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13. ABSTRACT (Maximum 200 Words) While watchful waiting is an accepted disease management strategy for localized prostate cancer, there is little information available on the impact of the disease and the expectant management on men's well-being. The few studies that have focused on these issues suggest that anxiety about untreated cancer and urologic and sexual impacts of the disease are important considerations in the selection of this approach to disease management. We have gathered data from prostate cancer patients selecting watchful waiting in lieu of an active treatment for their cancer in order to understand the psychosocial and symptom management burden that these men face. Our work builds on previous research on men selecting watchful waiting using a combination of qualitative and quantitative techniques to identify areas where patient education programs could be developed for these men to improve their quality of life. We have examined the psychological and interpersonal impact of prostate cancer in a semi-structured qualitative interview; assess the health-related quality of life (HRQoL) of 50 men with prostate cancer using the CaPSURE baseline data collection instrument; and compare the study respondents' HRQoL to the HRQoL of men in the CaPSURE database.				
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1. Introduction

While watchful waiting is an accepted disease management strategy for localized prostate cancer, there is little information available on the impact of the disease and the expectant management on men's well-being. The few studies that have focused on these issues suggest that anxiety about untreated cancer and urologic and sexual impacts of the disease are important considerations in the selection of this approach to disease management. In this project, we have gathered data from prostate cancer patients selecting watchful waiting in lieu of an active treatment for their cancer in order to understand the psychosocial and symptom management burden that these men face. Our work builds on previous research on men selecting watchful waiting using a combination of qualitative and quantitative techniques to identify areas where patient education programs could be developed for these men to improve their quality of life.

2. Body

The following tasks have been accomplished since the beginning of funding on 10/15/2004 (Table 1).

Table 1. Research tasks accomplished

Date	Task
7/21/2004	UCSF receives email notifying us project awarded
8/27/2004	UCSF submits project for review by UCSF Committee for Human Research (CHR)
9/14/2004	Project reviewed and approved by UCSF Genitourinary Oncology Scientific Review Committee
9/28/2004	Project determined to be exempt from review by UCSF Comprehensive Cancer Center Protocol Review Committee
10/15/2004	Project award begins
11/22/2004	Project approved by UCSF CHR
12/3/2004	Project approved by San Francisco VA Medical Center human subjects panel
1/14/2005	DOD Office of Research protections notifies UCSF that DOD will contact PI when a reviewer is assigned to project.
3/8/2005	First request for information received from DOD reviewer
4/26/2005	UCSF response to DOD reviewer. This packet of information was the largest and required the most time to assemble. Our response time also was impacted by vacation leave and attendance at a professional meeting for project investigators and staff.

Date	Task
5/23/2005	DOD reviewer informs us review begun
6/23/2005	Cancer anxiety in men on surveillance project using CaPSURE™ data begins
6/7/2005	Second request for information from DOD reviewer
6/29/2005	UCSF response to DOD reviewer
7/18/2005	Third request for information from DOD reviewer
8/5/2005	UCSF response to DOD reviewer
9/26/2005	Fourth request for information from DOD reviewer
10/10/2005	UCSF response to DOD reviewer
11/9/2005	DOD reviewer instructs UCSF to submit study materials to UCSF CHR
11/17/2005	UCSF submission to CHR of study materials including changes requested by DOD reviewer
01/20/2006	Dr. Latini leaves UCSF.
02/08/2006	UCSF alerts DOD reviewer on change of PI and asks for direction
02/16/2006	DOD Project Officer is notified of change of PI
2/25/2006	Cancer anxiety in men on surveillance poster presented at Multidisciplinary Prostate Cancer Symposium, San Francisco, CA
3/22/2006	UCSF directed to submit PI change to local IRB before receiving approval from DOD. (In past, DOD had to approve first, before submitting to local IRB.)
3/23/2006	UCSF submits copy of SFVAMC approval for "02A" modification to DOD reviewer
3/24/2006	Cancer anxiety in men on surveillance poster presented at Society of Behavioral Medicine meeting, San Francisco, CA
4/26/2006	UCSF receives appropriate paperwork and submits to local IRB and SFVAMC.
5/10/2006	Approval of project received from the UCSF IRB
05/15/2006	Revised statement of work submitted.
07/21/2006	UCSF responds to request of DOD reviewer for additional information on the protocol
09/14/2006	UCSF responds to request for additional information on the protocol as requested by the DOD reviewer
09/25/2006	UCSF responds to the request for additional information on the protocol as requested by the DOD reviewer
10/03/2006	DOD reviewer requests a major modification to the protocol

Date	Task
11/03/2006	Amendments for a major modification as requested by the DOD reviewer are sent to the UCSF IRB, the SFVAMC, and BCM IRB for review and approval
12/05/2006	Major modification in protocol approved by the UCSF IRB, awaiting approval from the SFVAMC and the BCM IRB
12/15/2006	Received acceptance of continuing review report and protocol amendment 1 from DOD IRB Chief
01/13/2006	Dr. Knight and Dr. Latini present invited papers on the psychosocial and patient education needs of men selecting watchful waiting at international conference on active surveillance for men diagnosed with localized prostate cancer, San Francisco, CA
01/23/2007	Approval of major modification approved by BCM, awaiting signed documents from SFVAMC
01/29/2007	Approval documents from BCM and SFVAMC sent to DOD for review. DOD reviewer requests separate letter from BCM IRB for waiver of consent and BCM protocol. BCM protocol sent to DOD reviewer
01/31/2007	Received acceptance of protocol amendment from DOD IRB Chief for work to be conducted at UCSF
02/02/2007	Received acceptance of protocol amendment from DOD IRB Chief for the work to be conducted at BCM
02/06/2007	SFVAMC receives notification from VA Central Office requiring a stand down of health services research in order to participate in national audit for data security. Dr. Knight's studies are included in the audit
04/02/2007	Manuscript from ancillary study on watchful waiting accepted for publication in Journal of Urology
05/16/2007	SFVAMC receives approval from VA Central Office that the audit has been completed, no data security problems are detected at SFVAMC, and studies at SFVAMC can be resumed
09/08/2007	Dr. Knight and Dr. Latini present preliminary results at the DOD Prostate Cancer Impact Conference in Atlanta, GA.
05/01/2008	Recruitment efforts continue with half of sample accomplished.
11/01/2008	Recruitment and accrual closed with sample accomplished.

3. Key research accomplishments

Because of the delay in our ability to collect original data due to the ongoing regulatory process, the investigators decided to explore other options for beginning to understand the psychosocial aspects of the surveillance process using an existing data source from one of the investigators other projects. The CaPSURE™ project, a 13,000 man national observational study collects more than 1,000 clinical and patient-reported variables on men diagnosed with localized prostate cancer. In June 2005, Dr. Latini, who was at the time Director of the Outcomes Research Core, the group responsible for carrying out analyses of CaPSURE data, and Dr. Knight began discussing how CaPSURE data might be used to understand the relationship between anxiety about cancer and the surveillance process. The investigators worked with CaPSURE staff to develop an analysis project exploring the impact of cancer anxiety on time to active treatment. The analysis was completed and abstracts were submitted to the Multidisciplinary Prostate Cancer Symposium and the annual meeting of the Society of Behavioral Medicine. The abstracts were both accepted and the investigators presented a poster reporting their results at both meetings. Both abstracts were published and a manuscript based on the work was published in the Journal of Urology.

1. Latini, D. M., Hart, S. L., Knight, S. J., Cowan, J. E., Ross, P. L., DuChane, J., Carroll, P. R., & the CaPSURE™ Investigators. (2006). Cancer anxiety predicts time to active treatment for men with localized prostate cancer on active surveillance: Data from CaPSURE™. *Proceedings of the Prostate Cancer Symposium: A Multidisciplinary Approach*. Abstract 281, p. 234. San Francisco, CA.
2. Latini, D. M., Hart, S. L., Knight, S. J., Cowan, J. E., Ross, P. L., DuChane, J., Carroll, P. R., & the CaPSURE™ Investigators. (2006). Cancer anxiety predicts time to active treatment for men with localized prostate cancer on active surveillance: Data from CaPSURE™. *Annals of Behavioral Medicine*, 31 (Suppl.), C132.
3. Latini, D.M., Hart, S.L., Knight, S.J., Cowan, J.E., Ross, P.L., DuChane, J., Carroll, P.R. (2007). The relationship between anxiety and time to treatment for prostate cancer patients on surveillance. *Journal of Urology*. 178, 821-827.

4. Reportable outcomes

Using data from the CaPSURE™ (Cancer of the Prostate Strategic Urologic Research Endeavor) study, a longitudinal, observational disease registry for men with biopsy-proven prostate cancer, Drs. Latini and Knight examined the relationship between cancer-related anxiety and time to active treatment for men initially selecting surveillance. As part of the CaPSURE study, sociodemographic and quality of life data are collected from patients at enrollment and at six-month intervals subsequently. Sites collect clinical data at enrollment and each time the patient returns for care. Follow-up prostate specific antigen (PSA) results are also reported.

As of April 2005, 11,804 patients were enrolled in the study. Participants included in the analysis were diagnosed with biopsy-proven localized prostate cancer between 1989 and 2003, selected surveillance rather than active treatment, had at least 2 cancer anxiety assessments on or after diagnosis, and had sufficient data to determine whether they received a treatment 6 or more months after diagnosis. Because of declining numbers of men with data beyond 4 years post-diagnosis, we restricted the sample to men with sufficient PSA and anxiety data in the 4 years post-diagnosis necessary to calculate the velocity measures. Our final sample included 116 men.

A 5-item fear of cancer recurrence measure was added to the CaPSURE patient questionnaire in 1999 and remained in the semi-annual questionnaire till 2002. The fear of recurrence scale measures patient beliefs and anxieties about disease recurrence. All items are rated on a 5-point Likert scale. The reliability and validity of this scale have been previously established.^{1,2} One previous analysis examining predictors of fear of recurrence using CaPSURE data was published in 2003.³

Table 2. Cancer Anxiety items

(Circle one number on each line.)	Strongly Agree	Agree	Not Certain	Disagree	Strongly Disagree
<i>Because cancer is unpredictable, I feel I cannot plan for the future</i>	1	2	3	4	5
I will probably have a relapse (recurrence) within the next five years	1	2	3	4	5
<i>My fear of having my cancer getting worse gets in the way of my enjoying life</i>	1	2	3	4	5
<i>I am afraid of my cancer getting worse</i>	1	2	3	4	5
I am certain that I have been cured of cancer	1	2	3	4	5

In this analysis, scores were *not* reversed, meaning higher scores indicated greater anxiety about cancer. The 3-item measure (**Table 3**, italicized items) used in the current study had a Cronbach coefficient alpha of .78. We transformed scores on each of the 3 items into a 0 to 100 score and then averaged the 3 items to create an overall cancer anxiety score.

Decisions to move from active surveillance to active treatment are frequently guided by examining changes in PSA levels over time using a formula proposed by Carter and colleagues.⁴ Three or more measures of PSA taken during a 2-year period or at least 12-18 months apart are used to calculate the rate of change in PSA over time. A higher rate of change in PSA is thought to be indicative of more rapid disease progression. We calculated PSA velocity for men in this study using the formula outlined by Carter and further detailed by Polascik.^{4, 5} We also calculated an “anxiety velocity” measure to examine the importance of the change in cancer-related anxiety for men in our study. We used the same formula as for PSA velocity.

Participants were divided into two groups based on whether they received a treatment for their prostate cancer during the observation period or not. Baseline clinical and sociodemographic characteristics for the two groups were compared using the chi-square test for discrete variables and t-test for continuous variables. We used survival analysis to determine independent predictors of time to undergoing active treatment. We fit a backwards-elimination Cox proportional hazards regression model to determine if anxiety velocity was an independent predictor of time to treatment after controlling for ethnicity, educational level, insurance type, relationship status, number of comorbid conditions at baseline, D’Amico risk group, age at diagnosis, and body mass index at baseline. We also included PSA velocity in the Cox model to control for disease progression.

There were no significant demographic or baseline clinical differences between the men who received an active treatment during the observation period and those who did not. One might expect that men who sought active treatment during the observation period would have presented with more advanced disease at baseline but there were no significant differences in PSA, Gleason score, or T-stage. There also was no difference between groups in baseline cancer anxiety.

As might be expected, the mean PSA velocity for men who sought active treatment was higher than for men who did not seek treatment (0.09 vs. -0.02), but this difference did not reach statistical significance ($p < .06$). The differences in anxiety velocity were larger: 0.39 for men who sought treatment vs. -0.25 for those who did not ($p < 0.001$). To understand the relationship between the 2 velocity measures, we calculated the Pearson product-moment correlation, which was modest (0.30, $p < .001$).

The figure below shows the differences in cancer anxiety over time for the two groups. In the Cox model (**Table 3**), we entered sociodemographic characteristics, baseline clinical characteristics, PSA velocity, and anxiety velocity to predict time to active treatment. None of the sociodemographic or baseline clinical characteristics were significantly related to time to treatment. Both PSA velocity and anxiety velocity were independent predictors of time to treatment ($p < .05$). We are carrying out further analyses to understand the

asymmetry of the confidence interval for the PSA velocity variable in our final Cox model. Once these adjustments to the model are complete, the manuscript will be revised accordingly and submitted for publication.

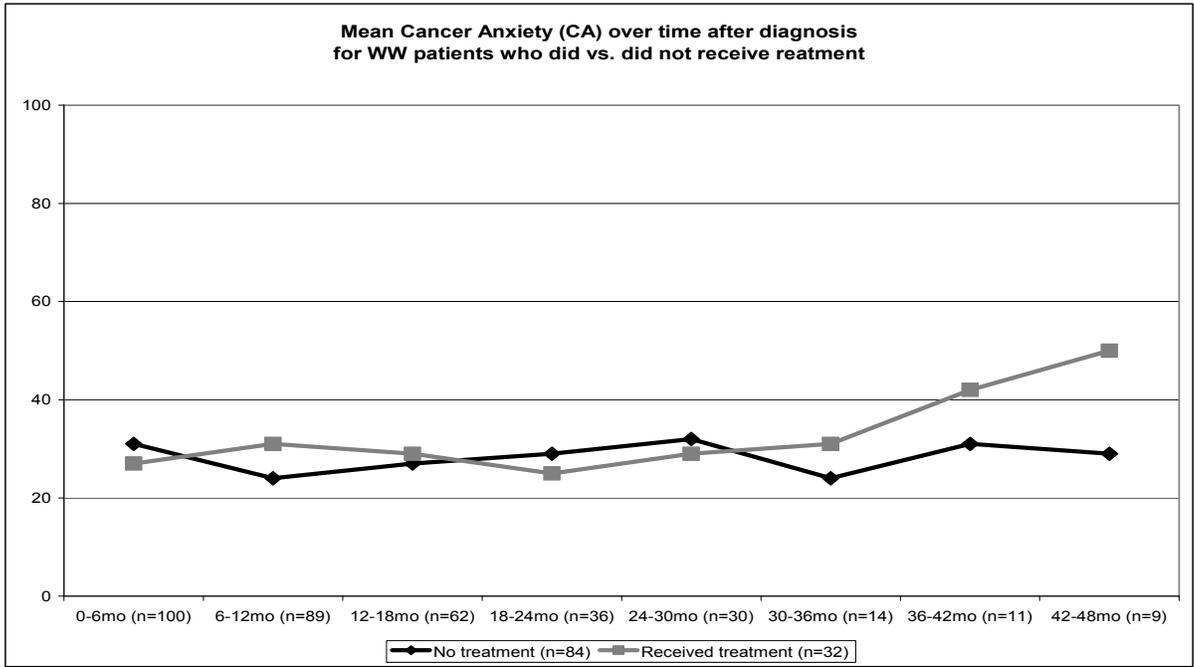


Table 3. Cox model to predict time to active treatment

Parameter	Estimate	Standard Error	Chi-Square	p-value	Hazard Ratio	95% Hazard Ratio Confidence Limits
PSA Velocity	2.05	0.96	4.57	.03	7.8	1.19 51.19
Cancer Anxiety Velocity	0.61	0.25	6.08	.01	1.85	1.13 3.01
Race			0.00	0.99		
Education			0.79	0.38		
Number of comorbidities	2.01			0.37		
Clinical risk group			3.49	0.17		
Insurance			1.83	0.18		
BMI at diagnosis			5.28	0.07		
Relationship			2.72	0.10		
Age at diagnosis			1.21	0.27		

Rather than being based solely on clinical disease progression, it appears men may allow cancer-related anxiety to influence decisions about treatment timing. Men should be provided with more psychosocial support to perhaps delay active treatment and the ensuing decrements in health-related quality of life.

5. Conclusions

For men who are older, who have less advanced prostate cancer, or who have more comorbid conditions, “watchful waiting” may be the most appropriate prostate cancer treatment. Over time, the proportion of men selecting watchful waiting in a national longitudinal prostate cancer registry dropped from 7.5% in 1989-1991 to 5.5% in 1998-2000.⁶ Even though the proportion of men selecting active surveillance may be dropping, the number of men choosing surveillance is still substantial. Using the American Cancer Society’s estimate of 234,460 new cases of prostate cancer and a rate of 5.5% of those men selecting active surveillance, there will be approximately 12,895 men choosing surveillance in 2006.

Watchful waiting is more frequently selected by non-White men, even after controlling for clinical characteristics at diagnosis.⁷ Thus, watchful waiters also may be those prostate cancer patients with the most difficulty securing the healthcare and resources they need to remediate the changes in their health-related quality of life (HRQoL), increasing the importance of understanding their unique experience of cancer. The majority (74%) of watchful waiters not dying from other causes have proceeded to active therapy by 7 years after diagnosis.⁸

Most of the research on psychosocial aspects of prostate cancer has focused on describing the impairments in HRQoL and psychological functioning of men with prostate cancer.⁹⁻¹⁵ While this literature on the HRQoL impacts of active treatment of prostate cancer is substantial, relatively few studies have explored the psychosocial and physical needs of men selecting watchful waiting. Over time, men selecting watchful waiting have worse mental HRQoL than men treated with surgery but better HRQoL than men treated with radiation.¹⁶ Men who select watchful waiting report substantial uncertainty and anxiety about their health status.¹⁷ Our preliminary results from our ancillary analysis of the CaPSURE anxiety data in men on surveillance supports this assertion that surveillance process carries a psychosocial burden that is not well understood and in fact may cause some men to seek active treatment sooner than is necessary.

The physical symptom profile of men selecting watchful waiting also differs from men who undergo active treatment. Men selecting watchful waiting were less likely to report erectile dysfunction (80% vs. 45%) and urinary leakage (49% vs. 21%) than men treated with a radical prostatectomy. However, urinary obstruction was significantly more common in men undergoing watchful waiting.¹⁸ Thus, watchful waiting is associated with psychosocial and physical burdens and needs distinct from those of active treatment.

One approach to relieving impairment in HRQoL that cancer patients experience has been the development of psychoeducational interventions.¹⁹ However, the number of such interventions developed specifically for prostate cancer patients is limited.²⁰ The more general interventions that include prostate cancer patients tend to include small numbers of them, relative to the number of participants who have other forms of cancer. For the few interventions that move beyond the support group model to provide educational and psychosocial support to prostate cancer survivors, all but one have focused on men selecting active treatment.²¹⁻²⁶

Based on the distinct impacts of watchful waiting as opposed to active treatment, it is unlikely that interventions targeting men who are undergoing or recovering from active treatment would adequately address the educational and psychosocial needs of watchful waiters. The one intervention focused on men selecting watchful waiting was able to show significant reductions in uncertainty in those men but the study was small (N=41) and has not yet been replicated. Thus, there is a critical gap in our understanding of the best methods for educational, decision-making, and psychosocial intervention for men selecting watchful waiting.²⁷ During the no-cost extension of this study, we will build on our preliminary results of the ancillary study by carrying out the qualitative interviews and paper-and-pencil data collection that will provide a more detailed understanding of the surveillance process necessary to develop a patient education and psychosocial support intervention for men on surveillance

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7. Appendices

“The relationship between anxiety and time to treatment for patients with prostate cancer on surveillance”

The Relationship Between Anxiety and Time to Treatment for Patients With Prostate Cancer on Surveillance

David M. Latini,* Stacey L. Hart, Sara J. Knight, Janet E. Cowan, Phillip L. Ross, Janeen DuChane, Peter R. Carroll and the CaPSURE™ Investigators

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Purpose: Little is known about psychosocial factors affecting the decision to move from surveillance to active treatment in men with localized prostate cancer. We examined the impact of cancer anxiety on the decision to move from surveillance to treatment.

Materials and Methods: We analyzed data from CaPSURE, a national observational prostate cancer registry. A total of 105 participants had localized disease, selected surveillance vs treatment and had at least 3 prostate specific antigen values available after baseline. Cancer anxiety was measured with a 3-item scale ($\alpha = 0.78$). We calculated the rate of change in prostate specific antigen with time (prostate specific antigen velocity) and used the same formula to calculate the rate of change in cancer anxiety. We fit a Cox regression model to determine predictors of receiving treatment in the 3-year observation period, controlling for prostate specific antigen velocity, demographics and baseline clinical characteristics.

Results: Prostate specific antigen velocity and the cancer anxiety change rate were significant independent predictors of treatment receipt (HR 1.02, 95% CI 1.004, 1.035, each $p < 0.01$). Men with higher prostate specific antigen velocity (1.51 ng/ml per year or greater) were significantly more likely to receive treatment than men with lower prostate specific antigen velocity (HR 3.18, 95% CI 1.122, 9.016). The 2 velocity measures correlated only modestly ($r = 0.29$, $p < 0.001$).

Conclusions: Rather than being based only on clinical presentation and disease progression, decisions about treatment receipt for some men are influenced by cancer related anxiety. Men should be provided with more psychosocial support to perhaps delay treatment and the ensuing decrements in health related quality of life.

Key Words: prostate, prostatic neoplasms, anxiety, prostate-specific antigen

Treatment guidelines outline the alternatives that men with PCa may select and the clinical characteristics important to consider in treatment selection.¹ For men who are older or who have less advanced PCa or more comorbid conditions surveillance may be appropriate. The proportion of men selecting surveillance in a national PCa registry ranges from 5.5% of all men to 8% of men presenting with low risk disease.² Some men remain on surveillance for substantial periods with almost 60% still on surveillance more than 18 months after diagnosis.³ Of men not dying of other causes 25% remain on surveillance as long as 7 years.⁴

If one calculates 5.5% of the estimated number of new PCa cases in the United States each year and adds the number of men diagnosed in previous years remaining on surveillance, the number of American men on surveillance may be substantial.⁵

Choosing active treatment for PCa over surveillance is not without drawbacks. Men undergoing treatment report localized and systemic symptoms, resulting in poorer HRQOL.⁶ Given the cost of treatment in dollars and decrements in HRQOL, there has been ongoing debate about the tight linkage between PCa detection and treatment, and whether some men with PCa need any treatment at all.^{7,8}

However, the surveillance process also imposes a burden.⁹ In a systematic review of studies of anxiety in men with PCa, of which most focused on men being screened for PCa or on men who had been treated and were presenting for PSA followup, Dale et al found that events such as a screening visit or followup PSA measurement evoked an increase in anxiety that decreased significantly after a normal result.¹⁰ These results are particularly relevant for men on surveillance because they must undergo repeated testing every 3 to 6 months and make repeated treatment decisions.

Earlier Patel et al reported that repeated testing and decision making cause some men to seek treatment before it

Submitted for publication January 4, 2007.

Study received approval from the institutional review boards at University of California-San Francisco and contributing sites.

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