RESEARCH ARTICLE

Standardized Breast Cancer Mortality Rate Compared to the General Female Population of Iran

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Abstract

  Introduction: Breast cancer is the most common cancer in women. Improvements of early diagnosis modalities have led to longer survival rates. This study aimed to determine the 5, 10 and 15 year mortality rates of breast cancer patients compared to the normal female population. **Materials and Methods:** The follow up data of a cohort of 615 breast cancer patients referred to Iranian Breast Cancer Research Center (BCRC) from 1986 to 1996 was considered as reference breast cancer dataset. The dataset was divided into 5 year age groups and the 5, 10 and 15 year probability of death for each group was estimated. The annual mortality rate of Iranian women was obtained from the Death Registry system. Standardized mortality ratios (SMRs) of breast cancer patients were calculated using the ratio of the mortality rate in breast cancer patients over the general female population. **Results:** The mean age of breast cancer patients at diagnosis time was 45.9 (±10.5) years ranging from 24-74. A total of 73, 32 and 2 deaths were recorded at 5, 10 and 15 years, respectively, after diagnosis. The SMRs for breast cancer patients at 5, 10 and 15 year intervals after diagnosis were 6.74 (95% CI, 5.5- 8.2), 6.55 (95% CI, 5-8.1) and 1.26 (95% CI, 0.65-2.9), respectively. **Conclusion:** Results showed that the observed mortality rate of breast cancer patients after 15 years from diagnosis was very similar to expected rates in general female population. This finding would be useful for clinicians and health policy makers to adopt a beneficial strategy to improve breast cancer survival. Further follow-up time with larger sample size and a pooled analysis of survival rates of different centres may shed more light on mortality patterns of breast cancer.

Keywords: Breast Cancer - SMR - survival - mortality rate - Iran

Introduction

  Breast cancer is the most common cancer in women worldwide. Based on the Iranian Cancer Registry Report in 2008, the total number of women diagnosed with breast cancer was 8,616 cases with Age Standardized incidence Rate (ASR) of 33.21 per 100,000 female populations.Cancer Office MOH (2009) The survival rate of breast cancer cases is an important issue to help physicians improve quality of patient care. Some studies have reported the survival rate of breast cancer in Iran. For example, in a study performed in 2007, the 7 years survival rate was estimated at 77.5% of patients registered in a screening program in shahre-cord between 1996-2006 (Khadivi et al., 2008). In another study conducted in 2008 in a private clinic in Tehran, the 5 year survival rate of 464 patients treated between 1994-2007 was 81%.(Akbari et al., 2008). A national study was conducted in 2010 on 6,147 breast cancer patients recorded in Iranian Cancer Registry System between 2001-2006. The study found that the five year survival rate of patients was 71% (Movahedi et al., 2011).

  Evidence suggests that breast tumors diagnosed in young women have biology distinct from breast tumors diagnosed in older women. Breast cancer in young women is associated with a markedly poorer overall survival and shorter recurrence-free survival relative to disease in older women. The -five year relative survival rates for women diagnosed prior to age 40 years are approximately 78-84% compared to over 90% among women diagnosed at age 60 years or older. This discrepancy in survival may be attributed to the fact that breast cancer is significantly less likely to be diagnosed at an early stage in young women than in older women (Christopher, 2010). On the other hand, many studies have shown that the age distribution of breast cancer in Iran is nearly one decade lower than their counterparts in developed countries (Mousavi et al., 2007). Since Iran has a relatively young population, it may affect breast cancer age distribution. Considering the prognostic effect of age on survival rate, this study aimed to calculate the mortality rate of breast cancer, standardized with normal women population and adjusted

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for age distribution. Standardized mortality rate (SMR), which is the ratio of the number of observed deaths to the number of expected deaths in a demographically matched standard population, was considered as a suitable index for this purpose.

Breast cancer is a common cancer with high survival rate. Demonstrating this disease survival time in sequential periods of life can help the health system adopt more beneficial strategies to overcome the disease. Most of the cost-effectiveness studies in the field of breast cancer are based on the knowledge of disease biology. So, this study may be helpful in providing an accurate disease transition model for measuring the effect and cost of different preventive, diagnostic and therapeutic modalities in breast cancer.

Materials and Methods

A total of 613 women diagnosed with breast cancer in Breast Cancer Research Center (BCRC) during 1997-2007 and followed up to 2012 have been used in this research. Survival status records of patients were completed through telephone interview. The observed mortality at 5, 10 and 15 year intervals was calculated for each age group. Observed mortality refers to the probability that a patient will die at a particular point in time (e.g., 5 years) after the date of diagnosis. It was assumed that the death rate pattern in missing patients were similar to present patients. So, the total number of observed death was calculated as the sum of true death and expected death in patients who had been missing during follow up.

As mentioned before, age is an important predictor of breast cancer survival and younger patients have shorter survival. In order to study breast cancer mortality probability during 15 years, the effect of age on mortality should be adjusted. Direct standardization method was applied to eliminate the age effect on mortality. To obtain the expected number of deaths for a standard population with the same age group, the probability of observing a death during the same follow-up period adjusted for normal population mortality was calculated.

General population mortality rate is recorded in Iranian Death Registry System established in 2002. So it was used as the standard population mortality rate in Iran. The last published data of Iranian mortality rate in 2007 was considered as the reference dataset (Death Office MOH, 2007).

To calculate the expected number of deaths, the annual death rate for each 5 year age group of the general female population was multiplied by the number of breast cancer patients in the same age group. Expected numbers of deaths were calculated separately for each follow up intervals.

The standardized mortality ratio (SMR) was calculated as the ratio of observed to expected mortality rate of patients. Considering a chi-square distribution on 1 degree of freedom for dataset, and exact test, Confidence Intervals on the standardized mortality ratio were calculated. If this interval included 1, then the evidence was consistent with the conclusion that the two populations might have the same survival distribution.

Mortality rate of patients for breast cancer during follow up time and SMR were calculated by SPSS version 20 and Epi Info software.

Results

Age distributions and clinical characteristics of patients have been summarized in Table 1. Since data records of some variables were not accessible, total count of patients in some of them is not 613.

The mean age of breast cancer patients at diagnosis time was 45.9 (±10.5) years with the age ranging from 24-74. About half of them were in stage II. Patients who underwent chemotherapy, radiation therapy and hormone therapy consisted o 89.6%, 75% and 87.1%, respectively.

Table 2 shows the mortality rate of general women population in Iran. The mean mortality rate of women less than 30 years has been considered for this sub group.

Table 1. Age Distributions and Clinical Characteristics of 613 Women with Breast Cancer in Tehran, Iran

Characteristics		No.	%
Age of diagnosis (years)			
	<30	39	6.4
	30-34	42	6.9
	35-39	89	14.5
	40-44	114	18.6
	45-49	125	20.4
	50-54	83	13.5
	55-59	59	9.6
	60-64	23	3.8
	65-69	22	3.6
	70-74	17	2.8
Disease staging	0	10	1.7
	I	98	16.9
	II	307	52.9
	III	143	24.7
	IV	22	3.8
Type of Surgery	Modified Radical Mastectomy	482	83.2
	Breast Preservation	97	16.8
Chemotherapy	No	64	10.4
	Yes	549	89.6
Radiotherapy	No	136	25
	Yes	408	75
Hormone therapy	No	79	12.9
	Yes	534	87.1

Table 2. Mortality Rate of Iranian General Women Population

Age Groups	Female Population	Mortality Rate/1000
<30	21222719	1.35
30-34	2380208	1.32
35-39	2049229	1.62
40-44	1785378	1.87
45-49	1484987	2.81
50-54	1104501	4.41
55-59	793427	6.51
60-64	615082	10.02
65-69	552674	16.52
70-74	447716	30.13
75-79	268808	55.88
80+	191575	129.26
All ages	32896304	4.03

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Table 3. Observed and Expected Deaths of Breast Cancer Patients Standardized to Population Mortality Rates at 5, 10 and 15 Year Intervals after Diagnosis

Age Groups	Number of patients in start of Study intervals			Expected deaths			Observed deaths		
	Baseline	5 y	10 y	5 y	10 y	15 y	5 y	10 y	10 y
<30	39	26	11	0.26	0.18	0.07	3.77	3	0
30-34	42	26	6	0.28	0.17	0.04	3.93	6.46	0
35-39	89	62	23	0.72	0.5	0.19	8.57	6.26	1.48
40-44	114	73	22	1.07	0.68	0.21	21.63	11.22	0
45-49	125	85	30	1.76	1.19	0.42	11.23	12.42	0
50-54	83	55	21	1.83	1.21	0.46	12.17	3.16	0
55-59	59	37	12	1.92	1.2	0.39	12.03	3.24	0
60-64	23	9	3	1.15	0.45	0.15	6.96	1.56	0
65-69	22	13	3	1.82	1.07	0.25	6.82	1.69	1.67
70-74	17	7	2	2.56	1.05	0.3	2.94	1.57	0
Total	613	393	133	13.36	7.72	2.48	90.05	50.59	3.14

Iranian Death Registry System established in 2002 and causes of death were coded based on ICD10 coding.

According to this data, about 65% of the female population (21,222,719) were less than 30 years old. The overall mortality rate of women is 0.4% with the range of 0.13% to 1.9% in different age groups.

Table 3 demonstrates the calculated observed and expected number of deaths in 5, 10 and 15 year intervals after diagnosis. It shows that from 613 patients entered in the study, 393 and 133 of them were accessible after 5 and 10 years of diagnosis, respectively.

By dividing the observed deaths by the expected ones in each interval of table 3, SMR and 95% Confidence Interval (CI) of breast cancer patients compared to general female population mortality rate were calculated. SMR and 95% CI in 5, 10 and 15 years after diagnosis were 6.74 (95%CI: 5.55-8.2), 6.55 (95%CI 5.03-8.09) and 1.27 (95%CI 0.65-2.9), respectively

Discussion

According to study results, the mortality rate of breast cancer at 5, 10 and 15 years after diagnosis is respectively 6.7, 6.5 and 1.26 times the expected rates in general women population. The observed mortality rate of breast cancer patients after 15 years of diagnosis is very similar to expected mortality rates in general women population.

According to Yavari study, the Proportional Mortality Ratios (PMRs) for neoplasms was fifth cause of death in Iranian population during 1979-81. It ranked 4th and 3rd cause of death in 1982-86 and 1987-90, respectively and was stabilized since then. (Yavari et al., 2003)Iranian Death Registry System recorded 993 deaths due to breast cancer in 2006. Mortality rates were 1.74 per 100,000 of total population and 3.47 mortality rates per 100,000 of women population (Death Office MOH, 2007).

In this study we compared the sequential mortality rate of a breast cancer patients' cohort with standard population mortality in 5 years intervals. The standardized mortality ratio has been used for defining this index since 1786. (Finkelstein et al., 2003) Many studies have compared the trend of breast cancer mortality at different time intervals. (Zahl and Maehlen, 2005; Erbas et al., 2007; Hirte et al., 2007; Jatoi et al., 2007; Cabanes et al., 2009)In spite of large sample size and long follow up duration of most studies(Tabar et al., 1992), the transition probability of mortality in a cohort of breast cancer patients during long period was not accessible.

Only one study was found which had calculated SMR of breast cancer for comparing standardized mortality in a sample population with other fetal diseases. In that study, in United States, they had investigated SMRs and PMRs in seafood workers, using the US general population for comparison. About 45% of the cohort was born after 1949 and they were followed up from 1966 to 2003. The SMRs for breast cancer was 0.5 (95% CI, 0.3-0.9). This cohort had excess deaths from stomach cancer and disorders of the thyroid gland, and deficit of deaths from breast cancer, stroke and ischemic heart disease.(Johnson et al., 2011) This result suggests that the observed mortality of breast cancer over a long period of time is less than expected mortality of normal female population.

One of the important and common questions of breast cancer patients in follow up visits is about "predicting the survival time". Most of them are worried about the future and they wish to know if they would have different survival probability from normal female population. According to opinion of expert surgeons and oncologists in breast cancer centers of Iran, survived patients up to 10-15 years can be considered as cured ones, but there is no definite cut point for it in literature. Demicheli, et al assessed the breast tumour recurrence, distant metastasis and mortality throughout 10 years of follow-up. They compared the first early peak of these events at about 24 months and second late peak at the sixth-seventh year for both estrogen receptor positive and negative tumours. (Demicheli et al., 2010) It seems that they had considered the critical survival time for patients less than 10 years. More information in this field can be useful for clinicians in planning a better and cost-effective follow up care. Thus, patients and their families can benefit from more suitable service and better quality of life.

Iranian Death registry Record System has been established since one decade before and its errors ought to be considered in our results. Besides, because of data collecting limitations, estimating population mortality rate excluding breast cancers is not possible. The aim of this study was comparing the SMRs of breast cancer in

5 years sequential intervals and it cannot be affected by mentioned error. Definitely providing more accurate data needs to data linkage of a cancer Registry data containing survival records and Death Registry records at the same time interval. At present, in Iran we do not have access to such data record systems.

It is important to note that breast cancer mortality data has been derived from a breast clinic in Tehran. Even though it is a referral centre from different cities of Iran, its results cannot be entirely generalized to the country. Different studies performed in governmental and non-governmental clinics of Iran have reported a wide range of 5 years survival between 58% - 89%.(Yaghmaii et al., 2007; Akbari et al., 2008; Khadavi et al., 2008; Khadivi et al., 2008; Mousavi Naiini et al., 2009; Movahedi et al., 2011). A meta-analysis study or a pooled data analysis of multiple centres of Iran which have recorded at least 15 years follow up data may provide more accurate and generalizable estimation of SMR for breast cancer.

This study demonstrated a highly drop in SMR after ten years survival. SMR at 15 years interval is 1.27 with 95% CI of 0.65-2.9. This interval included 1, indicating that the observed number of deaths in breast cancer patients after 15 years of diagnosis is not significantly higher than the expected number of deaths in general female population. Small sample size of patients who entered the third time transition cycle may have led to wide confidence interval. So a longitudinal study with larger sample size and longer follow up time is suggested for providing more accurate estimation of this index.

In spite of these limitations, this is a new epidemiologic point of view to breast cancer survival transition which may be beneficial for better understanding the tumour biology.

In many economic studies, health micro simulation models(Will et al., 2000) or mathematical procedures(Chen et al., 1998) are used to estimate quantitative patterns of disease incidence, progression and treatment consequences in a population. This study demonstrated that progression behaviour of breast cancer tumour may be halted after 10 years. So this study may provide useful information for cost-effectiveness modelling. It would help health policy makers to adopt a beneficial strategy to overcome breast cancer. Performing this study in other countries with larger database may have an important role in introducing the unknown aspects of this disease.

Acknowledgement

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