RESEARCH ARTICLE

Female Breast Cancer Mortality Rates in Turkey

Nurhan Dogan[1]*, Dilek Toprak[2]

Abstract

The main objective of this study was to analyze the mortality trends of female breast cancer in Turkey between the years 1987-2008. The rates per 100,000 age-standardized to the European standard population were assessed and time trends presented using joinpoint regression analysis. Average annual percent change (AAPC), anual percent change (APC) and 95% confidence interval (CI) was calculated. Nearly 23,000 breast cancer deaths occurred in Turkey during the period 1987-2008, with the average annual age-standardized mortality rate (ASR) being 11.9 per 100,000 women. In the last five years, significant increases were observed in all age groups, but there was no significant change over the age of 65. In this period, the biggest significant increase was in the 45-54 age group (AAPC=4.3, 95%CI=2.6 to 6.0).

Keywords: Breast cancer - mortality - joinpoint regression analysis - Turkey

Asian Pac J Cancer Prev, **15 (18)**, 7569-7573

Introduction

Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death among females, accounting for 23% (1.38 million) of the total cancer cases (6.038 million) and 14% (458,400 deaths) of the cancer deaths (3.346 million) in 2008. Breast cancer is also the leading cause of cancer death among women in economically developing (268,900 deaths, 12.7% of total) and developed countries (189,500 deaths, 15.5% of total). (Jemal et al., 2011)

Breast cancer is also the most common cause of cancer death among women (522,000 deaths in 2012) and the most frequently diagnosed cancer among women in 140 of 184 countries worldwide (Ferlay et al., 2013).

Although breast cancer is thought to be a disease of the developed world, almost 50% of breast cancer cases and 58% of deaths occur in less developed countries (Ferlay et al., 2010).

Globally, breast cancer incidence and mortality rates among women have been increasing rapidly in many Eastern European, Asian, Latin American, and African countries (Jemal et al., 2010). The lowest breast cancer mortality rates were found in Eastern Asia and Southeastern Asia and Pacific (Jemal et al., 2011).

Breast cancer was the leading cancer site in women in all countries of Europe in 2012. The range of mortality rates varies (15-36 per 100,000). Mortality rates were highest in Macedonia, Serbia, Belgium and Denmark, respectively (Ferlay et al., 2013, Ilic et al., 2013). Znaor et al found that in women, breast cancer mortality significantly declined in Slovenia, Croatia and Malta (AAPC -2%, -1% and -5%, respectively), but not elsewhere (Znaor et al., 2013).

In this research we aimed to evaluate temporal changes in mortality rates of female breast cancer in the population of Turkey between the years 1987-2008.

Materials and Methods

The study comprised the female population of the Turkey during the period 1987-2008. Cancer mortality data (provinces and districts) on women who died of breast cancer (codes 174 revision 9 and C50 revision 10 of the International Classification of Diseases (ICD) were obtained from the Turkish Statistical Institute death database (TurkStat, 2013). According to age groups' population distribution of years 1990 and 2000, the provincial and district centers, other years' midyear female population has been obtained. The rates were age-standardized (ASR per 100,000 person-years) using the direct method and the European standard population.

Statistical analysis

Joinpoint regression is a statistical modeling technique that explains the relationship between two variables by means of a segmented linear regression constrained to be continuous everywhere, in particular, in those places where the slope of the regression function changes. This technique is widely applied to the modeling of time trends in mortality or incidence series in epidemiological studies (Miguel et al., 2011).

Trends in age-standardized cancer mortality rates were calculated by joinpoint regression using Joinpoint software version 4.1.0 (Natinal Cancer Institutes, 2013). Joinpoint regression was used to detect points (i.e., "joinpoints") where the trends changed significantly. The

*[1]Department of Biostatistics and Medical Informatics, Faculty of Medicine, Afyon Kocatepe University, Afyonkarahisar, [2]Department of Family Medicine, Sisli Etfal Training and Research Hospital, Istanbul, Turkey *For correspondence: nurhandogan@hotmail.com*

analysis starts with the minimum number of joinpoints and tests whether one or more joinpoints are statistically significant and must be added to the model. Number of joinpoints were determined by performing permutation tests, each of which had a correct asymptotic significance level. These significance level were found using Monte Carlo methods and applying Bonferroni corrections (Kim et al., 2000). The final model shows (Fit an autocorrelated errors model based on the data), the best fitting joinpoints where the rate changes significantly. Each joinpoint informs of a statistically significant change, an estimated annual percent change (APC) and average annual percent change (AAPC) that are computed along with its 95% confidence intervals (95%CI). AAPC is the geometric mean of the annual changes from all of the partitions. Also AAPC takes into account trend transitions (Clegg et al., 2009).

In this study, each of detected trends were calculated by fitting a regression line to the natural logarithm of the rates, using calendar year as regressor variable [ln(rate)=a+bx], where x is calendar year; APC was estimated as. The APC was considered significant if the confidence interval does not include zero. The parameters were allowed with maximum of four joinpoints to enter the final model while having minimum of 4 years between two joinpoints. The analyses were applied with a significance level of 0.05.

Age standardized death rates per 100,000 people (using European standard population) were calculated for each calendar year using direct standardization the changes in the age-standardized mortality rate over the 22-year period were analyzed for cancer by fitting the joinpoint regression model. Ten-year age groups were used for the standardization. This approach adjusts crude rates according to the age distribution, so it is useful to compare populations of different cities or countries (Ahmad et al., 2001). The subgroup analyses were also performed; the age groups were divided in four strata and were created to approximate premenopause (25-44 years old), perimenopause (45-54 years old), the first ten years of the postmenopausal period (55-64 years old), and thereafter (≥65 years old), respectively. As there were very few breast cancer deaths, the results are not shown for ages <25 years.

Results

Nearly 23,000 breast cancer deaths occured in Turkey during the period 1987-2008, with the average annual age-standardized mortality rate (ASR) being 11.9 per 100,000 women. The standardized, or ASR increased from 9.2 per 100,000 women in 1987 to 14.9 per 100,000 in 2008. Also numerous year-to-year fluctuations in the mortality rate for females due to breast cancer are seen in the Figure 1 and 2.

Trends in breast cancer mortality were calculated using joinpoint regressions analysis. The results of the joinpoint regression analysis (i.e., the points in which the rates are changed significiantly), the APC for each trend and the AAPC for females (according to age-strata) are shown in Table 1.

Female breast cancer mortality is strongly related to age, with the highest mortality rates being in older women. In last 5 years, the most significant increase was in perimenapausal period by 4.3% per year. In the 25-44 years age group, during the 22 years observation period, a steady and significant increase in the mortality of breast cancer rates was observed (Table 1).

Among women 45-54 years old, two joinpoint model

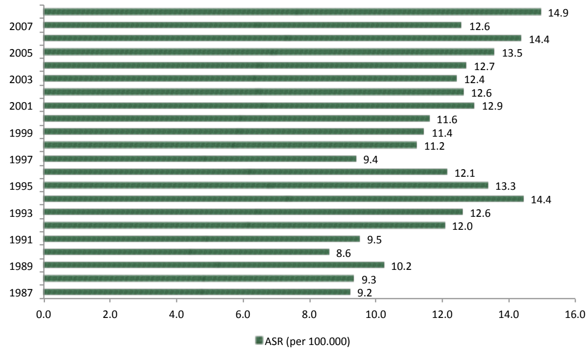

Figure 1. Age-Standardized Breast Cancer Mortality Rates by Years

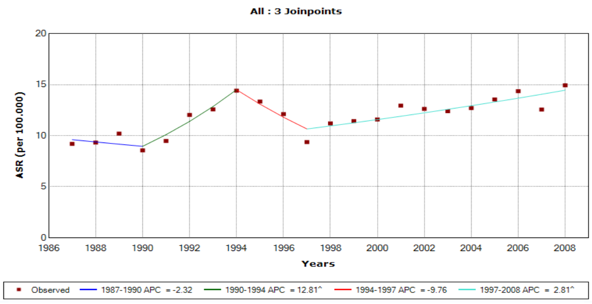

Figure 2. Joinpoint Regression Analysis of Female Breast Cancer Mortality Rates in Turkey (Provinces and Districts), 1987-2008

Table 1. Joinpoint Regression Analysis of Female Breast Cancer Mortality Rates per 100,000 in Turkey (Provinces and Districts), 1987-2008

Joinpoints (Years)	Time Period	APC[1] (95%CI[2])	AAPC[3] 2004-2008 (95%CI)
Age (years)			
25-44			^1.2 (0.3-2.2)
0 joinpoint	1987-2008	^1.2 (0.3-2.2)	
45-54			^4.3 (2.6-6.0)
2 joinpoint	1987-1994	^6.2 (2.9-9.7)	
	1994-1997	^-10.4 (-28.2-11.7)	
	1997-2008	^4.3 (2.6-6.0)	
55-64			^1.4 (0.7-2.2)
0 joinpoint	1987-2008	^1.4 (0.7-2.2)	
65+			0.5 (-1.6-2.7)
4 joinpoint	1987-1990	-4.5 (-13.1-5.0)	
	1990-1994	^15.7 (5.6-26.8)	
	1994-1997	-13.5 (-30.9-8.3)	
	1997-2001	8.2 (-1.3-18.6)	
	2001-2008	0.5 (-1.6-2.7)	
Overall			^2.8 (2.1-3.5)
3 joinpoint	1987-1990	-2.3 (-8.6-4.4)	
	1990-1994	^12.8 (5.9-20.2)	
	1994-1997	-9.8 (-23.1-5.9)	
	1997-2008	^2.8 (2.1-3.5)	

[1]APC annual percent change; [2]Confidence Interval; 3 AAPC average annual percent change; ^APC and AAPC are statistically significantly different from zero (two sided p<0.05)

were obtained as the best model. Breast cancer mortality rates presented a significant increase of 6.2% per year from 1987-1994, and a significant decline of 10.4% per year from 1994-1997, followed by a significant increase to the end of period in 1997 (by 4.3 per year).

In women 55-64 years age group, breast cancer mortality rates increased steadily during the 22 year observation period (with a significance increase, AAPC=1.4, 95%CI= 0.7-2.2).

In older age group (65 years and over), breast cancer mortality rates declined during the period 1987-1990 (by-4.5% per year), but this decline was not statistically significant. In this age groups, a significant increase in breast cancer mortality rates observed during the period 1990-1994 (by+15.7% per year) which was followed by non-significant decrease until 1997 and followed by a non-significant increase at the end of the period.

Age-specific rate differences were observed especially in 65 and over age group which were minimum in 1990 (21.16/100,000) and maximum in 2008 (40.9/100,000) between 1987-2008 (Figure 3).

Compared with the <45 age group, higher rates were observed in the perimenopausal period, and rates were highest in the postmenopausal periods of women's lives (Figure 3).

Mortality rates were higher in the postmenopausal periods (≥55 years). Regarding the Figure 4, we can see the steadily increase of breast Cancer Related Average Mortality Ages by years. Mortality rate is higher in perimenopausal period (45-54 years) than premenopause (<45 years), but in postmenopausal period (≥55years old) the mortality rate is the highest.

Table 2. Risk Factors for Breast Cancer

	Risk Factors for Breast Cancer	
Preventable	Nonpreventable	Partially Preventable
Birth control pills	Gender (Being female)	High Blood estrogen levels after meno-pause
Alcohol consump-tion	Family history of breast cancer	High Blood andro-gen or Prolactin hormone levels
Age of marriage and first pregnancy	Personal history of cancer	No/short period of breastfeeding
Number of birth and curretage	Older age	Occupation (Light at night and shift work)
Older age at meno-pause	High Bone density Age at first child-birth (older)	Socioeconomic factors (income, education etc.)
Sedentary life after menopause	Height (taller) BRCA1 or BRCA2 gene mutation	
Radiation exposure	High Breast density	
No/low consumption of Fruits and vegetables	Hyperplasia of the breast	
Smoking	Age of menarche (Younger Age)	
Overweight after menopause	Lobular carcinoma in situ (LCIS)	
Menopausal hormone therapy - estrogen + progestin	African American ethnicity	

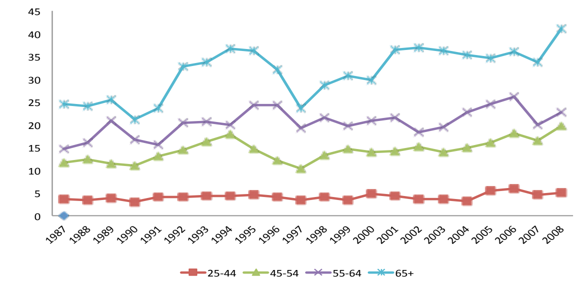

Figure 3. Mortality Rates Per 100,000 Women for Breast Cancer in Turkey by Years

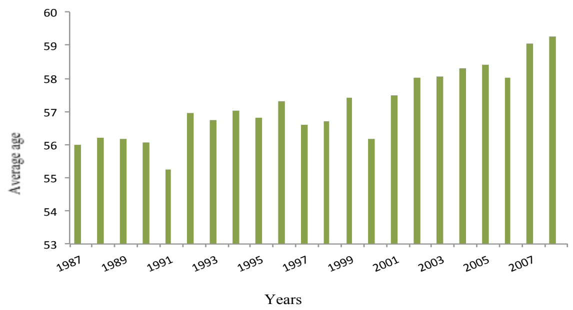

Figure 4. Breast Cancer Related Average Mortality Ages by Years

Discussion

Breast cancer is treatable and curable cancer type when diagnosed early (Eskiocak and Çatal B, 2005). Today although the increase in its incidence, with screening tests, early and easy diagnosis makes this cancer type more important (Parkin et al., 2005).

The present study demostrated that the average annual age-standardized mortality rate (ASR) is 11.9 per 100,000 women and breast cancer mortality has been increasing during the period 1987-2008 in Turkey. Regarding these mortality rates Turkey is among the countries with low breast cancer mortality rates however, a steady increase was observed through the years.

Considering the results of our study the increase of mortality rates can be defined as parallel to the increase of the population and general increase of breast cancer mortality rates in global world. Also this is partly because a shift in lifestyles. As the time passed, lifstyle of women changed in Turkey. This caused an increase of breast cancer risk factors like relatively late age at first birth, less/no breastfeeding, smoking and alcohol consumption.

The joinpoint regression Analysis (of Age-Specific) of Female Breast Cancer Mortality Rates per 100,000 women in Turkey (provinces and districts) between 1987-2008 increase significantly which means as the patient older, death from breast cancer increases. This is because of comorbid diseases and additional risk factors like sedentary life (physical inactivity) and overweight after menopause.

According to our study across all age groups, there was a significant increased trend in 45-54 age group (AAPC=2.5, 95%CI= 1.6-3.4), especially in last 5 years (AAPC=4.3, 95%CI= 2.6 to 6.0). This would be because of the hormonal factors, using more screening tests and more visit to physicians for menopause or any other complaint in those ages which causes more diagnosis.

Evaluating the age-standardized breast cancer mortality rates by years we can say that mortality rates especially increase in older ages. This may be as a result of new treatment methods and long life of women diagnosed as breast cancer.

Breast cancer mortality rates vary among countries and there are huge inequalities between rich and poor countries. For example it is the commonest incident form of cancer in African region. In women, cervix cancer and breast cancer were the commonest incident and fatal forms of cancer by a considerable margin in WHO South East Asia Region. Regional patterns in mortality rates are generally similar to the incidence patterns, although breast cancer is also a leading cause of cancer death in the less developed countries of the world. Incidence rates remain highest in more developed regions (Switzerland, U.S. whites, Italy, and many other European countries), but mortality is relatively much higher in less developed countries probably due to a lack of early detection and access to treatment facilities. For example, in western Europe, breast cancer incidence has reached more than 90 new cases per 100,000 women annually, compared with 30 per 100,000 in eastern Africa. In contrast, breast cancer mortality rates in these two regions are almost identical, at about 15 per 100 000, which clearly points to a later diagnosis and much poorer survival in eastern Africa. (IARC, 2008).

In our study the mortality rate is 1.6 fold in 20 years. This result should alert us for early diagnose and treatment. The most effective way of early detection is "education"; which is for physicians and also public education. By this way avareness can be raised.

Many researches showed that Turkish women not have sufficient knowledge about breast cancer and screening methods (Secginli and Nahcivan, 2004; Secginli and Nahcivan, 2006; Secginli and Nahcivan, 2007; Aslan et al., 2007). Similarly many reports about breast cancer documented that film mammography, clinical breast examination and breast self-examination were not performed as screening tests regularly, in many countries, like our country (Luszczynska, 2004; Avis et al., 2004; Sorenson et al., 2005; Danigelis et al., 2005; Secginli, 2007).

About 60% of the deaths are estimated to occur in economically developing countries. In contrast, breast cancer death rates have been decreasing in North America and several European countries over the past 25 years, largely as a result of early detection through mammography and improved treatment (Althuis et al., 2005; Ravdin et al., 2007; Jemal et al., 2010). In many African and Asian countries however, (Uganda, South Korea, India), incidence and mortality rates have been rising (Choi et al., 2005; Parkin, 2005; 2010).

With changes in reproductive patterns, physical inactivity, and obesity being the main contributory factors (Parkin, 2005; Jemal et al., 2010; Parkin et al, 2010). Increases in breast cancer awareness and screening activity may be responsible for the rising incidence in these populations. Maintaining a healthy body weight, increasing physical activity, and minimizing alcohol intake are the best available strategies to reduce the risk of developing breast cancer (Kushi et al., 2006). The relationship between alcohol consumption and breast cancer mortality and recurrence seems to be a dose-response. Gou et al found that only alcohol consumption of >20 g/d was associated with increased breast cancer mortality, but not with increased breast cancer recurrence (Gou et al., 2013).

The breast cancer incidence increases observed in many Western countries in the late 1980s and 1990s likely result from changes in reproductive factors as well as an increased screening intensity. Incidence rates in some of counties, sharply decreased from the beginning of the millennium, partly due to lower use of combined postmenopausal hormone therapy (Ravdin et al., 2007; Canfell et al., 2008; Seradour et al., 2009; Edwardset al., 2010). The factors that contribute to the international variation in incidence rates largely stem from differences in reproductive and hormonal factors and the availability of early detection services.

Comparing with the other country results Turkey has low mortality rate. This could be related with record problems or low risk factors of our women population like long period of breastfeeding in rural areas, limited use of hormone therapy, low alcohol consuption, high consuption of fruits and vegetable. On the other hand inrease of breast cancer mortality rates should alert us for the prevention projects.

Early detection through mammography has been shown to increase treatment options and save lives (Anderson et al., 2006). Recommended early detection strategies in include the promotion of awareness of early signs and symptoms and screening (Anderson et al., 2008). However the USPSTF recommends against routine screening mammography in women aged 40 to 49 years. The decision to start regular, biennial screening mammography before the age of 50 years should be an individual one and take into account patient context, including the patient's values regarding specific benefits and harms. (Grade C recommendation) The USPSTF recommends biennial screening mammography for women between the ages of 50 and 74 years (Grade B recommendation) and not to screen women 75 years or older. (I statement) (Calonge et al., 2009).

One of the aims of breast cancer programs should be to protect the young age and prevent them from the risks of breast cancer mentioned in Table 2. In this context, Turkish Ministry of Health and the European Union MEDA programme, carried out a new Project and Cancer Early Diagnosis, Screening And Training Center (KETEM) was established in 2006. In 2009, 122 KETEM centers were giving service for screening, diagnosis, treatment and awareness of cancer and public education in order to reduce the morbidity and mortality rates of cancer (KETEM). The results and success of these centers would be seen in the future by the decrease of cancer mortality and morbidity rates in Turkey. However, regarding the risk factors for breast cancer (Table 2) new strategies should be developed by Ministery of Health and social institutions.

References

Ahmad OB, Boschi-Pinto C, Lopez AD et al., (2001) Age Standardization of Rates: a new who standard, GPE discussion paper series: No.31, World Health Organization.
Althuis MD, Dozier JD, Anderson WF, Devesa SS, Brinton LA (2005). Global trends in breast cancer incidence and mortality 1973-1997. *Int J Epidemiol*, **34**, 405-12.
Anderson BO, Yip CH, Ramsey SD et al (2006). Breast cancer in limited-resource countries: health care systems and public policy. *Breast J*, **12**, 54-69.
Anderson BO, Yip CH, Smith RA, et al (2008). Guideline implementation for breast healthcare in low-income and middle-income countries: overview of the Breast Health Global Initiative Global Summit 2007. *Cancer*, **113**, 2221-43.
Aslan A, Temiz M, Yigit Y (2007). Knowledge, attitude and behaviors of nursing school students about breast cancer. *TSK Preventive Medicine Bulletin*, **6**, 193-8.
Avis NE, Smith KW, Link CL, Goldman MB (2004). Increasing mammography screening among women over age 50 with a videotape intervention. *Prev Med*, **39**, 498-506.
Calonge N, Petitti DB, DeWitt TG, et al (2009). Screening for breast cancer: U.S. preventive services task force recommendation statement. *Ann Intern Med*, **151**, 716-26.
Canfell K, Banks E, Moa AM, Beral V (2008). Decrease in breast cancer incidence following a rapid fall in use of hormone replacement therapy in Australia. *Med J Aust*. **188**, 641-4.
Choi Y, Kim YJ, Shin HR, Noh DY, Yoo KY (2005). Long-term prediction of female breast cancer mortality in Korea. *Asian Pac J Cancer Prev*, **6**, 16-21
Clegg LX, Hankey BF, Tiwari R, Feuer EJ, Edwards BK (2009). Estimating average annual per cent change in trend analysis. *Stat Med*, **28**, 3670-82.
Danigelis NL, Worden JK, Flynn BS, Skelly JM, Vacek PM (2005). Increasing mammography screening among low-income African American women with limited access to health information. *Prev Med*, **40**, 880-7.
Edwards BK, Ward E, Kohler BA, et al (2010). Annual report to the nation on the status of cancer, 1975-2006, featuring colorectal cancer trends and impact of interventions (risk factors, screening, and treatment) to reduce future rates. *Cancer*, **116**, 544-73.
Eskiocak P, Catal B (2005). Knowledge, attitude and behaviors of female students of fırat university elazığ health academy about self breast examination and breast cancer. 5. national nursing students congress, abstract book p.158, Sanliurfa.
Ferlay J, Shin HR, Bray F, et al (2010). Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer*, **127**, 2893-917.
Ferlay J, Soerjomataram I, Ervik M, et al (2013). GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer.
Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, et al (2013). Cancer incidence and mortality patterns in Europe: Estimates for 40 countries in 2012. *Eur J Cancer*, **49**, 1374-403.
Gou YJ, Xie DX, Yang KH, et al (2013). Alcohol consumption and breast cancer survival: a meta-analysis of cohort studies. *Asian Pac J Cancer Prev*, **14**, 4785-90.
IARC (2008). World cancer report 2008. Lyon, international agency for research on cancer. Edited by P. Boyle and B. E. Levin.
Ilic M, Vlajinac H, Marinkovic J, Vasiljevic S (2013). Joinpoint Regression Analysis of Female Breast Cancer Mortality in Serbia 1991–2010, *Women & Health*, **53**, 439-50.
Jemal A, Center MM, Desantis C, Ward EM. (2010). Global patterns of cancer incidence and mortality rates and trends. *Cancer Epidemiol Biomarkers Prev*, **19**, 1893-1907.
Jemal A, Bray F, Center MM et al (2011). Global cancer statistics. *CA Cancer J Clin*, **61**, 69-90.
KETEM, Handbook, http://www.kanser.gov.tr/Dosya/Bilgi-Dokumanlari/ketem-el-kitabi.pdf.
Kim HJ, Fay MP, Feuer EJ, Midthune DN (2000). Permutation tests for joinpoint regression with applications to cancer rates. *Stat Med*, **19**, 335-51.
Kushi LH, Byers T, Doyle C, et al (2006). American cancer society guidelines on nutrition and physical activity for cancer prevention: reducing the risk of cancer with healthy food choices and physical activity. *CA Cancer J Clin*, **56**, 254-81.
Luszczynska A (2004). Change in breast self-examination behavior: Effects of intervention on enhancing self-efficacy. *International J Behavioral Med*, **11**, 95-103.
Martinez-Beneito MA, Garcia-Donato G, Salmeron D (2011). A bayesian joinpoint regression model with an unknown number of break-points. *Annals Applied Statistics*. **5**, 2150-68.
National Cancer Institutes, Surveillance Research Program, 2013 (http://surveillance.cancer.gov/joinpoint)/
Parkin DM, Nambooze S, Wabwire-Mangen F, Wabinga HR (2010). Changing cancer incidence in Kampala, Uganda, 1991-2006. *Int J Cancer*, **126**, 1187-95.
Parkin DM, Whelan S, Ferlay J, Storm H, eds. (2005). Cancer incidence in five continents. Vol I to VIII. Cancer Base. No. 7. Lyon:IARC Press.
Parkin M, Bray F, Ferlay J, Pisani P (2005). Global cancer statistics, 2002. *Cancer J Clin*, **55**, 74-108.
Ravdin PM, Cronin KA, Howlader N et al (2007). The decrease in breast-cancer incidence in 2003 in the United States. *N Engl J Med*, **356**, 670-4.
Secginli S, Nahcivan NO (2006). Factors associated with breast cancer screening behaviors in a sample of Turkish women:a questionnaire survey. *Int J Nursing Studies*, **43**, 161-71.
Secginli S, Nahcivan NO (2007). Self breast examination: What are the new advices? *Health and Community J*, **16**, 13-8.
Secginli S (2007). Effects of Health Promotion Programme of Early Diagnosis of Breast Cancer on Screening Behaviours (thesis). Istanbul University Health Sciences Instutition.
Secginli S, Nahcıvan NO (2004). Reliability and validity of the breast cancer screening belief scale among Turkish women. *Cancer Nursing*, **27**, 287-94.
Seradour B, Allemand H, Weill A, Ricordeau P (2009). Changes by age in breast cancer incidence, mammography screening and hormone therapy use in France from 2000 to 2006. *Bull Cancer*, **96**, 1-6.
Sorenson J, Hertz A, Gudex C (2005). Evaluation of a Danish teaching program in breast self-examination. *Cancer Nursing*, **28**, 141-7.
TurkStat (2013), Turkish Statistical Institute, Death Statistics, Province and District Centers, (http://www.turkstat.gov.tr).
Znaor A, van den Hurk C, Primic-Zakelj M, et al (2013). Cancer incidence and mortality patterns in South Eastern Europe in the last decade: gaps persist compared with the rest of Europe, *Eur J Cancer*, **49**, 1683-91.