RESEARCH ARTICLE

Application of Cox and Parametric Survival Models to Assess Social Determinants of Health Affecting Three-Year Survival of Breast Cancer Patients

Maryam Mohseny[1], Farzaneh Amanpour[2], Alireza Mosavi-Jarrahi[1], Hossein Jafari[3], Mohammad Moradi-Joo[3], Esmat Davoudi Monfared[4]*

Abstract

Breast cancer is one of the most common causes of cancer mortality in Iran. Social determinants of health are among the key factors affecting the pathogenesis of diseases. This cross-sectional study aimed to determine the social determinants of breast cancer survival time with parametric and semi-parametric regression models. It was conducted on male and female patients diagnosed with breast cancer presenting to the Cancer Research Center of Shohada-E-Tajrish Hospital from 2006 to 2010. The Cox proportional hazard model and parametric models including the Weibull, log normal and log-logistic models were applied to determine the social determinants of survival time of breast cancer patients. The Akaike information criterion (AIC) was used to assess the best fit. Statistical analysis was performed with STATA (version 11) software. This study was performed on 797 breast cancer patients, aged 25-93 years with a mean age of 54.7 (±11.9) years. In both semi-parametric and parametric models, the three-year survival was related to level of education and municipal district of residence (P<0.05). The AIC suggested that log normal distribution was the best fit for the three-year survival time of breast cancer patients. Social determinants of health such as level of education and municipal district of residence affect the survival of breast cancer cases. Future studies must focus on the effect of childhood social class on the survival times of cancers, which have hitherto only been paid limited attention.

Keywords: Breast cancer - parametric survival - social determinants of health - Iran

Introduction

Breast cancer is the most common type of cancer diagnosed in women and is the main cause of cancer-related death in females. It accounted for 1.7 million cases of cancer and caused 521,900 deaths in 2012. Breast cancer alone comprises 25% of all cancers and 15% of cancer-related deaths in women (Torre et al., 2015).

According to the global statistics, incidence of breast cancer increases by 2% annually worldwide (DeSantis et al., 2011). The prevalence of breast cancer is the highest among the Iranian women in the age range of 40 to 49 years and its prevalence in this age range reaches 120 in 100,000 population (Mousavi et al., 2007). Differences exist in the prevalence and morbidity and mortality of breast cancer among different countries. A reduction in morbidity and mortality related to breast cancer has been reported in the north, south and west of Europe (Autier et al., 2011) while the trend of breast cancer-related morbidity and mortality is increasing in Asia, Japan, Korea and China (Katanoda and Yako-Suketomo 2010). Such variability may be related to several factors, and many studies have

focused on differences among the communities possibly affecting the prevalence and morbidity and mortality of diseases. Strong evidence suggests that such variability in diseases like breast cancer is related to social determinants of health (Adler and Stewart 2010). The center for disease control defined social determinants of health as social and economical conditions affecting the health of individuals and communities (Koh et al., 2011). Social determinants of health are factors that affect the interaction of people with the health care system (Dryden et al., 2012).

As a general consensus, people are classified according to their level of education, social class and place of residence, and their position in their community and at the social, national and global level is determined and judged based on the above-mentioned parameters (Kelly et al., 2006). An inverse correlation exists between the social class of individuals in the community and general rate of morbidity and mortality. Regarding breast cancer, the rate of cancer-related deaths among women in poor communities is higher than that among women in rich countries. Furthermore, rate of breast cancer-related deaths in low-income women has reported to be 1.46 times the

[1]Department of Community Medicine, [3]Taleghani Hospital,Shahid Beheshti University of Medical Sciences, [4]Department of Community Medicine, Baqiyatallah University of Medical Sciences, Tehran, [2]Department of Epidemiology and Biostatistics, School of Public Health, Shahroud University of Medical Sciences, Shahroud, Iran. *For correspondence:davoudimonfared@gmail.com

rate in high-income women (Sprague et al., 2011). Women from low socioeconomic classes are diagnosed with poor-prognosis breast cancer 1.35 times more than women from high socioeconomic classes (Hall et al., 2004).

Although many studies have focused on social determinants of health, some factors such as place of residence and childhood conditions have been less commonly addressed. Considering the high and growing prevalence of cancers and its correlation with social determinants of health (Heidarnia et al., 2013; Cheung et al., 2013), this study aimed to assess the correlation of social determinants of health with the three-year survival rate of breast-cancer.

Materials and Methods

This descriptive cross-sectional study was conducted on males and females diagnosed with breast cancer in Cancer Research Center of Shohada-E-Tajrish Hospital from March 20, 2006 to March 20, 2010.

Sampling was census. Sample size was calculated using the sample size calculation formula for survival studies taking into account α=5% and 80% power of study. The inclusion criteria were residing in Tehran, being diagnosed with breast cancer during the designated time period and initiation of treatment after definite diagnosis of breast cancer. A questionnaire was designed for the interview with patients.

Assessment of reliability of the questionnaire:

Years of education was used to determine the social class of patients since the previous studies have shown that years of education is a valid and reliable indicator for the studies on the correlation of health and social factors (Montazeri et al., 2005).

Financial status of patients was determined using the average per capita housing, which was calculated by dividing the floor area (square meters) of the house by the number of people living in the house. Previous studies have shown that level of income in Iran is not a reliable indicator of financial status (Montazeri et al., 2005) but the average per capita housing is a valid and reliable indicator of financial status (REF).

Social determinants of health were evaluated in different levels. Demographic factors including age, sex, marital status, financial status, place of residence (district), per capita housing and property tax were evaluated. Social class was determined by the level of education and occupational status of patients. Risky behaviors such as cigarette smoking were also questioned. Access to health care services, health insurance coverage, receipt of complete treatment and type of treatment were also addressed. Childhood conditions, place of residence in childhood, number of siblings, family history of breast cancer and family history of chronic diseases were evaluated as well.

The Urban HEART Study (Fereshtehnejad et al., 2010). was used to divide the municipal districts of Tehran into five major areas as follows: The north area included districts 1.0, 2.0, 3.0 and 6.0. The east area included districts 4.0, 7.0, 8.0 and 13. The west area included districts 5.0,

21.0 and 22.0. The central area included districts 9.0, 10.0, 11.0 and 12.0 and the south area included districts 14.0, 15.0, 16.0, 17.0, 18.0, 19.0, 20.0. For data collection, first, the contact information of patients was retrieved from the Cancer Registry Center of Shohada-E-Tajrish Hospital and patients were contacted by phone to assess their current state and calculate their three-year survival. Next, the questionnaire regarding social determinants of health was filled out for the patients over the phone. If the patient had passed away, the questionnaire was filled out by asking questions from the closest person to the deceased patient. The interviewer had academic education and had been instructed on how to interview the patients and ask questions. The same interviewer interviewed all patients. In case of unsuccessful attempt or incomplete questionnaire, the interviewer contacted the patient again to fill out the questionnaire.

Statistical analysis

Lognormal, log-logistic and the Weibull regression (as parametric models), and Cox proportional hazard model (as semi-parametric model) were used to assess the effect of possible risk factors on survival time and hazard ratio of breast cancer patients.

The interpretation of survival models depends on whether the model is an accelerated failure time (AFT) model or a proportional hazard (PH) model. The AFT models are applied to compare the survival times; whereas, the PH models are applied to compare the hazards. Cox is a PH model while lognormal and log-logistic are AFT models. The Weibull distribution is both a PH and an AFT model.

The AIC, which determines the goodness of fit of a statistical model, was used to compare different parametric distributions and Cox model. The distribution with the lowest AIC value fits the data the best.

Survival time was defined as the period between the diagnosis of disease and death or the end of third year. A binary variable was used to indicate whether a patient was censored or died of cancer.

Variables in the study included: Age (<50, ≥50), sex (female, male), inheritance (yes, no), chronic disease (yes, no), childhood residence (urban, rural), siblings (≤4, >4), smoking (yes, no), marital status (single, married, divorced, widowed), level of education (<high school, high school diploma, academic education), district (north, west, east, center, south), home ownership (yes, no), home size (<30, 30-60, >60 m2), complete treatment (yes, no), and treatment type (incomplete, complete).

Relative survival time and 95% confidence interval were estimated for the candidate parametric distribution. The hazard ratio and 95% confidence interval were estimated for the Cox model. All models were fitted using STATA (version 11) software.

Results

The study was performed on 797 breast cancer patients, aged 25-93 years with a mean age of 54.7 (±11.9) years and median age of 54 years. After three years of diagnosing with breast cancer, 700 (87.8%) patients were still alive

Table 1. Case summary and Overall Comparisons by Kaplan-Meier and Generalized Gamma with Regard to the Three-Year Survival of Breast Cancer Patients

Variable		Total No.	No. of Event	P value
Age	≥50.0	520.0	74.0	0.01*
	<50.0(ref)	277.0	23.0	
Sex	Female	686.0	88.0	0.46
	Male	114.0	12.0	
Marital status	Single	54.0	4.0	0.05
	Married	640.0	84.0	
	Divorced	36.0	0.0	
	Widowed	70.0	12.0	
Education	<High school diploma	258.0	46.0	<0.01*
	Diploma	264.0	36.0	
	Academic education (ref)	278.0	18.0	
Complete treatment	Yes	786.0	94.0	0.5
	No	10.0	2.0	
Childhood place of residence	Urban	690.0	92.0	0.03*
	Rural (ref)	106.0	6.0	
Chronic disease	Yes	150.0	20.0	0.44
	No	628.0	70.0	
Inheritance	Yes	268.0	30.0	0.5
	No	528.0	68.0	
Smoking	Yes	32.0	2.0	0.4
	Quit	28.0	2.0	
	No	736.0	94.0	
Siblings	>4.0	454.0	68.0	0.01*
	≤4.0(ref)	346.0	32.0	
Treatment type	Incomplete	170.0	4.0	<0.01*
	Complete (ref)	630.0	96.0	
Municipal district	North (ref)	162.0	8.0	0.01*
	East	124.0	14.0	
	West	90.0	8.0	
	Center	42.0	8.0	
	South	40.0	8.0	
Home ownership	Yes	640.0	80.0	0.72
	No	158.0	18.0	
Home size	<30.0	172.0	14.0	0.46
	30.0-60.0	162.0	8.0	
	>60.0	76.0	6.0	

* : Statistically significant (P<0.05)

while 97 (12.2%) patients had passed away.

Age, sex, inheritance, chronic disease, childhood place of residence, siblings, smoking, marital status, level of education, place of residence, home ownership, home size, completion of treatment and treatment type were entered separately into the Generalized Gamma (GG) model as well as Kaplan-Meier (KM) model. According to both models, the effects of age, level of education, childhood place of residence and siblings were significant (P<0.05). Case summary of variables and the results of overall comparison by KM method and GG model with regard to the three-year survival of breast cancer patients are shown in Table 1.

The results of parametric regression models and Cox model are shown in Table 2.

In all models, level of education and place of residence had significant effects on survival time of breast cancer patients.

The results of comparison between parametric models have been summarized in Table 2. According to the AIC statistic, all parametric models had better goodness of fit compared to Cox model; among parametric models, the lognormal was better than log-logistic and the Weibull distribution.

According to the lognormal model, patients with high

Table 2. Cox and Parametric Models of Breast Cancer Patients' Three-Year Survival

Variable		Cox (PH)	Weibull (PH)	Weibull (AFT)	Lognormal (AFT)	Loglogistic (AFT)
Demographic						
Age	≥50	1.2	1.2	0.9	1	0.9
		(0.5,2.6)	(0.5, 2.6)	(0.5,1.6)	(0.5, 1.9)	(0.5, 1.7)
	<50(ref)	1	1	1	1	1
Sibling	>4	1.7	1.7	0.7	0.7	0.7
		(0.9,3.2)	(0.9, 3.2)	(0.4, 1.1)	(0.4, 1.1)	(0.4, 1.1)
	≤4(ref)	1	1	1	1	
Child residence	Urban	2.3	2.3	0.5	0.4	0.5
		(0.6,9.6)	(0.5, 9.5)	(0.2, 1.6)	(0.2, 1.3)	(0.2, 1.5)
	Rural (ref)	1	1	1	1	1
Socioeconomic						
Education	<High school (ref)	1	1	1	1	1
	Diploma	0.9	0.9	1.1	1.3	1.2
		(0.4,1.8)	(0.4, 1.8)	(0.6, 2)	(0.7, 2.3)	(0.7, 2.1)
	Academic	0.4*	0.4*	2.1*	2.5*	2.3*
		(0.2,1)	(0.2, 1)	(1,4.4)	(1.2, 5.3)	(1.1, 4.8)
District	North(ref)	1	1	1	1	1
	East	2.9*	2.9*	0.4*	0.4*	0.4*
		(1.1,7.5)	(1.1, 7.5)	(0.2,1)	(0.2,0.9)	(0.2, 0.9)
	West	2.8	2.8	0.4	0.5	0.4
		(1,8)	(1, 8.2)	(0.2,1.0)	(0.2, 1.1)	(0.2, 1.0)
	Center	4.6*	4.8*	0.3*	0.4*	0.3*
		(1.6,13.6)	(1.6, 14.2)	(0.1,0.7)	(0.1,0.9)	(0.1, 0.8)
	South	4.5*	4.6*	0.3*	0.3 *	0.3*
		(1.5,13.6)	(1.5, 14)	(0.1,0.8)	(0.1, 0.8)	(0.11, 0.8)
AIC		505.2	329.9	329.9	325	328.6

* : Statistically significant (P<0.05)

school diploma or academic degree had higher survival time compared to patients with high school education, and the difference was significant for academic group of patients.

All municipal districts had lower survival time compared to the municipal district one, and the difference was significant for east, center, and south areas.

Discussion

Social determinants of health have been addressed in several studies. However, most previous studies have only focused on some of these factors. In the current study, we evaluated social determinants of health in breast cancer patients by focusing on personal aspects, socioeconomic status, occupational factors, high-risk behaviors, access to health care services, childhood conditions and family history.

Among the personal factors, age of onset of breast cancer was an important factor affecting the survival of patients. Evidence shows that age is a prognostic factor for breast cancer survival. Largillier et al (2008) reported a poor prognosis for breast cancer patients over 50 years of age. Some other studies have shown that pre-menopause women have a better prognosis than post-menopause

women with breast cancer (Dawood et al., 2010). Fallahzadeh et al. in their study in Iran reported that five-year survival rate of breast cancer patients over 50 years of age was lower than that of patients younger than 50 years (Fallahzadeh et al., 2014). Decreased survival rate of breast cancer patients by an increase in age may be due to the fact that in older ages, the prevalence of accompanying diseases increases as well. Presence of concomitant diseases causes secondary disabilities and adversely affects the process of treatment and compliance with cancer therapy by patients. All these factors negatively affect the survival rate. Moreover, the knowledge of older individuals about the importance of breast cancer screening may be poor. In the current study, high educational level and residing in better neighborhoods were associated with higher three-year survival rate for breast cancer. Some other studies showed that lower survival rate of breast cancer was correlated with lower level of education and living in areas with less-educated people (Sprague et al., 2011). Herndon et al (2013) reported a significant association between not completing high school and poorer prognosis in patients diagnosed with early-stage breast cancer. An epidemiologic study by Hussain et al (2008) showed that higher level of education was associated with more favorable survival of breast cancer patients.

Socioeconomic status in previous studies has been determined using different indicators. Morris et al. used the "ability to pay" (reflecting income, the number of dependents and insurance coverage) as an indicator of socioeconomic status. They reported that morbidity and mortality of breast cancer in women with low socioeconomic status was 1.69 times the rate in women with high socioeconomic status, even after adjusting for disease stage at the time of diagnosis, treatment and tumor histology (Morris et al., 2015). In a study by Ayanian et al (1993) type of insurance was used as an indicator of socioeconomic status and it was shown that rate of breast cancer-related deaths in uninsured women or in those with Medicaid insurance was approximately 40 to 50% higher than that in women with other types of insurance. In this study, place of residence was used as an indicator of socioeconomic status and level of education was used as an indicator of social class. Socioeconomic status can affect the survival rate of cancers particularly breast cancer via different mechanisms. Women with lower socioeconomic status are probably less commonly screened for early detection of breast cancer and their disease is often diagnosed at a later, more advanced stage. This hypothesis has been confirmed by some other studies as well (Morris et al., 2015). Moreover, women with lower socioeconomic status are probably more exposed to life style-related risk factors and environmental factors accelerating breast cancer. Furthermore, socioeconomic class determines the place of residence. People from lower socioeconomic classes often reside in areas with less medical services available for diagnosis and treatment of cancer (in terms of quality and quantity) and this can significantly affect the quality of treatment and survival rate of breast cancer patients. Other studies have also pointed to place of residence and distance from diagnostic and therapeutic medical centers as important factors affecting the survival rate of breast cancer patients (Dasgupta et al., 2012). Also, breast cancer patients from a lower socioeconomic class and with low income are less likely to complete their treatment course and show up for the follow-ups. Evidence shows that completion of the course of treatment positively affects the survival rate of breast cancer patients (Wheeler et al., 2013). Further studies are required to elucidate all socioeconomic aspects affecting the survival rate of cancer patients particularly those with breast cancer.

Social determinants of health such as age, level of education and place of residence (municipal district) affect the survival rate of breast cancer patients. Future studies are required to address the factors less commonly investigated in previous studies such as the childhood conditions of cancer patients.

Acknowledgements

References

Adler NE, Stewart J (2010). Health disparities across the lifespan: meaning, methods, and mechanisms. *Ann N Y Acad Sci*, **1186**, 5–23.

Autier P, Boniol M, Gavin A, et al (2011). Breast cancer mortality in neighbouring European countries with different levels of screening but similar access to treatment: trend analysis of WHO mortality database. *BMJ*, **28**, 343.

Ayanian JZ, Kohler BA, Abe T, et al (1993). The relation between health insurance coverage and clinical outcomes among women with breast cancer. *N Engl J Med*, **329**, 326-31.

Cheung MR (2013). Assessing the Impact of Socio-economic variables on breast cancer treatment outcome disparity. *Asian Pac J Cancer Prev*, **14**, 7133.

Dasgupta P, Baade PD, Aitken JF, et al (2012). Multilevel determinants of breast cancer survival: association with geographic remoteness and area-level socioeconomic disadvantage. *Breast Cancer Res Treat*, **132**, 701-10.

Dawood S, Broglio K, Ensor J, et al (2010). Survival differences among women with de novo stage IV and relapsed breast cancer. *Ann Oncol*, **21**, 2169-74.

DeSantis C, Siegel R, Bandi P, et al (2011). Breast cancer statistics, 2011. *CA Cancer J Clin*, **61**, 408-18.

Dryden R, Williams B, McCowan C, et al (2012). What do we know about who does and does not attend general health checks? Findings from a narrative scoping review. *BMC Public Health*, **31**, 1.

Fallahzadeh H, Momayyezi M, Akhundzardeini R, et al (2014). Five year survival of women with breast cancer in Yazd. *Asian Pac J Cancer Prev*, **15**, 6597-6601.

Fereshtehnejad M, Asadi-Lari M, Moradi Lakeh M, et al (2010). Estimation of life expectancy and its association with social determinants of health (SDH) in Urban population of different districts of Tehran in 2008 (Urban HEART Study). *Teb Va Tazkiyeh*, **77**, 103.

Hall S, Holman CD, Sheiner H, et al (2004). The influence on socio-economic and locational disadvantage on survival after a diagnosis of lung or breast cancer. *J Health Serv Res Policy*, **9**, 6-10.

Heidarnia MA, Monfared ED, Akbari ME, et al (2013). Social determinants of health and 5-year survival of colorectal cancer. *Asian Pac J Cancer Prev*, **14**, 5111-16.

Herndon JE, Kornblith AB, Holland JC, et al (2013). Effect of socioeconomic status as measured by education level on survival in breast cancer clinical trials. *PsycholOncology*, **22**, 315-23.

Hussain S.K., Altieri A., Sundquist J, et al (2008). Influence of education level on breast cancer risk and survival in Sweden between 1990 and 2004. *Int J Cancer*, **122**, 165-9.

Katanoda K, Yako-Suketomo H (2010). Comparison of time trends in breast cancer mortality (1990-2006) in the World, from the WHO mortality database. *Jpn J Clin Oncol*, **40**, 182-90.

Kelly MP (2006). The development of the evidence base about the social determinants of health. Geneva: World Health Organization.

Koh HK, Piotrowski JJ, Kumanyika S, et al (2011). Healthy People a 2020 vision for the social determinants approach. *Health Educ Behav*, **38**, 551-7.

Largillier R, Ferrero JM, Doyen J, et al (2008). Prognostic factors in 1038 women with metastatic breast cancer. *Ann Oncol*, **19**, 2012-19.

Montazeri A, Goshtasebi A, Vahdaninia M, et al (2005). The Short Form Health Survey (SF-36): translation and validation study of the Iranian version. *Qual Life Res*, **14**, 875-82.

Morris M, Woods LM, Rogers N, et al (2015). Ethnicity, deprivation and screening: survival from breast cancer among screening-eligible women in the West Midlands

diagnosed from 1989 to 2011. *Br J Cancer*, **113**, 548-55.

Mousavi SM, Montazeri A, Mohagheghi MA, et al (2007). Breast Cancer in Iran: An Epidemiological Review. *Breast J*, **13**, 383–91.

Sprague BL, Trentham Dietz A, Gangnon RE, et al (2011). Socioeconomic status and survival after an invasive breast cancer diagnosis. *Cancer*, **117**, 1542-51.

Torre LA, Bray F, Siegel RL, et al (2015). Global cancer statistics, 2012. *CA Cancer J Clin*, **65**, 87-108.

Wheeler SB, Reeder-Hayes KE, Carey LA (2013). Disparities in breast cancer treatment and outcomes: biological, social, and health system determinants and opportunities for research. *Oncologist*, **18**, 986-93.