.

Door to door visits begun in February 2007, women were explained about breast cancer, given some pamphlet when literate and invited to attend information sessions as well as the free breast clinic for breast complain or general screening. In 6 months, the 9240 women of the 8 villages targeted for the first phase of the project were visited. The door to door awareness activity is planned to be expended now to 27 village and subsequently to all the village of the district (N=52). The young pioneers have revealed to be very committed to their mission and, thanks to the very social character of their position, have been empowered as individuals in their communities.

Information sessions have been provided to 274 women (16 from Fakous city, 258 from the 8 1<sup>st</sup>-phase villages), as well as to 99 female student of Fakous city (aged 16-18) and their teachers.

The religious leaders of the 52 villages of the district have been informed about the program and asked to mention it in their Friday speech / sermon. The purpose was to raise breast cancer awareness in the male community and to inform about the early detection program.

A free breast cancer clinic has been opened in February 2007 at the Fakous Cancer Center. It hold twice a week and provide free check and whole radio diagnosis to positive cases. It receives around 15 women per month, most of them from Fakous city. Around 30% of them are referred for further investigations.

The impact of the program has not been evaluated yet as it is too early to get significant results. Given the female population of the Fakous district, around 70 new BC cases per year are expected, 11 of which from the 8 villages targeted by the public awareness program (according to the Gharbiah cancer registry incidence rate).

An important determinant to the feasibility of this pilot project has been the good relation of the Fakous Cancer Center with the local authorities and the primary health staff of the district. The fact that the well known figure of Prof. Sherif Omar is heading the project may have also been an important determinant for acceptance of the program by both the professionals and the general population of the Fakous district. The expansion of the program will include anti tobacco information.

#### 4.4 The Breast Cancer Foundation of Egypt (BCFE)

The Breast Cancer Foundation of Egypt was established in 2003 by a small group of health care professionals, survivors and public spirited citizens as a non-governmental, non-profit organization under the Ministry of Social Solidarity. At that time, there was no established BC awareness governmental program and no other NGO was working in this area. The public in general was not receptive to information about cancer. The topic was considered taboo in Egypt.

The BCFE philosophy is to advocate for BC awareness and services by serving the public in a manner that generates happy clients and positive recognition. BCFE partners with the National Cancer Institute (NCI) for teaching health care professionals. It is a mutually beneficial arrangement that does not involve the exchange of money.

To accomplish its mission, the initial strategy of BCFE involved:

- § Offer the public non-threatening information to demystify the subject and correct the widely believed misinformation
- § Offer this information in presentations to groups with minimal written material in a culture that prefers oral to written communication
- § Introduce the idea of screening following the verbal information sessions
- § Provide assistance to both public and private sectors upon request
- § Announce a philosophy of cooperation with government to fill the gap between what citizens need and what any developing country government with a large indigent population can realistically provide
- § Maintain a non-critical position regarding the lack of government progress towards BC awareness and services
- § Develop an on-going relationships with government agencies/facilities
- § Keeping the Minister of Health & Population informed of its activity

In the past few years BCFE has done educational presentations and opportunistic screening programs wherever asked for, i.e., private companies and ministries. The BCFE staff designed the screening program, all the tools for implementing it, and the training program for doctors and nurses to provide screening services. BCFE surveyed the facilities of hospitals that wanted to establish an early detection clinic and recommended changes to support a good patient flow, privacy and efficiency.

These services were provided free of charge to any facility requesting this assistance. The cost was supported by the sponsored screening program.

BCFE deals directly with many patients. Quick referral mechanisms and the link to treatment services are ensured. Poor patients are referred to free clinics of NCI. If they are covered by insurance they are advised WHERE and WHO to go to. If they do not want to go to NCI and are not covered by insurance,

BCFE arranges for treatment for them at a low cost facility, or through a doctor that will charge reasonably.

BCFE also implemented subsidized direct services to BC survivors from economically disadvantaged section, women who were not covered under the government's free or low cost health care system and women outside the government system who could not afford the full cost of an item or service.

Since BCFE has become recognized as the provider of BC education and services, many organizations have held events and contributed the proceeds to BCFE without BCFE being involved in the production of the event.

Currently as a result of BCFE work, BC early detection services have been set up in 41 clinics in Cairo, Alexandria, the Delta and Aswan including the National Cancer Institute(NCI), Tanta Cancer Center and four hospitals of the General Organization of Government Teaching Hospitals and Institutes (GOTHI), in Cairo and Aswan. More recently it has trained community health workers in four NGOs in Cairo. The training program is fully comprehensive targeting all players in the health clinics of the NGOs who have direct contact with the female population.

Unofficially, BCFE is recognized as the local expert in the area of BC early detection and is the agency to which requests for help are directed. In all its projects BCFE took a low key role and allowed credit for the project to be enjoyed by the government officials.

BCFE has never formally lobbied government to influence policy. It has developed a non-threatening position that allows for a cooperative rather than a competitive or judgmental relationship and allows BCFE to make progress without generating envy and criticism. BCFE has succeeded by offering needed education and services in a professional manner and only upon request. They have avoided militant advocacy and have tailored their advocacy strategies to the culture.

The BCFE success story has been reported in the WHO publication "Cancer Control modules: Policy and advocacy" published very recently and available on line at: [www.who.int/cancer/modules/en/index.html](http://www.who.int/cancer/modules/en/index.html).

*Source:* Information provided by Dr. Mohamed Shaalan, Professor of Surgery, BCFE Founding Chairman, Co-Director of prevention and early detection unit, NCI, and Lois Crooks, Volunteer Executive Director, General Secretary (2004-2008) and Founding Member.

BCFE website: <http://www.bcfе.org/>

## 5 CONCLUSIONS and RECOMMENDATIONS

### CONCLUSIONS

The main conclusions of this first-phase situation analysis can be summarized in five points:

1. BC in Egypt is still 4 times less frequent than in Western countries; however, due to delayed diagnosis of the disease and suboptimal treatment, the mortality/incidence ratio is higher than in Western countries
2. Given that the most important risk factors of BC are reproductive factors which are non-modifiable, prevention has no potential for major effect. Only secondary prevention (i.e., early diagnosis) has the power to achieve a significant reduction in mortality.
3. In Egypt as in many developing countries, BC is still diagnosed late, with tumors of size above 2 cm in 80% to 90% of cases.
4. Preliminary results suggest that the main barriers to early detection in Egypt are women's awareness about BC, but also first-line medical staff's knowledge and awareness about the disease. Thus, to strengthen knowledge about BC symptoms among first-line health staff and to streamline referral could potentially reduce delayed diagnoses. Training of first-line health staff have shown to be a cost-effective way to improve late-stage distributions in other countries with similar situations.
5. Screening programs are complex health interventions that demand significant time and resources to implement. The "clinical down-staging" approach recommended by the WHO, which includes an important component of medical training, appears to be an advantageous approach to fill the gap until screening reaches full coverage of the country.

### RECOMMENDATIONS

The idea of screening by clinical breast exam has received little support from the Egyptian medical community. A similarly low level of support may greet the clinical down-staging approach, all the more since it is a new concept introduced by the WHO less than two years ago. Demonstration projects together with advocacy are required to convince health professionals and decision makers of the potential benefit of such approaches.

Only a clear understanding of all the obstacles to early diagnosis and treatment will permit the building of a successful clinical down-staging program, it is therefore important to conduct barrier studies prior to action.

Therefore our main recommendations would be:

1. To study in depth the barriers to early diagnosis and treatment existing across Egypt, whether they are related to women's awareness and beliefs or to health-system shortages.
2. To conduct a demonstration program of clinical down-staging in one or several pilot communities, with careful evaluation and assessment.
3. To delay initiating national public awareness programs until women's barriers are well understood and the major health-system barriers are addressed.
4. To initiate studies of survival by stage in Egypt (see proposal 5.5 below). Such data are necessary to assess whether there is room to reduce BC mortality by improving some aspects of patient treatment and follow-up; to date, these data are lacking.

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## APPENDIX 1. The Gharbiah population-based cancer registry

Valid information about cancer incidence, prevalence and mortality in a population can only be provided by a population-based registry. Indeed hospital registries do not cover a well define population. Some patients resident in the governorate where the hospital is based may go for treatment elsewhere, while some patients from other governorates may come to the hospital, making the recruitment population of the hospital unclear.

The Gharbiah Cancer registry is a population-based registry which was established within the context of the Middle East Cancer Consortium joint cancer registration project, a NCI-US Office of International Affairs initiative. The registry is located in the Tanta Cancer Center of the MoHP. Tanta is the capital city of Gharbiah Governorate situated in the middle of the Nile delta about 100 km north of Cairo. The registry is jointly sponsored by the MECC and the MoHP of Egypt. The registry is composed of one coordinator/data-manager and 5 technicians and secretaries. In addition, medical doctors of the Tanta cancer center actively collect data through regular visits to all public and private centers and laboratories dealing with cancer patients in Gharbiah Governorate. Centers in Cairo, Mansoura and Menofia that deal with cancer patients are also visited regularly to collect data on Gharbiah patients who might be treated there. Death certificates are also reviewed.

In 1999, the registry started recording all incident cases among the approximately 3.5 millions residents of the Gharbiah Governorate. Although notification of cancer is not obligatory by law, a ministerial decree that was issued to request collaboration with the registry enhanced data collection effort. To date, the Gharbiah cancer registry has published two reports, one in 2002 covering year 1999 and one in 2007 covering years 2000-2002.

The data of the Gharbiah cancer registry have reached the quality criteria to be included in the 9<sup>th</sup> edition of the WHO-IARC regular publication "Cancer Incidence in Five Continents." "Cancer Incidence in Five Continents" (C15) is a worldwide recognised reference published since 1966. Today, to be included in the C15 constitutes the highest quality validation a cancer registry can expect.

The 1999-2002 incidence and age-specific incidence data of the Gharbiah cancer registry are available online, together with 225 other population-based registries data from all over the world, on the WHO-IARC website at <http://www-dep.iarc.fr/> (menu: C15 IX)

## APPENDIX 2. DEFINITIONS

### Incidence

Incidence is the number of new cases arising in a given period in a specified population. This information is collected routinely by cancer registries. It is usually expressed as a rate per 100,000 persons per year. It provides an approximation to the average risk of developing a cancer.

### Mortality

Mortality is the number of deaths occurring in a given period in a specified population. It can be expressed as an absolute number of deaths per year or as a rate per 100,000 persons per year.

### Survival

It is defined as the probability of survival, expressed as time elapsed since diagnosis (1,3 5-year survival). This *observed* survival probability is influenced by mortality both from cancer of interest and from other causes. For this reason, *relative* survival is usually calculated. It is defined as the ratio of the observed survival in the group of patients to the survival expected in a group of people in the general population, who are similar to the patients with respect to all possible factors affecting survival at the beginning of the follow-up period, except for the disease of interest.

### Crude rate

Data on incidence or mortality are often presented as rates. For a specific tumor and population, a crude rate is calculated simply by dividing the number of new cancers observed during a given time period by the corresponding number of people in the population at risk. For cancer, the result is usually expressed as an annual rate per 100,000 persons at risk.

### ASR (age-standardized rate or age-adjusted rate)

An age-standardized rate (ASR) is a summary measure of a rate that a population would have if it had a standard age structure. Standardization is necessary when comparing several populations that differ with respect to age because age has such a powerful influence on the risk of cancer. The most frequently used standard population is the World standard population. The calculated incidence rate is then called the World Standardized incidence rate. It is also expressed per 100,000.

### APPENDIX 3. Stage & TNM

Staging is the process of describing a cancer, such as where it is located, if or where it has spread, and if it is affecting the functions of other organs in the body. Doctors use diagnostic tests to determine the cancer's stage, so staging may not be complete until all of the tests are finished. Knowing the state of the disease helps the doctor plan a treatment and determine a prognosis (likely outcome or course of the disease). Cancer with a lower stage is usually associated with a better prognosis.

Many groups have developed different staging systems. The 2 major staging systems in use for BC in Egypt include: the SEER Summary Staging and the American Joint Committee on Cancer (AJCC) staging scheme based on the TNM System.

#### SEER Summary staging

Seer summary staging is the most basic way of categorizing how far a cancer has spread from its point of origin. It is also called Summary staging, General Staging, California Staging, and SEER Staging. It should be noted that this classifications in mainly used by registries and do not take into account tumor size or other pathological features as does the American Joint Committee on Cancer (AJCC) TNM (tumor, node, metastasis) classification. There are 4 categories in the Seer summary staging:

1. IN SITU: The presence of malignant cells within the cell group from which they arose; no penetration of basement membrane of the tissue; no stromal invasion.
2. LOCALIZED: A malignancy limited to the organ of origin; no spread beyond organ of origin; infiltration past basement membrane of epithelium into stroma of organ. Tumor can be widely invasive or even show metastases within the organ itself and still be considered "confined to organ of origin) or localized.
3. REGIONAL: Tumor extension beyond limits of organ of origin (by direct extension or to lymph nodes)
4. DISTANT: A tumor which has spread to areas of the body distant or remote from the primary tumor. Distant metastases are comprised of tumor cells which have broken away from the primary tumor and have traveled to other parts of the body. Also called metastatic.

#### TNM

The TNM Staging System is one of the most commonly used staging systems. This system was developed and is maintained by the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC). The TNM system is based on the extent of the tumor (T), the extent of spread to the lymph nodes (N), and the presence of metastasis (M). A number is added to each letter to indicate the size or extent of the tumor and the extent of spread.

T = Tumor Size: T1 = 0-2 cm, T2 = 2-5 cm, T3 = >5 cm, T4 = ulcerated or attached

N = Node Status: N0 = clear, or negative nodes, N1 = cancerous, or positive nodes

M = Metastasis: M0 = no spread of tumor, M1 = tumor has spread

AJCC staging

In the AJCC staging scheme, the TNM results are combined to determine the stage of cancer for each person. Stages are written as Roman numerals one through four (I, II, III, or IV).

Stage	T (tumor size)	N (node status)	M (metastasis)
<b>0</b>	Pre-cancerous		
<b>I</b>	T-1	N-0	M-0
<b>II</b>	T-0 to 2 T-2 T-3	N-1 N-0 N-0	M-0
<b>III</b>	T-Any T-3 T-4	N-2 or N3 N-1 or N-2 N-Any	M-0
<b>IV</b>	T-Any size	N-Any status	M-1

Correspondences between the SEER and AJCC staging systems

- § Localized corresponds roughly to stage I
- § Regional corresponds roughly to stage II and III
- § Distant corresponds to stage IV