A Case-Control Study of Risk Factors for Prostate Cancer in Iran

Mostafa Hosseini[*1], SeyedAhmad SeyedAlinaghi[2], Mahmoud Mahmoudi[1], and Willi McFarland[3]

[1] *Department of Epidemiology and Biostatistics, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran*

[2] *Iranian Research Center for HIV/AIDS (IRCHA), Tehran University of Medical Sciences, Tehran, Iran*

[3] *Department of Epidemiology and Biostatistics, University of California, San Francisco, USA*

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Abstract- Prostate cancer is a major cause of morbidity and mortality in Iran, yet there are few studies examining risk factors specific to the Iranian context. We conducted a case-control study to explore risk factors for prostate cancer in Mazandaran, Iran from 2005 to 2008. The cases were 137 men with clinicopathologically confirmed prostate cancer. Controls were 137 neighborhood and age match men without prostate cancer by PSA and digit examination. Analysis comprised an exploratory stage to identify potential risk factors, defined as variables associated with case status at the $P < 0.20$ level in conditional logistic regression. A second stage included all potential risk factors in multiple conditional logistic regression analysis, retaining those associated with prostate cancer at the $P < 0.05$ level. Potential risk factors for prostate cancer in exploratory analysis included family history of prostate cancer, history of other cancer, prostatitis, alcohol consumption, pipe or hookah smoking, walking to work, duration of occupational physical activity, intensity of occupational physical activity, body mass index, and older age. Multivariate analysis found intensity of occupational physical activity, prostatitis, and older age as independent predictors of increased risk for prostate cancer in this Iranian population. Our study confirms several recognized risk factors for prostate cancer, contributes evidence to the discussions of other hypothesized risk factors, and points to potentially new factors. Findings, along with confirmatory studies, can help guide efforts for early detection, treatment, and prevention for this common malignancy that is set to increase in Iran in future decades.

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Introduction

Carcinoma of the prostate is the most frequently diagnosed malignancy of men in Western countries. Prostate cancer is the second leading cause of cancer death among men in the United States of America, with an estimated 234,460 new cases and 27,350 deaths annually in the United States (1-9).

The incidence of prostate cancer is much lower in Asian than Western populations and the disease and its risk factors have been less studied in the region, including Iran. Nonetheless, prostate cancer is still a major cause of morbidity and mortality in Iran, ranking seventh most common underlying cause of cancer death for men (7-9). Cases may also be under-diagnosed. In autopsy series, the presence of histological prostate carcinomas was up to 29% in men aged 30–40 years, and 64% of men aged 60–70 years (7-9). Most studies investigating potential risk factors for prostate cancer have been conducted in the West, with consistent demographic findings including older age, family history, African American race, and residence in a Western nation (10, 11). Among endogenous factors, sex hormones, including elevated androgen levels, have been hypothesized with prostate cancer (11, 12). The sequelae of chronic inflammation and infection could potentially link prostatitis with the carcinoma of the prostate (9). Occupational risk factors have been investigated with mixed results. Exposures to cadmium, polynuclear aromatic hydrocarbons (PAH), lubricating oils, pesticides, and physical activity and work in farming and metal manufacturing industries have all been explored as potential risk factors, though there is inconsistency in the findings (13).

Given the differences in diet, lifestyles and potential exposures, the risk factors for prostate cancer in Iran

[*]**Corresponding Author**: Mostafa Hosseini
Department of Epidemiology and Biostatistics, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran
Tel: +98 21 88989125, Fax: +98 21 88989127, E-mail: Mhossein110@yahoo.com

may differ from those of other countries. The correct, local characterization of risk factors for prostate cancer can contribute to efforts to improve early detection, reduce morbidity and mortality through early treatment, and can also lead to modification of preventable exposures and behaviors. In present study, we explored potential risk factors for prostate cancer in a case–control study conducted in the Mazandaran Province in northern Iran.

Patients and Methods

We conducted a case–control study on risk factors for prostate cancer between 2005 and 2008 in the Mazandaran Province in northern Iran. A total of 137 male histologically confirmed prostate cancers whose addresses were taken from Mazandaran cancer registry were defined as the case series. Controls were as series of 137 men residing in the same neighborhood as each case. In selecting controls, the male neighbor closest in age to the case was chosen in order to help control for the strong effect of age on prostate cancer. For the majority of case-control pairs, the age difference was less than five years. However, some variation was still present, with cases being older than controls; therefore, we also controlled for the effect of age in the analysis stage. The controls had normal digital rectal examination and negative prostate specific antigen test result (i.e., <4 ng/mL).

Putative risk factors for prostate cancer included demographic information (e.g., age, education, occupational history), anthropometric measures (e.g., height and weight to construct the body mass index [BMI]), and responses to a specifically-prepared questionnaire on family history, health history, diet, lifestyle, and behaviors (e.g., smoking, alcohol, diet, and physical activity). Ethnicity was considered as a potential risk factor although majority of the subjects were of the predominant Mazandaran group. For family history of prostate cancer, first-degree (i.e., father, brother, or son) and second-degree relatives (i.e., grandfather or uncle) were considered. Interviewers were trained and visited both case and the matched control for consistency.

The analysis was conducted in two stages. The first stage was exploratory with the aim of identifying potential risk factors for prostate cancer in Iran. For this stage, variables of interest were those with an association with prostate cancer (i.e., case status) at the $P < 0.20$ level in bivariate conditional logistic regression analysis. Such variables were considered notable for future investigations and for inclusion in multivariate analysis. The second stage comprised multiple conditional logistic regression analysis, in which all potentially important bivariate risk factors at the $P < 0.20$ level were considered. The final model retained only those variables associated with prostate cancer at the $P < 0.05$ level. Data were entered and analyzed using STATA (8.0).

Written informed consent was provided by each subject. The study protocol was reviewed and approved by institutional review board of Tehran University of Medical Sciences.

Results

A total of 137 prostate cancer patients and 137 neighborhood and age group matched controls were studied. Most cases (83.2%) and controls (84.7%) were of Mazandaran Province; 80.7% of cases and 83.2% of controls lived in rural areas. The distribution of the three age groups (≤70 years, 71 to 80, and greater than 80) were 33.6%, 48.9%, 17.5% for cases and 47.5%, 46.0%, 6.5% for controls. In the majority of pairs (84%), cases and controls were within five years of each other and 62% were within three years. Cases and controls were similar in education level (10.9% of cases and 13.1% of controls had secondary education or more); 43.8% of cases and 45.2% of controls were farmers or ranchers; all subjects were married with 13.1% cases and controls married before the age of 20 years.

Table 1 shows bivariate comparisons between cases and controls, considering those variables with P <0.20 as potential risk factors. Family history of prostate cancer (OR 2.5, 95% CI 1.0-6.4), history of other cancer (OR 6.5, 95% CI 1.5-28.8), and history of prostatitis (OR 25.0, 95% CI 9.2-67.9) showed a positive tendency towards case status. Alcohol consumption (OR 2.2, 95% CI 0.8-6.3) and pipe or hookah smoking (OR 7.0, 95% CI 0.9-56.9) also showed a tendency to be higher among cases than controls. Markers for active versus sedentary lifestyle were mixed in their association with prostate cancer. On the one hand, walking more than ten hours per week to and from work tended to be protective of prostate cancer (OR 0.7, 95% CI 0.4-1.2), yet duration of occupational physical activity greater than 48 hours per week (OR 1.8, 95% CI 0.9-3.7) and highly active level of occupational physical activity (OR 2.0, 95% CI 1.0-4.3) were risk factors for prostate cancer. Moreover, and BMI greater than 25 (OR 0.4, 95% CI 0.2-0.8) was protective of prostate cancer. No tendencies for prostate cancer were noted at $P < 0.20$ for education level,

ethnicity, age at marriage, vasectomy, history of diabetes, family history of breast cancer (mother or sister), cigarette smoking, tea or coffee consumption, type of occupation, history of agrichemical exposure to pesticides, history of cadmium inhalation, occupational activity requirements (sitting, standing, or walking), sport physical activity, household physical activity, rate of walking to work (slow, moderate, rapid), dietary meat or dairy products consumption. Despite matching cases and controls on the three age categories, a strong residual association with age was found.

To control for residual age confounding and other potential confounding effects between the potential risk factors, multivariate conditional regression analysis was conducted including age and those variables associated with prostate cancer at the $P < 0.20$ level. Retaining only those variables associated with prostate cancer cases at the $P < 0.05$ level produced a final model with three risk factors (Table 2): high occupational physical activity (AOR 6.7, 95% CI 1.3-35. 1), history of prostatitis (AOR 31.5, 95% CI 9.2-170.5), and a continued effect of older age (over 80 years vs 70 or younger, AOR 299.1, 95% CI 5.3-16985.9).

Table 1. Characteristics of prostate cancer cases and controls; potential risk factors in bivariate analysis; Iran, 2005-2008.

Potential risk factor	Cases N (%)	Controls N (%)	OR (95% CI)	*p-value*
Family history of prostate cancer				
No	122 (89.1)	131 (95.6)	Referent	
Yes	15 (10.9)	6 (4.4)	2.5 (1.0 – 6.4)	0.058
History of other cancer				
No	124 (90.5)	135 (98.5)	Referent	
Yes	13 (9.5)	2 (1.5)	6.5 (1.5 – 28.8)	0.014
History of prostatitis				
No	21 (15.3)	117 (85.4)	Referent	
Yes	116 (84.7)	20 (14.6)	25.0 (9.2 – 67.9)	<0.001
Alcohol consumption				
None	124 (90.5)	130 (94.9)	Referent	
Any	13 (9.5)	7 (5.1)	2.2 (0.8 – 6.3)	0.144
Pipe or hookah smoking				
None	129 (94.2)	135 (98.5)	Referent	
Any	8 (5.8)	2 (1.5)	7.0 (0.9 – 56.9)	0.069
Walking to work (hours per week)				
≤10	102 (74.5)	93 (67.9)	Referent	
>10	35 (25.5)	44 (32.1)	0.7 (0.4 – 1.2)	0.17
Duration of occupational physical activity (hours per week)				
≤48	84 (62.2)	93 (68.9)	Referent	
>48	51 (37.8)	42 (31.1)	1.8 (0.9 – 3.7)	0.09
Intensity of occupational physical activity				
Inactive to moderately active	98 (71.5)	110 (80.3)	Referent	
Highly active	39 (28.5)	27 (19.7)	2.0 (1.0 – 4.3)	0.044
Body mass index (kg/m^2)				
≤25	105 (76.6)	83 (60.6)	Referent	
>25	35 (23.4)	54 (39.4)	0.4 (0.2 – 0.8)	0.003
Age group (years)				
≤70	46 (33.6)	65 (47.5)	Referent	0.002
71 – 80	67 (48.9)	63 (46.0)	7.0 (2.1 – 23.6)	<0.001
>80	24 (17.5)	9 (6.5)	56.9 (8.6 – 378.6)	0.002

Table 2. Independent associations with prostate cancer in multiple conditional logistic regression analysis; Iran, 2005-2008.

Risk factors	AOR*	95% CI	p-value
Intensity of occupational physical activity			
Highly active vs. inactive to moderately active	6.7	1.3 – 35.1	0.02
History of prostatitis			
Any vs. none	31.5	9.2 – 170.5	<0.0001
Age group			
71-80 vs. ≤70 years	7.7	0.7 – 80.1	0.08
>80 vs. ≤70 years	299.1	5.3 – 16985.9	0.006

*AOR: Adjusted odds ratio

Discussion

Characterizing preventable causes of cancer is an area of active research, including potential dietary, lifestyle, and environmental factors. Such factors can be particular to the cultural context and necessitate study within different settings. Few studies been conducted on the risk factors for prostate cancer in the Iranian context (7). Our case-control study explored potential associations with prostate cancer in a northern province of Iran and found ten risk factors meriting careful consideration.

Three factors that remained significantly associated with prostate cancer in multivariate analysis were older age, history of prostatitis, and more active occupational physical activity. Older age is a well known risk factor for prostate cancer (7, 14) and the association was evident in our study. Of note, our study design of matching on age group did not eliminate the effect – older age remained a strong predictor of prostate cancer case status despite the vast majority of controls being within five years of their matched cases. We also corroborated other epidemiological studies in showing a significant association of prostatitis and prostate carcinoma and possible mechanisms for the association have been hypothesized (9). Similar to our study, the scientific literature is less consistent on the association of measures of physical activity and prostate cancer.

On the face of it, our own data found inconsistent associations between prostate cancer, occupational physical activity, and other markers of active versus sedentary lifestyles. In the exploratory phase of analysis, high numbers of hours of walking to work was protective of prostate cancer, yet measures of the intensity and duration of occupational physical activity were higher among cases than controls. Moreover, we found no tendencies for sports physical activity, household physical activity, type of occupation physical activity, or rate of walking to work to be associated with prostate cancer. It is suggested that prostate cancer is a hormone-related or mediated disease and, as such, changes in hormone levels, specifically reduction of testosterone levels as a result of strenuous physical activity, may lead to reduced risk of prostate cancer. However, empirical evidence has not been conclusive and findings differ according to whether the physical activity is occupational, household, recreational, or other type (10, 13, 15). Inconsistency in findings may be due to differences in design and measures, or they may reflect a more complex or confounded relationship between prostate cancer, activity, lifestyle, and other possibly related factors.

The association between prostate cancer and obesity itself appears complex and to date inconclusive. As in our exploratory analysis, a case-control study from the USA noted an inverse association between BMI and prostate cancer (16). The study observed that men with a BMI greater than 29 kg/m^2 had the lowest risk of prostate cancer with a significant, protected odds ratio of 0.77 (95% CI: 0.56-1.06). Irani *et al.* attempted to counter potential confounding factors by comparing men with prostate cancer to those with benign prostatic hypertrophy (BPH) (17). The data found BMI not significantly associated with prostate cancer when compared with BPH, but in general obese men had 2.5 times the risk of having prostate cancer. One comprehensive analysis retrospectively studied 135,006 Swedish construction workers with a mean of 18 years of follow-up and found a non-significant positive correlation between BMI and prostate cancer incidence (18). Another study found obesity is associated with an increase in risk of high-grade prostate cancer but with a decrease in risk of low-grade tumors (19). In the final multivariate analysis of our present study, no significant association between BMI and risk of prostate cancer was observed.

Several other factors were associated with prostate cancer at the $p<0.20$ level in our exploratory analysis. While not definitive, these factors should be further studied, particularly as they pertain to the Iranian context. For example, alcohol consumption (illegal in

Iran and reported by only one in 14) had a tendency to be higher among cases. The association between alcohol consumption and prostate cancer has also not been consistent among studies (10, 15, 19, 20). A potential weak positive association between high levels of alcohol consumption and prostate cancer is noted in a review of the literature (10). Other studies have suggested that alcohol consumption may exert different effects at different ages on prostate cancer risk (15). Pipe and hookah smoking are also particular to the region, and a borderline association with prostate cancer was found in our exploratory analysis. In the literature, pipe and hookah smoking are not usually specifically defined and overall an association between smoking and prostate cancer risk has not been consistently demonstrated (4, 10). Finally, two other associations in exploratory analysis, family history of prostate cancer and history of other cancers, are consistent with other studies (3, 15).

Our study is notable for some negative findings on other hypothesized risk factors for prostate cancer. For example, we found no indication of associations with any dietary factors, such as tea, coffee, meat, and dairy consumption – each of which has been considered in other studies, yet data remain inconsistent (8, 10, 21, 22). We also did not find associations with potential exposures to agricultural chemicals. However, we acknowledge limitations in accurately gauging exposures to specific compounds. Finally, we also acknowledge that neighborhood matched controls may have "over-matched" for certain exposures and lifestyles, thus potentially contributing to negative findings in our study.

In conclusion, our study confirms recognized risk factors for prostate cancer, weighs in on some areas of on-going uncertainty, and additionally suggests potential risk factors specific to the Iranian context. Our study is one of very few to be conducted on the topic in Iran (7), a fact that belies the great morbidity and mortality caused by prostate cancer in our country. Iran's population is currently characterized as young; however, lifestyle risk factors and other exposures may take many years before their impact on cancer incidence is felt. Prostate cancer may therefore be poised to produce increased burden of disease in Iran in the coming decades unless preventive measures can be developed in the short- to mid- term.

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