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# Risk and associated factors of depression and anxiety in men with prostate cancer: Results from a German multicenter study

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## Abstract

**Objective:** In order to optimize psycho-oncological care, studies that quantify the extent of distress and identify certain risk groups are needed. Among patients with prostate cancer (PCa), findings on depression and anxiety are limited.

**Methods:** We analyzed data of PCa patients selected from a German multi-center study. Depression and anxiety were assessed with the PHQ-9 and the GAD-7 (cut-off ≥7). We provided physical symptom burden, calculated absolute and relative risk (*AR* and *RR*) of depression and anxiety across patient subsets and between patients and the general population (GP) and tested age as a moderator within the relationship of disease-specific symptoms with depression and anxiety.

**Results:** Among 636 participants, the majority reported disease-specific problems (sexuality: 60%; urination: 52%). AR for depression and anxiety was 23% and 22%, respectively. Significant RR were small, with higher risks of distress in patients who are younger (eg, $RR_{depression}$ = 1.15; 95%-CI: 1.06-1.26), treated with chemotherapy ($RR_{depression}$ = 1.46; 95%-CI: 1.09-1.96) or having metastases ($RR_{depression}$ = 1.30; 95%-CI: 1.02-1.65). Risk of distress was slightly elevated compared to GP (eg, $RR_{depression}$ = 1.13; 95%-CI: 1.07-1.19). Age moderated the relationship between symptoms and anxiety ($B_{urination}$ = −0.10, $P$ = .02; $B_{sexuality}$ = −0.11, $P$ = .01).

**Conclusions:** Younger patients, those with metastases or treatment with chemotherapy seem to be at elevated risk for distress and should be closely monitored. Many patients suffer from disease-specific symptom burden, by which younger patients seem to be particularly distressed. Support of coping mechanisms associated with disease-specific symptom burden seems warranted.

**KEYWORDS**
anxiety, cancer, depression, oncology, prostatic neoplasms

# 1 | INTRODUCTION

Prostate cancer (PCa) has a relatively good prognosis with 5-year survival rates exceeding 98% in most affluent countries.[1] Nevertheless, PCa patients may experience particularly high levels of anhedonia (the incapability to experience joy),[2] anxiety related to prostate specific antigen levels[3] or distress by the fact that they remain untreated.[4] Accordingly, a meta-analysis including 27 studies (n = 4494 patients) demonstrated high prevalence rates of both depression and anxiety, but also found considerable differences between studies (depression: 14%-18%; anxiety: 15%-27%).[5] A more recent study (n = 1643) pointed to low depression, but high anxiety rates (6% vs 20%).[6]

Apart from small sample sizes (mostly ≤100), these inconsistencies may be caused by insufficient assessment and reporting of internationally established medical data such as TNM-classification.[5] As a result, few studies stratified their samples by medical characteristics such as type of treatment or disease stage[5] in order to identify groups who suffer from particularly high levels of distress.

Regarding sociodemographic factors, it is still unclear whether depression increases or decreases with age[7,8] or whether age affects only anxiety or depression, respectively.[6,8] As an explanation for these inconsistencies, older and younger patients may differently cope with medical side effects which in turn would result in different psychological reactions.[7,9] Given the high frequency of disease-specific symptoms such as urination and sexual dysfunction[6] and their negative impact on psychological outcomes,[8,10] it may be helpful to investigate whether and how different emotional reactions to these disease-related symptoms may contribute to discrepant age effects in depression and anxiety.

Finally, few previous studies contrasted depression and anxiety in PCa patients with norm values in order to disentangle the effect of cancer-related stressors from general life circumstances.[5]

To overcome some of the limitations outlined above, we investigated depressive and anxious symptomatology in 636 PCa patients selected from a German multi-center study.[11] We (a) comprehensively describe the sample in terms of medical and physical symptom burden, (b) compare depression and anxiety rates between patient subsets, (c) explore the moderating effect of age within the relationship of disease-specific symptoms with depression and anxiety and (d) contrasted depression and anxiety in patients with normative values of the general population.

# 2 | PATIENTS AND METHODS

## 2.1 | Patients and study design

This sample represents a subset of a German multicenter study across all cancer types originally designed to estimate the prevalence of mental disorders in a representative sample of cancer patients.[11] Patients were consecutively recruited from all German clinical care settings, that is, from inpatient hospital wards, outpatient oncology clinics and cancer rehabilitation centers in/around five study centers across all parts of Germany (Freiburg, Hamburg, Heidelberg, Leipzig and Würzburg). The sample was proportionally stratified based on the distribution of incidence rates of tumor entities in Germany. Patients were eligible if they were (a) between 18 and 75 years old, (b) proficient in German and (c) free from cognitive or verbal impairments interfering with their ability to give informed consent. Participants were given the questionnaire in the treatment center, including a pre-stamped envelope to be returned within 2 weeks.

For this sub-study, we selected patients with a confirmed diagnosis of a malignant tumor of the prostate and available PHQ-9 sum score (which was the central screening measure for the overall study).[11]

To compare patients with norm values in depressive (PHQ-9) and anxious (GAD-7) symptomatology, we used representative data sets drawn from the German general population (PHQ-9: n = 5018[12]; GAD-7: n = 5030[13]). Persons in each sample were selected with the random-route-technique sampling persons with respect to *sample point*, *household* within these sample points and *target person* within the household.

The study was approved by all ethics committees (file numbers: Hamburg: 2768; Schleswig-Holstein: 61/09; Freiburg: 244/07; Heidelberg: S-228/2007-50 155 039; Würzburg: 107/07; Leipzig: 200-2007). All participants provided written informed consent in accordance with the Declaration of Helsinki and data were processed according to German data protection laws (§§27-30a BDSG).

## 2.2 | Measures

*Depressive symptomatology* was assessed with the validated German version of the PHQ-9[14,15] based on the DSM-IV criteria of major depression (which remained unchanged in the DSM-5). Patients rate the symptoms over the previous 2 weeks on a four-point Likert-scale from 0 (*not at all*) to 3 (*almost every day*). The sum score ranges from 0 to 27.[14] The diagnostic accuracy of the PHQ-9 among the total study sample was shown to be best (maximum Youden index) at a cut-off ≥7.[16]

*Anxious symptomatology* was assessed via the validated German version of the GAD-7 questionnaire,[17,18] measuring the seven most prominent symptoms of the DSM-IV diagnostic criteria for generalized anxiety disorder over the previous 2 weeks on a four-point Likert scale from 0 (*not at all*) to 3 (*almost every day*). The sum score ranges from 0 to 21. The diagnostic accuracy of the GAD-7 among the total study sample was shown to be best (maximum Youden index) at a cut-off ≥7.[19]

*Physical symptom burden* was assessed using the standardized problem checklist (PL) from the validated German version of the NCCN Distress Thermometer.[20,21] Across the 34 items, patients report whether they were distressed by the respective symptom (yes/no). For the present analysis, we selected the set of physical symptoms (21 items) encompassing both generic (eg, nausea) and PCa-specific (eg, incontinence) symptoms.

*Medical information* was obtained from hospital records and included treatment setting, cancer diagnosis (ICD-10), date of current

cancer diagnosis, tumor stage (UICC TNM classification), type of treatment and information on treatment intention. Performance status was assessed with the ECOG scale.

*Sociodemographic data* including age, relationship, school education and work situation were collected using standardized questionnaires.

## 2.3 | Statistical analyses

In the overall study,[22] non-responders with PCa were identified only based on the broader diagnostic category of *genital organ cancer*. Therefore, all analyses related to non-responders could not be performed specifically for PCa patients, but for all eligible men with genital organ cancers (proportion of PCa patients in this group: 94%). Responder-analyses with respect to age, time since diagnosis, education and treatment setting were conducted via multiple logistic regression models.

Medical information and physical symptom burden was provided via percentages and means.

To assess the risk of depression and anxiety in different subgroups, we stratified the total sample by variables that were chosen according to research gaps[5] and clinical relevance in other oncological studies.[23] In detail, we split the sample by (a) a binary variable which combined all TNM-information into a clinically relevant outcome (*localized* vs *non-localized*; algorithm see Figure S1), (b) occurrence of distant metastases (*yes* vs *no*), (c) completed/ongoing treatment with surgery, radiation, chemotherapy or androgen deprivation therapy (*yes* vs *no*), (d) under active treatment (yes vs not), (e) age (*below* vs *above the median of 67 years*) and (f) time since diagnosis (*below* vs *above the median of 3 months*).

The *absolute risk* (AR) of depression/anxiety was calculated as the prevalence of patients exceeding the respective cut-off (sum score ≥ 7). To statistically compare AR between patients subsets, we calculated *relative risks* (RR)[24] with 95%-confidence intervals (CI) using normal approximation (Wald-method). Analyses of covariance (ANCOVA) with depression and anxiety as continuous variables were applied to check whether factors that led to significant RR remain significant after adjustment for all other significant factors. Multicollinearity of these factors were determined by bivariate correlations.

RR was also used to contrast patients with the comparison groups from the general population (GP), which were matched by gender and age in the ratio 1:1.

For the moderation analyses, we first tested the effect of disease-specific symptoms (urination and sexuality) on depression and anxiety via univariate regression analyses using $f^2$ as effect size.[25] The moderating effect of age (here used as continuous variable) was investigated by analyzing the effect of the interaction terms (age × urination/sexuality) on both depression and anxiety, resulting in four separate models. Significant interaction effects were further investigated via interaction plots.

In this sub-study, missing data for each item of the PHQ-9 and the GAD-7 was ≤1.3% and ≤7.1%, respectively, and sum scores were computed if more than 50% of the respective items were available. Listwise deletion was applied in all analyses. All tests were two-sided, the level of significance was set at .05. Analyses were performed using IBM SPSS Statistics, Version 24 (IBM Corporation, 2016) and R (version 3.5.0, 2018, the R Foundation for Statistical Computing).

## 3 | RESULTS

Out of all eligible men with genital organ cancers, 78% were included for the analyses (Figure 1). Patients more recently diagnosed (OR = 0.99, *P* < .01), better educated (OR = 3.96, *P* < .01) and recruited from rehabilitation centers (OR = 2.29, *P* < .01) were significantly more likely to participate.

Among the participants with PCa, about 75% were classified as T2- or T3-stage, and 9% had metastases (Table 1). Patients were mostly treated with surgery (72%) and radiation (34%). The most frequently reported symptoms were disease-specific, that is, sexual problems (60%) and changes in urination (52%; Figure 2).

Among the total sample, AR for depression and anxiety was 23% and 22%, respectively (Table 2). Across the stratified subsets, AR ranged from 18% to 46% (depression) and from 17% to 29% (anxiety). Younger patients had a higher risk for both depression and anxiety.
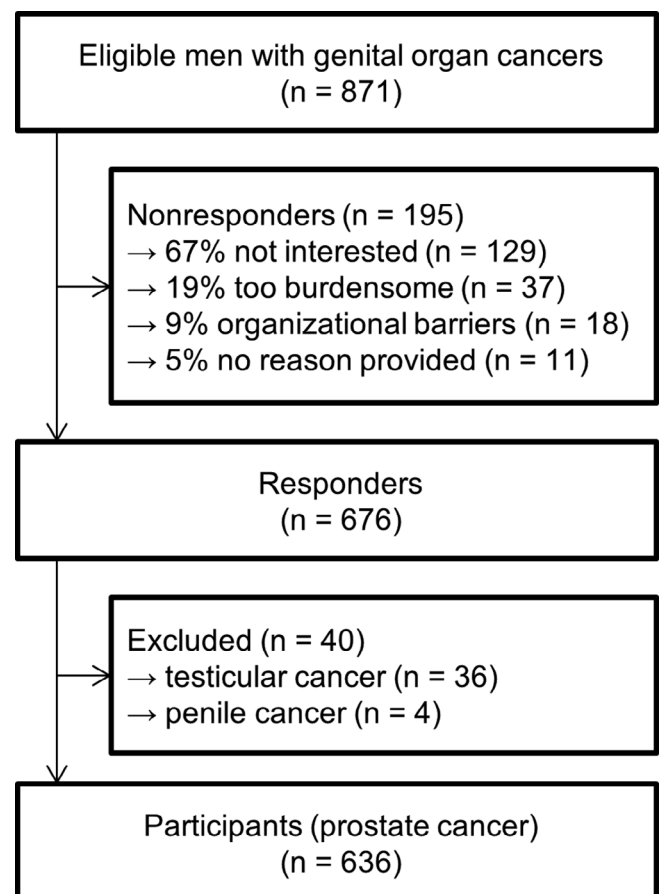


**FIGURE 1** Participant flow including reasons for nonparticipation

**TABLE 1** Sample characteristics among 636 men with prostate cancer

| | Counts |
|---|---|
| | n (valid %) |
| Age, years | |
|     Overall (mean, SD) | 65 (7) |
|     ≤55 | 59 (9) |
|     56 to 65 | 231 (36) |
|     66 to 75 | 343 (54) |
| In a relationship | |
|     No | 54 (9) |
|     Yes | 532 (91) |
| School education, years | |
|     ≤10 | 340 (53) |
|     >10 | 296 (47) |
| Work situation | |
|     Employed | 188 (30) |
|     Unemployed | 57 (9) |
|     Retired | 387 (61) |
|     Husband | 4 (1) |
| Months since diagnosis (mean, SD) | 11 (19) |
| Cancer care setting | |
|     Inpatient | 298 (47) |
|     Outpatient | 191 (30) |
|     Rehabilitation | 147 (23) |
| TNM-T[a] | |
|     Tis: in situ | 1 (<1) |
|     T1: too small to be scanned or felt | 52 (8) |
|     T2: inside the prostate gland | 278 (44) |
|     T3: broken through prostate gland | 177 (28) |
|     T4: spread into other body organs | 16 (3) |
|     Tx: not assessable | 101 (16) |
| TNM-N[b] | |
|     N0: no lymph node metastasis | 405 (77) |
|     N1-3: lymph node metastasis | 56 (11) |
|     Nx: not assessable | 65 (12) |
| TNM-M[c] | |
|     M0: no distant metastasis | 386 (74) |
|     M1: distant metastasis | 47 (9) |
|     Mx: not assessable | 87 (17) |
| Binary disease staging[d] | |
|     Non-localized | 197 (39) |
|     Localized | 307 (61) |
| Treatment intention | |
|     Curative | 485 (89) |
|     Palliative | 62 (11) |
| Type of treatment (current or completed) | |
|     Surgery | 457 (72) |
|     Radiation | 213 (34) |

(Continues)

**TABLE 1** (Continued)

|  | Counts |
|---|---|
|  | n (valid %) |
| Chemotherapy | 39 (6) |
| ADT | 112 (18) |
| Other treatment | 17 (3) |
| Active treatment | |
| Yes (any ongoing treatment) | 161 (25) |
| No (treatment completed/scheduled/ not intended) | 475 (75) |
| ECOG performance status | |
| 0: asymptomatic | 385 (63) |
| 1: ambulatory | 178 (29) |
| 2: <50% in bed | 39 (6) |
| 3: >50% in bed | 6 (1) |
| 4: bedbound | 0 (0) |

Note: Valid, rounded percentages (may not add up to 100).
Abbreviations: ADT, androgen deprivation therapy; ECOG, Eastern Cooperative Oncology Group.
[a]Tumor staging via size and extent of the tumor.
[b]Tumor staging via degree of spread to regional lymph nodes.
[c]Tumor staging via presence of distant metastasis.
[d]Combination of all TNM-information into a clinically relevant binary categorization (see Figure S1).
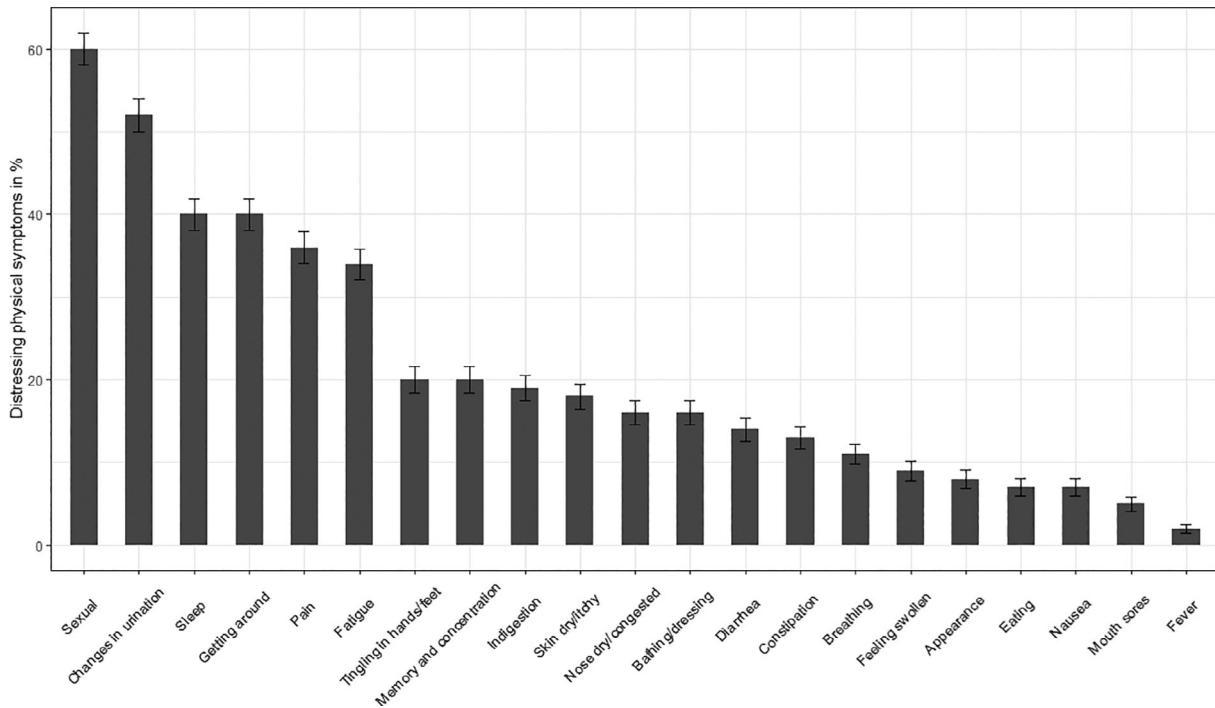


**FIGURE 2** Occurrence of distressing physical symptom burden among 636 patients with prostate cancer; error bars indicate standard errors using the formula SE = $\sqrt{(p \ast [1-p])/n}$

Additionally, a higher risk for depression was found for patients with metastases and for those treated with chemotherapy. Even though all significant RR were small in size (RR ≤1.46), results were replicated when controlled for the respective other two significant factors (Table S1). Among the three significant factors (age, chemotherapy and metastases), only metastases and chemotherapy showed a significant, but still moderate correlation[25] with r(430) = .40, P < .001.

Among the matched GP, the AR of depression and anxiety was lower compared to patients, with 13% and 16%, respectively. Statistically, the respective RR were small, but significant for both depression

**TABLE 2** Absolute risk (prevalence) of depression and anxiety and relative risk (ratios of AR) across subsamples of a sample of prostate cancer patients (N = 636)

| | Depression | | | Anxiety | | |
|---|---|---|---|---|---|---|
| | Included N | AR in % | RR[a] [95%-CI] | Included N | AR in % | RR[a] [95%-CI] |
| Total sample | 633 | 23 | | 596 | 22 | |
| Age | | | **1.15 [1.06;1.26]** | | | **1.14 [1.04;1.24]** |
| <67 years | 313 | 29 | | 294 | 27 | |
| ≥67 years | 317 | 18 | | 300 | 17 | |
| Time since diagnosis | | | 1.06 [0.97;1.16] | | | 0.98 [0.90;1.07] |
| <3 months | 216 | 19 | | 213 | 22 | |
| ≥3 months | 352 | 24 | | 344 | 21 | |
| Staging | | | 0.99 [0.89;1.09] | | | 1.02 [0.93;1.14] |
| Localized | 306 | 25 | | 286 | 22 | |
| Non-localized | 196 | 24 | | 187 | 25 | |
| Distant metastasis | | | **1.30 [1.02;1.65]** | | | 1.00 [0.84;1.20] |
| No metastases | 384 | 23 | | 362 | 23 | |
| Metastases | 47 | 40 | | 42 | 24 | |
| Type of treatment | | | | | | |
| Surgery | | | 1.08 [0.99;1.18] | | | 1.02 [0.93;1.13] |
| Yes | 455 | 25 | | 432 | 23 | |
| No | 175 | 19 | | 161 | 21 | |
| Radiation therapy | | | 0.95 [0.87;1.04] | | | 1.01 [0.92;1.10] |
| Yes | 212 | 20 | | 201 | 23 | |
| No | 416 | 24 | | 390 | 22 | |
| Chemotherapy | | | **1.46 [1.09;1.96]** | | | 1.09 [0.88;1.35] |
| Yes | 39 | 46 | | 35 | 29 | |
| No | 589 | 21 | | 556 | 22 | |
| Hormone therapy | | | 1.02 [0.91;1.15] | | | 1.04 [0.92;1.17] |
| Yes | 111 | 24 | | 109 | 25 | |
| No | 517 | 23 | | 482 | 22 | |
| Active treatment[b] | | | 0.92 [0.84;1.01] | | | 0.99 [0.90;1.09] |
| Yes | 147 | 19 | | 133 | 22 | |
| No | 486 | 25 | | 463 | 22 | |

Abbreviations: AR, absolute risk (prevalence); CI, confidence interval; RR, relative risk.
[a]RR was calculated as the ratio of AR in one group and the AR in the other group; RR whose CI do not include 1 are considered significant (in bold font).
[b]Yes: any ongoing treatment; no: treatment completed/scheduled/not intended.

and anxiety, with RR of 1.13 (95%-CI: 1.07-1.19) and 1.08 (95%-CI: 1.02-1.14), respectively.

Both disease-specific symptoms had significant, but small relationships[25] with both depression ($F_{urination}(1596) = 12.9$, $P < .001$, $f^2 = 0.02$; $F_{sexuality}(1587) = 24.6$, $P < .001$, $f^2 = 0.04$) and anxiety ($F_{urination}(1585) = 7.2$, $P < .01$, $f^2 = 0.01$; $F_{sexuality}(1576) = 38.7$, $P < .001$, $f^2 = 0.07$).

Age moderated the relationship of symptoms with anxiety ($B_{urination} = -0.10$, $P = .02$; $B_{sexuality} = -0.11$, $P = .01$), but not with depression ($B_{urination} = -0.05$, $P = .3$; $B_{sexuality} = -0.08$; $P = .08$). Interaction plots for significant moderations showed that the relationship between symptoms and anxiety was stronger in younger patients (Figures S2 and S3).

## 4 | DISCUSSION

### 4.1 | Main findings

In this sample of PCa patients selected from a German multicenter study, over half of the patients reported disease-specific symptom burden. More than 20% exceeded the clinical cut-offs for depression and anxiety, and risks were slightly higher than in the general population. Patients who were younger, treated with chemotherapy or had metastases were at increased risk of clinical levels of distress. The elevated distress of the younger patients may be explained by a stronger impact of disease-specific symptoms on psychological well-being.

## 4.2 | Integration into previous research

Patients mostly suffered from disease-specific symptom burden occurring in up to 60% of the sample. This finding is in line with a previous study among 197 prostate cancer patients using the same assessment.[26] The relatively high frequency/severity of these symptoms was also found in studies using other instruments and other survivorship phases, that is, before the beginning of any treatment (n = 1438)[6] and long-term survivors (n = 3348).[6] Furthermore, a previous article within the present multi-center study investigated all male cancer including PCa (n = 1881)[22] and found that the most frequently reported problems were not related to urination and sexuality, but fatigue and sleep,[27] which in turn implies that PCa patients suffer from distinct symptom burden.

We found that about one in five patients reported clinically relevant levels of depression and anxiety, with rates considerably differing between subsamples. Our rates are slightly higher than rates of a meta-analysis pointing to prevalence rates ranging from 14% and 18% (depression) and 15% and 27% (anxiety).[5] These higher rates are likely caused by our applied cut-offs, which were relatively low compared to previous studies.[16,19] Contrary to Lane et al,[6] we could not find a general higher rate of anxiety compared to depression. As an explanation, patients of this previous study were assessed in earlier disease stages and before any treatment[6] which may have resulted in a predominance of anxiety.[28]

Nevertheless, we observed that patients treated with chemotherapy or having metastases had elevated risk of depression; in these groups, depression was much more prevalent than anxiety. These effects may be explained by functional impairments in these groups resulting in high levels of anhedonia.[2] Since we showed that chemotherapy and metastases were correlated with each other, however, these two subgroups may simply represent advanced cancer patients, which are particularly vulnerable to depression.[29] Contrary to previous findings,[30,31] we did not find an effect of hormone therapy. An explanation could be that this category not only contained androgen deprivation therapy (ADT), but may also have included medication such as finasteride, which is not directly associated with psychological outcomes.[32] The effect of ADT, however, may be indirectly shown in our study given that the potentially ADT-related sexual problems were significantly associated with depression and anxiety.

Younger age was associated with a higher risk for both depression and anxiety. Whereas the association of higher anxiety in younger age is in line with previous studies (n = 736[7]; n = 1438[6]), it contradicts findings indicating that younger age is associated with lower depression (n = 736).[7] The moderating effect of age in the relationship between disease-related symptoms and anxiety supported the hypothesis that the association of younger age and anxiety may result from different coping between age groups[7,9]: Given that younger patients may be more active in sexuality and social life, they may experience more anxiety if such disease-specific symptoms occur. The fact that there was a moderating effect of age on anxiety, but not on depression may explain previous inconsistencies of age effects: Possibly, both outcomes are (partly) determined by coping with specific side effects/symptoms and thus inconsistent age effects across studies may result from specific symptom constellations among the samples. Apart from these hypotheses, previous studies differed in the mean age of the samples and the way they entered age in the analyses, for example, as dichotomous variable (our study), 5-year age groups[6,7] or other grouping strategies.[8] The impact of such methodological issues and other aspects such as time since diagnosis should also be investigated.

PCa patients had a significantly higher risk of both depression and anxiety when compared to matched norm values. Even though the effect was small, it is possible that a higher cut-off may have resulted in fewer cases in the general population and thus to a larger group effect between patients and norms. Most important, our finding is supported by methodologically similar studies, for example, two previous studies (n = 291[33] and n = 265[34]) which found that general mental health was worse in PCa patients than in the general population.

## 4.3 | Study limitations

As a central limitation, the cross-sectional design does not allow to interpret any results as causal effects. Generalizability may be limited given that the sample was largely evenly distributed with respect to early (T1-T2) and late disease stage (T3-T4) and thus does not fit to the distribution among general incidence rates which shows a higher percentage of patients in early stages.[35] Furthermore, responders were better educated and patients from cancer rehabilitation centers were overrepresented, suggesting a slight bias towards patients with higher socioeconomic status and in less acute cancer treatment stages. We also did not assess whether patients were on active surveillance. Even though cut-offs were based on recent findings,[16,19] the self-reported questionnaires cannot provide definite diagnoses of mental disorders.

## 4.4 | Clinical implications

The large sample selected from a German-wide multi-center study, the combination of data from hospital charts and patient-reported outcomes, the stratification across subsets and the investigation of different age effects provide novel results that may be used in clinical care.

It is to note that rates of depression and anxiety were relatively low compared to other cancer populations and that significant RR were relatively small in size. However, in light of the potentially adverse impact of depression and anxiety on cancer patients,[36,37] even relatively small prevalence rates and effects may have practical relevance. As patients were shown to suffer from distinct symptom burden, disease-specific screening for these symptoms in order to offer specific interventions such as coping skills to reduce distress resulting from sexual problems or support to reduce the impact of erectile dysfunction on spousal role activities seems needed.[38]

Younger patients and those in advanced stages may be more vulnerable to distress and thus should be closely monitored with respect to psycho-social issues. Younger patients may be particularly frightened by disease-specific symptoms and thus the occurrence of such fears should be explored. Despite the general high degree of supportive care need across patient groups,[39] specific efforts to motivate male cancer patients to seek psychological support seem warranted.[40]

## 4.5 | Conclusions

In this study, we showed that younger patients, those with metastases or treatment with chemotherapy were at risk for elevated distress and should be closely monitored. The majority of patients suffered from disease-specific symptom burden, which may particularly burdensome for younger patients. Psychological interventions should address coping mechanisms associated with disease-specific symptom burden.

### CONFLICT OF INTEREST
The authors have declared no conflict of interest.

### DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available on request from the corresponding author.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.