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The Impact of Body Mass Index and Waist Circumference on Health-related Quality of Life Among Colorectal Cancer Survivors: Results from the PROFILES Registry

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ABSTRACT

Background: We aimed to assess the association of waist circumference (WC) and body mass index (BMI) with health-related quality of life (HRQL) among colorectal cancer (CRC) survivors. **Methods:** CRC survivors diagnosed between 2000 and 2009 completed questionnaires in August 2013 (with self-reported weight, height, and self-assessed WC) and January 2014 (with HRQL using the EORTC-QLQ-C30). Clinical characteristics were retrieved from the Netherlands Cancer Registry. In multivariable linear regression analyses associations of BMI only, WC only and both BMI and WC with HRQL outcomes were assessed. **Results:** 1,111 CRC survivors were included of whom 34% had a normal weight ($18.5 \leq \text{BMI} < 25 \text{ kg/m}^2$), 49% had overweight ($25 \leq \text{BMI} < 30 \text{ kg/m}^2$), 17% had obesity ($\text{BMI} \geq 30 \text{ kg/m}^2$), and 44% had an increased WC (i.e., >102 and >88 cm for men and women, respectively). Both BMI and WC were separately associated with worse global health status, functioning, and more symptoms of fatigue. Increased WC was associated with lower physical, role and emotional functioning, regardless of BMI, with average differences ranging between 3 and 5 points. **Conclusion:** Future research on HRQL among CRC survivors should consider both BMI and WC. Furthermore, weight reduction trials should not only focus on general weight loss but also on the loss of abdominal fat.

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Introduction

Colorectal cancer (CRC) is the third most common cancer in men (746,000 incident cases, 10.0% of all cancer cases) and the second in women (614,000 incident cases, 9.2% of all cancer cases) and the incidence is still increasing worldwide (1,2). At the same time, mortality has decreased, due to earlier diagnosis and improved therapies, leading to an increase in the prevalence of CRC (3). Because of the high number of CRC survivors, studying health-related quality of life (HRQL) and understanding factors associated with HRQL becomes a major issue.

Several studies have addressed HRQL of long-term (≥ 5 yr) CRC survivors. Two systematic reviews showed that CRC survivors had a good overall HRQL, but may have slightly lower physical functioning and more psychological problems, including depression, anxiety and distress than the general population (4,5). Furthermore, survivors reported to suffer from bowel problems and

sexual dysfunction (4,6). Apart from having a stoma and recurrence of the disease, mainly socio-demographic and health-related factors such as age, social network size, income, education, body mass index (BMI) and the number of comorbidities were associated with HRQL (4,5).

BMI is also considered to be associated with HRQL in CRC, but the literature is not conclusive on this matter. A cross-sectional survey showed that obese CRC survivors reported significantly poorer physical functioning and mental health compared with overweight or normal weight CRC survivors (7). Three studies among CRC survivors showed that a higher BMI was associated with worse scores in physical functioning, role functioning, bodily pain, general health, fatigue and vitality (8–10). However, Rodriguez et al. found no association between BMI and physical, mental, and overall quality of life

among 5- to 7-yr CRC survivors (11). The discrepancy in results might be due to the lack of information about the amount of abdominal fat, which is considered to have more influence on cancer, prognosis and HRQL than BMI (12–14). Waist circumference (WC) has been suggested to be a reliable estimate for abdominal obesity (15). Several studies show that WC is associated with complications after rectal cancer surgery, and a reduced disease specific survival (16–18). However, as far as we know, the association between WC and HRQL among CRC survivors has not been studied yet.

In this study, we therefore aimed to assess the association between WC, BMI and HRQL among long-term CRC survivors. We hypothesized that WC is associated with HRQL outcomes independent of BMI.

Methods

Setting and Study Population

Data from a large population-based study among CRC patients were used. All CRC patients diagnosed between January 2000 and June 2009 were sampled from the southern area of the Netherlands Cancer Registry (NCR). The NCR contains clinical data on all newly diagnosed cancer patients in the Netherlands. The southern area comprises 2.4 million inhabitants, 10 hospitals and 2 radiotherapy institutes. After the initial patient selection, the Patient Reported Outcomes Following Initial Treatment and Long term Evaluation of Survivorship (PROFILES) registry was used for the longitudinal patient reported data collection (19). Patients with cognitive impairments, unverifiable

addresses and patients who died prior to the study started were excluded from the initial selection. The initial data collection started in 2010. In the current study, we present data regarding weight, height and WC which were collected in August 2013 and data regarding HRQL which were collected in January 2014 (Fig. 1). Ethical approval for the study was obtained from the local certified Medical Ethics Committee of the Maxima Medical Centre Veldhoven. A complete overview of the selection process can be found elsewhere (20). Data from this longitudinal study are (partly) available online for noncommercial scientific research, subject to study question, privacy, and confidentiality restrictions, and registration from PROFILES (www.profilesregistry.nl).

Data Collection

CRC patients were invited for participation via a letter from their (former) attending physician. The letter included a secured link with login and password to the online questionnaire, or patients could request a paper version of the questionnaire, whichever they preferred. After two months, a reminder with a paper questionnaire was sent. Patients were reassured that nonparticipation had no consequences for their follow-up care or treatment.

Body Composition, Sociodemographic and Clinical Characteristics

Weight (kg) and height (cm) were self-reported and used to calculate BMI (kg/m^2). BMI was categorized as normal

Figure 1. Flowchart of the study population.

weight ($18.5 \leq \text{BMI} < 25 \text{ kg/m}^2$), overweight ($25 \leq \text{BMI} < 30 \text{ kg/m}^2$) or obesity ($\text{BMI} \geq 30 \text{ kg/m}^2$). Patients with underweight ($\text{BMI} < 18.5 \text{ kg/m}^2$) were excluded. A measuring tape was provided with the questionnaire and patients were instructed to measure their WC (narrowest circumference of the waist), while standing, without bulky clothing on. Increased WC was defined as $>102 \text{ cm}$ and $>88 \text{ cm}$ for men and women, respectively (21). Age, gender and clinical information including cancer treatment and stage were derived from the NCR. Educational level was derived from the questionnaire distributed in 2013.

Health-Related Quality Of Life (HRQL)

The validated European Organization for Research and Treatment of Cancer – Quality of Life Questionnaire (EORTC-QLQ)-C30 was used to assess HRQL (22). As the previous research showed that obesity among CRC patients was mainly associated with functioning scales and more symptoms of fatigue (10,23) and to prevent spurious findings, only functioning scales (i.e., physical, emotional, social, cognitive, and role functioning), fatigue, and global health status were included in the analyses. All items were scored on a 4-point Likert scale ranging from “not at all” to “very much”, except for the items regarding global health status which were scored from 1 (very poor) to 7 (excellent). All scores were linearly transformed to a 1–100 scale. Higher scores on functioning and global health status represent better functioning, while a higher score on fatigue symptoms correspond to more fatigue.

Statistical Analyses

Differences in baseline characteristics between CRC patients with normal weight, overweight or obesity were assessed using one-way ANOVA (for continuous variables) and χ^2 analyses (for categorical variables). Similarly, differences in mean HRQL scores according to BMI categories and WC were assessed with one-way ANOVA or independent-samples *t*-test. The interaction between gender*BMI on HRQL was tested in adjusted linear regression models; similarly the interaction between gender*WC was tested. Both interaction terms were not significant and omitted in further analyses. Also, the interaction effect of BMI*WC on HRQL was tested. In case the term was not significant, both BMI and WC were included in the model to test for their independent effect; if this interaction term was significant, results for the outcomes were stratified by BMI. A significant interaction between BMI*WC was observed for fatigue and global health status. Four multivariable linear regression models were constructed. Both the association of BMI,

not adjusted for WC, with HRQL (Model 1) and the association of WC, not adjusted for BMI, with HRQL were assessed (Model 2). For those outcomes where no interaction between BMI and WC was observed, Model 3 was constructed in which the association of both BMI and WC with HRQL was assessed. As the interaction between BMI and WC was significant for fatigue and global health status, results were stratified for normal, underweight, and obese CRC survivors (Model 4). All models were adjusted for confounding factors determined a priori: age, sex, educational level, time since cancer diagnosis, cancer stage, and type of treatment.

A *p*-value <0.05 was regarded as statistically significant. In order to prevent multiple testing and associated type 1 errors, all *p*-values <0.01 were also shown. All analyses were conducted using the Statistical Package for Social Sciences (SPSS) version 17.0 (IBM).

Results

Characteristics of the Study Population

Of the 1,625 CRC survivors who were invited in August 2013, 1,111 (68%) were included (Fig. 1). Nonrespondents did not differ regarding gender, time since cancer diagnosis or cancer treatment as compared to respondents. Nonrespondents were slightly younger (69.4 ± 10.7 vs. 70.7 ± 9.2 yr) and differed regarding cancer stage at diagnosis (27% vs. 31% with stage I disease). Respondents with unknown weight, height, WC or with underweight ($n = 48$) did not differ regarding time since diagnosis, cancer treatment or stage, but were slightly older (75 ± 10 vs. 70 ± 9 yr) and differed regarding gender (62% vs. 42% female) as compared to the full sample ($n = 1,111$). Among the 1,111 included CRC survivors, 34% had a normal weight, 49% were overweight and 17% were obese. The majority of overweight (66%) and obese patients (56%) were male as compared to 48% in the normal weight group ($p < 0.01$). No differences were found regarding age, educational level, time since diagnosis, received cancer treatment, and cancer stage between the different BMI categories (Table 1). In total, 493 (44%) CRC survivors had increased WC which differed according to BMI category ($p < 0.01$, Fig. 2). Twelve percent of normal weight survivors had an increased WC, whereas 49% of overweight and 11% of obese survivors had a normal WC. The correlation between waist and BMI was $r = 0.57$.

Health-Related Quality of Life

Patients with increased WC reported worse physical functioning and higher fatigue scores than those with

Table 1. Sociodemographic and clinical characteristics of the study population in different BMI categories.

	Normal weight <i>n</i> = 377 (34%) <i>n</i> (%) or mean $\pm$ SD	Overweight <i>n</i> = 546 (49%) <i>n</i> (%) or mean $\pm$ SD	Obesity <i>n</i> = 188 (17%) <i>n</i> (%) or mean $\pm$ SD	<i>P</i> -value
Male	181 (48)	360 (66)	105 (56)	<0.01
Age (yr)	71 $\pm$ 9	71 $\pm$ 9	70 $\pm$ 9	0.60
BMI (kg/m ²)	23 $\pm$ 2	27 $\pm$ 1	33 $\pm$ 5	<0.01
WC (cm)	86 $\pm$ 12	98 $\pm$ 11	109 $\pm$ 14	<0.01
<i>n</i> (%) increased WC ^a	46 (12)	279 (51)	168 (89)	<0.01
Time since diagnosis (yr)	8 $\pm$ 3	8 $\pm$ 3	8 $\pm$ 3	0.84
Educational level ^b				
Low	34 (9)	63 (12)	29 (16)	0.09
Medium	232 (62)	350 (64)	115 (63)	
High	108 (29)	131 (24)	40 (22)	
Cancer stage				
I	122 (32)	172 (32)	57 (30)	0.51
II	139 (37)	174 (32)	60 (32)	
III	93 (25)	172 (32)	62 (33)	
IV	11 (3)	13 (2)	5 (3)	
Unknown	12 (3)	15 (3)	4 (2)	
Surgery	374 (99)	544 (100)	187 (99)	n/a
Chemotherapy	97 (26)	176 (32)	59 (31)	0.09
Radiotherapy	126 (33)	187 (34)	57 (30)	0.61

^aIncreased waist circumference > 102 cm (male) and > 88 cm (female).

^bEducation levels included the following categories: low = no/primary school; medium = lower general secondary education/vocational training; or high = pre-university education/high vocational training/university.

n/a no valid *p*-value could be calculated because low counts in cells without surgery.

normal WC, for all BMI categories (Table 2). Moreover, patients with a normal BMI and increased WC had worse role and emotional functioning and poorer global health status scores than those with normal BMI and normal WC. Additionally, patients with overweight and increased vs. normal WC reported worse role functioning. CRC survivors with obesity and increased WC reported worse emotional functioning as compared to those with normal WC (Table 2). Survivors with normal weight, overweight, and obesity but normal WC reported similar HRQL scores.

Multivariable linear regression models showed that being obese, but not overweight, vs. normal weight was significantly associated with lower scores on all functioning scales, a lower global health status and a higher level of fatigue (Table 3, Model 1). Similarly increased WC vs.

normal WC was associated with lower scores on all functioning scales, a lower global health status and more fatigue (Table 3, Model 2). After assessing the association of both BMI and WC with HRQL (Table 3, Model 3), BMI and waist were independently associated with worse physical and role functioning. Increased vs. normal WC, but not BMI was associated with worse emotional functioning (beta = -2.7; 95% CI: -5.3/-0.1). Moreover, being obese vs. normal weight, but not WC, was associated with worse cognitive and social functioning. As the association of WC on global health status and fatigue differed across separate BMI categories, results were stratified (Table 3, Model 4). Only survivors with normal weight, but not overweight and obesity, and increased WC scored significantly lower on global health status compared to survivors a normal WC with (beta = -6.1; 95% CI: -11.7/-0.4). Normal weight and obese CRC survivors with increased WC reported higher fatigue scores (beta = 10.6; 95% CI: 3.3/17.8 and beta = 13.7; 95% CI: 1.7/25.7, respectively) compared to CRC survivors with a normal WC.

Discussion

In the present study, 66% of CRC survivors had excess weight and 44% had increased WC. Both increased BMI and increased WC were associated with worse functioning scores and more symptoms of fatigue. Moreover, WC and BMI were independently associated with lower physical- and role functioning. In addition, increased WC was associated with lower global health status among patients with normal weight and with increased

Figure 2. Percentage of normal and increased WC according to BMI categories.

Table 2. HRQL scores according to BMI and WC groups.

	BMI					
	Normal		Overweight		Obesity	
	Normal WC N = 331	Increased WC N = 46	Normal WC N = 267	Increased WC N = 279	Normal WC N = 20	Increased WC N = 168
Physical Functioning [*]	86 ± 18	72 ± 20 ^b	86 ± 17	80 ± 18 ^b	85 ± 19	73 ± 22 ^a
Role Functioning [*]	86 ± 23	79 ± 24 ^a	87 ± 21	81 ± 27 ^a	86 ± 20	74 ± 30
Emotional Functioning [*]	89 ± 16	84 ± 17 ^a	90 ± 15	88 ± 17	92 ± 14	84 ± 21 ^a
Cognitive Functioning [*]	89 ± 18	89 ± 15	87 ± 19	87 ± 18	84 ± 22	83 ± 22
Social Functioning [*]	91 ± 20	89 ± 18	90 ± 20	89 ± 20	92 ± 17	83 ± 25
Global Health status [*]	80 ± 17	73 ± 19 ^a	80 ± 17	79 ± 16	81 ± 15	72 ± 20
Fatigue [#]	17 ± 21	31 ± 27 ^b	17 ± 20	21 ± 22 ^a	15 ± 18	28 ± 25 ^a

Independent-samples *t*-test between normal and increased WC within each BMI group.

^{*}Higher scores represent better functioning or better global health status.

[#]Higher scores represent a higher level of fatigue.

^a*p* < 0.05.

^b*p* < 0.01.

fatigue among normal and obese individuals. These results suggest that WC, besides BMI, should be considered in future studies assessing HRQL among CRC survivors. Furthermore, weight reduction trials should not only focus on general weight loss but also investigate the effect of nutrition and physical activity on the loss of abdominal fat.

As far as we know, no studies in CRC survivors focused on the association between WC and HRQL. Previous studies mostly assessed the association between WC and (disease-specific) survival showing a poorer (disease-specific) survival with increased WC (16,24). In our study, both BMI and WC were associated with HRQL. Moreover, WC was associated with worse physical, role, and emotional functioning, regardless of BMI. In addition, patients with obesity or overweight but with a normal WC had the same HRQL scores as compared to patients with normal weight and normal WC (Table 2), which remained apparent in multivariable analyses (data not shown). This indicates that WC might be stronger associated with HRQL than BMI. This is in accordance with studies on complications and survival of CRC patients, where WC was found to be a stronger predictor than BMI (16–18,25).

If WC can be seen as a proxy for abdominal fat, our results are in accordance with previous literature. Although not studied among cancer patients, several studies showed an association between abdominal obesity and poorer HRQL (14,26,27). Our results suggest that the so-called “metabolically unhealthy obese” (i.e., those with overweight/obesity and an unfavorable metabolic profile including more abdominal fat) have worse outcomes than the so-called “metabolically healthy obese” (i.e., those with overweight/obesity and a favorable metabolic profile). Several studies suggest that the metabolically healthy obese might be at lower risk for cardiovascular disease and mortality as compared to the

metabolically unhealthy obese (28,29). Adipose tissue has previously been shown to contribute to inflammation, insulin resistance and dyslipidemia, which in turn can promote the development of chronic diseases (30) and impair HRQL. Future studies should therefore investigate the mechanisms behind the development of metabolically healthy vs. unhealthy obesity and whether changes in lifestyle can influence the amount of abdominal fat. Weight reduction trials in cancer patients should not only focus on weight reduction in general but especially focus on the effects of nutrition and physical activity on abdominal fat reduction which can be measured by WC.

Strengths of the study are the large study population and the population-based character. This study also has some limitations. First, the BMI and WC data were collected half a year before the collection of the HRQL data. However, we do not expect large changes in BMI, WC and HRQL within half a year in this population of long-term CRC survivors. Unfortunately, no information on comorbid conditions, socioeconomic deprivation, and physical activity was available which are known to have a significant impact on HRQL (31,32). However, we did adjust for educational level, which was used as a proxy for socioeconomic deprivation. Due to the lack of data on comorbidity and physical activity and due to the cross-sectional study design, we cannot draw conclusions on causality regarding the association between WC, BMI, and HRQL. Moreover, body height and body weight were self-reported. Previous research shows high correlations between self-reported and objectively assessed BMI, with the exception of elderly (>60 yr) who often over-report their height resulting in an underreported BMI (33). This might have led to an underestimation of the effect of BMI. In addition, WC was self-assessed which did not differ from professionally measured WC in a previous study (34). However, in some groups,

Table 3. The association between BMI and WC with HRQL using multivariable linear regression.

Models	Physical Functioning	Role Functioning	Emotional Functioning	Cognitive Functioning	Social Functioning	Global Health status	Fatigue
1 BMI only [#]							
BMI							
Overweight vs. Normal	-2.1 (-4.5/0.3)	-1.8 (-5.2/1.6)	0.1 (-2.2/2.5)	-1.7 (-4.3/0.8)	-1.2 (-3.9/1.6)	-0.2 (-2.6/2.1)	1.3 (-1.7/4.3)
Obesity vs. Normal	-10.7 (-14.0/-7.5) ^b	-10.5 (-15.0/-6.0) ^b	-3.4 (-6.5/-0.3) ^a	-6.2 (-9.6/-2.8) ^b	-6.6 (-10.2/-2.9) ^b	-6.1 (-9.2/-3.0) ^b	8.4 (4.4/12.3) ^b
2 WC only [#]							
WC							
Increased vs. Normal	-7.2 (-9.4/-5.0) ^b	-6.8 (-9.8/-3.7) ^b	-2.7 (-4.9/-0.6) ^a	-2.5 (-4.9/-0.2) ^a	-2.9 (-5.4/-0.4) ^a	-3.2 (-5.3/-1.0) ^b	6.2 (3.5-8.9) ^b
3 BMI and WC [#]							
BMI							
Overweight vs. Normal	0.1 (-2.5/2.8)	0.2 (-3.5/4.0)	1.2 (-1.4/3.8)	-1.7 (-4.5/1.2)	-0.8 (-3.8/2.3)	NA	NA
Obesity vs. Normal	-6.6 (-10.5/-2.8) ^b	-6.2 (-11.5/-0.9) ^a	-1.5 (-5.2/2.2)	-5.4 (-9.5/-1.4) ^b	-5.8 (-10.2/-1.5) ^b		
Waist							
Increased vs. Normal	-5.2 (-7.9/-2.5) ^b	-4.8 (-8.5/-1.1) ^a	-2.7 (-5.3/-0.1) ^a	-0.3 (-3.1/2.5)	-1.1 (-4.1/2.0)		
4 BMI and WC [#] Stratified by BMI							
Normal weight							
Increased vs. normal WC	NA	NA	NA	NA	NA	-6.1 (-11.7/-0.4) ^a	10.6 (3.3/17.8) ^b
Overweight							
Increased vs. normal WC						0.1 (-2.9/3.1)	2.4 (-1.3/6.2)
Obese							
Increased vs. normal WC						-7.2 (-16.6/2.2)	13.7 (1.74/25.7) ^a

Results were expressed as unstandardized beta [95% confidence interval (CI)].

[#]All the models were adjusted for age, gender, educational level, time since diagnosis, cancer treatment (radio- and chemotherapy), and cancer stage.

NA: Not applicable.

If no significant interaction between BMI and WC was observed Model 3 was constructed, in case of a significant interaction between BMI and WC results were stratified by BMI in Model 4.

^a $p < 0.05$.^b $p < 0.01$.

mainly obese men, the false-negative rate of self-measurements exceeded 20% (34). Only 9% of our sample consisted of obese men; therefore, the influence of self-assessed WC might be negligible. Moreover, WC is an indirect way of estimating abdominal fat. More direct measurements like Computed Tomography (CT) scans might be more reliable but are expensive and not viable in clinical practice (35). However, WC was found to be a valid surrogate marker of intra-abdominal fat (36).

Conclusion

This study showed that higher BMI and increased WC are both associated with worse functioning, lower global health status and more symptoms of fatigue. Moreover, increased WC was associated with lower physical, role, and emotional functioning, regardless of BMI. Future research on HRQL among CRC survivors should take both BMI and WC into account. Furthermore, weight reduction trials should not only focus on weight loss in general but also investigate the effect of nutrition and physical activity on the reduction of abdominal fat.

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Conflict of interest statement

The authors declare that they have no conflict of interest.

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