Clinical and Epidemiologic Characteristics of Castration Resistant Prostate Cancer Patients in Sulaimaniyah, Iraqi Kurdistan

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ABSTRACT

Prostate cancer is prevalent among men aged over 65 and has been reported as the fourth most common cause of mortality of males all over the world. In addition to age, family history, and race, there are some lifestyle features such as diet, obesity, alcohol, and smoking are believed to play a role in its development. The present study was carried out in order to examine the clinical and epidemiologic characteristics of castration-resistant prostate cancer patients identify predictive factors for development of resistance to hormonal therapy. The present retrospective cohort study was carried out on 150 patients who were diagnosed with prostate cancer at Hiwa Cancer hospital in Sulaimania, Iraqi Kurdistan over the period of 2009-2014. The collected data were analyzed using descriptive statistics, one-sample Kolmogorov-Smirnov test, independent samples t-test, Mann Whitney test, and Pearson's Chi-square test through SPSS 20.0.

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INTRODUCTION

Among men, prostate cancer (PC) has been referred as the most common and as the fourth common cause of mortality among men all over the world (Ferlay *et al.*, 2014). As shown by the statistics published by GLOBOCAN 2012, PC has the highest incidence rate in western countries with 85 to 100 cases per 100,000 and the lowest in Asia with 11.2 cases per 100,000 (Ferlay *et al.*, 2015). Most cases of PC occur in men aged 65 years and more; therefore, it has been regarded

as a serious health challenge in countries with higher proportions of elderly men (Quinn and Babb, 2002). The data obtained from GLOBOCAN 2018 revealed that age-standardized incidence and mortality rates of prostate cancer in Iraq are respectively 6.6 and 2.0 per 100,000 (WHO, 2018). Moreover, according to the data obtained from Hiwa hospital located in Sulaimania, the Kurdistan region of Iraq, the incidence rate of prostate cancer in 2008, 2012, and 2013 was respectively 36, 67, and 41 cases (Ministry of Health, 2014). Although it has been pointed out that the causes of PC are not known yet (Marks, 2010),some risk factors have been mentioned to play a significant role in increasing the odds of prostate cancer development including age (National Cancer Institute, 2003), family history, race (American Cancer Society, 2014), diet (Hardin et al., 2011), diabetes (Tseng, 2011), obesity (Dimitropoulou et al., 2011), smoking (Huncharek et al., 2010), sexually transmitted diseases (STDs) (Fernandez, 2004), and alcohol (Nilsen et al., 2000). Among these risk factors, age has been referred to as the most important one, such that 93% of prostate cancer occur in men aged over 60 years, and only 7% of cases fall under this age (National Cancer Institute, 2003; American Cancer Society, 2014).

In the early stages, prostate cancer is asymptomatic and produces no clinical signs; however, once its symptoms emerge, they look like those of benign hyperplasia enlargement of the prostate (Harris and Lohr, 2002). In symptomatic cases, localized PC has been reported to be associated with urinary symptoms such as slow or weak urinary stream, inability to stream or difficulty starting or stopping the urine flow, frequency of urination particularly at night, hematuria, impotence, and hematospermia. Moreover, advanced stages of PC might present with rectal obstruction, pain in the hips, back and chest, numbness of legs or feet, and loss of bladder or bowel control due to the tumor pressing on the spinal cord (Huncharek et al., 2010; Philippou and Dev, 2014).

Over the last 20 years, prostate-specific antigen (PSA) and transrectal ultrasonography (TRUS) have widely been utilized to diagnose prostate cancer, leading to an increase in incidence rates, a decrease in mean age of development, and the most common stage at diagnosis being the stage of localized disease (Nelen, 2007; Roberts et al., 2018). The final diagnosis of PC is only possible through positive prostate biopsy. A highly significant factor in treatment of PC is determining the stage of the disease, which is usually carried out based on the American Join Committee on Cancer (AJCC) TNM system which is based on 5 key pieces of information includ-

ing the extent of the primary tumor (T category), whether the cancer has spread to nearby lymph nodes (N category), the absence or presence of distant metastasis (M category), the PSA level at the time of diagnosis, and the Gleason score based on the prostate biopsy (or surgery) (American Cancer Society, 2014). Depending on the stage of the disease, prostate cancer can be treated through different methods including surgery, radiation therapy, hormone therapy, cryotherapy, chemotherapy, and biological therapy (American Cancer Society, 2014; Adult Treatment Editorial Board, 2019).

The first line of treatment of PC is androgen deprivation therapy. Response rate is usually very high but over time, 80-90% of patients develop resistance to anti-androgen therapy. This is known as hormone refractory or castration-resistant prostate cancer (CRPC) which is defined by disease progression despite androgen-deprivation therapy (ADT) and may present as one or any combination of the following: a continuous rise in serum levels of PSA, progression of pre-existing disease, or appearance of new metastases (Hotte and Saad, 2010). CRPC is an advanced form of prostate cancer associated with poor survival rates, and now it is the second most common cause of male cancer-related mortality (Kirby et al., 2011). Although chemotherapy has been recommended as the first-line treatment method in advanced stage disease, it is not well tolerated by all CRPC patients who were often elderly men with limited bone marrow reserve and concurrent medical conditions (Amaral et al., 2012) . Given the significance of early diagnosis of castration-resistant prostate cancer (CRPC) and non-castration-resistant prostate cancer (non-CRPC) and due to their negative effects of quality of life particularly among elderly males, the present study was carried out in order to specify the clinical characteristics of such patients so as to help with early diagnosis and efficient management of the diseases.

MATERIALS AND METHODS

Using a retrospective cohort design with a nested case-control study approach, the study was carried out on patients with prostate cancer at Hiwa Cancer Hospital located in Sulaimaniyah, the Iraqi Kurdistan in 2014. The study sample was selected from among all 257 patients who were diagnosed with prostate cancer through laboratory investigations (biopsy and elevated PSA) at Hiwa Cancer Hospital from July 1, 2009 to July 1, 2014, which led to selection of 150 cases (75 with CRPC, 75 with PC showing response to hormonal therapy). The sam-

ple size was determined using Statsdirect statistical software, based on the assumption of an event rate of 0.2 in the control group.

The patients were assigned into a case group (who developed resistance to androgen deprivation therapy) and a control group (who did not develop resistance to androgen deprivation therapy within the first three years of prostate cancer treatment).

Data collection

After the patients' consent was obtained, collecting data of the patients' socio-demographics, medical history of chronic diseases, PC-related risk factors, and anthropometric measurements was carried out using a researcher-administered questionnaire through structured interviews with the patients either on phone or face-to-face at their homes. Moreover, the patients' clinical data were retrieved from their hospital records under the supervision of the managing physicians. It should be noted that no examination was performed in the present study to obtained required data.

Statistical analysis

The collected data were analyzed through SPSS (version 20) after they were revised and coded. For this purpose, descriptive statistics were used, and the results were presented as means ($\pm$standard deviation). Moreover, one-sample Kolmogorov-Smirnov test, Mann Whitney test, and Pearson's Chi-square test were run. The level of statistical significance was set at $p<0.05$ for all of the statistical tests.

Ethical considerations

To take the ethical considerations into account, the study protocol was approved by the IRB and research ethics committee of the High Institute of Public Health (HIPH) - Alexandria University, Egypt, and after approval was obtained from the Ministry of Health/Kurdistan Region - Iraq and Directorate of Health Sulaimaniyah, anofficial letter which was obtained from Directorate of Health Sulaimaniyah was delivered to Hiwa Cancer Hospital. Finally, informed consent was obtained from the participants whose information was strictly kept confidential.

RESULTS AND DISCUSSION

The current study was conducted in order to determine the clinical characteristics of patients with prostate cancer. For this purpose, 150 PC patients (75 with castrated resistance and 75 with no castrated resistance). The study reviewed the records of 257 patients who were identified with PC over the period of 2009-2014.

Analyzing the collected data revealed that the proportion of castration resistance was 63.03%.

The results also showed that most of the patients (60% of the cases and 58.7% of the controls) aged between 65 and 80 years. It was seen that patients aged 56-80 years were 1.4 times more prone to develop CRPC than those less than 65 years, and those aged over 80 were 1.5 times more prone to have CRPC. These differences; however, were not significant ($p>0.05$).

Regarding the participants' educational level, it was observed that most of the participants (26 % of the cases and 42.7% of the controls) were illiterate, who were followed by primary school with 12% of the controls and 13.3% of the cases, reading and writing level with 10.7% of the controls and 13.3% of the cases, and secondary school with 12% of the cases and 12% of the controls. In this regard, the difference between the two groups was not significant ($p>0.05$) (See Table 1).

Regarding the patients' family history of PC, the results revealed that 12% of the cases and 14.7% of the controls had a positive family history, and this difference was not significant ($p>0.05$). Moreover, patients with a family history of PC in their first-degree relatives were 2.1 times more likely to develop CRPC than those with second-degree relatives; however, this difference was not significant (See Table 2).

With regard to physical activities, the results showed that patients who did not stretch, walked less than 30 minutes per week, did not swim, or do aerobics were respectively 1.5, 1.1, 8.2, and 1.1 times more likely to develop CRPC. It was concluded that the two groups were not significantly different in terms of physical activities at a p-value of 0.492 (See Table 3).

Regarding the patient's habits, the results indicated that there was no significant difference between the two groups regarding their habits including alcohol consumption and smoking ($p>0.05$). However, those who consumed alcohol and smoke were respectively 1.6 and 0.88 times more likely to develop CRPC (See Table 4).

Regarding the patients' dietary habits, the results revealed that there was a significant difference at a p-value of 0.001 between the cases and controls in terms of consuming red meat, such that the cases ate more red meat (with median of 400 vs. 200 mg, respectively). They were also significantly different regarding consuming vegetables at a p-value of 0.025, such that the cases ate more vegetables than the controls (2.5 vs. 2, respectively) (See Table 5).

Table 1: Distribution of PC cases and the controls according to sociodemographic data

Socio demographic characteristics	Group				X2(P)	OR (95% CI)
	Controls		Cases			
	No	%	No	%		
Age in years					0.43	
50-	11	14.7	8	10.7	(0.511)#	1
65-80	44	58.7	45	60.0		1.4 (0.51-3.4)
80+	20	26.7	22	29.3		1.5 (0.51-4.5)
Education level					2.5	
Illiterate	32	42.7	20	26.7	(0.112)#	0.71 (0.22-2.3)
Read and write	8	10.7	10	13.3		1.4 (0.36-5.6)
Primary school	9	12.0	10	13.3		1.3 (0.33-4.9)
Secondary school	9	12.0	9	12.0		1.2 (0.29-4.5)
Preparatory school	5	6.7	13	17.3		2.9 (0.69-12.6)
Institute	4	5.3	6	8.0		1.7 (0.34-8.6)
University/more	8	10.7	7	9.3		1

OR: Odds ratio; #: X2for linear trend; ^ P value based on Mont Carlo exact probability; CI: Confidence interval

Table 2: Comparison of the cases the controls according to family history of PC and their affected degree of family history

Family history	Group				X2(P)#	OR (95% CI)
	Controls		Cases			
	No	%	No	%		
Family history					0.23	
No	64	85.3	66	88.0	(0.631)	1
Yes	11	14.7	9	12.0		0.79 (0.31-2.1)
Degree	N= 11		N= 11		0.178!	
First degree	9	81.8	9	100.0		2.1 (0.27-6.8)
Second degree	2	18.2	0	0.0		1

OR: Odds ratio; #: X2for linear trend; ^ P value based on Mont Carlo exact probability; CI: Confidence interval

Regarding the patients' body mass index (BMI), it was seen that the two groups were not significantly different (p>0.05) (See Table 6).

Regarding the patients' clinical characteristics, the results demonstrated that the CRPC and non-CRPC patients were significantly different in terms of histopathology, stage of the disease, and extent of the disease respectively at p-value of 0.043, 0.001, and 0.001, such that the patients at stage IV were most likely (16.5 times) to develop CRPC, followed by those at stage III being 2.6 times more likely, and stage II being 2.1 time more prone to develop CRPC. Moreover, patients with metastatic disease were 9.2 times more likely to develop CRPC, followed by those with locally advanced extent of disease being 1.9 times more prone to CRPC (See Table 7).

Prostate cancer is responsible for 10% of male mortality from cancer. After diagnosis, it is significant to identify lifestyle factors which affect the clinical course of the disease in order to help with manage and prevent the disease progression.

Due to the shift toward Western lifestyle and changes in dietary habits and also the effect of chemical hazard of the Iraqi/Iranian war, there have been numerous environmental and epidemiological changes in the Kurdistan region of Iraq which have increased the risks if cancer in the region (Othman et al., 2011).

Table 3: Distribution of prostate cancer cases and their controls regarding physical activities

Stretching		Group			X2(P)	OR (95% CI)
	Controls		Cases			
	No	%	No	%		
Stretching					0.694!	
None	72	96.0	73	97.3		1.5 (0.25-9.4)
Less than 30 min/week	3	4.0	2	2.7		1
Walk for exercise					0.09 (0.771)#	
None	5	6.7	5	6.7		1.0 (0.22-4.5)
less than 30 min/week	15	20.0	17	22.7		1.1 (0.37-3.5)
30-60 min/week	23	30.7	23	30.7		1.0 (0.35-2.9)
1-3 hrs/week	22	29.3	20	26.7		0.91 (0.31-2.6)
More than 4 hrs/week	10	13.3	10	13.3		1
Swimming					3.8 (0.050)*#	
None	59	78.7	69	92.0		8.2 (0.41-161.5)
Less than 30 min/week	10	13.3	2	2.7		1.7 (0.06-43.8)
30-60 min/week	3	4.0	4	5.3		9.0 (0.34-96.7)
1-3 hrs/week	3	4.0	0	0.0		1
Aerobics					1.2 (0.264)#	
None	69	92.0	73	97.3		1.1 (0.11-10.4)
Less than 30 min/week	3	4.0	1	1.3		0.43 (0.02-8.3)
30-6- min/week	2	2.7	0	0.0		0.2 (0.001-8.8)
1-3 hrs/week	1	1.3	1	1.3		1
Total score						
Median (Range)	3.0 (0-7)		3.0 (0-6)		0.492&	

OR: Odds ratio; #: X2for linear trend; ^ P value based on Mont Carlo exact probability; CI: Confidence interval

Table 4: Comparison between the CRPC and non-CRPC patients regarding their habits

Habits		Group			X2(P)	OR (95% CI)
	Controls		Cases			
	No	%	No	%		
Alcohol consumption					1.1 (0.288)	
No	64	85.3	59	78.7		1
Yes	11	14.7	16	21.3		1.6 (0.68-3.7)
Smoking					0.13 (0.723)	
No	51	68.0	53	70.7		1
Yes	24	32.0	22	29.3		0.88 (0.44-1.8)

OR: Odds ratio; #: X2for linear trend; ^ P value based on Mont Carlo exact probability; CI: Confidence interval

Table 5: Distribution of CRPC cases non-CRPC patients according to their dietary habits

Dietary habits	Group		Z	P
	Controls	**Cases**		
Gm Red meat/week			3.4	0.001*
Minimum	0	0		
Maximum	900	1500		
Median	200	400		
Vegetable/week			2.2	0.025*
Minimum	0	0.25		
Maximum	7.5	7.5		
Median	2.0	2.5		

Z: Mann-Whitney test; * P < 0.05 (significant); Gm : Gram

Table 6: Comparison between the CRPC and non CRPC patients regarding their body mass index

BMI	Group				X2(P)	OR (95% CI)
	Controls		Cases			
	No	%	No	%		
Under weight	4	5.3	2	2.7	0.27 (0.605)#	0.53 (0.09-3.1)
Normal weight	49	65.3	46	61.3		1
Over weight	17	22.7	25	33.3		1.6 (0.75-3.3)
Obese	5	6.7	2	2.7		0.43 (0.08-2.3)

OR: Odds ratio; #: X2for linear trend; CI: Confidence interval

Table 7: Comparison between the CRPC and non-CRPC patients regarding their clinical characteristics

Clinical characteristics	Group				X2(P)	OR (95% CI)
	Controls		Cases			
	No	%	No	%		
Histopathology					0.043*!	
Adenocarcinoma	71	94.7	75	100.0		9.5 (1.2-179.1)*
Sarcoma	4	5.3	0	0.0		1
Stage					17.9 (0.001)*#	
Stage I	26	34.7	11	14.7		1
Stage II	34	45.3	30	40.0		2.1 (0.88-4.9)
Stage III	12	16.0	13	17.3		2.6 (1.0-7.3)*
Stage IV	3	4.0	21	28.0		16.5 (4.1-67.1)*
Extent of Disease					11.6 (0.001)*#	
Primary local	58	77.3	41	54.7		1
Locally advanced	15	20.0	21	28.0		1.9 (1.0-4.3)*
Metastatic	2	2.7	13	17.3		9.2 (2.2-42.9)*

OR: Odds ratio; #: X2for linear trend; !P value based on Fisher exact probability; CI: Confidence interval; * P < 0.05 (significant)

Age has been referred to as the most significant risk factor for prostate cancer (Williams and Powell, 2009). With regard to the age at first presentation, the results of the present study revealed that two thirds of the patients aged between 65 and 80 years. This finding is in good agreement with those of the study carried out in Mazandaran, Iran from 2005 to 2008 (Hosseini et al., 1970). It is also in line with the fact that prostate cancer is more prevalent among older age groups (National Cancer Institute, 2003; American Cancer Society, 2014). The results of the present study indicated that the two groups (i.e. patients with CRPC and non-CRPC) were not significantly different in terms of their educational level, and most of them in both groups were illiterate. Similarly, the results of a study conducted in Iran reported similar educational levels in the two groups (Pourmand et al., 2007).

Regarding the family history, the results indicated that 12% of the cases and 14.7% of the controls had a positive family history of PC. Family history has been reported to increase PC incidence rate more in males younger than 65 years (Kiciński et al., 2011). It was also seen that 9 patients in each group had a first-degree relative with PC, and the two groups were not significantly different in this regard. Similarly, it has been reported than PC incidence increases among men with first-degree family history (Bruner et al., 2003; Johns and Houlston, 2003).

According to the results, lack of physical inactivity increased the odds of developing PC. It was also observed that lack of stretch, walking, swimming, and aerobics increased the likelihood of developing CRPC. This finding is in line with the results of other studies that reported a significant association between physical inactivity and incidence of PC (Jian et al., 2005; Kenfield et al., 2011). Regarding drinking alcohol, the results showed that those who consume alcohol are at a higher risk of developing PC; however, no significant association was observed, because drinking alcohol is not common among Kurdish people and is prohibited by the religion. However, it has been reported that there is a significant relationship between drinking alcohol and incidence of prostate cancer (Dennis and Hayes, 2001; Platz et al., 2004). In terms of smoking, the results of the present study showed that smokers are 1.6 times more likely to develop CRPC; however, this association was not significant. This finding is in line with previous studies which pointed out that smokers have a higher risk of PC but also shows the association between CRPC and smoking (Villeneuve et al., 1999; Giovannucci et al., 1999).

Regarding dietary habits, it was observed that there was a significant difference between the two groups in terms of consuming red meat and vegetables, such that those who consume red meat and vegetables are at a higher risk of developing CRPC. Similar findings have been reported regarding the effect of consuming red meat on increased risk of PC incidence (Tseng, 2004; Rohrmann et al., 2007). Regarding the patients' BMI, the results revealed no significant difference between the two groups. However, it was seen that overweight patients are 1.6 time likely to develop CRPC. This finding is in line with the results of the study reporting obese men are at a higher risk of developing advanced stage of PC (Wilson et al., 2012).

As shown by the results of the present study, all cases and 94% of the controls were diagnosed with adenocarcinoma, while none of the cases and a small percentage of the controls (5.3%) were diagnosed with sarcoma, and the two groups were significantly different in this regard. This finding is in good agreement with the results of the studies in Iran (Tanago and Mcaninch, 2003; Alizadeh and Alizadeh, 2014). Therefore, it can be concluded that there is a significant association between adenocarcinoma and development of CRCP. Most of the patients in the present study were diagnosed at stages I and II. Studies have shown that PC survival rate increases, if it is diagnosed at stages I and II when the tumor is still confined to the prostate (Chattopadhyay et al., 2018).

The results also revealed that the cases and the controls were significantly different in terms of the extent of the disease. It was seen that a larger number of cases had metastatic and locally advanced tumors, while most of the controls had localized tumors. Studies have indicated that survival rates are lower in PC patients with metastatic tumors than those with locally advanced tumors, and those with locally advanced tumors than those with localized tumors (Ries et al., 1988; Matsuda et al., 2011). Advanced stage was associated with higher incidence of CRPC. This is a biologically expected result and may be related to the appearance of resistant clones of PC cells over time and cancer progression.

CONCLUSIONS

As concluded in the present study, males aged 65 to 80 years are at a higher risk of developing prostate cancer than those less and more than 65 years. Also, males with a positive family or first-degree relative history are at a higher risk of developing PC. Moreover, lifestyle habits such as physical inactivity, alcohol consumption, smoking, and eat-

ing red meat and vegetables increase the odds of developing prostate cancer. Furthermore, underweight, overweight, and obese patients are more prone to develop PC. Most patients with PC have adenocarcinoma which increases the odds of developing castration-resistant prostate cancer 9.5 folds. Given the advances in PC diagnoses, most cases are detected at stages I, II, and II, which increases the patients' survival. Patients with CRPC are more likely to have locally advanced and metastatic PC; therefore, their survival rate is remarkably lower. Early diagnosis at early stage of PC can increase the patients' survival.

Conflict of Interest

None.

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