


# Symptoms of Anxiety and Depression Among Colorectal Cancer Survivors From the Population-Based, Longitudinal PROFILES Registry: Prevalence, Predictors, and Impact on Quality of Life

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**BACKGROUND:** The aims of this study were to prospectively assess symptoms of anxiety and depression among survivors of colorectal cancer (CRC), to compare these survivors with a normative population, and to identify subgroups at risk for experiencing symptoms of anxiety and/or depression across a 4-year time period. Also, the impact on health-related quality of life (HRQOL) was studied. **METHODS:** The population-based Eindhoven Cancer Registry was used to select patients diagnosed with CRC between 2000 and 2009. The Hospital Anxiety and Depression Scale and the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (HRQOL) were completed by patients in 2010 ( $n = 2625$  [73% response rate]), 2011, 2012, and 2013 and by an age- and sex-matched normative sample ( $n = 315$ ) in 2011. **RESULTS:** Patients reported a significantly higher prevalence of depression (19.0% vs 12.8%) and anxiety (20.9% vs 11.8%) in comparison with the norm. Anxiety was stable, whereas depression scores changed over time, although this was not clinically relevant. A longer time since diagnosis was associated with fewer depressive symptoms over time, whereas older age and being male were associated with less anxiety and more depression. Being married was associated with less anxiety and depression, and a low education level and comorbid conditions were associated with more anxiety and depression. Higher levels of symptoms of depression and anxiety were associated with a lower global quality of life and lower physical, role, cognitive, emotional, and social functioning over time. **CONCLUSIONS:** Because of the increased prevalence of depression and anxiety among patients with CRC and their negative effect on HRQOL, screening and referral are of the utmost importance, especially among those who are single, have a low educational level, and have comorbid conditions, even years after diagnosis and treatment. *Cancer* 2018;124:2621-8. © 2018 The Authors. *Cancer* published by Wiley Periodicals, Inc. on behalf of American Cancer Society. This is an open access article under the terms of the Creative Commons Attribution NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

**KEYWORDS:** anxiety, colorectal cancer, depression, normative population, quality of life.

## INTRODUCTION

Although survival rates for patients with colorectal cancer (CRC) are relatively high (58% are alive > 10 years after their diagnosis),<sup>1</sup> a large proportion of this group is confronted with continuing physical and psychosocial problems because of the cancer and its treatment.<sup>2</sup> This could have a negative impact on their health-related quality of life (HRQOL).<sup>3</sup> Although considerable attention is paid in the literature to the physical side effects of CRC and its treatment,<sup>4</sup> there is less focus on the psychosocial problems among CRC survivors. A recent review concluded that very few studies focused on symptoms of anxiety and depression among long-term CRC survivors.<sup>5</sup> The authors, therefore, argued that further research is needed to establish predictors of mental health outcomes in long-term CRC survivors.<sup>5</sup> They also pointed out that many studies included relatively small sample sizes, were cross-sectional, contained little information on cancer treatment, and did not include all disease stages and that a comparison with a normative population was often lacking.<sup>5</sup>

Therefore, we performed secondary analyses of our large population-based, longitudinal study of stage I to IV CRC survivors diagnosed between 1 and 10 years ago at the time of study inclusion. We included clinical data and compared our results with a normative population. The goals of this study were 1) to compare the baseline prevalence of anxiety and depression among CRC survivors with an age- and sex-matched normative population; 2) to prospectively assess the

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course of symptoms of anxiety and depression over a 4-year period; 3) to identify subgroups with high, fluctuating, and low levels of anxiety and depression over time; and 4) to assess the impact of having symptoms of anxiety and depression on HRQOL.

## MATERIALS AND METHODS

### *Participants*

A longitudinal, population-based cohort study was performed among CRC survivors registered within the Netherlands Cancer Registry, which records data on all patients newly diagnosed with cancer. We selected patients in the southern part of the Netherlands, an area with 2.4 million inhabitants.<sup>6</sup> All patients diagnosed with stage I to IV CRC between 2000 and 2009 were eligible. Patients who had unverifiable addresses, had a cognitive impairment, died before the start of study or were terminally ill, had stage 0 disease/carcinoma in situ, or were already included in our 2009 CRC study or another study (n = 169) were excluded. A complete overview of the selection of patients can be found on our Web site under data and documentation ([https://www.dataarchive.profilesregistry.nl/study\\_units/view/22](https://www.dataarchive.profilesregistry.nl/study_units/view/22)).

Ethical approval for the study was obtained from the medical ethics committee of the Maxima Medical Centre in Veldhoven, the Netherlands (approval number 0822). All participants gave informed consent.

### *Data Collection*

Data collection was performed within Patient-Reported Outcomes Following Initial Treatment and Long-Term Evaluation of Survivorship (PROFILES).<sup>7</sup> The study started in December 2010 (time 1 [T1]), and respondents received yearly subsequent questionnaires in 2011 (time 2 [T2]), 2012 (time 3 [T3]), and 2013 (time 4 [T4]). In 2010, survivors received a letter from their (former) attending specialist to inform them about the study. The letter included a link to a secure Web site, a login name, and a password so that interested patients could provide consent and complete questionnaires online. Those who preferred written communication could return a postcard, after which they received our paper and pencil informed consent form and questionnaire. Nonrespondents were sent a reminder letter and a paper and pencil questionnaire within 2 months.

### *Sociodemographic and Clinical Characteristics*

Information on survivors' sociodemographic and clinical characteristics was available from the Netherlands Cancer Registry. Other relevant sociodemographic and clinical

factors were obtained through the questionnaires (eg, marital status, educational level, and current occupation). Comorbidity in the last 12 months was assessed with the adapted Self-Administered Comorbidity Questionnaire.<sup>8</sup>

### *Symptoms of Anxiety and Depression*

We used the Hospital Anxiety and Depression Scale (HADS) to assess self-reported symptoms of anxiety and depression.<sup>9</sup> The HADS consists of 14 items: 7 items for depressive symptoms and 7 items for anxiety. It assesses levels of symptoms in the last week. The questions can be answered on a 4-point Likert scale, and the total score for each scale can range from 0 to 21. The cutoff value for symptoms of anxiety and depression is indicated by a score  $\geq 8$ .<sup>9-11</sup>

### *HRQOL*

The European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30; version 3.0) was used to assess cancer-specific HRQOL.<sup>12</sup> It contains 5 functional scales, the Global Quality of Life scale, 3 symptom scales, and 6 single items. The symptom scales and single items were not used in this study. Each item is scored on a 4-point Likert scale except for the Global Quality of Life scale, which has a 7-point Likert scale. Scores are linear-transformed to a 0 to 100 scale.<sup>13</sup> A higher score on the functional scales and Global Quality of Life scale means better functioning and HRQOL.

### *Normative Population*

Norm data were obtained in 2011 from the Health and Health Complaints project from CentERdata (<https://www.centerdata.nl/>). It is representative of the Dutch-speaking population in the Netherlands and includes those without Internet access. Panel members who were 18 years old or older received an online version of the HADS, the EORTC QLQ-C30, and the Self-Administered Comorbidity Questionnaire. Nonrespondents were reminded a week later. In total, 2040 panel members (82%) responded. An age- and sex-matched normative sample without cancer (1 person per panel-household) was selected from this group to match the age and sex distribution of the CRC sample. For matching, 10 strata were formed with sex and age (5 categories). Within each stratum, a maximum number of persons from the reference cohort were randomly matched according to the strata frequency distribution of patients. This resulted in 315 matched cancer-free individuals for the 2625 CRC survivors.

### Statistical Analyses

Differences in baseline sociodemographic and clinical characteristics between respondents and nonrespondents or patients with unverifiable addresses were compared with a chi-square or *t* test. Then, differences in baseline sociodemographic characteristics between patients who completed 1 questionnaire and patients who completed more questionnaires were examined by means of a chi-square or *t* test. Furthermore, baseline sociodemographic characteristics between CRC patients at T1 and an age- and sex-matched normative population were also compared with a chi-square or *t* test.

Prevalence rates of symptoms of anxiety and depression for CRC patients at T1 were compared with the Dutch normative population with chi-square tests.

The course of reported symptoms of anxiety and depression by the total group of CRC survivors was analyzed for anxiety and depression separately with linear mixed effects models (ie, a covariance pattern model with an unstructured error covariance matrix and a maximum likelihood estimation).<sup>14</sup> Time was analyzed as a regular categorical predictor with 4 levels (ie, the 4 time points). Sociodemographic and clinical variables were analyzed as time-invariant predictors (ie, baseline characteristics were used). To correctly interpret all model parameters, all continuous variables were grand mean-centered.<sup>14,15</sup> In addition, 3 groups were formed on the basis of the survivors' reported symptoms of anxiety or depression over time: always reporting symptoms of anxiety or depression (consistently high score  $\geq 8$  on all measurement occasions), sometimes reporting symptoms of anxiety or depression (fluctuating score), and never reporting symptoms of anxiety or depression (consistently low score  $\leq 8$  on all measurement occasions). We subsequently identified sociodemographic and clinical factors associated with group membership with a multinomial logistic regression analysis (consistently high, fluctuating, and consistently low reported symptom levels of anxiety or depression).

The impact of symptoms of anxiety and depression on global quality of life over time was analyzed with linear mixed effects models.<sup>14</sup> Anxiety and depression scores were analyzed as continuous time-varying predictors<sup>14</sup> (separate models and simultaneously), and sex, age, and number of comorbidities were entered as covariates into both models. Clinically relevant differences were determined with the guidelines for interpretation of the EORTC QLQ-C30.<sup>16</sup> Norman's rule of thumb was used for the HADS, whereby a  $\pm 0.5$  standard deviation difference (ie, 1.9 points) indicated a threshold of discriminating change in scores.<sup>17,18</sup> Analyses were

performed in IBM SPSS 24.0 with a significance level of  $\alpha = .05$ .

## RESULTS

### Respondents and Nonrespondents at T1

The questionnaire was completed by 73% ( $n = 2625$ ) at T1, 83% ( $n = 1643$ ) at T2, 82% ( $n = 1458$ ) at T3, and 81% ( $n = 1241$ ) at T4. Respondents at T1 were significantly younger, more often male, more often diagnosed with stage I disease, and more often treated with radiotherapy and surgery in comparison with nonrespondents (all *P* values  $< .05$ ; data not shown). Furthermore, respondents at T1 were more often male and more often received radiotherapy in comparison with patients with unverifiable addresses ( $P < .05$ ; data not shown).

### CRC Survivors and Normative Population

In total, 2625 patients with CRC completed the questionnaire at T1. Approximately half (44.9%) were female (Table 1). The mean age at T1 was 69.4 years with a mean time since diagnosis of 5.2 years. Colon cancer was diagnosed in 61.1%, and approximately one-third of the patients (29.3%) received chemotherapy in addition to surgery, whereas 30.6% received radiotherapy in combination with surgery.

Patients were matched by age and sex with a normative population. However, the normative population was on average 2 years younger, reported fewer comorbidities, was more highly educated, and less often had a partner than CRC patients (Table 1).

### Differences Between CRC Survivors Who Completed 1 Questionnaire and Those Who Completed More Than 1 Questionnaire

CRC survivors who completed 1 questionnaire were significantly older, were more often female and single, had a lower educational level, and less often had a job than those who completed 2 or more questionnaires. In addition, they were significantly more often diagnosed with 2 or more comorbid conditions and stage IV disease, they more often reported symptoms of anxiety (24% vs 19%) and depression (28% vs 15%), they more often underwent surgery, and they less often received radiotherapy in addition to surgery in comparison with those who completed more questionnaires. No differences were found in the time since diagnosis or the receipt of chemotherapy in addition to surgery as the primary treatment (data not shown).

**TABLE 1.** Sociodemographic and Clinical Characteristics at Time 1 of CRC Survivors (n = 2625) and Respondents From an Age- and Sex-Matched Normative Population (n = 315)

|   | CRC Patients | Normative Population | P    |
|---|--------------|----------------------|------|
| Sex: female, No. (%)                    | 1178 (44.9)  | 142 (45.1)           | .95  |
| Age, mean (SD), y                       | 69.4 (9.5)   | 67.4 (13.2)          | <.01 |
| Time since diagnosis, mean (SD), y      | 5.2 (2.8)    | —                    | NA   |
| Tumor type, No. (%)                     |              | —                    | NA   |
| Colon                                   | 1605 (61.1)  |                      |      |
| Rectal                                  | 1020 (38.9)  |                      |      |
| Stage, No. (%)                          |              | —                    | NA   |
| I                                       | 780 (29.7)   |                      |      |
| II                                      | 948 (36.1)   |                      |      |
| III                                     | 722 (27.5)   |                      |      |
| IV                                      | 113 (4.3)    |                      |      |
| Unknown                                 | 62 (2.4)     |                      |      |
| Chemotherapy: yes, No. (%) <sup>a</sup> | 770 (29.3)   | —                    | NA   |
| Radiotherapy: yes, No. (%) <sup>a</sup> | 802 (30.6)   | —                    | NA   |
| No. of comorbid conditions, No. (%)     |              |                      | .04  |
| 0                                       | 614 (25.0)   | 95 (30.2)            |      |
| 1                                       | 709 (28.9)   | 72 (22.9)            |      |
| ≥2                                      | 1129 (46.0)  | 148 (47.0)           |      |
| Partner: yes, No. (%)                   | 1984 (76.2)  | 216 (68.6)           | .01  |
| Educational level, No. (%)              |              |                      | <.01 |
| Low                                     | 520 (20.0)   | 25 (8.0)             |      |
| Middle                                  | 1568 (60.4)  | 167 (53.3)           |      |
| High                                    | 508 (19.6)   | 122 (38.9)           |      |
| Quality of life, mean (SD) <sup>b</sup> |              |                      |      |
| Global Quality of Life                  | 77.1 (19.1)  | 77.3 (16.8)          | .01  |
| Physical Functioning                    | 79.9 (20.7)  | 85.6 (18.5)          | .01  |
| Role Functioning                        | 79.7 (27.5)  | 84.2 (24.7)          | <.01 |
| Emotional Functioning                   | 85.9 (19.4)  | 88.5 (15.8)          | <.01 |
| Cognitive Functioning                   | 84.9 (20.4)  | 90.5 (15.3)          | <.01 |
| Social Functioning                      | 86.5 (22.4)  | 92.2 (17.5)          | <.01 |
| HADS, mean (SD)                         |              |                      |      |
| Anxiety                                 | 4.6 (3.8)    | 3.5 (3.3)            | <.01 |
| Depression                              | 4.4 (3.7)    | 3.8 (3.0)            | <.01 |

Abbreviations: CRC, colorectal cancer; EORTC, European Organisation for Research and Treatment of Cancer; HADS, Hospital Anxiety and Depression Scale; NA, not applicable; QLQ-C30, Quality of Life Questionnaire Core 30; SD, standard deviation.

<sup>a</sup>All patients underwent surgery as their primary treatment.

<sup>b</sup>A higher score on the EORTC QLQ-C30 functional scales and Global Quality of Life scale represent a higher level of function.

### Symptoms of Anxiety and Depression in Comparison With a Normative Population

The baseline prevalence level of depressive symptoms in CRC patients at T1 was 19.0%, whereas it was 12.8% in the normative population ( $P < .01$ ), and the prevalence of symptoms of anxiety was 20.9% in patients and 11.8% in the normative population ( $P < .001$ ; Supporting Fig. 1).

### Course of Symptoms of Depression and Anxiety

At the group level, HADS depression scores changed over time, with the largest change between T1 and T4 ( $P < .01$ ), although this mean change of 0.89 points was not clinically relevant (ie, it was not higher than the 0.5 standard deviation difference of 1.9 points; Table 2). No change was observed in HADS anxiety scores during the 4 assessments. When analyzing the course of depression and anxiety over time, we simultaneously included information on sociodemographics (eg, age and marital status)

and clinical variables (eg, comorbidity and cancer treatment). The results furthermore showed that a longer time since diagnosis was associated with fewer depressive symptoms over time but not anxiety. Older age and being male were significantly associated with fewer symptoms of anxiety and more symptoms of depression over time. Being married was associated with fewer symptoms of anxiety and depression, whereas a low education level and comorbid conditions were associated with more symptoms of anxiety and depression. No association was observed between radiotherapy, chemotherapy, disease stage, and HADS anxiety or depression scores over time.

### Identifying Subgroups With High Levels of Symptoms of Depression and Anxiety

When exploring changes within individuals, we saw that across the 4 time points, 8.3% of the patients with CRC always reported depressive symptoms (continuously

**TABLE 2.** Times and Sociodemographic and Clinical Factors Associated With HADS Anxiety and Depression Among Patients With Colorectal Cancer

| Variable                          | HADS Anxiety |       | HADS Depression |       |
|-----------------------------------|--------------|-------|-----------------|-------|
|                                   | $\beta$      | $P^a$ | $\beta$         | $P^a$ |
| Time variables                    |              |       |                 |       |
| Time                              |              |       |                 |       |
| T4 vs T1                          | -0.06        | .42   | -0.89           | <.01  |
| T4 vs T2                          | 0.05         | .53   | -0.42           | <.01  |
| T4 vs T3                          | -0.12        | .12   | -0.42           | <.01  |
| Time since diagnosis <sup>b</sup> | -0.03        | .25   | -0.05           | .05   |
| Sociodemographic variables        |              |       |                 |       |
| Age <sup>b</sup>                  | -0.02        | .01   | 0.03            | <.01  |
| Sex: male                         | -0.80        | <.01  | 0.38            | .02   |
| Married: yes                      | -0.40        | .04   | -0.35           | .07   |
| Education                         |              |       |                 |       |
| High-low                          | 1.21         | <.01  | 1.53            | <.01  |
| High-medium                       | 0.78         | <.01  | 0.96            | <.01  |
| Clinical variables                |              |       |                 |       |
| Comorbidities <sup>b</sup>        | 0.27         | <.01  | 0.22            | <.01  |
| Radiotherapy: no                  | -0.06        | .74   | -0.11           | .50   |
| Chemotherapy: no                  | -0.10        | .65   | -0.16           | .46   |
| Stage                             |              |       |                 |       |
| IV vs I                           | -0.86        | .07   | -0.73           | .11   |
| IV vs II                          | -0.71        | .13   | -0.60           | .18   |
| IV vs III                         | -0.82        | .07   | -0.84           | .06   |

Abbreviations: HADS, Hospital Anxiety and Depression Scale; T1, time 1; T2, time 2; T3, time 3; T4, time 4.

<sup>a</sup>Bolded  $P$  values are significant.

<sup>b</sup>Continuous variables are grand mean-centered.

high), 21.1% sometimes experienced depressive symptoms (fluctuating), and 70.6% never reported depressive symptoms (continuously low). Also, 9.6% of the patients always experienced symptoms of anxiety (continuously high), 22.3% sometimes experienced these symptoms (fluctuating), and 68.1% never reported symptoms of anxiety (continuously low).

Identifying sociodemographic and clinical factors independently associated with group membership (ie, continuously high, fluctuating, or continuously low symptoms of anxiety or depression over time) showed that a lower number of comorbidities, a higher educational level, being male, and a lower disease stage were more often associated with a decreased risk of having fluctuating or constantly high symptoms of anxiety or depression (Table 3). More specifically, those with 0 or 1 comorbid conditions, in comparison with those with 2 or more comorbidities, had lower risks of reporting fluctuating or continuously high symptoms of depression or anxiety versus continuously low symptoms of depression or anxiety (Table 3). In contrast, those with a low or medium educational level had a higher risk of fluctuating anxiety scores

and fluctuating or high depression scores. Males had a lower risk of fluctuating or high levels of anxiety, but no effect on depression was found. Younger patients had a higher risk of fluctuating anxiety scores, whereas older patients had a higher risk of fluctuating depression scores. Finally, those with stage I disease (vs stage IV disease) had a lower risk of fluctuating anxiety scores, whereas those with stage III disease (vs stage IV disease) had a lower risk of fluctuating depression scores. Chemotherapy or radiotherapy, the time since diagnosis, and having a partner did not significantly influence fluctuating or high levels of anxiety or depression.

### Association of Symptoms of Depression and Anxiety With HRQOL

Higher levels of symptoms of depression and anxiety were significantly associated with lower values for the EORTC QLQ-C30 Global Quality of Life, Physical Functioning, Role Functioning, Cognitive Functioning, Emotional Functioning, and Social Functioning scales over time (all  $P$  values < .01; Table 4) when we controlled for age, sex, and number of comorbidities. Depressive symptoms were negatively related to all 6 EORTC QLQ-C30 scales, with the smallest relations for Physical Functioning ( $\beta_{\text{between}} = -2.39$ ;  $\beta_{\text{within}} = -1.00$ ) and the largest for Role Functioning ( $\beta_{\text{between}} = -3.31$ ;  $\beta_{\text{within}} = -1.96$ ). Likewise, symptoms of anxiety were negatively related to all 6 EORTC QLQ-C30 scales, with the smallest relations for Physical Functioning ( $\beta_{\text{between}} = -1.49$ ;  $\beta_{\text{within}} = -0.540$ ) and the largest for Role Functioning ( $\beta_{\text{between}} = -3.64$ ;  $\beta_{\text{within}} = -2.23$ ). Levels of symptoms of depression and anxiety remained significantly associated with lower quality of life when they were simultaneously entered into the model while we controlled for age, sex, and number of comorbidities.

Those who always reported depressive symptoms had Global Quality of Life scores that were on average 25.9 to 28.6 points lower than the scores of those never reporting depressive symptoms (Supporting Fig. 2). Patients who always reported symptoms of anxiety reported Global Quality of Life scores that were on average 20.6 to 23.2 points lower than the scores of patients never reporting symptoms of anxiety. The aforementioned differences in quality of life are of large clinical relevance (ie, > 15-point difference).<sup>16</sup>

### DISCUSSION

In the growing population of CRC survivors, more attention is desired for the psychosocial consequences of CRC. Although this is a rapidly emerging research area, more

**TABLE 3.** Multivariate Analyses: Odds Ratios and 95% Confidence Intervals for the Individual Independent Variables

| Variable                   | HADS Anxiety                  |                               | HADS Depression               |                               |
|----------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|
|                            | Fluctuating                   | High                          | Fluctuating                   | High                          |
| Sex: male vs female        | 0.66 (0.51-0.84) <sup>a</sup> | 0.52 (0.36-0.75) <sup>a</sup> | 1.11 (0.86-1.44)              | 1.03 (0.71-1.51)              |
| Age                        | 0.99 (0.97-0.99) <sup>b</sup> | 0.99 (0.97-1.00)              | 1.02 (1.01-1.04) <sup>a</sup> | 0.99 (0.97-1.01)              |
| Stage                      |                               |                               |                               |                               |
| I vs IV                    | 0.49 (0.25-0.99) <sup>b</sup> | 0.88 (0.27-2.84)              | 0.60 (0.29-1.23)              | 0.42 (0.16-1.15)              |
| II vs IV                   | 0.57 (0.29-1.12)              | 1.02 (0.32-3.20)              | 0.53 (0.26-1.09)              | 0.43 (0.16-1.14)              |
| III vs IV                  | 0.56 (0.29-1.07)              | 1.11 (0.37-3.36)              | 0.45 (0.22-0.88) <sup>b</sup> | 0.51 (0.20-1.28)              |
| Chemotherapy: no vs yes    | 1.04 (0.73-1.47)              | 1.04 (0.63-1.73)              | 0.98 (0.68-1.41)              | 1.02 (0.60-1.71)              |
| Radiotherapy: no vs yes    | 0.79 (0.61-1.03)              | 0.97 (0.66-1.42)              | 0.89 (0.68-1.17)              | 0.81 (0.54-1.20)              |
| Time since diagnosis       | 0.99 (0.95-1.03)              | 0.96 (0.90-1.02)              | 0.97 (0.93-1.01)              | 0.93 (0.87-1.00)              |
| No. of comorbid conditions |                               |                               |                               |                               |
| 0 vs 2                     | 0.44 (0.32-0.61) <sup>a</sup> | 0.35 (0.22-0.57) <sup>a</sup> | 0.51 (0.36-0.71) <sup>a</sup> | 0.21 (0.12-0.37) <sup>a</sup> |
| 1 vs 2                     | 0.55 (0.41-0.73) <sup>a</sup> | 0.39 (0.25-0.59) <sup>a</sup> | 0.69 (0.51-0.92) <sup>a</sup> | 0.34 (0.21-0.53) <sup>a</sup> |
| Educational level          |                               |                               |                               |                               |
| Low vs high                | 1.64 (1.08-2.48) <sup>b</sup> | 1.80 (0.99-3.27)              | 2.35 (1.54-3.58) <sup>a</sup> | 3.02 (1.59-5.74) <sup>a</sup> |
| Medium vs high             | 1.43 (1.04-1.96) <sup>b</sup> | 1.52 (0.94-2.46)              | 1.70 (1.21-2.39) <sup>a</sup> | 2.00 (1.17-3.44) <sup>a</sup> |
| Partner: yes vs no         | 0.92 (0.68-1.25)              | 0.73 (0.49-1.09)              | 0.83 (0.61-1.13)              | 0.65 (0.43-1.00)              |

Abbreviation: HADS, Hospital Anxiety and Depression Scale.

The odds ratios and 95% confidence intervals (in parentheses) are displayed for patients in a certain category of an independent variable (vs the reference category; column) to be in a certain category of a dependent variable (vs the reference category; row).

<sup>a</sup>P < .01.

<sup>b</sup>P < .05.

**TABLE 4.** Generalized Linear Mixed Model Estimating Independent Inter- and Intra-Individual Effects of Depressive and Anxiety Symptoms on Health-Related Quality Of Life

|                                     | EORTC QLQ-C30 β        |                      |                    |                       |                       |                    |
|-------------------------------------|------------------------|----------------------|--------------------|-----------------------|-----------------------|--------------------|
|                                     | Global Quality of Life | Physical Functioning | Role Functioning   | Cognitive Functioning | Emotional Functioning | Social Functioning |
| HADS scales individually            |                        |                      |                    |                       |                       |                    |
| HADS Depression                     |                        |                      |                    |                       |                       |                    |
| Depressive symptoms between (inter) | -2.75 <sup>a</sup>     | -2.39 <sup>a</sup>   | -3.31 <sup>a</sup> | -2.85 <sup>a</sup>    | -3.22 <sup>a</sup>    | -3.20 <sup>a</sup> |
| Depressive symptoms within (intra)  | -1.77 <sup>a</sup>     | -1.00 <sup>a</sup>   | -1.96 <sup>a</sup> | -1.48 <sup>a</sup>    | -1.92 <sup>a</sup>    | -1.83 <sup>a</sup> |
| HADS Anxiety                        |                        |                      |                    |                       |                       |                    |
| Anxiety symptoms between (inter)    | -2.26 <sup>a</sup>     | -1.49 <sup>a</sup>   | -2.31 <sup>a</sup> | -2.58 <sup>a</sup>    | -3.64 <sup>a</sup>    | -2.51 <sup>a</sup> |
| Anxiety symptoms within (intra)     | -1.32 <sup>a</sup>     | -0.54 <sup>a</sup>   | -1.10 <sup>a</sup> | -1.24 <sup>a</sup>    | -2.23 <sup>a</sup>    | -1.44 <sup>a</sup> |
| HADS scales simultaneously          |                        |                      |                    |                       |                       |                    |
| HADS Anxiety                        |                        |                      |                    |                       |                       |                    |
| Anxiety symptoms between (inter)    | -0.87 <sup>a</sup>     | 0.13                 | -0.31              | -1.34 <sup>a</sup>    | -2.87 <sup>a</sup>    | -0.80 <sup>a</sup> |
| Anxiety symptoms within (intra)     | -0.74 <sup>a</sup>     | -0.18 <sup>b</sup>   | -0.38 <sup>b</sup> | -0.78 <sup>a</sup>    | -1.76 <sup>a</sup>    | -0.86 <sup>a</sup> |
| HADS Depression                     |                        |                      |                    |                       |                       |                    |
| Depressive symptoms between (inter) | -2.14 <sup>a</sup>     | -2.47 <sup>a</sup>   | -3.08 <sup>a</sup> | -1.9 <sup>a</sup>     | -1.19 <sup>a</sup>    | -2.64 <sup>a</sup> |
| Depressive symptoms within (intra)  | -1.44 <sup>a</sup>     | -.91 <sup>a</sup>    | -1.78 <sup>a</sup> | -1.16 <sup>a</sup>    | -1.17 <sup>a</sup>    | -1.46 <sup>a</sup> |

Abbreviations: EORTC, European Organisation for Research and Treatment of Cancer; HADS, Hospital Anxiety and Depression Scale; QLQ-C30, Quality of Life Questionnaire Core 30.

Continuous variables are grand mean-centered.

<sup>a</sup>P < .01.

<sup>b</sup>P < .05.

attention is needed, especially because *psychosocial* is a broad concept, and research focusing on long-term CRC survivors is still relatively scarce.

Our study showed prevalence rates of approximately 1 in 5 for survivors and 1 in 8 for the normative population for both anxiety and depressive symptoms.

Prevalence rates were relatively stable across the 4 assessments. On average, 1 in 12 patients reported depressive symptoms on all 4 assessments, and 1 in 10 always experienced anxiety. A comparison of our observed prevalence rates with those of other studies was difficult, not only because of the low number of studies on this topic<sup>5</sup> but

also because of the wide variation in the studied populations (eg, stage and time since diagnosis), small sample sizes, and different cutoffs used.

A shorter time since diagnosis, being male, and older age were associated with more depressive symptoms. Interestingly, being male and advanced age were associated with fewer symptoms of anxiety. Marital status was associated with fewer symptoms of anxiety and depression, whereas a low education level and comorbid conditions were associated with more. Our findings are comparable with the literature on this matter.<sup>19-21</sup> An unexpected finding was that treatment and disease stage were not associated with symptoms of anxiety and depression in our study. The literature on this matter is scarce.<sup>5</sup> However, disease stage did predict high global distress in an Australian study of patients with CRC up to 5 years after their diagnosis.<sup>19</sup>

As expected, those with high levels of anxiety and depression reported lower HRQOL across the 4 time points. However, we did not expect that the differences in HRQOL between patients who always reported symptoms of depression or anxiety and patients who never reported these symptoms would be so high. Differences ranged from 25.9 to 28.6 points for depressive symptoms and from 20.6 to 23.2 points for symptoms of anxiety. Only 2 other studies examined the association between the HADS and EORTC QLQ-C30 in patients with CRC, and they also showed that more symptoms of anxiety and depression were associated with lower HRQOL.<sup>22,23</sup> However, differences in EORTC QLQ-C30 scale scores between those with low and high levels of symptoms of anxiety and depression were not presented in these studies except for the Emotional Functioning subscale, which was indeed 24 points lower for those with anxiety and 9.9 points lower for those depressed.<sup>22</sup> Our results show that both depression and anxiety are independently related to HRQOL; hence, both psychological factors have an individual effect on patients' well-being.

The high prevalence of survivors who reported persisting symptoms of anxiety and depression years after their diagnosis—approximately 1 in 5—highlights the importance of screening programs for identifying those patients in need, even long after the primary treatment has ended. This immediately sets the first challenge: how do we identify those in need of help? The results of our study show that single CRC survivors with 1 or more comorbid conditions who have a lower educational level and a high disease stage are most vulnerable to experiencing feelings of depression and anxiety. Second, after successful screening, it is vital to know whether these

survivors actually want psychological help to reduce their feelings of depression and anxiety. In a recent study of cancer patients, only 36% of distressed patients were willing to accept help for their psychological difficulties.<sup>24</sup> Obviously, future research on screening and patients' need for help is warranted because a significant proportion of patients suffer from feelings of depression and anxiety, and they could possibly benefit from psychological or pharmaceutical treatment. This is especially vital not only because it is related to poorer HRQOL but also because one of our previous studies concluded that cancer survivors (including those with CRC) with depressive symptoms had a 2-fold risk for all-cause mortality, even after adjustments for major clinical predictors.<sup>25</sup> It is important to examine whether improvements of feelings of depression and anxiety would also lead to improved HRQOL and lower mortality rates among CRC patients.

The current study has a number of limitations that should be mentioned. First, although information was present regarding sociodemographic and clinical characteristics of nonrespondents, it remains unknown whether they declined to participate because of poor health or depressive feelings. Because depressed patients are less likely to show initiative and thus answer questionnaires, it is plausible that a higher proportion of depressed patients were nonrespondents. Second, although patients were matched by age and sex to a normative population, the normative population was significantly younger, reported fewer comorbidities, was more highly educated, and less often had a partner than CRC patients. A more optimal match was not possible. Third, although our study had a longitudinal study design, it was difficult to determine causality because associations could also be influenced by variables not measured. For instance, information on the prescription of antidepressants or anxiolytics and the use of professional psychological therapy was not available. One of the major strengths of this study is the fact that symptoms of anxiety and depression were assessed prospectively in a large population-based study with a high response rate, which provides information on their perseverance over time in a representative group of CRC patients. Also, results could be put into perspective by comparison with an age- and sex-matched normative population.

In conclusion, approximately 1 in 5 survivors reported persisting symptoms of anxiety and depression years after their diagnosis (a rate higher than that for the normative population, ie, approximately 1 in 8), and these numbers were quite stable over time. Higher levels of symptoms of depression and anxiety were independently

associated over time with a lower quality of life. Screening for these symptoms is, therefore, of the utmost importance, especially among survivors who are single, have a low education level, and have comorbid conditions, even years after their CRC diagnosis and treatment. Proper referral to mental health specialists is warranted,<sup>26,27</sup> not only because of the symptoms themselves and their association with low HRQOL but also because studies have shown that cancer survivors with depressive symptoms have an increased risk for all-cause mortality even after adjustments for major clinical predictors.<sup>25,28</sup> In current clinical practice, the mere question of whether CRC patients experience feelings of depression or anxiety should be addressed. Furthermore, providing all CRC patients with information on where to go when they are in need of psychological help, not only while being treated but also after their oncological care discharge, is a vital first step.

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## CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

## AUTHOR CONTRIBUTIONS

**Floortje Mols:** Funding acquisition, investigation, and writing. **Dounya Schoormans:** Conceptualization and editing. **Ignace de Hingh:** Conceptualization and editing. **Simone Oerlemans:** Conceptualization and editing. **Olga Husson:** Conceptualization, editing, and formal analysis.

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