RESEARCH COMMUNICATION

The Risk Factors of Prostate Cancer: A Multicentric Case-Control Study in Iran

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Abstract

Prostate cancer (PC), in Iran, is the third most frequently diagnosed visceral cancer among men and the seventh most common underlying cause of cancer mortality. We evaluated the relation between speculated factors and PC risk using data from a multicentric case-control study conducted in Iran from 2005 to 2007 on 130 cases of incident, clinicopathologically confirmed PC, and 75 controls admitted to the same network of hospitals without any malignant disease. Odds ratios (OR) and corresponding 95% confidence intervals (CIs) were estimated using conditional logistic regression models. The risk of PC was increased with aging (OR: 5.35, 95% CI: 2.17-13.19; P<0.0001), and with the number of sexual intercourse ≥2 times/week (OR: 3.14, 95% CI: 1.2-8.2; P=0.02). One unit elevation in serum estradiol and testosterone concentration was related to increase (OR: 1.04, 95% CI: 1.01-1.06; P=0.006) and decrease (OR: 0.79; 95% CI: 0.64-0.96; P=0.02) of PC risk, respectively. Cases were less likely to have a history of diabetes (OR: 0.34, 95% CI: 0.12-0.98; P=0.04). Increasing in dietary consumption of lycopene and fat was associated with declined (OR: 0.45, 95% CI: 0.09-2.12) and increased (OR: 2.38, 95% CI: 0.29-19.4) PC development, respectively. Other factors including educational level, marriage status, dietary meat consumption, vasectomy and smoking have not been shown to affect PC risk in the Iranian population. Our study adds further information on the potential risk factors of PC and is the first epidemiologic report from Iran. However, justification of these results requires more well-designed studies with a larger number of participants.

Key Words: Prostate cancer - risk factor - case-control study - Iran

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Introduction

Prostate cancer (PC) is the most commonly diagnosed non-skin cancer among men in most western countries and the third in Iran; yet the etiology of this disease remains largely unknown (Hsing et al., 2000; Hsing et al., 2001;Center for Disease Control, 2004). The incidence of PC and its mortality rates are remarkably different in diverse geographic regions and among various racial/ ethnic populations, with by far the highest rate in north America and the lowest in Asia (Hsing et al., 2000; Quinn et al., 2002).

Despite the fact that the PC has a great impact on public health and it is increasingly becoming clear that genetic, environmental, lifestyle and cultural factors are intimately tied with the incidence and mortality rate of this disease, we have yet to fully determine the risk factors and establish competent strategies for prohibiting its spread (Pienta, 1993).The widely accepted risk factors are age, ethnicity and family history of PC. There have also been some uncertain factors that affect PC risk including educational level, occupation, dietary meat, fat, lycopene and garlic consumption, smoking habit, alcohol use, marital status, vasectomy, sexual behavior, having diabetes mellitus, and etc. In addition, hormonal factors such as sex steroid hormones and insulin-like growth factor have been discussed as the probable risk factors (Pienta,1993; Haas et al., 1997; Chan et al., 1998; Sasagawa et al., 2001; Bostwick et al, 2004). However, there is controversy reports over the risk factors of PC from around the world.

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It is noteworthy that the recent data from Asia has demonstrated that a general trend toward the increasing incidence of PC, with some low risk regions such as oriental countries, reporting a more rapid increase than some high-risk countries in Europe and USA (Hsing et al., 2000; Sasagawa et al., 2001;Sim et al., 2005). As demographic incidence of PC has shown the significant difference between Asian and Western populations, it merits the thorough investigation regarding this matter with respect to the risk factor verification of this common health problem cancer. This study is sought to further evaluate the speculated risk factors of PC in a different demographic setting as a preliminary report from Iran, and aimed at assessing the effect of characteristic, lifestyle and environmental factors, as well as hormonal and genetic factors, on the occurrence of this disease.

Materials and Methods

Study Population

The data were derived from a case-control study of PC, conducted prospectively between August 2005 and May 2007 in eight provinces of Iran: Tehran, Isfahan [Central Iran], Hamadan, Lorestan [west of Iran], Khorasan [East of Iran], Gilan, Mazandaran [North of Iran] and Fars [South of Iran]. Cases were 130 men with incident, clinicopathologically confirmed PC, admitted to the major referral and teaching hospitals in the areas under surveillance. Controls were 75 men, residing in the same geographical areas and the same period of time and admitted to the same network of hospitals of cases, who had no evidence of PC (normal digital rectal examination and prostate specific antigen (PSA) level) or any other malignant disease. Subjects with history of metabolic disease, immune deficiency disorders or any previous intervention on prostate (surgery, hormonal therapy or radio therapy) were not included in our study. The study was performed in accordance with the Declaration of Helsinki and subsequent revisions and approved by ethics committee at Tehran University of Medical Sciences. Meanwhile, before the study performance, written informed consents had been obtained from all of the participants.

Data Collection

All interviews for cases and controls were conducted in hospital by well-trained interviewers using a structured questionnaire. There was no refusal in answering the questions and the response rate did not vary in different districts. The questionnaire included information on sociodemographic factors; interviewer administrated anthropometric variables, general lifestyle habits such as smoking, alcohol, sexual behavior (pre and post marriage sexual relationship and number of intercourses per week), frequency of intake of selected food items, personal medical history and family history of PC. Information on diet referred to the last two months before the onset of the disease that led to hospital admission and included the frequency of consumption of 13 foods, food groups, or dishes, consisted of major dietary meat (red meat and poultry) in Iranian diet (beef, ham, lamb, liver, chicken and etc.), and foods with the highest content of dietary fat (eggs, cream, fish, milk and etc). In addition, specific questions on intake of tomato (tomato extract, dressing) and garlic were asked from all participants. The patients' characteristics and the dietary intake of each group are presented in Tables 1 and 2 respectively.

Table 1. Comparison of Demographic and Baseline Characteristics of Patients in both Groups

Characteristic	Control group [n=75] (%)	Cancer group [n=130] (%)	P-value
Mean Age ±SD(yrs)	65.66±9.87	70.55±8.28	0.001
Education			0.2‡
Illiterate	19 (25.4)	52 (40.0)	
Technical Level	39 (52.0)	45 (34,6)	
University Degree	17 (22.6)	33 (25.4)	
Occupation			0.74‡
Farmer	17 (22.7)	32 (24.7)	
Industrial Worker	18 (24.0)	31 (23.8)	
Clerical Worker	10 (13.3)	11 (8.5)	
Other	30 (40.0)	56 (43.0)	
Location			0.21†
Urban	52 (69.3)	79 (60.8)	
Rural	23 (30.7)	51 (39.2)	
Ethnicity in Iran			0.7‡
Fars	53 (70.7)	84 (64.6)	
Turk	6 (8.0)	15 (11.5)	
Lor	9 (12.0)	13 (10.0)	
Gilak	3 (4.0)	12 (9.2)	
Other (Kurd, Arab, etc.)	4 (5.3)	6 (4.7)	
Marital Status			0.5†
Married	72 (96.0)	122 (93.8)	
Single	3 (4.0)	8 (6.2)	
Family History of Prostate Cancer			0.8†
Negative	70 (93.3)	121 (93.1)	
Positive	5 (6.7)	9 (6.9)	
Smoking Status			0.57†
Negative	58 (77.3)	96 (73.8)	
Positive	17 (22.7)	34 (26.2)	
Alcohol Consumption			0.8†
Negative	69 (92.0)	121 (93.1)	
Positive	6 (8.0)	9 (6.9)	
Vasectomy			0.17†
Negative	66 (88.0)	120 (92.3)	
Positive	9 (12.0)	10 (7.7)	
Diabetes Mellitus			0.2†
Negative	62 (82.7)	115 (88.5)	
Positive	13 (17.3)	15 (11.5)	
History of Sexually Transmitted Disease			0.28†
Negative	29 (38.7)	61 (46.9)	
Positive	46 (61.3)	69 (53.1)	
Mean years of sexual activity ±SD	41.9±10.70	46.87±9.25	0.002*
Sexual activity (per week)			0.03†
≤ 2	61 (81.3)	91 (70.0)	
> 2	14 (18.7)	39 (30.0)	

SD: standard deviation; * Independent samples t test, † Fisher's Exact test, ‡ Chi-square test

Laboratory Assays

Two serum samples, 10 ml each, were drawn from all

participants and collected in 2 tubes. One tube was sent to the clinical laboratory of the current centre for measuring of the erythrocyte sedimentation rate (ESR, normal range: <20 mm/h) level. In order to avoid the bias in reporting the laboratory results, the other tube was immediately transported on ice to our core laboratory for urology researches in Tehran for measuring of the remaining tests such as fasting blood sugar (FBS, normal range: 65-126 mg/dl), total PSA level (normal range: <4 ng/ml), sex hormone binding globulin (SHBG, normal range: 14.5-48.5 mmol/L), total testosterone level (T, normal range: 2.8-8 ng/ml), estradiol (E, normal range: 13.5-59.5 pg/ml), calcium (Ca, normal range: 8.1-10.4 mg/dl), albumin (Alb, normal range: 3.5-5.5 g/l) and triglyceride (TG, normal range: 200-400 mg/dl). The serum samples were stored at -70°C until analysis. Serum PSA, T, E and SHBG were measured using electrochemiluminescent (Roche, Basel, Switzerland). Biochemistry tests for assessment of FBS, Ca, Alb, TG and ESR were performed using COBAS Plus Chemistry Analyzer (Roche, Basel, Switzerland).

Data Analysis

All the data were recorded and the statistical analysis were performed using STATA version 8.0 (Stata Corp Statistical Software Program, Texas, USA). Continuous variables were compared between the two groups by independent samples t test. Chi-square test or Fisher's exact test were used for comparison of categorical variables between the two groups. The effect of different parameters on the risk of PC was estimated by odds ratios (OR) and corresponding 95% confidence intervals (95% CI), which were derived from the conditional logistic regression models and potential confounders were included as covariates in the models. The cut-off points for variables were based on their distributions in controls. The goodness of fit for the logistic model was assessed by Hosmer-Lemeshow test. All P-values were based on two-tailed tests and a value of less than 0.05 was considered statistically significant.

Table 2. Dietary Meat, Fat, Tomato and Garlic Consumption in Our Participants

Dietary Consumption	Control group [n=75] (%)	Cancer group [n=130] (%)	P-value
Meat (gr/week)			0.2‡
≤150	25 (33.3)	45 (34.6)	
151-300	33 (44.0)	38 (29.2)	
> 300	17 (22.7)	47 (36.2)	
Lipid (gr/week)			0.08‡
≤ 50	27 (36.0)	44 (33.9)	
51-200	34 (45.3)	41 (31.5)	
> 200	14 (18.7)	45 (34.6)	
Tomato (gr/week)			0.03‡
≤ 10	33 (44.0)	47 (36.2)	
11-100	17 (22.7)	52 (40.0)	
> 100	25 (33.3)	31 (23.8)	
Garlic			0.24†
No	36 (48.0)	73 (56.2)	
Yes	39 (52.0)	57 (43.8)	

† Fisher's Exact test, ‡ Chi-square test.

Table 3. Laboratory Test Results in our Study Population

Laboratory test	Control group [n=75] (%)	Cancer group [n=130] (%)	P-value
Prostate-specific Antigen (ng/ml)			0.0001‡
< 4	36 (48.0)	28 (21.5)	
4-10	11 (14.7)	25 (19.2)	
>10	28 (37.3)	77 (59.3)	
Mean Sex hormone binding globulin ±SD (mmol/L)*	61.25±30.35	58.62±27.08	0.55
Mean estradiol* level ±SD (pg/ml)	17.15±17.52	22.8±20.76	0.07
Mean* testosterone level ±SD (ng/ml)	2.9±2.53	2.5±2.45	0.26
Triglyceride (mg/dl)			0.42†
≤ 200	62 (82.7)	99 (76.2)	
> 200	13 (17.3)	31 (23.8)	
Erythrocyte sedimentation rate (mm/h)			0.18†
≤ 20	59 (78.7)	90 (69.2)	
> 20	16 (21.3)	40 (30.8)	

SD: standard deviation; * Independent samples t test, † Fisher's Exact test, ‡ Chi-square test.

Results

The total number of 205 subjects (130 cases and 75 controls) entered the study. The mean age (range) of the cases and controls was 70.55 years (52-89) and 65.66 years (43-85) respectively. Demographic and baseline characteristics, dietary consumption, and laboratory results of the participants are presented and compared in Tables , 2 and 3 respectively. The cases of PC tended to be older than the controls with lower level of education. The proportion of men with a family history of PC was higher among cases than controls, although the association was not statistically significant (p= 0.80).

The relation between different factors and PC risk are shown in Table 4. In the multivariable analysis, we observed that age particularly over 60 years, had statistically significant association with the increased risk of PC (OR: 5.35, 95% CI: 2.17-13.19; P<0.0001). Compared with controls, cases were less likely to have a history of diabetes (OR: 0.34, 95% CI: 0.12-0.98; P=0.04). Subjects with history of more than two times sexual intercourse per week had a higher risk of developing PC than those who had two or less than two times per week (OR: 3.14, 95% CI: 1.2-8.2; P=0.02).

The risk of PC declined with increasing in dietary consumption of lycopene (tomato and tomato products); however, it was not statistically significant (OR: 0.45, 95% CI: 0.09-2.12; P=0.31). Moreover, along with the dietary consumption of lipid, the PC risk increased, but it was not statistically significant (OR: 2.38, 95% CI: 0.29-19.4; P=0.42).

An increase of one unit in the serum E concentration was associated with a significant increase in the risk of PC (OR: 1.04, 95% CI: 1.01-1.06; P=0.006), and an increase of one unit in serum T concentration was related

Table 4. Association between Different Factors and Risk of Prostate Cancer in Conditional Logistic Regression Model

Variable	Odds Ratio	95% Confidence Interval	P value
Age (yrs)			
≤ 60	1.0	-	-
> 60	5.35	2.17-13.19	<0.0001
Diabetes Mellitus			
Negative	1.0	-	-
Positive	0.34	0.12-0.98	0.04
Sexual Activity (per week)			
≤ 2	1.0	-	-
> 2	3.14	1.2-8.2	0.02
Lipid Consumption(gr/week)			
≤ 50	1.0	-	-
51-200	1.7	0.35-8.2	0.5
> 200	2.38	0.29-19.4	0.42
Tomato Consumption (gr/week)			
≤ 10	1.0	-	-
11-100	1.88	0.39-8.97	0.4
> 100	0.45	0.09-2.12	0.3
Serum estradiol level (pg/ml)	1.04	1.01-1.06	0.006
Serum testosterone level (ng/ml)	0.79	0.64-0.96	0.02

to a significant decrease in PC risk (OR: 0.79; 95% CI: 0.64-0.96; P=0.02).

Overall, our finding implied that ethnicity, educational level, occupation, marriage status, dietary meat consumption, smoking, alcohol consumption, dietary garlic, history of vasectomy, prostatitis or any other sexually transmitted diseases, years of having sexual activity, and blood tests such as serum SHBG level, TG, Ca and Alb had not a statistically significant correlation with increase or decrease risk of PC.

Discussion

To our knowledge, this is the first, hospital-based, prospective study of PC risk factors from Iran. In this case-control study, some potential factors (age, family history, smoking, diet, and etc) were evaluated and compared with other reports from all over the world.

Cancer of the prostate is the third most frequently diagnosed visceral cancer among men in Iran (7.75% of all new cancer cases) and the seventh most common underlying cause of cancer death, accounting for about 6.03% of all cancer mortality (Center for Disease Control, 2004). The annual incidence of PC in Iran (age-adjusted by world standard population) is 7.24 per 100,000 men, within the range of overall rates from South-Eastern Asia (7.0), Western Asia (10.9) and Northern Africa (5.8). It is substantially lower than the Northern America (119.9), Southern Europe (35.5) and Eastern Europe (17.3), and higher than the other countries in South-Central Asia (4.4) and Eastern Asia (1.6) (Center for Disease Control,2004; Parkin et al., 2002). After late in 1980s, the occurrence of PC and its mortality rate increased in Iran which was in line with the worldwide occurrence. The reasons for this increase are not known completely; however, it seems to have been influenced by the developing the novel diagnostic methods and practices, using PSA testing for screening of PC (Haas et al., 1997; Hsing et al., 2000). Despite many etiological studies on PC in the world, no modifiable risk factors have been clearly established, particularly in Iran.

Age: The prevalence of PC increases with age, especially over the age of 60, both incidence and mortality rates due to PC increase strikingly (Haas et al., 1997; Chan et al., 1998; Sasagawa et al., 2001; Bostwick et al., 2004). Overall, in Iran, the incidence of PC increased from 6.52 to 214.08 per 100,000 men in the age ranges of 55–59 and 80-84 years in 2004 (Center for Disease Control, 2004). Our results also showed the direct correlation between aging and the risk of PC which was in consistent with others such as Veieroid and colleagues (1997). However, Schuurman et al (1999) reported no association between age and PC risk in a cohort of 58,279 cases.

Family history: It is claimed that PC has a hereditary component. (Haas et al., 1997; Chan et al., 1998). Men with a family history of PC are at increased risk of developing PC from 1.5 to 4 times more than the general population (Haas et al., 1997;Negri et al., 2005). Nevertheless, in line with Deno-pellegrini et al (1995) and Schuurman et al (1999) we found no correlation between PC and positive family history of PC which might be due to the small sample size of our study.

Diet: The dietary differences between diverse geographic regions and various racial/ethnic populations provide an interesting possible explanation for differences in the incidence and mortality of PC (Yu et al., 1991; Sasagawa et al., 2001). The diet of Iranian males is low in animal fat and high in fiber content and this may be related to the lower incidence of PC in the Asia compared with Western countries.

Most (Whittemore et al., 1995; Hayes et al., 1999; Ramon et al., 2000; Dennis et al., 2004), though not all (Mettlin et al., 1989; Severson et al., 1989), reports have found a positive association between animal fat and PC risk, particularly for advanced cancers. Whittemore and associates (1995) in a large, multicenter study found a positive association of PC risk and total fat intake in all ethnic groups. It was in line with earlier findings (Hayes et al., 1999; Ramon et al., 2000) as well as the current study and a meta analysis conducted by Dennis et al (2004). The large cohort study by Severson and colleagues (1989) did not demonstrate an association between dietary fat and PC development.

The relationship between dietary consumption of lycopene (tomatoes and tomato products) and the development of PC has been reviewed previously by Giovannucci (1999). Consistent with our results, several studies have demonstrated an inverse association between the high intake of tomatoes/tomato products and PC risk (Tzonou et al., 1999; Hodge et al., 2004; Jian et al., 2005). In contrast to these findings, some studies have shown no effect for dietary tomato consumption and PC risk (Nomura et al., 1997; Kirsh et al., 2006).

Consumption of meat, particularly red meat, has been proposed as a possible modifiable risk factor for PC, although results from epidemiologic studies are mixed (Rodriguez et al., 2006). Our study did not support the

hypothesis that greater intake of meat may contribute to the higher PC risk which was in accordance with some studies (Deneo-Pellegrini et al., 1999; Schuurman et al., 1999; Bosetti et al., 2004; Cross et al., 2005) and was in contrast with some other reports (Veierod et al., 1997; Michaud et al., 2001; Sonoda et al., 2004). The reason might be related to the low recruiting sample size and also the fact that most Iranian people consume dietary poultry more than red meat.

Similarly, we did not find any correlation between the intake of garlic and PC risk. By contrast, Hsing et al (2002) and Hodge et al (2004) suggested that consumption of garlic reduced risk of PC.

Smoking status and alcohol consumption: The effects of smoking and alcohol on the epidemiology of PC are inconclusive and difficult to interpret (Pienta et al., 1993; Haas et al.,1997). Hsing and colleagues (2002) demonstrated a relative risk of 1.8 for smoking. In line with our findings, most of the studies, although not all, that used incident PC cases in analyses observed no association among smoking status, alcohol consumption and risk of PC development (Fincham et al., 1990; Hickey et al., 2001;Crispo et al., 2004; Hodge et al., 2004; Jian et al, 2005).

Diabetes mellitus: It is stated that men with diabetes mellitus appear to have a lower risk of developing PC, which was consistent with our reports (Crawford, 2003). Hence, having diabetes might be a protective factor against PC. However, some studies showed no material association between diabetes and PC risk (Lightfoot et al., 2004; Tavani et al., 2005).

Sex steroid hormones: Although hormones play an important role in normal and cancerous prostate physiology including growth, differentiation and progression; their relationship to the risk of PC remains undefined and needs to be interpreted with caution (Pienta et al., 1993; Haas et al., 1997;Chan et al., 1998; Sasagawa et al., 2001).

Some studies have found elevated T and/or E levels among those with cancer, whereas others either did not detect any differences or actually found lower T and/or E levels (Pienta et al., 1993; Haas et al., 1997; Chan et al., 1998; Sasagawa et al., 2001;Bostwick et al., 2004; Sim et al., 2005). Shaneyfelt and colleagues (2000) performed a meta-analysis on hormone predictors of risks for PC and found that men with serum total T in the highest quartile are 2.34 times more likely to develop PC. Furthermore, high circulating levels of T, low estrogen levels, or low levels of SHBG may elevate the risk (Gann et al., 1996). However, data from some other major studies showed no association between high levels of circulating androgens and PC risk (Mohr et al., 2001; Chen et al., 2003). Platz et al (2005) suggested no association between E, SHBG and PC and also claimed that the increased level in serum T was correlated with the decreased PC risk, but it was not statistically significant. We observed that SHBG level had not any relation to the risk of PC. In addition, the increased level in serum T and serum E, were correlated with the decline and increase of PC risk, respectively, which might reflect differences in genetic and/or environmental factors of Iranian population. Justification of these results requires further well-designed studies with larger number of participants.

Sexual behavior and vasectomy: Some studies suggest that PC is related to the frequency of sexual activity, early intercourse, number of sexual partners, sexually transmitted diseases, prostatic infection, fertility, marital status and vasectomy. Nevertheless, there are some controversy results in this regard (Pienta et al.,1993;Haas et al., 1997; Chan et al., 1998; Lightfoot et al., 2004; Jian et al., 2005; Patel et al., 2005). Our findings did not support the significance of exposure to sexually transmitted microbial agents, history of prostatitis, number of years since having sexual activity and vasectomy in the natural history of PC; however, a significant increased risk was observed in subjects who reported having sexual intercourse more than two times per week compared to those who reported a weekly frequency of two times or fewer. It was in consistent with Fernandez et al (Fernandez et al., 2005) report and also Dennis and Dawson (Dennis et al., 2002) review. Therefore, the increase of sexual activities might be considered as a potential PC risk factor.

We decided not to match cases and controls. Matching on factors that are affected by exposure or disease can irreparably bias the study data (Rothman, 1998). We assumed that this could be the case for age, smoking status and etc which their possible confounding effect was controlled by using multivariable logistic regression model. This strategy can be considered as the strength of our study. Among other strengths here, cases and controls were drawn from similar catchment areas, interviews were conducted in the same hospital setting for cases and controls and participation was almost complete, much greater than in most population-based studies.

We realize that the study could bear some limitations including: its low statistical power as a result of recruiting low number of cases and controls, the possibility that the cancer might have been affected by the nutritional status and thereby serum T and E concentrations which produces a reverse causality problem and finally the single assessment of serum concentrations. We also lacked data on the treatment procedure, Gleason score and/or cancer stage. Depending on the nature of the exposure, risk factor associations often have been stronger for advanced PC than earlier cases of the disease.

In conclusion, the findings of our hospital-based, case-control study revealed that age, the increased sexual activity, and serum E level could be considered as some potential risk factors for developing PC in Iranian males. Moreover, having diabetes mellitus and increased level of serum T were found to have protective effects in the incidence of this disease. Further investigations with adequate sample size are yet to be performed to fully comprehend these mentioned associations. In addition, higher intake of dietary lycopene and lower consumption of dietary fat are encouraged.

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