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# Impact of chemotherapy on health status and symptom burden of colon cancer survivors: A population-based study

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ABSTRACT

*Background:* This population-based study assessed the impact of chemotherapy on general and disease-specific health status of resected colon cancer survivors up to 10 years post-diagnosis.

*Patients and methods:* Colon cancer survivors diagnosed between 1998 and 2007 were selected from the Eindhoven Cancer Registry. Survivors completed the SF-36 and the EORTC colorectal module (EORTC-QLQ-CR38). Comparisons to a normative population were conducted. Multiple linear regression analyses investigated the association between treatment and health status.

*Results:* Eight hundred and forty eight survivors were evaluated: 29% had chemotherapy (CT); 71% without chemotherapy (nCT). Survivors had similar SF-36 scores and scored better than the normative population on several domains. On the EORTC-QLQ-CR38, male nCT survivors had more sexual problems than CT survivors ($p = 0.01$). Among the sexually active respondents, the survivors reported sex to be less enjoyable than the normative population ($p = 0.02$). In multivariate analyses, CT predicted better physical function, and less male sexual dysfunction and weight loss problems than nCT.

*Conclusions:* Overall, CT survivors have general health status scores comparable to nCT survivors and the normative population up to 10 years since initial diagnosis. Sex-related problems among survivors suggest more attention on this often sensitive issue is required in clinical management.



## 1. Introduction

Colon cancer accounts for over 6000 new cases annually in The Netherlands.[1] Survival after colon cancer has increased with earlier detection and the provision of adjuvant chemotherapy for stage III tumours.[2] Indication for adjuvant chemotherapy is broadening to include patients with prognostic unfavourable stage II disease.[3]

The number of colon cancer survivors in The Netherlands is projected to double from 34,000 in 2000 to approximately 67,000 by 2015,[4] of whom >50% will be long-term survivors (>5 years after diagnosis).[5] Data on the long-term effects of

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chemotherapy on general well-being in colon cancer survivors are limited.[6,7] Patient-reported outcomes such as health status is regarded as an important indicator of treatment efficacy.[8]

Research suggests that the health status of colon cancer survivors improves over time since diagnosis[9,10] and that prior treatment was not associated with symptom prevalence.[11] However, small sample sizes,[12–14] use of non-validated health status questionnaires[11] or inclusion of rectal cancer survivors[12] call for cautious interpretation of these results.

Our study aimed to assess the general and disease-specific health status of resected colon cancer survivors up to 10 years post-diagnosis who either received chemotherapy (CT) or did not receive chemotherapy (nCT). We hypothesised that CT survivors will have poorer general and disease-specific health status compared to nCT survivors, independent of time.

## 2. Methods

### 2.1. Setting and participants

This study is part of a long-term follow-up assessment of colon cancer survivors registered with the Eindhoven Cancer Registry (ECR). The ECR compiles data of all individuals newly diagnosed with cancer in southern Netherlands, an area with 10 hospitals serving 2.3 million inhabitants.[15] For this study, all patients identified from ECR and diagnosed with colon cancer in 1998–2007 were eligible for participation. From the 3281 eligible patients, we randomly selected 1481 survivors using weights based on sex and year of diagnosis (Fig. 1). The weights were derived from the total distribution of colon cancer survivors in the ECR region. Survivors with shorter years since diagnosis were oversampled for inclusion in future follow-up assessments. Data collection started in January 2009. A local certified Medical Ethics Committee approved this study.

### 2.2. Data collection

Colon cancer survivors were informed of the study with a letter from their (ex)-attending surgeon. The letter explained that by completing and returning the enclosed questionnaire, survivors consented to participate in the study and agreed to the linkage of the questionnaire data with their disease history in the ECR. Survivors were reassured that non-participation had no consequences on their follow-up care or treatment. Non-respondents were sent a reminder letter and the questionnaire within 2 months.

### 2.3. Measures

General health status was assessed with the validated Dutch version of the SF-36 questionnaire which has eight subscales: physical function, role limitations due to physical health, bodily pain, general health perceptions, vitality, social function, role limitations due to emotional health and general mental health.[16] All scales were converted to a 0–100 linear scale according to standard scoring procedures. Higher scores indicate better health status. The SF-36 scores of the patient sample were compared to an age- and sex-matched Dutch normative population.[16]

Disease-specific health status was assessed with the Dutch validated European Organization for Research and

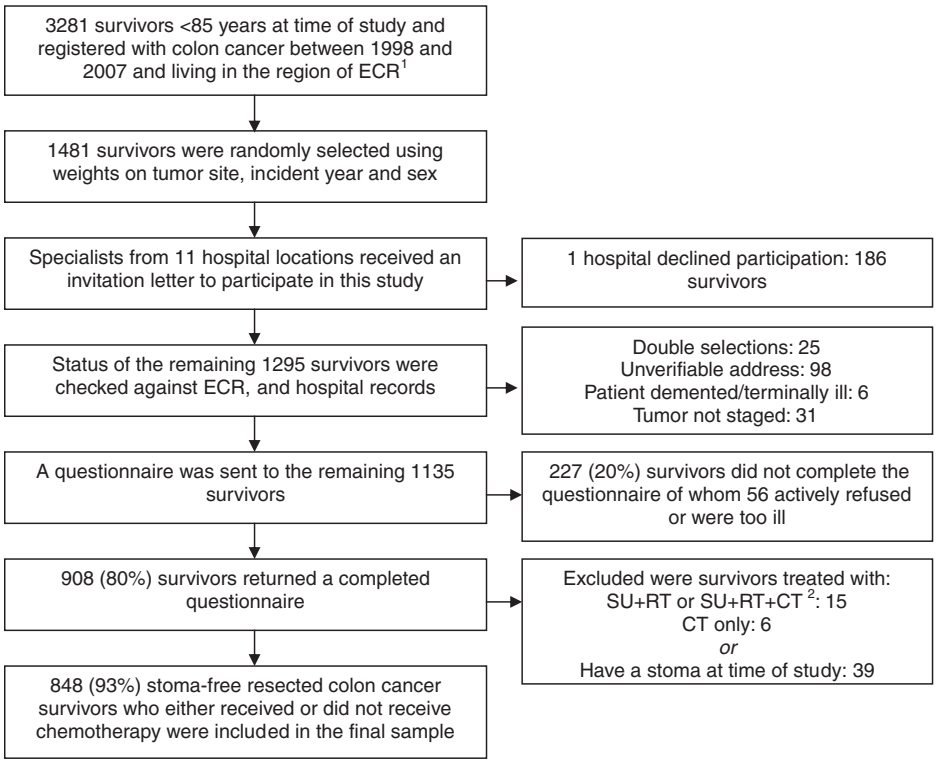


**Fig. 1 – Flow-chart of the data collection process. [1]ECR: Eindhoven Cancer Registry; [2]SU: surgery; RT: radiotherapy; CT: chemotherapy.**

Treatment of Cancer (EORTC) module Quality of Life Questionnaire-Colorectal 38 (QLQ-CR38).[17] This questionnaire assessed both functioning and symptom burden. Function incorporates two multi-items scales on body image and sexual function, and two single-item scales, future perspective and sexual enjoyment. There were seven symptom scales on: micturition, defecation, gastrointestinal symptoms, chemotherapy side-effects, male- and female-related sexual dysfunction, and weight loss (1-item). The items ranged from 1 (not at all) to 4 (very much). All scales were converted to a 0–100 linear scale according to standard scoring procedures. For the function (including the two single-item) scales, higher scores indicated better function; for the symptom scales and the single item on weight loss, higher scores indicated higher symptom burden.

In 2009, our research group assigned CentERdata, a research institute specialising in online research at Tilburg University, to collect normative data on sexuality via the CentERpanel.[18] The CentERpanel is an online household panel consisting of over 2000 households which are representative of the Dutch-speaking population in The Netherlands. For households without internet access, additional provisions were provided to assist in data collection. In total, 1613 (75%) panel members with no history of cancer and $\geqslant$18 years completed three items on sexuality from the EORTC-QLQ-CR38. For this analysis, we included only members 30 years and older ($n$ = 1497) to reflect the age distribution of our survivor sample. Members were asked to what extent over the past 4 weeks were they: (1) interested in sex; (2) sexually active; and for those who were sexually active, (3) to what extent was sex enjoyable for them. These three items were scored according to standard EORTC-QLQ-CR38 procedures.[17,18] Sociodemographic data, such as age, sex, marital status and comorbidity were collected.

Comorbidity at the time of survey was categorised according to the adapted Self-administered Comorbidity Questionnaire (SCQ).[19] The SCQ also assesses survivors' perceived severity and burden of the comorbid condition.

Survivors' sociodemographic and clinical information were available from the ECR. The ECR routinely collects data on tumour characteristics, including date of diagnosis, tumour stage and grade according to the tumour-node-metastasis clinical classification,[20] treatment and patient background characteristics including date of birth and comorbidity at the time of diagnosis. Follow-up data on recurrence (local and regional) and metastasis were derived from chart records. Socioeconomic status was determined by an indicator developed by Statistics Netherlands based on individual fiscal data from the year 2000 on the economic value of the home and household income, and provided as aggregate level for each postal code (average 17 households),[21] which were then categorised into tertiles. Body mass index, marital status, educational level, employment status and smoking were also assessed.

### 2.4. Statistical analyses

All statistical analyses were performed using SAS (version 9.1 for Windows, SAS Institute Inc., Cary, NC). Differences in demographic and clinical characteristics between treatment groups were compared with chi-square test on categorical variables. The non-parametric Wilcoxon test was applied when normality and homogeneity assumptions of continuous variables (age at survey and years since diagnosis) were violated.

The SF-36 and EORTC-QLQ-CR38 mean scores of the two treatment groups, stratified by years since diagnosis (short-term: <5 years; long-term: $\geqslant$5 years), were compared with ANCOVA. An interaction term (treatment * years since diagnosis) was also included. Confounding background variables included for adjustment in these analyses were determined *a priori*:[22] age at diagnosis, years since diagnosis, marital status, comorbidity, body mass index, sex, initial treatment, cancer stage and grade, disease progression and the interaction term.

Independent sample $t$-tests compared the SF-36 scores of the patient sample with an age- and sex-matched normative population.

Sexual function and sexual enjoyment scores of patients and normative population were compared with ANCOVA. The interactions between age and sex and group status (normative population and survivors) on health status were explored in two interaction terms: age * group and sex * group. Variables included for adjustment were age, sex, marital status, comorbidity, and the two interaction terms.

Multiple linear regression models using only the survivor sample investigated the association between health status and treatment and years since diagnosis. A range of sociodemographic and clinical variables were controlled for in multivariate models. Multicollinearity was determined if the variance inflation factor (VIF) was greater than 10.[23]

Statistical differences were indicated if $p < 0.05$ and reported $p$-values were two-sided. Clinically meaningful differences on the generic and disease-specific health status subscales were determined with Norman's 'rule of thumb', whereby a difference of approximately 0.5 SD indicates a threshold of discriminant change in health status scores of a chronic illness.[24]

## 3. Results

Response rate was high, with 908 (80%) of the 1135 colon cancer survivors returning a completed questionnaire (Fig. 1). Respondents, non-respondents and survivors with non-verifiable addresses had similar demographic and clinical characteristics, except for age; non-respondents were older whereas survivors with non-verifiable addresses were younger than the respondents (Table 1).

In total, 848 (606 nCT and 242 CT) colon cancer survivors were included in the final analysis (Fig. 1). As our objective was to assess the impact of chemotherapy on health status, we excluded those survivors who were treated with either radiotherapy or radiotherapy + chemotherapy following resection ($n$ = 15), received chemotherapy without resection ($n$ = 6), or had a stoma at the time of survey ($n$ = 39).

Baseline characteristics of the 848 survivors, stratified by treatment, suggested that CT survivors were more likely to be younger, to have a more recent diagnosis, to be higher educated, to be working, to have stage 3 or 4 and grade 3 disease, and to have a metastasis during follow-up (Table 2). CT

**Table 1 – Demographic and clinical characteristics of selected sample by response status.**

| (%) | Respondents ($n$ = 908) | Non-respondents ($n$ = 227) | Non-verified addresses ($n$ = 98) | $p$-Value |
|---|---|---|---|---|
| Mean age at time of survey | 69.4 ± 9.6 | 71.6 ± 10.0 | 69.0 ± 11.2 | 0.0002 |
| Mean years since initial diagnosis | 3.9 ± 2.5 | 4.0 ± 2.5 | 4.3 ± 2.6 | 0.1 |
| *Years since diagnosis* | | | | |
| <5 | 679 (75) | 162 (71) | 68 (69) | |
| 5 or more | 229 (25) | 65 (29) | 30 (31) | 0.3 |
| *Stage of cancer (TNM)* | | | | |
| 1 | 201 (22) | 51 (22) | 21 (21) | |
| 2 | 393 (43) | 114 (50) | 44 (45) | |
| 3 | 260 (29) | 57 (25) | 26 (26) | |
| 4 | 54 (6) | 5 (2) | 7 (7) | 0.2 |
| *Tumour grade (TNM)* | | | | |
| 1 | 72 (8) | 22 (10) | 12 (12) | |
| 2 | 605 (67) | 152 (67) | 58 (59) | |
| 3 | 144 (16) | 32 (14) | 14 (14) | |
| Unknown | 87 (9) | 21 (9) | 14 (14) | 0.4 |
| *Primary treatment* | | | | |
| SU only | 631 (69) | 172 (76) | 69 (70) | |
| SU + RT | 7 (1) | 2 (1) | 0 | |
| SU + CT | 256 (28) | 47 (21) | 28 (29) | |
| SU + RT + CT | 8 (1) | 4 (2) | 0 | |
| CT only | 6 (1) | 2 (1) | 1 (1) | 0.3 |

SU: surgery; RT: radiotherapy; and CT: chemotherapy.

survivors were less likely to have comorbid heart disease or hypertension at the time of study than nCT patients.

### 3.1. ANCOVA of general and disease-specific health status

Table 3 outlines the SF-36 mean scores, stratified by treatment and years since diagnosis. Generally, short- and long-term survivors had similar SF-36 domain scores. No significant interaction effects were noted on all SF-36 domains. Main treatment effects were noted on physical function ($p$ = 0.03) whereby CT survivors reported statistically but not clinically significantly better scores, independent of time since initial diagnosis. A statistically significant main treatment effect was also found for role limitations due to physical health ($p$ = 0.03), whereby short-term CT survivors had poorer scores but long-term CT survivors, higher when compared to their respective nCT counterparts.

There were no statistically significant differences on most EORTC-QLQ-CR38 domains between short- and long-term survivors, independent of treatment (Table 3). CT survivors reported having significantly more chemotherapy-related side-effects ($p$ = 0.03) than nCT survivors. There was a borderline significant interaction effect on sexual function ($p$ = 0.06) with CT survivors reported having greater sexual interest, especially among the long-term survivors. Male nCT survivors experienced more male-related sexual problems ($p$ = 0.01) than CT survivors, independent of time since initial diagnosis.

The adjusted mean scores of the SF-36 and EORTC-QLQ-CR38 subscales for the groups were similar to raw mean scores reported in Table 3.

Secondary analyses limited only to survivors with stages II and III tumours, and disease-free survivors had similar results (data not shown) to those reported above.

Similarly, CT predicted better scores for physical function on the SF-36 and less male sexual dysfunction on the EORTC-QLQ-CR38 in multivariate linear regression (Table 4). CT survivors also had fewer problems with weight loss. Years since diagnosis were positively associated with physical function and role limitations due to physical health scores on the SF-36 but not with any EORTC-QLQ-CR38 domains. Of the other clinical predictors, comorbidity, higher stage of disease, and having metastasis strongly predicted poorer scores on various SF-36 and EORTC-QLQ-CR38 domains. Being male was associated with better scores on several SF-36 domains, and higher scores on EORTC-QLQ-CR38 sexual function and sexual enjoyment but less chemotherapy-related problems. No violation of the multicollinearity assumption was noted in all domains tested as the average VIF was around 1.

To ensure that the above-reported multivariate analyses results were not influenced by the strong association between metastasis and poorer general health status and higher symptom burden, we performed secondary analyses with only disease-free survivors. These results were comparable to those using the full sample (data not shown).

### 3.2. Comparisons with normative population

The SF-36 scores of the treatment groups were compared to an age- and sex-matched Dutch population (Fig. 2). Both nCT and CT survivors had fewer complaints with bodily pain and higher scores on mental health than the normative population. CT survivors reported better physical function than the normative population. On social function and role limitations due to emotional health domains, nCT survivors scored better than the normative population.

**Table 2 – Demographic and clinical characteristics at the time of survey of resected colon cancer survivors who either received or did not receive chemotherapy.**

| (%) | nCT ($n$ = 606) | CT ($n$ = 242) | $p$-Value |
|---|---|---|---|
| Mean age at time of survey | 71.7 ± 9.4 | 66.1 ± 9.2 | <0.0001 |
| Mean years since initial diagnosis | 4.1 ± 2.5 | 3.4 ± 2.2 | <0.0001 |
| *Years since diagnosis* | | | |
| <5 | 434 (72) | 195 (81) | |
| 5 or more | 172 (28) | 47 (19) | 0.007 |
| *Tumour site* | | | |
| Caecum | 80 (13) | 52 (21) | |
| Appendix | 4 (1) | 1 (1) | |
| Ascending colon | 102 (17) | 40 (16) | |
| Hepatic flexure | 42 (7) | 14 (6) | |
| Transverse colon | 40 (7) | 23 (9) | |
| Splenic flexure | 25 (4) | 9 (4) | |
| Descending colon | 37 (6) | 11 (5) | |
| Sigmoid colon | 276 (45) | 92 (38) | 0.06 |
| *Stage of cancer (TNM)* | | | |
| 1 | 184 (30) | 0 | |
| 2 | 354 (58) | 24 (10) | |
| 3 | 61 (10) | 185 (76) | |
| 4 | 7 (1) | 33 (14) | <0.0001 |
| *Tumour grade (TNM)* | | | |
| 1 | 51 (8) | 14 (6) | |
| 2 | 412 (68) | 160 (66) | |
| 3 | 75 (12) | 59 (25) | |
| Unknown | 68 (11) | 9 (4) | <0.0001 |
| *Disease progression during follow-up* | | | |
| Local/regional recurrence | 4 (1) | 4 (2) | 0.1 |
| Metastasis | 25 (4) | 26 (10) | 0.0003 |
| *Comorbidity at time of study* | | | |
| None | 174 (29) | 92 (38) | |
| 1 | 173 (28) | 62 (26) | |
| >1 | 259 (43) | 88 (36) | 0.1 |
| *Most common comorbid conditions at time of survey* | | | |
| Heart disease | 137 (30) | 38 (22) | 0.02 |
| Hypertension | 195 (44) | 60 (33) | 0.01 |
| Arthritis | 163 (38) | 63 (36) | 0.6 |
| Back pain | 157 (38) | 51 (30) | 0.1 |
| Male | 321 (53) | 121 (50) | 0.4 |
| *Marital status* | | | |
| Married | 403 (69) | 180 (77) | |
| Single/divorced | 52 (9) | 21 (9) | |
| Widowed | 125 (21) | 34 (14) | 0.1 |
| *Educational level*[a] | | | |
| Low | 147 (26) | 41 (18) | |
| Medium | 325 (57) | 139 (60) | |
| High | 100 (17) | 51 (22) | 0.03 |
| *Employment status* | | | |
| Not working/retired | 497 (87) | 178 (77) | |
| Working | 71 (12) | 53 (23) | 0.0002 |
| *Socioeconomic status* | | | |
| Low | 146 (25) | 55 (23) | |
| Medium | 226 (38) | 89 (37) | |
| High | 198 (34) | 89 (37) | 0.6 |
| *BMI* | | | |
| <18.5 | 4 (1) | 2 (1) | |
| 18.5–24.9 | 182 (34) | 71 (32) | |
| 25.0–29.9 | 261 (48) | 110 (50) | |
| ⩾30 | 94 (17) | 38 (17) | 0.9 |
| Currently smoking | 60 (10) | 24 (10) | 0.5 |

nCT: did not receive chemotherapy; CT: received chemotherapy.

[a] Education: low (no or primary school); medium (lower general secondary education or vocational training); high (pre-university education, high vocational training, university).

**Table 3 – Raw mean scores (±SD) of general and disease-specific health status of colon cancer survivors by treatment and years since diagnosis.**

| | nCT | | CT | | Ancova[b] | | |
|---|---|---|---|---|---|---|---|
| | <5 years (*n* = 434) | ⩾5 years (*n* = 172) | <5 years (*n* = 195) | ⩾5 years (*n* = 47) | Treatment effect | Years since diagnosis effect | Treatment * years since diagnosis |
| *SF-36* | | | | | | | |
| General health | 62.7 ± 21.9 | 63.3 ± 21.3 | 61.0 ± 23.0 | 64.4 ± 25.0 | | | |
| Physical function | 67.2 ± 29.6 | 70.9 ± 26.7 | 70.9 ± 27.0 | 77.3 ± 27.3 | 0.03 | | |
| Role function – physical | 65.7 ± 42.2 | 66.9 ± 41.7 | 60.6 ± 43.7 | 77.3 ± 37.7 | 0.03 | | |
| Bodily pain | 76.1 ± 24.7 | 77.4 ± 23.9 | 74.6 ± 25.0 | 74.7 ± 23.0 | | | |
| Vitality | 65.3 ± 21.2 | 66.8 ± 19.4 | 64.0 ± 21.4 | 65.8 ± 22.2 | | | |
| Social function | 82.7 ± 21.9 | 83.1 ± 20.7 | 80.5 ± 22.6 | 82.9 ± 22.1 | | | |
| Role function – emotional | 80.9 ± 35.8 | 85.2 ± 32.0 | 80.7 ± 36.0 | 78.8 ± 36.0 | | | |
| Mental health | 77.2 ± 17.3 | 78.5 ± 16.5 | 78.0 ± 18.0 | 78.1 ± 19.7 | | | |
| *EORTC-QLQ-CR38*[a] | | | | | | | |
| Body image | 88.1 ± 19.6 | 87.2 ± 18.3 | 82.7 ± 22.4 | 88.6 ± 16.7 | | | |
| Future perspective | 71.9 ± 26.2 | 74.9 ± 25.0 | 63.2 ± 31.3 | 72.6 ± 25.9 | | | |
| Sexual function | 22.2 ± 22.7 | 21.3 ± 23.1 | 24.0 ± 23.1 | 30.0 ± 27.4 | | | 0.06 |
| Sexual enjoyment | 53.8 ± 30.4 | 56.4 ± 32.3 | 60.0 ± 29.7 | 59.0 ± 31.7 | | | |
| Micturition problems | 26.4 ± 18.8 | 24.7 ± 17.9 | 24.1 ± 17.8 | 19.7 ± 16.6 | | | |
| Chemotherapy side-effects | 13.1 ± 16.8 | 11.2 ± 15.6 | 19.2 ± 20.5 | 16.5 ± 21.0 | 0.03 | | |
| Gastrointestinal problems | 18.3 ± 15.1 | 16.6 ± 13.5 | 20.7 ± 15.3 | 19.8 ± 14.8 | | | |
| Male sexual problems | 36.0 ± 36.5 | 40.5 ± 37.1 | 31.6 ± 37.0 | 33.3 ± 37.0 | 0.01 | | |
| Female sexual problems | 19.0 ± 23.8 | 23.6 ± 28.2 | 28.2 ± 31.8 | 23.3 ± 31.4 | | | |
| Defecation problems | 11.9 ± 10.3 | 12.9 ± 10.7 | 13.2 ± 11.2 | 12.0 ± 8.8 | | | |
| Weight loss | 7.8 ± 18.6 | 8.1 ± 19.7 | 6.6 ± 18.5 | 3.7 ± 10.6 | | | |

nCT: did not receive chemotherapy; CT: received chemotherapy.

[a] Body image, future perspective, sexual functioning and sexual enjoyment scales: higher scores indicate better functioning; for the other symptom scales, higher scores indicate higher symptom burden.

[b] *p*-Values were adjusted for: age at diagnosis, years since diagnosis, marital status, comorbidity, body mass index (as continuous variables); sex (except for male and female sexual problems), initial treatment, cancer stage, cancer grade, local/regional recurrence, metastasis; interaction term (treatment * years since diagnosis).

There were no significant main differences between the normative population and survivor sample on sexual function following adjustments of age, sex, marital status and comorbidity (Fig. 2). However, both adjusted interaction terms of age * group ($p = 0.01$) and sex * group ($p = 0.01$) were significant on sexual function (data not shown). Among the sexually active respondents, there was a significant adjusted group main effect ($p = 0.02$), with the normative population scoring the highest mean scores on sexual enjoyment (72.4 ± 24.2) and nCT survivors, the lowest (54.5 ± 30.9). The adjusted interaction terms of age * group ($p = 0.007$) and sex * group ($p < 0.0001$) were significant for sexual enjoyment (data not shown).

## 4. Discussion

Overall, CT and nCT survivors had comparable general health status up to 10 years since initial diagnosis. Both treatment groups reported significantly better scores on several general health status domains than the sex- and age-matched normative population. On disease-specific health status, treatment effects impacted on sexual function and chemotherapy-related side-effects. CT survivors, both short- and long-term, had fewer problems with male sexual dysfunction.

Compared with other studies, our sample reported better general health status scores. A small study of 30 long-term colon cancer survivors with comparable demographics and clinical characteristics to our sample reported SF-36 mean scores that were considerably lower than those of our sample, for example 44.8 for physical function and 51.5 for role limitations due to emotional health.[14] The survivors in that study were somewhat older than our sample, with a mean age of 69 and all were surgically treated, of whom 73% also received chemotherapy and 13% radiotherapy + chemotherapy. These factors could explain the lower SF-36 scores when compared to our sample. Moreover, the scores of our sample were comparable to or better than that of the Dutch normative population.

Scores on several EORTC-QLQ-CR38 domains in our study were comparable to colorectal cancer survivors up to 6 years since diagnosis.[13] However, our sample reported higher scores on problems with micturition, chemotherapy side-effects and defecation, indicating a higher symptom burden on these domains than in the other study.

Compared with CT male survivors, nCT men had more sexual dysfunction problems independent of the years since diagnosis. nCT men were less likely to be interested in sex or be sexually active than CT men, even after correction for age and comorbidity. Tumour location could explain this

**Table 4 – Standardised betas of multivariate linear regression analyses evaluating the association of independent variables with the SF-36 and EORTC-QLQ-CR38 subscales, all patients combined ($n$ = 848).**

| | Independent variables | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Age | Years since dx | Marital status | Sex | BMI | Comorb | CT | Tumour stage | Tumour grade | Recur | Metas |
| *SF-36 subscales* | | | | | | | | | | | |
| GH | −0.2** | | 4.6* | | | −10.6*** | | −17.8** | | −19.6** | −16.6** |
| PF | −0.8*** | 0.9* | | 6.4** | −0.9*** | −11.0*** | 7.8* | −15.8** | | | −12.3** |
| RP | −0.5** | 1.4* | | | | −15.2*** | | −34.4** | −11.2* | | −19.8** |
| BP | | | | 5.4** | | −14.7*** | | | | | |
| RE | −0.3* | | 6.3* | 6.9* | | | | | −9.3* | | −12.4* |
| SF | | | 5.1** | | | −8.1*** | | −9.9* | | | −9.8* |
| VT | | | | 4.5** | | −9.3*** | | −9.6* | | | −8.0* |
| MH | | | 4.2** | 4.4** | | −4.0** | | | | | |
| *EORTC-QLQ-CR38 subscales* | | | | | | | | | | | |
| BI | | | | | | −4.1* | | −11.7* | | | |
| FP | | | | | | −10.2*** | | −22.2** | | | −20.7*** |
| SX | −0.8*** | | 9.0*** | 12.6*** | | | | | | | |
| SE | −0.7*** | | 12.1** | 18.7*** | | | | | | | |
| MP | 0.4** | | | | | 4.0** | | | | | |
| CT | 0.3** | | | −5.6*** | | 5.6** | | 13.2** | | | 8.7** |
| GI | | | | | | 5.0*** | | | | | |
| $M_{sex}$ | 1.2*** | | | | | | −20.4** | 27.6** | | | |
| $F_{sex}$ | | | 13.6* | | | | | | | | |
| DP | | | | | | 2.6** | | 4.8* | | | |
| WL | | | | | −0.4** | | −4.6* | 12.5** | | | 9.2** |

(1) BMI = body mass index; comorb = comorbid conditions; treat = treatment, recur = recurrence, and metas = metastasis.
(2) Marital status: not married versus married; sex: female versus male; comorbidity: no versus yes; CT: no chemotherapy versus chemotherapy; tumour stage: 1, 2, 3 versus 4; tumour grade: 1 versus 2, 3; recurrence: no versus yes; metastasis: no versus yes.
(3) Age, years since diagnosis and BMI: continuous variables.
(4) SF-36 ($n$ = number of observations in model): GH = general health ($n$ = 723); PF = physical functioning ($n$ = 720); RP = role functioning – physical ($n$ = 698); BP = bodily pain ($n$ = 739); RE = role functioning – emotional ($n$ = 694); SF = social functioning ($n$ = 742); VT = vitality ($n$ = 724); MH = mental health ($n$ = 724).
(5) EORTC-QLQ-CR38 ($n$ = number of observations in model): BI = body image ($n$ = 724); FP = future perspective ($n$ = 734); SX = sexual function ($n$ = 664); SE = sexual enjoyment ($n$ = 321); MP = micturition problems ($n$ = 721); CT = chemotherapy side-effects ($n$ = 713); GI = gastrointestinal problems ($n$ = 707); $M_{sex}$ = male sexual problems ($n$ = 335); $F_{sex}$ = female sexual problems ($n$ = 139); DP = defecation problems ($n$ = 675); and WL = weight loss ($n$ = 731).
* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.0001$.

disparity as distally located tumours would be more symptomatic and tended to be detected and treated at an earlier stage. Treatment for these distal tumours in turn could increase the risk of nerve damage to sexual organs within close proximity, with negative consequences for sexual function. Male nCT survivors reported having more erection problems than CT men. However, as tumour location in both survivors groups was similar ($p$ = 0.06), we do not have a clear explanation for our results.

We are currently unaware of any study that has explored the effect of combining chemotherapy with surgery on sexual function of colon cancer survivors. Most research on sexual function of cancer survivors tended to focus on either prostate or breast cancer. A study of long-term breast cancer survivors who received adjuvant chemotherapy reported that the clinical group reported significantly poorer sexual function scores when compared with a healthy non-cancer group.[25] Similarly, the survivors in our study were less likely to be interested in sex and were less sexually active when compared with the normative population. Although age could also influence sexual function,[26] our results corrected for age still showed a strong treatment effect in this domain.

We found that the scores on male sexual problems were generally higher in comparison to the other symptom domains in both survivor samples. Furthermore, a treatment effect was noted on male sexual dysfunction but not with females. This result is comparable to a small study of long-term colon cancer survivors.[14] In that study, men reported having severe problems with sexual function, even after adjustments for age and race. In comparison with the normative population, colon cancer survivors reported poorer scores on sexual function, although these differences were not significant following adjustments. Comorbid conditions could reduce sexual activity as this variable was significant ($p$ = 0.001) in the adjusted model. For those respondents who were sexually active, a treatment effect was noted as there were significant differences in sexual enjoyment between the groups, with the normative population reporting the highest and the nCT survivors, the lowest. These results suggest that the clinical management of colon cancer survivors could

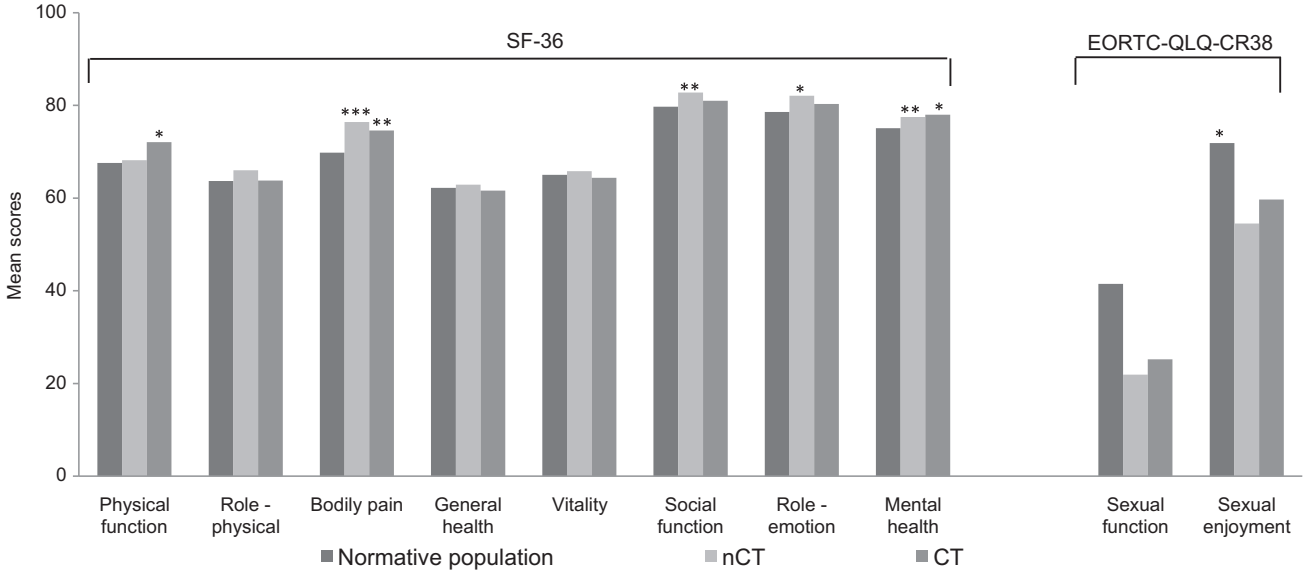


**Fig. 2 – Mean SF-36 and EORTC-QLQ-CR38 (sexual function and sexual enjoyment) subscale scores of survivors according to treatment in comparison with a Dutch normative population. For the S-36, when a subgroup of patients has a difference in the mean score to the age- and sex-matched normative population, then an asterisk is placed above that subgroup (as indicated from independent sample t-tests). For the EORTC-QLQ-CR38, an asterisk above the normative population indicates a group difference (ANCOVA, adjusted for age, sex, marital status, and comorbidity). nCT: did not receive chemotherapy; CT: received chemotherapy. $^{***}p < 0.0001$; $^{**}p < 0.01$; $^{*}p < 0.05$.**

focus more attention on this often sensitive issue, taking into consideration not only the clinical but also psychological factors that could impact on sexual function and enjoyment.[27]

The strength of comorbid conditions as a predictor of health status in our sample suggests that more attention to concomitant diseases should be considered when delivering clinical care. Comorbid conditions have been associated with socioeconomic status whereby persons of low socioeconomic status were more likely to have concomitant conditions.[28] Similarly, a review of colorectal cancer indicated that patients with low socioeconomic status were less likely to receive (neo)adjuvant treatment and had poorer survival rates.[29] We noted a greater percentage of survivors with >1 comorbid condition compared to those with no comorbid conditions among the low socioeconomic status group (29% versus 20%) than in the high socioeconomic status group (31% versus 38%), although these differences were not significantly different.

CT survivors had significantly more chemotherapy-related side-effects than nCT survivors. Although this result should not surprise, it is of interest that significantly more CT survivors reported having quite a bit/very much problem in the past week of thin/dull hair as a result of their disease and/or treatment and changes in the taste of food/drinks (16% versus 7%, $p < 0.0001$, and 13% versus 5%, $p < 0.0001$ respectively). This suggests that these symptoms, often considered to be acute rather than long-term effects of chemotherapy, could continue to affect survivors up to 10 years post-diagnosis. In a study of 321 cancer survivors which included colorectal cancer, 22% reported a current problem of hair loss of whom 38% attributed to cancer even though these were all long-term survivors with mean 10.4 years since diagnosis.[30] Nevertheless, the long-term effects of chemotherapy in colon cancer are relatively understudied. More study into the long-term effects of chemotherapy and especially its association with health status is recommended as the chemotherapy use is increasing in this patient group.

An unexpected finding was that colon cancer survivors reported better scores than the normative population on several SF-36 domains. For example, both nCT and CT survivors reported better scores on the bodily pain and mental health domains than the normative population. Similar findings have been found with other cancer types.[12,31] This suggests the resilience of cancer survivors to adapt to the demands of cancer and its treatment. This reconceptualisation of health status over the disease trajectory has been termed 'response shift'.[32]

In contrast to many studies of breast cancer survivors which reported strongly diminished health status even in the long-term after chemotherapy, these findings were not observed in colon cancer (as seen in our study and that of Bouvier et al.[7]). Comparisons are difficult as breast cancer survivors are more likely to be women and younger than colon cancer survivors. A possible factor for these differences in health status following chemotherapy could be the different standard chemotherapy regimens used in these two cancers. The TAC (docetaxel + doxorubicin + cyclophosphamide) regimen commonly used for breast cancer could have a different toxicity profile with greater impact on the health status and well-being than that of 5-fluorouracil (5-FU)-based regimen as prescribed for colon cancer.

Another possible explanation for the relatively good health status of our CT sample in comparison to that of the nCT survivors could be an issue of patient selection for chemotherapy in the ECR region. A previous study on the trends of

chemotherapy administration in the ECR region reported that increasing age and comorbidity were associated with decreasing chemotherapy administration in patients with stage III colon cancer.[33] Therefore, the CT survivors included in our sample were more likely to be younger and healthier before they were treated with chemotherapy.

Our inclusion of long-term survivors could introduce survival bias into our sample selection. This might not be a problem as we oversampled short-term survivors and there was a lack of difference in general health status between short- and long-term survivors. Second, possible confounding by indication could be present as treatment is linked to cancer stage and grade. A randomised control trial comparing the late effects of treatment could address this problem, although its feasibility would be hampered by reasons including lack of patient interest or poor institutional commitment.[34] As such, our population-based study is a suitable alternative. Our results suggest that widening indication for chemotherapy could be feasible as the treatment seems well-tolerated and long-term morbidity is comparable to that of nCT survivors.

Another limitation is the lack of information from the ECR on the types of chemotherapeutic agents used over time as the effects of different chemotherapy treatments on health status could be variable. According to the clinical experience of one of the authors (GJC), the most commonly prescribed chemotherapy treatment in the ECR region is that of 5-FU + leucovorin, administered following either the Mayo or Roswell Park regimen.[35] Since 2004, younger patients (<70 years) could also be treated with the FOLFOX (5-FU + leucovorin + oxaliplatin)[36] or XELOX (capecitabine + oxaliplatin)[37] regimen; for the older patients or those with comorbidity, either the monotherapy capecitabine or the Mayo regime are prescribed. However, we found no main effects of time since diagnosis on general and disease-specific health status, suggesting that possible differences in chemotherapy regimes over time is not an issue in our sample.

Fourth, missing information especially on female sexual problems could be >60%. Female nCT survivors were most likely to skip these items compared to the normative and CT samples: dryness of vagina during sex ($n = 648$; 66% versus 57% and 56% respectively, $p = 0.02$) and pain during sex ($n = 651$; 67% versus 57% and 57% respectively, $p = 0.01$). Therefore, we cannot draw conclusions on the extent of sexual dysfunction among female survivors.

Nevertheless, the high response rate of the large population-based sample and the use of validated health status questionnaires for comparison with a Dutch normative population are strengths of this study.

## Conflict of interest statement

None declared.

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