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14. ABSTRACT

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 propose to gather 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. The proposed study will build 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 will examine 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 (25 Caucasian, 15 African-American and 10 Latino) 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. The study will provide necessary information to create needed psycho-educational interventions for this understudied group of men living with prostate cancer.

15. SUBJECT TERMS
prostatic neoplasms, quality of life, patient education

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1. Introduction

Previous research on prostate cancer has generally focused on men selecting active treatments such as surgery or radiotherapy. In this project, we will collect both qualitative and quantitative data to provide a better understanding of the psychosocial and physical symptom burden of men undergoing watchful waiting. Data will be collected from 50 men (25 Caucasian, 15 African-American, 10 Latino) who have been diagnosed with biopsy-proven localized prostate cancer and have selected watchful waiting, rather than active treatment such as surgery or radiation. Qualitative data will be analyzed using a mixture of content analysis and grounded theory techniques. Qualitative data will be analyzed using standard analytic techniques, such as t-tests and analysis of variance for continuous data and chi-square tests for discrete data. Results will inform psychoeducational interventions for men selecting watchful waiting.

However, the regulatory review and approval process has been much longer than originally anticipated. While waiting for approval to begin collecting original data, the investigators have worked with an existing data set from the CaPSURE™ study that can provide answers to some of questions posed in the original application to the DOD. Those results are detailed in sections 3 and 4. The investigators feel that using CaPSURE data has allowed them to move the longer term research goals of the DOD-funded project forward while adhering to the need for complete regulatory approval before beginning original data collection. Once final approval has been given to collect new data, the investigators will build on these initial results from CaPSURE to provide the more detailed and nuanced description of the psychosocial aspects of the surveillance process outlined in the original proposal.

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

Date	Task
	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.
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.
02/08/06	UCSF alerts DOD reviewer on change of PI and asks for direction
02/16/06	DOD Project Officer is notified of change of PI
2/25/2006	Cancer anxiety in men on surveillance poster presented at

Date	Task
	Multidisciplinary Prostate Cancer Symposium, San Francisco, CA
3/22/06	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.)
3/23/06	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
4/26/06	UCSF receives appropriate paperwork and submits to local IRB and SFVAMC.
5/8/2006	Verbal approval has been received from the UCSF IRB and an approval letter will be forthcoming.

Based on the longer than anticipated time required to meet DOD human subjects requirements, we are suggesting the following changes in the project scope of work

REVISED STATEMENT OF WORK

We will gather 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. The current study will build on previous research with men selecting active treatment carried out by the investigators and others by focusing 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 will examine the psychological and interpersonal impact of prostate cancer; assess the health-related quality of life (HRQoL) of 50 men (25 Caucasian, 15 African-American and 10 Latino) with prostate cancer; and compare the study respondents' HRQoL to the HRQoL of men in the CaPSURE database. The study will provide necessary information to create needed psychoeducational interventions for this understudied group of men living with prostate cancer.

Specific tasks accomplished over the grant timeline will include:

Table 2. Revised scope of work

Month	Task
1-18	1. Secure project review and approval by DOD, UCSF, and VA human subjects and scientific review committees. a. Outline and conduct analyses for ancillary study using CaPSURE data to understand the impact of anxiety on time to active treatment b. Present data from ancillary study at professional meetings c. Prepare manuscript from ancillary study for publication
18-28	2. Recruit and enroll 50 men (25 Caucasian, 15 African-American, 10 Latino) who have been diagnosed with biopsy-proven localized prostate cancer and have selected watchful waiting, rather than active treatment such as surgery or radiation.
18-28	3. Collect general and disease-specific HRQoL data using the CaPSURE data collection instruments.
18-28	4. Provide additional contextual information to use in interpreting the qualitative data described below by computing descriptive statistics for the respondents' HRQoL data and comparing the respondents' data to HRQoL data for men in the CaPSURE database.
18-28	5. Conduct qualitative interviews that will address the psychological and interpersonal impact of prostate cancer, as well as the physical symptoms these men experience; perceived needs for prostate cancer education materials; values and themes that would promote better psychosocial adjustment and physical symptom management; and suggestions and feedback related to the development of a tailored prostate cancer education program.
26-30	6. Analyze the qualitative data using grounded theory and content analysis techniques to identify the predominant themes and issues reported by the respondents.

We anticipate receiving permission to begin enrolling participants in the study in May 2006 after securing DOD and UCSF/SFVAMC approval of the change in Principal Investigator. Once we have secured permission to enroll, we will carry out the recruitment plans as outlined in the protocol, including flyers in our clinics, emails to the list of men attending prostate cancer support groups, and recruitment at community-based events. It is anticipated that the revised scope of work will require a request for a 12-month no-cost extension of the end of the grant period.

3. Key research accomplishments

See Table 1, Section 2.

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:

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.

A draft manuscript has been prepared (see Appendix) and will be submitted to a journal by the end of May 2006. As Drs. Latini and Knight were receiving limited salary support from the DOD project during the regulatory approval phase of the project and the CaPSURE analysis project addresses one aspect of the psychosocial burden of watchful waiting, the investigators have acknowledged DOD support in their manuscript.

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 3. Cancer Anxiety items

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

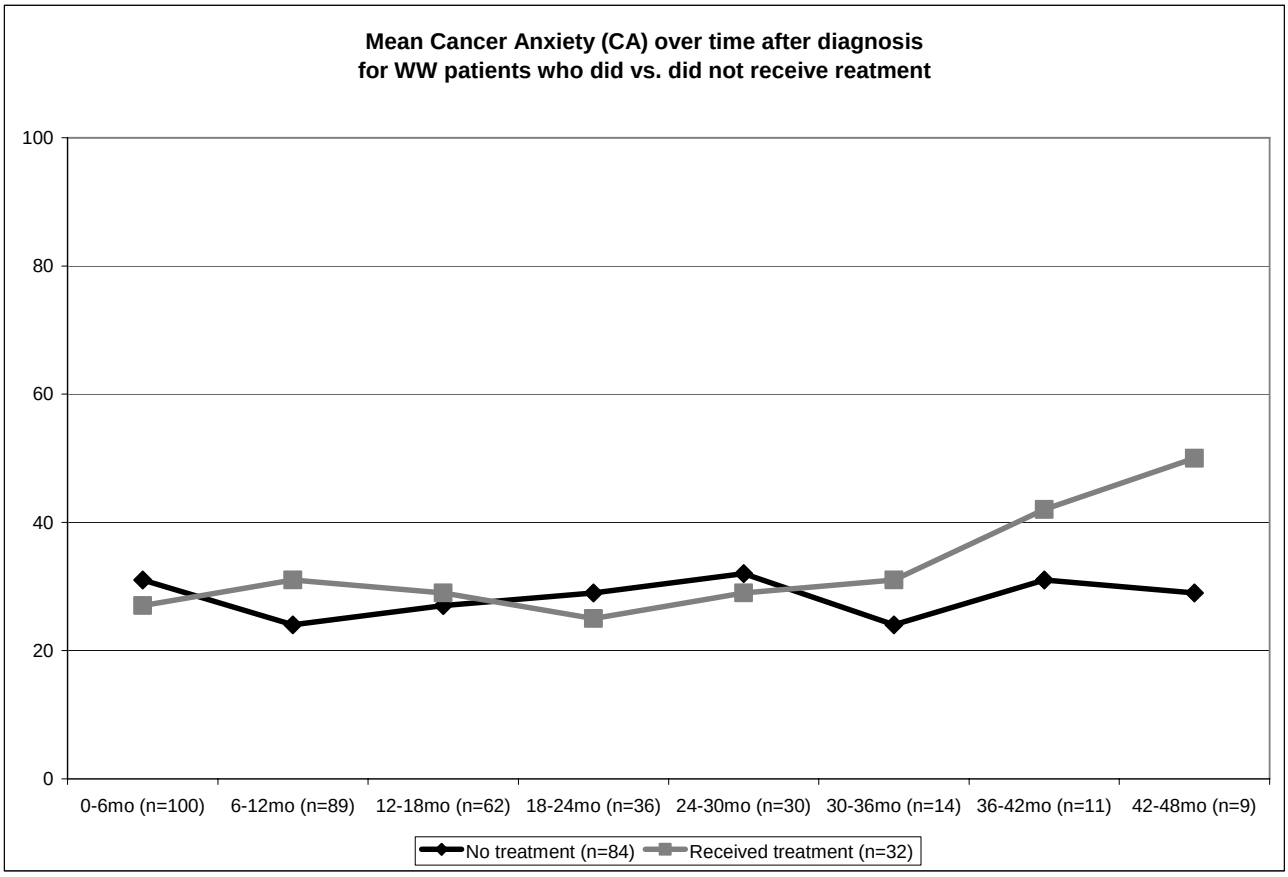

Table 4. Cox model to predict time to active treatment

	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 prostate cancer patients on surveillance"

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

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Running head: Cancer Anxiety Predicts Time to Active Treatment

Key Words: prostatic neoplasms, anxiety, active surveillance

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Abstract

Purpose: Little information is available describing the impact of anxiety on treatment choices made by men with localized prostate cancer. We examined the relationship between anxiety and timing of active treatment, while controlling for baseline patient characteristics.

Methods: Data were drawn from CaPSURE,™ a national observational prostate cancer registry. Participants (n=116) had localized prostate cancer, selected surveillance (vs. active treatment) had at least 2 PSA values and/or had active treatment data at or after 6 months post-baseline. Analyses were restricted to men with data within 4 years of diagnosis. Cancer anxiety was measured with a 3-item scale (Cronbach coefficient alpha=.78). We calculated the rate of change in PSA over time (PSA velocity; Carter et al, 1992) and used the same formula to calculate the rate of change in cancer anxiety ("anxiety velocity"). We fit a Cox proportional hazards mode to determine the impact of anxiety on time to active treatment, controlling for PSA velocity, demographics, and baseline clinical characteristics.

Results: PSA velocity (HR=7.8) and anxiety velocity (HR=1.85) were each significant (both $p < .05$) independent predictors of time to active treatment. The 2 velocity measures were only modestly correlated ($r = .30$, $p < .001$).

Conclusions: Rather than being based solely on baseline clinical presentation and disease progression, some men 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.

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Introduction

Prostate cancer has recently surpassed lung cancer to become the most common cancer of American men. The estimated number of new prostate cancer cases in the U. S. for 2006 is expected to be 234,460, up from 198,000 in 2002.[28, 29] Prostate cancer continues to disproportionately affect minority men.[29]

Treatment guidelines have been established outlining the alternatives men with prostate cancer may select from and the clinical characteristics important to consider in selecting a treatment.[30] For men who are older, who have less advanced prostate cancer, or who have more comorbid conditions, "active surveillance" may be the most appropriate treatment. Over time, the proportion of men selecting active surveillance 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 in the U. S. choosing surveillance in 2006. These men are in addition to an unknown number of men who previously selected surveillance and have neither progressed to active treatment nor died from other causes.

Most prostate cancer psychosocial research has focused on either men being screened for prostate cancer or on men who have sought active treatment; few studies have described the psychosocial status of men selecting active surveillance. Men who have completed active treatment report both localized and systemic symptoms that

result in poorer quality of life and increased bother.[31-35] Given the cost of active treatment in both decrements in health related quality of life and dollars, there has been an ongoing debate about the tight linkage between prostate cancer detection and treatment.[36-40]

However, the surveillance process imposes a different kind of burden.[27] In a systematic review of studies of psychological distress in men with prostate cancer, authors found most studies focused on men being screened for prostate cancer or on men who had been treated and were presenting for PSA follow-up. Events such as a screening visit or a follow-up PSA evoked a rise in anxiety that decreased significantly after a normal result.[41] These results are particularly relevant for men on surveillance as they must undergo repeated testing and treatment decisions related to their prostate cancer. The majority of men selecting surveillance proceed to active treatment within a few years of prostate cancer diagnosis. One study found 41% of men on surveillance had proceeded to active treatment within a median of 1.7 years after diagnosis.[42] Another study reported the majority (74%) of men choosing surveillance and not dying from other causes had proceeded to active therapy by 7 years after diagnosis.[8]

Earlier work has shown that the anxiety of repeated testing and decision-making causes some men to seek treatment before it may be medically necessary. In one study of 88 men on surveillance, 7 men who did not show progression based on objective measures of disease status requested treatment because of anxiety.[43] To determine whether this held true in a larger cohort using a standard measure of cancer anxiety, we examined longitudinal measures of anxiety as a predictor of time to active treatment.

We hypothesized that anxiety would be an independent predictor of time to treatment, after controlling for sociodemographic characteristics, baseline disease status, and disease progression as represented by PSA velocity.

Patients and Methods

Sample

~~Participants~~. We drew men from the CaPSURE™ (Cancer of the Prostate Strategic Urologic Research Endeavor) study, a longitudinal, observational disease registry for men with biopsy-proven prostate cancer. Sociodemographic and quality of life data are collected from patients at enrollment and at six-month intervals subsequently. CaPSURE™ sites collect clinical data at enrollment and each time the patient returns for care, including history of prostate cancer diagnosis, biopsies, pathology, staging tests, primary and subsequent prostate cancer treatments, Karnofsky performance status scores, and medications. Follow-up prostate specific antigen (PSA) results are also reported. The institutional review board at the University of California, San Francisco and the contributing sites approved the data collection protocols and other study methods.

As of April 2005, 11,804 patients were enrolled in the study. The group of men currently being followed numbers more than 7,000**.** Participants are actively enrolled from a core group of 31 urologic practice sites (40 sites have ever enrolled patients into CaPSURE). The sample is primarily drawn from community-based practices, with only about 8% of the participants from academic or Veterans Administration practices. A

more detailed description of the CaPSURE project methods has been previously published.[44, 45]

Participants included in the analysis were diagnosed with biopsy-proven localized prostate cancer between 1989 and 2003 (N=9,340), 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 (N=629). 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.

Cancer anxiety. 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]

The original scale was intended to measure fear of recurrence in persons who have been treated for cancer. In the current study, we examine responses to 3 of the items on the scale relevant to men on active surveillance. The 3 items included “Because cancer is unpredictable, I feel I cannot plan for the future,” “My fear of having my cancer getting worse gets in the way of my enjoying life,” and “I am afraid of my

cancer getting worse." In CaPSURE, the original 5-response Likert-type scale was used, with options from "Strongly agree" to "Strongly disagree." These 3 items are now part of the 4-item fear of recurrence subscale of the Memorial Anxiety Scale for Prostate Cancer.[46] In the previous CaPSURE analysis, raw scale scores were reversed and transformed from a 5 to 25 scale to a 0 to 100 scale to make the scores easier to compare to scores from health-related quality of life instruments where higher scores represent better functioning. In this analysis, however, scores were *not* reversed, meaning higher scores indicated greater anxiety about cancer. The 3-item measure 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.

Statistical analysis. Decisions to move from 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. To calculate, the change in anxiety we adapted the 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 analyzed PSA and Gleason scores as both continuous measures and using categories determined to be important in our previous studies.

Clinical risk was based on a modification of the risk groups defined by D'Amico et al.[47] Patients were considered low risk if they had PSA ≤ 10ng/ml, Gleason sum < 7 with no primary or secondary Gleason of 4 or 5, and clinical T-stage T1-T2a; intermediate risk if they had PSA 10.1-20 ng/ml or Gleason sum 7 or Gleason secondary 4 or 5, or T-stage cT2b-2c; and high risk if they had PSA > 20 ng/ml, or Gleason sum > 7 or Gleason primary 4 or 5, or T-stage cT3a. We also characterized risk using a newer technique – the Cancer of the Prostate Risk Assessment (CAPRA) score, which combines preoperative PSA, Gleason score, clinical T stage, biopsy results and age into an easily computed measure with predictive accuracy similar to the Kattan nomogram.[48]

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

model to control for disease progression. All analyses were performed with version 9.1 of SAS software.

Results

Baseline analyses

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. Men in this study were generally older (> 75 years), well-educated (47% had some college), and white (96%; **Table 1**). 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 (**Table 2**). Accordingly, there were no significant differences between groups in either the D'Amico risk classification or CAPRA scores, although the proportion of men classified as high risk using the D'Amico algorithm was higher in the men who were eventually treated (21% vs. 12%). Most men had one or more comorbid conditions and more than half were overweight or obese. At baseline, men who were later treated reported somewhat higher cancer anxiety but the difference was not significant.

Longitudinal analyses

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 (**Table 2**, $p < .06$). **Figure 1** shows the mean PSA readings over time by group. The differences in anxiety velocity were larger: 0.39 for men who sought treatment vs. -0.25 for those who did not ($p < 0.001$). **Figure 2**

shows the mean cancer anxiety scores over time for each group. The negative anxiety velocity for the untreated men is reflected in the general downward slope for their line, while the line for treated men slopes upward. One possibility was that a man's anxiety was tightly linked to his rising PSA. To understand the relationship between the 2 velocity measures, we calculated the Pearson product-moment correlation, which was modest (0.30, $p < .001$).

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 ($p < .05$).

Discussion

Men diagnosed with localized prostate cancer who select surveillance in lieu of active treatment face an ongoing series of repeated PSA tests and other diagnostic procedures usually culminating in a decision to undergo active treatment within a few years of their initial diagnosis. This process can raise men's anxiety about their current and future health, and cause substantial distress.[27] We examined the relationship between anxiety about cancer and time to active treatment for men on surveillance for localized prostate cancer. Clinical disease status information was collected upon entry to the study. Anxiety was measured using 3 questions from a previously validated measure of fear of recurrence at baseline and at 6-month intervals. PSA data were collected at baseline and over time as further PSA testing was performed. Using

survival analysis, we modeled time to active treatment for men who where treated during the observation period versus those who were not. After controlling for baseline sociodemographic and clinical characteristics, disease progression as represented by the rate of change in PSA over time (PSA velocity), we found the rate of change in anxiety (anxiety velocity) was an independent predictor of time to treatment. That is, some men's increasing anxiety caused them to be treated sooner than an objective measure of disease progression indicated was necessary.

Previous studies have found heightened anxiety in men on surveillance.[27, 43, 49] Our current results extend these previous findings in several ways. One study reported patients requesting treatment because of anxiety in spite of no objective evidence of disease progression.[43] However, it is unclear how anxiety was assessed. It may be that the patient's anxiety was simply noted during a clinical interview. While the 3-item measure used in the current study has not yet been validated, it is a subset of a 5-item measure that has been validated in men with prostate cancer.

Other studies focusing on distress in men on surveillance have been based on Mishel's Uncertainty in Illness theory.[50] The theory states illness increases uncertainty about one's current status and the future and heightens psychological distress, leading to decrements in quality of life. These studies, while based on small samples, have provided valuable insight into the antecedents of uncertainty and have shown signficiant reductions in uncertainty through increased cognitive reframing and improvements in quality of life.[24, 27, 49] What is unclear from their work is whether increase in cognitive reframing and improvements in quality of life were sufficient to encourage men on

surveillance to defer treatment till medically necessary. Building on their research and the results presented in this paper, further work is needed to understand the effect of reducing uncertainty on treatment decision-making and healthcare utilization. Another study has shown that uncertainty varies by ethnicity,[51] meaning new interventions to reduce uncertainty and anxiety must be tailored for different ethnic groups and take into account existing differences in treatment preferences and utilization by ethnic groups and literacy level.[52]

Some limitations of our study must be noted. The CaPSURE data base, while geographically diverse, may not adequately represent the modal U. S. prostate cancer patient. Because little work has been done on anxiety in men on surveillance, no measures of cancer anxiety have been validated in this population. The 5-item version of the measure included in the CaPSURE questionnaire had been used in other studies of cancer patients and has been incorporated into a new validated measure, the Memorial Anxiety Scale for Prostate Cancer, which also focuses on men who have been treated.[46]

Strengths of our study include the predominance of community-based urology patients in the sample, rather than being limited to academic series. Men are enrolled from sites in 25 states representing each area of the U. S. Clinical data are collected on standardized forms and our primary variable of interest (anxiety) was measured with a standardized, paper-and-pencil measure. One particular strength of the CaPSURE database is the longitudinal nature of the study, allowing the test of hypotheses such as the one examined in this paper.

Conclusions

Rather than being based solely on clinical disease progression, men may allow cancer-related anxiety to influence decisions about treatment timing. Further work is needed to determine whether providing men with more psychosocial support could active treatment and the ensuing decrements in health-related quality of life.

Table 1 Socio-Demographic Characteristics

	Overall		No active treatment N=84		Active treatment N=32		p-value
	N	(%)	N	(%)	N	(%)	
Age at diagnosis							0.27
<75	38	33	30	36	8	25	
>=75	78	67	54	64	24	75	
Mean age at diagnosis (SD)	75.6 (5.92)		75.2 (6.12)		76.5 (5.32)		0.28
Ethnicity							0.91
White	112	97	81	96	31	97	
Other	4	3	3	4	1	3	
Education							0.24
<HS	27	25	16	20	11	37	
HS graduate	36	33	28	35	8	27	
Some college	19	17	16	20	3	10	
College graduate	28	25	20	25	8	27	
Income							0.98
<$30,000	42	48	30	48	12	48	
$30,000-50,000	22	25	16	26	6	24	
$50,000-75,000	11	13	8	13	3	12	
>$75,000	12	14	8	13	4	16	
Relationship status							0.28
In relationship	93	84	66	81	27	90	
Single	18	16	15	19	3	10	
Insurance status							0.69
Medicare Supplement	58	53	41	53	17	53	
Medicare	21	19	15	19	6	19	
Private	15	14	12	16	3	9	
Other	15	14	9	12	6	19	

Table 2. Clinical characteristics

	Overall		No active treatment N=84		Active treatment N=32		p-value
	N	(%)	N	(%)	N	(%)	
Anxiety at baseline, Mean (SD)	29.6 (20.79)		30.7 (21.19)		26.7 (19.83)		0.38
PSA category at diagnosis							
<=4	16	16	13	18	3	10	
4.1-10	57	55	42	57	15	52	
10.1-20	25	24	16	22	9	31	
>20	5	5	3	4	2	7	
PSA at diagnosis, Mean (SD)	8.4 (6.06)		8.1 (6.33)		9.1 (5.35)		0.43
T-stage at diagnosis							0.30
1	75	68	57	71	18	58	
2	35	32	22	28	13	42	
3	1	1	1	1	0	0	
Gleason total							0.35
2-4	12	11	10	13	2	6	
5-6	78	70	57	71	21	68	
7	18	16	12	15	6	19	
8-10	3	3	1	1	2	6	
Gleason group							0.26
no 4-5	90	81	67	84	23	74	
1-3/4-5	11	10	8	10	3	10	
4-5/1-5	10	9	5	6	5	16	
Gleason at diagnosis, Mean (SD)	5.9 (0.99)		5.8 (1.02)		6.1 (0.91)		0.20
Risk category							0.19
Low	53	52	42	58	11	38	
Intermediate	34	33	22	30	12	41	
High	15	15	9	12	6	21	
CAPRA score, Mean (SD)	3.6 (1.61)		3.4 (1.58)		3.8 (1.68)		0.25

	Overall		No active treatment N=84		Active treatment N=32		p-value
	N	**(%)**	**N**	**(%)**	**N**	**(%)**	
Comorbidities							0.81
None	11	10	8	10	3	10	
1-2	48	44	34	42	14	48	
3+	51	46	39	48	12	41	
BMI category							0.63
Normal (<25.0)	45	42	35	44	10	34	
Overweight (25.0-29.9)	45	42	31	39	14	48	
Obese (30.0+)	18	17	13	16	5	17	
PSA velocity, Mean (SD)	0.01 (0.27)		-0.02 (0.29)		0.09 (0.21)		< .06
Anxiety velocity, Mean (SD)	-0.08 (1.03)		-0.25 (1.08)		0.39 (0.71)		< .01

Table 3. Cox regression model predicting 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			

Figure 1. Mean PSA values over time for patients who received active treatment vs. those who did not

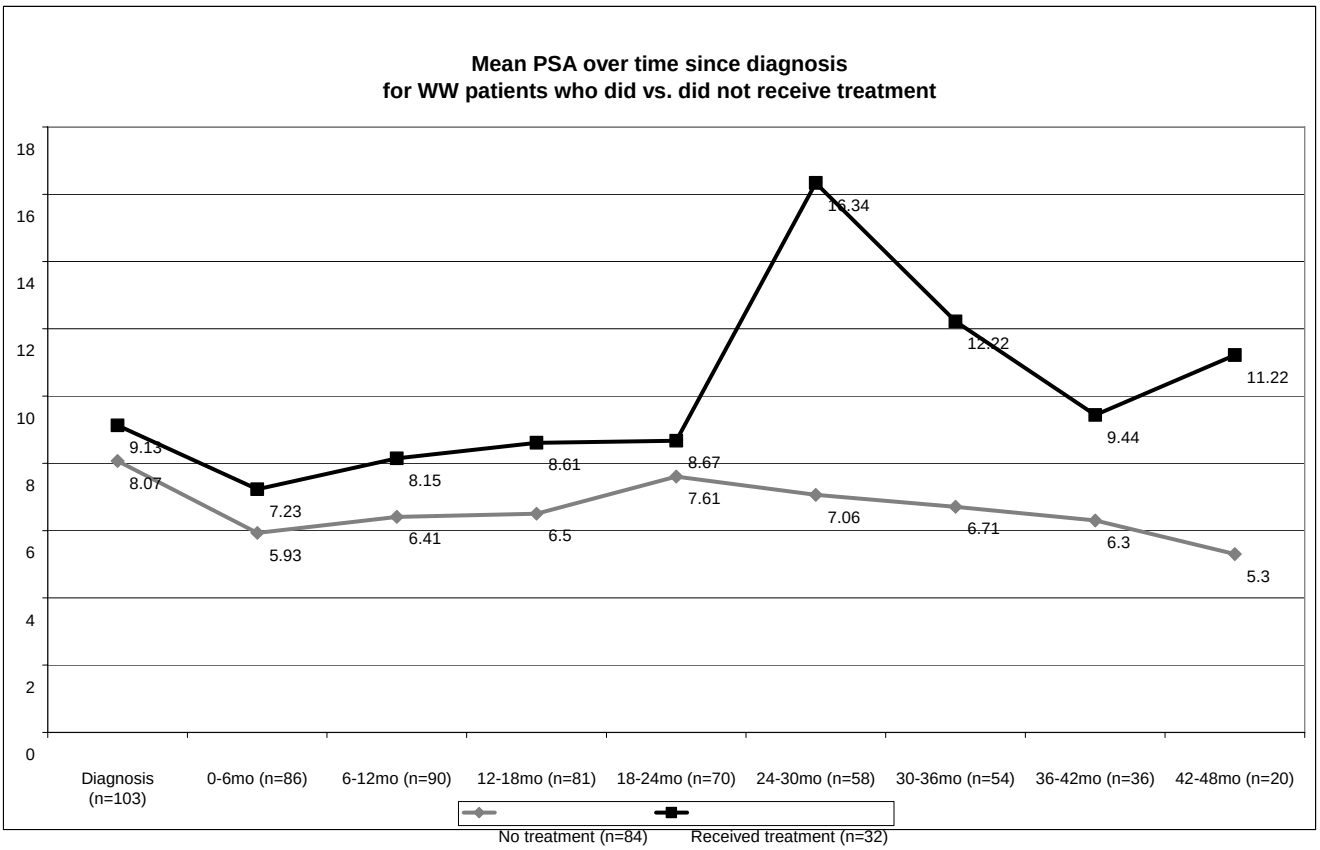
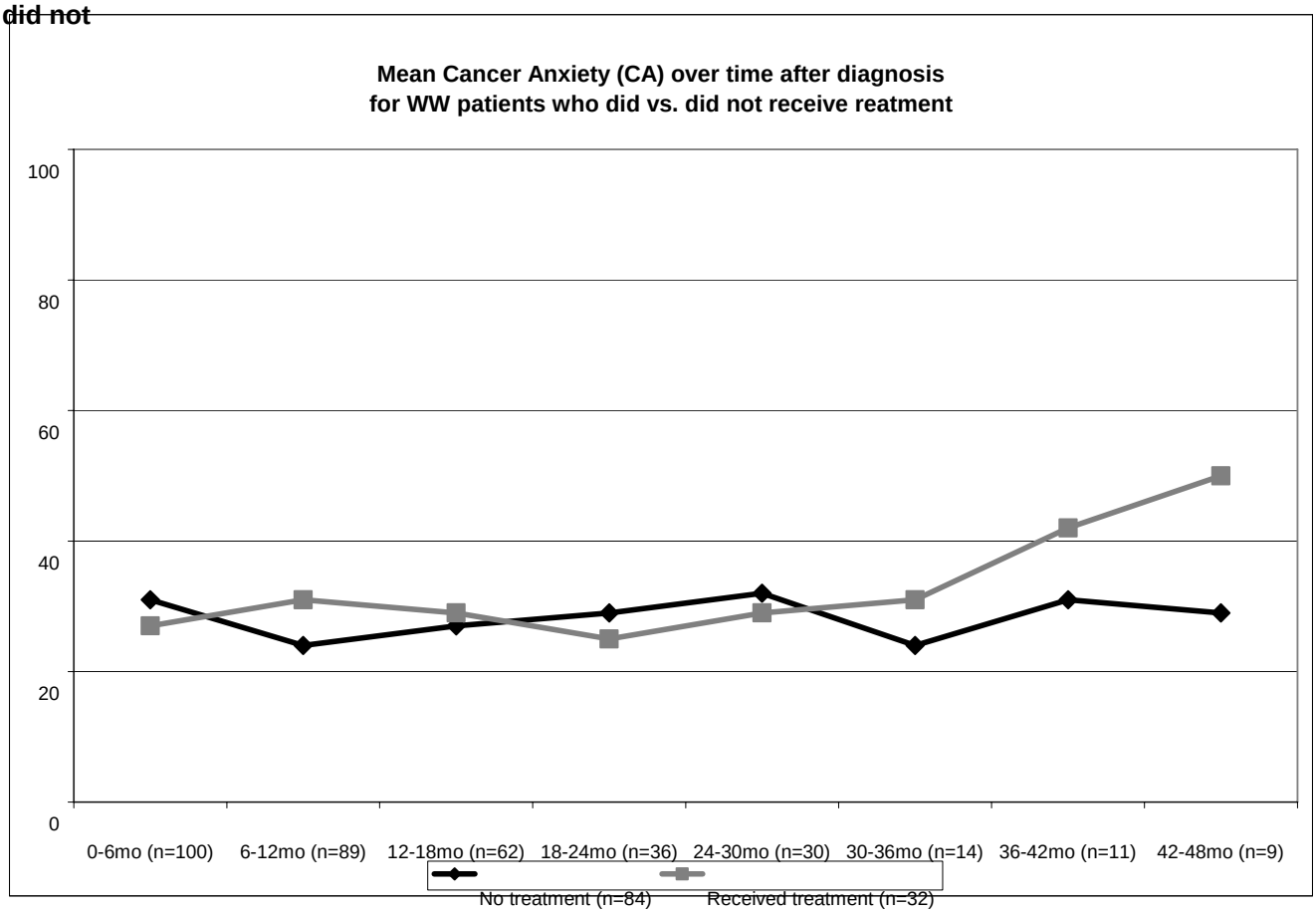


Figure 2. Mean cancer anxiety over time for patients who received active treatment vs. those who did not



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