Comorbidities, rather than older age, are strongly associated with higher utilization of healthcare in colorectal cancer survivors
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Published in:
Journal of the National Comprehensive Cancer Network
DOI:
10.6004/jnccn.2021.7030
Published: 31/05/2022

Document Version
Peer reviewed version

Link to publication on the UWS Academic Portal

Citation for published version (APA):

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ABSTRACT

Background
Colorectal cancer (CRC) survivors generally have a higher healthcare utilization than the general population due to cancer burden. However, it is unclear which factors are associated with this increased uptake. Our study aimed to: (1) compare CRC-related and non-CRC visits to general practitioners (GP) and medical specialists (MS) by comorbidities, and (2) assess whether healthcare utilization differs by demographic, clinical, and psychological factors.

Methods
We used data from a German population-based cohort of 1718 stage I-III CRC survivors diagnosed in 2003-2010 who provided information on healthcare utilization at 5-year follow-up. Multivariable linear regression was used to calculate least square means of CRC-related and non-CRC healthcare utilization according to Charlson comorbidity index and comorbidity cluster, adjusting for relevant demographic, clinical, and psychological characteristics.

Results
A higher comorbidity level was associated with more CRC-related MS visits and non-CRC GP visits. Besides being strongly associated with non-CRC GP visits, comorbidity cluster was also associated with CRC-related visits to GP and MS but its association varied by specific cardio-metabolic comorbidities. Healthcare utilization was less dependent on prognostic factors for CRC such as age and tumor stage but was strongly associated with disease recurrence, depression, and emotional functioning.

Conclusion
Comorbidities, rather than age or tumor stage, was related to healthcare utilization, suggesting that CRC survivors utilize healthcare mainly for reasons other than cancer 5 years post-diagnosis. Improved communication between primary and tertiary healthcare providers could enhance the medical care of cancer survivors with complex health needs and thereby also reduce healthcare costs.
INTRODUCTION

Global demographic aging, early diagnosis, and improvement colorectal cancer (CRC) treatments have increased the number of CRC survivors in many countries. In Germany, the 5-year relative survival rate increased from ~60% in 2012 to ~62% in 2016.¹ CRC is predominantly diagnosed at older age, when chronic conditions such as diabetes and cardiovascular diseases (CVD) are common.²³ Comorbidity prevalence in CRC survivors is high, ranging 46%-62%,⁴⁶ when compared with non-cancer controls (11%-50%).⁷

Besides being associated with poorer health outcomes such as higher symptom burden, lower health-related quality of life, and higher mortality,⁸¹¹ comorbidity is also associated with higher healthcare utilization (HCU) among cancer survivors than non-cancer controls.¹²¹⁴ Age could explain this HCU excess. However, two Dutch studies which used data from the same national primary care registry, reported contradictory results despite having comparable sampling time frame. The first study included all registered cancer survivors, reported that GP consultations increased with age and number of comorbid conditions, similar for cancer survivors and matched controls.¹³ In contrast, the second study that sampled only survivors of breast, prostate, and colorectal cancers reported that this difference in GP visits was more prominent among younger CRC survivors and those without comorbid disease.¹⁵ These studies did not account for severity of comorbid conditions, however, but reported either on selected individual comorbid conditions or sum of the selected comorbid conditions. Furthermore, distinct clusters of comorbidities in CRC survivors are differentially associated with treatment and survival.⁵ Stage III CRC survivors with pre-existing vascular or respiratory conditions were less likely to receive guideline-recommended therapy than survivors with other comorbidities. However, we found no published results on the association between comorbidity clusters and HCU.

The growing number of older CRC survivors with complex health issues could have considerable impact on the healthcare system.¹⁶ A better understanding of their healthcare needs could inform healthcare providers in improving efficiency and reduce costs of care delivery. Our study aims are: (1) to compare HCU (CRC-related and non-CRC visits) among CRC survivors by comorbidity scores (based on severity of comorbid conditions) and by specific comorbidity clusters (e.g. CVD, metabolic diseases),⁵ and
(2) to assess whether and to what extent HCU differs by demographic, clinical, and psychological factors in CRC survivors surviving beyond five years.

METHODS

Setting and participants

We used data from the population-based DACHS study, an ongoing case-control study with additional follow-up of CRC cases. The DACHS study was primarily designed to assess the effect of endoscopic screening on CRC prevention. It was started in 2003 in collaboration with 22 hospitals located in southwest Germany. Cases are additionally followed up for evaluation of treatment-related and prognostic factors. Eligible CRC patients with a newly diagnosed and histologically confirmed primary CRC (ICD 10: C18-20), were identified by their treating clinicians during their hospital stay for CRC surgery or were contacted by mail shortly after discharge by clinicians or clinical cancer registries. Details of the DACHS study have been reported elsewhere. All respondents to the baseline assessment received a 5-year follow-up. The current study reports on participants diagnosed with stage I-III CRC cancer between 2003 and 2010 who completed a HCU survey at 5-year follow-up between 2009 and 2016 (Supplementary Figure 1).

The ethics committee of the University of Heidelberg and the state medical boards of Baden-Württemberg and Rhineland-Palatinate approved the DACHS study. All participants provided written informed consent.

Data collection

At baseline, trained interviewers collected detailed socio-demographic, clinical, and lifestyle history from study participants. Attending physicians provided detailed treatment, recurrence, and incident comorbidity information at the 3-year follow-up, and they verified recurrence or new cancers (‘disease recurrence’) reported by participants at 5-year follow-up. At 5-year follow-up, ~86% of participants who were alive completed a mailed questionnaire that included information on HCU, depressive symptoms, fear of recurrence, emotional well-being, and changes in medical or recurrence history. Relevant sociodemographic and clinical data from baseline and 3-year follow-up, and patient-reported outcomes
such as HCU and psychological well-being collected at the 5-year follow-up were combined for this analysis.

Ascertainment of comorbidities

Comorbidities that pre-existed or were diagnosed at the time of CRC diagnosis were ascertained with ICD-10 codes abstracted from medical records. We used a modified Charlson comorbidity index (CCI) to calculate an overall comorbidity score. The definition of ‘other cancers’ in the CCI considered all primary cancers other than CRC and basal cell carcinoma. Survivors were grouped into 3 categories according to the overall comorbidity score: 0 (no comorbidity), 1, or 2+ (severe comorbidity). We used the CCI to derive comorbidity clusters: CVD (myocardial infarction, chronic heart failure, peripheral vascular disease, stroke with/without hemiplegia), metabolic (diabetes mellitus, chronic renal disease, liver disease), other (dementia, chronic obstructive pulmonary disease, other cancers, peptic ulcer, rheumatoid disease).

HCU

Participants provided the number of CRC-related and non-CRC visits to the general practitioner/family physician (GP) or medical specialist (MS) in the past 12 months. Visits to the MS for CRC-related matters included visits to oncologists, internists or gastroenterologists. For non-CRC matters, MS visits could include visits to oncologists, internists, gastroenterologists or psychologists.

Psychological well-being

Geriatric Depression Scale (GDS)

The validated and reliable 15-item GDS was answered with either a ‘yes’ or a ‘no’. Out of a maximum score of 15, 5-10 suggests mild depression (‘mild depression’) and ≥11 suggests severe depression (‘severe depression’).

Fear of recurrence
We used the item ‘fear of disease progression’ from the validated Questionnaire on Distress in Cancer Survivors. The item is scored from 0 (‘not applicable’) to 5 (‘a very serious problem’). We defined a priori that a score of 4 or 5 indicated moderate/high level of fear of recurrence.

Emotional well-being

The emotional functioning subscale from the validated European Organization for Research and Treatment of Cancer Quality of Life Core-30 (EORTC QLQ-C30) questionnaire assessed emotional well-being. The subscale comprises 4 items and answers range from 1 (not at all) to 4 (very much). Raw scores were linearly transformed to a scale of 0-100 using standard procedures. Higher score indicates better functioning.

Statistical analyses

Differences in the distributions of demographic and clinical characteristics by CCI score were tested for statistical significance using either ANOVA for continuous variables or chi-square test for categorical variables.

We used multivariable linear regression to calculate the least square means, separately, of CRC-related and non-CRC HCU for overall CCI score and comorbidity cluster. Covariates, selected a priori for adjustment, were age at diagnosis, sex, marital status, health insurance, cancer stage, disease recurrence, GDS score, fear of recurrence, and emotional functioning. We tested for interactions between comorbidity (CCI and cluster) and sex, disease recurrence, or depression (GDS score) on HCU.

Multiple linear regression was used to explore whether and to what extent demographic, clinical, and psychological characteristics are associated with HCU (separate for CRC-related and non-CRC visits).

We conducted sensitivity analyses on the above linear regression models excluding survivors with disease recurrence.

All analyses were conducted with SAS (version 9.4 for Windows, SAS Institute Inc., Cary, NC). Statistical significance was determined at $P<0.05$ (two-sided). The $P$-values were not adjusted for multiple testing and referred to the individual tests rather than a global test for differences.
RESULTS
Survivors' characteristics
This study included 1718 stage I-III CRC cancer survivors (Supplementary Figure 1). The majority of the respondents (70%) had no comorbid condition reported in the medical records (Table 1). Survivors with no pre-existing comorbidities were more likely to be younger, female, employed, higher educated, have BMI <25kg/m², a non-smoker, less likely to be depressed according to the GDS, had chemotherapy, and have private insurance when compared with survivors with comorbid conditions (Table 1).

Mean HCU
CCI score
Numbers of both CRC-related GP and MS visits, and non-CRC GP and MS visits increased with increasing CCI score, even though differences between groups were statistically significant only for CRC-related MS visits and non-CRC GP visits (Figure 1).

Comorbidity clusters
There were no significant differences between the comorbidity clusters in CRC-related GP or MS visits (Figure 2). For non-CRC GP visits, survivors with no comorbidities reported the lowest number of visits when compared with survivors in specific clusters of comorbidities, all significantly different except for multiple comorbidity clusters. Survivors in the CVD cluster reported the highest number of non-CRC GP visits. No significant differences in MS visits were noted between the clusters.

Factors associated with HCU
By comorbidity definition
The CCI was not associated with CRC-related GP visits (Table 2). However, a moderate/severe CCI score remained significantly associated with CRC-related MS visits, even after adjusting for demographic, clinical, and psychological factors. In comorbidity clusters analyses, CVD was significantly associated with CRC-related GP visits but not MS visits. In contrast, the metabolic cluster was significantly associated with CRC-related MS visits but not GP visits.
For non-CRC visits, mild and moderate/severe CCI were significantly associated with more GP visits, even after adjustments for demographic, clinical, and psychological factors (Table 3). No significant association was found between CCI and MS visits. In comorbidity clusters analyses, CVD, metabolic, and other clusters were significantly associated with increased non-CRC GP visits. Comorbidity clusters were not associated with non-CRC MS visits.

Interactions between comorbidity and sex on HCU were generally not significant, except for the comorbidity cluster*sex interaction for CRC-related GP visits, where the effect was more prominent among female survivors with CVD (Supplementary Table 1). The CCI*disease recurrence interaction on CRC-related and non-CRC MS visits was more prominent among survivors with disease recurrence ($P_{interaction}<0.001$). The comorbidity cluster*disease recurrence interactions suggest that survivors with recurrence and CVD or metabolic disease made more CRC-related GP visits. Survivors with recurrence and metabolic disease comorbidity more often visited the MS for CRC-related reasons.

Other factors

Age was not significantly associated with CRC-related GP or MS visits (Supplementary Table 2). Disease recurrence was significantly associated with CRC-related GP or MS visits, regardless of adjustment that included the CCI or comorbidity clusters. Depression was associated with more CRC-related MS visits.

For non-CRC HCU, age was not significantly associated with GP or MS visits (Supplementary Table 3). Lower education was associated with increased non-CRC GP visits. In contrast, being single was associated with fewer non-CRC GP visits. Chemotherapy, stage III CRC, and disease recurrence were significantly associated with non-CRC MS visits. Disease recurrence was associated with more non-CRC GP visits in analyses which adjusted for comorbidity clusters but not for the CCI. Mild depression was associated with more non-CRC MS visits and severe depression was associated with more GP and MS visits. Higher emotional functioning was associated with fewer GP visits.
Sensitivity analysis

After excluding survivors with disease recurrence, similar patterns of associations between comorbidity (CCI or clusters) and CRC-related GP and MS visits were observed. However the magnitude of the association was attenuated slightly, especially for MS visits (Supplementary Table 4). For non-CRC GP visits, results were similar to those from the whole sample. In contrast, disease-free survivors with pre-existing comorbidity showed a tendency for fewer non-CRC MS visits, but the difference was not statistically significant. There was no longer a significant interaction between comorbidity (CCI or clusters) with sex. Contrary to whole sample, there was a significant interaction between comorbidity clusters and depression for non-CRC GP visits, specifically among survivors with CVD or metabolic conditions and mild depression symptoms.

Regarding other factors associated with CRC-related visits, the association between private health insurance and MS visits almost doubled and reached statistical significance, in contrast to results using the whole sample (Supplementary Table 5). The magnitude of association between severe depression and CRC-related MS visits was attenuated and lost statistical significance after excluding survivors with disease recurrence. Results that were adjusted for CCI scores were similar to those adjusted for comorbidity clusters (data not shown).

DISCUSSION

Due to the aging population and improvement in treatment, the number of CRC survivors is increasing in many countries, including Germany. Like other cancer survivors, CRC survivors utilize healthcare more frequently than age-matched non-cancer controls. However, it is unclear which factors are associated with the HCU among long-term cancer survivors. In a cohort of stage I-III CRC survivors assessed at 5-year follow-up, we found that comorbidity rather than older age was strongly associated with more frequent healthcare visits. Other factors independently associated with more HCU were lower education, chemotherapy, disease recurrence, and depression. By contrast, cancer stage III and higher emotional functioning were associated with fewer healthcare consultations.

Our data suggest that survivors with disease recurrence made significantly more CRC-related GP and MS visits. This increased HCU is clinically plausible as these survivors were likely to have further treatment. In accordance with German clinical guidelines for stage I-III CRC, follow-ups are
recommended if the disease recurrence has therapeutic consequences, but a programmed follow-up is not necessary for survivors with good prognosis.\textsuperscript{27}

Comorbidity showed strong associations with non-CRC GP visits. This is in line with previous studies in which cancer survivors with comorbidity visited the GP more often than survivors without comorbidity or non-cancer controls.\textsuperscript{12-14} This association remained strong even after excluding survivors with disease recurrence. Of note, the magnitude of associations with HCU did not differ significantly between the two comorbidity definitions. It is well known that information gleaned from comorbidity clusters could be more specific than that from the CCI, which is a weighted summation of conditions. Significant interactions were more likely to be found when using comorbidity clusters rather than the CCI, indicating that survivors with CVD or metabolic conditions were more likely to visit their healthcare providers. The prognostic utility of comorbidity clusters for health outcomes research should be further assessed in future studies.

We found associations between psychological factors and HCU. Higher levels of emotional functioning was associated with fewer consultations but depression was associated with increased visits to healthcare professionals, similar to previous evidence.\textsuperscript{28} Medical expenditure for cancer survivors with psychological distress were significantly higher than that of survivors without psychological distress or non-cancer controls with psychological distress.\textsuperscript{29} Fear of recurrence could be associated with more frequent medical consultations.\textsuperscript{30} Cancer survivors with an elevated fear of disease recurrence consulted medical and psychosocial personnel more often within 18-months after cancer surgery.\textsuperscript{31} We did not find an association between HCU and fear of recurrence. Possible reasons for this disparity could be that previous studies included survivors of heterogeneous cancers up to 10-years post-diagnosis\textsuperscript{30} or were younger and better educated females with predominantly breast cancer.\textsuperscript{31} Our sample consisted of survivors with at least 5-year survival. It is possible that within these 5 years, access to regular follow-ups with a cancer specialist in accordance with clinical guidelines\textsuperscript{27} could have attenuated the association between fear of recurrence and HCU.

GP consultations generally increase with age.\textsuperscript{12, 13, 15, 32} Although we noted a similar trend in our study, this association was not significant. This difference in results could be that previous studies compared HCU with non-cancer controls and did not correct extensively for other potential demographic, clinical, and psychological factors as in our study. Instead, we noted that lower education was associated
with more frequent GP visits. For these survivors, visits to their GP could serve as a coping mechanism for illness-related psychological distress.\textsuperscript{28} We found that survivors with lower education were more likely to have depressive symptoms ($p<0.001$, data not shown). It is also possible that survivors feel more comfortable communicating with their GP than the MS even for CRC-related matters. Cancer survivors spoke of not feeling known or heard by their oncology healthcare team.\textsuperscript{33} Provision of clear information (e.g. using less technical language) could reduce psychological distress and improve functional health literacy in cancer survivors,\textsuperscript{34,35} especially among cancer survivors with lower level of education in whom multi-morbidities are also more common.\textsuperscript{36}

**Clinical implications**

Cancer specialists might consider the management of comorbid conditions beyond their role or expertise,\textsuperscript{37,38} and would prefer GPs to manage pre-existing cardiometabolic or psychiatric conditions of cancer survivors.\textsuperscript{39} In contrast, GPs are less comfortable with managing potential cancer-related symptoms.\textsuperscript{37} In our study, we observed that survivors would visit the GP for CRC-related matters. Previous studies suggest that cancer survivors with multi-morbidity might have fragmented care across medical specialties and have increased risk of potentially inappropriate medications due to polypharmacy. These may increase HCU and costs.\textsuperscript{40,41} This suggests that provision of care to cancer survivors with comorbidity needs to be better integrated and coordinated between cancer specialists and GPs.\textsuperscript{40,42}

Chemotherapy was associated with increased non-CRC-related MS visits in our study, probably due to long-term adverse treatment effects such as neuropathy or fatigue. These symptoms can persist and have a negative impact on functioning.\textsuperscript{43,44} Our results suggest that improved communication about risk of potential chronic treatment-related effects could be a point of focus for healthcare providers. Provision of clear information may also assist CRC survivors to better adapt to and self-manage these persistent side effects.\textsuperscript{45-47}

Depressive symptoms were associated with HCU, even after excluding survivors with disease recurrence. However, we used the GDS which is a screening instrument. Hence, depression needs to be confirmed with a clinical interview. Detailed evaluation not only assists treatment planning but also rules out possible fatigue which is associated with depression.\textsuperscript{47} Healthcare providers should therefore monitor cancer survivors for possible psychological distress and refer to psychological care, if necessary. Cancer
survivors treated for depression had lower total annual healthcare expenditure when compared with those with untreated depression.\textsuperscript{48}

\section*{Strengths and limitations}
Our study collected detailed baseline comorbidity information from a large population-based sample who completed uniform follow-ups. Nevertheless, our study has limitations. We explored the association between baseline comorbidity and HCU at 5-year post-diagnosis, even though comorbidity prevalence might have increased post-cancer.\textsuperscript{49} Visits to healthcare providers were self-reported, thereby increasing the possibility of recall bias. We do not have information on HCU from healthcare providers for corroboration. Also, we only assessed the frequency of HCU and we lacked information on the specifics of the visits. Furthermore, we do not have a standardized criterion to determine excessive HCU. Given that a number of psychological factors were assessed at the time of evaluating HCU (cross-sectional), we were not able to infer any causal relationship between psychological factors and uptake of healthcare.

\section*{Conclusion}
Among CRC survivors, HCU at 5-year follow-up was less dependent on age and tumor stage but was largely related to comorbidities, suggesting that uptake of healthcare is based mainly on reasons other than cancer. Improved communication between primary and tertiary healthcare providers, and with cancer survivors could benefit the care of cancer survivors with complex health needs and thereby also reduce healthcare costs.

\section*{CONFLICT OF INTEREST}
The authors report no conflict of interest.

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