Original Article

Fear of Cancer Recurrence and Disease Progression in Long-Term Prostate Cancer Survivors After Radical Prostatectomy: A Longitudinal Study

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BACKGROUND: Although fear of cancer recurrence (FCR) or disease progression is among the most endorsed unmet needs and concerns of cancer survivors, research on the course of FCR in long-term survivors is scarce. The objective of this study was to assess longitudinally the prevalence and predictors of FCR in long-term prostate cancer (PCa) survivors. **METHODS:** In all, 2417 survivors from the multicenter German Familial Prostate Cancer Database completed the Fear of Progression Questionnaire–Short Form on average 7 years (T1 in 2010) after radical prostatectomy and at follow-up 9 years later (T2 in 2019). Hierarchical multivariable logistic regression was used to assess predictors of FCR at follow-up. **RESULTS:** The mean age at the initial assessment was 69.5 years (standard deviation, 5.9 years); 6.5% and 8.4% of patients reported clinical FCR at the initial assessment (T1) and at the follow-up (T2), respectively. In a multivariable analysis controlling for concurrent associations, longitudinal predictors of FCR 9 years later included a lower level of education (odds ratio [OR], 4.35; 95% confidence interval [CI], 2.33-8.33), years since radical prostatectomy (OR, 1.10; 95% CI, 1.03-1.18), biochemical recurrence (OR, 1.67; 95% CI, 1.02-2.72), no current adjuvant therapy (OR, 2.38; 95% CI, 1.19-4.76), FCR (OR, 10.75; 95% CI, 6.18-18.72), and anxiety (OR, 1.35; 95% CI, 1.06-1.72). **CONCLUSIONS:** FCR remains a burden to certain PCa survivors even many years after their diagnosis and treatment. Health care professionals should monitor for FCR and identify patients at risk to provide appropriate psychosocial care because FCR is leading to limitations in quality of life and psychological well-being. ***Cancer* 2021;127:4287-4295**.

KEYWORDS: fear of cancer recurrence, longitudinal study, prostate cancer, radical prostatectomy, survivorship.

INTRODUCTION

Prostate cancer (PCa) is the second most frequently diagnosed cancer in men in the United States and Europe.[1,2] In light of high survival rates that translate PCa survivorship into a long-lived experience, improvements in quality of life (QOL) and psychological well-being are fundamental considerations in care after diagnosis and treatment. Recent research has shown that fear of cancer recurrence (FCR) or disease progression is among the most commonly endorsed unmet needs and concerns in cancer survivors, and it is frequently accompanied by a clinically significant impact on QOL.[3-5] FCR has been defined as "fear, worry, or concern about cancer returning or progressing," and such fears can arise at diagnosis and continue throughout the survivorship trajectory.[6] A moderate amount of FCR has been found to promote adequate screening uptake, whereas too little or too much FCR can lead to avoidance of screening uptake and maintenance to identify recurrence in a timely fashion.[7,8]

A longitudinal study of 519 patients with PCa found a significant decline in FCR after treatment followed by stable levels over the subsequent 2 years.[9] A cross-sectional study in long-term PCa survivors with a median postsurgery follow-up of 7.1 years found that a third still suffered from high levels of FCR, with younger age, lower QOL, distress, and the receipt of adjuvant radiotherapy being associated with high FCR.[10]

To date, previous research on FCR in PCa survivors has mostly focused on short-term follow-up care after diagnosis and treatment. Longitudinal studies examining risk factors for long-term FCR in PCa survivors surviving

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decades and more because of improved treatment are needed to improve patient management, surveillance, and psychological care. Thus, on the basis of a large sample of long-term PCa survivors after radical prostatectomy (RP), the objectives of this study were to 1) assess the prevalence of FCR, 2) prospectively evaluate changes in the trajectory of FCR over a 9-year period, and 3) identify and assess predictors of high FCR in long-term PCa survivors.

MATERIALS AND METHODS

Database and Study Procedure

The current analysis is based on data from the multicenter German Familial Prostate Cancer Database, which comprises more than 36,000 index patients and their relatives. Since 1993, this prospective study has consecutively recruited and surveyed newly diagnosed patients with PCa independently of their family history. Patients are referred by urologists and cooperating clinics throughout Germany. Briefly, the database is updated annually via questionnaires providing information about sociodemographic and clinicopathological data as well as family history. Relatives subsequently diagnosed with PCa are included in the database. Informed consent is obtained from each patient. The study was approved by the ethical review committee of the Technical University of Munich. More detailed descriptions of the database itself have been provided previously.[11,12]

For the current analysis, the eligibility criteria included 1) RP as the primary treatment and 2) the submission of FCR questionnaires in October 2010 (T1) and October 2019 (T2). The response rate was 63.0% in 2010 (at the T1 assessment) and 61.7% in 2019 (at the T2 assessment). A nonresponder analysis in 2010 showed that the 3566 patients who did not return the annual questionnaire (n = 2544) or did not fill out questions on FCR (n = 1022) were older at the survey (72.9 vs 71.6 years; $P < .001$) and at RP (64.2 vs 63.7 years; $P = .001$) and more often had locally advanced disease (37.7% vs 32.5%; $P < .001$) and biochemical recurrence (BCR; 45.4% vs 31.0%; $P < .001$) in comparison with respondents in 2010 (T1; n = 6072). The dropout analysis in 2019 (at the T2 assessment) showed that the 1502 patients who did not return the annual questionnaire (n = 691) or did not fill out questions on FCR (n = 811) differed significantly in their age at the survey (80.7 vs 78.4 years; $P < .001$) and at RP (63.8 vs 62.1 years; $P < .001$) and more often had locally advanced disease (31.5% vs 28.4%; $P = .036$) and BCR between 2010 and 2019 (40.1% vs 36.9%; $P = .046$) in comparison with respondents in 2019. In addition, depressive symptoms (7.8% vs 4.8%) and anxiety symptoms (7.7% vs 4.9%) in 2010 were more prevalent ($P < .001$) in nonrespondents in comparison with respondents in 2019 (n = 2417), but FCR did not differ (mean Fear of Progression Questionnaire–Short Form [FoP-Q-SF] score, 21.7 vs 21.2; $P = .136$; Supporting Table 1). Figure 1 outlines the flow of PCa survivors through the study.

Measures

Fear of cancer recurrence

We used the 12-item short version of the Fear of Progression Questionnaire (FoP-Q-SF), which is a validated and reliable instrument to measure fear of disease progression in chronically ill persons as well as FCR in patients with cancer.[13,14] Items are scored on a 5-point Likert scale ranging from 1 (never) to 5 (very often), with higher values indicating higher levels of fear. High FCR was defined as an FoP-Q-SF total score of 34 or higher.[15] The Cronbach α values in the current sample were 0.88 and 0.87 in 2010 (T1) and 2019 (T2), respectively.

Sociodemographic characteristics

Sociodemographic characteristics included age at the survey in 2010 and 2019 (≤70, <70 to 80, or >80 years), level of education (low, intermediate, high, or tertiary), partnership (yes vs no), and children (yes vs no).

Clinicopathological characteristics

Clinicopathological characteristics included age at RP (≤55, <55 to 65, or >65 years), years since RP (≤5, <5 to 10, <10 to 15, <15 to 20, or >20 years), prostate-specific antigen (PSA) level at diagnosis (ng/mL), organ-defined disease, positive PCa family history (defined as a patient with at least 1 affected relative with PCa), secondary cancer, BCR (defined as a PSA value ≥ 0.2 ng/mL) between RP and 2010 and between 2010 and 2019, and current therapy (radiation, androgen deprivation, and chemotherapy vs none) in 2010 and 2019. Depression and anxiety symptoms were assessed with the Patient Health Questionnaire 4 module, an ultrabrief screening tool consisting of a 2-item depression scale (Patient Health Questionnaire 2 [PHQ-2]) and a 2-item anxiety scale (Generalized Anxiety Disorder 2 [GAD-2]). The German version

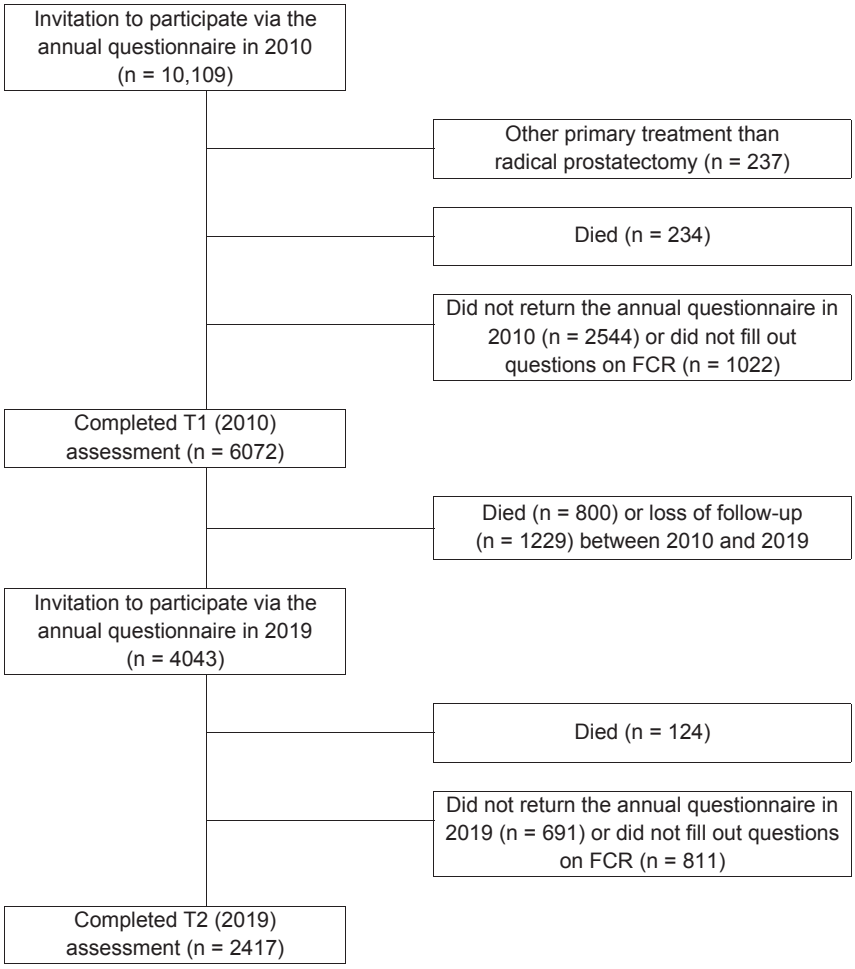

Figure 1. Flowchart of the study design and number of participants. FCR indicates fear of cancer recurrence.

has been proven to be reliable and valid, with a cutoff score ≥ 3 indicating clinical levels of depression and anxiety.[16] The Cronbach α coefficients in the current sample were 0.79 and 0.66 for the depression scale and 0.77 and 0.75 for the anxiety scale in 2010 and 2019, respectively.

Statistical Analysis

Descriptive statistics calculating counts and percentages for categorical variables and means and standard deviations (SDs) for continuous variables were used to present participant characteristics in 2010 (T1) and in 2019 (T2). In accordance with previous studies,[17-19] patients were categorized into 4 subgroups based on the cutoff score of our measure: resilient (stable low; low FCR in 2010 and 2019), incident (low FCR in 2010 and high FCR in 2019), recovered (high FCR in 2010 and low FCR in 2019), and chronic (stable high; high FCR in 2010 and 2019). Group differences were analyzed with χ^2 or Fisher exact tests for categorical variables and with analyses of variance or Wilcoxon-Mann-Whitney tests for continuous variables. Hierarchical multivariable logistic regression models were calculated to identify and assess predictors of FCR in 2019 via characteristics available in 2010 (step 1) and via characteristics available in 2019 (step 2). FCR was dichotomized, and clinical FCR was defined as a total FoP-Q-SF score of 34 or higher. In addition to the logistic approach, a linear multivariable regression analysis was conducted as a sensitivity analysis assessing FCR as a continuous variable. Likert-scaled predictors were entered into the regression analyses as continuous variables. All tests were 2-sided. P values $< .05$ were considered statistically significant. All analyses were performed with SAS 9.4.

TABLE 1. Sociodemographic, Clinicopathological, and Psychological Characteristics of the Study Population (N = 2417)

	T1 (2010)	T2 (2019)
Sociodemographic characteristics		
Age at survey, mean (SD), y	69.5 (5.9)	78.4 (5.9)
Age at survey, No. (%)		
≤70 y	1176 (48.7)	221 (9.1)
>70 to 80 y	1187 (49.1)	1174 (48.6)
>80 y	54 (2.2)	1022 (42.3)
Level of education, No. (%)		
Low	928 (39.5)	
Intermediate	416 (17.7)	
High	280 (11.9)	
Tertiary	728 (30.9)	
Partnership, No. (%)		
Yes	2256 (94.6)	2240 (92.8)
No	129 (5.4)	173 (7.2)
Children, No. (%)		
Yes	2147 (89.0)	
No	266 (11.0)	
Clinicopathological characteristics		
Age at RP, mean (SD), y	62.1 (5.9)	
Age at RP, No. (%)		
≤50 y	298 (12.3)	
>55 to 65 y	1314 (54.4)	
>65 y	805 (33.3)	
Years since RP, mean (SD)	7.3 (3.1)	16.3 (3.1)
Years since RP, No. (%)		
≤5	667 (26.6)	
>5 to 10	1309 (54.2)	
>10 to 15	392 (16.2)	1030 (42.6)
>15 to 20	49 (2.0)	1099 (45.5)
>20		288 (11.9)
PSA at diagnosis, median (IQR), ng/mL	7.3 (6.0)	
PSA at diagnosis, No. (%)		
≤4 ng/mL	218 (9.6)	
>4 to 10 ng/mL	1353 (59.9)	
>10 ng/mL	688 (30.5)	
Organ-defined disease, No. (%)		
Yes	1706 (71.7)	
No	675 (28.3)	
Secondary cancer, No. (%)		
Yes	103 (4.3)	331 (13.7)
No	2314 (95.7)	2086 (86.3)
Positive PCa family history, No. (%)		
Yes	799 (33.1)	910 (37.6)
No	1618 (66.9)	1507 (62.4)
BCR between RP and 2010 (T1), No. (%)		
Yes	610 (25.2)	—
No	1807 (74.8)	—
BCR between 2010 (T1) and 2019 (T2), No. (%)		
Yes	—	274 (12.7)
No	—	1890 (87.3)
Current therapy		
Yes	223 (9.2)	318 (13.2)
No	2194 (90.8)	2098 (86.8)
Psychological characteristics		
Fear of cancer recurrence, mean (SD)	21.2 (7.3)	22.2 (7.4)
Fear of cancer recurrence, No. (%)		
Yes	156 (6.5)	202 (8.4)
No	2261 (93.5)	2215 (91.6)
Depression, No. (%)		
Yes	115 (4.8)	336 (14.3)
No	2259 (95.2)	2013 (85.7)
Anxiety, No. (%)		
Yes	116 (4.9)	247 (10.6)
No	2256 (95.1)	2089 (89.4)

Abbreviations: BCR, biochemical recurrence; IQR, interquartile range; PCa, prostate cancer; PSA, prostate-specific antigen; RP, radical prostatectomy; SD, standard deviation.
The presented numbers are from the completed entries and do not always add up to the total sample size. The maximum percentage of missing data is 10.5%.

RESULTS

Characteristics of the Study Population

Sociodemographic, clinicopathological, and psychological characteristics of the study population of 2417 former RP patients in 2010 (T1) and in 2019 (T2) are presented in Table 1. The mean age at the initial assessment in 2010 was 69.5 years (SD, 5.9 years); 11.9% had a high level of education, and 30.9% had a tertiary level of education. The mean time since RP was 7.3 years (SD, 3.1 years) in 2010 and 16.3 years (SD, 3.1 years) in 2019; 25.2% of the patients had BCR between RP and 2010, and 12.7% did between 2010 and 2019.

At the initial assessment in 2010, 6.5% of the patients had high FCR, and this percentage increased to 8.4% 9 years later ($P = .001$). The average total short form score out of a total of 60, with higher values indicating greater fear, for the population was 21.2 (SD, 7.3) and 22.2 (SD, 7.4) in 2010 and 2019, respectively. The prevalences of clinical levels of depression (PHQ-2 score ≥ 3) and anxiety (GAD-2 score ≥ 3) were 4.8% and 4.9%, respectively, in 2010 and 14.3% and 10.6%, respectively, in 2019 (Table 1).

As shown in Table 2, most patients (88.4%) reported low FCR in 2010 (T1) and 2019 (T2; "resilient"), 3.2% had high FCR at both time points ("chronic"), 5.2% reported low FCR in 2010 but high FCR in 2019 ("incident"), and 3.2% had high FCR in 2010 and low FCR in 2019 ("recovered"). Almost two-thirds of the chronic subgroup (66.2%) reported a low level of education, whereas one-third (33.1%) of the resilient subgroup reported a tertiary level of education ($P < .001$). Patients in the resilient subgroup more often had organ-defined disease in comparison with patients from the other groups ($P = .012$). Both depression and anxiety showed the highest prevalence in the chronic subgroup ($P < .001$; Table 2).

Hierarchical Multivariable Logistic Regression Analysis

To investigate long-term predictors of FCR, patient factors measured in 2010 (T1) were tested for an

TABLE 2. Distribution of Characteristics Among 4 Patient Subgroups According to Their Fear of Cancer Recurrence Between 2010 and 2019

Characteristic	Chronic (n = 78 [3.2%])	Incident (n = 124 [5.2%])	Recovered (n = 78 [3.2%])	Resilient (n = 2137 [88.4%])	*P*
Level of education					<.001
Low	66.2	57.9	45.2	37.2	
Intermediate	16.2	16.5	15.1	17.9	
High	13.5	12.4	13.7	11.8	
Tertiary	4.1	13.2	26.0	33.1	
Partnership					
In 2010 (T1)	97.4	93.6	98.7	94.4	.267
In 2019 (T2)	96.2	91.9	98.7	92.6	.101
Children	92.3	93.6	94.9	88.4	.069
Age at RP, mean (SD), y	60.0 (6.4)	63.0 (5.6)	58.4 (6.2)	62.3 (5.9)	<.001
Years since RP, mean (SD)	7.0 (2.8)	7.9 (3.4)	6.9 (3.0)	7.3 (3.1)	.167
PSA at diagnosis					.544
≤4 ng/mL	8.0	5.2	9.7	10.0	
>4 to 10 ng/mL	60.0	66.7	54.2	59.7	
>10 ng/mL	32.0	28.1	36.1	30.3	
Organ-defined disease	61.5	62.3	65.3	72.7	.012
Secondary cancer					
In 2010 (T1)	1.3	4.8	6.4	4.3	.404
In 2019 (T2)	14.1	16.9	14.1	13.5	.751
Positive PCa family history					
In 2010 (T1)	34.6	29.8	32.1	33.2	.867
In 2019 (T2)	42.3	31.5	38.5	37.8	.424
BCR between RP and 2010 (T1)	39.7	42.7	37.2	23.3	<.001
BCR between 2010 (T1) and 2019 (T2)	14.5	15.5	8.0	12.6	.479
Current therapy					
In 2010 (T1)	15.4	12.9	23.1	8.3	<.001
In 2019 (T2)	24.4	30.7	20.5	11.5	<.001
Depression					
In 2010 (T1)	39.5	5.9	27.0	2.8	<.001
In 2019 (T2)	48.7	44.2	31.2	10.7	<.001
Anxiety					
In 2010 (T1)	42.7	7.6	32.9	2.4	<.001
In 2019 (T2)	42.1	42.0	20.5	7.2	<.001

Abbreviations: BCR, biochemical recurrence PCa, prostate cancer; PSA, prostate-specific antigen; RP, radical prostatectomy; SD, standard deviation.
All numbers are percentages except where indicated.

association with high FCR 9 years later in 2019 (T2) via a multivariable logistic regression including all as main effects (Table 3, step 1). Higher levels of education were strongly associated with a lower risk of FCR (tertiary level of education odds ratio [OR], 0.24; 95% confidence interval [CI], 0.14-0.41). A higher age at RP (OR, 1.05; 95% CI, 1.01-1.08) and more years since RP (OR, 1.09; 95% CI, 1.03-1.15) were both associated with a higher risk of FCR 9 years later. BCR and anxiety between RP and 2010 predicted higher FCR 9 years later (OR for BCR, 1.87; 95% CI, 1.28-2.71; OR for anxiety, 1.62; 95% CI, 1.31-2.01; Table 3, step1). High FCR in 2010 was the strongest predictor of FCR in 2019 (OR, 9.31; 95% CI, 5.70-15.20).

To control for concurrent risk factors in 2019 (T2) in addition to the long-term predictors in 2010 (T1), risk factors measured in 2019 in addition to those measured in 2010 were entered into a second logistic regression model for FCR in 2019. A tertiary level of education remained a strong predictor for low FCR (OR, 0.23; 95% CI, 0.12-0.43). Age at RP no longer showed an association with a higher risk of FCR when factors at T2 were added. Patients under PCa therapy in 2010 had a lower risk for FCR in 2019 (OR, 0.42; 95% CI, 0.21-0.84), whereas patients under PCa therapy in 2019 had a nearly 3 times higher risk of high FCR at 2010 (OR, 2.82; 95% CI, 1.59-5.00). High FCR in 2010 was the strongest predictor of FCR in 2019 (OR, 10.75; 95% CI, 6.18-18.72). Anxiety in 2010 (OR, 1.35; 95% CI, 1.06-1.72) and 2019 (OR, 1.69; 95% CI, 1.37-2.09) was associated with higher FCR in 2019. Depression in 2010 was not associated with FCR in 2019 (OR, 0.82; 95% CI, 0.63-1.06), but depression in 2019 was associated with a higher risk of FCR in 2019 (OR, 1.45; 95% CI, 1.19-1.78; Table 3).

Results of the additional linear regression analysis, which was conducted as a sensitivity analysis, largely confirmed previous results. In particular, those variables with

TABLE 3. Hierarchical Multivariable Logistic Regression Analysis to Test for FCR at T2

	Step 1			Step 2		
	OR	95% CI	*P*	OR	95% CI	*P*
Level of education (reference: low)			<.001			<.001
Intermediate	0.75	0.48-1.19		0.65	0.37-1.12	
High	0.62	0.37-1.05		0.56	0.31-1.01	
Tertiary	0.24	0.14-0.41		0.23	0.12-0.43	
Age at RP[a]	1.05	1.01-1.08	.004	1.02	0.99-1.06	.228
T1: years since RP[a]	1.09	1.03-1.15	.005	1.10	1.03-1.18	.006
T1: secondary cancer (reference: no)	0.81	0.34-1.93	.628	0.47	0.14-1.62	.234
T1: PCa family history (reference: no)	1.04	0.72-1.51	.837	0.49	0.16-1.46	.199
BCR between RP and T1 (reference: no)	1.87	1.28-2.71	.001	1.67	1.02-2.72	.040
T1: current therapy (reference: no)	0.81	0.47-1.41	.460	0.42	0.21-0.84	.015
T1: FCR (reference: no)	9.31	5.70-15.20	<.001	10.75	6.18-18.72	<.001
T1: depression[a]	1.00	0.80-1.25	.996	0.82	0.63-1.06	.123
T1: anxiety[a]	1.62	1.31-2.01	<.001	1.35	1.06-1.72	.015
T2: secondary cancer (reference: no)				1.11	0.59-2.10	.758
T2: PCa family history (reference: no)				2.24	0.77-6.50	.140
BCR between T1 and T2 (reference: no)				1.57	0.86-2.86	.139
T2: current therapy (reference: no)				2.82	1.59-5.00	<.001
T2: depression[a]				1.45	1.19-1.78	<.001
T2: anxiety[a]				1.69	1.37-2.09	<.001

Abbreviations: BCR, biochemical recurrence; CI, confidence interval; FCR, fear of cancer recurrence; OR, odds ratio; PCa, prostate cancer; RP, radical prostatectomy.
[a]Variables were entered continuously.

higher ORs in the logistic regression analysis were confirmed by the linear approach. In contrast to the main analysis, BCR between 2010 and 2019 was associated with higher FCR in 2019 in the linear regression analysis ($\beta = 0.045$; $P = .006$; Supporting Table 2).

DISCUSSION

The primary objectives of the current study were to assess the prevalence and evaluate the trajectory of FCR in long-term PCa survivors and to identify predictors of FCR. After a mean time of 7.3 years (2010; T1) after diagnosis and treatment, 6.5% of the survivors reported high levels of FCR. In 2019 (T2), approximately 9 years later, 8.4% of the survivors reported high FCR; this suggested that FCR increased slightly over time. A hierarchical multivariable logistic regression analysis revealed several factors in 2010, such as level of education, BCR in the first years after treatment, years since RP, current therapy, FCR, and anxiety, to be important predictors of FCR approximately 9 years later in long-term PCa survivors.

The main results of the current study showed that high FCR in 2010 was the strongest predictor and was associated with a 10-fold increase in the odds of having FCR 9 years later. Therefore, patients should be monitored for FCR early after treatment to identify those at risk and start early psychological interventions; this underlines the clinical implications of the results of the current study. A recent review and meta-analysis of the effect of psychological interventions showed that cognitive behavioral therapies were effective in reducing FCR, with effects maintained at follow-up.[20]

In the current analysis, the prevalence of FCR (6.5% in 2010 and 8.4% in 2019) was lower than rates reported in previous studies. For instance, using the same validated FoP-Q-SF cutoff score, Hinz et al[14] reported that 16.7% of patients with cancer scored high levels of FCR 6 months after their diagnosis. Recently, using the aforementioned cutoff score, Götze et al[21] reported similar rates in long-term cancer survivors. In a 5-year cohort, 19% of the cancer survivors showed high levels of FCR, and 13% did so in a 10-year cohort. However, it is noteworthy that both samples were not restricted to homogeneous subgroups of cancer types. It is well established that the prevalence of FCR is higher in patients with breast, lung, or ovarian cancer than patients with PCa.[22] Similarly, the

mean FoP-Q-SF scores of the current analysis (21.2 in 2010 [T1] and 22.2 in 2019 [T2]) were lower than the mean scores reported in the previous studies of Hinz et al (24.9) and Götze et al (25.1 [5-year cohort] and 23.7 [10-year cohort]). In a prospective study, Mehnert et al[23] reported that at the beginning of cancer rehabilitation, on average 11 months after diagnosis, approximately 18% of patients with cancer reported high FCR. After 1 year, this rate remained almost stable, and 17% still had high levels of FCR. However, the prevalence rates and severity of FCR must be interpreted with caution because FCR is usually not experienced constantly and can be triggered by specific situations, such as clinical check-ups or environmental triggers (eg, television or internet).[24]

Confirming previous research, we observed a strong association between a lower educational level and higher FCR.[22,25,26] The link between level of education and FCR possibly might be due to a better understanding of the disease, more effective coping strategies, or higher standards of living.

In step 1 of the hierarchical multivariable logistic regression analysis, a higher age at RP was associated with higher FCR in 2019. However, this observed effect disappeared when factors of 2019 (T2) were added in step 2. A meta-analysis by Simard et al[22] showed strong evidence that younger age is a consistent predictor of high FCR. However, a closer look revealed that studies showing no significant relationship were mainly investigating samples comprising men (eg, testicular cancer and PCa),[22] and this is in line with our findings. Reasons that younger men may be more vulnerable to FCR include the unexpectedness of cancer and the fact that a diagnosis poses a threat to important life projects such as marriage, having children, and building careers.[27] PCa survivors of the current analysis were approximately 70 years old in 2010 and 79 years old in 2019; therefore, marriage, having children, and building careers might not be relevant factors anymore in their life, and this partly explains the lack of correlation.

A positive family history of PCa and secondary cancers of the patients were both unrelated to FCR among PCa survivors in the current analysis. This finding is in line with previous research.[22,28] Although a positive family history is a well-known risk factor for developing PCa, it is not associated with worse long-term outcomes for PCa survivors.[29]

FCR, however, is present not just in cancer survivors. Partners of patients and family caregivers are also affected by concerns about cancer recurrence. For instance, higher FCR predicted a higher likelihood of PCa screening maintenance among male caregivers.[30] In a longitudinal study investigating the trajectory of FCR from pretreatment to 1 year later in patients with PCa and their spouses, spouses experienced even greater FCR than patients with PCa over time.[31]

Results of the current study revealed interesting findings concerning the role of BCR. BCR between RP and the first assessment in 2010 was associated with higher FCR. This is consistent with most studies in which recurrence or metastatic diagnosis was significantly associated with FCR.[22,32] Late BCR between the first assessment (mean time since RP, 7.3 years) and the second assessment (mean time since RP, 16.3 years) was not associated with higher FCR in the logistic regression analysis. Interestingly, in the linear regression analysis, late BCR was associated with higher FCR. To our knowledge, the current study is the first study investigating the influence of recurrence on FCR in long-term survivors with such a long follow-up. Apparently, indicators of illness severity such as BCR might be losing weight through the survivorship trajectory; however, it is not clear yet to what extent.

Currently receiving therapy (ie, chemotherapy, radiation therapy, or androgen deprivation therapy) in 2019 was associated with almost 3-fold higher odds of FCR. In line with earlier studies, having chemotherapy was associated with higher FCR.[22,25,28,33] Likewise, evidence was observed between radiotherapy and FCR[22,28,34,35] and between hormone therapy and FCR.[21] Interestingly, among survivors of the current study, receiving therapy in 2010 was associated with an even lower risk of FCR 9 years later. A possible explanation for this finding is that having experienced cancer recurrence with a consecutive treatment many years before might lead to the feeling that the treatment was successful and that a new cancer recurrence could be treated the same way.

Depression and anxiety in 2019 were both associated with higher FCR. FCR has continuously been described in the literature as being associated with depression and anxiety, although a causal direction of the relationship is unknown.[36,37] Furthermore, there is evidence that intrusive thoughts, hypochondriasis, symptom distress, or posttraumatic stress disorder is likewise associated with FCR,[21] and this makes FCR the result of different interpretations and cognitions of the threat of cancer.

To date, the current study is the largest registry study assessing the prevalence and predictors of FCR longitudinally over a mean follow-up period of approximately 9 years. This provides information on the perseverance over time of FCR in a representative group of PCa survivors

treated with RP. The fact that we included only patients after RP indicates very rigorous patient selection; however, it allows excellent comparability and precise factor evaluation.

Nevertheless, our study is not devoid of limitations. First, PCa survivors were treated with RP and hence are not representative of all PCa survivors as a result of selection bias. Second, data for the main outcome measures were self-reported and at risk for exaggeration and misrepresentation, and they may have been affected by social desirability reactions. Third, there was a notable number of PCa survivors who were lost to follow-up or did not answer questions on FCR (Fig. 1). These long-term survivors were noncompliant and could have contributed to nonrandom missing data because they may have had greater FCR than those analyzed in the study. Fourth, although the current study was conducted in Germany and some unique cultural aspects might differ in comparison with PCa survivors from other countries, there is currently no evidence that this could influence the experience of FCR in a significant manner. However, other health care systems differ considerably from the German system; these differences may include higher uninsured rates or economic and racial/ethnic disparities leading to unequal access to health and cancer care.[38] Therefore, the results of the current study have to be interpreted with caution and might not be applicable to men with hampered access to health care.

In conclusion, the results of the current study illustrate that FCR is a burden that is still present in some PCa survivors even many years after their diagnosis and treatment. FCR was the strongest predictor of FCR 9 years later. Early monitoring for FCR and the identification of patients at risk are crucial for starting early psychological interventions. A lower level of education, years since RP, BCR in the first years after treatment, no current adjuvant therapy, and anxiety symptoms were further important predictors of FCR in these patients. Therefore, treating health care professionals should be aware of these factors in clinical practice to provide appropriate psychosocial care when needed because FCR is among the most endorsed unmet needs and concerns in cancer survivors leading to limitations in their QOL and psychological well-being.

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AUTHOR CONTRIBUTIONS
Valentin H. Meissner: Conception and design of the study; interpretation of the data; administrative, technical, or material support; drafting of the manuscript; and revision of the manuscript for important intellectual content. **Lisa Olze:** Interpretation of the data, acquisition of the data, and revision of the manuscript for important intellectual content. **Stefan Schiele:** Statistical analysis; administrative, technical, or material support; and revision of the manuscript for important intellectual content. **Donna P. Ankerst:** Statistical analysis; interpretation of the data; administrative, technical, or material support; and revision of the manuscript for important intellectual content. **Matthias Jahnen:** Interpretation of the data and revision of the manuscript for important intellectual content. **Jürgen E. Gschwend:** Study supervision; administrative, technical, or material support; and revision of the manuscript for important intellectual content. **Kathleen Herkommer:** Conception and design of the study, development of methodology, acquisition of the data, study supervision, and revision of the manuscript for important intellectual content. **Andreas Dinkel:** Conception and design of the study, development of methodology, interpretation of the data, drafting of the manuscript, and revision of the manuscript for important intellectual content.

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