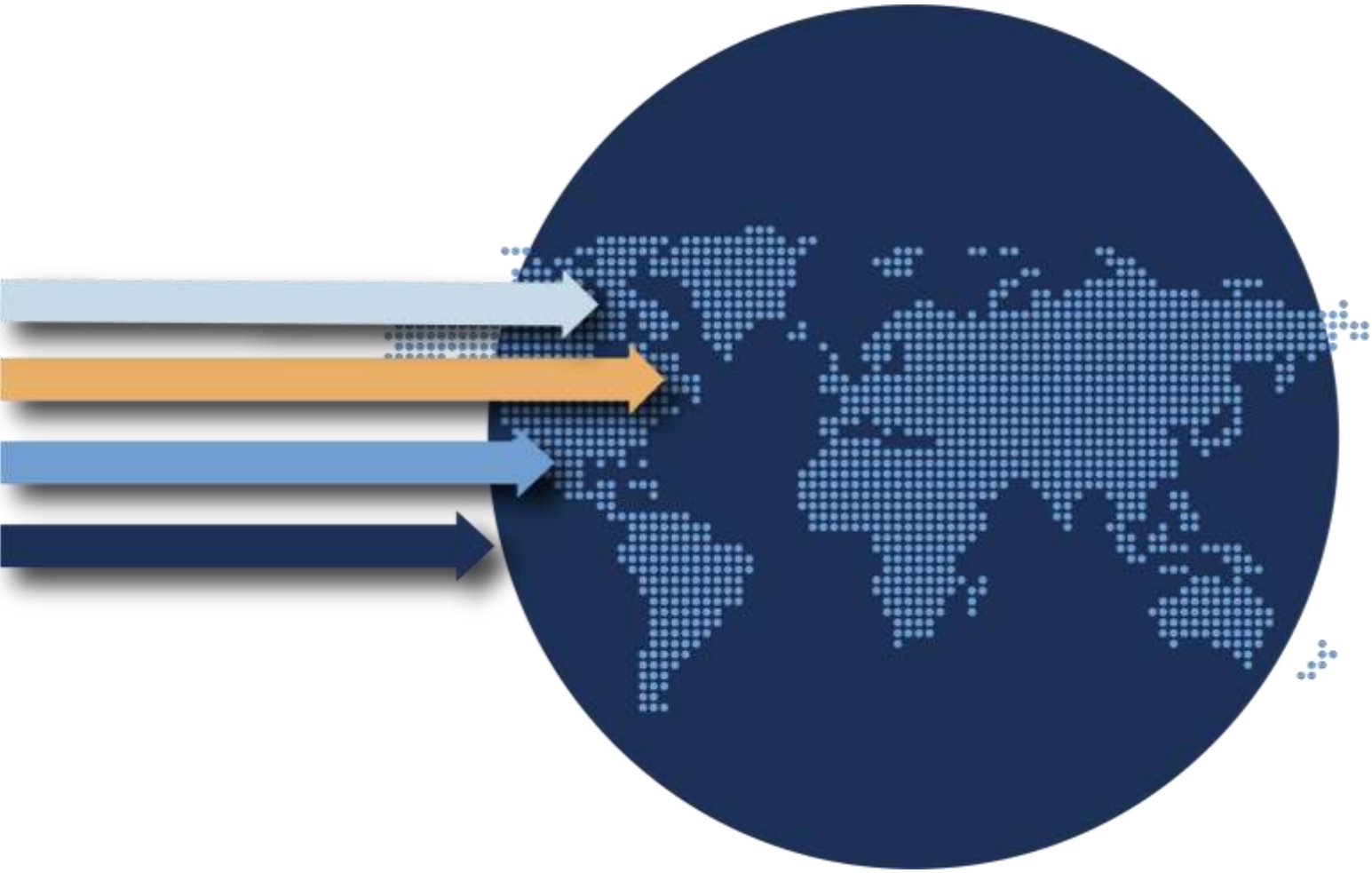
AN ASSESSMENT OF BREAST CANCER AND ITS MANAGEMENT IN IRAN



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Executive Summary

This research report aims at identifying the burden of breast cancer in Iran and explore how the health care system's organization, financing and resource management impact services and outcomes for breast cancer. The project aims to support Iranian health authorities in identifying and prioritizing policy options for improving breast cancer care and patient outcomes.

The report is entirely based on publicly available data (in English).

Chapter 1 – Health burden and cost of breast cancer in Iran

This chapter presents a summary of the epidemiology, the health burden and available data on costs.

- The age-standardized incidence for breast cancer in Iranian women is 31 per 100,000 population (WHO 2018); the latest update from the Iranian Registry indicates 34.5 per 100,000 population. These estimates are close to the average in less developed regions (31/100,000) but much less than the average in more developed regions (78/100,000). Incidence is expected to increase particularly in older women.
- The age-standardized mortality of breast cancer is 8.7 per 100,000 population which is among the lowest reported for any country. The ratio of mortality to incidence is about 1:3.
- 5-year prevalence is estimated at around 42,800 cases, 50% lower than in Turkey with a similar size population and age structure (68,300 cases).
- Breast cancer accounts for 15% of disability-adjusted life-years (DALYs) in Iranian women, with three quarters of the loss occurring in the age group 30-59 years.
- Data on direct and indirect costs for breast cancer are limited, but it has been estimated that indirect mortality costs constitute the largest part of costs.
- Drug sales data from 2016 indicate a cost in range of 180 M USD, of which trastuzumab (HER2 positive breast cancer) accounts for one third.

Chapter 2 – Medical review of breast cancer

This chapter reviews and summarizes current knowledge of breast cancer and its management, including data and studies from Iran when available, and addresses

- Breast cancer definition, diagnosis and prognosis
  - Biology of tumour cells and new innovative treatments
  - Prevention of breast cancer
  - Early detection of breast cancer
  - Breast cancer diagnostic techniques
  - Prognostic and predictive factors in breast cancer

- Therapy
  - Surgery
  - Radiotherapy
  - Medical treatment
  - Supportive care
- Clinical guidelines
- Clinical effectiveness

Over the last forty years, several new methods for management of breast cancer have been introduced, with documented improvements in both survival and quality of life. Since these new options have different costs and different outcomes, dependent on how they are implemented, it has become more complicated to make policy decisions that optimize the use of resources for management of best cancer.

Chapter 3 - Policy options, analysis, conclusions and recommendations

From the review in chapters 2 and 3, one can conclude that

- the number of breast cancer cases in Iran will increase as demographics change
- breast cancer appears today under-diagnosed
- breast cancer is currently diagnosed late compared to other countries, and consequently patients will have poorer prognosis
- prevention and screening programs are limited and, when existing, show low participation rates
- data on use of surgery, radiotherapy and medical therapy are limited, making it difficult to assess the appropriateness of existing clinical practice
- regional differences in detection and treatment appear large indicating a potential for improvement
- data on the direct and indirect cost of breast cancer are scarce, but indirect costs due to premature mortality appear to constitute the highest cost

We have not found a clearly expressed vision and mission for breast cancer care, based on defined objectives for survival and quality of care. This is important for mobilizing and allocating resources, and for assessing progress, for health care systems that focus on patient relevant outcomes and value-based care.

The observed improvements in outcomes from breast cancer management are a consequence of several different actions in combination. The number of alternatives is also increasing through continuously improved medical knowledge and innovation. New methods for prevention, early detection, surgery, radiotherapy and new cancer medicines can all contribute to improved outcome, and the difficult choice is to find the right balance suitable for each patient. But policy is not only

about doing the right things, it is increasingly important to do things right; i.e. implementation in clinical practice. Thus, there is a shift from evidence generated through experimental clinical trials, towards real world evidence generated from data and studies in clinical practice.

Thus, the major issue in Iran, as in other health care systems, is a lack of properly organised data that would allow developing appropriate policies for breast cancer care, and for evaluation of their implementation and outcomes.

Recommendations

The major recommendation is thus the need for development of an information structure to support policy, resource allocation and clinical decisions for breast cancer management. This includes not only epidemiological data such as collected in the registry, but also data about treatment patterns, resource use and outcomes (including quality of life) in clinical practice.

A second recommendation is to develop a system for assessing the costs and cost-effectiveness of different management strategies for breast cancer management in clinical practice. The number of alternatives for breast cancer management will increase, and questions about efficiency, i.e. outcome in relation to resource use, will be of increasing importance for health policy. This is not only important for eliminating waste and inappropriate use, but also for an evidence-based introduction of new diagnostic and therapeutic alternatives. Without a proper account of the present use of resources and outcomes achieved, it is not possible to define policy options for improvement, and monitoring of progress towards defined objectives.

Observing the issues around under diagnosis and late diagnosis of breast cancer, a third key recommendation is to run awareness and education campaigns with the aim to achieve earlier diagnosis in an even fashion across all regions. Such campaigns can be supported with well-designed prevention and screening programs for defined risk groups. Such programs should be carefully followed-up and adjusted according to the experience from their implementation.

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Table of Contents

Chapter 3

Foreword

Cancer is the second leading cause of death in the world. The disease panorama differs across regions and countries, but the burden of cancer is increasing everywhere. It is therefore perhaps not surprising that cancer policy in many places has taken center stage in the policy debate.

Among women, breast cancer is the most prevalent form of cancer. It is an area where there have been significant medical advances leading to 5-year survival rates around 90 % in the best performing health care systems today. Ensuring correct and early diagnosis and access to the relevant treatments thus become key.

In this report, the authors give a comprehensive overview of breast cancer in Iran. This is done by analyzing not only the epidemiology of the disease but also its associated costs and disease burden along with an overview of the medical developments in the field. A range of important issues pertaining to health policy in this area are discussed. Although the disease burden of breast cancer in Iran is high and increasing, medical advances and improved infrastructure help alleviate the problem.

This work was funded by a grant from Roche Pars. Responsibility for the analysis and conclusions lies solely with the authors.

Lund, Sweden, September 2019

Peter Lindgren
Managing Director, IHE

Chapter 1

Health burden and cost of breast cancer in Iran

Table of Contents

List of Figures

List of Tables

1. Health burden and cost of breast cancer in Iran

1.1. Introduction

The World Health Organization (WHO) defines cancer as follows: "Cancer is a generic term for a large group of diseases characterized by the growth of abnormal cells beyond their usual boundaries that can then invade adjoining parts of the body and/or spread to other organs". Other common terms used are malignant tumours and neoplasms. Cancer can affect almost any part of the body and has many anatomic and molecular subtypes that each requires specific management strategies.

Cancer is the second leading cause of death globally, accounting for 9.5 million deaths in 2018. It is the leading cause of death in high-income countries, accounting for nearly one quarter of total mortality. It is generally classified as a disease associated with ageing, although it affects people in all ages. In men, lung, prostate, colorectal, stomach and liver cancers are the most common types, while breast, colorectal, lung, cervix and stomach cancers are the most common cancers in women.

The health burden of cancer varies between countries but is increasing everywhere over time due to a changing disease panorama and the aging of populations. It can be described and quantified in different ways, and the different measures are complementary. Incidence and mortality are the basic parameters, while survival is a calculated measure based on these. Disability adjusted life years (DALY) is a measure that combines morbidity and mortality to express total burden and is used for comparisons between diseases and countries.

According to WHO (Globocan 2018), the overall cancer incidence in ***Iran*** (age standardised rate, ASR to world population, excluding non-malignant skin cancer) is 138 per 100,000, which is lower than the world average (198/100,000) and the WHO European region (255/100,000), but above the average of the WHO East Mediterranean region (124/100,000). (The most recent data from the Iranian Cancer Registry (2014) estimates the total cancer incidence at 142.5 per 100,000, and at 129.5 per 100,000 in females.) The mortality rate is 74 per 100,000, which is lower than for Sweden (84) and Switzerland. However, the ratio of mortality to incidence is significantly lower in these countries (0.3) compared to Iran (0.5).

The age standardized incidence for breast cancer in Iranian women in 2018 was 31 per 100,000 (WHO). This is close to the average in lower-middle income countries (31/100,000) but much lower than the average in high income countries (78/100,000). The latest update of the Iranian

Cancer Registry (2014) estimates the ASR at 34.5 per 100,000 (13,120 patients). The age-standardized mortality of breast cancer is 8.7 per 100,000, among the lowest reported for any country. The ratio of mortality to incidence is about 1:3.

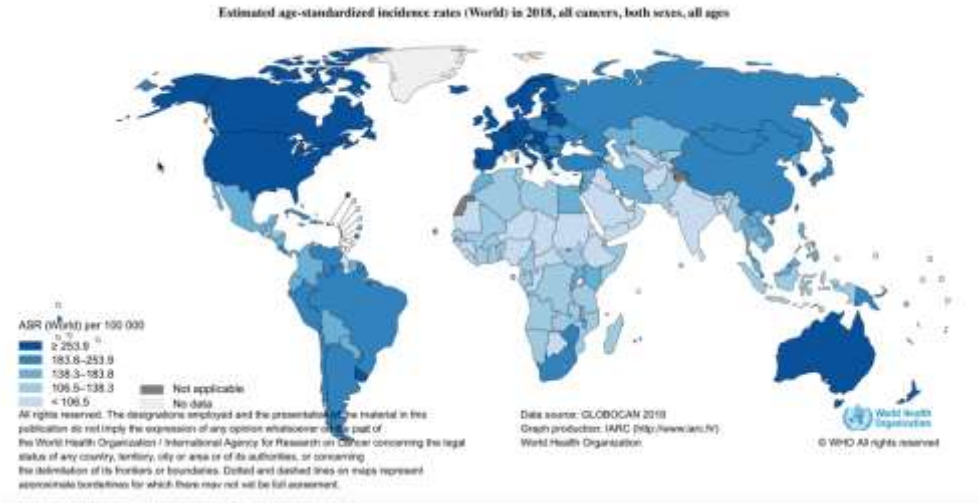


Figure 1-1 *- Estimated age-standardized rates of incidence cases, both sexes, all cancers worldwide, 2018*

Source: World Health Organization, Department of Health Statistics and Information Systems, August 2019

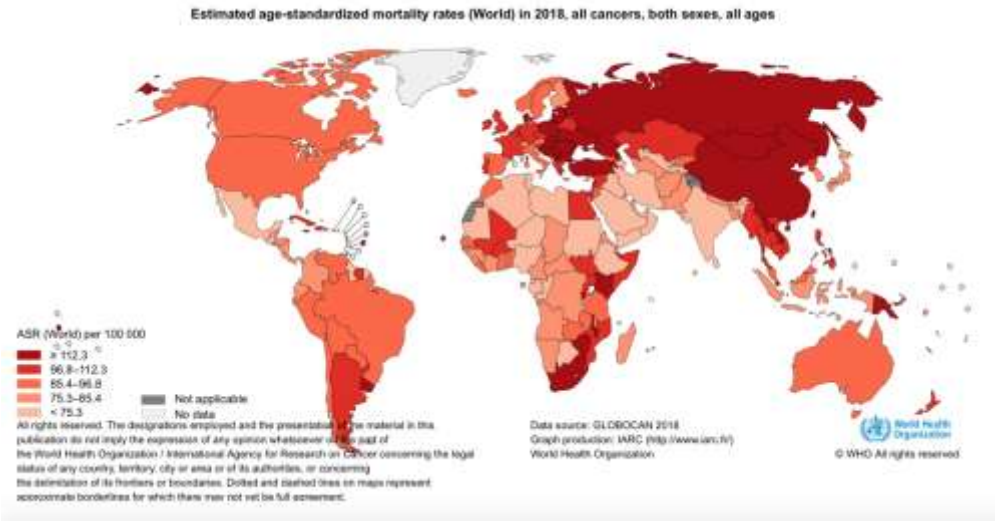


Figure 1-2 *- Estimated age-standardized rates (World) of deaths, both sexes, all cancers worldwide in 2018*

Source: World Health Organization, Department of Health Statistics and Information Systems, August 2019

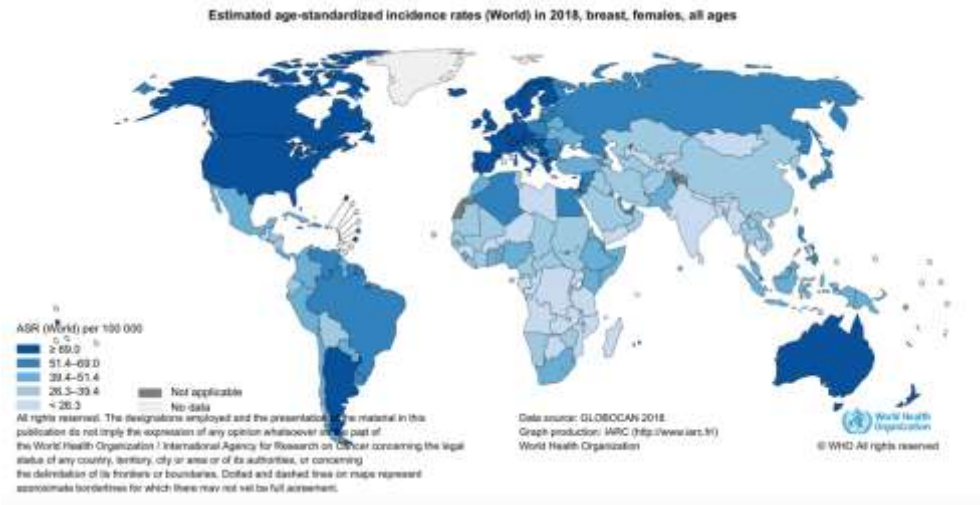


Figure 1-3 *- Estimated age-standardized rates of incident cases, female breast cancer, worldwide in 2018*

Source: World Health Organization, Department of Health Statistics and Information Systems, August 2019

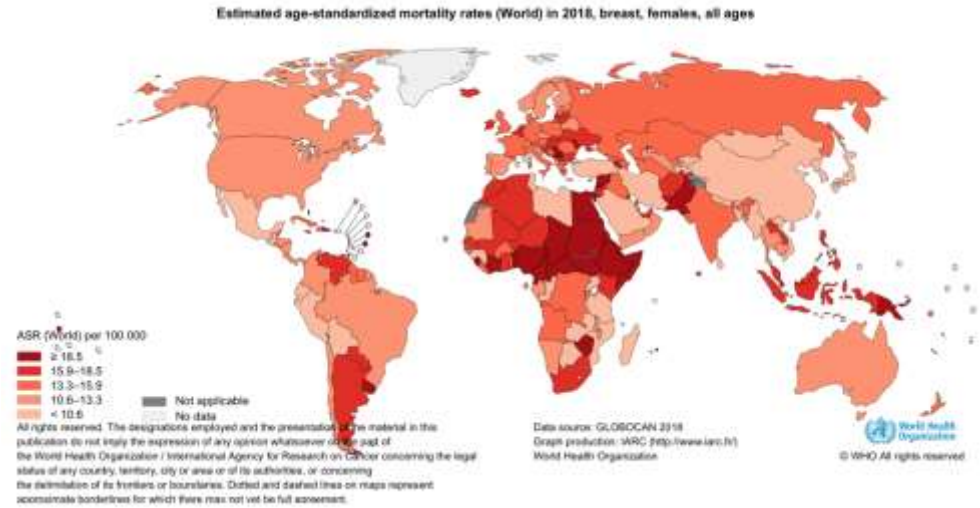


Figure 1-4 *- Estimated age-standardized rates of deaths, female breast cancer, worldwide in 2018*

Source: World Health Organization, Department of Health Statistics and Information Systems, August 2019

Cancer accounted for 7% of all DALYs in 2000 and increased to 7.5% in 2012 and 9.2% in 2016 in ***Iran***. The increasing share of cancer is seen in other countries as well, but cancer accounts for a smaller share of all health losses in Iran than, for example, in Western Europe; in many Western European countries cancer is the major health burden, accounting for about one fifth of all DALYs. Breast cancer accounts for 8% of all DALY lost due to cancer in the Iranian population and for 17% in Iranian women, with three quarters of the loss occurring in the age group 30-59 years. It is estimated that 23% of new breast cancer cases in low-and-middle income countries (LMIC) occur in women below 50, compared to 10% in high-income countries. According to data from Globocan 2018, in Iran this proportion is 56%.

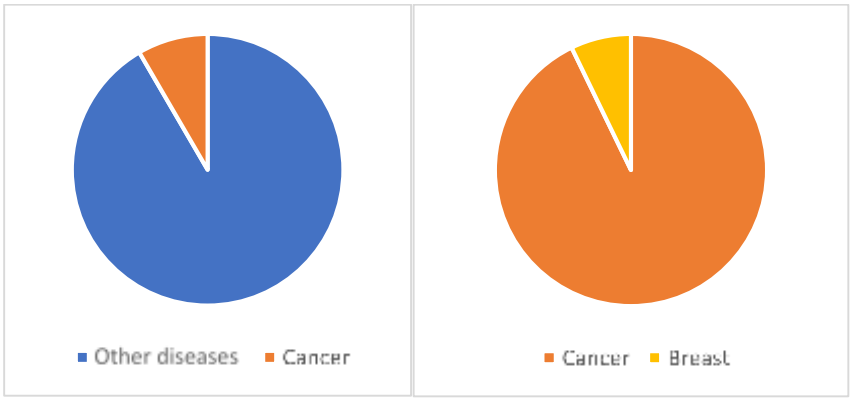


Figure 1-5 *- DALYs in Iran 2016. Share for cancer of all diseases (9.15%) and share of breast cancer of all cancers (7.74%)*

Source: World Health Organization, Department of Information Evidence and Research, June 2018. Estimated DALYs ('000) by cause, sex and WHO Member State, 2016

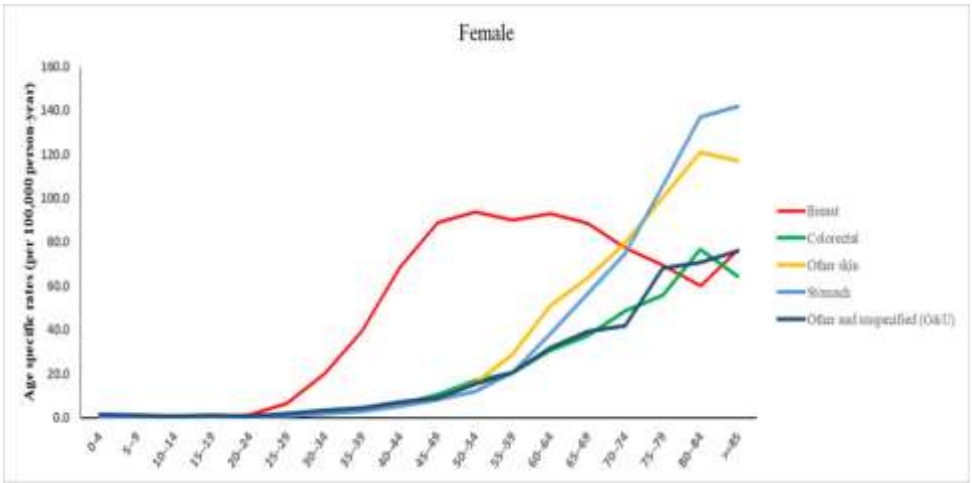


Figure 1-6 *– Age specific incidence rates, 5 most common cancers in women (Iran 2014)*

Source: Annual Report 2014, Iranian Cancer Registry

1.2. Health burden of breast cancer

1.2.1. Incidence

A review of the epidemiology of breast cancer in **Iran**, published in 2007, concluded that it was well studied, but that uncertainties around estimates still remained.[1] The incidence of breast cancer in women was estimated at 22 per 100,000 and the 5-year prevalence at 120 per 100,000. Stage I was diagnosed in 18%, stage II in 57% and stage III in 25% of the cases. In potentially curable cases, stage I was about 72% of the patients were diagnosed with a tumour larger than 2 cm. Sixty-three per cent of patients had lymph node involvement at the time of diagnosis. For comparison, the incidence rate in Turkey was estimated at 35.8 per 100,000 in 2004-6.

In a study of the first 10 years of the national cancer registry (NCR) of Iran, a total of 52,068 cases were found with the coding of primary breast cancer. [2] Women constituted 97.1% of the cases, with a mean age of 49.6 years (95%CI 49.5-49.6). Breast cancer was the leading type of cancer in Iranian women, accounting for 24.6% of all cancers. Most of the cases (95.7%) were registered as invasive. The most common morphology of primary breast cancer was invasive ductal carcinoma (ICD-O 8500/3), followed by invasive lobular carcinoma (ICD-O 8520/3) with relative frequencies of 77.8% and 5.2%, respectively. The average annual crude incidence of primary breast cancer in females was estimated at 22.6 (95%CI 22.1-23.1) per 100,000 women, with an age-standardized rate (ASR) of 27.4 (95%CI 22.5-35.9).

The latest data from Globocan (2018) report a total of over 13 000 cases (*Table 1.1*), which mirrors the estimate of 10,000 incident cases in 2010 in a paper by Rashidian and colleagues [3] and the most recent update on data from the Iranian Cancer Registry.

More recently a higher number of actual incident cases were recorded in the Iranian cancer registry (13,120 cases, ASR 34.5/100,000, Figure 1-7). [Data on file, cancer registry]. This indicates increased coverage. But there may still be underreporting due to limited access to and participation in opportunistic screening. The magnitude of this is difficult to estimate, and different estimates may have different policy implications, but a comparison with Swedish and Turkish data can be of interest, at least as a background for a policy discussion.

Table 1-1 - *Incidence and mortality of breast cancer (ICD 10 code C50) in different age groups in Iran*

Age group	Incidence	Incidence rate	Mortality	Mortality rate
0 - 14	3	0.0	2	0
15 - 39	3897	15.2	525	2.0
40 - 54	5258	75.3	1132	16.3
55 - 69	3649	86.4	1203	29.1
70 +	969	76.2.	664	50.8
All	13 776	31.0	3526	8.7*

*ASR (W).
Source: GLOBOCAN 2018

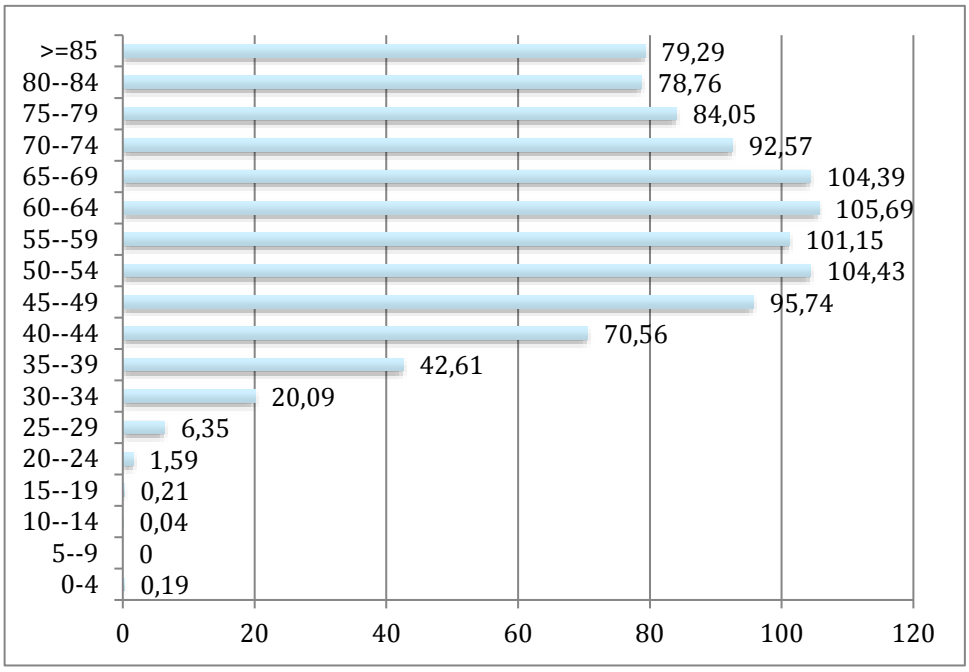


Figure 1-7 *– Updated incidence data from the Iranian Cancer Registry (2018)*

Data from the Iranian cancer registry shows that the highest incidence is in the age group 50-69 years, and a rapidly increasing incidence with age in the group 25-49 years.

Table 1-2 below shows that the crude incidence in Iran is five times higher in Sweden. This is partly explained by the higher age of the Swedish female population (the difference in the ASR is only slightly under three-fold), and a higher detection rate through more screening. The difference in the age standardized mortality rate is only about 25% between Sweden and Iran. Table 1-2 also indicates that it is in the older age groups where mortality in Sweden is higher, indicating that under-diagnosis in Iran is more frequent in these age groups.

Comparing Turkey to Iran, both crude incidence and mortality are about 55% higher in Turkey, with a similar distribution across age groups. According to Globocan, the incidence of breast cancer in women in Turkey was 46 per 100,000 in 2018.

The size of the population is similar in the two countries (around 80 million inhabitants) and so is the age structure (24% below 15 and 6% above 65 in Turkey; 27% below 15 and 5% above 65 in Iran). The incidence and mortality differences thus give an indication of under-diagnosis in Iran. However, other causes for these findings may be differences in risk factor profiles: Smoking is more frequent in Turkey (14% versus 1% of females in Iran) and obesity is more prevalent (40% of females compared to 32% in Iran)

Table 1-2 *- Comparisons of breast cancer incidence and mortality in Iran to Turkey and Sweden*

		Incidence rate			**Mortality rate**		
	Iranian Registry 2014	**GLOBOCAN 2012**					
Age group	***Iran***	Iran	Turkey	Sweden	Iran	Turkey	Sweden
15-39		10.7	16.6	20.5	2.7	4.1	1.6
40-44	***70.56***	55.6	75.8	110	14.5	18.9	11.1
45-49	***95.74***	76.1	97.9	162	20.9	26.5	19
50-54	***104.43***	87	112.8	218	26	33.2	28.9
55-59	***101.15***	87.9	119.6	271	29.4	39.2	39.3
60-64	***105.69***	81.2	116.5	312	32.9	45.7	49.6
65-69	***104.39***	76.3	112.6	327	37.3	52.7	59.4
70-74	***92.57***	71.8	106.2	329	42.2	60.2	73.3
75+		68	97.6	300	48	68.1	136
All	***34.5 (34.5)****	26.3 (28.1)*	40.8 (39.1)*	139 (80.4)*	8.9 (9.9)*	13.9 (13.4)*	30.5 (13.4)*

*ASR (W).
Source: GLOBOCAN 2012, IARC - 28.10.2017

Another way of looking into the magnitude of a potential underestimation is to compare incidence and mortality rate in different regions of Iran. The figure below illustrates differences in cancer incidence in females in Iran. The four-fold difference in the incidence of all cancers is similar to that seen for breast cancer.[4] As for variations seen between countries, population age structure and a number of other variables may explain the regional variations observed within the country, but evaluation would require more in-depth studies.

While regional variations can be useful as a basis for policy analysis, the conclusions are not obvious and depend both on the quality of the data and the precise question.

Jazayeri and colleagues report data on breast cancer from four regions, showing a higher than average incidence in Ahvaz and Shiraz provinces, 35 per 100,000 and 44 per 100,000, respectively, and a lower than average incidence in Mashad and Tabriz provinces, 25 per 100,000 and 23 per 100,000, respectively.[2] Mahdavifar and colleagues report more detailed data on regional variations in the period 2005-6, with the highest incidence in Teheran (43/100,000) and the lowest (below 12/100,000) in four regions, with an average for the country of 33 per 100,000.[4] Ten years later, a new report from the Iranian cancer registry on regional incidence in 2014 shows very similar, large variations between 13 and 51 per 100,000 cases. (National Report of the Cancer Registry, in publication.)

Figure 1-8 *Age-standardized incidence rates of all cancers per 100,000 females in Iran 2005-2006*

Source: [4]

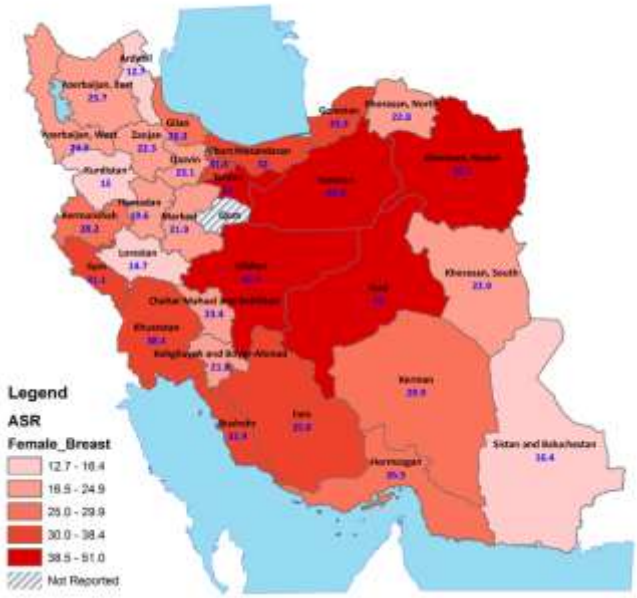


Figure 1-9 *Age-standardized incidence rates of breast cancer per 100,000 females in Iranian regions (2014)*

Source: Report of the National Cancer registry, in publication 2018.

In Turkey, regional differences have been identified in survival studies [5]. According to the authors of the study, a lower rate is explained by advanced stage at diagnosis, lack of breast cancer awareness and other societal, educational, cultural and economic barriers to early diagnosis and effective treatment. One could argue that these conditions also apply in parts of Iran.

Several studies from Iran indicate that incidence of cancer is increasing over time.[6, 7] However, they are based on short-term series, and changes in reporting over time make it difficult to make precise conclusions about the magnitude of the increase and the impact on it by different factors.

1.2.2. Mortality

A number of studies in **Iran** have estimated mortality from breast cancer. Mostafa Enayatrad and colleagues estimated the number of deaths caused by breast cancer during 2006 to 2010 in 29 provinces.[8] In women, breast cancer mortality increased from 3.93 in 2006 to 4.92 per 100,000 inhabitants in 2010. A study focusing on metastatic breast cancer reports that 6,160 cases are diagnosed each year of which 1,063 lead to death.[9] A study by Valipour estimates mortality to 3304 cases in 2012 and 3742 in 2015.[10] Daroudi et al report deaths for 10-year age groups for 2010 (see table below).[11]

Table 1-3 *- Mortality in different age groups in Iran*

Age group	Number of deaths
>20	4
20-29	84
30-39	487
40-49	994
50-59	960
60-69	682
70<	687
Total	3898

Source: Daroudi et al (2015)

Breast cancer mortality in Iran is increasing due to both population growth and population aging and thus an increase in incidence. At the same time, it is decreasing due to reductions over time in age standardized mortality rates. The net effect is an increase over time.[10, 12, 13] The table below shows a prediction of future incidence and mortality of breast cancer.[10]

The total burden of breast cancer mortality will increase over time, but since mortality is postponed to higher ages, the number of life years lost during economically active years is decreasing.

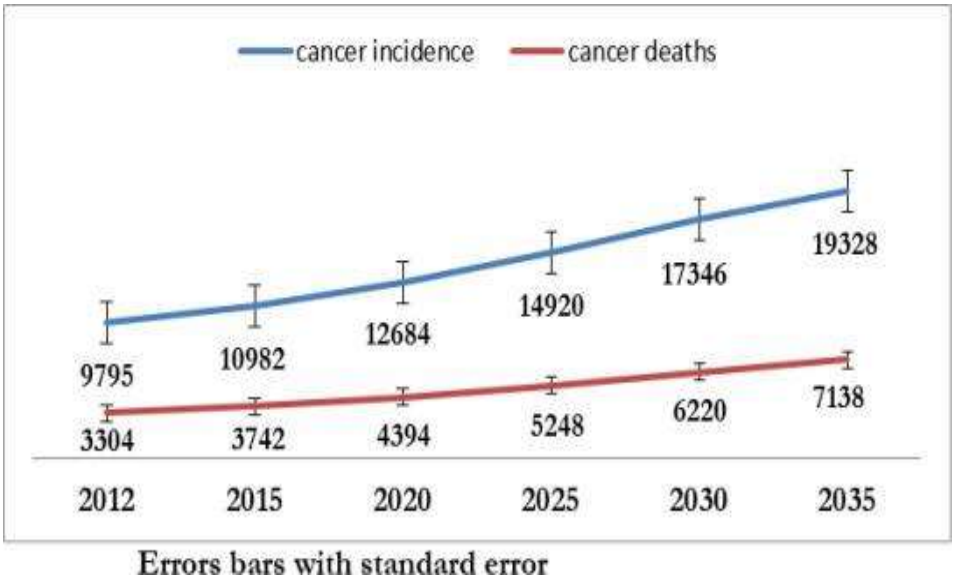


Figure 1-10 *-- Predicting future incidence and mortality of breast cancer in Iran 2012-35*

Source: Valipour et al, 2017

1.2.3. Survival

Three recent studies present estimates of survival after breast cancer diagnosis based on systematic reviews and meta-analysis. [14-16]

Table 1-4 *- Survival in breast cancer in Iran*

Study	1-year	3-year	5-year	10-year
Rezaianzadeh (2017)			67.6%	
Rahimzadeh M (2016)	95.6 %	80.8%	69.5%	55.9%
Abedi G (2016)	95.8% (94.6-97.0)	82.4% (79.0-85.8)	69.5% (64.5-74.5)	58.1% (39.6-76.6)

A national study investigating survival rates published in 2012 evidenced differences in survival by geographic region. The study identified 25,618 cases in the period 2001-2006, of which 24% could be interviewed (patients and/or family); there was no statistical difference between the total population and the study subjects. Men represented 2.8% of cases, 55% were aged 50 or less and 90% had invasive ductal carcinoma. Five-year survival ranged from 62.1 (SD 0.043) to 76.2 (0.025) depending on the region. [17]

For comparison, the Surveillance, Epidemiology and End Results (SEER) program of the US National Cancer Institute showed a 5-year survival rate of 89%. This compares to an average age-adjusted rate of 57% in developing regions and a rate as low as 46% in India. In Turkey, a difference in 5-year survival rates was observed within the country, with estimates of 86% in Istanbul to 60% in East Anatolia.[5]

Rezaianzadeh and colleagues (2017) report an increasing five-year survival rate in Iran over time, with the latest estimate at 75%. While improved survival is one of the most, if not the most important, outcomes and policy objectives, there are a number of issues involved in interpretation of both variations between and within countries and over time. The survival rate of breast cancer is lower in Iran compared to high-income countries, indicating a potential for improvement. In high-income countries, early diagnosis increases incidence through early detection, and thus the ratio mortality/incidence may be reduced without a reduction in mortality. Careful analysis of the determinants of inter-temporal and inter-regional variations is necessary in order to conclude which actions have a potential to improve the situation. However, increased incidence and improved survival will lead to increased prevalence of breast cancer, with more patients in need of care within the health care systems and will live with a diagnosis of breast cancer.

1.2.4. Prevalence

Breast cancer accounts for about a quarter of all cancer cases in women in Iran when we look at incidence, but one third of all cases if we compare 5-year prevalence.

Table 1-5 - Estimated incidence and 5-year prevalence of cancer per 100,000 adult female population in Iran (2018)

Cancer	Incidence	Prevalence
All cancers excluding non-malignant melanoma	110 115	248 392
Breast	13 776	40 825
Stomach	11 644	15 722
Lung	6 695	6 461
Colon	6 556	15 822
Bladder	6 041	17 284
Prostate	6 004	13 841
Leukaemia	5 437	15 561
Brain, central nervous system	4 639	12 345
Oesophagus	4 372	4200
Thyroid	3 963	13 812
Liver	3 492	2 671
Rectum	3 085	7 947
Non-Hodgkin lymphoma	2 988	8 394
Pancreas	2 257	1 460
Larynx	2 004	4 654
Kidney	1 983	5 091
Ovary	1 773	4 928)
Multiple myeloma	1 514	3 492
Corpus uteri	1 370	4 271
Lip, oral cavity	1 282	3 634
Hodgkin lymphoma	1 140	4191
Cervix uteri	917	2 613
Gallbladder	849	977
Testis	544	2 052
Melanoma of skin	499	1 492
Nasopharynx	364	1 123
Salivary glands	361	893
Anus	223	576
Oropharynx	112	336
Kaposi sarcoma	102	276
Hypopharynx	96	151
Vagina	54	156
Vulva	51	166
Mesothelioma	44	49
Penis	28	84

Source: GLOBOCAN 2018

Comparing with incidence and prevalence numbers for breast cancer in Turkey provides a further indication of the underdiagnosis of breast cancer in Iran. Five-year prevalence is 50% higher in

Turkey according to Globocan data for 2018 (see below), having increased by 17.5% between 2007 and 2012.[5]

Table 1-6 *- Comparison of incidence and 5-year prevalence of breast cancer in Iran and Turkey (2018)*

	Incidence	Prevalence*
Iran	13 776 (31.0)	40 825(100)
Turkey	22 345 (45.6)	68 288 (164)

Source: GLOBOCAN 2018. * Per 100 000

Daroudi and colleagues estimated that the number of new breast cancer cases was about 10,000 and the 5-year prevalence was 39,316 in 2010.[11] This is close to the estimate from Globocan 2012. This prevalence rate excludes women diagnosed more than five years ago. With a 10-year survival of 58% [16], the 10-year prevalence will be about 55,000, and an estimate of all women living with a diagnosis of breast cancer about 80,000. For reference, in Sweden and in the US the prevalence of breast cancer is more than ten times higher than the incidence.

It is positive that the population of survivors is expected to continue growing. But a consequence is that many survivors face a number of challenges even after their cancer has been "cured", for example long-term side effects of treatment and/or psychological effects that can affect quality of life. Survivorship is drawing attention and prompts studies about these effects and how to mitigate them. Survivorship programs can make a big difference in the length and quality of survivors' lives. Survivorship also extends to caregivers and family members. See the American Cancer Society (ACS) and the American Society of Clinical Oncology (ASCO) guidelines on breast cancer survivorship care published on Dec. 7, 2015 in *CA: A Cancer Journal for Clinicians*. (American Society of Clinical Oncology Breast Cancer Survivorship Care Guideline. http://ascopubs.org/doi/full/10.1200/jco.2015.64.3809)

1.2.5. Burden of disease measured as DALY

Increasing incidence and prevalence indicate that the health burden of breast cancer is increasing in Iran. [18, 19] However, increasing survival and postponing death reduce the health burden in terms of life years lost. The DALY used by WHO to evaluate the health burden illustrates the effect of combined changes in morbidity and mortality. The table below shows the estimates for 2000 and 2012 for Iran, with 113,800 and 127,000 DALYs for breast cancer. For comparison, DALYs in Turkey are 140,600 and 189,400. With an average equal life-expectance in the two countries (75 years), the difference is explained by the lower incidence and prevalence in Iran.

***Table 1-7** - Estimated DALYs ('000) by cause in Iran. Women in 2000, 2012 and 2016*

Type of cancer (cause)	2000	2012	2016
All malignant neoplasm	736,0	764,8	825,9
Breast cancer	113,8	127,0	137,6
<15	0	0	0
15-29	7.1	6.9	3.7
30-59	86.7	93.5	101.1
60-69	13.5	16.6	22.8
70+	6.6	10.0	10.0
Stomach cancer	67,8	66,8	67.9
Colon and rectum cancers	56,1	62,8	72.4

Source: World Health Organization, Department of Information Evidence and Research, June 2018. Estimated DALYs ('000) by cause, sex and WHO Member State, 2016

The estimates above indicate an increase in the health burden of cancer overall and of breast cancer for women in Iran between 2000 and 2016. Data for stomach and colon/rectum cancers, the second and third most common in females in Iran, are provide for reference. It is, however, important to keep in mind that the data used in these estimates are limited to one region in Iran. Also, the estimate of DALYs for cancer is dominated by calculations of life years lost, and thus primarily derived from mortality estimates. For females, breast cancer accounts for 15% of all DALYs lost from cancer, and three quarters of the loss is in the age group 30-59 years. Stomach and colon/rectal cancers are second and third in terms of DALYs from cancer for females. Due to the better survival in breast cancer compared to other cancers, the share of DALYs for breast cancer is lower than the share for incidence and prevalence.

1.3. Economic burden of breast cancer

The economic burden of cancer is not limited to the health care resources used for patients with cancer. Resources are also used for public and private care of cancer patients outside the health care sector (e.g. palliative care, care provided by family members), as well as through the loss of productive contributions by individuals with cancer.

While primary care is almost exclusively provided by the public system, specialist care is provided by both public and private actors. According to WHO estimates, private care accounts for 10-20% of services, and patients are subject to co-payments.

Among private service providers, throughout Middle-Eastern countries, non-governmental organisations (NGOs) provide a broad spectrum of services ranging from running full service

cancer hospitals to support with co-payment for drugs. In ***Iran*** NGOs have 3 important roles in cancer management: Prevention, treatment and palliation. They typically run information and prevention campaigns on cancer, on ways of early detection, self-examination particularly in breast cancer, etc. In the treatment setting, a small number of them (e.g. Behnam Daheshpoor) provide full service for cancer care including chemotherapy and radiotherapy, but limit themselves to financial and non-financial support such as co-payment for drugs, transfer and housing for patients from other provinces and cities, transportation of patients to treatment places as necessary, etc. Finally, some of them provide palliative care services.

Informal care by family and friends is an important complement to professional care, and estimates indicate that this amounts to between one third to half of the costs of formal care.[20] However, few studies of the cost of cancer formally include these costs.

Indirect costs related to the loss of production for persons with cancer are estimated to be of the same magnitude as the direct health care expenditures. Indirect costs related to premature mortality dominate the estimate of indirect costs, but those costs have declined over time, despite increasing incomes, due to reduction in mortality of cancer in the economically active age groups. Estimates of indirect costs due to morbidity are uncertain, and vary significantly between published studies.

> *On the side lines of the first conference on prevention and early diagnosis of cancer held around the World Cancer Day on February 4, 2017, Iraj Harirchi, the Iranian deputy health minister, pointed to the burden of the disease and its direct and indirect costs. (Financial Tribune February 05, 2017. https://financialtribune.com/articles/people/58864/cancer-costs-iran-25b-annually)*
> *"Cancer costs $2.5 billion (100,000 billion rials) each year, of which $750 million (30,000 billion rials) are direct costs (for costly medications)", he noted. Stating that sales data on cancer drugs from the Health Ministry is used to calculate the share of direct costs of the disease, he said, "Around $375 million (15,000 billion rials) is spent on chemotherapy drugs, which is the cheapest way to enhance the five-year survival rate for the disease." According to Iraj Harirchi, "about 83% of the direct costs are paid by the government and the remaining is paid out of pocket by the patients."*
> Since total health care expenditures in Iran amount to about $90 billion according to WHO ($82 billion in 2014), cancer accounts for about 3.3% of total health care expenditures. This is in line with data from other countries, showing the share of direct health expenditures on cancer to be significantly lower than the share of cancer on the disease burden (DALYs).
> *Indirect costs are resources lost due to inability to work and cancer death. According to Iraj Harirchi, the latest estimated annual mortality of cancer in Iran was 30,000 deaths (today over 50 000), accounting for 8% (today 15%) of all deaths in the country. Although the rate of cancer deaths has significantly*

decreased compared to earlier decades, the average survival rate of 30 to 35% is far lower than the global rate of 66%.

A full accounting for the costs of cancer should include an estimate of the health burden of cancer. Loss of quality-adjusted life years (QALY) can be measured and valued based on the willingness to pay for a QALY. Such estimates are possible to derive from decisions about allocating resources for cancer. There are few estimates of these costs, but available studies indicate that the intangible costs of lost QALYs are by far the dominating cost of cancer. [21]

Daroudi and colleagues have published a comprehensive estimate of the economic burden of breast cancer in Iran for 2010. The study found that indirect costs due to premature mortality dominate costs, representing 77% of total costs. Medical costs are dominated by costs of chemotherapy and terminal care. The results are summarized below.

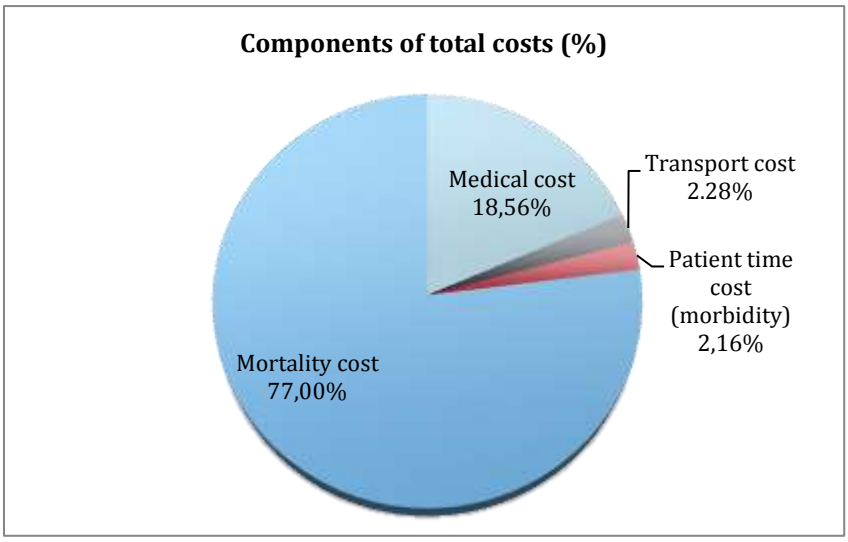


***Figure 1-11** - Share of different costs in breast cancer (Daroudi et al, 2015)*

1.3.1. Comments on estimates of the cost of breast cancer in Iran

In the following sections, we comment on the specific estimates in this study.

1.3.1.1. Direct cost calculations

Daroudi et al used a cross-sectional study in Isfahan to calculate the direct medical costs of breast cancer among women. The medical records of all patients registered in Seyed Al-Shohada Hospital between March 2005 and March 2010 were reviewed and the relevant data on resource utilisation extracted. The direct costs of medical services received were calculated with both public and private tariffs.[22] A total of 467 patients in various disease stages of disease with a mean age of 49 years were included into the study.

The average direct cost per patient per month in stages I to IV were US$ 222.17, 224.61, 316.51 and 828.52, respectively. The cost of surgery was the main cost for stages I and II, using private tariffs, while the cost of medication was the main cost component for stages III and IV.

Direct medical costs were estimated for three different categories: inpatient care, outpatient care and terminal care. Inpatient costs were estimated using medical records in one hospital of the Cancer Institute of Iran. Because the tariff for medical services is identical across Iran, the results from this center were generalized to the country. The public tariff may differ from actual costs and probably the private sector tariff is a better indicator of real cost than the public.

All costs are estimated as per patient costs, including the drug costs, and then multiplied with the estimated number of patients in each resource category. This "bottom-up" method is a natural choice with the data used, but has the disadvantage that errors in the estimation of per patient costs will be multiplied in the calculation of total costs. There is thus a need for a validation of the aggregate estimate.

The table below shows the direct medical cost estimates.[11]

Table 1-8 *- The direct medical costs of breast cancer in Iran, 2010 (in US $)*

Procedures	Number of patients	Mean cost, $US	Total cost, $US	Total cost (percent)
Diagnosis/staging	10000	158.91	1,589,100	0.90
Surgery	10000	1287.85	12,878,500	7.32
Radiotherapy	8120	923.48	7,498,658	4.26
Chemotherapy	9500	4760.68	45,226,460	25.72
Trastuzumab	2400	13137.20	31,529,280	17.93
Hormone Therapy & Fallow-up	34756	632.64	21,988,036	12.50
Terminal care	3867	14261.85	55,150,574	31.36
Total	-	-	175,860,607	100.00

The calculation is based on an estimate of the number of patients who in a given year have diagnosis/staging and surgery (equal to the incidence), radiotherapy (81%), chemotherapy (95%),

trastuzumab (24%), hormone therapy and follow up (5-year prevalence), and terminal care (equal to mortality). Thus, the method can be described as a prevalence study based on incidence and mortality. It fits the bottom-up approach, but makes it difficult to relate the final estimate to traditional descriptions of medical costs, such as hospital care, ambulatory care and drugs.

It is difficult to extrapolate costs estimated in 2010 to current costs without more detailed data. Sales data from Amarnameh (sales report from the MoH) indicate that total trastuzumab costs have more than doubled from US$ 32 million in 2010 to US$ 67.5 million in 2016. As the MoH reports sales by drug, not by indication, it is impossible to extract sales for all treatments used in breast cancer. The table below shows sales for drugs exclusively used in breast cancer.

Table 1-9 - *Sales of breast cancer drugs in Iran (2016)*

Drug name	US$ (mid-year exchange rate 2016)
LAPATINIB 250MG TAB	29,258
TAMOXIFEN CITRATE 20MG TAB	313,176
TAMOXIFEN CITRATE 10MG TAB	355,104
PERTUZUMAB 420MG/14ML VIAL	118,133
LETROZOLE 2.5MG TAB	5,142,093
TRASTUZUMAB 440MG VIAL	45,172,710
TRASTUZUMAB 150MG VIAL	22,327,074
EXEMESTANE 25MG TAB	2,828,051

Source: Amarnameh (MoH Annual Report) 2016

Transportation costs were the only cost outside health care included in the estimation of direct costs in the study, excluding thus informal care by family or by private providers (including NGOs). In the initial phase of care patients were estimated to have had around 50 trips; after the first year, they had about 7 trips per year, at a mean cost per journey of about US$29. Patients were thus estimated to have spent US$21,606,293 on transportation during their treatment. This appears high, as is the same as the cost of hormone therapy and follow-up, twice the cost of surgery, two thirds of the cost of Trastuzumab and more than patients' time cost (sick leave, see indirect costs). Also, a single trip costs 30% more than the average daily income for employed and three times the income for women not working.

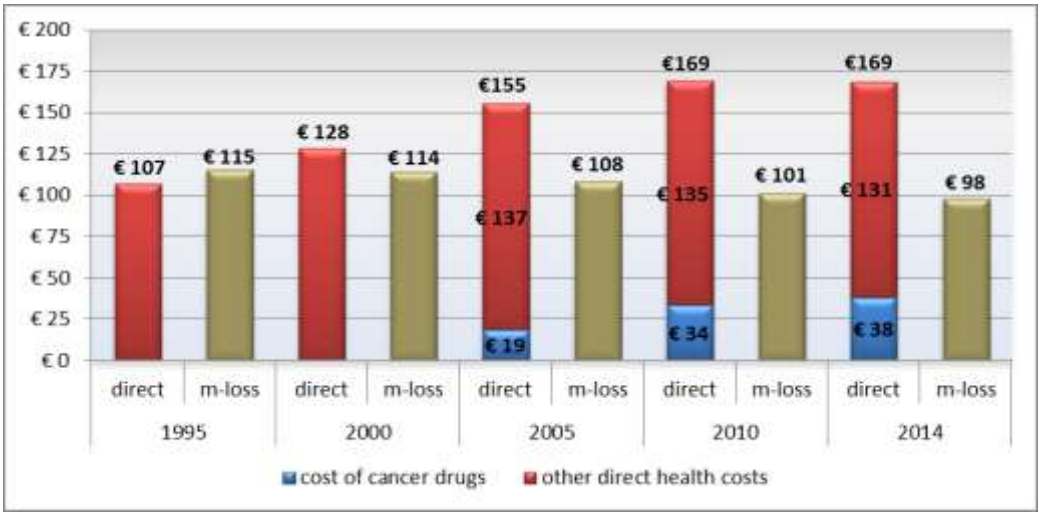
In view of the importance of real-world data, a recent claims data analysis estimated the direct medical cost of HER2-positive breast cancer management. [23]. The authors identified 1295 women in the Social Security Organisation (SSO) in the period of March 2011 to March 2014. Patients were classified as "early", "loco-recurrent" and "advanced" and costs (both public and private sector) estimated for the period. The mean age in the three groups was 45, 46 and 48 years,

with a follow-up of one year. Medical costs were estimated at $11796, $8253 and $17742, respectively. These estimates in a subgroup of patients are, however, difficult to relate to the overall direct costs in Iran.

1.3.1.2. Indirect cost calculations

Indirect costs due to loss of production from breast cancer are of two types: related to morbidity (absence from work) and to mortality (premature death). In the sample used by Daroudi et al, the mean time of absence from work during treatment and follow-up was 23.63 days. With a mean daily wage for employed and unemployed women of US$22.35 and US$9.67, respectively, patients' time cost was estimated at about $20 million in 2010 (or less than 3% of total indirect costs).

The mortality of breast cancer in 2010 in Iran was estimated at 3898 cases. Most patients who died were in the age groups of 40–49 and 50–59 years and the total mortality cost was estimated at $729 million, or 97% of total costs. While it is expected that indirect costs due to mortality will be dominating in Iran (considering the young age at diagnosis and low survival rate due to a aggressive tumours in younger females, late diagnosis and partially limited access to treatment), these results may still indicate that indirect costs due to morbidity are underestimated. Studies from high-income countries estimate indirect costs of mortality to about 60% of total indirect costs. Comparing indirect costs due to mortality with direct health care costs in Iran, the ratio is 4:1, which can be compared to 1:1 in Sweden (excluding the costs of screening). Again, this has to be seen in the light of younger age at diagnosis and more aggressive tumour types. The figure below illustrates the development of direct and indirect costs over time in Europe. Direct costs have increased and stabilized, while indirect costs due to mortality have decreased in real terms. [24]



"direct" = direct health cost of cancer; "m-loss" = productivity loss due to premature mortality from cancer. Cancer is defined as ICD-10 C00-D48 for direct health costs, and C00-C97-B21 for productivity loss.

***Figure 1-12** - Relationship between direct and indirect costs over time in Europe (2014 prices; IHE Report 2016:4)*

1.3.1.3. Approach to a revised estimate of the economic burden of breast cancer in Iran

To better understand the economic burden of breast cancer in Iran the study by Daroudi et al requires both interpretation and updating. One way to interpret costs is to compare to both different and similar countries. Updating will require verifying whether the use of individual types of resources has increased more than others, both as a consequence of new treatments and of changed incidence/prevalence, or whether costs have essentially increased according to GDP.

The table below shows an approach to a comparison. Two Swedish studies one decade apart illustrate how costs have developed (expressed in 2010 USD). We observe a two-fold increase in cost of screening, a moderate increase in cost of ambulatory care, a four-fold increase drug costs and a small reduction in indirect costs. Changes in direct costs are very much as expected, with the increased focus on screening in Sweden, a trend towards outpatient care, and the introduction of high-priced drugs. Changes in indirect costs on the other hand are more difficult to interpret, as a large number of factors both related to the disease and to other economic conditions exert an influence. Most obvious is the declining costs due to mortality, a consequence of improved survival and reduction of mortality for women diagnosed with breast cancer at working age. Indirect costs for morbidity may increase with longer treatment periods and improved survival, but may decrease due to a shift to ambulatory treatment and less adverse side effects of treatments. Estimates are also hampered by access to relevant data, which makes comparisons of estimates over time problematic.

Table 1-10 *- Estimates of costs of breast cancer (USD millions, in 2010)*

Cost item	Daroudi 2010	Lidgren 2003 Sweden	Lundquist 2013 Sweden	Percent increase	Iran 2016 (extrapolation)
Direct Health care cost	176	125	210	68%	260-80
Screening		28	54	94%	
Ambulatory care	24	40	53	32%	30
Inpatient care	75	45	50	10%	85
Drugs	77	12	57	389%	155
Direct costs outside the health care system					
Transportation	21				
Informal care			634		
Indirect cost	749	294	277	-6%	
Morbidity	20	140	113	-19%	
Mortality	729	154	164	6%	
Intangible cost		919	-		

Source: [21] [20]

Sweden as a country is not very comparable to Iran, but has the advantage to provide abundant and good quality data. Using this cost development over a decade as basis for a rough estimate of current costs in Iran, taking into account the actual doubling in sales of trastuzumab (see above), we would expect total health care costs to reach around 260-280 million USD, of which drugs would represent about 60%.

In conclusion, the Daroudi study should be updated, and more detailed data on consumption provided. Ideally, such an update should include data on ambulatory care (separate by primary and specialized care), inpatient care (separate by public and private inpatient care), surgery (by type of surgery), radiotherapy (by type), drugs (hormone therapy, chemotherapy, trastuzumab); in addition, transportation costs and informal care should be included. For indirect costs, the cost of mortality and morbidity should be reassessed.

1.3.2. Financing

Although financing, i.e. who pays for what, is not part of the burden of a disease, it can influence, or sometimes explain, consumption, both under-consumption and over-consumption. It is thus interesting to briefly summarize the financing of breast cancer care in Iran.

According to WHO, the share of government expenditure of total health care represented 53.4% in 2015, up from 36.9% in 2005. This indicates a substantial effort in public financing of health care, but the share remains below the average of around 75% in OECD countries. On the other hand, the share of health care in total government expenditures of 22.6% is is similar to OECD countries. There are four main health insurance organisations that benefit from government financing at various levels (the Social Security Insurance Organisation, the Medical Services Insurance Organisation, the Armed Forces Medical Services Insurance Organisation and the Imdad Committee Health Insurance). Private expenditure represents just under half of total health expenditure (46.6%), and the majority (85%) are out-of-pocket payments.

1.4. Discussion and conclusions

The incidence of breast cancer in Iran is lower than in high-income countries and in low-middle-income neighbouring countries.

Screening programs of breast cancer in Iran have failed to enhance the early detection of breast cancer. The difficulties to implement effective screening programs make it interesting to consider targeted programs for prevention.

The development of a national cancer registry has improved collection of data on cancer care as information for rational policy decisions, but the register for breast cancer is not yet accurate enough to be able to monitor the effect of screening programs or determining the current status of breast cancer treatment in Iran.

There were no data on survival, staging or biological markers of the breast cancer registered cases [2].

Data on direct and indirect costs are limited, but necessary for development of rational policies for improvements of outcome.

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Chapter 2

Medical review of breast cancer

Table of Contents

List of Figures

List of Tables

2. Medical review of breast cancer

2.1. Introduction

Breast cancer is not one disease, but a variety of diseases with different characteristics requiring different therapeutic approaches. Breast cancer management is also characterized by a multimodal therapy approach including screening, diagnosis, surgery, radiotherapy and an increasing number of anti-tumour drugs. Optimal management of breast cancer requires multidisciplinary teams including at least surgeons, radiation oncologist, medical oncologists, diagnostic radiologists, pathologists. The contributions by the different experts will actually provide better foundation for early detection and cure of breast cancer [1].

In this chapter we will provide an overview of current breast cancer management and – where relevant, and if data is available - reflect on the situation in ***Iran***.

2.2. Breast cancer definition, diagnosis and prognosis

2.2.1. Biology of tumour cells and new innovative treatments

Knowledge about the human cell and the genome, and progress in molecular medicine has led to a better understanding of breast cancer evolution and cancer cell characterization by defects in the DNA repair mechanisms, leading to an accumulation of genetic defects. The development of invasive breast cancer is a process with many steps, with an accumulation of genetic aberrations occurring over a long-time period (5-20 years). Cells have important repair mechanisms (P53 is the most known), and not until several and concurrent genetic aberrations occur cancer cells can develop, and the tumour is a fact.

Oncology is in a new paradigm with novel innovative drugs targeting different functions and pathways in the cancer cell (compared to earlier treatments targeting all fast dividing cells). This knowledge may reduce the need for unselective and highly cell-toxic treatments, with problematic side-effects. At the same time the targeted drugs have different toxicity panorama, also requiring surveillance. Today most of the research of breast cancer drugs focus on the aspects of targeting cell functions. [2].

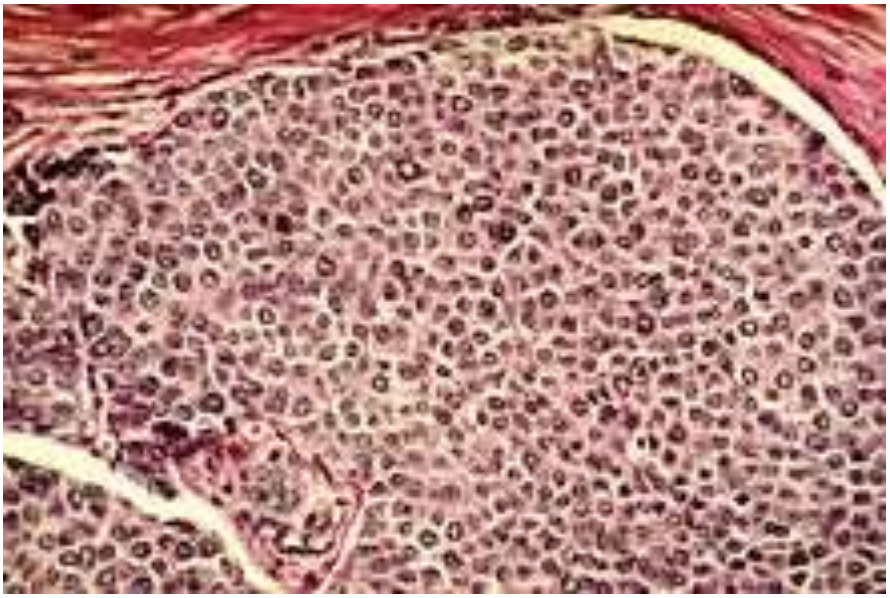


Figure 2-1 *- Breast cancer cells*

2.2.2. Prevention of breast cancer

Epidemiological research has shown that breast cancer risk is associated with various external and lifestyle factors such as high alcohol consumption, obesity, low exercise habits and exposure to certain viruses. Also, different hormonal treatments influence breast cancer risk, and combination treatments of oestrogen and progesterone (contraception, hormone replacement therapy) may increase the risk. In a small case control study in 521 ***Iranian*** women, family history, oral contraceptives usage, low parity, employment and shorter period of breast feeding were related to a higher risk of breast cancer in young women [3].

It is generally estimated that 20–30% of breast cancers are related to genetic factors that in combination with lifestyle factors can lead to an increased risk of development of the disease. Around 4-7% of breast cancer cases are directly attributable to certain genetic mutations, most commonly in the BRCA1 and BRCA2 genes, which predispose women to a 60-80% life-time risk of developing breast cancer, often at a young age. For women with a high genetic predisposition for breast cancer, preventive measures should be taken, including more frequent screening or chemoprevention with endocrine therapy. These latter drugs may, however, have a limited impact, since BRCA1 carriers are frequently endocrine unresponsive. The most established strategy is preventive surgery including removal of the breasts, although the evidence base for this strategy is limited [4].

The relationship between hormone exposure and breast cancer was the rationale for the first chemoprevention trials with the anti-hormone tamoxifen in women with an increased genetic risk of breast cancer. Treatment with tamoxifen, raloxifene or aromatase inhibitors resulted in a 50-60% risk reduction[5-7]. A recent review confirms that the use of tamoxifen and raloxifene reduces

the incidence of invasive breast cancer. Subgroup analyses and decision models suggest that high-risk women, particularly those who have had a hysterectomy, have the greatest benefit with the least harm [6, 8-11]. The fact that there are agents that can prevent cancer is in itself an important milestone in oncology.

In March 2010, a group of breast cancer experts met to develop a consensus statement on breast cancer prevention, with a focus on medical interventions. Of the two approved drugs, tamoxifen was considered the better choice that can be used even in pre-menopausal women, although raloxifene has fewer side-effects. Two newer drugs in this class, lasofoxifene and arzoxifene, have also shown to be efficacious, with possibly a better overall risk-benefit profile. However, they need further assessment. Aromatase inhibitors might be more efficacious based on results from prevention trials. New contralateral tumors in women with breast cancer might be useful as model for prevention, as has been seen for tamoxifen. Such a model would facilitate the design of simpler, cheaper, and better-focused trials for assessing new agents [12].

The American Society of Clinical Oncology (ASCO) has recently issued updated clinical guidelines for chemoprevention. In women at increased risk of breast cancer and aged ≥ 35 years, tamoxifen (20 mg per day for 5 years) should be discussed as an option to reduce the risk of estrogen receptor (ER)–positive breast cancer. In postmenopausal women, raloxifen (60 mg per day for 5 years) and exemestane (25 mg per day for 5 years) should also be discussed. According the National Cancer Institute Breast Cancer Risk Assessment Tool or an equivalent measure, increased breast cancer risk is defined as individuals with a 5-year projected absolute risk of breast cancer ≥ 1.66% or women diagnosed with lobular carcinoma in situ. Use of other selective estrogen receptor modulators or other aromatase inhibitors is not recommended outside clinical trials. Health care providers are encouraged to discuss the option of chemoprevention with women at increased breast cancer risk. The discussion should include the specific risks and benefits associated with each chemo preventive agent [13].

Cancer prevention is complex and involves social, political and medical aspects. Lifestyle changes can have an important effect on cancer incidence (primary prevention), as can good awareness of breast cancer. From a medical perspective, the main challenge is finding preventive agents/measures that are non-toxic and well tolerated.

There is limited information on preventive measures in ***Iran***. The focus has been on early detection by mammography screening (secondary prevention), but awareness of breast cancer and the risk associated with it (primary prevention) have been assessed. Balouchi et al found that, 62.4% of women in rural areas had a fair awareness of breast cancer risk factors, and around 50% had good awareness of mammography screening. Dianatinasab et al showed that diagnosis was almost 90 days

delayed among illiterate women. Several studies have concluded that in a country like ***Iran*** with a very diverse population base, the awareness factor is key. [14-16].

Based on a new program for early diagnosis of breast cancer in ***Iran*** a pilot phase started in 2015 then expanded; one of the main components is face-to-face awareness about risk factors and prevention options for breast cancer. Other strategies was promotion of public awareness regarding prevention and early detection of breast cancer in a national campaign for cancer around world cancer day (4 February) -that has been held annually in Iran from 2013- and specifically for breast cancer in October, each year.

2.2.3. Breast cancer early detection

It is needed to differentiate screening from early diagnosis. **Screening** is the process of identifying apparently healthy, asymptomatic persons who are at high risk of having clinically undetectable early disease while **early diagnosis** aims to detect cancer in its early stages, when treatment is simple and affordable, resulting in higher cure-rates.

Screening involves routine application of a screening test at specified intervals and referring those with "abnormal" (positive) screening tests for further diagnostic investigation. A screening test may be offered to many asymptomatic in a population; **population-based screening,** or it may be offered by to asymptomatic individuals during routine health care interactions, when it is called **opportunistic or spontaneous screening**.

Population-based screening programs are characterized by centralized screening invitations to a well-defined target population; systematic call and recall for screening; timely delivery of test results, diagnostic investigations, treatment and follow-up; centralized quality assurance; and a program database with linkages to other information systems (such as cancer- and death registration) for monitoring and evaluation of the program [17].

Mammography is the most common screening technique, although there is a certain level of false positives and therefore a risk of over-diagnosis. Mammography screening reduce the risk of death by about one third, according to Kalager et al. It is estimated that more than 70% of breast cancer deaths occur in non-screened women. The benefit of screening is related to the overall breast cancer risk, and the benefit is higher in high-risk groups. [1, 17] Mammography screening started in the 1980s in Sweden based on several randomized trials preformed during the 1970-80s [18]. More countries have followed, and currently mammography screening is offered in most western countries to women between ages 40/50 – 70 years. In middle income countries, mammography screening is also increasing as the standard of living improves [19]. However, population-based breast cancer

screening is a complex process and may not be feasible everywhere, as it requires expertise and well-established logistics. Screening programs need to be adapted to each specific country and situation.

World Health Organization (WHO) in the "position paper on mammography screening" categorized countries to three levels:

- Well-resourced settings
- Limited resource settings with relatively strong health care systems
- Limited resource settings with weak health care systems

In limited resource settings with relatively strong health systems, WHO suggests considering an organized, population-based mammography screening program for women aged 50−69 years only if the conditions for implementing an organized program specified in that guide are met by the health-care system, and if shared decision-making strategies are implemented so that women's decisions are consistent with their values and preferences. (Conditional recommendation based on moderate quality evidence) [18].

In ***Iran***, opportunistic or spontaneous screening mammography can be offered by a physician to asymptomatic individuals during routine health care interactions and is covered by insurance companies. A free-of-charge mammography screening pilot program was implemented in 2007-2009 in major provinces/cities in lower socioeconomic groups of women (comprising 29% of the population) in Iran. However, attendance was low (27%), and reasons for non-attendance were, for instance, shame, pain, fear of the risk of dying.

Below, we summarize graphically the information from *Iranian* studies on screening, extracted with permission from a literature review by Buchardt et al, 2018 (Masters Thesis, Karolinska Institute, Stockholm).

***Table 2-1** Summary of studies reporting on screening in Iran*

	Study design	Sample size	Screening (%)			Regular screening (%)			Never performed screening (%)		
			BSE	CBE	MMG	BSE	CBE	MMG	BSE	CBE	MMG
Jarvandi 2002	Cross-sectional	n=708	43	-	-	6	-	-	57	-	-
Montazeri 2003	Cross-sectional	n=410	56	-	-	6	-	-	44	-	-
Montazeri 2008	Cross-sectional	n=1402	37	-	-	17	-	-	63	-	-
Fouladi 2013	Cross-sectional	n=380	27.4	-	6.8	-	-	-	-	-	-
Hajian-Tilaki 2014	Cross-sectional	n=500	38.4	25.2	28.7 (>40yo)	10.2	4.2	-	61.6	74.8	-
Shiryazdi 2014	Cross-sectional	n=441	41.9	-	10.6	-	-	-	-	-	-
Ghahramanian 2016	Cross-sectional	n=370	43	23.8	39 (>40yo)	5.1	-	-	-	-	-
Anbari 2017	Cross-sectional	n=457		-	-	10.3	3.3	2.4		81.2	
Behbahani 2017	Cross-sectional	n=307	47.4	-	4.5	-	-	-	-	-	-
Farzaneh 2017	Cross-sectional	n=1134	53.8	9.8	29.9 (>40yo)	36.6	5.6	16.5 (>40yo)	-	-	-

BSE = breast self-examination; CBE = clinical breast examination; MMG = mammography

Clinical breast examination as an alternative low-cost screening tool in limited resource settings, and seems to be a promising approach. To date, there is no evidence from randomized controlled trials or observational studies that clinical breast examination -as a stand-alone primary screening modality for asymptomatic women- leads to reduction in breast cancer mortality compared to population-based screening programs. A shift towards early stage diagnosis has been observed in two ongoing randomized controlled trials of clinical breast examination in India, but no breast cancer mortality decline has yet been observed and further follow-up is continuing. Clinical breast examination as a screening tool leads to referral of around 5% of women for further assessment, which could consume health care resources in low- and middle-income countries. [17].

In limited resource settings with weak health systems, where the majority of women with breast cancer are diagnosed in late stages and mammography screening is not cost-effective and feasible, early diagnosis of breast cancer through universal access of women with symptomatic lesions to prompt and effective diagnosis and treatment should be high on the public health agenda [18].

The underlying foundation of every breast cancer early detection program should be the promotion of early diagnosis of breast cancer through both public awareness and professional education regarding signs and symptoms of cancer. It entails recognizing possible warning signs and taking prompt action, and requires education of the public to improve cancer awareness, training of health care professionals to improve their professional awareness and skills in recognizing early signs and symptoms of common cancers, prompt refer of suspected cases, availability, affordability and good access to diagnostic and staging investigations, treatment services and follow up care in public health services [17, 19].

Based on a new program for early diagnosis of breast cancer in Iran a pilot phasestarted in 2015 then expanded, one of the main components is face-to-face awareness about risk factors and prevention options for breast cancer. In this program women aged 30−69 years are assessed by midwifes at primary health care level regarding history of breast and ovarian cancer in the family and any suspicious symptoms of breast cancer are clinically examined. If women belong to high risk groups or if any finding in clinical breast examination, she is referred to second level for further evaluation a including visit of general physician or surgeon and mammography or sonography. Based on results of pilot phase, around 5% of women evaluated at first level need second level evaluation.

Other strategies for promotion of public awareness regarding prevention and early detection of breast cancer is a national campaign for cancer around world cancer day (4 February) that has been held annually in Iran from 2013 and specifically for breast cancer in October.

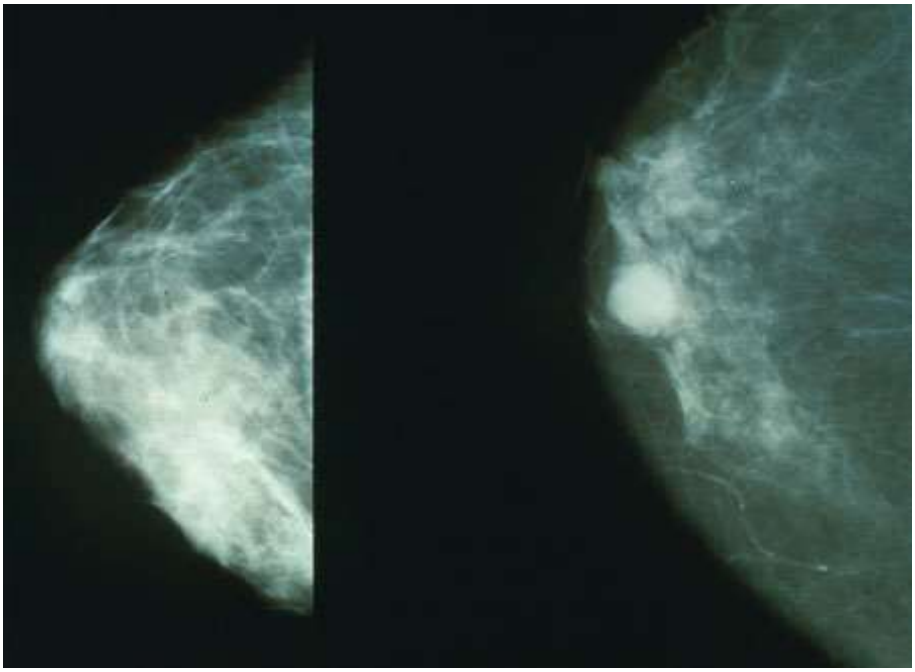


Figure 2-2 *- Mammography of normal breast tissue (left) and of cancer (right)*

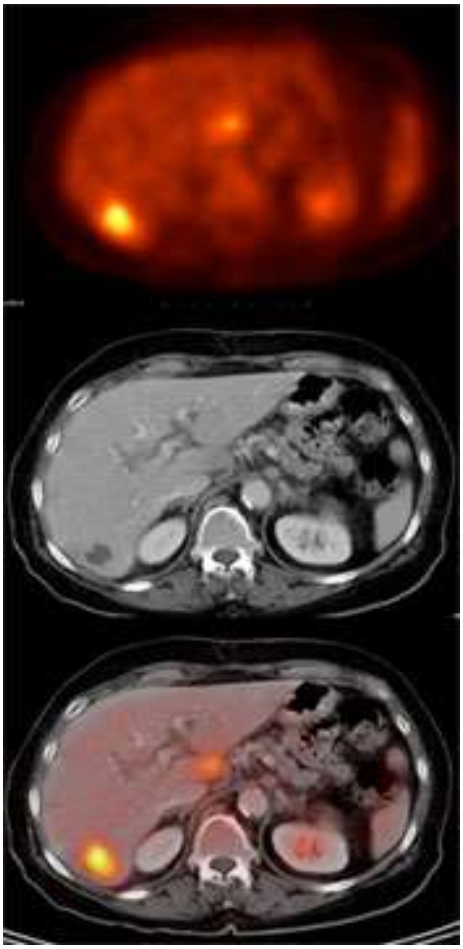


Figure 2-3 *- PET image (on top), CT middle, and PET/CT (bottom)*

2.2.4. Breast cancer diagnostic techniques

Different forms of radiology have come to play a key role in oncology, not only as a diagnostic tool but also as a method of evaluating efficacy of treatment by measuring progression or regression of tumors and metastatic lesions. The introduction of new radiological methods in the 1980s and 1990s such as Computerized Tomographic Scanning (CT) and Magnetic Resonance Imaging (MRI) have improved the accuracy of diagnosing potential metastatic lesions. MRI has improved the diagnostic ability, especially in patients with dense breasts (although there is a high proportion of false positives, ~30%). MRI can also be used for evaluation of treatment response. Currently, Positron Emission

Tomography (PET) in combination with CT (PET/CT) is increasingly used in clinical practice in many countries, as it differentiates between viable and non-viable tumor tissue. PET/CT provide better view of viable tumor tissue and distinction between organs.

Core Needle Biopsy (CNB) and Fine Needle Aspiration (FNA) Cytology are important tools in the diagnostic procedure. Fine Needle Aspiration cytology is very useful to confirm the primary diagnosis and for the follow-up of recurrences. Biopsy provides histologic material and is essential for primary diagnosis for detailed tumor specifications [20]. Core Needle Biopsy (CNB) is also necessary for primary diagnosis when medical treatment is considered as first treatment (neo-adjuvant treatment).

Advanced analyses of surgical specimen are cornerstones in molecular medicine. For instance, gene- and protein profiling techniques have contributed to an increased understanding of cell and cancer biology and provided a more accurate classification of various tumour forms. By analysing the gene expression of a wide range of breast cancer tumors, it has been possible to identify genes that provide tumour-specific characteristics. In some cases, it is also possible to predict if an individual tumour will respond to certain treatments [21, 22].

We did not find any data on usage of other radiological diagnostic techniques in ***Iran*** in the literature. One recent ***Iranian*** study by Ahmadinejad states that fine needle aspiration cytology is useful for lymph node staging [14, 15, 23-25] According to the **Iranian** cancer registry annual report (2014), cytology/pathology is performed for 77% of subjects with breast cancer.

2.2.5 Prognostic and predictive factors in breast cancer

The classical prognostic/predictive factors in breast cancer are tumour size, lymph node involvement, metastatic spread, morphology, hormone receptor status and age. For tumour specific diagnostics, the established methods apply in ***Iran*** (tumour size, lymph node involvement, metastases, TNM,

oestrogen receptor status, progesterone receptor status, HER2 status, proliferation). Molecular typing is being used in Iran but there is limited information in the literature to what extent.. One recent study in ***Iran*** noted that Ki67 (indicator for proliferation) is a good prognostic tool. Ki67 is routinely used in high-income countries [20-22].

- Tumour size: A primary tumour larger than 2 cm indicates a worse prognosis, with 20-year disease free survival of 64% compared to 79% with tumours of less than 2cm. In a review in the US (SEERS data) 30% of the small tumours was non-invasive, 30% had invasive tumours less than 1cm, and 37% had tumours 1-2cm. The 20-year survival rate was 98%, 93% and 88% for non-invasive tumours, invasive tumours less than 1cm, and invasive tumours 1-2cm, >2 cm, respectively. A recent study in Brazil by Freitas et al showed that only 27% of tumours are < 2cm at diagnosis [23-25].
  This compares to data from ***Iran*** that show that only 18.9% of patients are diagnosed with tumours less than 2cm [21, 26].
- Lymph node involvement: In untreated patients without tumour involvement of lymph nodes, the 5-year survival rate is 85%; if 4 or more lymph nodes have tumour involvement, the survival rate is only 26%. In the study from Brazil 75% of patients had no or < 3 nodes involved [25, 27].
  In ***Iran*** around 68% of patients have tumour involvement of lymph nodes at diagnosis [26].
- Metastasis: Metastatic spread of breast cancer to other organs at diagnosis is a sign of poor prognosis and shorter survival time. Around 25% of patients in the Brazilian study had advanced or metastatic disease. In Lebanon around 30-40% present with metastatic disease. Several studies show that lymph node status is prognostic also in metastatic disease, with 60% increased risk of death. This may be related to difference in the behaviour of tumour dissemination [2, 25, 28, 29]. Harirchi et al show that in ***Iran*** over 60% of breast cancer patients present with metastatic spread, although this study did not provide information on lymph node status [26].
- Oestrogen receptor and progesterone receptor status: oestrogen receptor positive breast cancer is the most common breast cancer sub-type with around 50-80% (related to age) of all cases [30, 31]. A positive oestrogen receptor status is also a predictor of response to endocrine therapy [32-34]. Progesterone receptor status is a prognostic factor (positive progesterone status better prognosis) but not treatment predictive, as it does not alter response to endocrine therapy. Again, in the data from Brazil show that 67% of patients had oestrogen receptor positive breast cancer and 60% progesterone positive breast cancer [25, 35, 36].
  In ***Iran*** these proportions are somewhat lower (57-62.3% oestrogen receptor positive and 47-51.8% progesterone positive) according to Mousavi et al in 2007, and this may be due to the fact that many patients present with more aggressive disease [37].
- Age: Mean and median age at diagnosis in most high-income countries is around 63-65 years. Younger women with a breast cancer diagnosis have a worse outcome (50% increased mortality), even if survival has improved over time related to use of adjuvant treatments [38-42].
  In ***Iran*** the mean age at diagnosis is much lower (below 50 years) than the mean age of around 64 years in many countries. Also, according to the 2008 World Bank Report, the population pyramid of ***Iran*** indicates that the number of breast cancer cases in the younger ages will remain high in the years to come [37, 43, 44].

- Molecular subtypes and signal transduction pathways inform on prognosis and predict use of more or less aggressive treatment. All but Luminal A subtype are generally highly proliferative [45-47].
    - Luminal A is the most common subtype occurring in 50-60% of cases that also includes most of the hormone receptor positive tumours. This is a subgroup with relatively good prognosis and would require only adjuvant hormonal treatment [48]. In ***Iran*** the proportion of patients with oestrogen receptor positive tumours is 10-30% lower, which means that the number of patients requiring endocrine treatment only would also be lower [37].
    - Luminal B cancers occur in around 10-20% of cases and are more aggressive than Luminal A disease, and patients should be offered chemotherapy [49]. According to the data, the rate of Luminal B cancers would be higher in ***Iran*** at around 30% [21].
    - HER2 enriched cancers represent about 15-30% of all primary cancers. Untreated, these tumours have a poor prognosis. Patients with treated HER2 positive breast cancers will have improved survival (8-year 12.4% untreated vs 21.2% treated) [50]. Related to the higher proportion of large and aggressive tumours in ***Iran*** the proportion of HER2 enriched tumours could be higher. In the only study we found from ***Iran*** by Madani et al in 260 patients 40.8% had HER2 positive breast cancer, but that may be an overestimation [21], compared to other countries. This could be -for instance- related to technical errors of HER-2 testing or classifying HER-2 (2+) as HER-2 positive.
    - Basal-like cancers (also called triple negative; negative oestrogen and progesterone receptor status as well as negative HER2 status) constitute about 10% of all breast cancers. Publications show that the proportion of triple negative breast cancers is higher in ***Iran*** at 15-22.5%, [22, 51].
    - Claudin-low tumours indicate immune deactivation. It is a rare subtype and that is mainly seen in the basal-like subtype but could also occur in other subtypes. This is an interesting development as immune response enhancement is now gaining great attention in breast cancer research, and may be a way forward for this aggressive subtype [52-54].

Below, we summarize graphically the information from ***Iranian*** studies on prognostic factors at diagnosis, extracted with permission from a literature review by Dr Norah Buchardt 2018 (Masters Thesis, Karolinska Institute, Stockholm, Sweden).

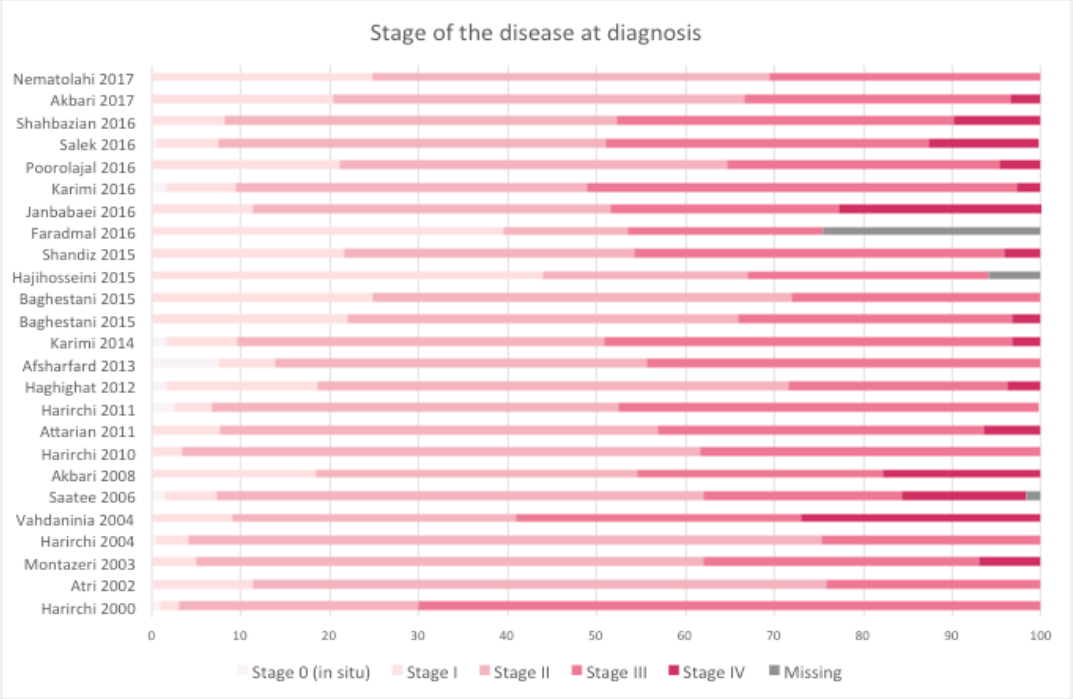


Figure 2-4 *Summary of studies reporting on stage at diagnosis in Iran*

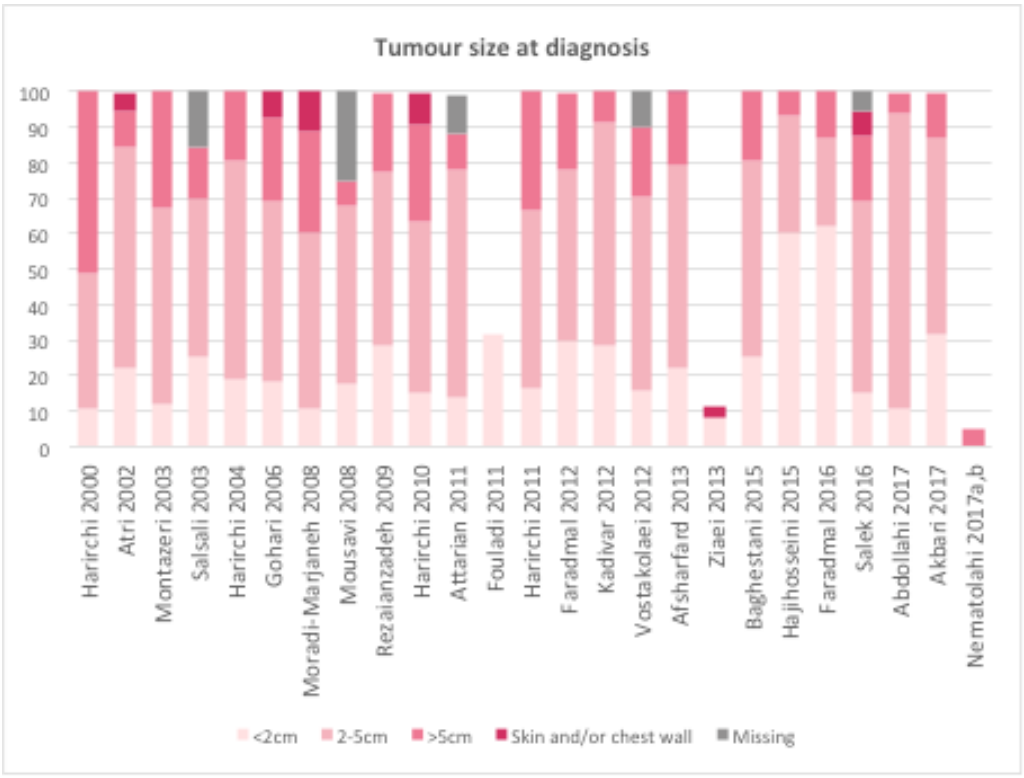


Figure 2-5 *Summary of studies reporting on tumor size at diagnosis in Iran*

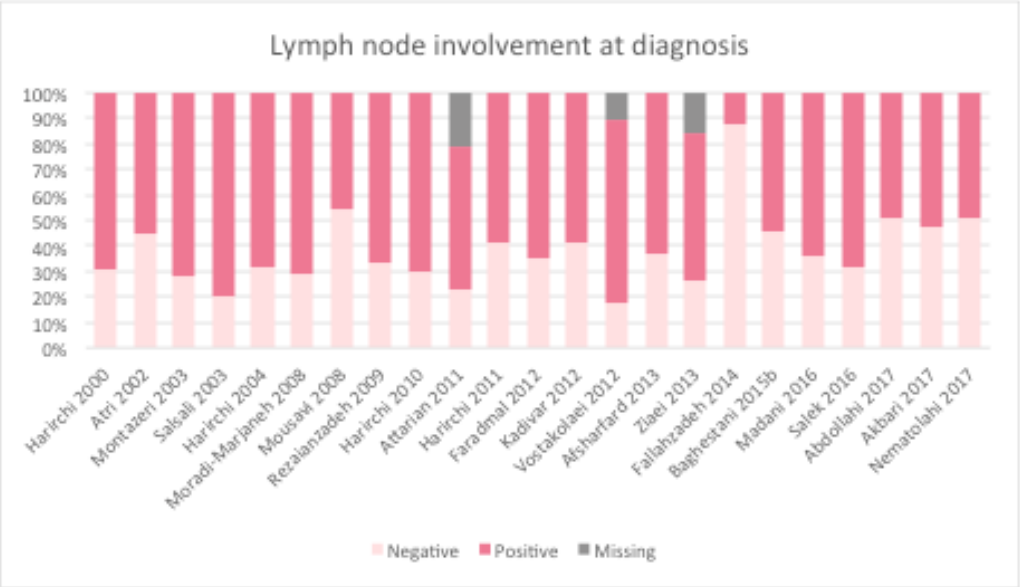
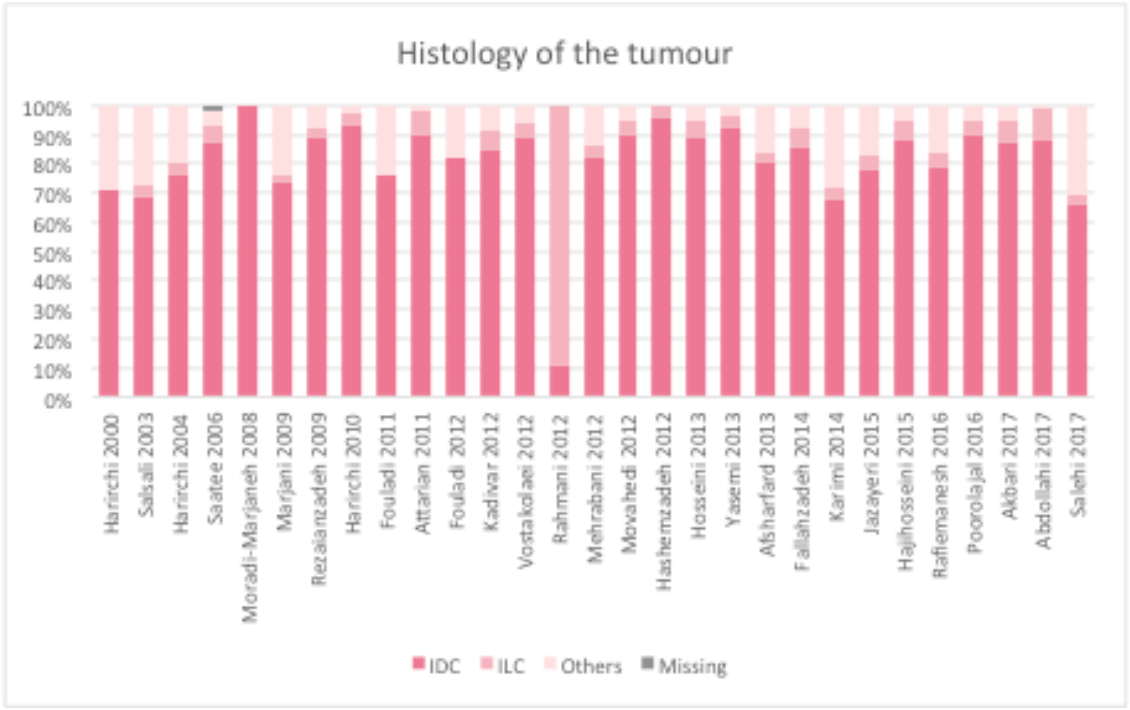


Figure 2-6 *Summary of studies reporting on lympnode involvement at diagnosis in Iran*



IDC=invasive ductal carcinoma; invasive lobular carcinoma

Figure 2-7 *Summary of studies reporting on histology at diagnosis in Iran*

2.3. Therapy

The long-term survival rates in breast cancer are around 80% in most western countries. In patients receiving adjuvant treatment (treatment before/after surgery), the mortality risk is reduced and the long-term survival rates are improved, in part related to treatment [40, 55]. Around 50% of patients with local relapse and around 20% of patients with regional relapse will obtain long-term survival/cure. In the recent study from Brazil in 2,273 patients the 5-year survival was 72% and the 10-year survival was 58% [25, 56, 57].

In ***Iran*** one study in 1,500 patients the 5-year survival rate was lower compared to other countries, at 72% (95% CI 69-74%), and with large differences between regions of 67-79% [43]. Recent studies indicate a five-year survival rate of around 72-75% [17-19].

2.3.1. Surgery

Breast tumours in early stages can be completely removed by surgical resection. Survival rates for surgery alone are around 50-60% [40]. Surgical procedures include breast-conserving surgery, mastectomy, and axillary lymph node examination. A mastectomy involves removing all of the breast tissue, sometimes with other nearby tissues. In breast-conserving surgery, only a part of the affected breast is removed, depending on size and location of the tumour. For most women with small tumours and no spread to axillary lymph nodes, breast conservation therapy (lumpectomy/partial mastectomy plus radiation therapy) is as effective as mastectomy [58, 59]. However, breast-conserving surgery requires high-quality imaging and radiotherapy and thus, in settings with limited resources modified radical mastectomy is still recommended [60].

Lymph node dissection is part of the staging process and the results will determine subsequent treatments. A sentinel lymph node biopsy is the identification and removal of the first lymph node(s) into which a breast tumour drains and will most likely contain cancer cells if spread outside the breast. Axillary lymph node dissection is performed if there are tumour cells in the sentinel nodes, or if the cancer has spread to other organs. Between 10 to 20 lymph nodes are removed, as with these numbers the risk of a false negative result is considered acceptable. A possible long-term adverse effect of removing axillary lymph nodes is lymphedema, occurring in 25% of women [61].

As many patients in ***Iran*** are diagnosed with large tumours, mastectomy is predominant. If combined with intra operative radiotherapy the procedure may be more limited. Lymph node dissection should be a common procedure, as the majority of patients will have tumour cells present in lymph nodes.

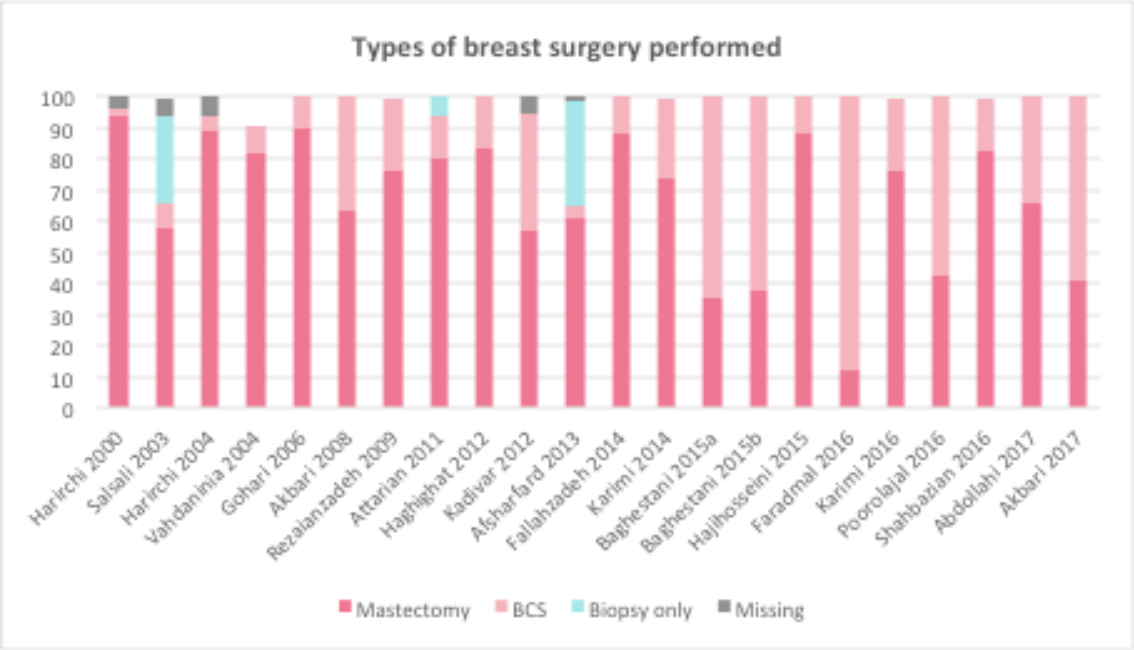


Figure 2-8 *Types of breast surgery performed*

2.3.2. Radiotherapy

It has been estimated that 45-55% of breast cancer patients benefit from radiotherapy [62, 63].

Radiotherapy aims at destroying cancer cells remaining in the breast, chest wall, or lymph node areas after breast-conserving surgery with high-energy rays or particles. A meta-analysis revealed that radiotherapy is an important complement to surgery, decreasing the risk of loco-regional relapse by two-thirds compared to surgery alone [64]. External beam radiation is the most common type of radiation therapy for breast cancer. If breast-conservation surgery was performed, the entire breast receives radiation, and sometimes an extra boost of radiation is given to the area of the cancer. Depending on the size and extent of the cancer, radiation may include the chest wall and lymph node areas as well.

Brachytherapy, also known as internal radiation, is another way to deliver radiation therapy. Instead of directing radiation beams from outside the body, radioactive seeds or pellets are placed directly in the breast tissue next to the area of the cancer. It is often used to add an extra boost of radiation to the tumour site along with external radiation to the whole breast. Tumour size, and location, as well as other factors select patient suitable for radiation.

Clinical linear accelerators are the most common device for external radiation therapy. In some countries, cobalt machines are used; these are less efficient but also less costly. In Europe, guidelines for radiotherapy equipment recommend that the coverage of linear accelerators should be at least

four per million inhabitants (or one per 450 patients), although this varies from country to country. In these guidelines, cobalt machines are considered having half the capacity of a linear accelerator [65].

According to the DIRAC (DIrectory of RAdiotherapy Centres) database, there are less than one linear accelerator and less than one cobalt machine per million inhabitants in ***Iran*** (see table 1 below). Following the European guidelines above, ***Iran*** should have around 320 linear accelerators using inhabitants (80 million) as the criteria, or 200 machines using the number of cancer cases (90,000). The total number of machines available in Iran (table 1) (assuming 50% efficiency for cobalt machines) is about four times less, translating into one machine per 1600 cancer cases. There a publication showing an interest in use of hyper-fractioning of radiotherapy, reducing the number of machines required [66, 67].

Table 2-2 *- Number of Radiotherapy equipment in the different regions of Iran*

Region	Total linear accelerators per region *	Total cobalt machines per region *	Linear accelerators per million inhabitants **	Cobalt machines per million inhabitants **
Teheran	22	16	0.94	0.69
Isfahan	5	2	0.38	0.15
Tabriz	3	3	0.38	0.15
Kermanshah	5	0	0.43	0
Mashad	8	2	0.62	0.15

*) Data from the DIRAC database July 2017.
**) Population data from Wikipedia July 2017

2.3.3. Medical treatment

Progress in medical treatments of cancer has been made in almost every area. In most tumours, stepwise and relatively modest improvements have -over time- resulted in an impressive increase in the proportion of patients considered cured. For instance, the overall breast cancer mortality in the USA and the UK was reduced by 25% from the 1980-ies to the year 2000. This progress is to some extent the result of screening programs, enabling earlier detection of the disease, but it is also a true reduction in mortality due to important improvements in adjuvant treatment [68, 69]. Anthracycline based chemotherapy reduces the annual breast cancer death rate by about 38% for women younger than 50 years and by about 20% for those in the age of 50-69 years. Additional use of 5 years tamoxifen treatment in oestrogen receptor positive disease results in a reduction of the annual breast cancer death rate by around 50%. Some patients are now receiving prolonged treatment to 10 years.

Improved chemotherapeutic regimens have increased survival further and recently, adjuvant treatment with the monoclonal antibody trastuzumab in patients with HER2-positive disease has shown a 50% decreased relapse risk and a 33% reduced mortality risk [40, 69].

2.3.3.1. Primary treatments

The first generation of adjuvant chemotherapy was developed during the 1970-ies. Better regimes have been developed over time and currently combination of two to three drugs with different mechanisms of action is recommended. Regimes containing taxanes and anthracyclines have been shown to be most effective [40, 70-73]. In ***Iran,*** where the majority of patients have aggressive disease at diagnosis (luminal B, lymph node involvement, large tumours, metastatic spread), the proportion of patients requiring adjuvant chemotherapy would be high.

Anti-hormonal therapy started with tamoxifen in 1975, and its broad indication in advanced disease and as adjuvant therapy (as well as prevention in the USA) represented a major breakthrough in breast cancer treatment. The aromatase inhibitors (anastrazole, exemestane, letrozole) are in part (in postmenopausal women) replacing tamoxifen. A meta-analysis of longitudinal studies involving almost 200,000 women published in 1998 has been an important step in recognising the value of adjuvant endocrine therapy; follow-up data are regularly published [64, 70, 73-75]. Results show that adjuvant chemotherapy reduces the relative annual risk of death by almost 40% for women <50 years and by 20% for women 50-69 years of age, while endocrine therapy with tamoxifen in estrogen-receptor positive patients reduces the relative annual mortality risk by 30% [70, 75, 76]. As the proportion of patients in ***Iran*** with hormone receptor positive breast cancer is comparatively low, as mentioned earlier, the proportion of patients receiving anti-hormonal treatments will be proportionally lower than in other countries.

Biological treatments entered into the breast cancer therapy field in the late 1990-ies and have changed e.g. the outcome for women with HER2-positive breast cancer. Trastuzumab is a monoclonal antibody that attaches to a growth-promoting cell surface protein known as HER2 that is increased in about 15% of women with early breast cancer and 20-30% of women with advanced breast cancer. Trastuzumab can suppress HER2 stimulated tumour growth and may also activate the immune system to more effectively attack the cancer. Treatment with trastuzumab has led to marked prolonged survival in metastatic breast cancer [77]. One-year adjuvant treatment with trastuzumab in women with HER2 positive breast cancer leads to a 50% reduced risk of recurrence [78-80]. As the proportion of patients with HER2 positive disease appears to be relatively high in ***Iran***, the proportion of patients expected to be treated with anti-HER2-drugs would also be relatively high.

Cell signalling pathways are nowadays in focus for treatment targeting. Examples are PI3K/AKT, CDK4/6 and PARP. Also, immune modulating agents are in focus of research, as PD1 agents [46, 81, 82]. See figure 2-4 below.

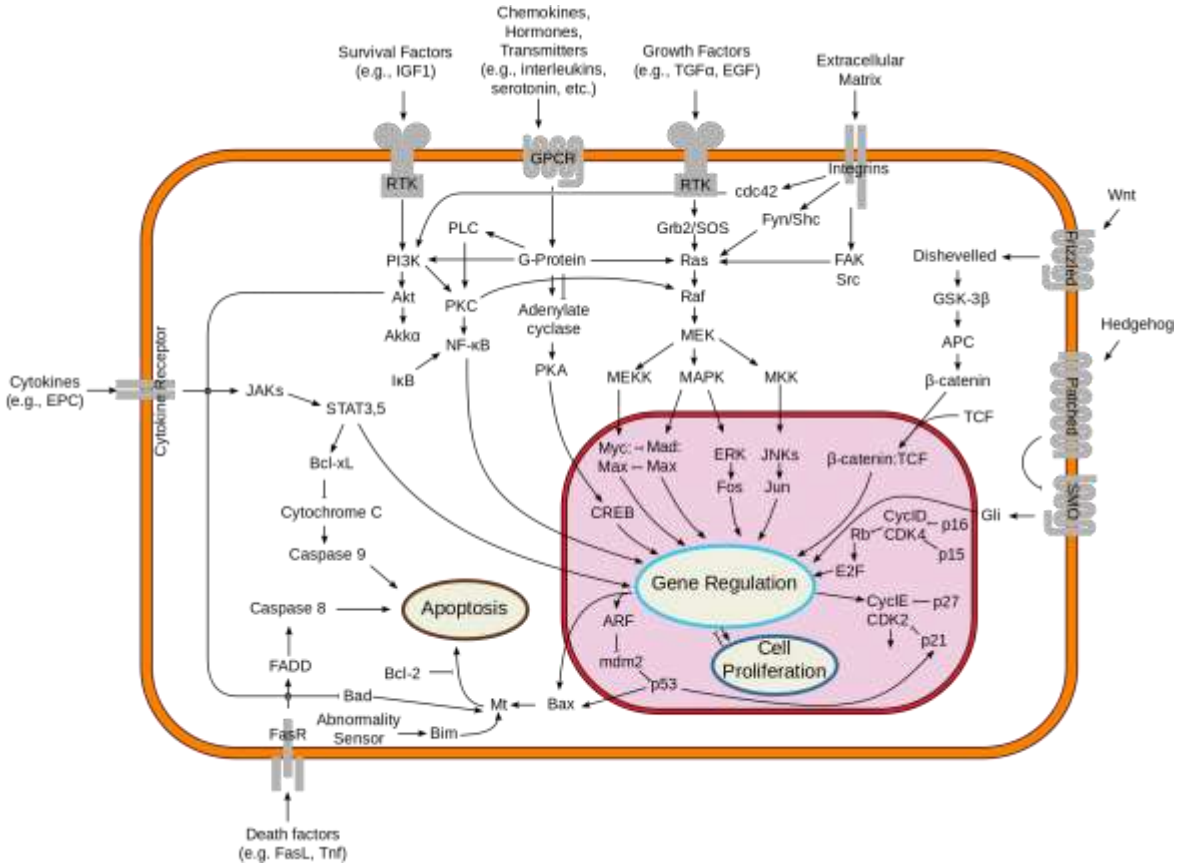


Figure 2-9 *- Cell signalling transduction pathways (simplified)*

Adjuvant chemotherapy is commonly given for a period of 5-6 months, followed by endocrine therapy for 5 years for hormone-sensitive patients, either 5 years of tamoxifen or anastrazole or a sequence of first tamoxifen and then exemestane or letrozole. Some high-risk patients may also be subject to prolonged use with tamoxifen followed by letrozole with a total treatment time of up to 10 years. Today, the optimal period of adjuvant treatment with trastuzumab is 1 year in combination with, or subsequent to, chemotherapy (5-6 months) and may be followed by endocrine therapy for at least 5 years. Generally, chemotherapy combinations containing anthracyclines and taxanes are used in different schedules. Furthermore, in postmenopausal women 2-5 years of bisphosphonates will significantly reduce recurrence (RR 0.86, 95% CI 0.78-0.94; 2p=0.002), distant recurrence (0.82, 0.74-0.92; 2p=0.0003), bone recurrence (0.72, 0.60-0.86; 2p=0.0002), and breast cancer mortality (0.82, 0.73-0.93; 2p=0.002). [76, 83, 84].

Data on different chemotherapy regimens used in ***Iran*** is scarce. The old version of national practice guideline on HER2 positive breast cancer recommended 9 weeks of anti-HER2 treatment, based on the FINNHER study. There is also one study by Ansaripour et al suggesting a treatment time of trastuzumab of 6 months [87-89]. The new version of national practice guidelines recommends 6 months of trastuzumab for early breast cancer and 12 months for advanced non-metastatic breast cancer.

2.3.3.2. Treatments for metastatic breast cancer

Treatments for metastatic breast cancer focus on palliation and prolonged survival. Treatments are individualised and should be adjusted according to each patient's tumour and quality of life aspects. In cancer, quality of life and survival are equally important. A Swedish study in metastatic breast cancer patients has shown that quality of life was relatively high, especially in the elderly patients [85, 86].

To manage patients correctly, information on tumour specifics is essential, as management of patients may change as tumour characteristics change. It has been shown that changes in tumour behaviour will also affect survival. Thus, tumour biopsies should be sampled at recurrence of breast cancer [2, 29, 85, 87-90].

Treatments used are: Surgery or radiotherapy for localized disease or medical treatments for disseminated metastatic disease; anti-hormonal treatments as long as the tumour retains hormonal sensitivity; different chemotherapeutic agents such as anthracyclines, taxanes, biological treatments for relevant subgroups; anti HER2 treatments in patients with HER2 positive disease. The dual HER2 blockade with trastuzumab and pertuzumab has been shown to be superior to trastuzumab alone in the metastatic setting. [29, 88, 91].

2.3.3.3. Companion diagnostics

A key challenge with all agents, but particularly biological therapies, is to predict responders.

Tumour status of receptors and genes or proteins can be determined with different tests, as an important step in eligibility for treatment. For instance, in general, the proportion of patients with a positive status is 70-80% for hormone receptors and is 15% for HER2 in breast cancer, and no other patient is expected to respond to given therapy.

The importance of companion diagnostics can be illustrated with HER2 positive breast cancer and trastuzumab treatment. In an interesting comparison of treating only HER2 positive patients with trastuzumab versus treating an unselected patient population, 23,586 patients would have been

required to detect the same survival differences as seen in the pivotal studies including only 469 patients [92].

Technical aspects related to use of companion diagnostics relate to sensitivity and specificity of methodologies and cut-off levels. The methods may change over time as knowledge increases, and cut-off levels may change. Also, in view of tumour heterogeneity re-testing of recurrences is required.

The use of companion diagnostics still need to be developed in ***Iran***, as no data was found on this matter [93].

2.3.4. Supportive care

Supportive drugs enable intensified treatment schedules and improved quality of life for patients suffering adverse symptoms of the cancer or the treatment. Patients treated with chemotherapy often develop fatigue, low levels of red blood cells (anaemia), decreased white blood cell counts (neutropenia) and nausea.

The fatigue of cancer patients is often multifactorial: It may be related to side effects of treatment or psychological stress. Many tumours also secrete substances (cytokines) that may cause fatigue. However, fatigue is primarily caused by anaemia. Chemotherapy is often associated with bone marrow depression, which may delay consecutive doses of treatment. The development of erythropoietin, G-CSF (filgrastim, pegfilgrastim), broad-spectrum antibiotics and platelet transfusion techniques has decreased morbidity and enabled intensified treatment schedules. There are several agents to prevent/reduce nausea (e.g. ondansetron, granisetron). Finally, bisphosphonates (e.g. pamidronat, zoledronic acid), and RANKL (denosumab), reduce the risk of skeletal events (fractures) as well as relief pain caused by skeletal metastases.

A different type of supportive care, discussed at the 2017 meeting for American Society of Clinical Oncology, is a web-based system with direct contact between patient and treating clinic. This provides a unique opportunity to on a day-to-day basis manage treatment and adverse effects. In a controlled follow-up study, survival in patients with metastatic cancer was 5 months longer in the web-based arm than the control arm (31.2 vs. 26.0 months, p = 0.03). [94].

There are several publications on supportive care and quality of life aspects in ***Iran.*** They focus mainly on quality of life during and after breast cancer treatment[95-98].

2.4. Clinical guidelines

Anti-tumour treatment guidelines exist in most countries both at national, regional or hospital level. These guidelines are based on results from clinical studies and of clinical consensus. The adherence to guidelines and outcome of compliance is rarely evaluated in any country. Many oncology drugs are approved on the surrogate end-point progression free survival, although the translating to overall survival benefit is uncertain [99].

In general, ***Iran*** appears to use international clinical guidelines, but there are no data on how well they are followed. One study on HER2 positive breast cancer and treatment guidelines made the general comment that treatment guidelines are not always followed (as also experienced in other countries. [100].

From 2017 national practice guidelines -for 12 chemotherapy drugs and most frequent cancers- have been developed by the ministry of health in ***Iran*** and insurance companies use them for coverage of drugs and services.

2.5. Clinical effectiveness and real-life data

Clinical effectiveness is a measure of the extent to which a particular intervention works in clinical practice. If the intervention is shown to be efficacious in controlled conditions, clinical effectiveness will assess outcome using real life data from clinical practice. These studies will indicate which treatments work in which patients, assess safety in heterogenous patient populations and provide information on areas where more research is needed.

Tumour heterogeneity is a key challenge when treatments are entering clinical practice as the methods in clinical practice may differ from those in clinical trials. Tumour development from primary tumour to recurrence may include selection of clones that may be treatment related. This is rarely discovered in clinical trials and large cohorts may be required. Co-morbidities may affect both treatments proposed and outcome of treatments, and the sequence and combinations of treatments differ from the strict programs in clinical trials. Side effects may result in dose reductions thereby reducing the total amount of drug delivered [101, 102].

Real world data may answer questions not possible in clinical trials, as patient groups in clinical practice are heterogenous and have co-morbidities and other pre-conditions. Real-world data from Sweden shows that survival is worse in breast cancer patients with HER2 negative/discordant HER2 status compared to HER2 positive primary and metastatic breast cancer; 2-5 times poorer outcome,

and change in oestrogen receptor status from oestrogen positive to oestrogen negative will increase the risk of death with almost 50%.

In the global database IARC (International Agency for Research on Cancer) data from ***Iran*** was previously based on the register from the Golestan province solely [70] but recently it refers to national population-based cancer register data from 2014.

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Chapter 3

Policy options, analysis, conclusions and recommendations

Table of Contents

List of Figures

List of Tables

3. Policy options, analysis, conclusions and recommendations

3.1. Introduction

Breast cancer is a growing challenge for health care systems, not only in high-income countries, but increasingly also in low and middle-income countries, as life-expectancy increases and socioeconomic conditions change.

While the medical technologies available for management of breast cancer are similar in most countries, policies for improving the delivery of services and outcomes must be adapted to different economic and social conditions. Issues of affordability (availability of resources) and access for different segments of the population (equity) are important aspects of cancer policy in both global and national perspectives.

As the options for disease management increase, the choices involved in allocation of resources become ever more complicated. The table below illustrates the development over time of the different technologies to manage breast cancer. Within each type of technology, several options have been developed.

Table 3-1 *– Development of health care technology for breast cancer*

Development of health care technology for management of breast cancer	
Mortality reduction and improved survival	**Improved quality of life and potentially cost-saving**
Mammography screening and adjuvant radiotherapy	Breast conserving surgery combined with radiotherapy
Hormonal treatment	Testing for sentinel node involvement
Cytotoxic medicines	Advances in palliative care
Targeted therapies	Shift from inpatient to ambulatory care
Multidisciplinary medical care	

At the same time the objectives for efficiency and equity become more explicit. The multi-modality approach to breast cancer management means that policies cannot focus on a single factor, but need to address several factors simultaneously. A further challenge for policy guidelines is that, as they include many different aspects that are changing over time, they require frequent updates.

Thus, more information is needed about resource allocation and the potential outcomes and cost-effectiveness of different available options. The development of a cancer registry with the relevant information is key to the development of rational policies, and the evaluation of the impact of different options in clinical practice. Real world data on patient characteristics, treatments and outcome are necessary for developing guidelines for an efficient and equitable cancer management.

It is, however, important to differentiate between policy guidelines and clinical guidelines:

- A policy guideline is a high-level statement, uniform across organizations, providing guidance for decisions for groups of patients and for priorities and resource allocations.
- A clinical guideline is a document containing advice on how to act in a given situation, based on consensus [1]. It summarizes and evaluates all currently available evidence on a particular issue with the aim of assisting physicians in selecting the best management strategy for an individual patient with a given condition.

A number of policy papers have been published by Lancet Oncology that provide a background for defining and assessing policy options for breast cancer management in a global perspective that is relevant for ***Iran***. These policy papers address prevention and cost-effective cancer treatment [2], early detection [3], surgery [4] as well as palliative care [5]. A number of clinical guidelines for breast cancer have been developed by international and national organizations. However, their implementation at the national and local level is seldom followed-up and the actual impact of the guidelines is unknown or low.

3.2. Summary of issues for policy in Iran

The previous two chapters describe challenges and opportunities for breast cancer detection and treatment in general, and highlight the data that are publicly available regarding Iran. The main findings are summarized here once again.

From these Iranian data, one can conclude that

- breast cancer will increase as demographics change
- there still appears to be under-diagnosis
- breast cancer is currently diagnosed late and in younger women compared to other countries, with consequently a poorer prognosis
- prevention and screening programs have been limited and, when existing, show low participation rates

- data on use of surgery, radiotherapy and medical therapy are limited
- regional differences in detection and treatment appear large
- data on direct and indirect costs due to breast cancer are scarce but premature mortality appears to constitute the highest cost

These points are briefly addressed below. But in conclusion it becomes evident that there is a lack of appropriate data for all parts of breast cancer management for development of rational policies.

3.2.1. Under-diagnosis

According to the Iranian cancer registry the age-standardized incidence for breast cancer in Iranian women is estimated at 31 per 100,000. This is close to the average in low middle-income countries (31.4/100,000) but much less than the average in high income countries (78.3/100,000). The estimated number of new cases is 13,000 per year.

Five-year prevalence was estimated at 39,300 in 2010 (excluding women diagnosed >5 years ago). The latest estimates in Globocan 2018 sets it at 40,800. With a 10-year survival of 58%, the 10-year prevalence will be about 55,000, and an estimate of all women living with a diagnosis of breast cancer about 80,000. For reference, in Sweden and in the US prevalence of breast cancer is more than ten times higher than the incidence.

Cancer incidence in Iran has been predicted to increase as a consequence of demographic change. One estimate forecast a doubling between 2012 and 2035, while another based on the Iranian registry predicts a 65% increase between 2018 and 2040.

3.2.2. Late diagnosis

Larger tumour size, lymph node involvement and metastatic spread predict a poorer prognosis.

A primary tumour of >2 cm has a worse prognosis, but in Iran only 18.9% of patients are diagnosed with tumours of <2cm. (This compares to 27% in Brazil and 67% in the USA.)

Five-year survival with no lymph node involvement is 85%; with 4 or more lymph nodes involved survival is only 26%. In metastatic disease, positive lymph node status increases the risks of death by 60%. In Iran, an estimated 50% of patients have tumour involvement of lymph nodes at diagnosis and as many as 10% present with metastatic spread. (This compares to around 33% with lymph node involvement in the USA and 22-25% in the screening population in Sweden, and an estimated 25% and 30-40% with metastatic disease at diagnosis in Brazil and Lebanon, respectively.)

As a consequence, 5-year survival is low and currently estimated at 67-79% depending on the region, with a mean for the country of 71%. This compares to 60%-86% (depending on the region) in Turkey, and to 89% in the USA.

3.2.3. Prevention and screening

Awareness of breast cancer in rural areas is low and limited (62% with some awareness) and only half of these had a good awareness of mammography. Recently, the Ministry of Health started an early detection program focusing on people with suspicious symptoms (early diagnosis) and high risk groups.

Prevention focuses on mammography, but data on screening and follow-up of screening are scarce. One free-of-charge program in lower socioeconomic groups of women representing 29% of the population showed low attendance (27%), due to, for instance, shame, pain and fear of dying.

3.2.4. Treatment

In theory, all options for treatment – surgery, radiotherapy, chemotherapy – are available, but data on their precise use are lacking.

- Surgery is dominated by mastectomy as a consequence of late diagnosis. Surgery is performed both by breast cancer specialists and other surgeons and usage data or data on outcome are not available.
- Radiotherapy is likely underused, due to an overall lack of machines and partly inefficient technology (cobalt machines). Again, no usage data are available.
- Data on use of cancer medicines are sketchy, and cannot be directly related to the different needs by different patient groups. The high proportion of younger patients with bad prognostic factors in Iran also makes international comparisons difficult. Indeed, Iran appears to have a lower proportion of oestrogen receptor positive cancers than is generally estimated, hence endocrine treatment would be lower than elsewhere. On the other hand, the proportion of more aggressive tumours (luminal B) appears higher, requiring more chemotherapy. The number of patients with HER2 enriched tumours has been estimated to be higher than elsewhere (40% compared to 25-30%), which would mean high usage of trastuzumab – but these estimates have not been confirmed and could be influenced by both, the younger patient population or issues in the testing procedure itself.

3.2.5. Regional differences

All components of breast cancer - awareness, detection, treatment and outcome - vary by region, as the population is very heterogeneous.

3.2.6. Costs

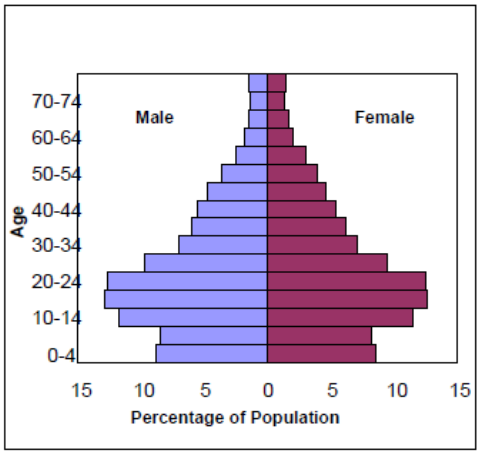
Due to the absence of detailed information on resource use, data on costs are limited. The only available study estimates the ratio of indirect to direct costs at 4:1, which can be compared to 1:1 in Sweden, excluding the costs of screening. Across Europe, direct costs are higher than production losses. Even with low access to or underusage of certain treatment modalities, this ratio would indicate that a part of health care costs is not captured in the published studies and/or have been mortality costs overestimated. In order to estimate the effectiveness of policies to detect, diagnose and manage breast cancer more current and more detailed data will be required.

3.3. Policy options in Iran

3.3.1. Population at risk

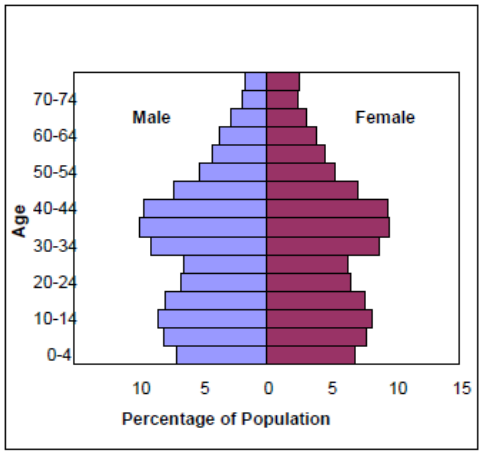
To define the future burden of breast cancer, it is important to estimate the number of women at risk. The figure below illustrates the estimated age development of the population in Iran between 2005 and 2025.

Figure 6
IR Iran Population Pyramid
2005



Source: World Development Indicators 2006 (World Bank 2008).

Figure 7
IR Iran Population Pyramid
2025



Source: World Development Indicators 2006 (World Bank 2008).

Figure 3-1 *- Population in Iran in 2005 and 2025*

As seen in the figure above, the population in ***Iran*** is relatively young but will increase in age over the next decade. This will lead to an increase in breast cancer incidence and requires active measures to adapt the health care system. With a population growth of 1.0-1.1 % in Iran, we estimate that the female population will increase by around 15% by 2030. This means that over 50% of the female population will be over the age of 40 and thus have an increased risk of breast cancer [6].

The figure below represents an estimate of the effect of population changes on the number of breast cancer cases, assuming constant age-adjusted incidence. The total number of cases increases from just under 10,000 cases in 2010 to 15,000 cases in 2025 and slightly over 20,000 cases by 2040. Around 25% of the increase is due to increase in population size, and 75% to population ageing.

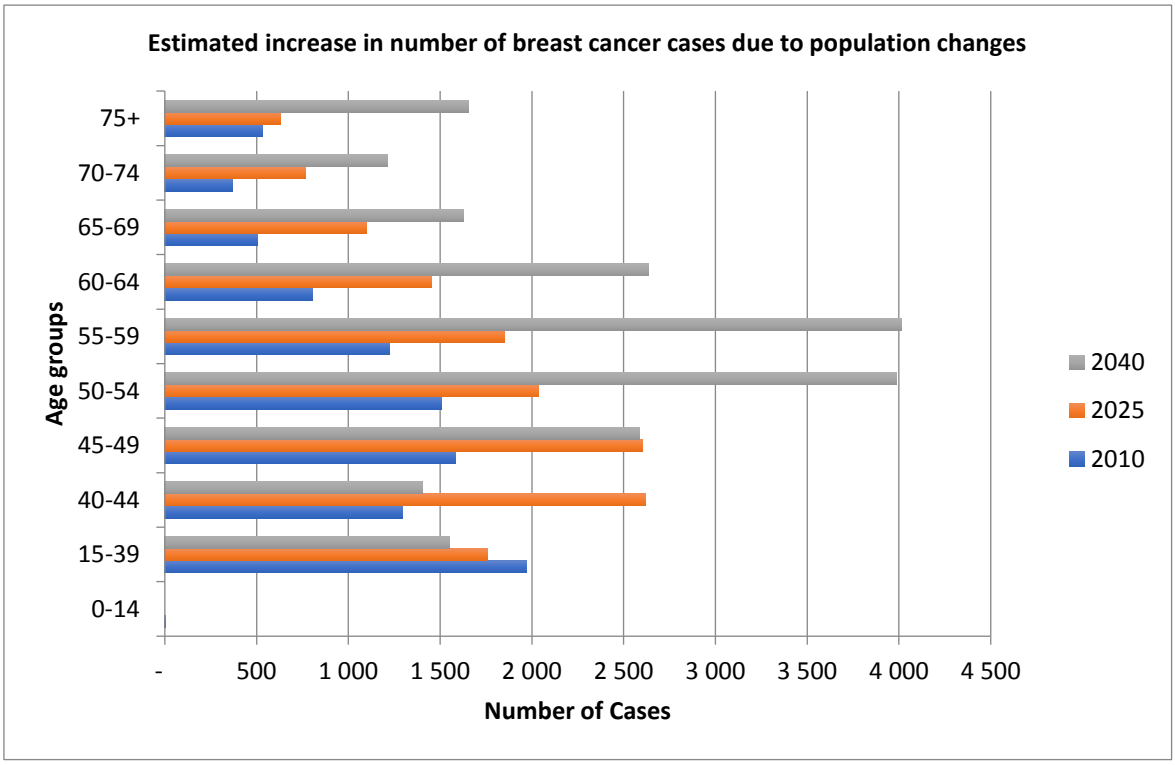


Figure 3-2 *- Effect of population changes on breast cancer cases*

Source: Own estimates using population data from "Population Pyramids of the World (https://www.populationpyramid.net/iran-islamic-republic-of/2040/

Estimated age standardized rates of breast cancer in Iran for 2004 were between 0.06 - 101.15 per 100,000, increasing for 2010 to between 20.85 - 329.68 per 100,000. These latter estimates highlight a large variation between regions. Breast cancer is more common in Central and Northern Iranian provinces and in women at higher socioeconomic status. It has been suggested that this disparity can be reduced through special programs such as education, screening, and preventive measures [7, 8].

3.3.2. Primary prevention

Primary prevention measures aim at reducing the risk factors for a specific disease. Primary prevention is more difficult to achieve in breast cancer than in some other cancers, for example lung cancer (reducing smoking).

- Life-style risk factors: Risk factors specific to breast cancer that are susceptible to primary prevention measures include: reduced breast feeding, obesity after menopause, high calorie diet, high alcohol intake, low physical activity, use of oral contraception and use of post-menopausal hormonal treatment [9] . Successful implementation of primary prevention campaigns depends on the level of awareness of breast cancer.
- High risk population. It is generally estimated that 20–30% of breast cancers are related to genetic factors that in combination with lifestyle factors can lead to an increased risk. For these women, preventive measures should be taken, including more frequent screening or chemoprevention with endocrine therapy when warranted. The most established strategy is, however, preventive surgery including removal of the breasts, although the evidence base for this strategy is limited [10].
- Tamoxifen and raloxifen have been available for use as preventive agents in the US for many years. They were recently approved in Europe for preventive use. It is estimated that about 3% of the female population would benefit from chemoprevention. However, experience from the US market shows that fewer women actually take the treatment, mainly due to the side effects involved.
- The biggest challenge is to identify high-risk women who may benefit the most from preventive treatment. There is research indicating that it may be possible to identify the gene patterns that predict best effect of treatment [11]. Since the chemo-preventive drugs are generic, costs and cost-effectiveness of their use in high-risk groups are not debatable. However, the resources required for identification and follow-up of risk groups can be considerable and need consideration when establishing preventive policies.

In a country like ***Iran***, a key to earlier detection of breast cancer is awareness of the disease. According to available literature, parts of the population need education about woman health issues, including breast diseases. In these activities, it is important to point out that breast cancer is not by definition a deadly disease. On the contrary, early detection, as well as access to early treatment, has the potential to cure the disease. If primary prevention is introduced with a focus on breast cancer being potentially preventable or curable, women may opt for a preventive strategy, particularly if they feel that the curative options are more limited in Iran compared to the US and Western Europe. A strategy for primary prevention with endocrine drugs may thus have a better acceptance compared to the US and Western Europe [12].

Currently, preventive measures for ***Iran*** focus on early detection by examination and screening (secondary prevention) and increase the awareness of breast cancer [13-15]. Awareness in combination with basic education about breast cancer may provide a basis for an earlier diagnosis of breast cancer.

Awareness and educational campaigns can be combined with clinical examination by health care workers who focus on women's health, but do not have to have a formal education as registered nurses or MDs. There is some experience from low- and middle-income countries of breast diagnosis made by health care workers [16]. These health care workers can perform basic clinical breast examinations and make referrals to clinical mammography. An alternative to mammographic examination may be ultrasound [17]. Trained health care workers can perform clinical breast examination on symptomatic women including ultrasound and even perform clinically directed biopsies or refer women to clinical mammography examinations including biopsies. In more remote areas mobile units could be used for screening of breast cancer but also other form of cancer like cervical cancer and colorectal cancer [18].

3.3.3. Secondary prevention/early diagnosis

The aim of secondary prevention is to reduce the severity of disease (risk of recurrent and/or metastatic disease) and the risk of dying from breast cancer. As discussed earlier, outcomes are significantly better if a breast cancer is detected before it has spread outside the breast. Importantly, early-stage breast cancer is not symptomatic in all patients. There is strong association between stage at diagnosis (or tumor size) and survival [19].

The principal secondary prevention measure in breast cancer is population-based mammography, combined with ultrasound examination in dense breasts. This has been shown to improve outcomes, as it leads to a larger share of breast cancers being diagnosed at an early stage in the screened population [19, 20]. For most types of breast cancer, the likelihood of lymph node invasion and worse tumor grade increases as tumor size increases [21, 22]. Nevertheless, in many countries with limited availability of screening, the majority of tumours are detected when women consult after having noticed a breast lump. A recent retrospective 'failure analysis' of mortality in over 7,000 women found that >70% of deaths from breast cancer occurred in women who did not attend regular screening mammography [23].

This emphasizes again the importance of awareness campaigns. A critical factor in relation to this is access to well organized breast cancer care, including diagnostic work-up, surgical and non-surgical treatment [24].

A number of studies have addressed the issue of screening and early detection in Iran.

- In a cross-sectional study from 2014, a random sample of 561 women aged 40 years and older without the history of breast cancer and identified with Kurdish background in Baneh county, *Iran*. The mean age of women was 43.64 (SD = 5.17). The participation rate in the mammography program was 16.8% (95% CI: 13.7-19.8%). The lowest level of participation was found among women aged 60 and older, illiterate and post-menopausal women [25]. As an indication, this compares to a participation rate of 70% in a city like Stockholm in Sweden in 2010 (Lind et al.)
- One study in *Iran* suggests that knowledge, attitude and practice of breast cancer screening are associated with women's literacy. In order to improve women's health and breast cancer providing equal educational opportunities for women seems necessary [26].
- Another study concludes that planning to enhance the women's awareness about breast cancer and the methods of early diagnosis and educational programs can be an important step to reduce deaths and disabilities caused by this disease among women in less developed areas of *Iran* [27].

This indicates that breast cancer prevention and early detection programs can only be successfully implemented after or together with intensive awareness and educational campaigns, with a particular focus on those parts of society with limited resources.

Table illustrates how breast cancer screening can be performed, based on level of resources and awareness. In Iran, all levels of resources are present.

Table 3-2 *– Level of resources and breast cancer screening*

Table 2: Early detection and access to care

Level of resources	Detection method(s)	Evaluation goal
Basic	Breast health awareness (education ± self-examination) Clinical breast examination (clinician education)	Baseline assessment and repeated survey
Limited	Targeted outreach/education encouraging CBE for at-risk groups Diagnostic ultrasound ± diagnostic mammography	Down staging of symptomatic disease
Enhanced	Diagnostic mammography Opportunistic mammographic screening	Opportunistic screening of asymptomatic patients
Maximal	Population-based mammographic screening Other imaging technologies as appropriate: high-risk groups, unique imaging challenges	Population-based screening of asymptomatic patients

Source: [24]

3.3.4. Cost-effectiveness of breast cancer screening

Cost-effectiveness analyses compare the costs and health effects (outcomes) of an intervention to no or other interventions to determine the extent to which it provides value for money. This can be used to inform decision on where and how to best allocate resources. The cost-effectiveness of breast cancer screening varies by country and depends on many factors e.g. disease epidemiology, health care system, costs and compliance rate. The majority of studies has been conducted in high-income countries and cannot be directly translated to the situation in ***Iran***. Many of the cost-effectiveness analyses in breast cancer screening have focused on comparing different strategies for screening, e.g. age range, screening test, frequency of screening [28-33].

Cost-effectiveness estimates vary greatly, in part due to the uncertainties about the clinical outcome of screening, partly due to differences in the costs and the cost-calculations (where all costs for screening, diagnosis and treatment need to be included): estimates range from 1,000 to 30,000 Euro per life year gained [28, 29]. We illustrate a calculation below:

Assuming that mammography screening reduces mortality in breast cancer by 20%, 43 deaths are avoided per 10,000 screened using figures from the UK screening program [29]. The same source gives the estimate of 17 years of life gained per death avoided, which gives 0.073 life years gained per screened woman. In a study in Norway/Sweden/Finland, costs vary from 34 Euro to 127 Euro per woman screened [34]. We use 100 Euro as the base case estimate. Let us further assume that over a 20-year period, there are seven screening occasions. This will give a cost per life year gained of 10,000 Euro, which is in the lower range of estimates above. This example indicates that screening can be a cost-effective method for improving outcomes in breast cancer compared to no screening.

However, screening with mammography may reduce mortality with only 5-15% and leads to over-diagnosis in a magnitude of about 15-40%. Careful design of the program including follow-up and treatment is necessary for mammography screening to provide a positive net benefit.[35, 36]

In a recent review "Population Screening for Cancer in High-Income Settings: Lessons for Low-and Middle-Income Economies", the authors point out the discrepancy between breast screening efficacy and effectiveness in clinical practice, and make the following conclusions: "In limited-resource settings, addressing the social, political, and economic determinants of late presentation of patients with cancer is what matters, not mammographic screening, as well as putting in place high-quality, affordable breast cancer care". [37]

Cost-effectiveness analyses of screening programs are complicated and include a number of uncertainties and methodological decisions:

- Outcome (life years gained) is difficult to assess without thorough follow-up.
- Also, life years gained should be adjusted to quality adjusted life years (QALYs) gained to take into account that all life years gained are not of full quality and that diagnosis and treatment impact quality of life.
- In addition, it is both conceptually and empirically difficult to estimate the incremental costs of screening:
    - How much of the treatment costs that should be included in the cost of screening? Without a screening program, breast cancers may be detected later, with a different stream of costs.
    - Changes in survival also have an impact on costs for treatment of other diseases, and it is debated if changes in costs for treatment of other diseases should be included or not.
    - The inclusion of changes in indirect costs due to reduced morbidity in women who are of working age, and the inclusion of costs for added years of life will also affect the estimates of cost-effectiveness.
    - Finally, cost-effectiveness is determined by the design of the screening program, and will differ between patient characteristics, such as age.

Despite the uncertainties surrounding cost-effectiveness analyses, decisions about implementation and design of screening programs will be influenced by these estimates. The increasing number of options for early detection of breast cancer makes it also necessary to use cost-effectiveness to define the detection programs providing the most value for money. It is therefore better if studies are performed explicitly and in a systematic way, with data limits recognized and uncertainties around estimates discussed, rather than left to speculation. One advantage of this is that systematic studies usually lead to improvements in the data and improved understanding of the drivers of cost-effectiveness, which can make better decisions and thus better outcomes. Finally, although many cost-effectiveness studies of mammography have been performed, determinants of both relative effectiveness and costs change over time. Thus, new studies need to be performed that take into account changes in epidemiology, technology and progress in treatments, as well as changing social and economic conditions.

In a review of low- and middle-income countries, the evidence-base to guide strategies for breast cancer control is limited and of poor quality. It suggests nevertheless that screening strategies may be economically attractive. Yet, there is very little evidence to provide specific recommendations on screening by mammography versus clinical breast examination [38]. This situation may change in the near future, as data will mature from two large ongoing trials in India, evaluating clinical breast examination (CBE) as screening tool [39].

As the average age at primary breast cancer is generally younger in low-and middle-income countries, it has been suggested that breast-cancer screening programs begin at an earlier age, although this would considerably increase the cost of such programs. However, the age at diagnosis is mainly driven by

the age distribution of the population, with fewer older women, rather than by higher age-specific incidence rates in younger women. Resources might thus be better used to raise awareness and encourage more women with palpable breast lumps to seek care [3].

Mammography as a tool for opportunistic or spontaneous screening was introduced in Iran long time ago, but population based screening was introduced in ***Iran*** in a pilot phase ten years ago. In a recent study the incremental cost-effectiveness ratio was 6,264 US$ per disease adjusted life year gained with screening intervention compared with no-screening intervention. The authors state that in view of this cost, breast cancer screening programs may not be recommended as long as the target group has a low participation rate [40]

3.3.5. Treatment

3.3.5.1. Breast cancer surgery

Surgery remains the first cornerstone in the treatment of breast cancer and it is thus important that surgical care is organized in a structured way. The European Society of Breast Cancer Specialists (EUSOMA) criteria recommend surgery in defined breast cancer units [4, 41].

Two surgical procedures dominate, either modified radical mastectomy with lymph node sampling or partial mastectomy with lymph node sampling. Partial mastectomy in combination with postoperative radiation provides the same local control as modified radical mastectomy (without radiation). It has therefore become the dominant approach in many high-income countries, for example in US (see figure below). In countries with limited resources and late diagnosis, modified radical mastectomy still remains standard of care.

In country like Iran where women become more aware about breast cancer symptoms in recent years, tumor size and probability of lymph node involvement have been decreased. Surgeons in Iran have also become more familiar with Breast Conserving Surgery (BCS) comparing to ten years ago (4) and studies confirm the rate of BCS have been increased. In the most recent study, around 60% of patients undergone BCS. It seems that BCS become standard of care in most of the cases in Iran, so simultaneously the number of radiotherapy machine should increase and technique of treatment should improve [5, 42, 43].

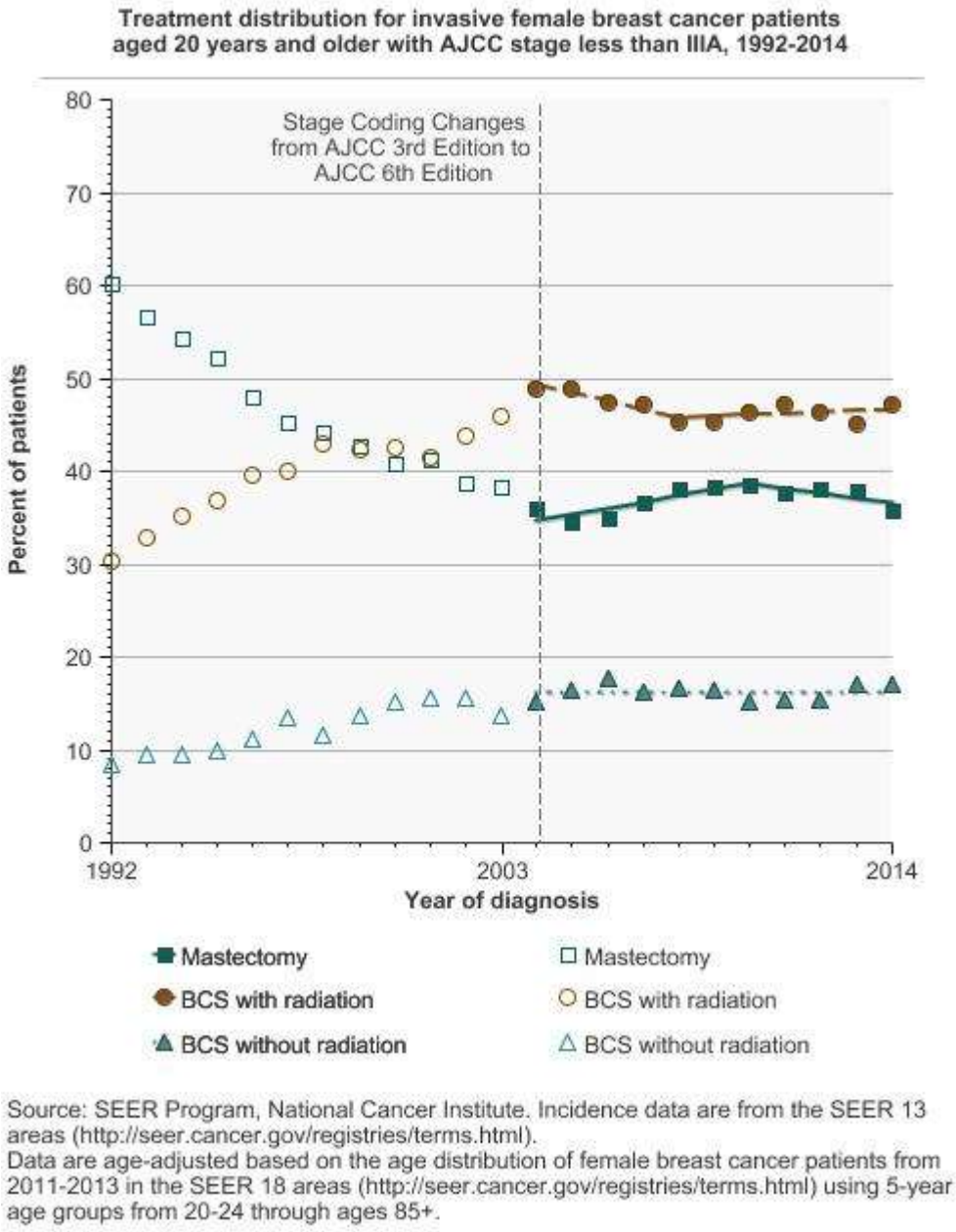


Figure 3-3 *– Surgery for invasive female breast cancer patients 1992-2014 (USA)*

3.3.5.2. Pathology

High quality pathology is key in the decision making of breast cancer care. In order to properly select relevant adjuvant therapy, clinicians need information on tumor size, nodal involvement, proliferation rate and hormone receptor status as well as HER2 status. Quality assurance linked to the postoperative work-up of tumor samples is thus important. [44].

There is limited information regarding pathology in ***Iran***, making it difficult to assess whether post-surgical care is appropriate.

3.3.5.3. Radiation

The shortage of radiation facilities in Iran can be a limitation to breast conserving therapy but even after modified radical mastectomy (MRM), patients with positive lymph node or tumor with large size need adjuvant radiotherapy therefore increase the number and better distribution of radiotherapy machines across country so that they can deliver new techniques is inevitable. Intraoperative radiotherapy (IORT) with small and mobile radiation machines is a safe and cost-effective alternative to conventional external radiotherapy [43-45]. However, this technology is still investigational, and has been suggested conditionally for smaller tumor size without lymph node involvement. It requires dedicated and well-educated staff so it may not yet be suitable for the specific situation in Iran.

3.3.5.4. Adjuvant therapy

Based on the pathology, the most suitable adjuvant therapy is proposed to the patient.

- If the tumor is hormone receptor positive, tamoxifen or aromatase inhibitors are indicated. It is recommended that the length of treatment follow international guidelines, i.e. 5 years or longer, and follow-up routines include means to ensure compliance. It has indeed been shown that low compliance reduces the efficacy of adjuvant hormonal therapy [45]. The increasing number of cases in older age groups, that are more often hormone sensitive, makes it important to implement optimal adjuvant hormone therapy in the future.
- In the case of aggressive or metastatic disease, chemotherapy is indicated. In Iran where patients present late, chemotherapy is thus expected to be used more than e.g. in high-income countries with efficient screening programs. Adjuvant chemotherapy can, however, be complicated to administer in health care settings with limited resources, as it requires safe venous access. There are nevertheless reports of successful applications of complex health care procedures like the use of central venous access devices in health care systems with very limited resources [46, 47]
- For patients with HER2 positive disease, trastuzumab should be offered as adjuvant therapy for a period of one year. In some countries, including Iran, only short-term treatment was reimbursed which, according to present knowledge, was sub-optimal. This has now been changed and 1-year treatment is standard and covered by insurance.

The information on actual usage of adjuvant therapy in ***Iran*** is too limited to make any assessment regarding the adequacy of treatment. A recent review of breast cancer mortality in the United States in the period 1975 to 2010 concludes that increased use of adjuvant therpy, rather than prevention and screening, is responsible for the observed decline in breast cancer mortality. [48]

3.3.5.5. Follow-up

Breast cancer can recur many years after primary treatment. Awareness of symptoms of recurrent disease is essential both for affected women and within the health care system is essential, and easy access to dedicated breast cancer units for patients with a previous diagnosis of breast cancer should be ensured. This information needs to be incorporated into the general awareness campaigns.

3.3.6. Supportive care, palliative care and survivorship

Although metastatic breast cancer is an incurable state of the disease, there are multiple treatment options. First, it is essential to have proper diagnostic work-up of metastatic disease including, if possible, verification of disease (tumor sample) including repeated analysis of hormone receptor status as well as HER2 status as these molecular features may change over time [49, 50]. Second, it is of great importance that palliative care focus on patient needs, and especially of disease related symptoms. Proper treatment of pain, respiratory symptoms, etc is key in order to achieve good palliation.

The Breast Health Global Initiative formed in 2005 has presented a number of guidelines and convened three expert panels to develop resource allocation recommendations for supportive and palliative care programs in low- and middle-income countries. Each panel focused on a specific phase of breast cancer care: during treatment, after treatment with curative intent (survivorship), and after diagnosis with metastatic disease. The panels' consensus statements were published in 2013, with recommendations covering physical symptom management, pain management, monitoring and documentation, psychosocial and spiritual aspects of care, health professional education, and patient, family, and caregiver education for low-and middle-income countries, and these are mainly based on the level of resource use from basic (home care by relatives) to maximal (specialists at palliative care centers) [5].

Palliative care is important in all countries, yet the problem is of greater relative importance in countries where patients have more advanced disease at diagnoses.

3.4. Conclusions and recommendations

The disease burden of breast cancer in Iran is high and growing. However, breast cancer is also the cancer where we see most progress in options for management of the disease over the past 40 years: mammography for early detection, hormonal and cytotoxic medicines, breast conserving surgery and radiotherapy, lately targeted medicines and breast cancer management through multidisciplinary teams.

The long-term prognosis for breast cancer patients has also improved significantly over time. In those countries with the best outcome, 10-year survival rates are now 80% compared to survival rates of just over 50% some 50 years ago. The improvement in survival rates is due to a combination of earlier diagnosis and better treatment. Outcomes differ significantly between and within countries, including between those with comparable levels of resources dedicated to healthcare, indicating opportunities for improvement of outcomes and a more efficient allocation of resources.

The development of new approaches to prevention, early detection and treatment of breast cancer have increased the alternatives available for policy makers, payers, providers and patients. This makes choices to define the best use of medical progress more complicated. It requires more data and analyses to inform decisions. Breast cancer care has developed into a complex process including many different activities that need to be coordinated to ensure best outcomes.

One major conclusion and recommendation is the need for development of an information structure to support policy, resource allocation and clinical decisions for breast cancer management. This includes not only epidemiological data, but also data about treatment patterns, resource use and outcomes (including quality of life) in clinical practice. Without a proper account of the present use of resources and outcomes achieved, it is not possible to define policy options for improvement and monitoring of progress towards defined objectives.

A second key observation is that, as there are many options with different costs attached to them and different clinical outcomes, it is important to assess cost-effectiveness of alternative options, both preventive, curative and for improvement of quality of life. Since research and development continuously creates new options, comprehensive cancer centers that integrate research and quality cancer care can play an important role in introducing and evaluating diagnostic and therapeutic interventions.

Finally, it is crucial to run awareness and education campaigns with the aim to achieve earlier diagnosis, equal access to care and reductions in the disparity of outcomes across regions and population groups.

3.4.1. Data

- A high quality National Cancer Registry has been implemented in Iran. Such registries are key to obtaining accurate data on breast cancer incidence and mortality at the national level and allow analysis of variations between segments of the population and over time, as well as documentation, assessment and communication of the burden of the disease. With relevant data collection, analyses over time allow to assess the progress of breast cancer management as well as the impact of policy guideline developments. Currently, there is still a lack of detailed, patient linked, data on outcome in relation to treatment patterns and stage at diagnosis that limits analyses of how changes in clinical practice affect outcome.
    - Therefore, the National Cancer Registers needs to be updated with relevant information about patient characteristics, treatment, and selected outcome measures. It should be used not only for epidemiological studies, but also for policy evaluation.
- Available data show that the breast cancer incidence and mortality rates in Iran have increased over time. This increase is mainly related to population growth and increased life expectancy. Age adjusted incidence rates are also increasing in low- and middle-income countries related to lifestyle changes, e.g. women having fewer children.
    - This development reinforces the need for collecting data on the burden and cost of breast cancer to inform policies about allocation of resources for management of breast cancer to optimize outcome.
- As survival rates increase with better treatment, more women will be living with/after the disease. This makes **quality of life** during and after treatment increasingly important and puts supportive and palliative care into focus. Iran lacks data on both, quality of life at different stages of the disease, and related to different treatment options on the **quality of care**.
    - Such data are helpful for monitoring treatment and assessment of outcome, and development of specific policies.

3.4.2. Prevention, early diagnosis and screening

- There is a marked correlation between stage at diagnosis and overall survival rates in breast cancer, with earlier diagnosis related to improved outcome. Methods for early detection have both costs and potential harms (false positives), as well as benefits (in terms of better survival), and must be designed according to evidence of the balance between costs and improved outcome. Development of policies for early diagnosis requires careful analysis: why is it needed, what are the alternatives, what are the costs and benefits, and what are the issues for implementation. Intervention programs require careful implementation and follow-up. Explicit calculations of costs and

effectiveness/outcomes of different alternative actions should be part of program development and evaluation.

- Diagnosis in Iran appears to be delayed, with a high proportion of women presenting with advanced disease despite the younger age. A key to improving outcome in Iran are thus regular and intensive **awareness and education campaigns**, combined with screening programs.
- **Screening or early diagnosis programs with clinical breast examination (BE)** for earlier detection of breast cancer are thus an important component of a strategy to improve breast cancer survival in Iran. However, such programs must be designed to meet the specific situation in different regions and for different segments of the population, in order to balance potential benefits and harms, as well as cost-effectiveness and affordability.
- New data have shown the benefit of **primary prevention** with medicines such as tamoxifen and raloxifen. Considering the late diagnosis, and the difficulty and cost to implement effective screening, this strategy should be considered in Iran.

- There is great **uncertainty** around estimates of reductions in mortality and the magnitude of over-diagnosis from screening, but it is possible to conclude that breast cancer screening provides important benefits. The benefits and cost-effectiveness of screening programs are, however, very much influenced by the specific design of the program (e.g. target population, screening intervals).
  - Data on cost-effectiveness of alternative screening strategies are limited and should be developed using data from Iran.

3.4.3. Surgery, adjuvant treatment, treatment of advanced breast cancer and survivorship

- Information on the appropriateness of breast cancer **management** in Iran is not accessible. From the data available to us, it is impossible to assess the number and type of **surgical interventions** performed, and by whom, in relation to the diagnosed population. Nor is it possible to assess the use and the benefits of **radiotherapy**. The latter appears however insufficient, considering the apparent lack of machines. Similarly, good data on **use of cancer medicines** appear limited, and without data on the characteristics of the diagnosed cancer it is not possible to draw any conclusion regarding the levels of usage of the individual classes of treatments. Finally, there is no information on the implementation of multidisciplinary breast cancer care nor the organization of palliative care.
  - Consequently, it is of utmost importance to collect and assess the data currently available in the health care sector, organize adequate data collection both within the registry but also within hospitals.

3.4.4. Economic burden

The largest survival improvements over the last decades have been seen in patients diagnosed with stage II or III disease, which is mainly due to early detection and to the introduction of adjuvant treatment. Currently, we witness a rapid introduction of new effective drugs, including in the late stages of the disease, which improve survival but also increase the costs. Economic data are thus an important complement to data on health burden, and for decisions about resource allocation for prevention and treatment. They are also necessary for comparative studies, between countries but above all between regions within countries, to identify best practices and adapt programs for prevention, early detection and treatment.

- Data on the **economic burden** of breast cancer in ***Iran*** in terms of direct and indirect costs are sparse. According to the most recent and most complete study, costs are dominated by indirect costs, partly due to the fact that most cases occur in women of working age. Direct health care costs attributable to breast cancer vary between studies.
    - The information on cost should be reassessed and updated with more complete data in order to estimate the cost-effectiveness of interventions.
- Two general conclusions about **evidence and cost-effectiveness** have been made. First, strong systems (as opposed to technology-driven solutions) can drive the development and implementation of evidence-based frameworks for prevention and management of cancer in an equitable and affordable way. For this to succeed, different stakeholders—including national governments, global donors, the commercial sector, and service delivery institutions—must work together to address the growing burden of cancer across economies of low, middle, and high income. [2] Second, the oncology community needs to take greater responsibility, especially when using expensive tests and treatments with marginal value. Patients, payers, and pharmaceutical communities should be constructively engaged to communicate medically and economically possible goals to be able to reduce use and costs. Diagnostic tests and treatments should have to show true value to be added to existing protocols. [51].

3.4.5. Guidelines

Health policy guidelines aim at providing guidance for decisions for groups of patients and for prioritization and resource allocation. Policy guidelines are explicitly aimed at administrative as well as clinical decisions and should therefore include an assessment of economic consequences. They are used for vertical as well as horizontal priorities and have a wide involvement of stakeholders.

The objectives of **academic practice guidelines**, such as the ESMO and ASCO guidelines for breast cancer, are to provide guidance for clinical decisions for individual patients and to summarize clinical

evidence and experience. They never include an explicit consideration of cost-effectiveness. The strength of academic guidelines is that they are based on scientific studies and experience of leading practitioners. They are also an important part of medical education and may have a strong influence on clinical decisions such as prescribing drugs. However, there may be limited influence on other stakeholders, such as patients and payers. Academic guidelines also are often accused for a bias towards the interests of specialists and industry.

- Clinical guidelines exist in ***Iran***, but there is a need for revision and local adaptation, and such work is ongoing.
- Policy guidelines with recommendations for prevention, screening, treatment, follow-up and terminal care should be developed/updated both at national and local levels, involving all stakeholders. International guidelines must be adapted to national and local conditions to provide best outcome and cost-effectiveness, as well as to facilitate implementation.

A general problem with guidelines is that they are often not followed, due to a lack of systematic implementation and follow-up. Locally developed guidelines are often the most influential ones. Inclusion of all stakeholders in the development, links to resource allocation and/or pay for performance may improve adherence. Above all, the development of registries should provide the necessary data to assess implementation and may thus improve adherence.

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This research report aims at identifying the burden of breast cancer in Iran and explore how the health care system's organization, financing and resource management impact services and outcomes for breast cancer. The project aims to support Iranian health authorities in identifying and prioritizing policy options for improving breast cancer care and patient outcomes.

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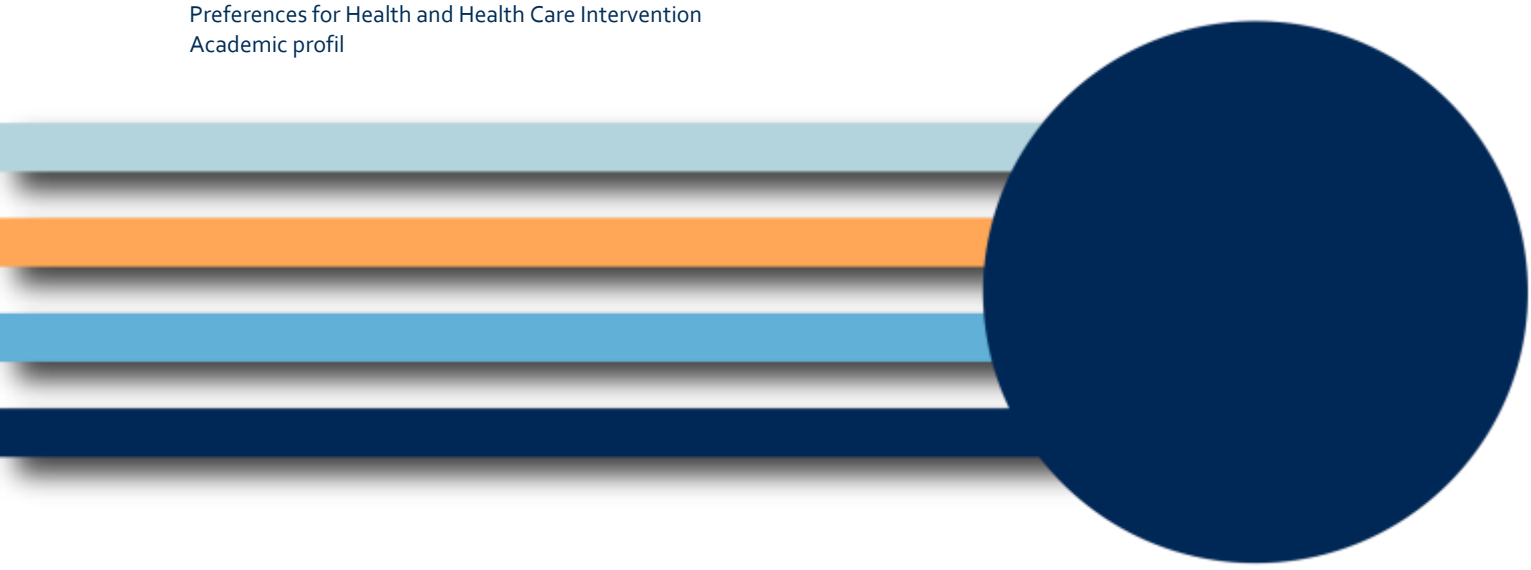

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