



Pre-treatment Depression and Anxiety Disorder in Men with Cancer of the Prostate in South Western Nigeria

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Authors' contributions

This work was carried out in collaboration among all authors. All authors contributed to the conceptualisation, data collection and final writing of the article. Data analysis was done by authors APT and DMU. All authors read and approved the final manuscript.

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ABSTRACT

Aim: The aim of the study is to determine the pre-treatment prevalence and associated factors of anxiety and depression in men with cancer of the prostate.

Study Design: This is a prospective, cross-sectional study.

Place and Duration: The urology unit of Ekiti State University Teaching Hospital, Ado-Ekiti. Ekiti State, Nigeria. The study period was from 1st January 2018 to 31st December 2019.

Methodology: A total of 46 consented male participants recently diagnosed with cancer of the prostate (CAP) were assessed for depression and anxiety disorders using the Hospital Anxiety and Depression Scale (HADS). Participants also completed a sociodemographic questionnaire, an 8-item International Prostate Symptoms Score (IPSS) and a quality of life questionnaire (BS).

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Results: Forty-three and half percent (43.5%) of the participants suffered depression; anxiety disorder occurred in 21.7% of the participants. Only 2.2% of the participants had anxiety disorder without depression, while 23.9% had depression without anxiety disorder. Significant level of poor quality of life (QoL) was found among participants with depression and anxiety disorder. Having one psychiatric morbidity was associated with having another. Age of participants and other sociodemographic parameters were not associated with psychiatric morbidity.

Conclusion: There is a high prevalence of anxiety disorder and depression among patients with cancer of the prostate. Assessment of these disorders should be included in the management of patients with prostate cancer to enhance early detection and prompt treatment for better patients' clinical outcome.

Keywords: Cancer; prostate; anxiety disorder; depression.

ABBREVIATIONS

<i>CAP</i>	: <i>Cancer of the prostate</i>
<i>HADS</i>	: <i>Hospital Anxiety and Depression Scale</i>
<i>IPSS</i>	: <i>International Prostate Symptoms Score</i>
<i>LUTS</i>	: <i>Lower urinary tract symptoms</i>
<i>QOL</i>	: <i>Quality of life</i>
<i>BS</i>	: <i>Bother Score</i>
<i>PSA</i>	: <i>Prostate-specific antigen</i>
<i>DSM</i>	: <i>Diagnostic and statistical manual</i>
<i>Yrs</i>	: <i>Years</i>
<i>Corr. Co-eff</i>	: <i>Correlation coefficient</i>

Risk factors for psychiatric morbidities among prostate cancer patients include being unmarried, low education, advanced prostate cancer, low physical or cognitive functioning, younger age, and medical co-morbidities, unemployment, low income, past depressive episodes, and poor coping skills [7, 9].

Explanation of the relationship or cause of depression in prostate cancer patients could be multifactorial. And these include biological factors, psychological factors, environmental factors, and behavioral factors [10-13]. Depression has also been associated with certain prostate cancer treatment types (e.g. androgen deprivation therapy) and complications (e.g., erectile dysfunction) [14,15].

1. INTRODUCTION

Psychological morbidities such as anxiety and depression are commonly experienced by patients with cancers including patients with prostate cancer. (CAP) [1]. Psychological distress may be experienced at time of diagnosis, during and after completion of treatment [2]. Various prevalent rates have been reported for anxiety and depression among this group of patients. A 12-month U.S. prevalence of any DSM (Diagnostic and Statistical Manual)-IV anxiety disorder for prostate cancer was reported to be 11.08% [3, 4]. The pre-treatment depression prevalence of 17.27% was reported by Watts et al in men with prostate carcinoma in a systemic review and meta-analysis of 4,494 patients [5]. Other researchers have reported a prevalence of common depressive disorders (major and persistent depressive disorders or depression) of up to 25-28% in cancer survivors (vs 5-6% in non cancer controls [6]. Another study had reported much higher prevalence of 33% [7]. Anxiety disorders prevalence between 28% and 39% were reported by various authors [7,8].

Co morbidity of psychiatric disorder and prostate cancer is associated with some complications and negative prognosis. One of the worst complications is death by suicide. The risk of death by suicide in patients with prostate cancer has been reported to be higher than in general population [16-18]. The absolute risk of suicide among these patients is estimated to be approximately 1 in 1,000 men, which is almost twice that of the general population [19]. The rates of suicidal ideation are, however much higher among these patients. One study had estimated approximately 12% of prostate cancer patients experience suicidal ideation [20].

Also, studies have associated a diagnosis of depression as a risk factor for worse outcomes of prostate cancer. Using the SEER database, Prasad et al. reported that patients with clinically localized prostate cancer and a diagnosis of a depressive disorder were less likely to undergo definitive treatment for the prostate cancer and experienced poorer survival outcomes including increased mortality [21,22]. Mohamed et al. also reported that baseline depression significantly

predicted worse post-treatment sexual and urinary quality of life [23].

In contrast to most studies, some researchers suggested psychiatric morbidity, especially depression, may have been a risk factor for the development of prostate cancer in some cases. The pathophysiology of this link is hypothesized to relate to immune system dysfunction [24].

To the best of our knowledge, available studies on the pre-treatment prevalence of depression and anxiety in prostate carcinoma were done mainly among Caucasians with very limited studies done in sub-saharan Africa. This study was therefore designed to determine the pre-treatment prevalence and associated factors of anxiety and depression in men with CAP in South Western Nigeria.

2. MATERIALS AND METHODS

This is a prospective, cross-sectional study of anxiety and depression in men with CAP presenting with lower urinary tracts symptoms [LUTS] to the urology unit of the hospital. The study period was from 1st January 2018 to 31st December 2019.

Inclusion criteria comprised all cases of histologically diagnosed prostate cancer presenting to the clinic for the first time, and who consented to participate in the study. Exclusion criteria included men who have had previous prostatic surgery, non-histologically diagnosed CAP, those with neurogenic bladder of any cause, bladder calculi or contracture, urethral stricture, bladder malignancy and any other causes of LUTS aside prostate cancer. Patients who had previous diagnosis of a psychiatric morbidity or who did not give their consent were also excluded.

The process of data collection was carried out without undue risks to the patients. There was no financial cost to the subjects at any stage of the study.

A sociodemographic questionnaire was used for the sociodemographic details of the subjects while anxiety and depression were measured using the Hospital Anxiety and Depression Scale (HADS). This is a 14-item questionnaire asking respondents to rate the degree or frequency of feelings experienced during the past week on a four-point scale (scored 0 to 3). Seven items form an anxiety subscale and seven in a depression subscale, each with a possible score

ranging from 0 to 21. A score of 7-10 is a mild case, score of 11-14 is moderate while score of 15-21 is a severe case [25,26]. Patients also completed an 8-item International Prostate Symptoms Score (IPSS) [27]. The bother Score [BS] which was the assessment of the [quality of life] QoL was classified into two groups of Good quality of life [BS≤3] versus poor quality of life [BS>3] [28].

2.1 Histological Diagnosis

Any patient who had a PSA≥10.0ng/dl was sent for trucut needle biopsy and specimen sent for histological analysis.

2.2 Specimen Collection for PSA

Patients were encouraged to abstain from sexual activities for three days prior to blood collection. Likewise, direct rectal examination was also avoided before venepuncture. Prolonged tourniquet application was avoided during the collection of 5ml blood for the PSA. Serum PSA concentration was estimated by ELISA methodology using ACCUBIND kit.

Data collected were analyzed with a multi-purpose computer analysis program, Statistical Package for the Social Sciences version 23 (IBM; SPSS, Chicago, IL, USA). Statistically significant value was set at P<0.05.

3. RESULTS AND DISCUSSION

A total of 46 patients were recruited for the study. The mean age of the participants was 72.6±9.44 years. About forty-eight percent (47.8%) of them were currently doing one job or the other while most of them (89.1%) were currently married. A high percentage (80.4%) of the participants denied current consumption of alcohol while only about a quarter (28.3%) of them denied ever smoking cigarettes. A high percentage of the participants (78.3%) started having LUTS about 3yrs before they were diagnosed as having cancer of the prostate (Table 1).

There was a high prevalence of depression (43.5%) among the participants. Anxiety disorder on the other hand was reported in about 21.7% of them. Only 2.2% of them had only anxiety disorder without depression while 23.9% had only depression without anxiety disorder. About 19.6% of the participants had both anxiety disorder and depression (Table 2).

There was no significant association between having depression or anxiety and the sociodemographic details (such as age, employment status or marital status) including smoking and alcohol consumption, BMI (Table 1).

However there was a significant association between depression/anxiety and high BS score (signifying poor quality of life). Most people that had an anxiety disorder were found to also have depression as shown by the significant correlation between anxiety and depression scores. (corr. Co-eff (r)= 0.597, $p = 0.000$). Also, the IPSS scores of the patients was

significantly correlated with the BS scores ($r = 0.309$, $p = 0.018$).

One of the major findings in this study is the high prevalence of psychiatric morbidity among patients with cancer of the prostate. This study found prevalent rates as high as 43.5% and 21.7% for depression and anxiety disorder respectively. These rates are high when compared to studies among similar patients done in the western world. For instance, a study in USA reported a prevalence of 11.08% for anxiety disorder [3, 4]. While other authors in similar environment reported prevalence rates ranging from 17-28% for depression [5,6].

Table 1. Sociodemographic characteristics of study population

Variable	Frequency (n=46)	Percentage (%)	Depression	Anxiety disorder
			Test statistic P-value	Test statistic p-value
Occupation				
Employed	22	47.8%	$\chi^2 = 0.43$	$\chi^2 = 0.314$
Unemployed	24	52.2%	$p = 0.736$	$p = 0.575$
Marital status				
Married	41	89.1%	$\chi^2 = 0.028$	$\chi^2 = 1.558$
Widowed/separated	5	10.9%	$p = 0.868$	$p = 0.212$
Alcohol use in last 6 months				
No	37	80.4%	$\chi^2 = 0.469$	$\chi^2 = 3.108$
Yes	9	19.1%	$p = 0.383$	$p = 0.078$
Smoking (lifetime)				
No	13	28.3%	$\chi^2 = 0.783$	$\chi^2 = 0.019$
Yes	33	71.7%	$p = 0.373$	$p = 0.890$
Duration of symptoms before diagnosis				
<1 yr	20	43.5%		
1-3 yrs	16	34.8%		
3-5 yrs	7	15.2%		
>5 yrs	3	0.5%		
Quality of life (BS score)				
Good	3	6.5%		
Poor	43	93.5%		
Severity of depression				
None	26	56.5%		
Mild	11	23.9%		
Moderate	6	13.0%		
Severe	3	6.5%		
Severity of anxiety disorder				
None	36	78.3%		
Mild	7	15.2%		
Moderate	3	6.5%		
Severe	0	0.0%		

Table 2. Psychological morbidity of study population

Variable	Anxiety only	Depression only	Both anxiety and depression	No morbidity	ANVA	P-Value
Prevalence	2.2%	23.9%	19.6%	54.3%		
Mean age	78	73 ±7.95	69.89	73.16 ± 10.48	0.449	0.64
Mean BMI	34.67	26.94 ±4.57	24.35 ±3.79	25.27 ± 3.39	2.088	0.09
Mean PSA	97.80	48.18 ±3.62	72.31 ± 3.54	73.32 ± 3.1	1.672	0.20
Mean BS score	4.0	5.09±0.54	5.22 ± 0.67	4.48 ± 1.35	1.891	0.162
Mean IPSS score	26.0	22.09± 8.15	22.22 ± 8.13	21.12 ± 6.57	0.163	0.850

On the other hand, some authors reported a much higher prevalence rates for anxiety disorder (28-39%) [7,8]. Reasons for the varying prevalent rates among the various studies could be because of the instrument used in assessing for psychiatric morbidity, or the different populations been studied. A possible explanation for the high rates of depression in this study compared to others could be that some of the patients might have underlying mood symptoms which were not diagnosed before onset of LUTS. This is not uncommon in our environment where retired people are lonely and financially incapacitated due to unpaid pensions and lack of other activities to keep themselves busy. Such patients experiencing mood symptoms might not present to the hospital due to either ignorance or stigma associated with mental illness. Also, men are unlikely to report mental health symptoms or seek mental healthcare [29, 30].

Anxiety disorder on the other hand have been reported to be higher around the time of diagnosis, especially while awaiting result of biopsy [31]. Also worries about cancer recurrence or future diagnostic tests could also increase rates of anxiety in these patients [32]. Some authors had also explained the high rate of anxiety disorder in the context of patients who might have a specific form of situational anxiety called Prostate Cancer Related Anxiety (PCRA) [33,34].

One of the important findings in the study was the high level of poor quality of life among patients with depression and anxiety disorder. Similar findings of poor quality of life were also reported by other authors [33-36]. These patients with poor quality of life were also found to have more LUTS (high IPSS scores). Previous study done in this environment among patients with CAP also reported poor quality of life in those with severe LUTS [37]. Possible explanation for the these associations could be

that patients having more physical symptoms find it difficult coping with daily activities and are likely to worry more about their symptoms compared to patients with few symptoms. The discomfort could, invariably, lead to poor quality of life and consequently psychiatric morbidity. Conversely, the depressive or anxiety symptoms could also be the cause of poor quality of life.

Having a psychiatric morbidity was associated with having another psychiatric morbidity. In this instance, having depression was associated with having anxiety disorder and vice versa. This is however not surprising as individuals who are having one form of emotional distress or the other are at risk of a major psychiatric disorders [38]. Erim et al also reported a prevalence of probable depression of about seven times higher in participants with PCRA compared with those without PCRA [38].

Another possible explanation is that the same factor may, independently, lead to multiple psychiatric disorders. The American Cancer Society prostate cancer survivor care guidelines noted that survivors with significant or persistent PSA anxiety may be at heightened risk of depressive symptoms [39].

Our study, similar to some others, confirms the lack of a relationship between psychiatric morbidity and factors such as PSA level, age of the patient [40].

A major strength of the study was that we were able to identify cases of depression and anxiety disorder using a simple instrument, but a limitation of this study is the small sample size. Future studies may focus on recruiting more participants to increase the power of the study.

4. CONCLUSION

In conclusion, this study found a high rate of anxiety and depression among CAP patients. In addition, it showed significant association

between psychiatric morbidity and poor quality of life; similarly, between poor quality of life and LUTS. This study revealed risk of having depression was increased in those with anxiety disorder.

Due to the high rate of anxiety and depression among CAP patients, assessing patients for these disorders and initiating prompt treatment may reduce the morbidity and mortality in these patients.

CONSENT

Written informed consent of the patients was obtained before they were included in the study. Those who declined consent were not victimized in any way.

ETHICAL APPROVAL

Ethical approval was obtained from the Ethical Committee of Ekiti State University Teaching Hospital, Ado-Ekiti. Ethical approval no is EKSUTH/A67/2020/06/002.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics. *CA Cancer J Clin.* 2017;67:7–30.
2. Bobridge A, Bond MJ, Marshall V, Paterson J. An investigation of the support needs of men and partners throughout the prostate cancer journey. *Psychooncology.* 2015;24:341–347.
3. Essink-Bot M-L, Koning HJ, Hijs HG, Kirkels WJ, Van der Maas PJ, Schroder FH. Short-term effects of population-based screening for prostate cancer on health-related quality of life. *J Natl Cancer Inst.* 1998;90:925–931.
4. Lintz K, Moynihan C, Steginga S et al. Prostate cancer patients' support and psychological care needs: survey from a non-surgical oncology clinic. *Psycho Oncology.* 2003;12:769–783.
5. Atlanta GA. American Cancer Society. Cancer facts and figures for African Americans; 2016-2018.
6. Massie MJ. Prevalence of depression in patients with cancer. *J Natl Cancer Inst Monogr.* 2004;32:57-71.
7. Heo J, Noh OK, Chun M, Oh Y-T, Kim L. Psychological distress among prostate cancer survivors in South Korea: A nationwide population based, longitudinal study. *Asia-Pac J Clin Oncol.* 2019;1-6.
8. Korfage IJ, Essink-Bot M, Janssens AC, Schroder FH and De Koning HJ. Anxiety and depression after prostate cancer diagnosis and treatment: 5-year follow-up. *British Journal of Cancer.* 2006;94:1093 – 1098.
9. Skolarus TA, Wolf A, Erb NL et al. American Cancer Society prostate cancer survivorship care guidelines. *CA Cancer J Clin.* 2014;64:225-249.
10. Edwards B, Clarke V. The psychological impact of a cancer diagnosis on families: the influence of family functioning and patients' illness characteristics on depression and anxiety. *Psychooncology.* 2004;13:562-576.
11. Linden W, Vodermaier A, MacKenzie R, Greig D. Anxiety and depression after cancer diagnosis: Prevalence rates by cancer type, gender, and age. *J Affect Disord.* 2012;141:343-351.
12. DiMatteo MR, Lepper HS, Croghan TW. Depression is a risk factor for noncompliance with medical treatment: Meta-analysis of the effects of anxiety and depression on patient adherence. *Arch Intern Med.* 2000;160:2101-2107.
13. Rost K, Zhang M, Fortney J, Smith J, Coyne J, Smith GR. Persistently poor outcomes of undetected major depression in primary care. *Gen Hosp Psychiatry.* 1998;20:12-20.
14. Pirl WF, Greer JA, Goode M, Smith MR. Prospective study of depression and fatigue in men with advanced prostate cancer receiving hormone therapy. *Psycho Oncology.* 2008;17:148-153.
15. Nelson CJ, Mulhall JP, Roth AJ. The association between erectile dysfunction and depressive symptoms in men treated for prostate cancer. *J Sex Med.* 2011;8:560-566.
16. Fall K, Fang F, Mucci LA, Ye W, Andren O, Johansson JE et al. Immediate risk for cardiovascular events and suicide following a prostate cancer diagnosis:

- Prospective cohort study. *PLoS Med.* 2009; 6:1000197.
17. Fang F, Keating NL, Mucci LA, Adami HO, Stampfer MJ, Valdimarsdottir U et al. Immediate risk of suicide and cardiovascular death after a prostate cancer diagnosis: Cohort study in the United States. *J Natl Cancer Inst.* 2010;102:307–14.
 18. Bill-Axelsson A, Garmo H, Lambe M, Bratt O, Adolfsson J, Nyberg U et al. Suicide risk in men with prostate-specific antigen-detected early prostate cancer: A nationwide population-based cohort study from PCBaSe Sweden. *Eur Urol.* 2010;57:390–5.
 19. Smith DP, Calopedos R, Bang A, Yu XQ, Egger S, Chambers S et al. Increased risk of suicide in New South Wales men with prostate cancer: analysis of linked population-wide data. *PLoS One.* 2018;13:0198679.
 20. Recklitis CJ, Zhou ES, Zwemer EK, Hu JC, Kantoff PW. Suicidal ideation in prostate cancer survivors: understanding the role of physical and psychological health outcomes. *Cancer.* 2014;120:3393–400.
 21. Prasad SM, Eggener SE, Lipsitz SR, Irwin MR, Ganz PA, Hu JC. Effect of depression on diagnosis, treatment, and mortality of men with clinically localized prostate cancer. *J Clin Oncol.* 2014;32:2471–8.
 22. Jayadevappa R, Malkowicz SB, Chhatre S, Johnson JC, Gallo JJ. The burden of depression in prostate cancer. *Psychooncology.* 2012;21:1338–45.
 23. Mohamed NE, Bovbjerg DH, Montgomery GH, Hall SJ, Diefenbach MA. Pretreatment depressive symptoms and treatment modality predict post-treatment disease-specific quality of life among patients with localized prostate cancer. *Urol Oncol.* 2012;30:804–12.
 24. Currier MB, Nemeroff CB. Depression as a risk factor for cancer: from pathophysiological advances to treatment implications. *Annu Rev Med.* 2014;65:203–21.
 25. Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. *Acta Psychiatr Scand.* 1983;67:361- 370.
 26. Vordermaier A, Linden W, Siu C. Screening for emotional distress in cancer patients: A systematic review of assessment instruments. *J Natl Cancer Inst.* 2009;101:1464-1488.
 27. Barry MJ, Fowler FJ, O’Leary MP, Bruskewitz RC, Holtgrewe HL, Mebust WK et al. The American Urological Association symptom index for benign prostatic hyperplasia. *J Urol.* 1992;148:1549-57.
 28. O’leary MP. Validity of “bother score” in the evaluation and treatment of symptomatic benign prostatic hyperplasia. *Rev Urol.* 2005;7(1):1-10.
 29. Addis ME, Mahalik JR. Men, masculinity, and the contexts of help seeking. *Am Psychol.* 2003;58(1):5.
 30. Real T. I don’t want to talk about it: Overcoming the legacy of male depression. New York: Fireside; 1997.
 31. Heo J, Noh OK, Chun M, Oh Y-T, Kim L. Psychological distress among prostate cancer survivors in South Korea: A nationwide population based, longitudinal study. *Asia-Pac J Clin Oncol.* 2019;16(2):125-130.
 32. Deimling GT, Bowman KF, Sterns S, Wagner LJ, Kahana B. Cancer-related health worries and psychological distress among older adult, long-term cancer survivors. *Psychooncology.* 2006;15:306-320.
 33. Roth A, Nelson CJ, Rosenfeld B et al. Assessing anxiety in men with prostate cancer: further data on the reliability and validity of the memorial anxiety scale for prostate cancer (MAX-PC). *Psychosomatics.* 2006;47(4):340-347.
 34. Roth AJ, Rosenfeld B, Kornblith AB et al. The memorial anxiety scale for prostate cancer: validation of a new scale to measure anxiety in men with prostate cancer. *Cancer.* 2003;97(11):2910-2918.
 35. Nelson CJ, Starr TD, Macchia RJ, Hyacinthe L, Friedman S, Roth AJ. Assessing anxiety in Black men with prostate cancer: further data on the reliability and validity of the Memorial Anxiety Scale for Prostate Cancer (MAX-PC). *Support Care Cancer.* 2016;24(7):2905-2911.
 36. Dale W, Bilir P, Han M, Meltzer D. The role of anxiety in prostate carcinoma: A structured review of the literature. *Cancer.* 2005;104(3):467-478.
 37. Adegun PT, Adebayo PB, Areo PO. Severity of lower urinary tract symptoms among middle aged and elderly Nigerian men: Impact on quality of life. *Adv Urol.* 2016;1015796.
Available: <https://doi.org/10.1155/2016/1015796>

38. Erim DO, Bennett AV, Gaynes BN, Basak RS, Usinger D, Chen RC. Associations between prostate cancer-related anxiety and health-related quality of life. *Cancer Med.* 2020;9(12):4467-4473.
39. Skolarus TA, Wolf AM, Erb NL et al. American Cancer Society prostate cancer survivorship care guidelines. *CA Cancer J Clin.* 2014;64:225-249.
40. Sánchez Sánchez E, González Baena AC, González Cáliz C, Caballero Paredes F, Moyano Calvo J, Castiñeiras Fernández J. Prevalence of anxiety and depression in prostate cancer patients and their spouses: An unaddressed reality. *Prostate Cancer*; 2020. DOI: 10.1155/2020/4393175

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