Long-term Trend in Prostate Cancer Mortality in Turkey

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Abstract: The main objective of this study was to analyze the mortality trends of prostate cancer in Turkey between the years 1987-2008. The age-standardized mortality rates (per 100,000) were calculated using the direct method, according to the World standard population. Temporal trends were assessed using the joinpoint regression. Average annual percent change (AAPC), anual percent change (APC), and a 95% confidence interval (CI) was calculated. During the period, the average annual age-standardized mortality rate (ASR) being 3.86 per 100,000 male. In the last five years, while significant decreases observed under the age of 65, there were also significant increases in the 65 and over age group. In this period, the biggest significant increase was in the over the age of 75 (AAPC=10.6, 95%CI=1.3 to 20.9). Increasing survival and an aging population have led more men to die from prostate cancer especially in older ages.

Keywords: Prostate cancer, Mortality, Joinpoint regression analysis.

1. INTRODUCTION

Prostate cancer is the second most common cancer among men. Looking at 2008 data, it is the sixth leading cause of cancer deaths among men worldwide, accounting for about 14% of total new cases and 6% of total deaths in men. According to the American Cancer Society, 1 in 7 people will be diagnosed with prostate cancer in their lifetime, and 1 in 38 people will die of prostate cancer [1]. Men who live in more developed countries have more risk than men living in undeveloped countries [1,2].

An estimated 150,000 new cases of cancer every year in Turkey is seen. In our country, among the frequent cancer types in Turkey, prostate cancer is in the 5th line with 6% in men. Respectively these cancers are lung (30.13), prostate (24.33), skin (18.91), breast (17.96), stomach (9.92) cancer with an incidence of per 100 thousand [3].

In a study by Akpolat *et al*, in Turkey, in autopsy and radical cystoprostatectomy studies, prostate carcinoma that is clinically silent and undetected in routine screenings has been found at high rates [4].

Zorlu *et al*. (Total 4150 male patients) overall age-standardized incidence rate of prostate cancer in Turkey 35 / 100,000 is the highest rate in Istanbul (43.7 / 100,000), Ankara (42.7 / 100,000), such as in major cities have been identified and the lowest rate in the city of Edirne (17.7/100.000). According to this study, incidence rates were less than 1 / 100,000 in people under the age of 40, and over 300 / 100,000 in people over 70 [5].

Prostate cancer usually affects men over the age of 50 and is rarely found in young men. The median age of prostate cancer patients is 67. Prostate-specific antigen (PSA) is used for screening prostate cancer. This laboratory test generally helps us to diagnose the disease befor the metastasis. PSA (gamma-seminoprotein / kallikrein-3) is a glycoprotein enzyme. In differential diagnosis elevated PSA levels, besides cancer, should also make us think prostatitis, benign prostate hyperplasia, and other prostate disorders. However, this should be underlined that PSA testing changes prostate cancer incidence data (25 fold) more than mortality data (10 fold). This results in more differences in incidence (25 fold) data than mortality data (10 fold) of prostate cancer [1, 4].

In Turkey, a project named KETEM (Cancer Early Diagnosis and Screening Centre) was initiated in 1996 with the cooperation of the European Union and the Turkish Ministry of Health. The aim of this Project is early diagnosis of cancers especially cervix and breast as well as prostate cancers, with the population-based screening programs which give the possibility for treatment and management of the disease [6].

Prostate cancer is not cancer with a high mortality rate, it has a high survival rate. The ten-year relative survival of prostate cancer is 97.8% at 10 years and 91.4% at 15 years adjusted for age, sex, and race [7].

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E-ISSN: 2313-0946/20

As remarkable social, economic and lifestyle changes have occurred in Turkey, it is important to identify the trends of prostate cancer mortality rates in our country. In this research, we aimed to evaluate temporal changes in mortality rates of prostate cancer in the population of Turkey between 1987 and 2008.

2. MATERIALS AND METHODS

The study covers the period 1987-2008 Turkey male population. Cancer mortality data (provinces and districts) for men who died of prostate cancer (codes 185 revision 9 and C61 revision 10) of the International Classification of Diseases was obtained from the Turkish Statistical Institute (TurkStat) [8]. As the detailed (province/district and age distribution) data were given till the year 2008, we evaluated the mortality rates between limited years: from 1987 to 2008. Also, estimates of the population at risk in each year were obtained from TurkStat. Rates were age-standardized (per 100,000 persons) using direct method and World standard population. However, after the year 2008 regarding TurkStat, although the number of deaths per year was declared, no data about gender, age, and also province/urban distributions were given.

Statistical Analysis

Trends in ASR were calculated by joinpoint regression using Joinpoint Regression Program, Version 4.0.4; Statistical Methodology and Applications Branch, Surveillance Research Program, National Cancer Institute [9]. The number of junction points was determined by performing permutation tests, each with an accurate asymptotic level of significance. This level of significance was found using Monte Carlo methods and applying Bonferroni corrections. [10]. The final model shows the best fitting joinpoints (Fit an autocorrelated error model based on the data) where the ratio varies significantly. Each joinpoint provides information on a statistically significant change, estimated annual percentage change (APC), average annual percentage change (AAPC) calculated with 95% confidence intervals (95% CI). AAPC is the geometric mean of annual changes from all regions. It also takes into account the AAPC trend transitions [11]. Explaining the change, the terms increase or decrease were used when the AAPC was statistically significant (if the confidence interval didn't contain zero); otherwise, the term stable was used.

Parameters are allowed to enter the final model with a maximum of four junction points, with a minimum of 4 years between two joinpoints. Analyzes were applied at the 0.05 significance level.

Age-standardized mortality rates (ASR) per 100,000 people (using the world standard population) were calculated for each calendar year using direct standardization, changes in ASR over 22 years were analyzed for cancer by fitting a joinpoint regression model. Ten-year age groups were used for standardization. This approach adjusts crude rates by age distribution, so it's useful to compare the populations of different cities or countries. [12]. Subgroup analyzes were also performed for age (divided into five strata: 35-44, 45-54, 55-64, 65-74, and 75 years and over), but the results were not shown for <35 years because prostate cancer deaths were so small.

3. RESULTS

In Turkey, about 19 880 prostate cancer deaths occurred between 1987 to 2008 and an average annual ASR is 3.86 per 100,000 men. ASR increased from 3.01 per100,000 men in 1987 to 4.46 per100,000 in 2008 (Table **1**).

Joinpoint Regression Analysis identified two joinpoints for the mortality series, separating three trends: 1987-2001, 2001-2004, and 2004-2008 (Table **2**, Figure **1**).

Prostate cancer mortality rates presented a significant increase of 3.61% per year from 1987 to 2000 and a decline of 11.28% per year from 2001 to 2004, but this decline was not statistically significant (because it was not in the range of CI), This was followed by a significant increase with 8.56% APC, which equates to the series' AAPC for the last five years (Table **2**).

Age-Specific Mortality Rates

The results of the joinpoint regression analysis, APC, and AAPC for each trend are shown in Table **2**.

Prostate cancer mortality was strongly related to age and differed by age. According to the last five years, the series was declining in young men (35-64 years of age) but increased in older men (≥65 years old) (Table **2**). The reduction in prostate cancer mortality in young men was present between 1987 and 2008, and was significant in the 35-44 age groups (AAPC = -4.7%), 45-54 years (AAPC = -4.1%), and 55-64 age groups (AAPC = -4.0%).). In males aged 55-

Table 1: Prostat Cancer Mortality Per 100,000 in Turkey

Year	Crude Rates	ASR	Number of Deaths	Number of Population
1987	6.57	3.01	462	7,029,741
1988	6.34	2.89	453	7,150,282
1989	7.84	3.52	570	7,274,311
1990	7.25	3.33	591	8,154,441
1991	6.50	3.01	529	8,139,691
1992	7.43	3.49	612	8,234,044
1993	7.45	3.48	620	8,327,257
1994	8.00	3.80	690	8,505,130
1995	8.22	3.84	711	8,653,071
1996	8.35	3.92	851	10,193,907
1997	8.95	4.19	925	10,336,895
1998	10.47	4.85	1,091	10,423,630
1999	9.15	4.30	968	10,573,817
2000	9.24	4.31	1,038	11,238,363
2001	10.38	4.87	1,135	10,932,953
2002	10.16	4.78	1,119	11,015,033
2003	7.24	3.42	808	11,159,378
2004	8.14	3.29	1,096	13,468,356
2005	9.54	3.83	1,301	13,636,007
2006	9.91	3.97	1,368	13,800,873
2007	10.85	4.40	1,441	13,283,980
2008	10.99	4.46	1,501	13,654,843
Average	8.59	3.86		

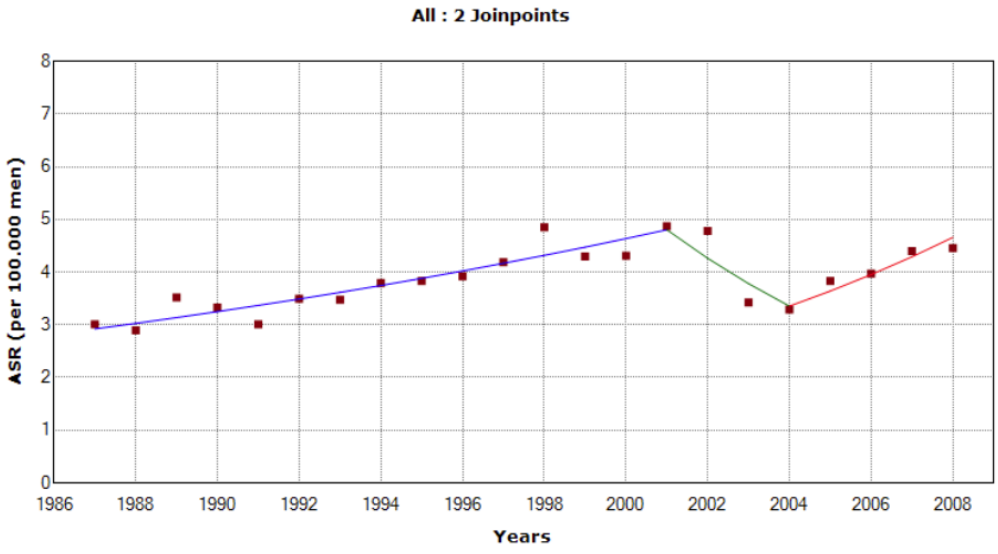

Figure 1: Joinpoint regression analysis of prostate cancer mortality rates in Turkey (provinces and districts), 1987-2008.

64, a significant increase in prostate cancer mortality was observed during 1987-1998 (2.3% per year). In all older age groups (≥65 years old), it was observed that prostate cancer mortality rates significantly increased during the 2004-2008 (AAPC = 1.1% per year and AAPC = 10.6% per year in Table **2**). The only exception was among men aged 75 and over years. In this age group, a non-significant decrease in prostate cancer mortality was observed in the period 2001-2004 (12.4% per year) which was followed by a significant increase at the end of 2008 (APC = 10.6% per year).

Table 2: Joinpoint Regression Analysis of Prostate Cancer Mortality Rates Per 100,000 men in Turkey (Provinces and Districts), between 1987 and 2008

Joinpoints (Years)	Time Period	APC (95%CI)	AAPC 2004-2008 (95%CI)
Age (years)			
35-44			
0 joinpoint	1987-2008	^-4.7 (-7.8 to -1.4)	^-4.7 (-7.8 to -1.4)
45-54			
0 joinpoint	1987-2008	^-4.1 (-5.5 to -2.7)	^-4.1 (-5.5 to -2.7)
55-64			
1 joinpoint	1987-1998	^2.3 (-0.6 to 5.3)	^-4.0 (-7.2 to -0.7)
	1998-2008	^-4.0 (-7.2 to -0.7)	
65-74			
0 joinpoint	1987-2008	^1.1 (0.2 to 1.9)	^1.1 (0.2 to 1.9)
75+	1987-2001	^5.9 (4.2 to 7.2)	^10.6 (1.3 to 20.9)
2 joinpoint	2001-2004	-12.4 (-37.1 to 22.0)	
	2004-2008	^10.6 (1.3 to 20.9)	
Overall	1987-2001	^3.6 (2.9 to 4.3)	
2 joinpoint	2001-2004	-11.3 (-27.8 to 9.0)	^8.6 (2.9 to 14.5)
	2004-2008	^8.6 (2.9 to 14.5)	

APC, annual percent change; CI, Confidence Interval; AAPC, average annual percent change.
^APC and AAPC are statistically significantly different from zero (two-sided p<0.05).

4. DISCUSSION

Cancer is the second-highest cause of death in Turkey [3]. In this study, we found that age-standardized prostate cancer mortality rates were increased significantly (8.6% each year) between 2004 and 2008. This result can be interpreted as an improvement in case finding and the effect of PSA screening in asymptomatic patients, as well as an increase in the incidence of prostate cancer as the time possibly caused by greater exposure to risk factors and population shifts. Also, population demographics in conjunction with economic development in Turkey, especially in urban areas varies considerably.

The development level of a country is an important factor for prostate cancer mortality rates. For example, in the Asia-Pacific region while in less developed countries such as the Philippines and Thailand, significant increases in mortality have been observed, in more developed countries it began to decrease [13].

Deaths from prostate cancer in the United States decreased significantly from 2001 to 2010 in men at a rate of 3.4% per year [9]. However, in Brazil, Colombia, and Cuba there were twofold upward trends that of the USA, between the years 2005-2009 [10]. Regarding our results, prostate cancer mortality rates were 7.24-10.99/100 000 in Turkey.

High death rates from prostate cancer are evident in Iceland, Norway, most of Sweden, Southern Finland, and Denmark; There were also rates above average in the Netherlands, Belgium and Northern France and Ireland. There were also high rates from Switzerland to Austria and western Hungary. Low rates are notable in Poland, Greece, and Italy, and most of Spain [14]. So it is clear that prostate cancer mortality was higher in developing countries (like Singapore, Poland) than in developed countries (like Australia, Canada, France, the United Kingdom, the United States) [15].

The largest average increase in prostate cancer mortality rates was seen in the Republic of Korea (7.8%), Moldova (6.5%), and Trinidad and Tobago (4.5% per year) [16]. Regarding our research, the mortality rate of 8.6% is also a significant increase among the world date.

As remarkable social and economic development, aging population, and great changes in lifestyle (including nutrition, occupation, migration to urban, sedentary life) have occurred in Turkey, increased trends of prostate cancer-related deaths might be a result of these changes.

The race is also detected as an important risk factor for prostate mortality rates. While it is high in the predominantly black population (like the Caribbean, sub-Saharan Africa), it is very low in Asia and intermediate in the Americas and Oceania [17].

Worldwide ASR of prostate cancer mortality, in 2012, ranged between 2.9 per 100,000 (in Eastern Asia) and 29.3 per 100,000 (in Caribbean) [14]. It is (per 100,000) 10.0 in more developed regions, 17.0 in Africa, 12.1 in Central America, 3.1 in Eastern Asia, 13.1 in Western Asia, and 10.9 in European Union. So there is a wide range of ASR between the regions. Regarding the location of our country (a bridge between Asia and Europe), the reflection of this feature can also be seen in our ASR (3.86) result, which is mostly Asian but also close to Southern Europe (Table **3**).

In contrast to the decline observed in Hungary and the Czech Republic, the death rate has increased in a few Eastern European countries (including a few former Soviet countries) [18]. It can be said that prostate cancer mortality rates are almost the same in developed and developing regions (136,000 and 122,000, respectively) [1]. In Western European countries like Great Britain, France, Germany, the Netherlands, and North American like Finland, Norway, the prostate cancer death rates are decreasing. On the other hand, there is an increase in Asian and Eastern European countries. And also improved treatment in North American (*e.g*. Finland and Norway) countries probably caused a decrease in prostate cancer rates. Meanwhile like in many regions in the world western-style foods, being inactive in daily life, obesity caused an increase in Asian and Eastern European countries [1, 19]. Like European countries, in Turkey also lifestyle is changing. The number of obese men in our country is approximately 27.3% [20]. Eventually, we are getting away from our traditional foods and eating more animal fat with a sedentary life. These risk factors may affect men population resulting in more risks and deaths from prostate cancers. However, no association between dietary patterns and prostate cancer has been discovered. As dairy products include high calcium, there would be a little higher prostate cancer risk which was not related to fat intake. On the other hand, alcoholic beverages are not found to be a risk factor for prostate cancer but colorectal and breast cancer [21].

In our study, the majority of prostate cancer deaths occurred in men aged 75 and over, and the proportion for this age group was increasing. In the last five years, while it was stable in the ages under 75, there was a drop among men aged 75 and over, between 2002-2004 which was followed by an increase in the next years. Like prostate cancer, all types of cancer risk factors increase by age, this might be the reason for the increasing trend of mortality.

Turkey has a high number of young people. With the aging of the young population, Turkey will become an older demographic structure of the population

Table 3: Prostate Cancer Mortality Worldwide in 2012 (GLOBOCAN 2012)

Region	ASR (per 100,000)	Region	ASR (per 100,000)
World	7.8	South America	16.6
More developed regions	10.0	Northern America	9.8
Less developed regions	6.6	Eastern Asia	3.1
Africa	17.0	South-Eastern Asia	6.7
Sub-Saharan Africa	20.9	South-Central Asia	2.9
Eastern Africa	18.7	Western Asia	13.1
Middle Africa	24.2	European Union (EU-28)	10.9
Northern Africa	7.0	Central and Eastern Europe	11.6
Southern Africa	24.4	Northern Europe	14.5
Western Africa	21.2	Southern Europe	9.1
Latin America and Caribbean	16.6	Western Europe	10.7
Central America	12.1	Oceania	13.0
Caribbean	29.3		

showing an increase of over 45, especially in later years. This reality made awareness for Turkey about take into consideration some projects about cancer prevention, control, and screening.

The most known risk factors for prostate cancer are aging, race and family history. Also, the role of environmental and genetic factors in pathogenesis should be considered to explain the different incidence patterns in various countries and races [5]. This situation also can be discussed for Turkey.

Regarding our study, a relative decrease was found in the mortality rate from prostate cancer in 2003-2004. This reduction can be explained by improvements in diagnosis and / or early detection. As age increases, the risk of death from prostate cancer increases. In a study in the UK, the highest mortality rates were in the 85+ age group, most of this group were aged ≥75 years, also more than 99% were in ≥55 years group [22].

The age-adjusted mortality rates have been significantly increasing over the last years for prostate cancer men in Serbia (1999–2009: 9.1/100,000-11.5/100,000) [23].

The trends of prostate cancer mortality rates differed as the years, regarding the country. For example, significant decreases of about 2% were observed at all ages in Australia (1998 to 2006), Japan (2004 to 2010) and New Zealand (1995 to 2008); Approximately 1% per year in Singapore (1980-2009) and South Korea (2002--2010), 2% per year in Hong Kong (1980-2009), 7% per year in the Philippines (1992-2008) and Thailand, there was a greater increase of 17% per year (1994–2006). The mortality rates did not change in men between the ages of 50 - 79 years in those countries [13].

Babb *et al.* found that in whites, blacks and Asians in South Africa, deaths from prostate cancer increased in all ages under 80 years old, but a decrease was observed over the ages 80 [24]. This would be probably because of the other death causes and life expectations.

The highest prostate cancer mortality in the world is in men of African descent in the Caribbean region. Although there is not a consensus on the reason, genetic features could be the main factor [25].

The use of PSA in early-stage diagnosis increased the number of patients detected as prostate cancer. However, this did not mean a decrease in prostate cancer-specific mortality in a combined meta-analysis of five randomized controlled trials. Although all current data demonstrate no significant reduction, only the European Randomized Study of Screening for Prostate Cancer reported a significant 21% reduction of prostate cancer-specific mortality in 55-69 years old group. The independent effect of digital rectal examination on mortality was not studied in any research [26]. As overdiagnosis and overtreatment depending on PSA screening results are common and are associated with treatment-related harms, men should be informed of this.

If a man has intermediate serum PSA concentration, percent of free PSA, PSA density of the whole prostate, and the transition zone are poor predictors of biopsy outcome. These parameters provide additional information if the prostate is smaller than 50 cc. Regarding the ethnic differences between the populations, different PSA results are possible between the studies [27].

PSA test is being used in our country also for many years. This screening approach improved the diagnosis and/or early detection; probably reflecting a relative reduction in mortality from prostate cancer in 2003-2004 that we found in our study.

Due to the non-invasive nature of this study, there may be some missing data such as morphological confirmation, comorbidities, BMI, and other sociodemographic characteristics as a limitation of our study.

In conclusion, prostate cancer, with a significant burden on healthcare resources is a major public health problem in Turkey continues to be. This population-based national data, since this work not covered by Turkey's National Cancer Registry Network also covers the provinces, offers a different perspective on the knowledge about the epidemiology of prostate cancer in Turkey. Increasing survival and the aging population have caused more men to die from prostate cancer, especially in older ages. So periodic health controls, especially in 65 and over age group, should include a digital rectal examination and serum PSA levels for early diagnosis; it is very important for men's health.

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Received on 25-7-2020 Accepted on 15-8-2020 Published on 5-9-2020

DOI: https://doi.org/10.12974/2313-0946.2020.05.01.2