RESEARCH ARTICLE

Prostate Cancer Incidence in Turkey: An Epidemiological Study

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Abstract

Background: This study aimed to determine the incidence of prostate cancer in Turkey in a population-based sample, and to determine clinical and pathological characteristics of the cases. Materials and Methods: All newly diagnosed prostate cancer patients were included in this national, multi-centered, prospective and non-interventional epidemiological registry study conducted in 12 cities representing the 12 regions of Turkey from July 2008 to June 2009. The population-based sample comprised 4,150 patients with a recent prostate cancer diagnosis. Results: Age-adjusted prostate cancer incidence rate was 35 cases per 100,000 in Turkey. At the time of diagnosis, median age was 68, median PSA level was 10.0 ng/mL. Digital rectal examination was abnormal in 36.2% of 3,218 tested cases. Most patients had urologic complaints. The main diagnostic method was transrectal ultrasound guided biopsy (87.8%). Gleason score was ≤6 in 49.1%, 7 in 27.8% and >7 in 20.6% of the cases. There was a statistically significant positive correlation between serum PSA level and Gleason score (p=0.000). The majority of patients (54.4%) had clinical stage T1c. Conclusions: This is the first population-based national data of incidence with the histopathological characteristics of prostate cancer in Turkey. Prostate cancer remains an important public health concern in Turkey with continual increase in the incidence and significant burden on healthcare resources.

Keywords: Prostate cancer - incidence - patient profile - histopathological characteristics - Turkey

Asian Pac J Cancer Prev, **15 (21)**, 9125-9130

Introduction

Prostate cancer is the third most common cancer in the world, and its geographical variability across the world is well known. It has been reported as a rare disease in Asia and Africa (approximately four-seven per 100,000) while it is frequently diagnosed as an ageing-related malignancy preferentially occurring in certain ethnic groups especially in the West (70-100 cases per 100,000 in Nordic European countries and North America) (Quaglia et al., 2003; Bostwick et al., 2004; Cheng and Sim, 2005; Wang et al., 2011). Indeed, with ageing populations and increasing use of prostate-specific antigen (PSA) screening, a sharp increase in the incidence of prostate cancer has been documented in the high-risk countries in the past decade (Majeed and Burgess, 1994; Potosky et al., 1995; Chirpaz et al., 2002). While the increasing age, race and family history are the only established risk factors, the incidence patterns in various countries and races indicate that the pathogenesis involves interplay between environmental and genetic factors (Henry et al., 2008). Changes in the prevalence of risks factors might be partially responsible for the increase in prostate cancer incidence, but variations in clinical practices have been considered the most important determinants of the time trends of the recent years (Potosky et al., 2001).

In Turkey, there was no reliable data on the prostate cancer incidence until the publication of the first extensive epidemiological study carried out in Izmir, the third largest city of Turkey, between 1993 and 2002 (Cal et al., 2009). Although it may not represent the whole country, the study reported prostate cancer to be the fifth most common cancer in Izmir with age-standardized incidence of 8.9/100.000 during the 1993-1997 time period. The same study showed that the prostate cancer had increased to 13.8/100.000 in Izmir between 1998 and 2002, while relatively lower rates were observed in most of the European countries and two to three times higher rates were reported in Asian population(s) in the same period (Cal et al., 2009).

As some small-scale regional studies performed in limited sample populations were insufficient to reflect the overall picture of urological cancers in Turkey, this study was designed to determine the incidence and clinico-pathological characteristics of prostate cancer among a large number of Turkish patients in 12 cities from 12 regions representing the general Turkish population across the country.

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Materials and Methods

Study population

All newly diagnosed prostate cancer patients were to be registered in this national, multi-center, prospective and non-interventional epidemiological registry study conducted in 12 cities each representing one of the 12 regions of Turkey during a 12-month period.

For the sampling of the cities and regions, a comparable and representative official statistical database, issued by the Turkish Statistics Institute in compliance with the Eurostats in NUTS (nomenclature of territorial units for statistics) was used. In addition, study centers in each region were located where both the Izmir Cancer Registry (KIDEM) and a sub-committee of the Turkish Association of Urooncology were also present as active organizations.

The study aimed to register every diagnosed prostate cancer patient in the selected 12 study regions (cities and districts) during an exact period of 12 months. To achieve this goal all registered urologists and pathologists were informed about this epidemiological study in these regions.

Patient related information was recorded on a three-page Data Collection Form (DCF) and each completed original DCF was sent to the data-recording center located at KIDEM, Izmir, via courier at monthly intervals. A copy of the DCF was filed by the Cancer Registry Associates (CRAs) who were also responsible for enrolling patients to the study.

The CRAs were responsible for collecting data in specific regions. They visited each urologist in the region of their responsibility, and registered every recently diagnosed prostate cancer patient to the study. The CRAs also visited the pathologists in the region to collect data on pathological confirmation. Each registry was made by contacting the physician of the patient. In case of any difficulty, the CRA asked for assistance from the Turkish Association of Urooncology's representative in the region.

Study parameters

a) Socio-demographic features: age, marital status, educational status, smoking status and alcohol consumption

b) Basic clinical features: body mass index (kg/m2), concomitant diseases, medical background, past history of vasectomy and family history of prostate cancer

c) Prostate cancer incidence: Age and place of residence

d) Physical examination: Digital rectal examination (DRE)

e) PSA levels: at the time of diagnosis

f) Diagnostic method

g) Histopathological findings: Gleason score, Perineural invasion (PNI)

h) Clinical staging: According to Union for International Cancer Control (UICC) 2002 TNM

Statistical analysis

Upon the non-interventional nature of the study, there were different numbers of missing data for different variables. All available data were used in the analyses. World Standard Population (segi) was used to calculate AAIRs. Statistical analysis was performed using computer software (Statistical Package for Social Sciences version 13.0, SPSS Inc. Chicago, IL, USA). Categorical variables were analysed with Chi-square or Fischer's Exact Test. Continuous variables were analysed with Student's t-test or Wilcoxon signed rank test depending on the variability of data. Total PSA values were grouped for age intervals and calculated according to binomial distribution with 95%CI. Data were expressed as "mean (standard deviation; SD)", median (minimum-maximum) and percent (%) and percentiles where appropriate. $p<0.05$ was considered statistically significant.

Results

Prostate cancer incidence

A total of 4150 male patients with a recent diagnosis of prostate cancer were registered between 01 July 2008 and 30 June 2009. As summarized in Table 1, overall age-adjusted incidence rate (AAIR) of prostate cancer was 35/100.000 in Turkey, with the highest rate identified in the city of Istanbul (43.7/100.000) and the lowest rate in the city of Edirne (17.7/100.000) (Figure 1).

Prostate cancer incidence rates was lower than 1/100.000 in patients younger than 40 years old, while it was higher than 300/100.000 in patients older than 70 years old. Prostate cancer incidence rate was determined to be highest between the ages of 75 and 79 (386.7/100.000; Table 2, Figure 2).

Socio-demographic features of patients

Median age of the patients (n=4118) was 68 years,

Table 1. Prostate Cancer Incidence Rates* in Turkey with Respect to Place of Residence

Province	Crude incidence rate	Age-adjusted rate (World Standard Population)
Adana	24.1	33.8
Ankara	35.2	42.6
Edirne	22.6	17.7
Erzurum	15.5	19.4
Eskisehir	24.4	21.6
Gaziantep	12.6	23.6
Istanbul	29.6	43.7
Izmir	25.7	25.1
Kayseri	23.6	28.7
Malatya	26.4	29.4
Trabzon	27.8	24.6
Zonguldak	27.2	26
Turkey	27.7	35

*per 100 000

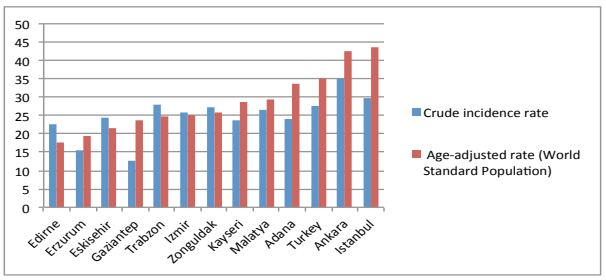

Figure 1. Prostate Cancer Crude and Age Adjusted Incidence Rates*

Table 2. Age Specific Incidence Rates* for Turkey

Age group	Incidence rate*
25-29	0.1
30-34	0.1
35-39	0.5
40-44	1.1
45-49	6
50-54	25.9
55-59	79.4
60-64	173
65-69	287.3
70-74	355.7
75-79	386.7
80-84	311.4
85+	335.7

*per 100 000

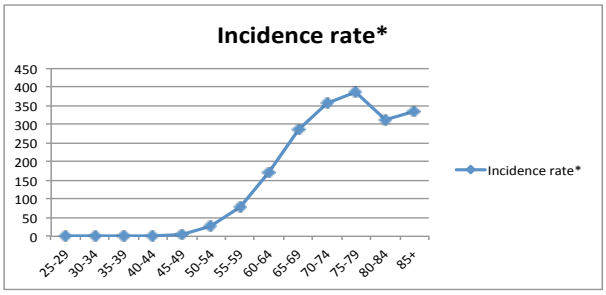

Figure 2. Age Specific Incidence Rates* for Turkey

Table 3. Distribution of the Patients According to BMI and PSA (ng/mL) Levels at the Time of Diagnosis

BMI (kg/m²)		n	Cumulative %	%
	<25	279	34.9	34.9
	25-30	407	50.9	85.8
	30-35	99	12.3	98.1
	≥35	15	1.9	100
	Total	800	100	
PSA levels	0.1-2.5	110	3.6	3.6
	2.6-4.0	355	11.6	15.2
	4.1-10.0	1128	36.8	52.0
	10.1-20.0	625	20.4	72.4
	>20	845	27.6	100
	Total	3063	100	

while most of the patients were older than 65. More than half (58.0%) of the prostate cancer patients with available data stated that they were elementary school graduates. Among the patients with known marital status, 89.7% (n=1005) were married; and 40.1% (n=327) had ≥4 children. Considering smoking and alcohol drinking habits, 18.4% of the patients (n=183) were active smokers, 36.8% were former smokers (n=367) and 44.8% were non-smokers (n=447); among the smokers, 70.4% were smoking one pack of cigarettes per day; and 11.8% were regular consumers of alcohol.

Basic clinical features

Body mass index was identified to be over 30 kg/m2 in 14.2% of the patients (Table 3). Hypertension (369/2188; 16.9%), cardiovascular disease (185/2167; 8.5%), diabetes mellitus (DM) (141/2197; 6.4%) and malignancy (36/2141; 1.7%) were the most commonly identified concomitant diseases by patients. Past history for vasectomy was evident in 0.1% patients (2/2243). Family history of prostate cancer in a first-degree relative was evident in 4.0% patients (83/2069). Of these, 42.1% and 40.8% had a history of father or a brother with prostate cancer, respectively.

Physical examination

Majority (89.1%) of patients with available data (n=1988) had urological complaints at the time of diagnosis. DRE was suspicious for prostate cancer in 36.2% of 3218 patients.

PSA (ng/mL) levels

The median PSA level was 10.0 ng/mL in the entire group (n=3063). The distribution of patients according to PSA levels of, 0.1-2.5 ng/mL, 2.6-4.0 ng/mL, 4.1-10.0 ng/mL, 10.1-20 ng/mL and >20 ng/mL were 3.6%, 11.6%, 36.8%, 20.4% and 27.6%, respectively (Table 3).

Diagnostic method

Transrectal ultrasound-guided biopsy was the main diagnostic method in 87.8% (2868/3266). The remaining methods were TURP (9.3%), digital-guided tru-cut biopsy (1.9%) and open prostatectomy (1.0%).

Histopathological findings

Of all patients, 49.1% had Gleason score of 6 or less;

Table 4. Histopathological Findings

Gleason Scores		n	%
	≤6	2039	49.1
	7	1152	27.8
	≥8	856	20.6
	Unknown	103	2.5
Distribution of Gleason Score-7	2+5	1	0.1
	3+4	729	63.3
	4+3	422	36.6

Table 5. Clinical Stage of Prostate Cancer (n=4133)

Primary tumour (T) (n=2329)	n	%
T1a	80	3.4
T1b	139	5.9
T1c	1266	54.4
T2a	267	11.5
T2b	142	6.1
T2c	252	10.8
T3a	84	3.6
T3b	39	1.7
T4	60	2.6
Regional lymph nodes (N) (n=898)		
NX	334	37.2
N0	490	54.6
N1	74	8.2
Distance Metastases (M) (n=906)		
MX	269	29.7
M0	488	53.9
M1		16.5
M1a	57	6.3
M1b	75	8.3
M1c	17	1.9

27.8 had Gleason score of 7 and 20.6% had Gleason score of ≥8. 6 was the most frequent Geason skore with 41.9%. Among the patients with Gleason score of 7, 63.3% were score of 3+4, 36.6% were score of 4+3 while only 0.1% was score of 2+5 (Table 4). PNI was detected in 40.9% of the patients. There was a statistically significant positive correlation between serum PSA level and Gleason score (rho= 0.15 p=0.000) and it remained after controlling for age with partial correlation (rho=0.154 p=0.000)

Clinical stage of prostate cancer

The distribution of patients in terms of clinical staging referring to UICC 2002 TNM was summarized in Table 5. Majority of the patients had clinical stage T1c (54.4%). Lymph node involvement was positive in 8.2% of the patients. Of all 16.5% patients had metastatic (M1a-c) disease.

Discussion

An AAIR as 22.3 per 100 000 in 2006 was reported as the first nationwide estimates for prostate cancer for the country. The authors had used data from 8 cancer registries in different regions of Turkey for the estimations (Eser S et al, 2010). In our study we collected data in 12 provinces including Istanbul and Ankara which are have the largest populations in the country. Our findings of overall age-adjusted incidence rate of prostate cancer was 35/100.000 in Turkey, ranging from 43.7/100.000 to 17.7/100.000 with respect to regional distribution seem to support consistent global increase as well as geographical variation in the prostate cancer incidence. Besides, compared to previously reported incidences of 8.9/100.000 in 1993-1997 and 13.8/100.000 in 1998-2002 in the first extensive epidemiological study conducted in the Aegean region of Turkey by Izmir Cancer Registry (KIDEM), a continual increase seems evident in prostate cancer incidence in our country while still lower than most of the European countries and higher than Asian population(s) due to global increase in the overall incidence (Cal et al., 2009); Auvinen et al., 2010).

Increasing trends were reported for the prostate cancer incidence, particularly in transition countries. In Hong Kong, an increasing trend in prostate cancer morbidity was reported with significant annual percent changes in 1995-2008 period (Xie et al., 2012). In Isfahan Iran, increasing trend in prostate cancer incidence (AAIRs from 5 in 2001 to 71.7 per 100 000 in 2015) was projected using mortality data (Moradpour F 2013). An increasing trend also was reported from 26 in 1999-2004 to 42 per 100 000 in 2005-2010 was reported in a rural area of North Western Greece (Grivas et al, 2012). However in Jordan quite low AAIRs (10.2 per 100 000) was reported in Jordan in 1996-2009 with no increase in time (Ismail et al., 2013).

Likewise, in a past overview concerning prostate cancer incidence and mortality trends in 37 European countries, an increase in prostate cancer incidence during the study period was observed in 24 of 37 countries included in the analysis that revealed a five-fold variation in the age-adjusted rates, from less than 30 in the Russian Federation to more than 150 per 100,000 in Finland and Sweden (Auvinen et al., 2010.)

At the time of diagnosis, the highest incidence rate was observed among patients aged between 75-79 years (386.7/100.000). This is compatible with the well-known characteristics of the disease that usually affects elderly subjects aged 65 years or more and is a rare disease before 50 years of age (Quaglia et al., 2003; Minana et al., 2012) reported their newly national prostate cancer registry in Spain. Median age was 69 years and of all 71% was over 65 years, which is compatible with our results. Similar results were obtained in studies from the USA (Konety et al., 2011; Jemal et al., 2012).

Additionally, our findings related to patient profile revealed most of the patients to be of non-smoker (44.8%) or former smokers (36.8%), who were graduated from elementary school (58.0%) and married (89.7%) with ≥4 children (40.1%).

A few researchers have reported a significantly reduced risk for prostate cancer which is associated with graduation from college or technical school with a significant trend of decreasing risk with increasing educational level (Perez et al., 2006). Concordant with this data, most of the patients had lower educational status, in our study.

The influence of sexual activity and marital status in the development of prostate cancer has been studied extensively, with their hypothetical relationship indicated to be related to the influence of inherent hormonal, infectious and cultural factors (Sobrino-Najul et al., 2011).

Consumption of alcohol only by 11% of our patients is consistent with most studies published to date that show no association between alcohol use and prostate cancer (Weed and Breslow, 1998). However a significant positive association with alcohol and prostate cancer were also reported in the literature with consideration as a stronger risk factor for higher-grade disease (Parker et al., 2000).

More than half of the patients were overweight in our population. In Spanish data, mean BMI was 27.49 kg/m^2. Giovannucci et al. (2003) reported the results of US health professionals and, of 2896 prostate cancer patients, 52.5% was overweight. Studies investigating the relation between BMI and prostate cancer presented conflicting results. Some studies report increased risk of prostate cancer with obesity (Freedland and Buschemeyer, 2007). Results from the Prostate Cancer Prevention Trial (Neuhouser et al., 2006), 10258 men undergoing biopsy, men with and without prostate cancer have similar BMI results (case: 27.1 *vs* control: 25.1). But they stated that men with high BMI were less likely to have low-grade cancer.

The presence of co-morbidities was lower than Spanish data in our study. They reported that of all co-morbidities 48.15% was cardiovascular diseases and %14.41 was DM. Most of the patients were older than 65 years old in both data. Many co-morbidities were associated with prostate cancer seen in higher age population. Our findings with low level (6.4%) co-morbidity with DM does not concordance with the present meta-analysis findings provide strong evidence that DM is associated with an increased risk of prostate cancer in Asians (Long et al, 2012)

In relation to well-recognized impact of genetic risks on the development of disease, prostate cancer occurs

often within a family, and the family history is an empirical indicator in prostate cancer diagnosis (Wang et al., 2011). Nonetheless, identification of positive family history for prostate cancer in first-degree relatives only in 4% of our patients is in line with the past reports indicating known susceptibility genes to be involved in only approximately 10% of cases despite a high heritability shown in twin studies (Auvinen et al., 2011).

Cozar et al. (Minana et al., 2012) reported that 34.5% of patients had abnormal DRE in Spanish data which was similar to our results. They also stated that 39.54% of patients had LUTS and 13.9% of patients had tumor related symptoms. Majority of our patients had urologic complaints, but they were not classified according to tumor-related symptoms. Since population-based screening for prostate cancer is not performed in our country, great majority of the patients who underwent biopsy were initially seen in urology clinics due to urological complaints.

Median PSA at the time of diagnosis was similar in two national data (10 ng/mL *vs* 8 ng/mL) and in a rural area of North Western Greece (10.8ng/mL) (Grivas et al., 2012). The proportion of patients with serum PSA level ≤ 10 ng/mL was 62.9% in Spanish study while it was 52% in our study. However, more patients had a PSA level ≤ 4 ng/mL in our study (15.2% *vs* 5.5%). A PSA threshold of 2.5 ng/mL has been used in most of the institutes in our country. A lower threshold may be the underlying cause of this controversy.

The contemporary diagnostic method for prostate cancer is TRUS-Bx. In our study, the ratio of prostate cancer diagnosed with TRUS or tru-cut biopsy was 89.7%, whereas it was 98.7% in Spanish data. The ratio of TURP or open prostatectomy as a diagnostic method was 10.3% in our study. Due to the low life expectancy, elderly patients with LUTS and co-morbidities are more likely to undergo TURP instead of TRUS-Bx. As expected, most of the patients (54.4%) were diagnosed with stage T1c disease. In Spanish study, this ratio was 62.42%. In the study in a rural area of North Western Greece most common clinical stage was cT2 (57.3%) (Grivas et al 2012).

Most of the patients had Gleason score of 6 or less in our data similar to Spanish data (49.1% *vs* 56.5%). Gleason score of 8 or more was seen in 20.6% of patients in our study, similarly 16.8% in Spanish data. Most common Gleason score was 6 as in the study done in a rural area of North Western Greece (Grivas et al., 2012) while it was reported as 7 in Saudi Arabia (Albasri et al., 2014) and Pakistan (Arshad et al., 2013). We found significant positive correlation between serum PSA level and Gleason score in accordance with the findings of the studies done in a rural area of North Western Greece (Grivas et al 2012) and Saudi Arabia ((Albasri et al., 2014).

Upon the non-interventional nature of this study, there might be some missing data as a limitation of our study.

In conclusion, we may conclude that, prostate cancer remains an important public health concern in Turkey with continual increase in the incidence and significant burden on healthcare resources. This population-based national data also gives a different standpoint for accumulated knowledge of the information on prostate cancer epidemiology in Turkey since this study covers the provinces which were not covered in the Turkish National Cancer Registry Network.

Acknowledgements

The authors would like to thank Cagla Ayhan, M.D. and Prof. Sule Oktay, M.D., Ph.D. from KAPPA Consultancy, Training and Research Ltd, Istanbul, Turkey, for their contributions to the manuscript preparation, and Ali F. Sahin, M.D. who provided editorial support.

This study was funded through a restricted grant and also sponsored by Sanofi Turkey. Technical assistance was provided by the Cancer Control Department of Ministry of Health of Turkey and the Turkish Association of Urooncology.

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