

Candidate Predictors of Health-Related Quality of Life of Colorectal Cancer Survivors: A Systematic Review

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Key Words. Colorectal cancer survivors • Candidate predictors • Health-related quality of life • Systematic review •

International Classification of Functioning, Disability and Health

ABSTRACT

The population of colorectal cancer (CRC) survivors is growing and many survivors experience deteriorated health-related quality of life (HRQoL) in both early and late post-treatment phases. Identification of CRC survivors at risk for HRQoL deterioration can be improved by using prediction models. However, such models are currently not available for oncology practice. As a starting point for developing prediction models of HRQoL for CRC survivors, a comprehensive overview of potential candidate HRQoL predictors is necessary. Therefore, a systematic literature review was conducted to identify candidate predictors of HRQoL of CRC survivors. Original research articles on associations of biopsychosocial factors with HRQoL of CRC survivors were searched in PubMed, Embase, and Google Scholar. Two independent reviewers assessed eligibility and selected articles for inclusion ($N = 53$). Strength of evidence for candidate HRQoL predictors was

graded according to predefined methodological criteria. The World Health Organization's International Classification of Functioning, Disability and Health (ICF) was used to develop a biopsychosocial framework in which identified candidate HRQoL predictors were mapped across the main domains of the ICF: health condition, body structures and functions, activities, participation, and personal and environmental factors. The developed biopsychosocial ICF framework serves as a basis for selecting candidate HRQoL predictors, thereby providing conceptual guidance for developing comprehensive, evidence-based prediction models of HRQoL for CRC survivors. Such models are useful in clinical oncology practice to aid in identifying individual CRC survivors at risk for HRQoL deterioration and could also provide potential targets for a biopsychosocial intervention aimed at safeguarding the HRQoL of at-risk individuals. *The Oncologist* 2016;21:433–452

Implications for Practice: More and more people now survive a diagnosis of colorectal cancer. The quality of life of these cancer survivors is threatened by health problems persisting for years after diagnosis and treatment. Early identification of survivors at risk of experiencing low quality of life in the future is thus important for taking preventive measures. Clinical prediction models are tools that can help oncologists identify at-risk individuals. However, such models are currently not available for clinical oncology practice. This systematic review outlines candidate predictors of low quality of life of colorectal cancer survivors, providing a firm conceptual basis for developing prediction models.

INTRODUCTION

Globally, the number of people surviving colorectal cancer (CRC) is growing [1, 2]. CRC and its treatment can be accompanied by adverse effects that may compromise the health-related quality of life (HRQoL) of CRC survivors [3, 4]. CRC treatment can cause symptoms such as pain, bowel dysfunction, and fatigue that can negatively impact physical

functioning and performance of activities of daily living [5, 6]. Additionally, a CRC diagnosis can have a strong psychological impact on emotional functioning, such as fear about the illness and death, that could lead to sleep disruption, anxiety, and depression [6, 7]. Furthermore, CRC survivors may experience restrictions in social and role functioning, particularly their

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ability to participate in community activities, engage in social networks, and perform work [8]. Thus, CRC survivors are frequently in need of care aimed at safeguarding their HRQoL.

Identification of CRC survivors at risk for HRQoL deterioration is crucial for providing appropriate care. Clinical prediction models of HRQoL can serve as an invaluable aid in practice to identify at-risk individuals, based on a multivariable set of HRQoL predictors [9]. These types of prognostic models estimate the probability of a future health-related outcome (e.g., HRQoL) on the basis of a multivariable combination of predictors. Such prior knowledge could help clinicians make informed decisions about tailored care in anticipation of possible future HRQoL deterioration [10]. However, no evidence-based prediction models for HRQoL of CRC survivors are currently available for clinical oncology practice. A broad overview of potential candidate predictors constitutes the first step toward developing evidence-based prediction models that incorporate relevant candidate HRQoL predictors based on the current best evidence from HRQoL studies in CRC survivors [11, 12].

Since the concept of HRQoL is complex and multidimensional, comprising physical, social, emotional, and cognitive aspects [13], use of a guiding theoretical framework is recommended to improve the identification of potential candidate HRQoL predictors [14]. The International Classification of Functioning, Disability and Health (ICF) can be used for that purpose as a health condition-specific classification and mapping system for HRQoL research [15]. The ICF is a biopsychosocial framework of health and functioning, developed by the World Health Organization [16], in which HRQoL is conceptualized as the subjective perception of an individual's level of functioning and health status within the context of environmental and personal factors (Fig. 1) [17, 18]. Recently, the applicability of the ICF for studying relevant aspects of HRQoL in CRC survivors was reported [19]. The ICF emphasizes both biomedical and psychosocial aspects of health and functioning, as well as contextual factors that influence functioning; therefore, the ICF framework is useful for comprehensive mapping of candidate HRQoL predictors.

The aim of this systematic literature review was to identify important candidate predictors of HRQoL of CRC survivors through an ICF-based biopsychosocial approach, thereby providing conceptual guidance for developing evidence-based prediction models of HRQoL of CRC survivors. Such prediction models are useful clinical aids for identifying individuals at risk for HRQoL deterioration following CRC diagnosis and treatment, and can also provide potential targets for behavioral (e.g., lifestyle) and psychosocial interventions aimed at safeguarding the HRQoL of at-risk CRC survivors.

MATERIALS AND METHODS

Search Strategy and Selection Criteria

The main research question for the systematic review was "What are relevant biopsychosocial candidate predictors of HRQoL of CRC survivors?" For the purpose of this systematic review, a CRC survivor was defined as any individual living with a CRC diagnosis (any tumor stage) from the time of diagnosis until the end of life [20]. HRQoL was defined as the QoL related

to one's health and functioning status (i.e., the subjective perception of an individual's level of functioning or disability in the context of the individual's health condition and environmental and personal factors) [17, 18, 21]. A candidate predictor was defined as any biopsychosocial factor (i.e., related to demographic, clinical, psychological, lifestyle, and social characteristics) having an association with HRQoL, either cross-sectionally or longitudinally.

PubMed, Embase, and Google Scholar were used for the systematic literature search (Table 1). Eligible for inclusion were original research articles describing results of multivariable analyses in CRC survivors, with HRQoL as primary outcome. Articles presenting results of only univariate analyses were considered not eligible because of the inherent multivariable nature of prediction models [9]. Detailed eligibility criteria are presented in Table 2. In total, 289 records were potentially eligible for inclusion (Fig. 2). The titles and abstracts of these records were systematically screened for eligibility by two independent reviewers (B.W.A.v.d.L., M.J.L.B) who reached consensus on excluding records at this stage only when those records were clearly not eligible (e.g., review articles or etiologic studies) and on the final selection of 49 records eligible for full-text screening. The two reviewers subsequently assessed eligibility of full-text articles. Through citation tracking, 73 additional records were identified and full texts of these articles were also assessed for eligibility. Finally, 53 articles were included in the review (Fig. 2).

Grading the Evidence

During data extraction, potentially relevant candidate HRQoL predictors were initially identified based on statistical significance (i.e., factors for which a statistically significant association with HRQoL was observed in individual studies). Next, the strength of evidence for identified factors was assessed by a straightforward, stepwise scoring and grading procedure, based on previously recommended procedures for assessing the quality of evidence from prognostic research [22, 23]. Briefly, the procedure consisted of three consecutive steps (Fig. 3).

First, a quality score was assigned to each individual study based on study design (longitudinal vs. cross-sectional studies) and sample size ($n < 100$ vs. $n \geq 100$). The methodological rationale behind the quality score was that longitudinal studies provide more valid prognostic evidence than cross-sectional studies and that larger studies provide more reliable evidence than smaller studies [22]. Second, the consistency of evidence for each of the identified factors was assessed across different studies by summing the quality scores from step 1 for individual studies that observed the same association of a particular factor with HRQoL. An established ICF linking procedure was used in this step to group factors that were conceptually alike by linking them to the corresponding ICF category [24]. The consistency of evidence was categorized as follows: A = highly consistent (sum score ≥ 6 points), B = moderately consistent (sum score of 4–5 points), and C = weakly consistent (sum score < 4 points). The third step comprised the grading of the overall strength of evidence for potential candidate HRQoL predictors. For each identified factor, the evidence was graded as "strong" if it was a factor

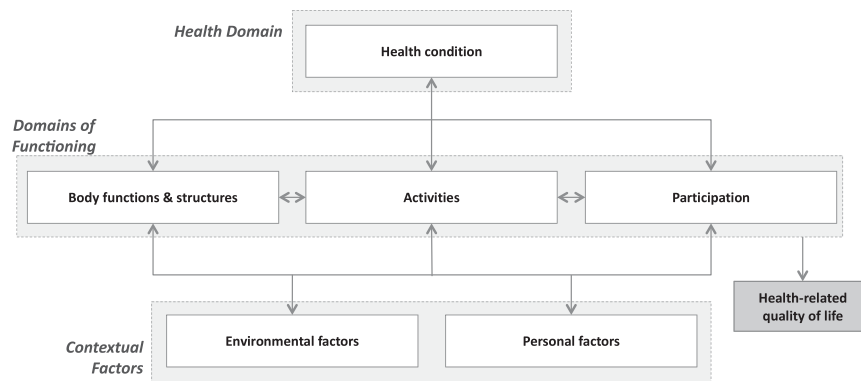


Figure 1. The biopsychosocial framework of the International Classification of Functioning, Disability and Health [16]. Health-related quality of life is conceptualized in the framework as the subjective perception of an individual's level of functioning or disability in the context of the individual's health condition and environmental and personal factors [17, 19].

Table 1. Search terms used for systematic literature search^a

Database	Search terms
PubMed ^b	((colorectal neoplasms AND survivor*) AND (health-related quality of life OR quality of life OR depression OR pain OR anxiety OR fatigue OR well-being) AND (predict* OR determinant* OR risk factors))
Embase ^c	((colorectal cancer AND survivor*) AND (health-related quality of life OR quality of life OR depression OR pain OR anxiety OR fatigue OR well-being) AND (predict* OR determinant* OR risk factors))
Google Scholar	((“colorectal neoplasms” AND survivor*) AND (health-related quality of life OR quality of life OR depression OR pain OR anxiety OR fatigue OR well-being) AND (predict* OR determinant* OR risk factors))

^aSearched databases were PubMed, Embase, and Google Scholar. The initial literature search was performed on September 8, 2014.

^bA combination of medical subject heading (MeSH) terms and free-text search terms was used. MeSH terms were as follows: “colorectal neoplasms,” “quality of life,” “depression,” “pain,” “anxiety,” and “fatigue.”

^cA combination of Emtree terms and free-text search terms was used. Emtree terms were as follows: “colorectal cancer,” “quality of life,” “depression,” “pain,” “anxiety,” and “fatigue.”

belonging to category A from step 2; “weak-to-moderate/inconclusive” if it was a factor belonging to categories B or C from step 2; or “inconsistent” in case of contradictory findings for the same factor in different studies, irrespective of the categories assigned in step 2.

Mapping Factors Into the ICF Framework

Identified factors were mapped into the appropriate domains of the ICF framework, based on the ICF linking procedure applied during step 2 of the evidence grading. For example, body mass index (BMI) was linked to the ICF category b530 “Weight maintenance functions,” which belongs to the body structures/functions domain of the ICF framework. In this way, a conceptual biopsychosocial model of potential candidate predictors of HRQoL was developed for CRC survivors.

RESULTS

Study Characteristics

Study populations consisted of CRC survivors ($n = 42$), or exclusively rectal cancer ($n = 7$) or colon cancer survivors ($n = 4$). In total, 36 studies were cross-sectional and 17 were longitudinal. The most frequently used cancer-specific HRQoL questionnaires were the Functional Assessment of Cancer

Therapy-Colorectal ($N = 19$) [25] and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ)-Core 30 ($N = 12$) [26], often supplemented with the CRC-specific module EORTC QLQ-CR38 ($N = 8$) [27]. The Short-Form Health Survey was the most frequently used generic HRQoL questionnaire ($N = 18$) [28]. The included articles ($N = 53$) were published between 1994 and 2014 (Table 3).

Strength of Evidence for Potential Candidate Predictors Within ICF Domains

The identified factors were mapped into the biopsychosocial ICF framework and arranged in accordance with the graded strength of evidence for their potential relevance as candidate HRQoL predictors (Fig. 4).

ICF Domains

Health Condition

Evidence was graded strong for the presence of a stoma and comorbidity. Twelve studies (5 longitudinal) consistently demonstrated that CRC survivors with a stoma reported lower HRQoL, both in early phases from 6 weeks up to 2 years postdiagnosis [29–34] and in later phases from 2 years to

Table 2. Eligibility criteria for selection of original research articles to be included in the review

Criteria category	Criteria
Inclusion	<ul style="list-style-type: none"> - Original research articles focusing on HRQoL in CRC survivors - Articles of observational or experimental studies describing results of multivariable analysis in CRC survivors with HRQoL as primary outcome - Articles published between 1990 and 2014 - Articles in English language of which full text was available
Exclusion	<ul style="list-style-type: none"> - Articles focusing not on HRQoL as a multidimensional construct, but only on specific domains (e.g., only the sexual functioning aspect of HRQoL) - Studies of CRC etiology - Studies in mixed cancer survivor populations (i.e., presenting results not specific for CRC survivors) - Studies presenting only results of comparisons between CRC survivors and other populations (e.g., population of healthy individuals) - Review articles, book chapters, articles in press, and abstracts

Abbreviations: CRC, colorectal cancer; HRQoL, health-related quality of life.

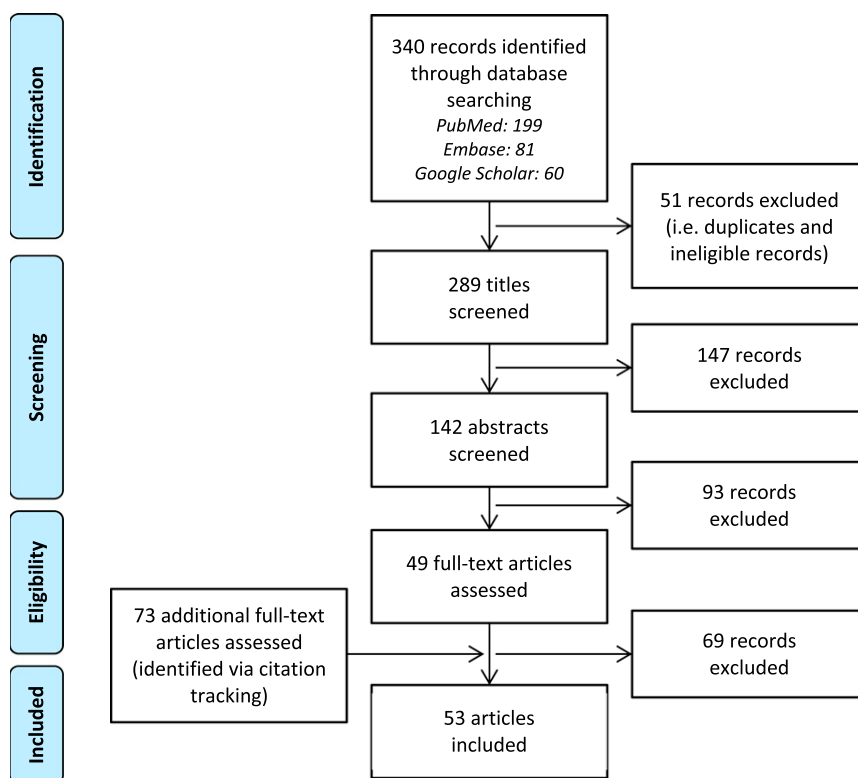


Figure 2. Flow diagram of record identification and screening phases, eligibility assessment, and number of included articles (according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses: the PRISMA statement [94]). During screening of titles and abstracts, only records that were considered clearly ineligible by two independent reviewers were excluded for further (full-text) screening (e.g., a review article or an etiologic study).

over 5 years postdiagnosis [35–40]. Additionally, 9 studies (2 longitudinal) showed that CRC survivors with 1 or more comorbid conditions reported lower HRQoL up to 10 years postdiagnosis [31, 36, 38–44].

Evidence was graded weak-to-moderate/inconclusive for chemotherapy-induced neuropathy symptoms and disease recurrence. Cross-sectional associations were observed of more peripheral neuropathy symptoms in CRC survivors [45, 46] and tumor recurrence in rectal cancer survivors [40] with

lower HRQoL. Evidence was graded inconsistent for tumor stage and localization. Either associations of higher tumor stage with lower HRQoL were observed [29, 33, 35, 40, 42, 43, 47, 48] or there was no significant association between tumor stage and HRQoL [32, 39, 41, 49–51]. Similarly, studies observed either no significant association between tumor localization and HRQoL [29, 32, 42, 51] or that rectal cancer survivors reported lower HRQoL than colon cancer survivors [35, 48].

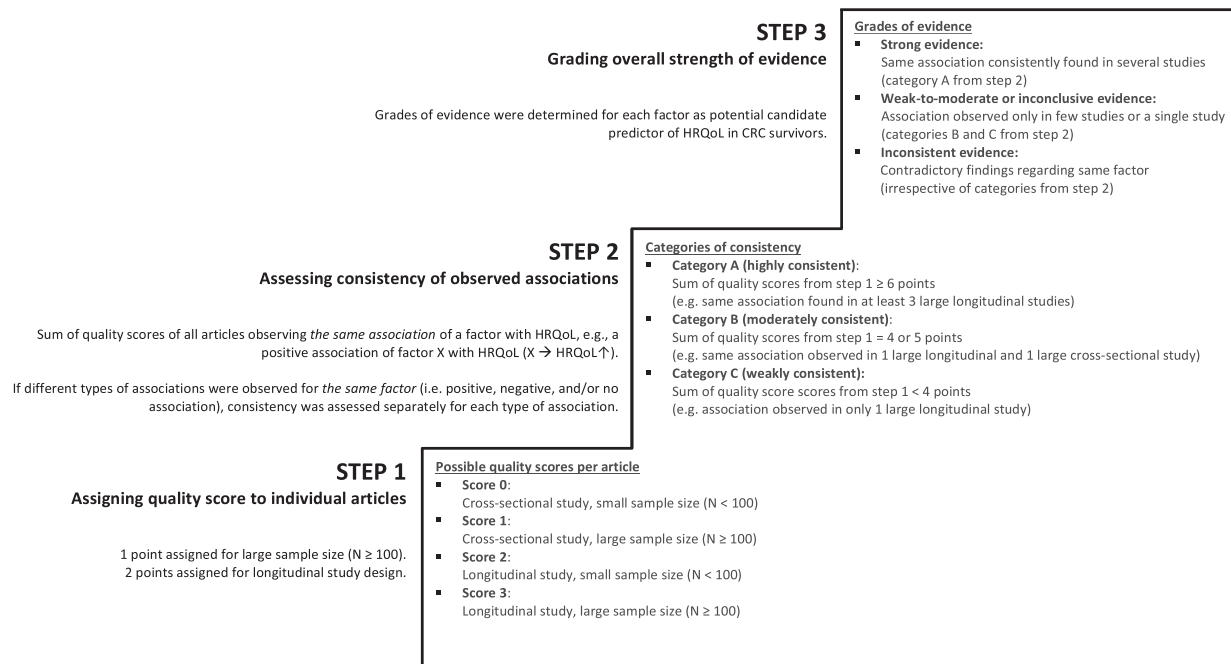


Figure 3. Stepwise scoring and grading procedure applied to assess the strength of evidence for candidate predictors of HRQoL of CRC survivors. In step 2, previously published linking rules for the International Classification of Functioning, Disability and Health (ICF) [24] were used to group factors that were conceptually alike by linking them to the corresponding ICF category. As an example, the factors psychological distress, anxiety, and depression correspond to the same ICF category: b152 Emotional functions. Articles observing similar associations of these factors with HRQoL were therefore grouped, and quality scores from step 1 for these articles could thus be summed to assess the consistency of evidence for associations of these particular factors with HRQoL.

Abbreviations: CRC, colorectal cancer; HRQoL, health-related quality of life.

Body Functions/Structures

Evidence was graded strong for BMI, fatigue, psychological distress, anxiety, and depression. Four studies (2 longitudinal) found that CRC survivors with higher BMI (i.e., >25–30 kg/m²) reported lower HRQoL in periods from 6 months up to 10 years postdiagnosis than survivors with lower BMI [31, 44, 52, 53]. Additionally, 2 longitudinal studies observed that higher levels of fatigue were associated with lower HRQoL reported by CRC survivors up to 5 years postdiagnosis [34, 35]. Four studies (2 longitudinal) found that CRC survivors with higher levels of psychological distress, anxiety, or depression reported lower HRQoL up to 5 years post-treatment [50, 51, 54, 55].

Evidence was graded weak-to-moderate/inconclusive for performance status, fecal control problems or incontinence, nausea, chronic diarrhea, constipation, pain, and smoking. Studies observed that poor performance status (i.e., problems with daily functioning) was associated with lower HRQoL reported by CRC [32] and colon cancer survivors [56]. Other studies observed associations of problems with fecal control or incontinence [34, 50], chronic diarrhea [32, 41], constipation [32], nausea [34], pain [38], and smoking [35, 57, 58] with lower HRQoL of CRC survivors.

Activities

Evidence was graded strong for physical activity. Ten cross-sectional studies showed that lower levels of total physical activity, light physical activity, and moderate-to-vigorous physical activity (MVPA), as well as not adhering to physical activity guidelines (i.e., MVPA ≥150 minutes/week) were

significantly associated with lower HRQoL in CRC survivors up to 10 years postdiagnosis [34, 53, 57–64]. Furthermore, 3 longitudinal studies found that CRC survivors who reported no change or a decrease of their habitual physical activity level postdiagnosis had lower HRQoL than survivors reporting to have increased their physical activity level up to 2 years postdiagnosis [65–67].

Ten cross-sectional studies showed that lower levels of total physical activity, light physical activity and moderate-to-vigorous physical activity (MVPA), as well as not adhering to physical activity guidelines (i.e., MVPA ≥150 minutes/week) were significantly associated with lower HRQoL in CRC survivors up to 10 years postdiagnosis.

Evidence was graded weak-to-moderate/inconclusive for factors related to sedentary behavior and health literacy. Associations were observed of increased television viewing time (a specific sedentary behavior) with decreased HRQoL [68]. Low subjective functional health literacy (i.e., basic reading/writing skills needed to understand health information) was associated with lower HRQoL of CRC survivors [58].

Participation

In the participation domain of the ICF, no factors were identified for which evidence was graded strong. Evidence

Table 3. Overview of articles included in the systematic review (N = 53)

Author (year)	Country	Sample characteristics	Study design	Candidate predictors	HRQoL measure(s)	Qualitative summary of main results	Quality score ^a
Andrykowski (2013) [71]	The Netherlands	1,300 stage I–IV CRC survivors; mean age: 69 years; 57% men; average 4 years postdiagnosis	Cross-sectional	SES as primary determinant; sociodemographic and clinical characteristics	SF-36	Lower SES associated with lower HRQoL	1
Anthony (2003) [75]	U.S.	71 male patients with stage I–IV CRC; median age: 66 years	Longitudinal; measurements at diagnosis (baseline) and 12 months postdiagnosis	Baseline HRQoL; sociodemographic and clinical characteristics	FACT-C	Lower baseline HRQoL and occurrence of perioperative complications associated with lower HRQoL	2
Baldwin (2009) [81]	U.S.	286 CRC survivors with ostomies; mean age: 72 years, 59% men; average 12 years postsurgery	Cross-sectional	Sex; sociodemographic and clinical characteristics	mCOH-QOL-Ostomy; SF-36	Female sex associated with lower HRQoL	1
Blanchard (2008) [57]	U.S.	1,918 stage I–IV CRC survivors; mean age: 70 years; 53% men; 2–10 years postdiagnosis	Cross-sectional	Lifestyle variables (meeting recommendations for PA, fruit and vegetable consumption, and smoking); lifestyle behavior cluster score; sociodemographic and clinical characteristics	SF-36	Not meeting PA, fruit and vegetable, and smoking recommendations (individually and combined in a lifestyle behavior cluster score) associated with lower HRQoL	1
Blanchard (2010) [52]	U.S.	668 stage I–IV CRC survivors; mean age: 70 years; 53% men; 2–10 years postdiagnosis	Cross-sectional	BMI (healthy weight, overweight, obese), PA (meeting recommendations yes/no); sociodemographic and clinical characteristics	SF-36	Higher BMI associated with lower HRQoL	1
Buffart (2012) [62]	The Netherlands	1,371 stage I–IV CRC survivors; mean age: 70 years; 56% men; average 4 years postdiagnosis	Cross-sectional	PA level; sociodemographic and clinical characteristics	SF-36	Lower levels of MVPA associated with lower HRQoL	1
Chambers (2012) [35]	Australia	763 stage I–III CRC survivors; age range: 20–80 years, 54% men	Longitudinal; measurements at 5 months (baseline) and 5 years postdiagnosis	Sociodemographic variables, health and lifestyle behaviors (including PA), psychological variables (optimism, cancer threat appraisal), and perceived social support	FACT-G; FACT-C	Higher disease stage, having a stoma, having a rectal tumor, not having received adjuvant treatment besides surgery, fatigue, smoking, female sex, being single, not having pets, no private health insurance, less perceived social support, negative cancer threat appraisal, lower optimism, and lower baseline HRQoL associated with lower HRQoL PA levels not significantly associated with HRQoL	3
Courneya (1999) [65]	Canada	53 CRC patients (85% stage II and III); mean age: 61 years; 60% men	Longitudinal; measurements approximately 2 months postsurgery (baseline) and then monthly over 4-month period postsurgery	Exercise behavior; baseline HRQoL	FACT-C	No increase in mild exercise from prediagnosis to postsurgery, and lower baseline HRQoL associated with lower HRQoL at follow-up	2

(continued)

Table 3. (continued)

Author (year)	Country	Sample characteristics	Study design	Candidate predictors	HRQoL measure(s)	Qualitative summary of main results	Quality score ^a
Dunn (2013) [47]	Australia	1,844 stage I–IV CRC patients; age range: 20–80 years; 60% men	Longitudinal; measurements at 5, 12, 24, 36, 48, and 60 months postdiagnosis	Psychological variables (optimism, cancer threat appraisal, perceived social support); sociodemographic and clinical characteristics	FACT-C	Poor social support, more negative cognitive appraisal, low optimism, younger age, socioeconomic disadvantage, female sex, and remoteness of residence (i.e., a proxy measure of lower SES) associated with lower HRQoL Educational level not significantly associated with HRQoL	3
Grimmett (2011) [59]	U.K.	495 stage I–III CRC survivors; mean age: 68 years, 59% men; average 2 years postdiagnosis	Cross-sectional	Lifestyle variables (PA, fruit and vegetable consumption, smoking status, alcohol use, and BMI), and health behavior score composed of smoking, alcohol use, PA and fruit and vegetable consumption; sociodemographic and clinical characteristics	EORTC QLQ-C30	Less PA, low fruit and vegetable consumption (<5 daily portions), nondrinking (vs. moderate drinking), normal weight (vs. overweight), and lower health behavior score associated with lower HRQoL Smoking not significantly associated with HRQoL	1
How (2012) [76]	U.K.	62 patients with stage I–III low rectal cancer; median age: 60–67 years; 66% men	Longitudinal; measurements presurgery (baseline) and 1 year postsurgery	Type of surgery (LAR vs. APR); sociodemographic and clinical characteristics	EORTC-QLQ-CR38; Coloplast stoma QoL questionnaire	Having undergone LAR (vs. APR) associated with lower HRQoL	2
Husson (2013) [72]	The Netherlands	139 stage IV (metastatic) CRC survivors; mean age: 66 years; 66% men; average 3 years postdiagnosis	Cross-sectional	Perceived receipt of information about the disease, medical tests, treatment and other care services; satisfaction with received information; sociodemographic and clinical characteristics	SF-36	Perceived receipt of more information about disease and other care services associated with lower HRQoL Satisfaction with received information not significantly associated with HRQoL	1
Husson (2014) [58]	The Netherlands	1,643 stage I–IV CRC survivors; mean age: 69 years; 57% men; average 4 years postdiagnosis	Cross-sectional	Subjective functional health literacy (i.e., basic reading and writing skills needed to understand health information), health behaviors (PA level, alcohol consumption in past 12 months, current smoking status); sociodemographic and clinical characteristics	EORTC QLQ-C30	Low subjective functional health literacy, not meeting PA guidelines, and current smoking associated with lower HRQoL Alcohol consumption and BMI not significantly associated with HRQoL	1

(continued)

Table 3. (continued)

Author (year)	Country	Sample characteristics	Study design	Candidate predictors	HRQoL measure(s)	Qualitative summary of main results	Quality score ^a
Hyphantis (2011) [54]	Greece	144 survivors with nonmetastatic CRC; mean age: 65 years; 67% men; average 2 years postdiagnosis	Longitudinal; measurements at approximately 21 months postsurgery (baseline) and 1 year follow-up (i.e., 12 months after baseline)	Psychological distress, personality variables (ego defense mechanisms, hostility, sense of coherence); sociodemographic and clinical characteristics	WHOQOL-BREF	Lower baseline HRQoL, increased psychological distress, more repression defense, weaker sense of coherence, and being divorced/widowed/separated associated with lower HRQoL	3
Inoue-Choi (2013) [80]	U.S.	383 female stage I–IV CRC survivors among mixed population of cancer survivors (including breast, gynecological, and other cancer types); mean age: 79 years; average 9 years postdiagnosis	Cross-sectional	Healthy lifestyle score based on adherence to WCRF/AICR 2007 [82] recommendations (BMI \leq 25 kg/m ² , moderate-to-high PA level, \geq 5 daily servings of fruits and vegetables, \geq 25 g/d dietary fiber intake, $<$ 80 g/d red meat intake, $<$ 14 g/d alcohol intake, $<$ 2,400 mg/d sodium intake); sociodemographic and clinical characteristics	SF-36	Adhering to fewer lifestyle recommendations associated with lower HRQoL	1
Jansen (2011) [78]	Germany	483 stage I–IV CRC survivors; mean age: 72 years; 38% women; average 5 years postdiagnosis	Cross-sectional	Benefit finding and posttraumatic growth; sociodemographic and clinical characteristics	EORTC QLQ-C30	Lower levels of posttraumatic growth associated with lower HRQoL Benefit finding not significantly associated with HRQoL	1
Johnson (2009) [60]	U.S.	843 stage I–IV CRC survivors; mean age: 82 years; 48% men; average 8 years postdiagnosis	Cross-sectional	PA level (total PA, MVPA, LPA); sociodemographic and clinical characteristics	SF-36	Lower levels of total PA and MVPA associated with lower HRQoL	1
Kerr (2003) [73]	Germany	329 stage I–IV rectal cancer survivors; 70% $<$ 70 years; 63% men	Longitudinal; yearly measurements between 6 months and 4 years postdiagnosis	Patient's satisfaction with hospital stay, physician communication, and aftercare, combined in overall communication variable (clear vs. unclear communication); sociodemographic and clinical characteristics	EORTC QLQ-C30	Unclear communication associated with lower HRQoL	3
Kilic (2012) [77]	Turkey	230 rectal cancer patients who had undergone postoperative adjuvant chemoradiotherapy; median age: 55 years, 55% men; median 5 years post-treatment	Cross-sectional	Type of surgery (LAR or APR) and time since completion of all treatments ($<$ 5 years vs. \geq 5 years post-treatment); sociodemographic and clinical characteristics	EORTC-QLQ-C30; EORTC-QLQ-CR38	Having undergone APR (vs. LAR) and shorter time post-treatment associated with lower HRQoL	1

(continued)

Table 3. (continued)

Author (year)	Country	Sample characteristics	Study design	Candidate predictors	HRQoL measure(s)	Qualitative summary of main results	Quality score ^a
Krouse (2009) [36]	U.S.	491 stage I–IV CRC survivors; mean age: 72 years; 62% men; average 12 years postdiagnosis	Cross-sectional	Presence of a permanent ostomy; sociodemographic and clinical characteristics	mCOH-QOL-Ostomy; SF-36	Presence of a permanent ostomy (vs. anastomosis), younger age, more comorbidity, lower household income, and work status associated with lower HRQoL	1
Lewis (2014) [66]	U.S.	453 stage II colon cancer survivors; mean age: 63 years; 40% men	Longitudinal; measurements at diagnosis (baseline) and at 12 months and 24 months postdiagnosis	PA level assessed over the previous 12 months and other self-reported health behaviors (diet, supplement use, tobacco use, and alcohol intake); sociodemographic and clinical characteristics	FACT-C; SF-12	Lower levels of vigorous PA at baseline and not increasing PA postdiagnosis associated with lower HRQoL	3
Liu (2010) [74]	U.S.	679 stage I–IV CRC survivors; age range: 39–96 years; 59% men; average 11 years postdiagnosis	Cross-sectional	Medical and surgical complications; sociodemographic and clinical characteristics	mCOH-QOL-Ostomy	Having enterocutaneous fistula (among patients with ostomies), and having late and ostomy-related complications (among rectal cancer patients) associated with lower HRQoL	1
Lundy (2009) [37]	U.S.	588 CRC survivors; mean age: 71 years; 59% men; median 10 years postsurgery	Cross-sectional	Household income; sociodemographic and clinical characteristics	mCOH-QOL-Ostomy; SF-36	Lower household income, younger age, and having an ostomy associated with lower HRQoL	1
Lynch (2007) [34]	Australia	1,966 CRC survivors (Duke's stage A to D); age range: 20–80 years; 60% men; average 5 months postdiagnosis.	Cross-sectional	PA level (prediagnosis levels retrospectively assessed); sociodemographic and clinical characteristics	FACT-C	Lower levels of PA, not being married, having a stoma, fatigue, nausea, and fecal problems associated with lower HRQoL	1
Lynch (2008) [67]	Australia	1,488 CRC survivors (Duke's stage A to D); age range: 20–80 years; 59% men	Longitudinal; measurements at 6, 12, and 24 months postdiagnosis	PA level (total PA, and meeting PA guidelines [i.e., inactive, insufficiently active, or sufficiently active]); sociodemographic and clinical characteristics	FACT-C	Lower levels of total PA, moderately and vigorously intense PA, and not meeting PA guidelines associated with lower HRQoL. Not increasing levels of total and moderate-intensity PA associated with decreased HRQoL	3
Lynch (2011) [68]	Australia	1,966 CRC survivors (Duke's stage A to D); age range: 60–80 years; 60% men	Longitudinal; measurements at 5, 12, 24, and 36 months postdiagnosis	Duration of television viewing (total time spent sitting and watching television on average day over past month); PA, BMI; sociodemographic and clinical characteristics	FACT-C	More time spent in television viewing (i.e., a specific sedentary behavior) associated with lower HRQoL	3

(continued)

Table 3. (continued)

Author (year)	Country	Sample characteristics	Study design	Candidate predictors	HRQoL measure(s)	Qualitative summary of main results	Quality score ^a
Mols (2013) [45]	The Netherlands	1,643 stage I-IV CRC survivors; mean age: 69 years; 57% men; average 6 years postdiagnosis	Cross-sectional	Chemotherapy-induced peripheral neuropathy; sociodemographic and clinical characteristics	EORTC QLQ-C30	Having more symptoms related to peripheral neuropathy (e.g., tingling, numbness, and aching or burning pain in toes and feet) associated with lower HRQoL	1
Mols (2014) [39]	The Netherlands	1,019 stage I-IV rectal cancer survivors; mean age: 69 years; 59% men; median 5 years postdiagnosis	Cross-sectional	Presence of an ostomy; sociodemographic and clinical characteristics	EORTC QLQ-C30; EORTC QLQ-CR38	Having a permanent ostomy, more comorbidity, shorter time since diagnosis, and not being married associated with lower HRQoL Tumor stage and treatment regimen not significantly associated with HRQoL	1
Paika (2010) [55]	Greece	162 stage I-IV CRC survivors; mean age: 65 years, 67% men; average 21 months postsurgery	Cross-sectional	Psychological distress, personality variables (ego defense mechanisms, hostility, sense of coherence); sociodemographic and clinical characteristics	WHOQOL-BREF	More psychological distress, less denial, weaker sense of coherence, more repression defense, and more hostility associated with lower HRQoL	1
Peddle (2008) [64]	Canada	413 stage I-IV CRC survivors; mean age: 61 years; 55% men; average 62 months postdiagnosis	Cross-sectional	Exercise behavior (PA level pre-diagnosis, during adjuvant therapy, and during past month); sociodemographic and clinical characteristics	FACT-C	Not adhering to PA guideline associated with lower HRQoL	1
Ramsey (2000) [49]	U.S.	173 stage I-IV CRC survivors; mean age: 70 years; 25% men; from 13 months to > 60 months postdiagnosis	Cross-sectional	Time since diagnosis, age, sex, race (white vs. nonwhite), income status, marital status, and tumor stage	FACT-C	Shorter time since diagnosis and lower income associated with lower HRQoL Tumor stage not significantly associated with HRQoL	1
Ramsey (2002) [41]	U.S.	227 stage I-IV CRC survivors; mean age: 74 years; 54% men; from 5 years to > 15 years postdiagnosis	Cross-sectional	Age, sex, race (white vs. nonwhite), income status, marital status, chronic diarrhea, comorbidity score, time since diagnosis, and tumor stage	FACT-C; SF-36	More comorbidities, lower income, and chronic diarrhea associated with lower HRQoL Time since diagnosis and disease stage not significantly associated with HRQoL	1
Rauch (2004) [38]	France	121 stage I-IV rectal cancer survivors; median age: 64 years, 65% men; median 60 months postdiagnosis.	Cross-sectional	Pain; sociodemographic and clinical characteristics	EORTC QLQ-C30; EORTC QLQ-CR38	Higher levels of pain, more comorbidity, younger age, and having a stoma associated with lower HRQoL	1

(continued)

Table 3. (continued)

Author (year)	Country	Sample characteristics	Study design	Candidate predictors	HRQoL measure(s)	Qualitative summary of main results	Quality score ^a
Rinaldis (2010) [29]	Australia	1,757 CRC patients (Duke's stage A–D); mean age: 65 years; 60% men	Longitudinal; measurements at 5 months (baseline) and 12 months postdiagnosis	Benefit finding; sociodemographic and clinical characteristics	FACT-C	Less benefit finding, lower baseline HRQoL, younger age, having a permanent stoma, higher disease stage, more treatments received (surgery and one or more adjuvant therapies vs. surgery only), and female sex associated with lower HRQoL	3
Ristvedt (2009) [50]	U.S.	80 stage I–III rectal cancer survivors; mean age: 68 years; 56% men	Longitudinal; measurements soon after initial treatment (baseline) and 2–5 years later (average: 4 years)	Trait anxiety; sociodemographic and clinical characteristics	FACT-C	High trait anxiety, fecal incontinence, male sex, and shorter time since diagnosis associated with lower HRQoL Having a stoma not significantly associated with HRQoL	2
Ross (2007) [30]	Denmark	249 CRC survivors (Duke's stage A–D); mean age: 67 years; 49% men	Longitudinal; measurements at 3, 6, 12, and 24 months postsurgery	Presence of a stoma; sociodemographic and clinical characteristics	EORTC QLQ-C30; EORTC QLQ-CR38	Having a stoma associated with lower HRQoL	3
Salsman (2011) [79]	U.S., Puerto Rico	826 stage I–IV CRC survivors from two studies: 1. 258 CRC survivors; mean age: 61 years; 57% men; average 17 months postdiagnosis 2. 568 CRC survivors; mean age: 67 years; 49% men; average 19 months postdiagnosis	Cross-sectional	Spiritual well-being (faith and meaning/peace subscales); sociodemographic and clinical characteristics	FACT-C	Less faith and meaning/peace associated with lower HRQoL	1
Sapp (2003) [70]	U.S.	259 female CRC survivors (both localized and nonlocalized extent of disease); mean age: 72 years; average 9 years postdiagnosis	Cross-sectional	Social network measures (social network summary scores: social network size, number of frequent contacts, and overall social connectedness); sociodemographic and clinical characteristics	SF-36	Worse social network measures (i.e., lower frequency of contacts with close relatives/friends, smaller network size, lower frequency of participating in religious/community events, and lower overall social connectedness) associated with lower HRQoL	1

(continued)

Table 3. (continued)

Author (year)	Country	Sample characteristics	Study design	Candidate predictors	HRQoL measure(s)	Qualitative summary of main results	Quality score ^a
Schag (1994) [56]	U.S.	117 stage I–IV colon cancer survivors; mean age: 65 years; 66% men; average 3 years postdiagnosis	Cross-sectional	Karnofsky performance status (i.e., patients' degree of problems with activities of daily life and general well-being), type of hospital, sex, work status, and medical comorbidity index	CARES QoL index	Worse performance status, not receiving treatment in private hospital, female sex, and not working associated with lower HRQoL Medical comorbidity index not significantly associated with HRQoL	1
Schlesinger (2014) [53]	Germany	1,389 stage I–IV CRC survivors; mean age: 69 years; 56% men; median 6 years postdiagnosis	Cross-sectional	Lifestyle score composed of four lifestyle factors: BMI, healthy diet index, PA, and smoking status; alcohol consumption; sociodemographic and clinical characteristics	EORTC QLQ-C30	Unfavorable lifestyle score (i.e., less favorable lifestyle factors), higher BMI, unhealthy dietary index, and less recreational PA associated with lower HRQoL	1
Sharma (2007) [33]	U.K.	104 stage I–IV CRC patients; mean age: 68 years; 67% men	Longitudinal; measurements at 5–12 days presurgery (baseline) and 6 weeks after hospital discharge	Baseline HRQoL; sociodemographic and clinical characteristics	FACT-C; EQ-5D	Lower baseline HRQoL, younger age, higher tumor stage, postoperative morbidity, and presence of a stoma associated with lower HRQoL	3
Soerjomataram (2012) [42]	The Netherlands	1,291 stage I–IV CRC survivors; age range: 50 to ≥80 years; 57% men; 2–10 years postdiagnosis	Cross-sectional	Sociodemographic and clinical characteristics	SF-36	Higher tumor stage, having one or more comorbid conditions at diagnosis, lower SES, and female sex associated with lower HRQoL Age, tumor site, time since diagnosis, and type of treatment regimen not significantly associated with HRQoL	1
Steginga (2009) [31]	Australia	1,822 CRC survivors (Duke's stage A–D); mean age: 65 years; 60% men	Longitudinal; measurements at 6 months (baseline) and 24 months postdiagnosis	Sociodemographic, medical, lifestyle-related, and psychological variables	FACT-C	Lower baseline HRQoL, negative cancer threat appraisal, lower optimism, more comorbidities, not having private health insurance, higher educational attainment, higher BMI, female sex, and having a stoma associated with lower HRQoL	3
Thong (2011) [43]	The Netherlands	848 stage I–IV colon cancer survivors; mean age: 69 years; 52% men; average 4 years postdiagnosis	Cross-sectional	Sociodemographic and clinical characteristics	EORTC-QLQ-CR38; SF-36	Shorter time since diagnosis, not having received chemotherapy, more comorbidity, higher tumor stage, being married, younger age, and female sex associated with lower HRQoL	1

(continued)

Table 3. (continued)

Author (year)	Country	Sample characteristics	Study design	Candidate predictors	HRQoL measure(s)	Qualitative summary of main results	Quality score ^a
Thong (2011) [40]	The Netherlands	340 stage I–III rectal cancer survivors; mean age: 69 years; 66% men; average 4 years postdiagnosis	Cross-sectional	pRT; sociodemographic and clinical characteristics	EORTC QLQ-CR38; SF-36	pRT (vs. surgery only), comorbidity, presence of a stoma, disease recurrence, and higher tumor stage associated with lower HRQoL	1
Thraen-Borowski (2013) [61]	U.S.	832 CRC survivors; mean age: 82 years; 48% men; average 8 years postdiagnosis	Cross-sectional	PA level and social participation (participation in social activities, such as visiting friends and doing volunteer work); sociodemographic and clinical characteristics	SF-36	Less social participation and lower levels of PA (i.e., lower levels of MVPA and LPA, less planned exercise, and not meeting PA recommendations) associated with lower HRQoL	1
Toftnagen (2013) [46]	U.S.	111 stage III–IV CRC survivors; mean age: 61 years; 51% men; average 3 years since initiation of chemotherapy	Cross-sectional	Chemotherapy-induced peripheral neuropathy, symptom experience scale (sensory and motor symptoms), and interference scale (interference with activities of daily living); sociodemographic and clinical characteristics	SF-36	More problems related to peripheral neuropathy (i.e., higher scores on symptom experience and interference scales) associated with lower HRQoL	1
Trentham-Dietz (2003) [44]	U.S.	307 female survivors of invasive CRC; mean age at follow-up: 72 years	Longitudinal; measurements at approximately 1 year (baseline) and on average 9 years (range: 7–11 years) postdiagnosis	Sociodemographic, clinical, and lifestyle-related characteristics	SF-36	Older age, more comorbidities, and higher BMI at follow-up associated with lower HRQoL	3
Tsunoda (2005) [51]	Japan	128 stage I–IV CRC patients; mean age: 69 years; 58% men; average 40 months since surgery	Cross-sectional	Psychological distress (anxiety, depression); sociodemographic and clinical characteristics	EORTC-QLQ-C30	Higher levels depression and anxiety associated with lower HRQoL Age, sex, tumor localization, and tumor stage not significantly associated with HRQoL	1
Vallance (2014) [63]	Canada, Australia	178 stage I–III colon cancer survivors; mean age: 64 years; 56% men; average 19 months postdiagnosis	Cross-sectional	Accelerometer-assessed PA level and sedentary time; sociodemographic and clinical characteristics	FACT-C	Lower levels of MVPA and not adhering to PA guideline associated with lower HRQoL Sedentary time not significantly associated with HRQoL	1

(continued)

Table 3. (continued)

Author (year)	Country	Sample characteristics	Study design	Candidate predictors	HRQoL measure(s)	Qualitative summary of main results	Quality score ^a
Wilson (2006) [32]	U.K.	201 CRC survivors (Duke's stage A-D); mean age: 68 years; 62% men; average 6 weeks after hospital discharge	Cross-sectional	Treatment factors and complications; sociodemographic and clinical characteristics	EORTC QLQ-C30; EORTC-QLQ-CR38; FACT-C; SF12, EQ-5D	Younger age, lower preoperative performance status, presence of a stoma, diarrhea, and constipation associated with lower HRQoL Tumor localization and stage not significantly associated with HRQoL	1
Wong (2013) [48]	China	515 stage I-IV CRC survivors; mean age: 63 years; 58% men; average 47 months postdiagnosis	Cross-sectional	Sociodemographic and clinical characteristics	SF-12; SF-6D	Higher tumor stage, rectal (vs. colon) tumor, and shorter time since diagnosis associated with lower HRQoL Presence of comorbidities and family history of CRC not significantly associated with HRQoL	1
Yost (2008) [69]	U.S.	568 stage I-IV CRC survivors; mean age: 67 years; 48% men	Longitudinal; measurements at approximately 9 months (baseline) and approximately 19 months postdiagnosis	Perceived quality of care (e.g., treatment and health information, access to cancer care, confidence in providers, and control of pain/discomfort and nausea/vomiting); sociodemographic and clinical characteristics	FACT-C	Lower baseline HRQoL, poorer self-reported general health; more perceived problems with treatment information, with control of pain/discomfort and with control of nausea/vomiting; male sex, Hispanic ethnicity, and not being married/living together associated with lower HRQoL	3

^a A quality score was assigned to each article based on study design and sample size: 0 points (cross-sectional study; $N < 100$); 1 point (cross-sectional study; $N \geq 100$); 2 points (longitudinal study; $N < 100$); and 3 points (longitudinal study; $N \geq 100$).

Abbreviations: APR, abdominoperineal resection; BMI, body mass index; CARES, Cancer Rehabilitation Evaluation System; CRC, colorectal cancer; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30; EORTC QLQ-CR38, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Colorectal 38; EQ-5D, EuroQOL 5 dimensions; FACT-G, Functional Assessment of Cancer Therapy-General; FACT-C, Functional Assessment of Cancer Therapy-Colorectal; HRQoL, health-related quality of life; LAR, low anterior resection; LPA, light physical activity; mCOH-QOL-Ostomy, modified City of Hope Quality of Life-Ostomy questionnaire; MVPA, moderate-to-vigorous physical activity; PA, physical activity; pRT, preoperative radiotherapy; SES, socioeconomic status; SF-6D, Short Form, Health Survey-6-Dimensions; SF-12, Short Form Health Survey-12; SF-36, Short Form Health Survey-36; SF-36v2, Short Form Health Survey-36 version 2; WCRF/AICR, World Cancer Research Fund/American Institute for Cancer Research; WHOQOL-BREF, World Health Organization Quality of Life Instrument, Short Form.

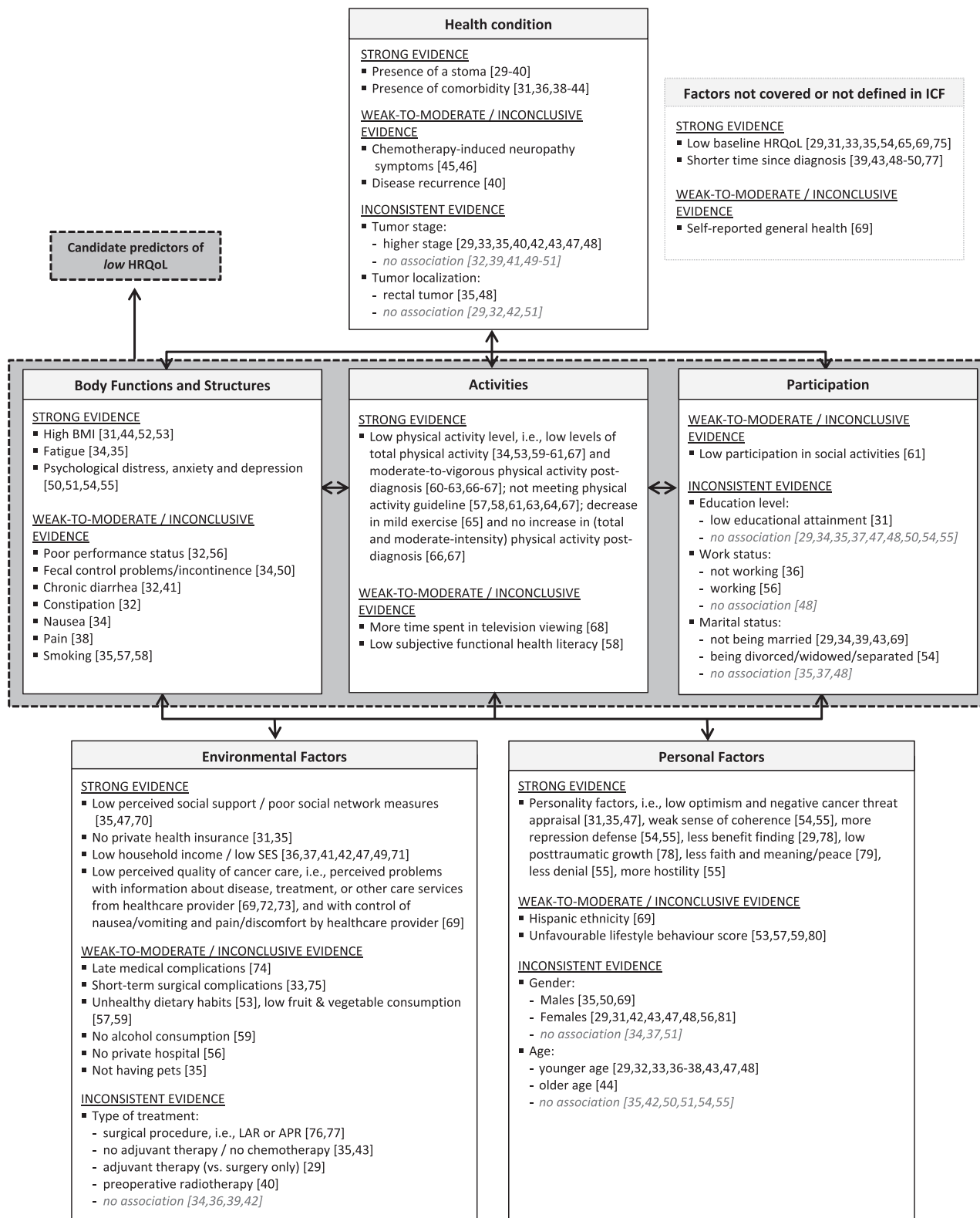


Figure 4. Candidate predictors of low HRQoL of colorectal cancer survivors, mapped into the biopsychosocial framework of the ICF. Candidate HRQoL predictors are arranged in the framework according to the graded strength of evidence (i.e., strong evidence, weak-to-moderate or inconclusive evidence, and inconsistent evidence).

Abbreviations: APR, abdominoperineal resection; BMI, body mass index; HRQoL, health-related quality of life; ICF, International Classification of Functioning, Disability and Health; LAR, low anterior resection; SES, socioeconomic status.

was graded weak-to-moderate/inconclusive for participation in social activities, with only one study observing that less participation in social activities (e.g., visiting family/friends) was associated with lower HRQoL of CRC survivors [61].

Evidence was graded inconsistent for education level, work status, and marital status. One study observed associations of lower educational attainment with lower HRQoL of CRC survivors [31], whereas nine other studies did not observe an association between education level and HRQoL [29, 34, 35, 37, 47, 48, 50, 54, 55]. Additionally, either working [56] or not working [36] was observed to be associated with lower HRQoL of CRC survivors, or no significant association between HRQoL and work status was observed [48]. Several studies observed either that not being married or being divorced, widowed, or separated was associated with lower HRQoL in CRC survivors [29, 34, 39, 43, 54, 69] or found no significant association between marital status and HRQoL [35, 37, 48].

Environmental Factors

Evidence was graded strong for perceived social support; for factors related to socioeconomic characteristics, including health insurance, household income, and socioeconomic status (SES); and for factors related to perceived quality of care. In 3 studies (2 longitudinal), less perceived social support and worse social network measures (e.g., fewer social contacts) were found to be associated with lower HRQoL reported by CRC survivors 5 or more years postdiagnosis [35, 47, 70]. Regarding socioeconomic factors, 2 longitudinal studies in CRC survivors observed significantly lower HRQoL 2–5 years postdiagnosis among survivors who did not have private health insurance at 5–6 months postdiagnosis [31, 35]. Furthermore, 7 studies (1 longitudinal) found that lower household income or lower SES were associated with lower HRQoL reported by CRC survivors between 5 months and 10 years postdiagnosis [36, 37, 41, 42, 47, 49, 71]. Finally, 3 studies (2 longitudinal) observed that perceiving more problems with provision of information by care providers (e.g., about the diagnosis, illness, treatments, complications, and care services) was associated with lower HRQoL reported by both CRC survivors and rectal cancer survivors 2–4 years postdiagnosis [69, 72, 73].

Evidence was graded weak-to-moderate/inconclusive for late medical complications, short-term surgical complications, factors related to dietary habits, having received treatment in a private hospital, and having pets. In rectal cancer survivors with ostomies, ostomy-related late medical complications (e.g., fistula or urinary retention) were observed to be associated with lower HRQoL [74]. Additionally, studies observed associations of short-term surgical complications and perioperative morbidity (e.g., wound infections) with lower HRQoL of CRC survivors [33, 75]. Studies also observed that CRC survivors reporting unhealthy dietary habits (i.e., low consumption of fruits, vegetables, and whole-grain bread; and high consumption of red and processed meat) reported lower HRQoL than survivors reporting healthy habits [53, 57, 59]. Furthermore, one study observed that CRC survivors who did not drink alcohol reported lower HRQoL than moderate alcohol drinkers [59]. Finally, not having received

treatment in a private hospital [56] and not having pets [35] were observed to be associated with lower HRQoL of CRC survivors.

Evidence was graded inconsistent for factors related to cancer treatment. Contrasting results were found regarding the association of different types of surgery with HRQoL in rectal cancer survivors [76, 77]. Additionally, studies in CRC survivors observed either no significant association of treatment-related variables with HRQoL [34, 36, 39, 42] or that not having received adjuvant therapy besides surgery was associated with lower HRQoL [35, 43]. In contrast, other studies observed that having received adjuvant therapy (vs. surgery only) [29] or preoperative radiotherapy [40] was associated with lower HRQoL in CRC and rectal cancer survivors, respectively.

Personal Factors

Evidence was graded strong for personality factors. In 8 studies (5 longitudinal), a number of psychological variables related to the personality of CRC survivors were shown to be associated with lower HRQoL up to 5 years postdiagnosis, including lower optimism and negative cancer-threat appraisal [31, 35, 47], a weaker sense of coherence [54, 55], more repression defense [54, 55], less benefit finding [29, 78], lower posttraumatic growth [78], less faith and meaning/peace [79], and less denial and more hostility [55].

Evidence was graded weak-to-moderate/inconclusive for factors related to ethnicity and personal lifestyle behavior. In a study from the U.S., a significant association was observed between Hispanic ethnicity and low HRQoL in CRC survivors [69]. Regarding lifestyle-related factors, studies have observed that CRC survivors reported lower HRQoL when meeting fewer healthy lifestyle recommendations [53, 57, 59, 80].

Evidence was graded inconsistent for sex and age. Several studies observed that either female CRC survivors reported lower HRQoL [29, 31, 42, 43, 47, 48, 56, 81] or that male survivors reported lower HRQoL [35, 50, 69]. Other studies, however, did not observe a significant association between sex and HRQoL [34, 37, 51]. Younger age was observed to be associated with lower HRQoL of CRC survivors [29, 32, 33, 36–38, 43, 47, 48], or no significant association between age and HRQoL was observed [35, 42, 50, 51, 54, 55]; a single study among female CRC survivors observed that older age was associated with lower HRQoL [44].

Factors Not Covered or Defined in ICF

Some potentially relevant candidate HRQoL predictors identified from the included articles could not be linked to an appropriate ICF category because the meaningful concept represented by these factors was either too broad to be defined by a single, specific ICF category or domain, or was not covered by any category in the ICF. These factors, therefore, could not be mapped into the ICF framework and are depicted separately in Figure 4.

Evidence was graded strong for baseline HRQoL and time since diagnosis, and weak-to-moderate/inconclusive for self-reported general health. In 8 longitudinal studies, it was shown that lower HRQoL reported by CRC survivors at an earlier time

point during the study (i.e., baseline) was associated with lower HRQoL reported at later time points during study follow-up from 6 weeks post-treatment up to 5 years postdiagnosis [29, 31, 33, 35, 54, 65, 69, 75]. Furthermore, six studies (one longitudinal) showed that shorter time since diagnosis was associated with lower HRQoL reported by CRC survivors [39, 43, 48–50, 77]. Finally, poorer self-reported general health was observed to be associated with lower HRQoL of CRC survivors [69].

DISCUSSION

This systematic literature review presents a qualitative overview of the current state of evidence for candidate predictors of HRQoL of CRC survivors, using a novel, ICF-based approach. A conceptual biopsychosocial HRQoL model was developed providing a comprehensive overview of potentially relevant candidate HRQoL predictors according to their level of evidence (Fig. 4). This framework may serve as an evidence base for selecting relevant candidate predictors when planning to develop a prediction model of HRQoL for identifying CRC survivors at risk of HRQoL deterioration. Evidence regarding candidate predictors of low HRQoL was found to be strongest for the presence of a stoma and comorbidity (ICF domain: health condition); for high BMI and high levels of fatigue and psychological distress, anxiety, and depression (body functions/structures); for low levels of physical activity (activities); for low perceived social support, for factors related to low SES, and for low perceived quality of care (environmental factors); for several personality factors including low optimism and negative cancer threat appraisal (personal factors); and for low baseline HRQoL and shorter time since diagnosis (factors not covered or defined in ICF).

Predictors related to modifiable behaviors or characteristics of CRC survivors may provide targets for tailored interventions to prevent HRQoL deterioration in at-risk individuals. As factors related to modifiable lifestyle behavior, physical activity and BMI emerged as the most relevant candidate HRQoL predictors. Because physical activity and BMI are related to dietary habits of CRC survivors and other lifestyle behaviors such as smoking and alcohol consumption [83], personal lifestyle behaviors of CRC survivors should preferably be regarded in combination for prediction of their HRQoL. Indeed, CRC survivors adhering to multiple healthy lifestyle behaviors were found to report better HRQoL than survivors adhering to less healthy behaviors [53, 57, 59, 80], and beneficial effects of multibehavior lifestyle interventions on CRC survivors' HRQoL have been shown [84–86]. In addition, several potentially modifiable psychological factors related to individual coping skills of CRC survivors were identified as relevant candidate HRQoL predictors. By influencing stress responses and ego defense mechanisms following major life events, such as a cancer diagnosis, these factors can contribute to the development of psychosomatic symptoms (e.g., fatigue, anxiety and depression) [87–89]. Interventions focusing on coping skills of CRC survivors in response to significant health stressors (e.g., cancer diagnosis/treatment, presence of a stoma or multimorbidity) may be a promising strategy to safeguard at-risk individuals against HRQoL deterioration [90].

Because physical activity and BMI are related to dietary habits of CRC survivors and other lifestyle behaviors such as smoking and alcohol consumption [83], personal lifestyle behaviors of CRC survivors should preferably be regarded in combination for prediction of their HRQoL.

Evidence was found to be inconsistent for tumor- and treatment-related factors, education level, work, marital status, sex, and age. Several reasons could be put forward for these inconsistent findings. First, it could be that the factor of interest is not a true predictor of CRC survivors' HRQoL. This might be the case for education level, for which no significant association with HRQoL was observed in the majority of studies. Second, it could also be that the factor of interest may be an effect modifier (e.g., sex and age [36]), for which prediction models should be stratified. Third, inconsistent findings may be attributable to heterogeneity of CRC survivor populations across studies. For instance, studies conducted at different times postdiagnosis could have affected observed associations of certain factors with HRQoL, such as tumor stage and type of treatment, which might be more relevant for predicting HRQoL in the short term, while becoming less important over time. This would suggest that prediction models need to be developed according to time since diagnosis—that is, separate models for estimating short-term versus longer-term HRQoL. Finally, between-study differences in measurement methods (e.g., of work or marital status) may have produced inconsistent findings regarding factors representing similar concepts.

Of note, weak-to-moderate or inconclusive evidence was found for a variety of factors in every ICF domain. Although several of these factors might be very relevant for HRQoL prediction in CRC survivors (e.g., chemotherapy-induced neuropathy, sedentary behavior, and dietary habits), they had only been examined in a single or few studies that mostly had a cross-sectional design. Strikingly, no factors within the participation domain of the ICF were identified as potentially relevant candidate HRQoL predictors, for which evidence could be graded strong. As the societal aspect of functioning, the level of participation of CRC survivors presumably is relevant for their HRQoL. More research on these factors is thus warranted, preferably through prospective studies.

A major strength of this systematic review was the use of the ICF framework as guiding conceptual model of HRQoL, constituting a novel approach that has resulted in a comprehensive overview of biopsychosocial candidate HRQoL predictors for CRC survivors (Fig. 4). Our model not only encompasses biomedical and somatic aspects of health and functioning (e.g., medical conditions and disease symptoms) but also psychosocial aspects (e.g., ability to perform activities and participate in social life) and environmental and personal factors that are likely to be relevant for predicting HRQoL. Previous systematic reviews focused only on a specific subpopulation of CRC survivors [3] or on a specific class of predictors [89, 91]. As a potential limitation, we cannot exclude the possibility of publication bias. Potentially relevant articles may have been missed in our literature search, which might

have been too specific. Furthermore, because there currently is a paucity of studies on prediction of HRQoL in CRC survivors, we had to rely on association studies for identification of potential candidate HRQoL predictors.

CONCLUSION

The results of this systematic review provide conceptual guidance for developing evidence-based prediction models for HRQoL of CRC survivors, which currently are not available. A crucial first step in prediction model development is a priori identification and evidence-based selection of relevant candidate predictors [11, 92, 93]. For that purpose, our ICF-based biopsychosocial conceptual model (Fig. 4) can be used to select candidate HRQoL predictors. Depending on available data for model development, we recommend including candidate predictors for which strong evidence was provided. Additionally, based on relevant subject matter knowledge, it is to be recommended to also consider factors for which evidence was found to be inconsistent, in order to assess their added value or potential role as effect modifiers (e.g., sex-specific models). Finally, depending on specific study circumstances and intended use of the prediction model, development of separate models (e.g., for different time periods after diagnosis or treatment) may be considered, as may selection of additional candidate predictors for which evidence was graded weak-to-moderate/inconclusive.

Importantly, the process of developing useful prediction models includes more than evidence-based selection of candidate predictors and statistical development of multivariable models. It must always include an internal validation step to optimize model performance by adjusting for overfitting (preferably using bootstrapping methods), and an external validation step to assess model performance in other, similar populations than the population used for model development (i.e., model transferability/generalizability). Finally, the usefulness of a validated prediction model also needs to be evaluated in impact studies to assess whether applying the model improves patient outcomes. Evidence-based prediction models can be used in clinical oncology practice to identify individuals at risk for future HRQoL deterioration and to provide potential targets for behavioral and psychosocial interventions

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that may ultimately enable better tailoring of individualized care aimed at safeguarding the HRQoL of CRC survivors.

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