Aus dem Institut für Epidemiologie
der Christian-Albrechts-Universität zu Kiel

Postdiagnostic dietary patterns, physical activity, and health-related quality of life and long-term survival after colorectal cancer

Dissertation

zur Erlangung des Doktorgrades
der Agrar- und Ernährungswissenschaftlichen Fakultät
der Christian-Albrechts-Universität zu Kiel

vorgelegt von
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aus Henstedt-Ulzburg

Kiel, 2018

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Zweiter Berichterstatter: Prof. Dr. Dr. Anja Bosy-Westphal
Tag der mündlichen Prüfung: 13. Juli 2018

Gedruckt mit Genehmigung der Agrar- und Ernährungswissenschaftlichen Fakultät
der Christian-Albrechts-Universität zu Kiel

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Ratjen I, Schafmayer C, di Giuseppe R, Waniek S, Plachta-Danielzik S, Koch M, Nöthlings U, Hampe J, Schlesinger S, Lieb W. **Postdiagnostic Mediterranean and Healthy Nordic Dietary Patterns Are Inversely Associated with All-Cause Mortality in Long-Term Colorectal Cancer Survivors**. *J Nutr* 2017;147(4):636-44.

Ratjen I, Schafmayer C, di Giuseppe R, Waniek S, Plachta-Danielzik S, Koch M, Burmeister G, Nöthlings U, Hampe J, Schlesinger S, Lieb W. **Postdiagnostic physical activity, sleep duration, and TV watching and all-cause mortality among long-term colorectal cancer survivors: a prospective cohort study**. *BMC Cancer* 2017;17(1):701.

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Ratjen I, Weber KS, Roden M, Herrmann ME, Müssig K. **Type 1 diabetes mellitus and exercise in competitive athletes**. *Exp Clin Endocrinol Diabetes* 2015;123(7):419-22.

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Index of Abbreviations

AICR	American Institute for Cancer Research
BMI	Body mass index
CI	Confidence interval
CRC	Colorectal cancer
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
FFQ	Food frequency questionnaire
HNFI	Healthy Nordic Food Index
HR	Hazard ratio
HRQOL	Health-related quality of life
IQR	Interquartile range
MET	Metabolic equivalent of task
MMDS	Modified Mediterranean Diet Score
OR	Odds ratio
PRO	Patient-reported outcome
QOL	Quality of life
RR	Relative risk
TV	Television
US	United States
WCRF	World Cancer Research Fund
WHO	World Health Organization

1 General introduction

Colorectal cancer (CRC) is the third most common cancer in men and the second most common cancer in women with nearly 1.4 million people diagnosed worldwide in 2012 [1]. It is expected that by 2030 the number of worldwide newly diagnosed cases will increase to 2.2 million annually [2, 3]. At the same time of globally increasing incidences, survival rates of CRC patients are rising due to earlier diagnoses and more effective treatment methods, leading to a growing group of CRC survivors [2, 4]. Thus, identifying and characterizing factors that affect these survivors' daily life and their survival time is becoming a more important global public health interest.

Lifestyle factors, like dietary behavior and physical activity, are evidentially associated with the incidence of a considerable number of different types of cancer [5-9] with CRC being one of the most lifestyle-influenced cancers [10, 11]. However, specific and official lifestyle recommendations for cancer survivors are still lacking. So far, dietary and physical activity recommendations for cancer survivors are the same recommendations as for cancer prevention, as released from the World Cancer Research Fund (WCRF)/American Institute for Cancer Research (AICR) in 2007 [12, 13]. Furthermore, as survival rates of CRC patients are improving and, thus, more people are living a life beyond CRC, health-related quality of life (HRQOL) in those CRC survivors is rising to a key issue.

Some previous studies investigated the associations of selected dietary factors, obtained some time after the cancer diagnosis ('postdiagnostic') with CRC mortality, including dairy products, calcium, vitamin D, sugar-sweetened beverages, red and processed meat, and the glycemic index, with the results being rather inconclusive [14-17]. Most of those studies investigated single foods, food groups, or nutrients. However, the complexity of diet is likely to be better represented by dietary pattern analyses which might also capture synergistic and antagonistic nutrient and food interactions [18, 19].

Physical activity has been shown to be associated with numerous beneficial health effects like reduced body weight and cardiovascular risk, decreased cancer risk, and improved survival in the general population and in different patient groups [7, 20-22]. Some prior studies examined the association between physical activity and mortality after CRC diagnosis and suggested higher amounts of physical activity being related to improved CRC survival [23-26]. However, most previous studies assessed physical activity within a relatively short time interval after CRC diagnosis. Thus, evidence regarding the association

of physical activity with mortality later on after diagnosis is still scarce. Additionally, the contribution of different types of activity (e.g., sports, cycling, housework) to the beneficial effect of total physical activity on CRC survival has not yet been investigated, so far.

Besides prolongation of life, improving HRQOL should be a key goal of CRC treatment [27]. Studies revealed that the HRQOL status of CRC survivors varies between populations, between individuals, and between different HRQOL domains [28-32]. The knowledge of factors affecting HRQOL in CRC survivors may facilitate the identification of individuals with an especially high risk of a low HRQOL or the adjustment of modifiable risk factors [33]. HRQOL of CRC survivors has been associated with mortality in several studies [34-38], but these previous studies assessed HRQOL primarily rather shortly after diagnosis or even before treatment initiation. Moreover, some studies focused particularly on individuals with an advanced (metastatic) cancer stage [37, 39]. Therefore, further studies are needed that examine the relation between HRQOL and mortality in CRC survivors in the long term after diagnosis.

The majority of studies that examined lifestyle factors in relation to CRC survival assessed diet and physical activity before cancer diagnosis in population-based studies [40]. Moreover, even those studies that assessed diet and physical activity after diagnosis are often very heterogeneous regarding timing of exposure (diet, physical activity, quality of life (QOL)) assessment. However, the survival time from diagnosis until exposure assessment might have a considerable effect on the relations between lifestyle factors and HRQOL and mortality. For example, studies have reported that many cancer survivors modify their dietary and physical activity habits after cancer diagnosis to improve health and prevent recurrence [41-45]. Furthermore, dietary behavior and physical activity during or shortly after therapy might be affected by adverse treatment effects [46-49]. Therefore, the timing of lifestyle factor assessment might play an important role for outcome manifestation and the assessment several years after diagnosis and treatment is more likely to reflect the real and long-lasting individual dietary and physical activity habits which might have the strongest and enduring influence on health and survival. Thus, long-term cancer survivors (>5 years survived after diagnosis) may embody a special group of interest in research settings.

1.1 Public health relevance

Colorectal cancer

CRC is a heterogeneous disease characterized by carcinomas in the colon or rectum which are both parts of the gastrointestinal (digestive) system [50, 51]. The majority of colorectal carcinomas arise slowly from adenomas or adenomatous polyps over years or even a decade, involving a series of histological, morphological, and genetic changes [52]. Evidentially, the development of CRC is associated with genetic, environmental, and lifestyle (e.g., physical inactivity, obesity, diet, smoking) factors [51, 53]. Approximately two-thirds of CRC patients undergo surgical tumor resection with curative intent [54, 55]. If indicated, patients additionally receive neoadjuvant (before surgery) or adjuvant (following surgery) therapies, including chemotherapy or radiation therapy, or a combination of both [51, 54, 56].

CRC is one of the most common malignancies in the Western world. It is the third most common cancer in men and the second most common cancer in women, affecting approximately 746.000 men and 614.000 women worldwide in 2012 [57]. Thus, CRC accounts for about 10% of all cancer cases [57]. In Germany, there were ~61.000 people diagnosed with CRC in the year 2014 [58]. Globally, the highest incidence rates are found in Japan, North America, Oceania, and Europe. Although current incidence rates are lower in developing as compared to developed countries, incidence is constantly rising in several developing countries [57, 59]. CRC incidence increases with age. The mean age at diagnosis is 75 years for women and 72 years for men in Germany. More than half of patients that are diagnosed with CRC are older than 70 years [60], though the incidence of CRC in younger individuals is increasing [61, 62].

In 2012, there were 694.000 deaths from CRC worldwide (8.5% of all cancer deaths) [57] and by 2030 there are 1.1 million deaths predicted [2, 3]. In Germany, CRC accounts for approximately 25.000 deaths per year [60]. However, due to substantial improvements in cancer detection and treatment strategies, the group of people surviving cancer is growing [4]. Death rates of CRC have fallen each year by on average 2% (1997-2007) in Europe and 2.5% (2005-2014) in the United States (US) and the 5-year relative survival is about 65% in the US and about 63% in Germany [58, 63, 64].

A ‘cancer survivor’ is defined as any person who has ever been diagnosed with cancer, from the time of diagnosis until the end of their life [65, 66]. Cancer survivorship is a continuum that comprises phases of treatment and recovery, long-term disease-free living or living with stable disease, and, in some cases, living with advanced cancer disease [67].

Each of these phases implies different needs and challenges for survivors [67]. One of these challenges is that individuals who have been diagnosed with cancer have an increased risk of second primary cancers [68] and are also more likely to develop other chronic diseases such as cardiovascular diseases, diabetes mellitus, and pulmonary diseases [69-73]. The concept of 'cancer survivorship' has its origin in North America [74] and has gained importance in Europe relatively recently [75]. With the increasing number of cancer survivors, the field of cancer survivorship, examining experiences and outcomes of cancer survivors, will continue to gain more attention in research and clinical settings [76].

Diet and physical activity as lifestyle factors influencing disease risk

Nutritional factors, dietary behavior, and physical activity are known to exert substantial influence on a large number of diseases (e.g., cardiovascular diseases, metabolic disorders, and cancer) as well as on physical and mental health conditions [7, 20-22, 77-82]. During the last decades, large parts of the population were getting less physically active, spent more time with sedentary activities (e.g., television (TV) viewing, using the computer), and increasingly adhered to a unhealthy diet with a high consumption of fast food and fortified foods [83]. Low levels of physical activity and energy-dense, fat-, and sugar-rich diets are evidentially related to overweight and obesity, which is an increasing public health problem [84]. Besides, suboptimal diet quality and physical inactivity have been shown to be among the leading modifiable causes of death and disability in the world [85]. As nutrition and physical activity are a natural part of everyone's daily life, the modification of these behavioral factors is conceptually a promising path for disease prevention and health promotion.

Cancer survivors are increasingly interested in lifestyle recommendations to prevent cancer recurrence and to improve QOL and survival after diagnosis [12, 67]. Therefore, informed lifestyle choices for cancer survivors are becoming particularly important. However, current dietary and physical activity guidelines for cancer survivors are the same as for cancer prevention in healthy individuals [13]. Major cancer-related research organizations like the WCRF are calling for research on lifestyle factors linked to cancer outcomes [86]. Because cancer survivors are also at higher risk for other chronic diseases, as for example cardiovascular diseases, when compared to the general population [69, 87], understanding the role of lifestyle factors for cancer-specific, noncancer, and overall outcomes is of clinical and public health relevance [88-90].

In nutritional epidemiology, dietary pattern analyses, instead of analyses of isolated nutrients or foods, are gaining importance since dietary patterns are more likely to exert an effect on health rather than just single dietary components [18, 19, 91]. One of the most established and widely known dietary patterns is the Mediterranean diet. It is characterized by high consumption of vegetables, fruits and nuts, legumes, fish, and unprocessed cereals and low consumption of dairy products, meat, and poultry. Furthermore, a high ratio of monounsaturated lipids to saturated lipids and a moderate alcohol intake (mainly in the form of (red) wine) is part of the Mediterranean diet [92, 93]. Besides its lipid-lowering effects through a low content of saturated lipids, the Mediterranean diet has been shown to exert a broad range of beneficial health effects [79, 82, 94-100]. To assess the degree of adherence to the Mediterranean diet, Trichopoulou et al. [92, 101] constructed an *a priori*, hypothesis-based Mediterranean diet scale enabling the application of this scale in analytical epidemiologic studies. In the past years, several modified variants of the Mediterranean diet scale have been constructed and introduced into research, mainly to slightly adjust the instruments to other countries' dietary behavior (e.g., the US and Non-Mediterranean Europe), for example by including also polyunsaturated fats in the ratio of unsaturated to saturated lipids [94, 102-104]. More recently, a dietary pattern which consists of typical healthy Northern European foods has gained attention. The *a priori*-defined 'healthy Nordic Food Index' has been developed by Olsen et al. [105] and comprises rye bread, oatmeal, apple and pears, cabbage, root vegetables, and fish/shellfish. It has been investigated in different observational studies that were able to confirm its positive effects on various health outcomes, including mortality, cancer, and cardiometabolic disease risk [105-109].

In the light of decreased physical activity participation and increased sedentary time in many populations around the globe, the importance of promoting physical activity as a public health intervention is actively being discussed and addressed [110-113]. Most studies dealing with physical activity focused on health effects of recreational physical activity. However, the impact of occupational physical activity (activities on the way to work or at work) and physical activities during the daily routine like, for example, housework, home repair, gardening, and stair climbing may as well provide substantial health benefits. The latter might be especially important for elderly individuals who retired and rather spend their time at home than at work. Additionally, older individuals might be less capable and motivated of engaging in high-intensity sports and exercise (e.g., playing soccer or doing resistance training) and, therefore, spend more time with light-intensity activities and daily routine activities like gardening and housework. Different physical activities are

heterogeneous regarding their types and intensities and, potentially, also regarding their effects on physical functioning and health [114].

Health-related quality of life

Patient-reported outcomes (PROs) are increasingly gaining importance as outcome measures in both observational and interventional studies, as well as in clinical practice [115-118]. PROs are measurements that are reported by the patients themselves and that can represent the patients' view on the burden of a disease and its treatment [116-118]. One of the most widely assessed and applied PROs is HRQOL [116, 118]. Thereby, treatment effects are evaluated not only by their influence on quantity of life but also on quality of life [118, 119]. QOL is a multidimensional, subjective, dynamic, and person-centered construct, consisting of physical, functional, emotional, and social dimensions [120]. The World Health Organization (WHO) has defined QOL as an 'Individuals' perception of their position in the context of the culture and value systems in which they live, and in relation to their goals, expectations, standards and concerns' [121]. Symptoms play an important role for HRQOL because they have a direct or indirect impact on QOL, e.g., by affecting daily activities or family and social life [122, 123].

Ideally, cancer survivors recover from disease- or treatment-related acute effects within weeks or months after therapy but sometimes side effects of treatment (e.g., fatigue, sleep disorders, pain) persist [29, 124-127]. In addition, latent detriments and some treatment effects (e.g., second cancers, cardiovascular diseases, osteoporosis) may become apparent months or years after treatment completion [126-130]. Thus, CRC survivors can be impaired in physical functioning and in everyday life by multiple disease- and treatment-related symptoms such as pain, fatigue, and bowel dysfunction and may be negatively affected in psychological, emotional, social, and role functioning because of fear, anxiety, distress, sleep disruption, and depression [123, 131-134]. Some cancer survivors are living with a permanent sense of uncertainty and fear of disease recurrence since diagnosis [76]. Furthermore, in some CRC survivors, the construction of a stoma might be necessary, which can mean both physical as well as psychological impairments [135-139]. Hence, international organizations, like the US Institute of Medicine, are highlighting the importance of caring for psychosocial needs of cancer survivors [140].

1.2 State of knowledge

Postdiagnostic diet and colorectal cancer survival

A few studies have investigated the association between dietary factors and survival after CRC diagnosis but most observations were not replicated in other studies [141, 142]. For example, high consumption of sugar-sweetened beverages after CRC diagnosis was not associated with overall survival in a study of stage III colon cancer patients [17]. However, in the same sample, higher dietary glycemic load and higher total carbohydrate intake were significantly associated with decreased survival whereas no association was found for dietary glycemic index [15]. In another cohort, higher postdiagnostic total fiber and whole grain intake were both significantly associated with CRC-specific and all-cause mortality [143]. Furthermore, in 953 stage III colon cancer patients, an improvement in survival was observed along with increasing coffee consumption, though the association was limited to caffeinated coffee [144]. Regarding nutrient intake, postdiagnostic folate and other one-carbon nutrients showed no association with CRC-specific death [145] and a higher postdiagnostic predicted 25-hydroxyvitamin D_3 score (including dietary and supplementary vitamin D intake) was associated with improved cancer-specific and overall mortality [146] while, in another study, the intake of vitamin D showed no association with mortality [14]. The postdiagnostic intake of calcium and milk was inversely associated with all-cause mortality [14]. In 1925 participants of a randomized trial on adjuvant therapies, the intake of total alcohol was not associated with colon cancer outcomes, however, when considering different types of alcohol, a higher consumption of red wine was associated with significantly better outcomes. Beer and liquor consumption were not associated [147]. Likewise, in 1599 CRC survivors, an association of postdiagnostic alcohol consumption and mortality could not be confirmed [148]. A higher consumption of red and processed meat after CRC diagnosis revealed no relation with survival [16] whereas a higher consumption of dark fish in colon cancer survivors was associated with improved overall survival [149]. However, the intake of marine n-3-polyunsaturated fatty acids was not statistically significantly associated with overall survival, but with disease-free survival [149].

So far, only few studies have examined dietary patterns in relation to CRC survival. Most studies focused on nutrients, foods, and food groups, as presented above. Additionally, those studies that investigated dietary patterns in relation to CRC survival were inconclusive. One prospective observational study with 1009 stage III colon cancer patients reported that a Western dietary pattern, characterized by high intakes of meat, fat, refined grains, and desserts, led to significantly decreased survival whereas a prudent pattern, characterized by high intakes of fruits and vegetables, poultry, and fish, was not significantly

associated with patient outcome [150]. Another study examined the association of five different dietary patterns with survival in 1201 women diagnosed with CRC, including the Alternate Healthy Eating-Index 2010, the alternate Mediterranean Diet score, the Dietary Approaches to Stop Hypertension score, a prudent (healthy), and a Western (unhealthy) dietary pattern. From these patterns, only the Alternate Healthy Eating-Index 2010 displayed a statistically significant inverse association with mortality [103].

Postdiagnostic physical activity and colorectal cancer survival

Several systematic reviews and meta-analyses reported significant inverse associations between postdiagnostic physical activity and all-cause mortality in CRC survivors [142, 151, 152]. Specifically, studies examining the impact of physical activity on cancer recurrence and cancer survival revealed 25-63% lower all-cause mortality for more active as compared to less active patients after CRC diagnosis [23-26, 153-155]. However, these prior studies assessed physical activity rather shortly after CRC diagnosis (several months to <5 years after diagnosis) and studies examining the effect of physical activity in long-term CRC survivors (>5 years after diagnosis) on mortality risk are scarce. Furthermore, evidence on the impact of different types of physical activity on survival is missing. In addition to frequency and duration of physical activity, also sedentary time, like TV watching hours, are of interest with respect to their association with mortality in CRC patients. In this context, two studies analyzed the association between postdiagnostic TV viewing and all-cause mortality in CRC survivors and observed an increase in mortality with more hours of TV watching, though the association failed to reach statistical significance [23, 156].

Health-related quality of life status and factors associated with health-related quality of life in colorectal cancer survivors

Most previous studies reported generally high HRQOL values in CRC survivors [157-162] and improvements in HRQOL over the course of months and years after diagnosis [28]. However, on a parallel note, several symptoms and medical issues (e.g., pain, diarrhea, fatigue, depressive symptoms, impaired daily functioning) have been reported by CRC patients, even years after diagnosis and treatment [30, 32, 158, 159, 161].

Different clinical, sociodemographic, and lifestyle factors have been identified to be associated with HRQOL in CRC survivors in previous epidemiological studies [28, 34, 163, 164], even though the results from different studies were partially inconsistent and conflicting. As an example, some studies reported higher [28] and some lower [31, 34, 122,

165] HRQOL in women as compared to men, whereas other studies observed no significant difference between men and women in HRQOL [164]. Older as compared to younger age was associated with a lower physical [34, 164] but a higher mental HRQOL [34] and with better overall HRQOL [31, 32]. A higher educational level was found to be related to higher QOL and higher physical functioning in different cohorts [34, 164, 165]. With respect to the association between family status and HRQOL, studies reported inconsistent results [28, 164-166]. Other studies found a lower social support to be associated with worse HRQOL [31, 167, 168]. Lifestyle factors, like higher physical activity [135, 169-171], a more beneficial diet [170, 171], nonsmoking [34, 165], and a normal weight or body mass index (BMI) [34, 163, 170], were positively associated with HRQOL in previous studies. Furthermore, malnutrition was found to be associated with worse QOL scores in 58 CRC patients [172]. Regarding tumor location, study results were largely conflicting with either no significant association with HRQOL [34], a lower HRQOL for rectal cancer survivors than for colon cancer survivors [28] or a lower physical functioning in colon tumor as compared to rectum tumor survivors [165]. In terms of treatment modalities, a French study of 207 rectal cancer survivors reported worse HRQOL in patients who received both chemotherapy and radiation as compared to patients receiving only radiation [173]. In a Dutch investigation, chemotherapy or radiation alone compared to none was not associated with HRQOL [174]. In contrast, two other studies found an increased HRQOL and better physical functioning in patients receiving adjuvant treatment as compared to patients not receiving adjuvant treatment [28, 175]. Additionally, a more advanced disease stage, more comorbidities, and cancer recurrence were associated with worse HRQOL [28, 31, 122, 164, 165, 176]. Several studies demonstrated that CRC survivors with a stoma had a decreased HRQOL, even in the long-term period of two to more than five years postdiagnosis [28, 137, 177]. As opposed to this, in one study of 121 rectal cancer patients, a stoma construction was found to be associated with a higher global QOL and less gastrointestinal problems [178] which was not true for rectal cancer patients in two other studies [136, 179].

Taken together, HRQOL of CRC survivors has been analyzed in prior studies, but most of these studies evaluated rather short-term (≤5 years after diagnosis) treatment- and disease-related effects on QOL and were mostly based on relatively small sample sizes [30, 165, 180-182].

Health-related quality of life and colorectal cancer survival

Lower HRQOL was associated with worse survival in CRC survivors in few prior studies [35, 37-39, 165, 180, 181]; some of those have been summarized in a literature review [183]. However, these studies mainly assessed HRQOL very shortly after diagnosis and therapy or even prior to treatment initiation and some of them assessed HRQOL specifically in patients with advanced (metastatic) cancer [37, 39, 181]. So far, only one study assessed HRQOL in long-term survivors of CRC and examined its association with mortality. This study provided initial evidence for an inverse relation between physical and mental HRQOL and mortality risk more than 5 years after diagnosis [34].

1.3 Aims of the present thesis

The research aims of this doctoral thesis were to investigate whether predefined dietary patterns, physical activity, and HRQOL after diagnosis were associated with all-cause mortality in long-term survivors of CRC. Further aims were to describe the HRQOL status in CRC long-term survivors and to examine correlates of HRQOL in these individuals. Specifically, the individual research aims were defined as follows:

I) To investigate whether the Modified Mediterranean Diet Score and the healthy Nordic Food Index, obtained post-diagnostically in long-term survivors of CRC, were associated with all-cause mortality in these individuals (Chapter 2).

II) To assess the association of postdiagnostic total physical activity, different types of physical activity (‘sports’, ‘cycling’, ‘walking’, ‘gardening’, ‘housework, home repair, and stair climbing’), hours of sleeping at night and day, and time spent watching TV with all-cause mortality in CRC long-term survivors (Chapter 3).

III) To describe the HRQOL status of CRC long-term survivors (Chapter 4).

IV) To identify sociodemographic and clinical correlates of HRQOL in long-term CRC survivors (Chapter 4).

V) To examine the association of HRQOL with all-cause mortality among long-term survivors of CRC (Chapter 4).

The research goals were addressed by analyzing data of a prospective cohort study initially consisting of 2733 CRC survivors who have been recruited by the biobank PopGen approximately 4 years after diagnosis [184]. Dietary intake, physical activity, and HRQOL were assessed on average (median) 6 years after CRC diagnosis using validated questionnaires [185-187]. The ascertainment of vital status was conducted via population registries and length of median survival follow-up, beginning at the date of exposure (diet, physical activity, and HRQOL) assessment, was 7 years. For details on the study design please see also **Figure 1** in the appendix. The background, analyses, results, and discussion of each aim will be presented in detail in three scientific articles (Chapter 2-4). Subsequently, findings will be summarized and discussed in Chapter 5.

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2 Postdiagnostic Mediterranean and healthy Nordic dietary patterns are inversely associated with all-cause mortality in long-term colorectal cancer survivors

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J Nutr 2017; 147(4): 636-44

The Journal of Nutrition
Nutritional Epidemiology

Postdiagnostic Mediterranean and Healthy Nordic Dietary Patterns Are Inversely Associated with All-Cause Mortality in Long-Term Colorectal Cancer Survivors[1–4]

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Abstract

Background: Dietary factors are known to affect the risk of new-onset colorectal cancer (CRC), but information on the extent to which postdiagnostic diet affects mortality in long-term CRC survivors is scarce.

Objective: We investigated the association of 2 a priori–defined postdiagnostic dietary patterns [Modified Mediterranean Diet Score (MMDS) and healthy Nordic Food Index (HNFI)] with all-cause mortality in long-term CRC survivors.

Methods: Diet was assessed at a median time of 6 y after cancer diagnosis in 1404 CRC survivors (median age: 69 y; 56% men) in a prospective cohort study in Northern Germany by using a semiquantitative food-frequency questionnaire. Cox proportional hazard models, adjusting for clinical and sociodemographic characteristics, were used to assess associations of the MMDS and the HNFI with all-cause mortality.

Results: A total of 204 patients died during a median follow-up time of 7 y after diet assessment. In multivariable-adjusted models, higher adherence to the modified Mediterranean diet was significantly associated with lower all-cause mortality (HR: 0.48; 95% CI: 0.32, 0.74 for highest compared with lowest score quartile and HR: 0.88; 95% CI: 0.81, 0.96 per 1-point increment in pattern score). Similarly, the HNFI was inversely associated with all-cause mortality when the highest was compared with the lowest index quartile (HR: 0.63; 95% CI: 0.39, 1.04) and when modeled as a continuous trait (HR: 0.90; 95% CI: 0.82, 0.99 per 1-point increment in the score).

Conclusions: Our results suggest that higher adherences to the Mediterranean diet and to the healthy Nordic diet after CRC diagnosis are associated with better overall survival in long-term CRC survivors. *J Nutr* 2017;147:636–44.

Keywords: dietary patterns, Modified Mediterranean Diet Score, healthy Nordic Food Index, colorectal cancer, survivors, mortality

Introduction

Colorectal cancer (CRC)[12] is the third most common cancer in men and the second most common cancer in women, affecting ~746,000 men and ~614,000 women worldwide in 2012 (1). Because of improved treatment strategies and earlier diagnoses, survival rates of patients with CRC have improved, leading to a growing number of long-term survivors after CRC diagnosis (2, 3). Besides primary CRC prevention, investigating factors that determine the prognosis in these long-term cancer survivors is an important field of research. Although cancer survivors are increasingly interested in lifestyle recommendations to improve quality of life and survival after diagnosis and therapy, current dietary guidelines for cancer survivors are based on cancer

[1] Supported by a Postdoctoral Research Fellowship from the German Research Foundation (Deutsche Forschungsgemeinschaft KO 5187/1-1) for MK and a Nurses' Health Study Biomedical Research Centre grant (Interventional Public Health) to SS.
[2] The funding sources had no role in the design or conduct of the study.
[3] Author disclosures: I Ratjen, C Schafmayer, R di Giuseppe, S Waniek, S Plachta-Danielzik, M Koch, U Nöthlings, J Hampe, S Schlesinger, and W Lieb, no conflicts of interest.
[4] Supplemental Methods 1 and Supplemental Tables 1–3 are available from the "Online Supporting Material" link in the online posting of the article and from the same link in the online table of contents at http://jn.nutrition.org.
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[12] Abbreviations used: CRC, colorectal cancer; HNFI, healthy Nordic Food Index; MMDS, Modified Mediterranean Diet Score.

Manuscript received November 15, 2016. Initial review completed December 14, 2016. Revision accepted January 25, 2017.
First published online February 22, 2017; doi:10.3945/jn.116.244129.

prevention guidelines (4–6) and are thus guidelines that aim to prevent the development of cancer in healthy individuals. Therefore, cancer charities, such as the World Cancer Research Fund, are calling for research on dietary recommendations for cancer survivors (7).

There is convincing evidence that several dietary factors are associated with the risk of new-onset cancer, especially of cancers within the gastrointestinal tract. High intakes of fat, red meat, refined sugar, and alcohol seem to increase the risk of CRC, whereas a high intake of dietary fiber, vegetables, and fruits shows a protective association against CRC development (8–12). However, the impact of postdiagnostic dietary factors on long-term survival of patients with CRC has not been adequately examined. Because foods and nutrients act in combination rather than isolation, dietary patterns are of particular interest (13). However, so far only a small number of studies have examined the association between dietary patterns and CRC survival, and results were inconsistent. For example, among patients with stage III colon cancer a higher adherence to a Western dietary pattern was associated with an ~2-fold elevated risk of mortality (14), whereas no such association could be observed in female CRC patients from the Nurses' Health Study (15).

We focused our analyses on 2 established dietary patterns that have been linked to health outcomes in prior studies but that have been scarcely examined with respect to CRC survival: the Mediterranean diet and the healthy Nordic diet. The Mediterranean diet, composed of traditional Mediterranean foods such as vegetables, fish, legumes, and beneficial fatty acids, has been widely shown to exert beneficial health effects and to reduce the risk of several diseases, including cardiovascular diseases and cancer, as well as mortality in population-based and clinical settings (16–18). Recently, a healthy Nordic diet also attracted scientific interest. Strong adherence to a healthy Nordic diet pattern, consisting of typical (healthy) Nordic food items, such as cabbage, apples and pears, fish, and oatmeal, has been associated with an 18% lower overall mortality among Swedish women (19). Similarly, a 35% lower CRC incidence for women who strongly adhered to a healthy Nordic diet than for women with poorer adherence was reported in a large Danish study (20).

Therefore, in the present study, we aimed to investigate whether the Modified Mediterranean Diet Score (MMDS) and the healthy Nordic Food Index (HNFI), obtained postdiagnostically in long-term CRC survivors, are associated with all-cause mortality in these individuals.

Methods

Study design and recruitment of the study population. The basic study design is depicted in **Figure 1**. Between 2004 and 2007, a total of 2733 patients with histologically confirmed CRC were recruited by the PopGen biobank and were followed up prospectively. Details of the study design have been reported elsewhere (21–24). Briefly, patients who were diagnosed with CRC between 2002 and 2005 were identified through medical records of surgical departments in 23 hospitals in Northern Germany and via the regional cancer registry. At the University Hospital Kiel, patients who were diagnosed from 1993 to 2005 were included. Patients were invited to participate in the study by their treating physicians and asked to fill in a questionnaire about clinical characteristics and sociodemographic and selected lifestyle factors. The study protocol was approved by the institutional ethics committee of the Medical Faculty of Kiel University. Written, informed consent was obtained from all study participants.

First follow-up survey. Between 2009 and 2011, a total of 2263 patients, who agreed to being recontacted, were asked to complete a questionnaire about clinical and sociodemographic factors, a web-based FFQ (25), and a questionnaire on health-related quality of life. Of the 2263 individuals contacted for this follow-up survey, 354 participants had died and 31 had moved with unknown addresses. Of the remaining 1878 individuals, 1685 (90%) participants responded to the general questionnaire, and of these 1452 (86%) completed the FFQ. Of the 1452 participants with information on diet, we excluded individuals with missing information on year of diagnosis (n = 21) and vital status (n = 21). Furthermore, we excluded participants who had a diagnosis of small intestine cancer instead of CRC (n = 3) and for whom information on follow-up length was implausible (n = 3). Therefore, the present analysis was based on 1404 participants.

Assessment of vital status. All-cause mortality was first determined by a combination of an active and passive follow-up in 2014. Individuals were contacted again via mail for an extension of their informed consent related to genetic analyses. Participants who did not respond or for whom spouses reported the study participant's death, vital status was obtained from population registries, and the date of death was recorded. An update on vital status of all patients was performed up to June 2016 via population registries, and the date of death was recorded if participants were deceased. Altogether, 204 deaths had occurred since the information on diet was obtained, and the date of death could be verified for all cases. The date of diet assessment was used as start of follow-up for this study. Individuals were censored at the verified date of death or at the date of last vital status assessment, whichever came first.

Clinical and sociodemographic characteristics. The assessment of clinical and sociodemographic characteristics has previously been reported elsewhere (23) and is described in **Supplemental Methods 1**.

Assessment of diet. Information on usual dietary intake, including alcohol consumption, was assessed by a validated, semiquantitative, web-based FFQ (a paper version was available on request and was preferred by 84% of participants) developed by the Department of Epidemiology at the German Institute of Human Nutrition in Potsdam-Rehbrücke (25). The FFQ consists of 112 food items and evaluates the consumption frequencies of predefined and labeled quantities of foods and beverages during the previous 12 mo. Frequencies were categorized into 4–11 options ranging from "never" and "once a day" to "11 times a day or more frequently." Quantities were given as portions, grams, milliliters, slices, pieces, or spoons. On the basis of consumption frequencies and standard portion sizes, intakes in grams per day were calculated for each inquired food or food group for each participant. Additionally, total energy intake per day was computed based on FFQ data.

Dietary patterns. The present analysis focused on 2 a priori–defined (hypothesis-based) dietary patterns, the Modified Mediterranean diet and the healthy Nordic diet. A score indicating adherence to the Mediterranean diet was constructed, as reported by Trichopoulou et al. (26), by assigning a value of 1 for an intake at or above the sex- and cohort-specific median of 5 beneficial components (vegetables, fruits and nuts, legumes, cereals, and fish) and for an intake below the median of 2 components presumed to be detrimental (meat and poultry products and dairy products); otherwise a value of 0 was assigned. For ethanol, a value of 1 was assigned to men who consumed between 10 and 50 g/d and to women who consumed between 5 and 25 g/d; otherwise a value of 0 was assigned (27). For fat intake, the ratio of unsaturated lipids to saturated lipids was calculated, which means we included not just monounsaturated but also polyunsaturated lipids in the numerator of the ratio, which leads to a slightly modified version of the Mediterranean diet pattern called the MMDS (16). We chose the MMDS for our analyses because in non-Mediterranean countries polyunsaturated lipids are the principal unsaturated lipids in diet and have established protective effects on coronary heart disease (16, 28). Individuals with a lipid ratio at or above the sex-specific median were assigned a value of 1, and those with a ratio below the median were assigned a value of 0. Thus, the total MMDS ranged from 0 (minimum adherence) to 9 (maximum adherence) (27).

The HNFI was originally developed by Olsen et al. (29) and is based on the following 6 traditional Nordic food items: cabbage, root

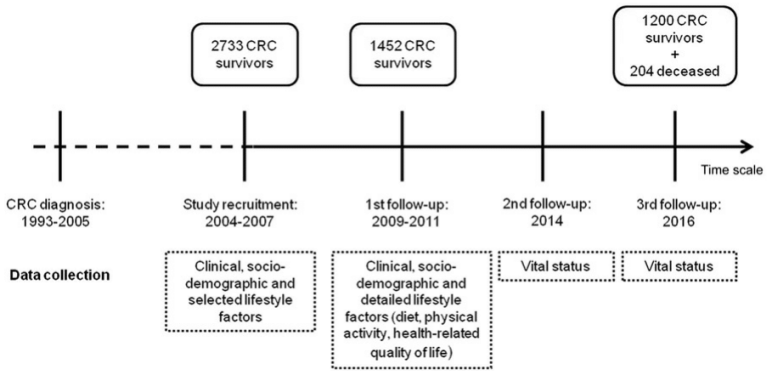

FIGURE 1 Study design of the PopGen CRC survivor cohort. CRC, colorectal cancer.

vegetables, rye bread, oatmeal, apples and pears, and fish and shellfish. As consumption of rye bread was not assessed specifically, we made one minor adjustment and included whole–grain bread instead of rye bread as a pattern component (19). The index is scored in a fashion similar to the Mediterranean diet score by Trichopoulou et al. (27). A value of 1 was given for an intake at or above the sex-specific median of the sample and a value of 0 was given if the intake was below the sex-specific median for each item and each participant. Thus, each participant could be scored between 0 (minimum adherence) and 6 (maximum adherence) (30).

Statistical analyses. First, anthropometric, lifestyle, and clinical factors were compared across quartiles of each dietary pattern score (MMDS and HNFI). Differences in medians of continuous variables were tested by using Wilcoxon's rank-sum test, and differences in categorical variables were assessed by using a chi-square test.

Second, Cox proportional hazard regression models were used to calculate HRs and 95% CIs for the association between adherence to MMDS or HNFI (each score considered separately) and all-cause mortality with the time interval from age at diet assessment to age at death or last follow-up as the underlying time variable. For these analyses, the exposure variable was modeled in 2 different ways. We calculated HRs for pattern score quartiles using the first quartile as the referent. We tested for linear trend across the quartiles by using the median values of the dietary pattern score quartiles as a continuous variable in the respective regression models. In another analysis, the dietary pattern score was included in the model as a continuous variable and we assessed the HRs and *P* values for all-cause mortality per a 1-point increment in dietary pattern score. To control for confounding, all models were adjusted for sex and age at diet assessment (model 1). A second model was additionally adjusted for BMI (in kg/m^2) at diet assessment, physical activity (continuous in metabolic equivalents of tasks per week), survival time from CRC diagnosis until diet assessment (continuous in years), tumor location (colon, rectum, both, or unknown), occurrence of metastases (yes, no, or unknown), occurrence of other cancers (yes, no, or unknown), chemotherapy (yes, no, or unknown), smoking status (never, former, current, or unknown), and total energy intake (continuous in kilocalories per day) (model 2). For categorical covariates indicator variables were used. Additionally, we calculated the multivariable-adjusted HR for all-cause mortality for individuals who were in the fourth quartile of both dietary pattern scores compared with all other participants. The assumption of proportional hazards was tested by the Schoenfeld residuals method and by including time-dependent variables in the models. Three variables (age, BMI, and metastases) did not meet the assumption of proportional hazards. Therefore, respective multiplicative time-covariate-interaction terms (time × age, time × BMI, time × metastases), with the time variable defined as the time interval from age at diet assessment to age at death or last follow-up, were included in the models.

Third, stratified analyses were conducted by categories of sex (men compared with women), age at diet assessment (<69 compared with ≥69 y), BMI (<25 compared with ≥25), physical activity (<95 compared with ≥95 metabolic equivalents of task–h/wk), tumor location (colon compared with rectum), and occurrence of metastases (yes compared with no). In addition, we stratified our analysis by side of colon cancer (left-sided compared with right-sided) in a subgroup with available information on colon cancer side (n = 466). We tested respective multiplicative interaction terms in the multivariable-adjusted models by including the cross product of the MMDS or the HNFI as a continuous variable and the potential effect modifier as a continuous or categorical variable, as appropriate.

Fourth, in sensitivity analysis, we examined the association of postdiagnostic dietary pattern scores with all-cause mortality, excluding CRC survivors who died within 12 mo of diet assessment to preclude those who changed their dietary behavior because of indisposition. In a second sensitivity analysis, we excluded individuals who had reported metastases at baseline or follow-up because in case of metastatic cancer the effect of dietary factors on survival might be weaker.

All statistical analyses were conducted by using SAS version 9.4 software (SAS Institute, Inc.). Two-sided *P* values of <0.05 were considered statistically significant.

Results

Basic characteristics of the overall study sample are provided in **Table 1**. Participants were, on average, age 62 y (median) at diagnosis. The median time interval between diagnosis and study recruitment was 3 y (IQR: 2–5 y). Diet was assessed at a median of 6 y after CRC diagnosis. Nearly all participants (99%) received surgery, and about half of them had no additional therapy. Twenty-two percent of all participants had chemotherapy, 3% had radiation therapy, and 21% underwent both chemotherapy and radiation therapy. Forty-seven percent of individuals had a tumor located in the colon and 42% in the rectum. A tumor in both locations, colon and rectum, was diagnosed in 5% of the patients. Seventeen percent of the participants reported a diagnosis of metastases and 21% the occurrence of other cancer. The median daily intakes of the individual dietary components on which the dietary pattern scores are based are shown separately for men and women (**Table 2**).

Association of dietary pattern scores with clinical and sociodemographic factors. Clinical and lifestyle characteristics according to quartiles of the MMDS and to quartiles of the HNFI are shown in **Tables** 1 and **3**, respectively. Participants with a higher adherence to the MMDS were more likely to be women, to be more physically active, and to have had a higher total energy intake (Table 1). Individuals with a higher HNFI had a slightly longer survival time from diagnosis until diet assessment and were more likely to report the occurrence of other cancer, to have never smoked, to be physically active, and to have had a higher total energy intake (Table 3).

TABLE 1 Characteristics of the overall sample of CRC survivors and across quartiles of the MMDS[1]

		Quartiles				
	Overall sample	1	2	3	4	P^2
Total individuals	1404 (100)	386 (27)	314 (22)	318 (23)	386 (27)	
Deaths	204 (100)	71 (35)	48 (24)	51 (25)	34 (17)	0.0014
Sex						0.0006
Men	788 (56)	251 (32)	169 (21)	169 (21)	199 (25)	
Women	616 (44)	135 (22)	145 (24)	149 (24)	187 (30)	
Age at diagnosis, y	62 (57–66)[3]	62 (58–67)	62 (56–66)	62 (57–67)	61 (56–65)	0.10
Age at diet assessment, y	69 (64–73)	70 (65–74)	69 (63–73)	69 (65–74)	68 (63–73)	0.09
Time between CRC diagnosis and diet assessment, y	6 (5–8)	6 (5–8)	6 (5–8)	6 (5–8)	7 (5–8)	0.83
BMI, kg/m^2	26.2 (23.9–29.3)	26.3 (24.2–29.0)	27.0 (24.0–29.4)	26.0 (23.9–29.4)	26.0 (23.4–28.7)	0.13
Tumor location						0.76
Colon	666 (47)	177 (46)	141 (45)	155 (49)	193 (50)	
Rectum	594 (42)	167 (43)	134 (43)	137 (43)	156 (40)	
Both	63 (5)	16 (4)	17 (5)	12 (4)	18 (5)	
Unknown	81 (6)	26 (7)	22 (7)	14 (4)	19 (5)	
Metastases						0.07
Yes	238 (17)	72 (19)	39 (12)	56 (18)	71 (18)	
No	928 (66)	253 (66)	206 (66)	210 (66)	259 (67)	
Unknown	238 (17)	61 (16)	69 (22)	52 (16)	56 (15)	
Other cancer						0.70
Yes	297 (21)	82 (21)	73 (23)	61 (19)	81 (21)	
No	1077 (77)	298 (77)	234 (75)	247 (78)	298 (77)	
Unknown	30 (2)	6 (2)	7 (2)	10 (3)	7 (2)	
Therapy						0.77
None	734 (52)	194 (50)	170 (54)	163 (51)	207 (54)	
Chemotherapy	313 (22)	84 (22)	67 (21)	71 (22)	91 (24)	
Radiation therapy	45 (3)	15 (4)	11 (4)	11 (3)	8 (2)	
Chemotherapy and radiation therapy	289 (21)	89 (23)	59 (19)	69 (22)	72 (19)	
Unknown	23 (2)	4 (1)	7 (2)	4 (1)	8 (2)	
Smoking status						0.98
Never	565 (40)	152 (39)	122 (39)	137 (43)	154 (40)	
Former	692 (49)	191 (49)	156 (50)	152 (48)	193 (50)	
Current	126 (9)	37 (10)	30 (10)	25 (8)	34 (9)	
Unknown	21 (2)	6 (2)	6 (2)	4 (1)	5 (1)	
Physical activity, METs/wk	95 (63–132)	84 (56–122)	86 (57–124)	100 (68–134)	108 (72–149)	<0.0001
Energy intake, kcal/d	2183 (1782–2605)	2090 (1705–2497)	2135 (1740–2584)	2194 (1778–2624)	2259 (1903–2722)	<0.0001

[1] Values are *n* (%) unless otherwise specified. CRC, colorectal cancer; MET, metabolic equivalent of task; MMDS, Modified Mediterranean Diet Score.
[2] Based on chi-square tests for categorical variables and Wilcoxon's rank-sum tests for continuous variables.
[3] Median; IQR in parentheses (all such values).

Association of dietary patterns with survival. During a median follow-up time of 7 y, 204 of the 1404 study participants died. In multivariable-adjusted proportional hazard regression analyses, the postdiagnostic MMDS showed a statistically significant association with better overall survival. The HR for all-cause mortality declined with each MMDS quartile. Individuals in the fourth MMDS quartile had an HR of 0.48 (95% CI: 0.32, 0.74) compared with individuals in the first quartile, after multivariable adjustment (**Table 4**). Per 1-point increment in MMDS, the hazard of mortality declined by 11% (HR: 0.89; 95% CI: 0.81, 0.96; $P = 0.004$) after adjusting for age and sex and by 12% (HR: 0.88; 95% CI: 0.81, 0.96; $P = 0.003$) after multivariable adjustment.

Likewise, greater adherence to the postdiagnostic HNFI was statistically significantly associated with an improved overall survival when the score was modeled as a continuous trait (HR: 0.89; 95% CI: 0.82, 0.98; $P = 0.01$ per 1-point increment in HNFI after age and sex adjustment and HR: 0.90; 95% CI: 0.82, 0.99; $P = 0.04$ after multivariable adjustment).

When quartiles of the HNFI were used, quartiles 2–4 showed a tendency toward lower hazards for mortality than quartile 1 in age- and sex-adjusted and multivariable-adjusted models (HR: 0.63; 95% CI: 0.39, 1.04 for the fourth compared with the first quartile after multivariable adjustment), although the multivariable-adjusted model did not reach statistical significance (P-trend = 0.06; Table 4).

A total of 35% of our participants were in identical quartiles for both dietary patterns (MMDS and HNFI). Comparing those individuals who were in the fourth quartile of both scores with all other individuals in our sample revealed an HR of 0.30 (95% CI: 0.15, 0.62) for all-cause mortality.

Assessment of interactions and sensitivity analyses. With respect to the association of the MMDS with all-cause mortality, we did not find any statistical interactions with sex, age at diet assessment, BMI, physical activity, tumor location, colon tumor side, and metastases. However, in a subgroup, despite a nonsignificant P value for interaction ($P = 0.94$), the results provided

TABLE 2 Daily intakes (g/d) of component food groups of the MMDS and the HNFI by sex in 1404 CRC survivors[1]

Dietary variable	Men	Women
MMDS		
Vegetables	182 (146–240)	185 (150–250)
Legumes	2 (2–7)	1 (1–1)
Fruits and nuts	192 (127–297)	245 (165–374)
Cereals	134 (111–164)	117 (96–146)
Fish	32 (20–57)	22 (12–35)
Dairy products	212 (131–341)	212 (137–308)
Meat	129 (88–180)	74 (47–104)
Unsaturated lipids	57 (47–68)	44 (37–54)
Saturated lipids	42 (35–52)	33 (27–40)
Unsaturated:saturated lipids (ratio)	1.34 (1.20–1.49)	1.34 (1.20–1.52)
Ethanol	11 (3–25)	4 (1–11)
HNFI		
Cabbage	26 (19–35)	21 (16–30)
Root vegetables	18 (13–28)	19 (14–30)
Whole-grain bread	25 (14–38)	28 (16–42)
Oatmeal	0 (0–2)	0 (0–6)
Apple and pears	118 (32–225)	118 (32–225)
Fish	32 (20–57)	22 (12–35)

[1] Values are medians (IQRs). Components of the food groups are as follows—vegetables: all vegetables, e.g., leafy vegetables, root vegetables, cabbage; legumes: all legumes; fruits and nuts: fruits, nuts, seeds, olives; cereals: e.g., flour, bread, rice, pasta; fish: fish and shellfish; dairy products: all dairy products, e.g., milk, cheese, yogurt, cream; meat: red meat, processed meat, and poultry; cabbage: all cabbages; root vegetables: all root vegetables; whole-grain bread: all whole-grain bread; oatmeal: all oatmeal; apples and pears: all apples and pears. CRC, colorectal cancer; HNFI, healthy Nordic Food Index; MMDS, Modified Mediterranean Diet Score.

some evidence for a stronger protective association of higher adherence to the MMDS on survival in patients with left-sided colon tumor than in those with right-sided tumor. In the analyses related to the HNFI, survivors whose tumor was located in the colon showed a slightly stronger association of adherence to the healthy Nordic diet with survival than individuals whose tumor was located in the rectum (*P*-interaction = 0.045). Interaction terms between the other tested covariates and the HNFI were not statistically significant regarding all-cause mortality (**Supplemental Table 1**).

In sensitivity analyses, excluding individuals who died within 12 mo of diet assessment (with 185 deaths remaining), results were largely unchanged (**Supplemental Table 2**). In analyses restricted to participants without known occurrence of metastases (with 149 deaths remaining), HRs were slightly but not substantially different. The direction of the association stayed the same, and the same associations as in the main model were statistically significant (**Supplemental Table 3**).

Discussion

Main findings. The key observations were as follows: First, greater adherence to a Mediterranean diet was associated with better survival, even after accounting for relevant potential clinical and sociodemographic confounders. Second, the healthy Nordic Food Index also provided evidence for an inverse association with mortality, although the *P* value for trend across quartiles just failed to reach statistical significance. When modeled as a continuous trait, a greater HNFI was significantly associated with improved survival in the multivariable-adjusted model.

To our knowledge, this is the first study that investigates the association of the HNFI and the MMDS with mortality in CRC survivors.

In the context of the published literature. Mounting evidence links the Mediterranean diet to improved health outcomes. A higher adherence to the Mediterranean diet has been shown to reduce the risk of new-onset cancer in initially healthy men and women (18, 31) and has been inversely related to mortality in different populations, including general population samples and elderly cohorts (16, 26, 27). Only one previous study used a design similar to our approach and investigated another version of the Mediterranean diet (adopted for the American population), obtained postdiagnostically, in relation to survival among 1201 women diagnosed with CRC (15). In that study, an inverse association with overall mortality (HR: 0.87; 95% CI: 0.63, 1.21) was also observed for the fifth quintile compared with the first quintile, although statistical significance was not reached. In the former study, diet assessment took place on average 21 mo (median) after diagnosis, whereas in our study, diet was assessed 6 y (median) after CRC diagnosis (15). It is conceivable that the effect of the Mediterranean diet on survival after CRC is slightly stronger in long-term survivors than in patients who had less follow-up time after completion of treatment. During and after treatment periods, disease consequences and treatment methods could influence appetite, digestion, and diet behavior (32, 33). Additionally, because the scoring of the Mediterranean diet score is based on cohort-specific medians for each component of the score, we do not know whether the absolute intake per food group is similar between studies, even if the adherence score is identical. In the Multiethnic Cohort Study of Diet and Cancer, a prediagnostically obtained alternate Mediterranean diet score was inversely related to CRC-specific and all-cause mortality in women but not in men. After stratification for ethnicity, the inverse relation was limited to African American women (34). We expand these analyses by showing that a higher adherence to the Mediterranean diet, obtained on average 6 y after CRC diagnosis, is related to an improved survival in long-term CRC survivors.

The HNFI was developed ~2 decades after the Mediterranean diet score and therefore has not been examined as comprehensively as the Mediterranean diet. However, some initial studies have reported associations between higher adherence to the healthy Nordic diet and lower all-cause and cause-specific mortality (19, 29), as well as lower risk of developing CRC (20) and type 2 diabetes (35) in the general population. With respect to CRC, one study reported a 35% (95% CI: 54, 6%) lower incidence of CRC in women with strong adherence to the HNFI than in women with low adherence, with similar tendencies observed in men (20). In a Swedish cohort, however, no significant association between HNFI adherence and CRC incidence was reported (36). To our knowledge, our study is the first to investigate the association between a healthy Nordic diet and all-cause mortality in CRC survivors.

Some previously published studies reported a better prognosis in CRC patients with left-sided colon cancer than in those with a right-sided tumor (37). In our subgroup analyses, we provide initial evidence that adherence to the Mediterranean diet might have a more consistent protective effect in patients with left-sided compared with right-sided colon cancer. We acknowledge, however, that this analysis was based on a small number of deaths and requires confirmation in independent samples. Although the comparison of CRC survivors with colon compared with rectum cancer suggested a stronger association between greater HNFI and better survival for CRC survivors with colon cancer (*P*-interaction = 0.045), the HRs between these groups differed only moderately.

TABLE 3 Characteristics of 1404 CRC survivors across quartiles of the HNFI[1]

	Quartiles				
	1	2	3	4	P^2
Total individuals	231 (16)	581 (41)	303 (22)	289 (21)	
Deaths	43 (21)	88 (43)	41 (20)	32 (16)	0.10
Sex					0.52
Men	139 (18)	327 (42)	165 (21)	157 (20)	
Women	92 (15)	254 (41)	138 (22)	132 (21)	
Age at diagnosis, y	62 (58–67)[3]	62 (57–66)	62 (57–65)	61 (56–66)	0.58
Age at diet assessment, y	69 (64–74)	69 (64–74)	69 (65–73)	69 (64–73)	0.80
Time between CRC diagnosis and diet assessment, y	6 (5–8)	6 (5–8)	6 (5–8)	7 (5–8)	0.05
BMI, kg/m^2	26.9 (24.1–29.1)	26.4 (24.2–29.3)	25.7 (23.4–29.4)	26.2 (23.7–28.7)	0.17
Tumor location					0.16
Colon	96 (42)	285 (49)	136 (45)	149 (52)	
Rectum	104 (45)	234 (40)	141 (47)	115 (40)	
Both	10 (4)	27 (5)	13 (4)	13 (5)	
Unknown	21 (9)	35 (6)	13 (4)	12 (4)	
Metastases					0.30
Yes	34 (15)	96 (17)	60 (20)	48 (17)	
No	151 (65)	378 (65)	203 (67)	196 (68)	
Unknown	46 (20)	107 (18)	40 (13)	45 (16)	
Other cancer					0.009
Yes	44 (19)	111 (19)	72 (24)	70 (24)	
No	177 (77)	463 (80)	228 (75)	209 (72)	
Unknown	10 (4)	7 (1)	3 (1)	10 (3)	
Therapy					0.47
None	126 (55)	313 (54)	141 (47)	154 (53)	
Chemotherapy	47 (20)	128 (22)	73 (24)	65 (22)	
Radiation therapy	5 (2)	19 (3)	10 (3)	11 (4)	
Chemotherapy and radiation therapy	50 (22)	115 (20)	73 (24)	51 (18)	
Unknown	3 (1)	6 (1)	6 (2)	8 (3)	
Smoking status					0.01
Never	75 (32)	222 (38)	136 (45)	132 (46)	
Former	117 (51)	301 (52)	142 (47)	132 (46)	
Current	34 (15)	50 (9)	21 (7)	21 (7)	
Unknown	5 (2)	8 (1)	4 (1)	4 (1)	
Physical activity, METs/wk	78 (48–113)	90 (60–128)	105 (73–141)	108 (72–141)	<0.0001
Energy intake, kcal/d	1891 (1567–2277)	2145 (1740–2541)	2217 (1838–2654)	2413 (2007–2988)	<0.0001

[1] Values are *n* (%) unless otherwise specified. CRC, colorectal cancer; HNFI, healthy Nordic Food Index; MET, metabolic equivalent of task.
[2] Based on chi-square tests for categorical variables and Wilcoxon's rank-sum tests for continuous variables.
[3] Median; IQR in parentheses (all such values).

Potential explanations for the observed association of MMDS and HNFI with mortality. The Mediterranean diet has been found to be associated with several clinical endpoints, some of them with relevant lethality, including coronary heart disease (17), stroke (38), type 2 diabetes mellitus (39), and cancer (18, 31). The main reasons for the health-promoting effects of the Mediterranean diet are assumed to be attributable to a combined consumption of virgin olive oil, nuts, fish, and plant foods (vegetables, legumes, and fruits) and a relatively low meat intake (40). The Mediterranean diet has been shown to be rich in antioxidants (vitamin C, carotenoids, phenols, and flavonoids), which may prevent cancer progression and recurrence and may be associated with lower plasma concentrations of inflammatory markers (11, 41). The healthy Nordic diet is also mainly characterized by plant foods with a range of beneficial health effects that are in part similar to those of the Mediterranean diet. Rye or whole-grain bread, fruits, legumes, and vegetables contain a lot of dietary fiber and micronutrients, which are beneficial for blood glucose concentrations, bowel function, and body weight (42–45). Especially for CRC, dietary fiber is suggested to have a protective effect for disease onset and may also be positive for CRC survivors by prohibiting recurrence (44, 45). The vegetables and fruits belonging to the healthy Nordic diet (cabbages, root vegetables, apples, and pears) are particularly rich in isothiocyanates, carotenoids, and a range of other phytochemicals (46). Olive oil, nuts, fish, and oatmeal deliver, among other things, essential fatty acids. Unsaturated lipids, especially ω-3 fatty acids, positively affect vascular function and play a positive role in prevention and treatment of cancer (47, 48).

We observed that 35% of the participants were in identical quartiles of both dietary pattern scores (MMDS and HNFI), indicating a moderate simultaneous adherence to both diets. As expected, individuals in the fourth quartile of both dietary patterns (indicating strong adherence to both diets) showed a better overall survival than the group of all other participants.

TABLE 4 Associations between quartiles of the MMDS and the HNFI and all-cause mortality in CRC survivors (n = 1404)[1]

	Quartiles				
	1	2	3	4	P-trend[2]
MMDS					
Individuals (deaths), n (%)	386 (71)	314 (48)	318 (51)	386 (34)	
Score[3]	3 (2–3)	4 (4–4)	5 (5–5)	6 (6–7)	
Age- and sex-adjusted model[4]	1 (Ref)	0.89 (0.61, 1.28)	0.90 (0.63, 1.29)	0.51 (0.34, 0.77)	0.003
Multivariable-adjusted model[4,5]	1 (Ref)	0.92 (0.64, 1.34)	0.85 (0.59, 1.23)	0.48 (0.32, 0.74)	0.001
HNFI					
Individuals (deaths), n (%)	231 (43)	581 (88)	303 (41)	289 (32)	
Score[3]	1 (0–1)	2 (2–3)	4 (4–4)	5 (5–6)	
Age- and sex-adjusted model[4]	1 (Ref)	0.82 (0.57, 1.19)	0.75 (0.49, 1.14)	0.58 (0.37, 0.92)	0.02
Multivariable-adjusted model[4,5]	1 (Ref)	0.87 (0.59, 1.27)	0.77 (0.49, 1.22)	0.63 (0.39, 1.04)	0.06

[1] Estimated with Cox proportional hazard models. CRC, colorectal cancer; HNFI, healthy Nordic Food Index; MMDS, Modified Mediterranean Diet Score; Ref, reference.
[2] Calculated by modeling the median value of dietary pattern score quartiles as a continuous variable.
[3] Values are medians (IQRs).
[4] Values are HRs (95% CIs).
[5] Adjusted for sex, age at diet assessment, BMI, physical activity, survival time from CRC diagnosis until diet assessment, tumor location, occurrence of metastases, occurrence of other cancer, chemotherapy, smoking status, total energy intake, time × age, time × BMI, and time × metastases.

With respect to the adherence of our sample to the 2 dietary patterns and the absolute (median daily) intake of the different dietary component food groups in our sample, a comparison with other, mainly general population cohorts led to the following results: the adherence of our cohort to the Mediterranean diet was in part lower than in cohorts of Mediterranean countries (27, 49) but similar to other non-Mediterranean or to mixed Mediterranean and non-Mediterranean cohorts (16, 50).

Furthermore, compared with other studies, the adherence to the healthy Nordic diet seemed to be relatively high in our cohort with a median daily intake that is in line with or even slightly above the median daily intake of other cohorts (19, 20, 29). In particular, the healthy Nordic diet might be an appropriate dietary pattern to analyze within our cohort because of the geographical proximity of our study area (Northern Germany) to the Scandinavian and Northern European countries where the HNFI was developed and primarily applied (29). It may be presumed that the Nordic diet is a common eating pattern in our study area, and it might be easier for a Northern German person to increase the intake of well-known foods, such as those belonging to the healthy Nordic diet, than to adapt a more unfamiliar dietary pattern such as the Mediterranean diet. Similar considerations might also apply to other Northern European or even Northern American populations, suggesting that the healthy Nordic diet could be a relevant health-promoting dietary pattern for certain populations (29).

Strengths and limitations. Our study has its strengths in a relatively large sample size, a standardized dietary assessment, a long duration of follow-up, and in a complete and validated vital status assessment. However, there are some limitations. We had information available only on all-cause mortality and not on disease-specific mortality. Thus, further studies on the association of dietary patterns with disease-specific mortality (e.g., cancer compared with noncancer causes of death) are warranted. The CRC diagnosis of our study participants occurred at a median of 6 y before diet assessment, which is why we characterize them as long-term cancer survivors. Therefore, the applicability of our results to all CRC patients is unknown. An indication for long-term survival is also the relatively small percentage of deaths in our cohort. Furthermore, information on tumor stage and comorbidities were unfortunately not available in our cohort. We had information only on metastases and other cancers. When we performed analyses stratified by occurrence of metastases, results were not substantially different. All our data were self-reported, which may have led to some information bias. However, we validated clinical data against medical records in a subset of 181 patients and obtained a concordance of ~87%.

In conclusion, our results suggest that long-term CRC survivors with a stronger adherence to the Mediterranean diet have a lower risk of all-cause mortality. The same tendency could be observed for adherence to the healthy Nordic diet. Our results, along with those of future studies, might help strengthen the evidence and develop dietary recommendations for cancer survivors.

Acknowledgments

IR, CS, UN, JH, and SS designed the research; IR, CS, MK, UN, JH, and SS conducted the research; IR, RdG, SW, SP-D, and SS analyzed the data or performed the statistical analysis; IR, SS, and WL wrote the manuscript; and IR and WL had primary responsibility for the final content. All authors read and approved the final manuscript.

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Supplemental Methods 1

Clinical and socio-demographic characteristics

Concerning self-reported clinical factors, information on tumor location, occurrence of metastases or other types of cancer (both reported at baseline and follow-up), as well as on neoadjuvant and adjuvant cancer therapies were obtained from each participant by questionnaires. In a subset of 181 patients, self-reported clinical data on tumor location, type of therapy, and metastases were validated against medical records with overall good agreement (87 % concordance). Likewise, information on socio-demographic factors were obtained from the participants using questionnaires. These questionnaires included information on sex, age at diagnosis, age at diet assessment (follow-up), smoking status at follow-up, and post-diagnostic body weight and height at baseline and follow-up. Body Mass Index (BMI; kg/m^2) was defined as weight divided by the square of height in meters. The FFQ [1] included additional validated questions concerning physical activity during the past 12 months [2]. Hours per week spent with different activities (walking, cycling, sports, gardening, housework, home repair, stair climbing) were derived from these questions. To obtain intensity levels, comparable among each other and to other studies, metabolic equivalent of task (MET) values, according to the 2000 Compendium of Physical Activity [3], were assigned to each corresponding activity [4].

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Supplemental Table 1: Multivariable-adjusted hazard ratios (HR)[1] and 95 % confidence intervals (95 % CI) of all-cause mortality in CRC survivors according to quartiles of MMDS and HNFI, stratified by potential effect modifiers (n=1404)

		Quartiles					
		Q1	Q2	Q3	Q4		
	Total no. of individuals (No. of deaths)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	p_{trend}[2]	$p_{interaction}$[3]
Modified Mediterranean Diet Score							
Sex							
Men	788 (147)	1 (Ref.)	0.86 (0.55-1.35)	0.75 (0.48-1.17)	0.57 (0.35-0.91)	0.02	
Women	616 (57)	1 (Ref.)	0.91 (0.45-1.85)	1.04 (0.52-2.10)	0.28 (0.11-0.70)	0.02	0.64
Age at diet assessment[4]							
< 69 years	662 (53)	1 (Ref.)	0.65 (0.29-1.49)	1.18 (0.57-2.45)	0.81 (0.37-1.76)	0.89	
≥ 69 years	742 (151)	1 (Ref.)	1.02 (0.67-1.55)	0.88 (0.58-1.36)	0.46 (0.27-0.76)	0.005	0.40
BMI							
< 25 kg/m²	536 (87)	1 (Ref.)	1.01 (0.57-1.78)	1.04 (0.59-1.86)	0.46 (0.23-0.90)	0.05	
≥ 25 kg/m²	868 (117)	1 (Ref.)	0.84 (0.50-1.39)	0.80 (0.49-1.31)	0.51 (0.30-0.88)	0.02	0.26
Physical Activity[4]							
< 95 METs/week	698 (127)	1 (Ref.)	0.89 (0.55-1.42)	0.93 (0.58-1.49)	0.53 (0.30-0.92)	0.05	
≥ 95 METs/week	706 (77)	1 (Ref.)	1.11 (0.59-2.08)	0.87 (0.47-1.61)	0.46 (0.24-0.90)	0.02	0.70

Supplemental Table 1 (continued)

		Quartiles					
		Q1	Q2	Q3	Q4		
	Total no. of individuals (No. of deaths)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	p_{trend}[2]	$p_{interaction}$[3]
Modified Mediterranean Diet Score							
Tumor location							
Colon	666 (87)	1 (Ref.)	1.19 (0.66-2.13)	1.15 (0.65-2.04)	0.44 (0.22-0.90)	0.05	
Rectum	594 (92)	1 (Ref.)	0.55 (0.31-0.99)	0.60 (0.35-1.05)	0.45 (0.25-0.82)	0.01	0.81
Colon tumor side[5]							
Right-sided	232 (22)	1 (Ref.)	3.32 (0.82-13.40)	1.77 (0.36-8.62)	1.07 (0.20-5.71)	0.74	
Left-sided	234 (31)	1 (Ref.)	0.48 (0.12-1.89)	0.78 (0.30-2.02)	0.27 (0.08-0.92)	0.06	0.94
Metastases							
Yes	238 (55)	1 (Ref.)	0.54 (0.22-1.31)	0.65 (0.32-1.34)	0.55 (0.26-1.18)	0.12	
No	928 (112)	1 (Ref.)	1.19 (0.73-1.92)	0.96 (0.58-1.60)	0.48 (0.26-0.89)	0.03	0.75
Healthy Nordic Food Index							
Sex							
Men	788 (147)	1 (Ref.)	0.82 (0.52-1.27)	0.75 (0.44-1.28)	0.50 (0.27-0.92)	0.04	
Women	616 (57)	1 (Ref.)	0.75 (0.36-1.58)	0.71 (0.29-1.69)	0.70 (0.29-1.71)	0.41	0.44

Supplemental Table 1 (continued)

		Quartiles					
		Q1	Q2	Q3	Q4		
	Total no. of individuals (No. of deaths)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	p_{trend}[2]	$p_{interaction}$[3]
Healthy Nordic Food Index							
Age at diet assessment[4]							
< 69 years	662 (53)	1 (Ref.)	0.90 (0.40-2.02)	0.90 (0.36-2.28)	1.07 (0.41-2.81)	0.93	
≥ 69 years	742 (151)	1 (Ref.)	0.90 (0.58-1.38)	0.79 (0.47-1.33)	0.55 (0.31-0.99)	0.05	0.53
Body Mass Index							
< 25 kg/m²	536 (87)	1 (Ref.)	0.86 (0.49-1.52)	0.64 (0.32-1.27)	0.50 (0.23-1.09)	0.05	
≥ 25 kg/m²	868 (117)	1 (Ref.)	0.85 (0.51-1.42)	0.84 (0.46-1.54)	0.68 (0.36-1.30)	0.02	0.07
Physical Activity[4]							
< 95 METs/week	698 (127)	1 (Ref.)	0.82 (0.53-1.28)	0.50 (0.27-0.94)	0.66 (0.36-1.21)	0.05	
≥ 95 METs/week	706 (77)	1 (Ref.)	0.93 (0.45-1.94)	1.28 (0.61-2.69)	0.60 (0.25-1.45)	0.51	0.06
Tumor location							
Colon	666 (87)	1 (Ref.)	0.75 (0.42-1.32)	0.62 (0.29-1.29)	0.41 (0.19-0.88)	0.02	
Rectum	594 (92)	1 (Ref.)	0.67 (0.38-1.17)	0.64 (0.34-1.20)	0.60 (0.29-1.25)	0.23	0.045
Colon tumor side[5]							
Right-sided	232 (22)	1 (Ref.)	0.91 (0.17-5.02)	1.61 (0.23-11.24)	0.81 (0.12-5.43)	0.94	
Left-sided	234 (31)	1 (Ref.)	0.94 (0.32-2.80)	0.33 (0.07-1.56)	1.24 (0.31-5.02)	0.77	0.60

Supplemental Table 1 (continued)

		Quartiles					
		Q1	Q2	Q3	Q4		
	Total no. of individuals (No. of deaths)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	p_{trend}[2]	$p_{interaction}$[3]
Healthy Nordic Food Index							
Metastases							
Yes	238 (55)	1 (Ref.)	0.45 (0.21-0.97)	0.37 (0.15-0.90)	0.51 (0.19-1.36)	0.08	
No	928 (112)	1 (Ref.)	0.98 (0.59-1.63)	0.95 (0.53-1.70)	0.55 (0.28-1.11)	0.13	0.69

[1] Estimated with Cox proportional hazard models; adjusted for sex, age at diet assessment, BMI, physical activity, survival time from CRC diagnosis until diet assessment, tumor location, occurrence of metastases, occurrence of other cancer, chemotherapy, smoking status, total energy intake, (time x age), (time x BMI), and (time x metastases); except the stratifying variable

[2] Calculated by modeling the median value of dietary pattern score quartiles as a continuous variable

[3] Calculated by entering into the model an interaction term of MMDS or HNFI as a continuous variable and the stratifying covariate

[4] Cutpoints chosen based on median values

[5] Derived from a subgroup of n = 466

CRC, colorectal cancer; HNFI, healthy Nordic Food Index; MET, metabolic equivalent of task; MMDS, Modified Mediterranean Diet Score

Supplemental Table 2: Sensitivity Analysis (n=1385): Hazard ratios (HR)[1] and 95% confidence intervals (95% CI) of all-cause mortality according to quartiles of dietary pattern scores after excluding individuals who died within 12 months after diet assessment

	Quartiles				
	Q1	**Q2**	**Q3**	**Q4**	**p_{trend}[2]**
Modified Mediterranean Diet Score					
Total no. of individuals (deaths), n	378 (27)	311 (22)	313 (23)	383 (28)	
Score, Median (IQR)	3 (2-3)	4 (4-4)	5 (5-5)	6 (6-7)	
Age- & sex-adjusted, HR (95% CI)	1 (Ref.)	0.96 (0.66-1.41)	0.90 (0.61-1.32)	0.52 (0.34-0.80)	0.005
Multivariable-adjusted[3], HR (95% CI)	1 (Ref.)	0.98 (0.67-1.45)	0.84 (0.57-1.24)	0.49 (0.31-0.76)	0.002
Healthy Nordic Food Index					
Total no. of individuals (deaths), n	233 (17)	577 (42)	291 (21)	284 (21)	
Score, Median (IQR)	1 (1-1)	2 (2-3)	4 (4-4)	5 (5-6)	
Age- & sex-adjusted, HR (95% CI)	1 (Ref.)	0.83 (0.57-1.21)	0.76 (0.48-1.19)	0.59 (0.37-0.96)	0.04
Multivariable-adjusted[3], HR (95% CI)	1 (Ref.)	0.87 (0.59-1.28)	0.79 (0.49-1.26)	0.63 (0.38-1.05)	0.09

[1] Estimated with Cox proportional hazard models

[2] Calculated by modeling the median value of dietary pattern score quartiles as a continuous variable

[3] Adjusted for sex, age at diet assessment, BMI, physical activity, survival time from CRC diagnosis until diet assessment, tumor location, occurrence of metastases, occurrence of other cancer, chemotherapy, smoking status, total energy intake, (time x age), (time x BMI), and (time x metastases)

Supplemental Table 3: Sensitivity Analysis (n=1166): Hazard ratios (HR)[1] and 95% confidence intervals (95% CI) of all-cause mortality according to quartiles of dietary pattern scores after excluding individuals with known occurrence of metastases

	Quartiles				
	Q1	**Q2**	**Q3**	**Q4**	**p_{trend}[2]**
Modified Mediterranean Diet Score					
Total no. of individuals (deaths), n	374 (32)	282 (24)	245 (21)	265 (23)	
Score, Median (IQR)	3 (2-3)	4 (4-4)	5 (5-5)	6 (6-7)	
Age- & sex-adjusted, HR (95% CI)	1 (Ref.)	1.04 (0.70-1.56)	0.88 (0.57-1.36)	0.60 (0.36-0.98)	0.04
Multivariable-adjusted[3], HR (95% CI)	1 (Ref.)	1.10 (0.73-1.66)	0.88 (0.56-1.39)	0.60 (0.36-0.99)	0.048
Healthy Nordic Food Index					
Total no. of individuals (deaths), n	190 (16)	486 (42)	237 (20)	253 (22)	
Score, Median (IQR)	1 (0-1)	2 (2-3)	4 (4-4)	5 (5-6)	
Age- & sex-adjusted, HR (95% CI)	1 (Ref.)	0.94 (0.61-1.45)	0.89 (0.53-1.48)	0.53 (0.30-0.94)	0.03
Multivariable-adjusted[3], HR (95% CI)	1 (Ref.)	1.07 (0.68-1.68)	1.06 (0.62-1.82)	0.65 (0.36-1.19)	0.18

[1] Estimated with Cox proportional hazard models
[2] Calculated by modeling the median value of dietary pattern score quartiles as a continuous variable
[3] Adjusted for sex, age at diet assessment, BMI, physical activity, survival time from CRC diagnosis until diet assessment, tumor location, occurrence of other cancer, chemotherapy, smoking status, total energy intake, (time x age), and (time x BMI)

3 Postdiagnostic physical activity, sleep duration, and TV watching and all-cause mortality among long-term colorectal cancer survivors: a prospective cohort study

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BMC Cancer 2017; 17(1): 701

Ratjen *et al. BMC Cancer* (2017) 17:701
DOI 10.1186/s12885-017-3697-3

BMC Cancer

RESEARCH ARTICLE Open Access

Postdiagnostic physical activity, sleep duration, and TV watching and all-cause mortality among long-term colorectal cancer survivors: a prospective cohort study

Ilka Ratjen[1*], Clemens Schafmayer[2], Romina di Giuseppe[1], Sabina Waniek[1], Sandra Plachta-Danielzik[1], Manja Koch[1,3], Greta Burmeister[2], Ute Nöthlings[4], Jochen Hampe[5], Sabrina Schlesinger[6†] and Wolfgang Lieb[1†]

Abstract

Background: Lifestyle recommendations for cancer survivors are warranted to improve survival. In this study, we aimed to examine the association of total physical activity, different types of physical activity, hours of sleeping at day and night, and hours spent watching television (TV) with all-cause mortality in long-term colorectal cancer (CRC) survivors.

Methods: We assessed physical activity in 1376 CRC survivors (44% women; median age, 69 years) at median 6 years after CRC diagnosis using a validated questionnaire. Multivariable-adjusted Cox regression models were used to estimate hazard ratios (HRs) for all-cause mortality according to categories of physical activities, sleep duration, and TV watching.

Results: During a median follow-up time of 7 years, 200 participants had died. Higher total physical activity was significantly associated with lower all-cause mortality (HR: 0.53; 95% CI: 0.36–0.80, 4th vs. 1st quartile). Specifically, sports, walking, and gardening showed a significant inverse association with all-cause mortality (HR: 0.34; 95% CI: 0. 20–0.59, HR: 0.65; 95% CI: 0.43–1.00, and HR: 0.62; 95% CI: 0.42–0.91, respectively for highest versus lowest category). Individuals with ≥2 h of sleep during the day had a significantly increased risk of all-cause mortality compared to individuals with no sleep at day (HR: 2.22; 95% CI: 1.43–3.44). TV viewing of ≥4 h per day displayed a significant 45% (95% CI: 1.02–2.06) higher risk of dying compared to ≤2 h per day of watching TV.

Conclusions: Physical activity was inversely related to all-cause mortality; specific activity types might be primarily responsible for this association. More hours of sleep during the day and a higher amount of TV viewing were each associated with higher all-cause mortality. Based on available evidence, it is reasonable to recommend CRC survivors to engage in regular physical activity.

Keywords: Postdiagnostic, Physical activity, Sleep duration, TV watching, Colorectal cancer, Survivors, Mortality

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Background

In 2012, there were nearly 1.4 million people diagnosed with colorectal cancer (CRC) and it is predicted that by 2035 the number of cases will increase to 1.36 million for men and 1.08 million for women worldwide [1]. On a parallel note, death rates of CRC have fallen by on average 2.5% each year from 2005 to 2014 in the US and the 5-year relative survival is about 64.9% in the US and about 63% in Germany [2, 3]. Rising survival rates and increasing numbers of newly diagnosed cases lead to a growing group of CRC survivors [4]. Therefore, as outlined by the World Cancer Research Fund [5], there is rising interest in to what extent behavioral factors affect the course of the disease and survival of patients with CRC [6].

Regular physical activity has a broad range of beneficial health effects, e.g., on obesity and other cardiovascular risk factors [7] and is associated with better overall survival in the general population and in many patient groups [8, 9]. Additionally, physically active people have a lower risk of developing different forms of cancer [10], including colon cancer [11]. A meta-analysis of 52 studies reported a risk reduction of colon cancer incidence of about 24% in physically active men and of about 21% in active women compared to inactive people [11]. Besides, evidence is growing that physical activity is also safe and well-tolerated by cancer patients during and after treatment [12, 13]. Furthermore, exercise has been shown to increase quality of life and to improve physical functioning among cancer survivors [14, 15].

Prior studies have investigated the association between physical activity and mortality in CRC patients and reported 25–63% lower disease-specific and all-cause mortality for more active as compared to less active patients after CRC diagnosis [16–23]. However, previous studies focused on physical activity that was assessed relatively shortly after diagnosis (range: 5 months to 4.2 years median) [16–23] and less is known about the impact of different types of physical activity on mortality of CRC survivors. Two studies examined the relation of postdiagnostic television (TV) viewing with all-cause mortality in CRC survivors and found a 25–45% increase in mortality for the highest category of TV watching, but statistical significance was not reached [16, 24].

Cancer survivors, especially CRC survivors, are mostly elderly. Colon and rectum cancer are most frequently diagnosed among persons aged 65–74 years [3]. In this predominant age group, physical activity can imply a lot of advantages in health, quality of life, and social life but might also represent a practical challenge for some people due to age-related comorbidities [25]. Therefore, resulting health benefits of physical activity should be investigated thoroughly.

In this study, we assessed the association of postdiagnostic total physical activity, different types of physical activity ('sports', 'cycling', 'walking', 'gardening', 'housework, home repair, and stair climbing'), hours of sleeping at night and day, and time spent watching TV with all-cause mortality among CRC long-term survivors.

Methods

Study sample

Between 2004 and 2007, a total of 2733 patients with histologically confirmed CRC (diagnosed between 1993 and 2005) were recruited by the biobank PopGen after identification through medical records from surgical departments in 23 hospitals in Northern Germany and through the regional cancer registry. Detailed information on this sample has been reported previously [14, 26, 27]. Patients filled in a questionnaire about clinical characteristics and socio-demographic and selected lifestyle factors. The study protocol was approved by the institutional ethics committee of the Medical Faculty of Kiel University and written informed consent was obtained from all study participants.

Between 2009 and 2011, 2263 patients who initially agreed to be re-contacted were asked to complete another questionnaire about clinical and socio-demographic factors, a food frequency questionnaire (FFQ) [28] with additional questions about physical activity [29], and a questionnaire on health-related quality of life (HrQol) [30]. Of the 2263 participants contacted, 1452 (64%) responded to the FFQ and to the questions on physical activity. Compared to non-responders (n = 694, 25.4%) and deceased (n = 354, 13.0%) individuals of the initial study sample of 2733 individuals, the participants who completed the physical activity questionnaire were younger at baseline and at CRC diagnosis, reported more often a family history of CRC, and had less often metastases or other types of cancer [14]. We excluded individuals with missing information on year of diagnosis (n = 21) and vital status (n = 21), those with implausible length of follow-up (n = 3), and participants with a diagnosis of small intestine cancer instead of CRC (n = 3). Finally, to eliminate outliers (extreme values) of physical activity, we excluded individuals above the 98th percentile of total physical activity (n = 28), leaving an analytical sample of 1376 participants (61% of the initial study sample contacted for follow-up).

Physical activity assessment

A validated questionnaire was applied to assess physical activity during the past 12 months [29]. From these questions, average hours per week spent with different activities, including walking, cycling, sports (physical exercise except for cycling), and gardening, each separately for summer and winter, as well as housework (e.g. cooking,

washing, cleaning), and home repair (do-it-yourself) were enquired. Additionally, stair climbing defined as floors per day, hours of sleeping at night and day, respectively and hours per day spent watching TV were quantified. Metabolic equivalent of task (MET) values, according to the 2000 Compendium of Physical Activity [31], were assigned to each corresponding activity [32]. One MET is defined as the energy expenditure for sitting quietly and MET-values are the ratio of the metabolic rate for a specific activity divided by the resting metabolic rate [31]. Thus, the number of hours per week spent with each activity (where applicable, the mean number of hours was calculated from summer and winter activities) were multiplied by the respective MET-values (walking: 3.0, cycling: 6.0, sports: 6.0, gardening: 4.0, housework: 3.0, home repair: 4.5, stair climbing: 8.0) [31, 32]. To derive MET-hours per week of total physical activity, the MET-hours of walking, cycling, sports, gardening, housework, home repair, and stair climbing were summed up.

Clinical and socio-demographic characteristics

The self-administered questionnaires about clinical characteristics included questions related to tumor location (colon, rectum, both lesions), occurrence of metastases or other types of cancer (both reported at baseline and physical activity assessment), and neoadjuvant and adjuvant cancer therapies. We validated these self-reported clinical data (tumor location, type of therapy, metastases) against medical records in a subset of 181 participants and observed overall good agreement (87% concordance). Among socio-demographic factors, sex, age at diagnosis, age at physical activity assessment, smoking status (never, former, current) at physical activity assessment, and postdiagnostic body weight and height at baseline and physical activity assessment were self-reported. Body Mass Index (BMI; kg/m^2) was defined as weight divided by the square of height in meters. Total energy intake has been calculated from FFQ data [28] and global health-related quality of life (gHrQol; score ranging from 0 to 100) was assessed by the EORTC-QLQ C30 (version 3.0) [30].

Vital status ascertainment

Vital status ascertainment has been described in detail elsewhere [27]. In 2016, vital status of all participants was updated via population registries and date of death was recorded if participants were deceased (date of death could be verified for all cases). The date of physical activity assessment was used as starting point for follow-up of this study and follow-up ended with date of death or last vital status assessment whichever came first.

Statistical analyses

Participant characteristics were compared across quartiles of total physical activity. Differences in categorical variables were tested using a chi-squared test and differences in distributions of continuous variables were tested with the Wilcoxon ranksum test.

The Kaplan-Meier curves and log-rank test were used to investigate (unadjusted) differences in the survival time distribution of CRC survivors according to quartiles of total physical activity.

HRs and 95% CIs for the association of total physical activity, different types of physical activity, hours of sleeping at night or day, and hours per day of watching TV with all-cause mortality were estimated using Cox proportional hazards regression models with age as the underlying time variable. Total physical activity was modeled in quartiles and individual activities, sleep duration, and TV watching were modeled in appropriate categories of MET-hours/week or hours/day. For sports, cycling, and gardening, categories of 0, >0–10, >10–20, and >20 MET-hours/week were chosen similar to a recent analysis in a German study that used the same physical activity questionnaire [33]. For walking and activities from housework, home repair, and stair climbing, categories of 0–10, >10–20, >20–30, and >30 MET-hours/week were used because these activities were reported with an overall higher amount of MET-hours/week and a low prevalence of 0 MET-hours/week. The categories for hours of sleeping at night (≤6, 7–8, and ≥9 h/day) were chosen based on sleep time duration recommendations of the National Sleep Foundation [34]. Categories for hours of sleeping at day (0, >0- < 1, 1- < 2, and ≥2 h/day) and hours of watching TV (≤2, >2- < 4, and ≥4 h/day) were chosen based on the distribution of reported values. HRs were calculated for each quartile/category using the first quartile/lowest category as the referent, except for sleeping at night where the recommended optimal level of 7–8 h/day was used as the referent. To control for confounding, all models were adjusted for sex and age at physical activity assessment. A second model was additionally adjusted for BMI at physical activity assessment (continuous in kg/m^2), survival time from CRC diagnosis until physical activity assessment (continuous in years), smoking status (never, former, current, unknown), alcohol intake (continuous in g/day), tumor location (colon, rectum, both, unknown), occurrence of metastases (yes, no, unknown), occurrence of other cancers (yes, no, unknown), and chemotherapy (yes, no, unknown). We also considered the presence of a stoma and family history of CRC as potential confounders but decided not to include those in the final model because the results did not change substantially (<10%). In addition, the individual activities 'cycling,' 'sports,' 'walking,' 'gardening,' and 'housework, home repair, and stair climbing' were mutually adjusted for. Furthermore, hours of sleeping at

night and hours of sleeping at day were mutually adjusted for. Time spent watching TV was additionally adjusted for total physical activity. We tested the proportional hazards assumption by the Schoenfeld residuals method and by including time-dependent variables in the models. Because age, BMI, and metastases did not meet the proportional hazards assumption, respective time-dependent multiplicative interaction terms (time x age, time x BMI, time x metastases) were included in the models. Tests for linear trend across quartiles or categories were performed by modeling the median value for each quartile/category as a continuous variable and by including this variable in the respective Cox regression model.

The degree of nonlinearity in the association of total physical activity with all-cause mortality was evaluated with restricted cubic spline regression, fitted with four knots (5th, 35th, 65th, and 95th percentile [35]) and a reference point located at the median (44 MET-hours/week) of the reference group (Quartile 1) of the main analysis. This model was adjusted for the same covariates as the main model (described above).

In subgroup analyses, HRs and 95% CIs of all-cause mortality for the fourth versus the first quartile of total physical activity were calculated stratified by sex (men vs. women), median age at physical activity assessment (<69 vs. ≥69 years), BMI (<25 vs. 25 - <30 vs. ≥30 kg/m^2), tumor location (colon vs. rectum), occurrence of metastases (yes vs. no), and smoking status (never vs. ever). We additionally stratified by the median of gHrQol (<75 vs. ≥75) to assess potential differences in the association of physical activity with all-cause mortality between individuals with a higher and a lower gHrQol. Respective multiplicative interaction terms were tested in the multivariable-adjusted models by including the cross product of total physical activity and the potential effect modifier.

To investigate the robustness of our findings, sensitivity analyses were performed. To account for reverse causality, we examined the association of postdiagnostic total physical activity with all-cause mortality after excluding CRC survivors who died within 12 months after physical activity assessment. In a second sensitivity analysis, we excluded participants who reported a diagnosis of metastases either at baseline or first follow-up because the occurrence of metastases could influence the ability of being physically active and the survival rate. In another sensitivity analysis we additionally added gHrQol (modeled on a continuous scale) to the multivariable-adjusted model in order to assess the effect of quality of life on the association between physical activity and survival and to further account for potential reverse causality. In addition, it might be possible that complete inactivity could be an indicator for disease status, reflecting individuals with very poor health status. Thus, in a sensitivity analysis, individuals with 0 MET-hours of total physical activity were excluded. In a fifth sensitivity analysis, we additionally adjusted the association of TV watching with all-cause mortality for total energy intake to assess the potential role of high intake of energy-dense foods associated with sedentary time for survival [36].

All statistical analyses were conducted using SAS version 9.4 software (SAS Institute, Inc., NC, USA). Two-sided p values of <0.05 were considered statistically significant.

Results

Participant characteristics

Characteristics of the overall study population and stratified by quartiles of postdiagnostic total physical activity are provided in Table 1. Of the 1376 individuals, 44% were women, the median age at diagnosis was 62 years, and the median time between CRC diagnosis and physical activity assessment was 6 years. Nearly half of the participants had a tumor located in the colon (48%), 42% had a rectum carcinoma, 17% of the participants reported a diagnosis of metastases, and 21% a diagnosis of other cancers either at baseline or first follow-up. More than half of the study population had only surgery and no other CRC therapy was carried out (Table 1). The study participants reported a median of 100 MET-hours/week (interquartile range: 65–145) of total physical activity. Compared with participants in the first quartile of postdiagnostic total physical activity, participants with a higher amount of total physical activity were more likely to be women, were younger at the time of diagnosis and at physical activity assessment, and had a higher consumption of alcohol (Table 1).

Postdiagnostic physical activity, sleep duration, and TV watching and all-cause mortality

After the assessment of physical activity, individuals were followed for a median time period of 7 years. During this period, 200 (14.5%) of the 1376 study participants had died.

Figure 1 displays significant differences in the survival time between quartiles of total physical activity (log-rank p value <0.0001), in the sense that higher quartiles of activity showed better survival as compared to lower quartiles. However, the difference in survival time between quartiles decreased with increasing quartile displaying less distinct differences between quartiles 3 and 4 with respect to cumulative survival. In a multivariable-adjusted Cox regression model, individuals in quartiles 2 to 4 of total physical activity all displayed statistically significantly longer survival as compared to individuals in the first quartile, with a 47% reduction of all-cause mortality in the fourth quartile (HR: 0.53; 95% CI: 0.36–0.80; p_{trend} = 0.0006; Table 2). Using cubic spline regression, we observed evidence for a statistically

Table 1 Characteristics of the overall sample of CRC survivors (n = 1376) and according to quartiles of total physical activity (in MET-hours/week)

		Quartiles of total physical activity				
Participant characteristics	Overall sample	Q1 (0–64.5)	Q2 (>64.5–99.7)	Q3 (>99.7–144.9)	Q4 (>144.9)	p^a
Total no. of individuals, n	1376	344	344	344	344	
No. of deaths, n (%)	200 (15)	85 (25)	47 (14)	33 (10)	35 (10)	<0.0001
Sex, n (%)						
Men	770 (56)	224 (65)	200 (58)	176 (51)	170 (49)	
Women	606 (44)	120 (35)	144 (42)	168 (49)	174 (51)	<0.0001
Age at diagnosis, y	62 (57–66)	63 (57–70)	62 (56–66)	62 (57–66)	61 (56–65)	0.0002
Age at physical activity assessment, y	69 (64–73)	70 (65–77)	69 (64–74)	69 (65–73)	68 (63–72)	0.0006
Time between CRC diagnosis and physical activity assessment, y	6 (5–8)	6 (5–8)	7 (5–8)	7 (5–8)	6 (5–8)	0.37
BMI, kg/m^2	26.2 (23.8–29.3)	26.6 (24.0–29.4)	26.0 (23.7–29.3)	26.1 (23.8–29.1)	26.0 (23.7–29.2)	0.63
Smoking status, n (%)						
Never	556 (40)	123 (36)	140 (41)	143 (42)	150 (44)	
Former	678 (49)	177 (51)	171 (50)	170 (49)	160 (47)	
Current	121 (9)	37 (11)	30 (9)	26 (8)	28 (8)	
Unknown	21 (2)	7 (2)	3 (1)	5 (1)	6 (2)	0.57
Alcohol intake, g/day	7 (2–20)	5 (1–20)	8 (2–23)	7 (3–18)	7 (2–18)	0.01
Tumor location, n (%)						
Colon	657 (48)	166 (48)	168 (49)	170 (49)	148 (43)	
Rectum	576 (42)	147 (43)	144 (42)	137 (40)	153 (44)	
Both	62 (5)	13 (4)	13 (4)	21 (6)	15 (4)	
Unknown	81 (6)	18 (5)	19 (5)	16 (5)	28 (8)	0.48
Metastases, n (%)						
Yes	234 (17)	70 (20)	48 (14)	54 (16)	56 (16)	
No	908 (66)	207 (60)	248 (72)	227 (66)	226 (66)	
Unknown	234 (17)	67 (19)	48 (14)	63 (18)	62 (18)	0.06
Other Cancer, n (%)						
Yes	292 (21)	73 (21)	79 (23)	68 (20)	72 (21)	
No	1054 (77)	261 (76)	260 (76)	268 (78)	265 (77)	
Unknown	30 (2)	10 (3)	5 (1)	8 (2)	7 (2)	0.84
Therapy, n (%)						
None	721 (52)	182 (53)	191 (56)	168 (49)	180 (52)	
Chemotherapy	305 (22)	85 (25)	68 (20)	80 (23)	72 (21)	
Radiation	45 (3)	6 (2)	18 (5)	11 (3)	10 (3)	
Chemotherapy and radiation	282 (20)	65 (19)	59 (17)	80 (23)	78 (23)	
Unknown	23 (2)	6 (2)	8 (2)	5 (1)	4 (1)	0.18

Values are n (%) or median (interquartile range)
Abbreviations: *BMI* body mass index, *CRC* colorectal cancer, *MET* metabolic equivalent of task
[a]Based on chi-squared test for categorical variables and Wilcoxon's rank-sum test for continuous variables

significant nonlinear association between total physical activity and all-cause mortality ($p_{nonlinear}$ = 0.01, Wald chi-square test). With increasing physical activity the survival benefit is growing until a plateau is reached around the third quartile (about 130 MET-hours/week; Fig. 2).

Considering individual types of physical activity, sports showed the strongest inverse association with all-cause mortality (HR: 0.34; 95% CI: 0.20–0.59, comparing >20 with 0 MET-hours/week, p_{trend} < 0.0001), independent of other types of physical activity. Similarly, also MET-hours of walking (HR: 0.65; 95% CI: 0.43–1.00 for >30 vs. 0–10 MET-hours/week, p_{trend} = 0.03) and of gardening activities (HR: 0.62; 95% CI: 0.42–0.91 for >20 vs. 0 MET-hours/week, p_{trend} = 0.01) were associated with survival in

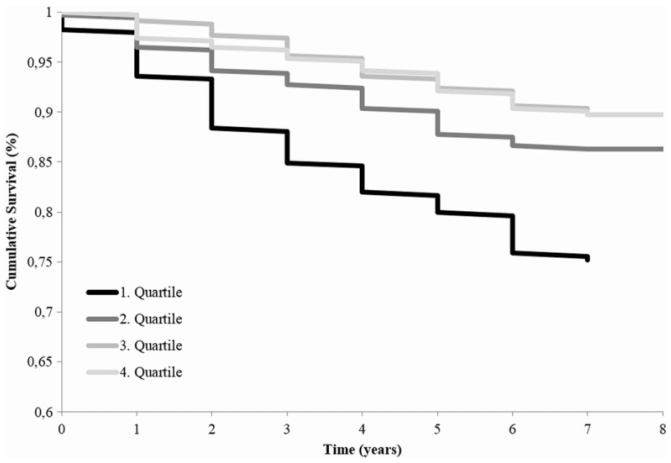

Fig. 1 Kaplan-Meier-Curves of overall survival of 1376 CRC survivors according to quartiles of total physical activity. The log-rank *p* value is <0.0001. Abbreviations: CRC, colorectal cancer

multivariable-adjusted models (Table 2). No statistically significant association with all-cause mortality after multivariable adjustment could be observed for cycling ($p_{trend} = 0.52$) and for the combination of activities from housework, home repair, and stair climbing ($p_{trend} = 0.99$; Table 2).

Notable differences with respect to their association with all-cause mortality were observed between hours of sleeping at night and hours of sleeping at day (Table 2). Whereas the sleep duration at night displayed no statistically significant association with survival time, individuals who slept ≥2 h during the day had more than twice the risk of dying (HR: 2.22; 95% CI: 1.43–3.44, $p_{trend} = 0.0004$) compared to individuals who did not sleep at day. Furthermore, ≥4 h/day spent watching TV displayed a significant 45% higher all-cause mortality compared with ≤2 h/day of TV viewing (HR: 1.45; 95% CI: 1.02–2.06, $p_{trend} = 0.04$; Table 2).

Stratified analyses by potential effect modifiers

The stratification by potential effect modifiers revealed significant quantitative interactions by sex, BMI, and tumor location (Fig. 3). The inverse association between total physical activity and all-cause mortality was stronger in women than in men ($p_{interaction} = 0.003$), stronger in individuals with a lower BMI (e.g. <25 kg/m^2 or 25 - < 30 kg/m^2) than in individuals with a higher BMI (e.g. ≥30 kg/m^2) ($p_{interaction} = 0.02$), and stronger in individuals with a colon carcinoma than in individuals with a rectum carcinoma ($p_{interaction} = 0.002$). There was no evidence for a statistically significant interaction by age, occurrence of metastases, smoking status, and gHrQol, although the association was slightly stronger in older than in younger individuals and in individuals with metastases than in those without metastases (Fig. 3).

Sensitivity analyses

After excluding participants who died within 12 months of physical activity assessment ($n = 19$), the results remained essentially unchanged (Additional file 1: Table S1). After exclusion of individuals who reported a diagnosis of metastases ($n = 234$), the association of physical activity with survival was a little weaker and slightly failed to reach statistical significance (probably because of the smaller sample size), but the inverse pattern of association was comparable to the overall sample (Additional file 1: Table S2). In another sensitivity analysis, we additionally adjusted the multivariable-adjusted Cox regression models and the restricted cubic spline regression for gHrQol. However, results did not change substantially. We observed that all associations were slightly attenuated and that the relation of walking with survival was rendered statistically nonsignificant (HR: 0.73; 95% CI: 0.47–1.14), upon adjustment for gHrQol. The restricted cubic spline regression still revealed a nonlinear trend ($p_{nonlinear} = 0.05$) (data not shown). Excluding participants who reported 0 MET-hours/week of total physical activity ($n = 8$) did not change the results appreciably (data not shown). Additionally adjusting the association of TV viewing with all-cause mortality for total energy intake did not cause any change in the results (data not shown).

Discussion

Principal observations

In this cohort of 1376 long-term CRC survivors, higher postdiagnostic total physical activity was associated with

Table 2 HRs[a] and 95% CIs of all-cause mortality according to quartiles of total physical activity and according to categories of individual activities, sleep duration, and TV watching in CRC survivors (n = 1376)

	Total no. of individuals	No. of deaths	Age- & sex-adjusted HR (95% CI)	Multivariable-adjusted[b] HR (95% CI)
MET-hours/week of total physical activity				
Quartile 1 (0–64.5)	344	85	1.00 (Ref.)	1.00 (Ref.)
Quartile 2 (>64.5–99.7)	344	47	0.61 (0.42–0.87)	0.65 (0.45–0.94)
Quartile 3 (>99.7–144.9)	344	33	0.45 (0.30–0.68)	0.52 (0.34–0.79)
Quartile 4 (>144.9)	344	35	0.51 (0.34–0.77)	0.53 (0.36–0.80)
p^{c}_{trend}			0.0004	0.0006
MET-hours/week of sports activities[d]				
0	708	150	1.00 (Ref.)	1.00 (Ref.)
> 0–10	146	10	0.42 (0.22–0.81)	0.41 (0.22–0.80)
> 10–20	261	25	0.56 (0.37–0.86)	0.58 (0.37–0.89)
> 20	261	15	0.33 (0.19–0.56)	0.34 (0.20–0.59)
p^{c}_{trend}			<0.0001	<0.0001
MET-hours/week of cycling activities[d]				
0	503	102	1.00 (Ref.)	1.00 (Ref.)
> 0–10	236	31	0.75 (0.50–1.14)	0.80 (0.52–1.22)
> 10–20	241	27	0.71 (0.45–1.10)	0.90 (0.57–1.41)
> 20	396	40	0.61 (0.42–0.90)	0.85 (0.57–1.27)
p^{c}_{trend}			0.02	0.52
MET-hours/week of walking activities[d]				
0–10	409	75	1.00 (Ref.)	1.00 (Ref.)
> 10–20	386	56	0.82 (0.58–1.16)	0.83 (0.58–1.19)
> 20–30	297	37	0.65 (0.44–0.96)	0.67 (0.45–1.00)
> 30	284	32	0.62 (0.41–0.94)	0.65 (0.43–1.00)
p^{c}_{trend}			0.01	0.03
MET-hours/week of gardening activities[d]				
0	297	69	1.00 (Ref.)	1.00 (Ref.)
> 0–10	358	48	0.72 (0.49–1.06)	0.81 (0.55–1.20)
> 10–20	264	23	0.38 (0.23–0.61)	0.41 (0.25–0.68)
> 20	457	60	0.55 (0.38–0.79)	0.62 (0.42–0.91)
p^{c}_{trend}			0.003	0.01
MET-hours/week of housework, home repair, and stair climbing activities[d]				
0–10	177	45	1.00 (Ref.)	1.00 (Ref.)
> 10–20	221	29	0.60 (0.37–0.95)	0.65 (0.40–1.05)
> 20–30	194	29	0.69 (0.43–1.10)	0.72 (0.45–1.17)
> 30	784	97	0.70 (0.48–1.01)	0.83 (0.55–1.23)
p^{c}_{trend}			0.35	0.99
Hours of sleeping at night[e]				
≤ 6	294	42	1.03 (0.72–1.45)	0.97 (0.68–1.38)
7–8	933	132	1.00 (Ref.)	1.00 (Ref.)
≥ 9	149	26	1.08 (0.71–1.65)	0.99 (0.65–1.53)
p^{c}_{trend}			0.95	0.87
Hours of sleeping at day[e]				
0	607	57	1.00 (Ref.)	1.00 (Ref.)

Table 2 HRs[a] and 95% CIs of all-cause mortality according to quartiles of total physical activity and according to categories of individual activities, sleep duration, and TV watching in CRC survivors (n = 1376) *(Continued)*

	Total no. of individuals	No. of deaths	Age- & sex-adjusted HR (95% CI)	Multivariable-adjusted[b] HR (95% CI)
> 0 – <1	98	7	0.58 (0.26–1.27)	0.53 (0.24–1.17)
1 – <2	558	94	1.19 (0.85–1.68)	1.17 (0.82–1.65)
≥ 2	113	42	2.63 (1.72–4.02)	2.22 (1.43–3.44)
p^{c}_{trend}			<0.0001	0.0004
Hours/day of watching TV[f]				
≤ 2	480	55	1.00 (Ref.)	1.00 (Ref.)
> 2 – <4	414	59	1.16 (0.80–1.68)	1.23 (0.85–1.79)
≥ 4	482	86	1.28 (0.91–1.80)	1.45 (1.02–2.06)
p^{c}_{trend}			0.16	0.04

Abbreviations: *BMI* body mass index, *CRC* colorectal cancer, *MET* metabolic equivalent of task; *TV* television
[a]Estimated with Cox proportional hazards regression models
[b]Adjusted for sex, age at physical activity assessment, BMI, survival time from CRC diagnosis until physical activity assessment, tumor location, occurrence of metastases, occurrence of other cancer, chemotherapy, smoking status, alcohol intake, (time x age), (time x BMI), and (time x metastases)
[c]Calculated by modeling the median value of physical activities, sleeping time, or TV watching categories as a continuous variable
[d]multivariable-adjusted models mutually adjusted for 'cycling', 'sports', 'walking', 'gardening', and 'housework, home repair, and stair climbing'
[e]multivariable-adjusted models mutually adjusted for hours of sleeping at night and hours of sleeping at day
[f]multivariable-adjusted models additionally adjusted for total physical activity

lower all-cause mortality. The observed association emerged as nonlinear with an approximately similar reduction of all-cause mortality for individuals with moderate and for individuals with high physical activity as compared to individuals with lower levels of activity. We identified significant effect modification by sex, BMI, and tumor location in the sense that the observed association between total physical activity and all-cause mortality was stronger in women, in individuals with a lower BMI, and in individuals with a colon carcinoma. Regarding individual types of physical activity, sports, walking, and gardening were particularly strongly inversely related to all-cause mortality. A greater amount of sleeping during the day was associated with shorter survival, whereas the amount of sleep at night was not associated with survival. More hours per day spent watching TV were associated with a higher all-cause mortality in our CRC survivor cohort.

In the context of the current literature

Our observation of a significant inverse association of postdiagnostic physical activity with all-cause mortality is consistent with a recent meta-analysis of 7 prospective cohort studies of patients with CRC, reporting a summary RR of 0.71 (95% CI: 0.63–0.81) for total mortality, associated with high levels versus low levels of physical activity [37]. With respect to the results obtained in individual cohorts, a 42% (95% CI: 0.47–0.71) reduction in the relative risk for all-cause mortality associated with 8.75 or more MET-hours/week (compared to less than 3.5 MET-hours/week) of recreational physical activity was reported in 2293 CRC survivors [17]. Of note, the time intervals between CRC diagnosis and physical activity assessment were much shorter in most prior studies (range: 5 months to 4.2 years median) [16–23] as compared to our study (6 years median). Thus, we expand the existing evidence by showing that the relation between higher physical activity and better overall survival is also present in long-term survivors of CRC.

Furthermore, to our knowledge, our study is the first one to investigate the association of different types of postdiagnostic physical activity (e.g. walking, cycling, sports, gardening, and housework) with mortality of CRC survivors. However, a randomized controlled trial investigated different intensities of physical activity with cardiorespiratory fitness and body composition in CRC survivors and observed a significantly enhanced cardiorespiratory fitness, increased lean mass, and decreased fat mass in individuals with high- vs. moderate-intensity exercise [38].

With respect to the association of watching TV with all-cause mortality, a prior study (n = 1759 participants) reported likewise an increased risk for all-cause mortality in individuals with ≥4 h per day of TV viewing compared to individuals with 0–2 h of TV watching per day (HR: 1.25; 95% CI: 0.93–1.67) [16]. Similarly, an HR of 1.45 (95% CI: 0.73–2.87) for ≥21 h/week of watching TV compared to 0–6 h of TV viewing was reported in a sample including 714 male CRC survivors [24]. However, in these two studies, statistical significance could not be reached.

In our analyses, the effect of total physical activity on all-cause mortality differed by sex, BMI, and tumor location. Specifically, the association was stronger in women, which is in line with observations in a study of 879 CRC survivors in Western Australia [20]. Furthermore,

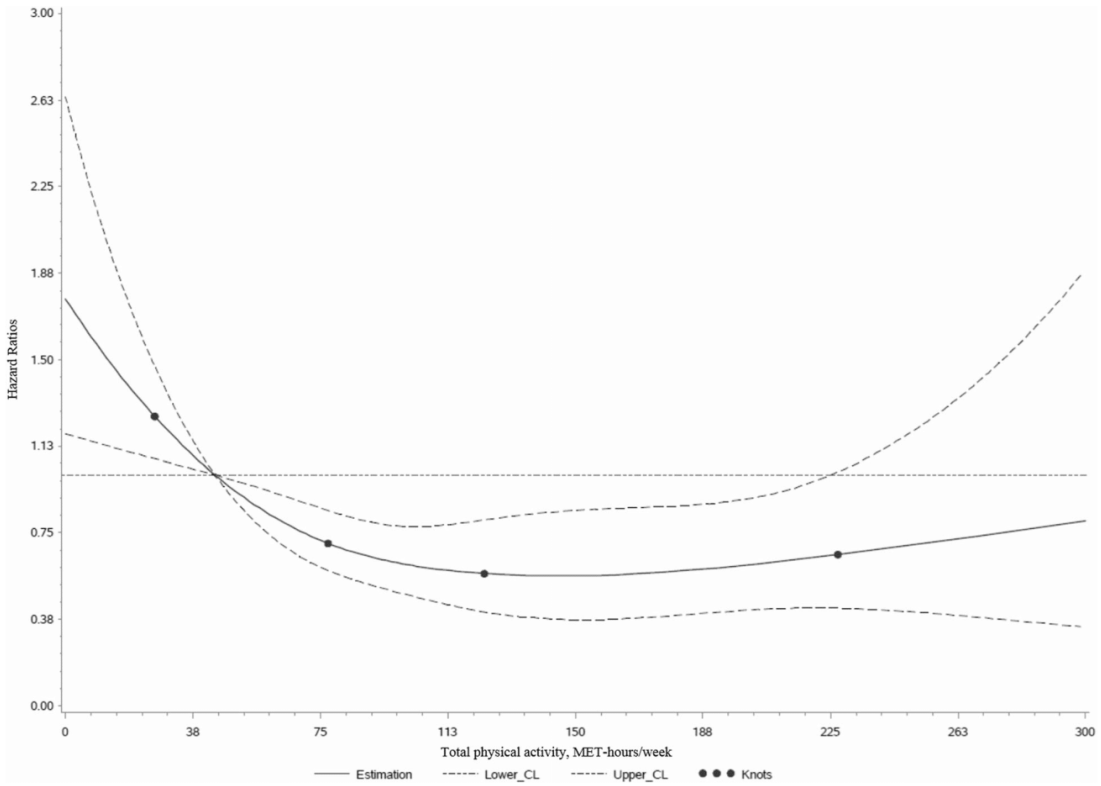

Fig. 2 Multivariable-adjusted hazard ratios of all-cause mortality according to total postdiagnostic physical activity in CRC survivors (n = 1376), calculated with restricted cubic spline regression. The solid line depicts hazard ratios and the dashed lines are the 95% CIs. The points indicate the knots on 5th, 35th, 65th, and 95th percentiles. The reference value is the median (44 MET-hours/week) of the first quartile of total physical activity. The model was adjusted for sex, age at physical activity assessment, BMI, survival time from CRC diagnosis until physical activity assessment, tumor location, occurrence of metastases, occurrence of other cancer, chemotherapy, smoking status, and alcohol intake. The p value for nonlinearity is 0.01 (Wald chi-square test). Abbreviations: BMI, body mass index; CRC, colorectal cancer; MET, metabolic equivalent of task

individuals with a lower BMI displayed a stronger association of physical activity with overall survival as compared to individuals with a higher BMI. Concerning this interaction, other studies revealed heterogeneous results [18–20]. In our cohort, individuals with a colon tumor had a stronger association of physical activity with overall survival than individuals with a rectum tumor. A similar but nonsignificant tendency was reported in an Australian study [19]. Additionally, in the European Prospective Investigation into Cancer and Nutrition, physical activity was associated with a reduction of colon cancer incidence, but not of rectum cancer incidence [32].

The average level of physical activity, measured in MET-hours per week, in our sample was higher than in most of the other studies of CRC survivors [17, 21, 23]. It has to be kept in mind, though, that in our cohort nearly all activities (leisure time activities (sports, cycling, walking), gardening, and housework activities (housework, home repair, stair climbing)) were enquired and included in the analyses, whereas most prior studies relied only on leisure time activities. Additionally, regarding the median age of 69 years, it can be assumed that the vast majority of our participants were no longer engaged in occupational activities when physical activity was assessed, so that almost every kind of usual activity should be recorded when leisure time physical activity and housework/gardening activities are gathered.

Potential explanations for the observed associations

Several beneficial health effects of physical activity have been reported, including improvements in metabolism, inflammatory processes, and vascular and cardiac function. Specifically, greater insulin sensitivity and lower levels of insulin [39] were related to increased physical activity. In prospective studies, higher circulating insulin and C-peptide levels have been associated with CRC risk [40], angiogenesis, tumor growth, and anti-apoptosis [41]. Another potential mechanism is that physical

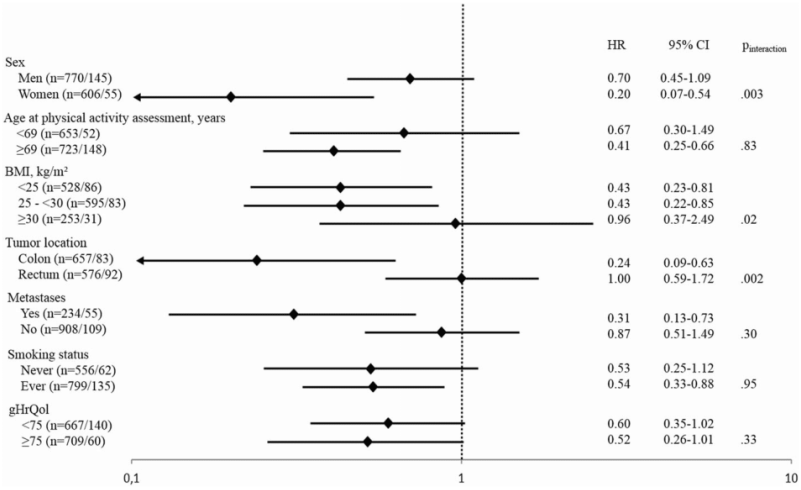

Fig. 3 HRs and 95% CIs for all-cause mortality in 1376 CRC survivors comparing the fourth to the first quartile of total physical activity, stratified by potential effect modifiers; for each stratum the total number of individuals/number of deaths is shown; HRs and 95% CIs were estimated with Cox proportional hazards models, adjusted for sex, age at physical activity assessment, BMI, survival time from CRC diagnosis until physical activity assessment, tumor location, occurrence of metastases, occurrence of other cancer, chemotherapy, smoking status, alcohol intake, (time x age), (time x BMI) and (time x metastases), except the stratifying variable; $p_{interaction}$ was calculated by entering into the model an interaction term of total physical activity as a continuous variable and the stratifying covariate; cutpoint for age at physical activity assessment and gHrQol was the respective median value. Abbreviations: BMI, body mass index; CRC, colorectal cancer; gHrQol, global health-related quality of life

activity decreases inflammatory adipocytokines and increases circulating concentrations of anti-inflammatory cytokines, which could affect cancer incidence and mortality [42]. Physical activity also improves structure and function of the cardiovascular system, e.g., by lowering blood pressure [7] and by positively affecting vascular remodeling [43]. In this context, a small intervention study in 47 CRC survivors revealed that a 4-week exercise program of high intensity as compared to moderate intensity led to a significant improvement in cardiorespiratory fitness and body composition [38]. The differences in the association between the different types of physical activity with all-cause mortality cannot be fully explained with our dataset because we do not know the exact type and intensity of activity within a given activity group (e.g. in sports, gardening, housework). As outlined in the methods section, we obtained the duration of each activity and then multiplied it with a recommended averaged MET-value [31, 32]. One potential explanation for the observed differences between the different types of activity could be that sports activities conducted by the participants included more high-intensity exercise as compared to cycling activities and that gardening activities may include more high-intensity exercise as compared to household activities. But these premises require further investigations with more detailed information on intensity level and type of activity. Another beneficial effect of gardening (as compared to household activities) could also be the outdoor exercise in fresh air with more sunlight exposure leading to an increased vitamin D synthesis. Previous studies reported an association between higher plasma vitamin D levels and lower all-cause mortality in CRC survivors [44, 45]. A high level of walking activities might reflect an active lifestyle in general which may have led to the reduction in all-cause mortality with more MET-hours/week of walking in our cohort.

With respect to the observed association between TV viewing and all-cause mortality, higher amounts of time spent watching TV have been associated with higher levels of cardiometabolic biomarkers and increased risk of cardiovascular disease and obesity [46], diabetes [47], and all-cause mortality [48]. One of the potential mechanisms for the observed association includes greater amounts of sedentary time in individuals watching more TV and a higher consumption of energy-dense food [36]. However, in a sensitivity analysis, we additionally adjusted the association of TV viewing with all-cause mortality for total energy intake and observed no differences in HRs and 95% CIs.

The observed association between more hours of sleeping at day and higher all-cause mortality could be explained by reduced physical activity and higher sedentary time leading to adverse biological consequences as mentioned above. However, it is also plausible that reverse causality may have influenced this association. It cannot be ruled out, that individuals with a worse health

status spend more time sleeping at day due to uncomfortable feeling and lack of energy.

Reverse causality might also play a role for the association between physical activity and mortality in general (e.g. less physical activity due to indisposition). Although we performed several sensitivity analyses to address this point (additional adjustment for gHrQol; exclusion of participants who died within 12 months after physical activity assessment; exclusion of individuals with 0 MET-hours/week of total physical activity), and the results remained largely unchanged in these analyses, reverse causality cannot entirely be ruled out.

The nonlinearity of the association between total physical activity and all-cause mortality reveals that compared to nearly no activity, a moderate level is associated with a lower risk of all-cause mortality whereas the differences in mortality risk between high activity and moderate activity were not so prominent. Thus, physical activity at all compared to nearly none might be beneficial for CRC survivors with moderate and high levels of physical activity conferring approximately similar benefits with respect to survival.

The difference in the association of physical activity with all-cause mortality between men and women and between individuals with a lower BMI and those with a higher BMI might be due to a generally healthier lifestyle in women than in men [49] and in individuals with a lower BMI, e.g., in the normal range or in the overweight category, as compared to individuals with a BMI in the obese category [50]. Additionally, obese individuals might be more prone to misreport physical activity which may have led to the lack of association in the obese participant group [51]. Regarding the difference between colon and rectum carcinoma, a hypothesized mechanism is that physical activity might accelerate bowel motility more intensely in the colon than in the rectum which can affect the gastrointestinal transit time and the time in which potential carcinogens have contact with the mucosa [52].

Strengths and limitations

Strengths of our study include the prospective design with a long follow-up period, a relatively large sample, and a comprehensive ascertainment of physical activity, its subtypes, and vital status.

However, some limitations need to be considered. We only had information available on all-cause mortality, but not on disease-specific mortality. Therefore, future studies on the association of physical activity, especially of different types of activities, with CRC-specific mortality are warranted. The CRC diagnosis of our study participants occurred at a median of 6 years prior to physical activity assessment, which is why we characterize them as long-term cancer survivors. Thus, the generalizability of our observations to all CRC patients is unknown. Additionally, information on tumor stage and comorbidities were not available in our cohort. We only had information on metastases and other cancers. Though, a recent study that investigated the association between prediagnostic physical activity and survival did not find any differences in the results after adjusting for comorbidities in a sensitivity analysis [33]. We also were not able to adjust the association between sleep during daytime and survival for medication use, even though some medication could influence fatigue and sleeping time as well as mortality. Furthermore, we had no information on prediagnostic physical activity. However, a previous study reported a significant association of postdiagnostic physical activity with mortality independent of prediagnostic activities [16]. Moreover, reported activities, especially in the category of sports, are likely to vary between participants in type or intensity, which has not been assessed specifically. The data on clinical and lifestyle factors were self-reported which may have led to some information or recall bias. Nevertheless, a validation of self-reported clinical data against medical records in a subset of 181 patients revealed a concordance of about 87%.

Conclusions

Our results strengthen the evidence on the association of higher postdiagnostic physical activity with reduced mortality risk in CRC survivors. Certain activity types might be primarily responsible for this association. The association of lifestyle factors (such as physical activity and sedentary behavior) after CRC diagnosis with survival is particularly interesting, because CRC survivors might be able to alter their behavior and actively improve their health outcome, a premise that could be addressed in further (interventional) studies. The fact that reverse causality is a common problem in observational studies underscores the need for randomized controlled trials of physical activity interventions in CRC survivors.

Furthermore, physical activity could be an attractive strategy to prevent cancer recurrence and to prolong life in cancer survivors because it potentially also prevents many other diseases which accumulatively appear in the elderly [53]. Based on the available evidence, it is reasonable to recommend CRC survivors to engage in regular physical activity.

Additional file

Additional file 1: Table S1. Sensitivity Analysis (n = 1357): HRs and 95% CIs of all-cause mortality according to quartiles of physical activity after excluding individuals who died within 12 months after physical activity assessment (n = 19); **Table S2.** Sensitivity Analysis (n = 1142): HRs and 95% CIs of all-cause mortality according to quartiles of physical activity after excluding individuals with known occurrence of metastases (n = 234). (DOCX 20 kb)

Abbreviations
BMI: Body mass index; CRC: Colorectal cancer; FFQ: Food frequency questionnaire; gHrQol: Global health-related quality of life; HrQol: Health-related quality of life; MET: Metabolic equivalent of task; TV: Television

Acknowledgements
Not applicable.

Funding
MK is recipient of a Postdoctoral Research Fellowship from the German Research Foundation (Deutsche Forschungsgemeinschaft, DFG, KO 5187/1–1). RdG is supported by the Deutsche Forschungsgemeinschaft Excellence Cluster "Inflammation at Interfaces" (grants EXC306 and EXC306/2). The funding sources had no role in the design and conduct of the study.

Availability of data and materials
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Authors' contributions
IR, CS, UN, JH, and SS designed and conducted research; IR performed the statistical analyses; IR, RDG, SW, SPD, MK, GB, and SS contributed to the design of the study, interpretation of the data, and manuscript preparation; IR, SS, and WL wrote the manuscript; IR, SS, and WL had primary responsibility for final content. All authors read and approved the final manuscript.

Ethics approval and consent to participate
The study protocol was approved by the institutional ethics committee of the Medical Faculty of Kiel University and written informed consent was obtained from all study participants.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interest.

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Received: 8 August 2017 Accepted: 19 October 2017
Published online: 25 October 2017

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Supplemental Table 1 Sensitivity Analysis (n=1357): HRs[1] and 95% CIs of all-cause mortality according to quartiles of physical activity after excluding individuals who died within 12 months after physical activity assessment (n=19)

	Total no. of individuals	No. of deaths	Age- & sex-adjusted HR (95% CI)	Multivariable-adjusted[2] HR (95% CI)
MET-hours/week of total physical activity				
Quartile 1 (0-65.2)	339	74	1.00 (Ref.)	1.00 (Ref.)
Quartile 2 (>65.2-100.7)	339	42	0.65 (0.44-0.95)	0.67 (0.46-0.99)
Quartile 3 (>100.7-147.0)	340	32	0.52 (0.34-0.79)	0.58 (0.38-0.89)
Quartile 4 (>147.0)	339	33	0.58 (0.38-0.88)	0.59 (0.39-0.90)
p_{trend}[3]			0.006	0.008

[1] Estimated with Cox proportional hazards models.

[2] Adjusted for sex, age at physical activity assessment, BMI, survival time from CRC diagnosis until physical activity assessment, tumor location, occurrence of metastases, occurrence of other cancer, chemotherapy, smoking status, alcohol intake, (time x age), (time x BMI), and (time x metastases).

[3] Calculated by modeling the median value of total physical activity quartiles as a continuous variable.

Abbreviations: BMI, body mass index; CRC, colorectal cancer; Ref., reference.

Supplemental Table 2 Sensitivity Analysis (n=1142): HRs[1] and 95% CIs of all-cause mortality according to quartiles of physical activity after excluding individuals with known occurrence of metastases (n=234)

	Total no. of individuals	No. of deaths	Age- & sex-adjusted HR (95% CI)	Multivariable-adjusted[2] HR (95% CI)
MET-hours/week of total physical activity				
Quartile 1 (0-65.5)	285	58	1.00 (Ref.)	1.00 (Ref.)
Quartile 2 (>65.5-100.2)	286	35	0.71 (0.46-1.08)	0.72 (0.47-1.11)
Quartile 3 (>100.2-143.5)	286	25	0.53 (0.33-0.85)	0.60 (0.37-0.97)
Quartile 4 (>143.5)	285	27	0.66 (0.41-1.05)	0.65 (0.40-1.04)
p_{trend}[3]			0.04	0.05

[1] Estimated with Cox proportional hazards models.

[2] Adjusted for sex, age at physical activity assessment, BMI, survival time from CRC diagnosis until physical activity assessment, tumor location, occurrence of other cancer, chemotherapy, smoking status, alcohol intake, and (time x age).

[3] Calculated by modeling the median value of total physical activity quartiles as a continuous variable.

Abbreviations: BMI, body mass index; CRC, colorectal cancer; Ref., reference.

4 Health-related quality of life in long-term survivors of colorectal cancer and its association with all-cause mortality: a German cohort study

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Under peer review with BMC Cancer

Abstract

Background: The group of colorectal cancer (CRC) survivors continues to grow worldwide. Understanding health-related quality of life (HRQOL) determinants and consequences of HRQOL impairments in long-term CRC survivors may help to individualize survivorship care plans. We aimed to i) examine the HRQOL status of CRC long-term survivors, ii) identify cross-sectional sociodemographic and clinical correlates of HRQOL, and iii) investigate the prospective association of HRQOL after CRC diagnosis with all-cause mortality.

Methods: We assessed HRQOL within a Northern German cohort of 1294 CRC survivors at a median of 6 years after CRC diagnosis using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30). Cross-sectional correlates of different HRQOL dimensions were analyzed using multivariable-adjusted logistic regression models with HRQOL as a binary variable. With multivariable-adjusted Cox proportional hazards regression models, hazard ratios (HR) of all-cause mortality were estimated per 10-point-increments of an HRQOL summary score, a global quality of life scale, and HRQOL functioning and symptom domains.

Results: The median HRQOL summary score was 87 (interquartile range: 75-94). Sex, age, education, tumor location, metastases, other cancers, type of therapy, and current stoma were identified as correlates of different HRQOL scales. After a median follow-up time of 7 years after HRQOL assessment, 175 participants had died. Nearly all HRQOL domains, except for cognitive functioning and diarrhea, were significantly associated with all-cause mortality. A 10-point-increment in the summary score decreased the risk of death by 24% (HR: 0.76; 95% CI: 0.70-0.82).

Conclusions: HRQOL in CRC survivors appeared to be relatively high in the long term. Various clinical and sociodemographic factors were cross-sectionally associated with HRQOL in long-term CRC survivors. Lower HRQOL was associated with increased all-cause mortality. Individualized healthcare programs for CRC survivors (including psychosocial screening and interventions) are needed to detect decreased HRQOL and to further improve long-term HRQOL and survival.

Keywords: health-related quality of life, long-term survivors, colorectal cancer, correlates, mortality

Background

As the group of patients surviving colorectal cancer (CRC) is growing, understanding and improving health-related quality of life (HRQOL) in these patients is becoming an important field of research [1, 2]. CRC survivors may be impaired in physical functioning and in everyday life by multiple disease- and treatment-related symptoms such as pain, bowel dysfunction, and fatigue and may be negatively affected in psychological, emotional, social, and role functioning because of fear, anxiety, sleep disruption, and depression [3-6]. Therefore, reconstitution of physical, social, psychological, and sexual function is pivotal [7]. Assessment of HRQOL in CRC survivors provides insight into their experiences of the disease, therapy, and recovery, helps to identify risk factors of low HRQOL, and might support the choice and design of appropriate interventions and survivorship care plans [8-10].

HRQOL in CRC survivors has been addressed in prior studies, but most of these studies evaluated rather short-term (≤5 years after diagnosis) treatment- and disease-related effects on quality of life (QOL) [11-14]. Long-term HRQOL after CRC diagnosis and, especially, its association with survival is not well described. A few studies investigated HRQOL in patients who survived at least 5 years after CRC diagnosis but most of them relied on relatively small sample sizes. In two studies in the US, a relatively high QOL was observed in 227 and 173 CRC survivors, respectively, with QOL obtained ≥5 years after CRC diagnosis [1, 15]. Nonetheless, higher prevalence of depression and anxiety in CRC survivors as compared to the general population have been reported [1, 10, 16]. With respect to factors influencing QOL, different clinical, sociodemographic, and lifestyle factors, including age, sex, tumor location, body mass index (BMI), stoma, and physical activity were associated with HRQOL of CRC survivors in previous epidemiological studies [8, 17-19], though findings were partially inconsistent in terms of their effect sizes and effect directions. In a previous investigation, we have examined the relation between selected lifestyle factors (diet, BMI, physical activity, and smoking status), modeled as a lifestyle index, and HRQOL in our CRC survivor cohort [20] and observed that a favorable diet, more physical activity, and lower BMI were significantly associated with higher HRQOL. In the present study, we will expand on this previous analysis by i) investigating the association of a broad panel of clinical and sociodemographic factors (not considered in our prior analyses [20]) with HRQOL and ii) relating HRQOL prospectively to all-cause mortality. To our knowledge, so far, only one study examined the association between HRQOL and mortality in long-term CRC survivors and provided initial evidence for an inverse relation between physical and mental component scores and mortality risk [18].

Thus, the aim of this study was three-fold: first, to describe the HRQOL status of a cohort of CRC long-term survivors; second, to identify sociodemographic and clinical correlates of

HRQOL in these CRC survivors; third, to investigate the association of HRQOL with all-cause mortality in these individuals.

Methods

Study population

Between 2004 and 2007, a total of 2733 patients with histologically-proven CRC, diagnosed between 1993 and 2005, have been identified through medical records review in collaboration with surgical departments of 23 hospitals in Northern Germany and with the regional cancer registry. These patients were enrolled in a prospective study, conducted by the biobank PopGen, as reported in more detail elsewhere [20-22]. Briefly, at the time of inclusion (baseline; 2004-2007), participants were asked to fill in a questionnaire on clinical and sociodemographic characteristics and on selected lifestyle factors (e.g. cigarette smoking, alcohol consumption). The study protocol was approved by the ethics committee of the Medical Faculty of Kiel University and written informed consent was obtained from all study participants.

A first follow-up assessment was conducted from 2009 to 2011, and 2263 participants who initially agreed to be re-contacted were asked to fill in another questionnaire about clinical and sociodemographic characteristics, as well as standardized and validated questionnaires on diet (food frequency questionnaire [23]), physical activity [24], and HRQOL [25].

Of the 2263 participants re-contacted, 354 individuals were deceased and 31 had moved with unknown addresses. From 1677 individuals who filled in the HRQOL questionnaire, we excluded individuals with incomplete HRQOL data (n=147), individuals with missing information on physical activity (n=169), year of diagnosis (n=30), and vital status (n=30), those with implausible length of follow-up (n=4), and participants with a diagnosis of small intestine cancer instead of CRC (n=3), leaving an analytical sample of 1294 participants.

Health-related quality of life assessment

For the assessment of HRQOL (conducted at first follow-up), the German version of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30; version 3.0) [25] was used. The 30-item self-report questionnaire is a validated cancer-specific instrument for the measurement of HRQOL. The QLQ-C30 is composed of a global QOL scale and of five multi-item functional scales that assess physical, role, emotional, cognitive, and social function. Furthermore, three multi-item symptom scales evaluate pain, nausea/vomiting, and fatigue, and six single-item scales measure constipation, diarrhea, appetite loss, dyspnea, insomnia, and financial difficulties. All items are scored on a scale from 1 (not at all) to 4 (very much), except for

global QOL, which is scored from 1 (very poor) to 7 (excellent). A scoring procedure was applied according to the EORTC QLQ-C30 Scoring Manual [26]. All scales were linearly transformed to standardize the raw scores to scores that range from 0 to 100. High functional scores and high global QOL scores indicate high (functional) QOL whereas high symptom scores represent more severe symptoms. A summary score was calculated from 13 scales (excluding global QOL and financial difficulties) with the symptom scales being reversed (100 - symptom scale) to obtain a uniform direction of all scales [27], as follows: *QLQ-C30 summary score = (physical functioning + role functioning + social functioning + emotional functioning + cognitive functioning + (100-fatigue) + (100-pain) + (100-nausea/vomiting) + (100-dyspnea) + (100-insomnia) + (100-appetite loss) + (100-constipation) + (100-diarrhea)) / 13*.

Assessment of sociodemographic, clinical, and lifestyle characteristics

The self-administered questionnaires on clinical and sociodemographic characteristics assessed date of diagnosis, tumor location, neoadjuvant and adjuvant types of therapy, occurrence of metastases or other types of cancer, sex, age at diagnosis, age at HRQOL assessment (first follow-up), education (≤9, 10, ≥11 years, unknown) and family status (single, married, in partnership, divorced, widowed, unknown) at first follow-up, current stoma at first follow-up, smoking status at first follow-up, and postdiagnostic body weight and height at baseline and first follow-up. BMI (kg/m²) was calculated with weight divided by the square of height in meters. We validated self-reported clinical data (tumor location, type of therapy, metastases) against medical records in a subset of 181 participants and observed overall good agreement (87% concordance). Information on physical activities during the past 12 months was obtained with validated questions [24]. Hours per week spent with different activities (walking, cycling, sports, gardening, housework, home repair, stair climbing) were derived from these questions. To obtain comparable intensity levels, metabolic equivalent of task (MET) values, derived from the 2000 Compendium of Physical Activity [28], were assigned to each corresponding activity [29].

Vital status ascertainment

All-cause mortality was first determined in 2014. Participants who did not respond when they were re-contacted for an extension of their informed consent, or for whom the spouse reported the study participant's death, vital status was attained from population registries and date of death was recorded. In 2016, vital status of all participants was updated via population registries and date of death was recorded if participants were deceased. Altogether, 175 participants had died since HRQOL assessment.

Statistical analyses

First, medians and interquartile ranges (IQR) were calculated for the summary score, global QOL, and for each functioning and symptom scale. For symptom scales, also prevalence (defined as a symptom scale >0) were computed.

Second, in order to determine potential correlates of the different HRQOL scores, odds ratios (ORs) and 95% confidence intervals (95% CIs), derived from multivariable-adjusted logistic regression models in cross-sectional analyses, were estimated with the respective score modeled as a binary outcome (below vs. above the score-specific median) and with sociodemographic (sex, age, education, family status) and clinical (tumor location, metastases, other cancer, type of therapy, current stoma) characteristics as exposures (and, thus, as potential correlates). These models were adjusted for the following variables, except the respective exposure variable of interest: sex, age at HRQOL assessment, BMI (continuous in kg/m²), physical activity (continuous in MET-hours/week), tumor location (colon, rectum both, unknown), occurrence of metastases (yes, no, unknown), occurrence of other types of cancer (yes, no, unknown), type of therapy (none, chemotherapy, radiation, both, unknown), and current stoma (yes, no, unknown).

Third, Cox proportional hazards regression models were used to estimate hazard ratios (HR) and 95% CIs of all-cause mortality for each 10-point-increment in the summary score, in the global QOL score, and in each functioning and symptom scale. The 10-point-increment was chosen because a 10-point change in QLQ-C30 scales was found to indicate a ("subjective significant") "moderate" change in HRQOL domains [30]. The date of HRQOL assessment was the starting point for survival follow-up of this analysis and follow-up ended with date of death or date of last vital status assessment whichever came first. We conducted a Cox model adjusting for sex and age at HRQOL assessment and a multivariable-adjusted model, which was additionally adjusted for BMI, physical activity, tumor location, time from diagnosis until HRQOL assessment, type of therapy, occurrence of metastases, occurrence of other cancers, current stoma, education (≤9, 10, ≥11 years, unknown), family status (single, married/in partnership, divorced, widowed, unknown), and smoking status (never, former, current, unknown). We tested the proportional hazards assumption by the Schoenfeld residual method and by including time-dependent variables in the statistical model. Because age did not meet the proportional hazards assumption, a respective time-interaction-term (age x time) was included in each Cox regression model.

Fourth, to test for nonlinearity in the association of HRQOL with all-cause mortality, a restricted cubic spline regression was conducted. For this analysis, the summary score (including information from nearly all functioning and symptom scales) was chosen as the independent variable. The knots were located on the 5th, 35th, 65th, and 95th percentile [31] and the reference value was the median (62.4 score points) of the first quartile of the

summary score. The model was adjusted for the same covariates as the multivariable-adjusted Cox regression model (mentioned above).

Fifth, stratified analyses were performed to examine the role of potential effect modifiers (sex, age, BMI, education, family status, smoking status, tumor location, therapy, metastases, and current stoma) on the association between the summary score and all-cause mortality. Furthermore, we formally tested for statistical interactions by including respective cross product terms (summary score x potential effect modifier) in the statistical model predicting all-cause mortality.

Sixth, to assess the robustness of our results we performed a sensitivity analysis, excluding all individuals who reported a diagnosis of metastases or other cancers because metastases and additional cancer diseases could influence HRQOL as well as survival. We also considered excluding all participants who died within 12 months of HRQOL assessment in a second sensitivity analysis but there was no individual who deceased within the first 12 months of follow-up.

Results

Participant characteristics

The characteristics of the study participants as a total sample and according to an HRQOL summary score below or at/above the median are presented in **Table 1**. Of the 1294 individuals, 43% were women and the median age at diagnosis was 62 years. HRQOL was assessed on average 6 years (median) after CRC diagnosis. Nearly half of the population (46%) reported a low educational status and 77% were married or in a partnership at time of HRQOL assessment. Sixteen percent of the individuals had a diagnosis of metastases, 21% reported a diagnosis of another cancer, and half of the participants (53%) had no additional cancer therapy except for surgery. A current stoma at time of HRQOL assessment was reported by 12% of the CRC survivor cohort.

Health-related quality of life status in long-term colorectal cancer survivors

The HRQOL summary score had a median of 87.3 (IQR: 75.3-94.4) (**Table 2**). The global QOL scored lower with a median of 75.0 (58.3-83.3). The highest scores of the five functional scales were observed for role (100 (66.7-100)) and social (100 (66.7-100)) functioning with the highest possible score as the median. Physical, emotional, and cognitive functioning were a little bit lower but roughly at a comparable level (between 83.3 and 86.7; **Table 2**). Of the nine symptom scales, fatigue and insomnia revealed the highest median scores (22.2 (0-33.3) and 33.3 (0-33.3), respectively) and also the highest symptom prevalence (70% and 52%, respectively), indicating a higher burden of these symptoms in the present cohort. Each of the other symptom scales had a median of 0, indicating on

average no or minor symptom burden. Nevertheless, more than one-third of the study participants reported any symptoms of pain (44%), dyspnea (38%), and diarrhea (36%), respectively (**Table 2**).

Correlates of health-related quality of life

Relevant correlates for low values (below the score-specific median) of the different HRQOL scales are provided in **Table 3**. In general, older age (except for emotional and social functioning), lower education, tumor location in both the colon and the rectum, metastases or other cancers, a combination of chemotherapy and radiation therapy, and a current stoma were statistically significant correlates of low HRQOL in cross-sectional analyses (**Table 3**).

Specifically, women had a statistically significantly higher risk of low physical functioning than men but a lower risk of low social and cognitive functioning as compared with men. With respect to age, younger survivors (<60 years) had higher odds and older survivors (≥80 years) had lower odds for low social functioning as compared to survivors aged 60-69 years. A high educational level was significantly associated with decreased risk of low global QOL and low physical functioning. Rectal tumor survivors were more likely to have a low physical and social functioning than colon tumor survivors. Individuals with a diagnosis in both locations had nearly two times the odds of a low summary score. Metastases had a negative impact on the HRQOL summary score and on social functioning whereas a history of other types of cancer affected the HRQOL summary score and global QOL, as well as role, social, and cognitive functioning. The combination of chemotherapy and radiation was associated with a low HRQOL summary score, low global QOL, and low role und social functioning. Individuals with a current stoma at time of HRQOL assessment were more likely to have a low physical, role, emotional, and social functioning, as shown in **Table 3**.

Association between health-related quality of life and all-cause mortality

After a median follow-up time of 7 years after HRQOL assessment, 175 (13.5%) of the 1294 participants had died. Higher scores of the HRQOL summary score and of the global QOL score were associated with improved survival (HR: 0.76; 95% CI: 0.70-0.82 and HR: 0.80; 95% CI: 0.75-0.86 for all-cause mortality per 10-point-increment, respectively) (**Table 4**). Restricted cubic spline regression revealed a linear association between the HRQOL summary score and all-cause mortality ($p<0.0001$ for overall association; $p=0.87$ for nonlinearity; **Figure 1**).

Furthermore, every functioning scale was statistically significantly inversely related to all-cause mortality, except for cognitive functioning which was borderline non-significant (HR:

0.95; 95% CI: 0.88-1.02), with physical functioning displaying the strongest association (HR: 0.80; 95% CI: 0.75-0.86; **Table 4**).

Each of the symptom scales, except for diarrhea (HR: 1.03; 95% CI: 0.97-1.09), was statistically significantly positively associated with all-cause mortality, with financial difficulties displaying the weakest (HR: 1.07; 95% CI: 1.01-1.13) and nausea and vomiting (HR: 1.31; 95% CI: 1.19-1.43), fatigue (HR: 1.20; 95% CI: 1.13-1.26), and appetite loss (HR: 1.18; 95% CI: 1.10-1.25) displaying the strongest associations after multivariable adjustment (**Table 4**).

The stratification by potential effect modifiers revealed a stronger association between the HRQOL summary score and survival for individuals who had no therapy in addition to surgery as compared to individuals who had either chemotherapy or radiation or both chemotherapy and radiation ($p_{interaction}$=0.02). Furthermore, participants with a high educational status showed a stronger association between HRQOL and all-cause mortality than participants with a low or middle educational status ($p_{interaction}$=0.03). The association was also stronger in individuals with a current stoma than in those without a stoma although the interaction term was not statistically significant ($p_{interaction}$=0.08; **Table 5**).

In a sensitivity analysis, after excluding participants who reported a diagnosis of metastases or a diagnosis of other cancers (n=414), the results remained largely unchanged (data not shown).

Discussion

In the present analyses, we describe in detail the HRQOL in long-term survivors of CRC, assess cross-sectional correlates of this HRQOL (and its different scales), and evaluate the prospective association of HRQOL with all-cause mortality in these CRC survivors. Our main observations were as follows: First, in general, the overall HRQOL, obtained approximately 6 years after the cancer diagnosis, seems to be relatively high. Role and social functioning reached the highest median scores out of the five functioning scales, while out of the nine symptom scales, fatigue and insomnia had the highest median scores, indicating the highest extent of these symptoms as compared to the other symptoms. Second, sex, age, education, tumor location, metastases, other cancers, type of therapy, and current stoma were statistically significant correlates of different HRQOL scales. Third, the summary score and the global QOL as well as nearly all functioning and symptom scales were statistically significantly associated with all-cause mortality in the sense that higher HRQOL and better functioning were associated with better overall survival and more symptoms were related to worse overall survival. Fourth, the inverse association between the HRQOL summary score and all-cause mortality was stronger in individuals who had no neoadjuvant or adjuvant therapy as compared to individuals with chemotherapy or both

chemotherapy and radiation and stronger in individuals with a high educational status than in individuals with a low or middle educational status.

Health-related quality of life status

Compared to our study, previous studies reported similar high HRQOL values in CRC survivors, which are considered to be an indication of overall good QOL [1, 15, 32, 33]. However, the HRQOL of our CRC survivor cohort is in several aspects (especially regarding emotional, cognitive, and physical functioning) still slightly lower when compared to European general (healthy) population samples, though the HRQOL values of elderly general population groups (age categories >60 years) approximate those of our CRC survivors [34]. Thus, it is conceivable that, on average, CRC survivors in the long term are able to gain HRQOL levels comparable to individuals from the general population with about the same age.

Association of sociodemographic characteristics with health-related quality of life in cross-sectional analyses

In our study, women had a higher risk of a low physical functioning than men but a lower risk of a low social and cognitive functioning as compared with men. In contrast to our observations, however, a recent US study including 593 CRC survivors reported no significant difference between men and women in physical HRQOL and female gender was associated with increased risk of a low mental HRQOL [8].

Similar to our findings, the above mentioned US study reported a tendency towards a lower physical HRQOL and higher mental HRQOL in the elderly as compared to younger individuals, even though the association between age and HRQOL lost statistical significance after multivariable adjustment [8]. However, in a study of the Seattle Colorectal Cancer Family Registry, the association between older age and a higher risk of a very low physical component summary score remained statistically significant even after multivariable adjustment [18]. One possible explanation for the association of older age with low physical functioning is the higher prevalence of frailty and multiple comorbidities in the elderly [35] which might lead to worse physical functioning and decreased overall HRQOL. Similarly, lower cognitive functioning might, as well, rather be a consequence of advanced age than of cancer history [36].

In our study, a higher educational level was associated with higher global QOL and higher physical functioning which is in accordance with the above mentioned study on 593 long-term CRC survivors [8]. However, we did not assess income level which is likely to be highly correlated with educational level and which was associated with physical, social, and emotional well-being in other studies [10, 37].

With respect to the association between family status and HRQOL, the published literature is partially conflicting. Whereas in our cohort, family status displayed no evidence for an association with HRQOL, other studies reported being single, divorced or widowed or being married or in partnership to be inconsistently associated with low or high HRQOL [8, 38].

Association of clinical characteristics with health-related quality of life in cross-sectional analyses

Regarding tumor location, other studies found either no significant association with HRQOL [18] or a lower HRQOL for rectal cancer survivors than for colon cancer survivors [17], which is in line with the observations from our analyses. This association might be explained by differences in symptoms, treatment modalities, and therapy duration between colon and rectum cancer affecting HRQOL [39].

Comparable to our results, a French study of 207 rectal cancer survivors reported worse role and social functioning and lower global QOL scales of the EORTC QLQ-C30 in patients who received both chemotherapy and radiation as compared to patients receiving only radiation [40]. Additionally, chemotherapy or radiation alone compared to none was not associated with HRQOL in our cohort which is in line with findings from a Dutch investigation in the PROFILES registry [41]. A combined therapy of radiation and chemotherapy is likely to be indicative of a worse disease status and it might be associated with more treatment side-effects which would explain the decreased HRQOL [42].

Several other studies demonstrated that CRC survivors with a stoma had a decreased HRQOL, even in the long-term period of two to more than five years postdiagnosis [17, 43, 44]. In our analyses, one of the strongest negatively influenced HRQOL component by the presence of a stoma was the social functioning, as similar reported by a systematic review including 10 studies [16]. Stoma patients often are affected by fear, worry, dissatisfaction, and embarrassment especially when dealing with it in public areas and social relations [45].

Of note, the ability to compare results across studies has been limited by the huge variety of applied HRQOL assessment instruments (e.g. EORTC-QLQ C30, FACT-C, SF36, SF12). Overall, our observations suggest that a more severe disease stage (e.g. tumor located on both sides, diagnosis of metastases and other cancers, chemotherapy and radiation, current stoma) is associated with lower HRQOL.

Prospective association of health-related quality of life with all-cause mortality

In our sample, a higher HRQOL was associated with a lower risk of dying which is in line with prior studies, although these studies mainly assessed HRQOL in patients with advanced disease stages [46]. Consistently, in our study, higher values in the different

functioning scales and lower values in the symptom scales were associated with longer survival. In agreement with these observations, a very low physical component score (<10th percentile) was associated with a higher risk of mortality in 1021 long-term CRC survivors of the Seattle Colorectal Cancer Family Registry (HRQOL approximately 5.5 years postdiagnosis; HR: 3.97; 95% CI: 2.95-5.34) [18].

A few studies used the same HRQOL assessment instrument as we did (EORTC QLQ-C30) and reported likewise significant associations with survival, but those studies assessed HRQOL of CRC patients very shortly after diagnosis and therapy (≤1 year) or even prior to cancer treatment [11, 47-51]; and some of these studies focused on advanced CRC [49, 50]. We expand those results by examining HRQOL in a relatively large sample (n=1294) of long-term CRC survivors.

The underlying mechanisms of the association between HRQOL and survival in cancer patients are not yet entirely clear. It is conceivable that individuals with a worse HRQOL have more severe CRC or more comorbid conditions. We adjusted our analyses for the prevalence of metastases and other cancers as well as for type of therapy, but we could not control for tumor stage, recurrence, and comorbidities because of lack of information regarding these clinical characteristics. Another potential explanation for the observed association between HRQOL and survival might be psychological distress. It has been reported that individuals with psychological distress rate their HRQOL lower and that psychological distress is associated with increased cancer mortality [52, 53] and increased all-cause mortality in the general population [54]. Psychological stress and depression might adversely affect cardiovascular physiology [55] and could lead to increased inflammatory responses and cortisol release by dysregulating the hypothalamic-pituitary-adrenal axis [56].

Out of the five functioning scales, we observed the strongest association with all-cause mortality for physical functioning (HR: 0.80; 95% CI: 0.75-0.86) which might be due to the fact that physical functioning is the most affected by bodily health and fitness which is related to morbidity and mortality [57]. The strong associations between nausea/vomiting and appetite loss and survival could be due to malnutrition, cachexia, or weight loss leading to increased morbidity and mortality [58-60]. Furthermore, fatigue which was also significantly associated with mortality in our cohort has been shown to be associated with mortality even in the general population [61].

Strengths and limitations

Strengths of our study include the large sample size, the prospective design regarding survival analyses with a long follow-up period (median, 7 years), and the validated

ascertainment of vital status. Furthermore, HRQOL was assessed with one of the most widely used cancer-specific instruments (EORTC QLQ-C30).

However, there are some limitations that should be noted. Our analyses on correlates of HRQOL were cross-sectional, precluding causal inferences. Furthermore, we did not have information on comorbidities although it is likely that HRQOL as well as survival are affected by certain comorbidities. Additionally, we only had information available on all-cause mortality, but not on disease-specific mortality. Also, information on tumor stage was not available in our cohort. We only had information on metastases and other cancers. Interestingly, a recent review reported inconclusive results regarding the association between tumor stage and HRQOL [62]. Furthermore, HRQOL was assessed only once in our cohort, so that we were not able to analyze changes of HRQOL over time. The data on clinical and lifestyle factors were based on self-report, which is why we cannot completely exclude the possibility of recall bias. However, the validation of self-reported clinical data against medical records in a subset of 181 patients revealed a concordance of about 87%.

Conclusions

The HRQOL in CRC survivors seems to be relatively high in the long term. Sex, age, education, tumor location, metastases, other cancers, type of therapy, and current stoma were associated with overall HRQOL (summary score and global QOL) and with different HRQOL scales. Furthermore, lower HRQOL was associated with increased all-cause mortality among CRC long-term survivors. Therefore, it is important to monitor HRQOL in long-term CRC survivors, particularly since various intervention programs, like physical activity interventions, educational programs, and psychotherapeutic interventions, might be helpful to further improve HRQOL [10]. Identifying risk factors for HRQOL deterioration may enable a better individualized care of CRC survivors. Thus, randomized controlled trials are needed to bring light into the causal relationship of clinical and sociodemographic, as well as lifestyle, determinants with HRQOL. Special support may be needed for individuals who have multiple risk factors for poor HRQOL.

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Declarations

Ethics approval and consent to participate: The study protocol was approved by the institutional ethics committee of the Medical Faculty of Kiel University and written informed consent was obtained from all study participants.

Competing interests: The authors declare that they have no competing interest.

Funding: RdG is supported by the Deutsche Forschungsgemeinschaft Excellence Cluster “Inflammation at Interfaces” (grants EXC306 and EXC306/2). The funding sources had no role in the design and conduct of the study.

Table 1 Characteristics of the total sample of 1294 CRC long-term survivors and according to an HRQOL summary score below or at/above the median

Participant characteristics	Total sample	Summary score < median	Summary score ≥ median
Total no. of individuals, n	1294	647	647
No. of deaths, n (%)	175 (14)	117 (18)	58 (9)
Sex, n (%)			
Men	740 (57)	362 (56)	378 (58)
Women	554 (43)	285 (44)	269 (42)
Age at diagnosis, y	62 (56-66)	62 (56-66)	61 (57-65)
Age at HRQOL assessment, y	69 (64-73)	69 (63-74)	69 (64-73)
Time between CRC diagnosis and HRQOL assessment, y	6 (5-8)	6 (5-8)	6 (5-8)
BMI, kg/m²	26.2 (23.9-29.2)	26.4 (24.0-29.4)	26.0 (23.7-28.9)
Physical activity, MET-hours/week	101 (65-149)	102 (64-144)	100 (66-152)
Education, n (%)			
Low	597 (46)	311 (48)	286 (44)
Middle	393 (30)	196 (30)	197 (30)
High	292 (23)	135 (21)	157 (24)
Unknown	12 (1)	5 (1)	7 (1)
Family status, n (%)			
Single	52 (4)	27 (4)	25 (4)
Married or in a partnership	991 (77)	482 (75)	509 (79)
Divorced	65 (5)	37 (6)	28 (4)
Widowed	147 (11)	76 (12)	71 (11)
Unknown	39 (3)	25 (4)	14 (2)
Smoking status, n (%)			
Never	509 (39)	238 (37)	271 (42)
Former	649 (50)	342 (53)	307 (47)
Current	116 (9)	56 (9)	60 (9)
Unknown	20 (2)	11 (2)	9 (1)
Tumor location, n (%)			
Colon	613 (47)	278 (43)	335 (52)
Rectum	552 (43)	293 (45)	259 (40)
Both	58 (4)	39 (6)	19 (3)
Unknown	71 (5)	37 (6)	34 (5)
Metastases, n (%)			
Yes	209 (16)	124 (19)	85 (13)
No	872 (67)	429 (66)	443 (68)
Unknown	213 (16)	94 (15)	119 (18)
Other Cancer, n (%)			
Yes	270 (21)	154 (24)	116 (18)
No	997 (77)	482 (75)	515 (80)
Unknown	27 (2)	11 (2)	16 (2)
Therapy, n (%)			
None	681 (53)	319 (49)	362 (56)
Chemotherapy	285 (22)	135 (21)	150 (23)
Radiation	40 (3)	21 (3)	19 (3)
Chemotherapy and radiation	268 (21)	164 (25)	104 (16)
Unknown	20 (2)	8 (1)	12 (2)

Table 1 (continued)

Participant characteristics	Total sample	Summary score < median	Summary score ≥ median
Current Stoma, n (%)			
Yes	151 (12)	89 (14)	62 (10)
No	1130 (87)	551 (85)	579 (89)
Unknown	13 (1)	7 (1)	6 (1)

Values are n (%) or median (interquartile range).

Abbreviations: BMI, body mass index; CRC, colorectal cancer; HRQOL, health-related quality of life; MET, metabolic equivalent of task.

Table 2 Median and IQR for the HRQOL summary score and its scales and symptom prevalence (defined as percent of individuals with any symptoms of the respective scale) among 1294 CRC long-term survivors

QLQ-C30 Scales	Median (IQR)	Symptom prevalence
Summary score	87.3 (75.3 - 94.4)	
Global QOL	75.0 (58.3 - 83.3)	
Functioning scales		
Physical functioning	86.7 (73.3 – 100)	
Role functioning	100 (66.7 – 100)	
Emotional functioning	83.3 (66.7 – 100)	
Cognitive functioning	83.3 (66.7 – 100)	
Social functioning	100 (66.7 – 100)	
Symptom scales		
Fatigue	22.2 (0 - 33.3)	70 %
Nausea and vomiting	0 (0 – 0)	12 %
Pain	0 (0 - 33.3)	44 %
Dyspnea	0 (0 - 33.3)	38 %
Insomnia	33.3 (0 - 33.3)	52 %
Appetite loss	0 (0 – 0)	14 %
Constipation	0 (0 – 0)	24 %
Diarrhea	0 (0 - 33.3)	36 %
Financial difficulties	0 (0 – 0)	23 %

Abbreviations: CRC, colorectal cancer; HRQOL, health-related quality of life; IQR, interquartile range; QLQ-C30, Quality of Life Questionnaire Core 30; QOL, quality of life.

Table 3 ORs[a] and 95% CIs for low (defined as values below the scale-specific median) HRQOL scales according to sociodemographic and clinical characteristics in CRC survivors (n=1294) from cross-sectional analyses

	n	Summary score <median	Global QOL <median	Physical functioning scale <median	Role functioning scale <median	Emotional functioning scale <median	Social functioning scale <median	Cognitive functioning scale <median
Characteristics		**OR (95% CI)[b]**	**OR (95% CI)[b]**	**OR (95% CI)[b]**	**OR (95% CI)[b]**	**OR (95% CI)[b]**	**OR (95% CI)[b]**	**OR (95% CI)[b]**
Sex								
Male	740	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
Female	554	1.19 (0.94-1.51)	0.95 (0.75-1.21)	**1.65 (1.29-2.11)**	0.96 (0.75-1.22)	1.01 (0.80-1.27)	**0.61 (0.48-0.78)**	**0.78 (0.62-0.99)**
Age, years								
< 60	192	1.31 (0.93-1.86)	1.21 (0.85-1.71)	0.85 (0.60-1.21)	1.21 (0.85-1.72)	1.38 (0.98-1.96)	**1.46 (1.02-2.10)**	1.19 (0.85-1.68)
60-69	520	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
70-79	479	1.21 (0.94-1.57)	1.20 (0.93-1.56)	**1.70 (1.31-2.22)**	1.15 (0.89-1.49)	0.97 (0.75-1.25)	0.77 (0.59-1.01)	**1.29 (1.00-1.66)**
≥ 80	103	**1.58 (1.00-2.49)**	**1.85 (1.15-2.96)**	**3.91 (2.34-6.52)**	**2.07 (1.30-3.29)**	0.89 (0.57-1.39)	**0.58 (0.36-0.94)**	**1.85 (1.17-2.91)**
Education								
Low	597	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
Middle	393	0.99 (0.76-1.30)	**0.68 (0.52-0.89)**	0.96 (0.73-1.26)	0.95 (0.73-1.25)	0.95 (0.73-1.23)	1.09 (0.82-1.43)	1.04 (0.80-1.35)
High	292	0.86 (0.64-1.16)	**0.58 (0.43-0.78)**	**0.67 (0.49-0.91)**	0.87 (0.64-1.17)	0.89 (0.66-1.19)	0.75 (0.55-1.02)	0.79 (0.59-1.06)

Table 3 (continued)

	n	Summary score <median	Global QOL <median	Physical functioning scale <median	Role functioning scale <median	Emotional functioning scale <median	Social functioning scale <median	Cognitive functioning scale <median
Family status								
Single	52	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
Married/in partnership	991	0.96 (0.54-1.72)	0.87 (0.49-1.57)	0.73 (0.40-1.34)	0.86 (0.48-1.54)	0.98 (0.55-1.74)	1.14 (0.63-2.09)	1.16 (0.65-2.07)
Divorced	65	1.35 (0.63-2.89)	0.98 (0.46-2.09)	0.99 (0.45-2.18)	0.97 (0.45-1.08)	0.97 (0.46-2.05)	1.09 (0.49-2.41)	1.21 (0.57-2.55)
Widowed	147	0.97 (0.50-1.89)	1.14 (0.58-2.24)	0.67 (0.33-1.37)	0.82 (0.42-1.60)	0.94 (0.49-1.82)	1.02 (0.51-2.06)	1.38 (0.71-2.67)
Tumor location								
Colon	613	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
Rectum	552	1.11 (0.84-1.45)	1.02 (0.77-1.33)	**1.33 (1.01-1.76)**	1.28 (0.98-1.69)	1.03 (0.79-1.35)	**1.41 (1.07-1.86)**	0.90 (0.68-1.17)
Both	58	**1.95 (1.08-3.54)**	1.48 (0.82-2.68)	1.39 (0.77-2.53)	1.23 (0.69-2.19)	0.83 (0.47-1.45)	1.19 (0.66-2.16)	1.14 (0.65-2.02)
Metastases								
No	872	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
Yes	209	**1.43 (1.02-2.01)**	1.11 (0.79-1.55)	1.29 (0.91-1.83)	1.04 (0.74-1.46)	1.14 (0.81-1.59)	**1.47 (1.03-2.10)**	1.33 (0.95-1.86)

Table 3 (continued)

	n	Summary score <median	Global QOL <median	Physical functioning scale <median	Role functioning scale <median	Emotional functioning scale <median	Social functioning scale <median	Cognitive functioning scale <median
Other Cancer								
No	997	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
Yes	270	**1.39 (1.05-1.85)**	**1.38 (1.03-1.83)**	1.32 (0.99-1.77)	**1.38 (1.04-1.84)**	1.03 (0.78-1.37)	**1.60 (1.20-2.15)**	**1.35 (1.02-1.79)**
Therapy								
None	681	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
Chemotherapy	285	0.90 (0.66-1.23)	1.03 (0.75-1.40)	1.13 (0.82-1.56)	1.07 (0.78-1.47)	0.90 (0.66-1.23)	1.21 (0.88-1.68)	0.93 (0.68-1.27)
Radiation	40	1.02 (0.52-1.99)	1.59 (0.79-3.20)	0.89 (0.44-1.82)	0.89 (0.45-1.76)	0.66 (0.34-1.29)	1.74 (0.87-3.50)	0.75 (0.38-1.46)
Chemotherapy + Radiation	268	**1.56 (1.11-2.18)**	**1.57 (1.12-2.20)**	0.96 (0.68-1.35)	**1.62 (1.16-2.27)**	1.04 (0.74-1.45)	**2.33 (1.64-3.31)**	1.33 (0.96-1.85)
Current stoma								
No	1130	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
Yes	151	1.11 (0.76-1.62)	1.30 (0.88-1.92)	**2.13 (1.42-3.20)**	**1.87 (1.27-2.77)**	**1.46 (1.00-2.14)**	**2.44 (1.60-3.71)**	1.03 (0.71-1.50)

[a] Calculated with a multivariable-adjusted logistic regression model.

[b] Adjusted for sex, age at HRQOL assessment, BMI, physical activity, tumor location, metastases, other cancer, therapy, and stoma; except the exposure variable of interest.

Abbreviations: BMI, body mass index; CI, confidence interval; CRC, colorectal cancer; HRQOL, health-related quality of life; MET, metabolic equivalent hours of task; OR, odds ratio; QOL, quality of life; Ref, reference.

Table 4 HRs[a] and 95% CIs of all-cause mortality per 10-point-increments of QLQ-C30 scales in CRC survivors (n=1294)

	Age- & sex-adjusted HR (95% CI)	**Multivariable-adjusted[b] HR (95% CI)**
Summary score[c]	0.76 (0.70-0.82)	0.76 (0.70-0.82)
Global QOL[c]	0.80 (0.75-0.85)	0.80 (0.75-0.86)
Functioning Scales[c]		
Physical Functioning	0.78 (0.74-0.83)	0.80 (0.75-0.86)
Role Functioning	0.86 (0.82-0.90)	0.87 (0.83-0.91)
Emotional Functioning	0.89 (0.84-0.94)	0.88 (0.83-0.94)
Social Functioning	0.86 (0.82-0.90)	0.87 (0.83-0.92)
Cognitive Functioning	0.94 (0.88-1.01)	0.95 (0.88-1.02)
Symptom Scales[d]		
Pain	1.11 (1.06-1.16)	1.11 (1.05-1.16)
Nausea/Vomiting	1.32 (1.21-1.44)	1.31 (1.19-1.43)
Fatigue	1.21 (1.15-1.27)	1.20 (1.13-1.26)
Insomnia	1.08 (1.03-1.13)	1.08 (1.03-1.13)
Dyspnea	1.15 (1.10-1.20)	1.13 (1.08-1.19)
Appetite Loss	1.19 (1.12-1.27)	1.18 (1.10-1.25)
Constipation	1.08 (1.03-1.14)	1.09 (1.03-1.15)
Diarrhea	1.02 (0.97-1.08)	1.03 (0.97-1.09)
Financial Difficulties	1.09 (1.03-1.15)	1.07 (1.01-1.13)

Values were calculated for a 10-point-increment in scales.

[a] Calculated with Cox proportional hazards regression model.

[b] Adjusted for sex, age at HRQOL assessment, BMI, physical activity, tumor location, time from diagnosis until HRQOL assessment, type of therapy, metastases, other cancer, current stoma, education, family status, smoking status, and (age x time).

[c] Higher scores of the summary score, the global QOL, and the functioning scales indicate a higher HRQOL or a higher functioning.

[d] Higher scores of the symptom scales indicate a higher extent of symptoms.

Abbreviations: BMI, body mass index; CI, confidence interval; CRC, colorectal cancer; HR, hazard ratio; QLQ-C30, quality of life questionnaire core 30; QOL, quality of life.

Table 5 HRs[a] and 95% CIs of all-cause mortality for a 10-point-increment in HRQOL summary score among CRC survivors (n=1294); stratified by potential effect modifiers

Potential effect modifiers	Total no. of individuals	No. of deaths	Age- & sex-adjusted HR (95% CI)	Multivariable-adjusted[b] HR (95% CI)	$p_{interaction}$[c]
Sex					
Men	740	126	0.74 (0.68-0.81)	0.74 (0.66-0.82)	
Women	554	49	0.78 (0.69-0.90)	0.75 (0.65-0.87)	0.40
Age at HRQOL assessment, years[d]					
<69	626	50	0.78 (0.67-0.91)	0.87 (0.74-1.03)	
≥69	668	125	0.73 (0.67-0.80)	0.72 (0.65-0.80)	0.75
BMI, kg/m²					
<25	497	72	0.69 (0.61-0.77)	0.66 (0.58-0.76)	
25-<30	558	75	0.78 (0.69-0.88)	0.82 (0.71-0.94)	
≥30	239	28	0.81 (0.68-0.97)	0.77 (0.61-0.98)	0.19
Education					
Low	597	96	0.78 (0.71-0.87)	0.79 (0.71-0.88)	
Middle	393	44	0.81 (0.69-0.96)	0.80 (0.66-0.97)	
High	292	34	0.60 (0.50-0.71)	0.57 (0.45-0.71)	0.03
Family status					
Married/in partnership	991	127	0.76 (0.69-0.84)	0.77 (0.69-0.85)	
Single, divorced or widowed	264	43	0.74 (0.63-0.87)	0.75 (0.63-0.89)	0.86
Smoking status					
Never	509	53	0.80 (0.69-0.93)	0.80 (0.68-0.94)	
Former	649	105	0.74 (0.67-0.82)	0.73 (0.65-0.81)	
Current	116	14	0.78 (0.60-1.03)	0.72 (0.47-1.09)	0.23
Tumor location					
Colon	613	72	0.76 (0.67-0.87)	0.78 (0.69-0.89)	
Rectum	552	84	0.77 (0.69-0.86)	0.76 (0.67-0.86)	0.15
Therapy					
None	681	95	0.68 (0.61-0.75)	0.67 (0.59-0.76)	
Chemotherapy or radiation	325	47	0.87 (0.75-1.00)	0.86 (0.72-1.03)	
Both	268	31	0.80 (0.66-0.96)	0.89 (0.72-1.10)	0.02
Metastases					
Yes	209	50	0.76 (0.66-0.89)	0.80 (0.68-0.94)	
No	872	95	0.77 (0.69-0.85)	0.76 (0.67-0.85)	0.88
Current stoma					
Yes	151	30	0.70 (0.58-0.85)	0.57 (0.43-0.76)	
No	1130	145	0.78 (0.71-0.85)	0.79 (0.72-0.86)	0.08

[a] Calculated with Cox proportional hazards regression model.

[b] Adjusted for sex, age at HRQOL assessment, BMI, physical activity, tumor location, time from diagnosis until HRQOL assessment, therapy, metastases, other cancer, current stoma, education, family status, smoking status, and (age x time); except the stratifying variable.

[c] Calculated by including the cross product of the summary score and the respective potential effect modifier in the Cox proportional hazards regression model.

[d] Cut-point based on median value.

Abbreviations: BMI, body mass index; CI, confidence interval; CRC, colorectal cancer; HR, hazard ratio; HRQOL, health-related quality of life.

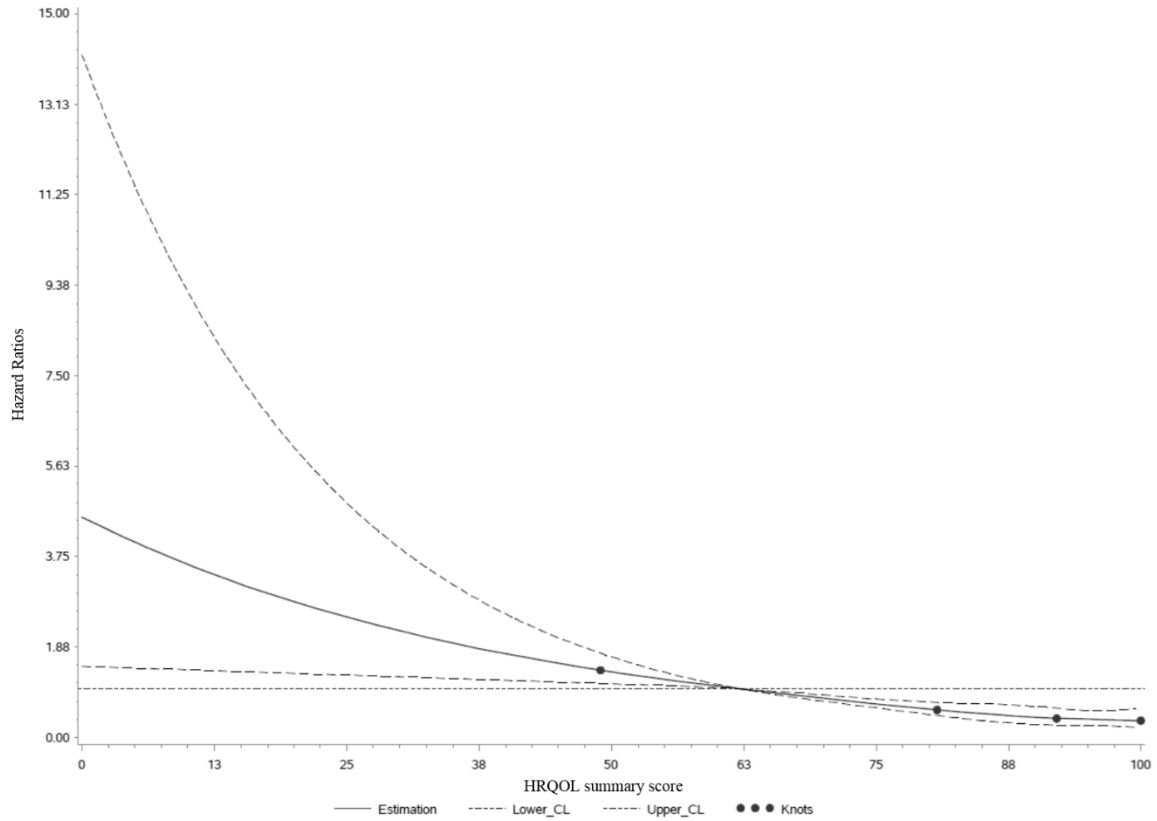

Figure 1 Multivariable-adjusted hazard ratios for all-cause mortality according to the HRQOL summary score in CRC survivors (n=1294), calculated with restricted cubic spline regression. The solid line depicts hazard ratios and the dashed lines are the 95% CIs. The points indicate the knots at the 5th, 35th, 65th, and 95th percentiles. The reference value is the median (62.4 score points) of the first quartile of the summary score. The model was adjusted for sex, age at HRQOL assessment, BMI, physical activity, survival time from CRC diagnosis until HRQOL assessment, tumor location, occurrence of metastases, occurrence of other cancer, therapy, education, family status, and smoking status. The p value for overall association is <0.0001 and the p value for nonlinearity is 0.87 (Wald chi-square test). Abbreviations: BMI, body mass index; CRC, colorectal cancer; HRQOL, health-related quality of life.

5 General discussion

As the group of individuals surviving CRC is constantly growing, lifestyle factors and QOL after CRC diagnosis are becoming increasingly important. This doctoral thesis systematically assessed the association of specific dietary patterns, physical activity, and HRQOL several years after diagnosis with all-cause mortality in CRC long-term survivors. Furthermore, the HRQOL status and important clinical and sociodemographic correlates of HRQOL in long-term survivors of CRC were evaluated. The results of this thesis were presented in three articles. The main observations were as follows:

I) Stronger adherence to the Modified Mediterranean diet was associated with better overall survival, even after accounting for relevant potential clinical and sociodemographic confounders. Also, the healthy Nordic Food Index was inversely associated with all-cause mortality when modeled as a continuous variable, even though quartiles of the healthy Nordic Food Index slightly failed to reveal a statistically significant association.

II) More postdiagnostic total physical activity was associated with significantly lower all-cause mortality as compared to less physical activity. Regarding individual types of physical activity, sports, walking, and gardening were particularly strongly inversely related to all-cause mortality. A greater amount of sleeping during the day was associated with shorter survival, whereas the amount of sleep at night was not associated with survival. More hours per day spent watching TV were associated with a higher all-cause mortality in this CRC survivor cohort.

III) The HRQOL generally seemed to be relatively high in CRC survivors approximately (median) 6 years after diagnosis. On average, the highest functioning was reported for role and social functioning. Fatigue and insomnia represented the symptoms with the highest extent out of nine symptom scales.

IV) Sex, age, education, tumor location, metastases, other cancers, type of therapy, and a current stoma were identified as sociodemographic and clinical correlates of overall HRQOL and of different HRQOL scales.

V) The summary score and the global QOL as well as nearly all functioning and symptom scales were statistically significantly associated with all-cause mortality in the sense that higher HRQOL and better functioning were associated with better overall survival and more symptoms were related to worse overall survival. Out of the functioning scales, physical functioning displayed the strongest positive association with HRQOL whereas cognitive functioning was not statistically significantly associated. Of the nine symptom scales, diarrhea was not related to all-cause mortality while fatigue, nausea/vomiting, and appetite loss revealed the strongest association with survival.

5.1 Extension of previous knowledge

In view of the fact that analyses on postdiagnostic dietary factors related to CRC survival were largely limited to nutrients, single foods, or food groups, and that dietary pattern analyses are scarce, this doctoral thesis adds to the previous knowledge by providing initial evidence for a positive association between two established dietary patterns (the Mediterranean diet and the healthy Nordic diet) and overall survival in CRC survivors. While the healthy Nordic diet has been examined for the first time with respect to its association with mortality after CRC diagnosis in this thesis, the Mediterranean diet (adopted for the American population) was obtained postdiagnostically and tested in relation to survival among CRC patients in one prior analysis [1]. In that study, also an inverse association with mortality was observed, but statistical significance could not be reached. However, this study assessed diet much earlier after diagnosis (median, 21 months) [1] as compared to the study of this thesis (median, 6 years).

With respect to physical activity, this thesis expands the existing evidence by showing that the positive association between physical activity and overall survival, already shown for physical activity earlier after diagnosis [2-4], also applies to long-term survivors (≥5 years) of CRC. Additionally, this thesis investigated for the first time the association of different types of postdiagnostically assessed physical activity with mortality in CRC survivors and revealed significant associations with survival primarily for sports, walking, and gardening. Furthermore, a higher amount of sedentary time (sleeping at day, watching TV) was significantly inversely associated with all-cause mortality. In two prior studies, more hours of TV viewing were also related to higher mortality, though not statistically significant [5, 6].

The relatively high HRQOL status of the present CRC survivor cohort confirms the findings of previously conducted studies [7-12]. The results regarding sociodemographic correlates of HRQOL were partially concordant (e.g. for age, education) [13-15] and partially

inconsistent (e.g. for sex, family status) [13-18] with prior studies. In terms of clinical correlates of HRQOL, for tumor location, differing results were observed in previous studies, partly supporting the findings of this thesis [19] and partly disagreeing [14, 15]. Likewise, for treatment modalities, some study results were similar [20, 21] to this thesis' findings whereas some studies found different associations [19, 22]. Previously, a more advanced disease stage, which likely includes the occurrence of metastases and other cancers, was associated with worse HRQOL [15, 17-19]. The majority of studies on stoma construction in relation to HRQOL were in accordance with the findings of this doctoral thesis, suggesting a lower HRQOL in individuals with a stoma [19, 23, 24].

Several studies provided some evidence for an association between a higher HRQOL and improved CRC survival as compared to a lower HRQOL, but these studies assessed HRQOL primarily rather shortly after CRC diagnosis or even before initiation of cancer therapy and some of them focused on patients with advanced cancer stage [15, 25-30]. Thus, this thesis extends the previous knowledge by revealing that the association between HRQOL and CRC survival is also present in long-term survivors of CRC, which, so far, has only been suggested in one prior study [14].

5.2 Implications for public health

While comprehensive guidelines for clinical practice regarding diagnosis and treatment of cancer exist, evidence-based clinical guidelines for posttreatment survivorship care are scarce. The increasing number of cancer survivors is challenging oncologists and primary care clinicians by demanding specified follow-up care [31, 32]. Physical activity and nutritional assessment and intervention are not traditional parts of cancer treatment and survivorship programs [33-35]. However, especially in the phase of long-term disease-free living or stable disease, an important focus should be on lifestyle goals like weight management, a healthy diet, and being physically active [36, 37]. Moreover, the knowledge of lifestyle factors after diagnosis that have an influence on cancer survival is particularly promising because cancer survivors are theoretically able to actively modify their behavior after diagnosis in order to improve cancer outcome, target comorbidities, and enhance general health [38-41]. Additionally, cancer survivors wish to have a more active role in their health care after diagnosis and are eager to know which lifestyle changes they should carry out [36, 42, 43].

Dietary patterns

This doctoral thesis was able to show that a higher adherence to the Mediterranean diet and to the healthy Nordic diet, respectively, were beneficially associated with overall survival in CRC long-term survivors. In the last decades, even apart from the Mediterranean countries where the Mediterranean diet has its origins, the Mediterranean dietary pattern has gained enormous popularity and implementation also in other regions like the US and Northern and Western Europe and is recommended by Health Services as a healthy diet choice [44, 45]. Besides its effect on cancer incidence and cancer mortality, the Mediterranean diet is also associated with a decline in total mortality and cardiovascular mortality in the general population [46, 47]. Frequently, nutritional scientists are discussing whether the traditional Mediterranean diet is implementable in Non-Mediterranean countries [48, 49]. Especially the high amount of monounsaturated fatty acids is suggested to be responsible for a large proportion of the health-promoting effect of the Mediterranean diet [49] and in Non-Mediterranean countries, the diet usually contains higher amounts of polyunsaturated than of monounsaturated lipids [50, 51]. However, alternatively to olive oil which is rich in polyunsaturated fatty acids and traditionally used in Mediterranean countries, it is also reasonable to advise patients or individuals to use canola oil or canola oil-based margarine, which is more common in Western Europe and Northern America, in addition to other Mediterranean foods like nuts and fatty fish to reproduce the fatty acid profile that is characteristic of the Mediterranean population [52]. Thus, modifications that keep the advantageous effects of the traditional dietary pattern are feasible [50].

Apart from the Mediterranean diet, evidence on the beneficial impact of the healthy Nordic diet indicate that the potential positive aspects of the traditional Nordic diet are not to be neglected [53-57]. Hence, the healthy Nordic diet might be a promising dietary pattern for health promotion especially for Northern German people, as represented in the cohort of this thesis, but as well for other Northern European and Northern American populations [53]. The healthy Nordic diet might be easier to implement and may be more sustainable because of its stronger familiarity and cultural acceptance in the Northern area as compared to the Mediterranean diet [53, 54]. In general, it might be reasonable to promote regional diets, like the healthy Nordic diet in Northern Europe, in order to enhance health and decrease disease burden, because this approach may increase the people’s compliance [58].

Physical activity promotion

During the last years, evidence has been growing that physical activity is not just beneficial in terms of survival, but that it is also safe and well-accepted by cancer patients during and after treatment [59, 60]. Additionally, exercise contributes to an increase in quality of life and to improvements of physical functioning among cancer survivors [61-65]. Moreover, physical activity also reduces cancer-related fatigue [66, 67]. In general, physical activity might be an attractive strategy to help preventing cancer recurrence and to prolong life in cancer survivors as it is likely to also substantially reduce the risk for many other diseases which accumulatively appear in cancer survivors, especially in the elderly, including coronary heart disease, stroke, type 2 diabetes, and dementia [68-70]. Furthermore, the Physical Exercise Across the Cancer Experience framework [71] suggests that physical activity contributes to the attenuation of adverse treatment effects and to coping with treatment during the immediate therapeutic phase.

Thus, the accumulating available evidence of numerous studies indicates that it is reasonable to encourage CRC survivors to be regularly physically active and to minimize TV viewing time. Some types of physical activity, as for example sports, lower-intensity activities like walking, and diverse activities like gardening, might have a stronger inverse association with mortality than other activities but more studies are needed to confirm these findings. Of note, cancer survivors, especially CRC survivors, are mostly of higher age because colon and rectum carcinomas are most frequently diagnosed in persons at the age of around 70 years [72, 73]. In this age group, physical activity can induce a lot of advantages in health, QOL, and social life but might also represent a practical challenge for some individuals due to age-related limitations or comorbidities [74-76]. Therefore, physical activity interventions and recommendations should always be individually adapted to every person’s preferences and physical abilities.

Lifestyle recommendations and interventions

The findings of this doctoral thesis, together with those of previous investigations and with results of future studies might be helpful to develop evidence-based lifestyle recommendations for cancer survivors. Such recommendations for cancer survivors would represent an important basis for physicians and other health professionals to guide cancer survivors towards optimal lifestyle choices [36]. However, before evidence-based recommendations can be issued, interventional studies need to demonstrate in a

randomized controlled setting that specific modifications in diet and physical activity indeed improve HRQOL and survival in long-term CRC survivors.

However, it might be necessary to also implement active support (e.g., supervised exercise programs, nutrition counseling) for CRC survivors, instead of only publishing recommendations, in order to improve lifestyle behavior because initiating and maintaining lifestyle changes without support may be a huge barrier to overcome for some affected individuals [36, 77]. Studies revealed that only 20-30% of cancer survivors will be physically active after recovery from treatment [78]. Furthermore, it might be beneficial to involve family members to provide more social support and to assist the cancer survivor in changing lifestyle behaviors [77]. CRC survivors also reported the wish to receive information about potential lifestyle support early after diagnosis to make autonomous and informed decisions during active treatment [77]. Thus, lifestyle recommendations and support should be routinely offered by oncology health care professionals to enable CRC survivors improving their lifestyle through informed decision making [77].

A randomized controlled trial in CRC patients reported that early individualized nutritional counseling and education had a long-term effect on cancer outcomes (e.g., survival), as well as on sustained nutritional intake, diet behavior, and QOL [79]. A similar randomized controlled trial was conducted focusing on physical activity. Patients who received an oncologist's exercise recommendation with an additional exercise motivation package significantly increased their level of exercise participation as compared with a group of patients only receiving the oncologist's exercise recommendation without a motivation package and compared with a control group without an intervention [80].

Health-related quality of life surveillance

Despite the fact that CRC survivors usually report a relatively high HRQOL, there is a wide range of factors (clinical, sociodemographic, lifestyle) that can potentially be targeted to further improve HRQOL in these individuals, especially in view of the fact that decreased HRQOL is associated with worse survival. Assessment of HRQOL in CRC survivors might provide insight into the individuals' experiences of the disease, therapy, and recovery and helps to identify risk factors of a low HRQOL [13, 81, 82]. Identifying risk factors for HRQOL deterioration may enable a better individualized care of CRC survivors, particularly among vulnerable subgroups of survivors. In addition to the assessment of HRQOL in clinical trials, the surveillance of HRQOL in clinical practice can reveal important information on disease

burden and physical and psychosocial detriments of cancer survivors. Therefore, it is important to monitor HRQOL early and regularly over a long period in CRC survivors [82].

Additionally, the findings of this doctoral thesis suggest that low levels of HRQOL identify CRC survivors with a higher risk of dying. To target physical and psychosocial deteriorations and to further improve HRQOL, various intervention programs, like physical activity interventions, educational programs, psychosocial interventions, and self-help groups, could be helpful and valuable. Educational programs might help to enhance cancer-related knowledge and, thus, improve emotional dealing with the disease and its treatment. Psychotherapeutic interventions may include support in emotional expression, increasing personal resources, improving coping skills, and regaining control in everyday life [82].

5.3 Methodological considerations

5.3.1 Survival analyses

Survivorship bias

The analyses of this doctoral thesis might be prone to survivorship bias because individuals with a generally higher risk of dying (e.g., with a more advanced cancer stage at diagnosis) might not have been included in the analyses as they might have died before exposure assessment (median, 6 years after diagnosis). On the one hand, this could lead to an overestimation of the benefit from being exposed [83]. On the other hand, it might be questionable whether or not the mortality of this CRC survivor cohort is still related to the former cancer disease. However, the objective of this thesis was to examine '*long-term*' survival after CRC diagnosis (in relation to lifestyle factors and HRQOL), and in the case of mortality of *long-term* cancer survivors it is less important whether these individuals die from cancer than, rather, when they will die (from any cause). Long-term cancer survivors are a special group of individuals characterized by their history of a cancer disease that, in the majority of cancer survivors, has a significant influence on their physical and psychological health for the rest of their lives.

All-cause vs. cause-specific mortality

Within this thesis, vital status of study participants was ascertained by requesting information on current residencies or, if a participant had deceased, date of death at the local population registries. Thus, only date of death (mortality from all causes), but no

causes of deaths were available for the survival analyses. Therefore, analyses on cause-specific, for example cancer-specific, mortality could not be conducted. However, since long-term cancer survivors have a higher incidence of other chronic disease conditions, mostly due to disease- and treatment-related effects, deaths of other causes than cancer-related ones are of essential importance. Long-term cancer survivors with high cancer-related survival rates often die of cardiovascular diseases instead of their cancer disease [84, 85]. In addition, cancer survivors have a higher risk of non-cancer deaths than age-standardized general population controls [85, 86]. When examining cancer-related mortality, only directly cancer-caused deaths are considered, whereas other deaths that are indirectly caused by the cancer (cancer-consequent; e.g., cardiovascular diseases induced by chemotherapy) are neglected [87, 88]. As a consequence, the total effect of the exposing factors may be underestimated.

Furthermore, the accuracy of analyses using disease-specific mortality depends on the correct adjudication of the cause of death (accuracy of death certificates) [87] which has been shown to be often unreliable and may introduce bias [88-90]. The clinical determination of the cause of death is a complex procedure that is susceptible to several sources of error [89]. All-cause mortality might, therefore, be a more reliable endpoint in scientific analyses [87].

Altogether, all-cause mortality is a hard and distinct endpoint [87] and it is likely to be the most relevant endpoint for cancer patients themselves. The cause of death might be important for the underlying pathology of death but for the patient it is more important whether to survive a period of time or not.

5.3.2 Exposure and covariate assessment

Physical activity

Although structured and validated questionnaires for the assessment of physical activity are widely established in epidemiological research [91, 92], self-reported physical activity is prone to recall and misclassification bias [93, 94]. It might, therefore, not be an entirely accurate and reliable measure for the amount and intensity of activities and, especially, for unstructured forms of activity (e.g., gardening and housework activities) [93, 95]. Alternatively, technical assessment tools, including accelerometry and pedometers, provide measurement methods that avoid these types of bias by objectively and technically measuring the duration and intensity of activities [96]. Thus, a combination of self-reported and objectively measured data might supply more precise and reliable information on

physical activity for analyses in research studies as compared to questionnaire-based assessment tools alone.

Disease stage

CRC can be divided into the following stages of disease: localized disease restricted to the bowel wall (stage I), regional disease spread through the bowel wall and to local organs (stage II) or spread to lymph nodes (stage III), and distant metastatic disease (stage IV) [37]. Disease prognosis is highly dependent on cancer stage. Stage I CRC has a 5-year survival rate of 90%, stage II and III diseases have a 5-year survival of 70%, and stage IV disease has a 5-year survival of 10% [37].

Unfortunately, in this cohort, data on cancer stage were not available. Therefore, the potential heterogeneity by disease stage in this sample could not have been considered as confounder in the survival analyses. However, because of the long survival time (median, 6 years) from CRC diagnosis until assessment of the exposure variables (diet, physical activity, HRQOL), the study participants were defined as 'long-term' cancer survivors and it is likely that most of the participants had a lower disease stage and a better general prognosis enabling them to survive until exposure assessment, which was essential for inclusion in the analyses. This argues for a rather homogenous study population in terms of cancer stage. Moreover, the analyses were adjusted for the occurrence of metastases or other types of cancer as well as for the type of adjuvant or neoadjuvant therapies which are factors that are associated with cancer staging and the severity of the disease [33, 37, 97, 98]. In addition, sensitivity analyses were conducted excluding I) individuals who reported a diagnosis of metastases or II) individuals who died within the first 12 months after exposure assessment.

Comorbidities

Comorbidities (coexisting diseases) are associated with poorer survival in cancer survivors, though they are not related to more advanced cancer stage or differences in tumor biology [99, 100]. Comorbidities are common in CRC survivors, probably because known risk factors for CRC (e.g., smoking, obesity, physical inactivity) are also risk factors for a range of other chronic disease conditions, such as cardiovascular disease [99, 100]. Especially in cancer patients with a generally good survival prognosis, the effect of comorbid diseases on mortality is relevant [99]. The data of the CRC survivor cohort, underlying this doctoral thesis, did not include comprehensive information on existing comorbidities. Therefore,

these potential confounders could not be considered in the multivariate analyses examining the association of lifestyle factors and HRQOL with survival in CRC survivors. Furthermore, the role of comorbidities as possible correlates of HRQOL could not be investigated, even though previous studies found evidence that HRQOL is affected by certain comorbidities [13, 18, 101].

5.4 Future research

To date, several studies provided evidence for significant associations of certain dietary factors and physical activity levels after diagnosis with CRC survival. However, the majority of research findings still need to be replicated in further studies with large sample sizes and comprehensive and validated exposure, covariate, and outcome assessment. More studies are warranted to examine lifestyle factors, including diet, physical activity, and sedentary behavior, as well as HRQOL among populations of long-term CRC survivors. In general, research on cancer survivorship issues should be further extended and encouraged in the future [102]. Examining the prevalence and burden of long-term and late effects of cancer disease and treatment is of high significance. This might be realizable by the expansion of national cancer registries with valid and complete data and a routine assessment of PRO data in these registries [103]. Generally, HRQOL studies with high methodological (e.g., prospective design) and reporting quality are warranted [102].

With respect to future research questions related to nutritional epidemiology in CRC survivors, a special focus should be on dietary pattern analyses to incorporate synergistic and antagonistic interactions of different nutrients and foods and to better depict the normal mixed diet [104, 105]. Regarding physical activity assessment, future studies examining type and intensity of physical activity with a combination of objective (e.g., accelerometry) and self-reported measures are needed. A longitudinal study on physical activity, fitness, and nutrition and its effect on quality of life, cancer recurrence, and survival in CRC survivors, using questionnaires, fitness tests, and accelerometry for physical activity assessment, is currently ongoing [106]. Additionally, more studies on the impact of different activity types on CRC survival are required to provide evidence for the development of specific activity recommendations. Future studies may also investigate how to introduce interventions to promote lifestyle factors in daily practice [102]. Another important aspect is the assessment of determinants of adherence to lifestyle recommendations in CRC survivors in order to address individual needs and to achieve sustainable lifestyle improvement in CRC survivors [77].

The majority of currently conducted studies, including the analyses of the present thesis, were observational and, thus, limited in their ability to evaluate causality. Hence, the current evidence calls for pilot intervention programs. Perspectively, more interventional studies like the current Norwegian randomized controlled food-based diet intervention, called the 'Norwegian Dietary Guidelines and Colorectal Cancer Survival study' [107], are needed to examine the effect of specific dietary factors on cancer outcome. Concerning physical activity interventions, a randomized controlled intervention program was recently started with the objective of examining the impact of a three-year physical activity program, beginning two to six months after completion of adjuvant therapy, on survival in CRC patients [108, 109]. Greater evidence on the utility of physical activity interventions in CRC survivors is expected from this trial. As well for HRQOL research in CRC survivors, more randomized controlled trials are needed to clarify whether modification of clinical and lifestyle characteristics ultimately improve patient outcomes, including HRQOL and survival.

5.5 Conclusion

As CRC diagnosis, treatment, and survival rates are improving, the issues and needs of long-term CRC survivors warrant special attention. To improve well-being and survival of these cancer survivors, lifestyle factors following diagnosis, like diet and physical activity, play an important role because cancer survivors are potentially able to actively modify these factors in their daily routine. In addition to prolongation of life, HRQOL is of huge importance for cancer survivors. Therefore, the identification and characterization of potential determinants of HRQOL are matters of increased research and public health interest. This doctoral thesis contributes to the current knowledge by revealing associations between higher adherence to a Mediterranean and to a healthy Nordic diet, respectively, with reduced all-cause mortality in CRC long-term survivors. Furthermore, the evidence regarding a significant relation between higher physical activity after diagnosis and improved survival was strengthened suggesting that particular types of activity (sports, walking, gardening) are primarily associated with mortality. Additionally, more time of physical inactivity was independently associated with a worse prognosis. The HRQOL status seemed to be relatively high in the long term in CRC survivors with several sociodemographic and clinical characteristics emerging as correlates of HRQOL after diagnosis. Nearly all domains of HRQOL were found to be associated with all-cause mortality in the sense that a higher HRQOL or better functioning was related to better survival whereas more symptoms were related to worse survival.

Further research is warranted to expand the evidence on dietary factors, physical activity, and HRQOL after CRC diagnosis in relation to overall survival in interventional studies or large prospective cohort studies. Nevertheless, the current evidence underscores the reasonableness of targeted lifestyle recommendations, interventions, and educational programs as well as psychological and psychosocial support for CRC long-term survivors. Therefore, dedicated survivorship care programs and screening modules are needed to be established in clinical routine and trained health professionals' work.

5.6 References

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6 Summary

Colorectal cancer (CRC) is one of the most common malignancies worldwide. Due to earlier diagnoses and more effective treatment strategies, the number of individuals surviving CRC is steadily growing. CRC survivors are highly interested in specific lifestyle recommendations to prevent disease recurrence and improve survival. Besides prolongation of life, health-related quality of life (HRQOL) of CRC survivors is a rising public health issue. This thesis evaluated the associations of defined dietary patterns, physical activity, and HRQOL, obtained on average 6 years after diagnosis, with mortality in CRC long-term survivors. In addition, the HRQOL status and correlates of HRQOL in long-term survivors of CRC were determined.

Specifically, within a prospective cohort study of initially recruited 2733 CRC survivors from Northern Germany, the associations of adherence to two *a priori*-defined dietary patterns, the Mediterranean diet and the healthy Nordic diet, with all-cause mortality were examined using Cox regression models. Furthermore, total physical activity, different types of physical activity, sleep duration at night and at day, and television (TV) watching hours were related to survival. In addition, the HRQOL status of long-term CRC survivors was determined and sociodemographic and clinical correlates of HRQOL in these individuals were identified with cross-sectional logistic regression analyses. Moreover, Cox regression analyses were performed to investigate the association between HRQOL and mortality.

A higher adherence to the Mediterranean and to the healthy Nordic dietary pattern was associated with reduced all-cause mortality, respectively. A higher amount of total physical activity, and specifically of sports, walking, and gardening activities was related to improved overall survival. More hours of sleep during the day and more hours of watching TV were associated with decreased survival. The HRQOL status of CRC survivors was relatively high. Sex, age, education, tumor location, metastases, other cancers, type of therapy, and a current stoma were statistically significant correlates of overall HRQOL and of different HRQOL domains. Higher HRQOL and better functioning was associated with lower all-cause mortality while more symptoms were associated with higher all-cause mortality.

Based on the existing evidence, it is reasonable to encourage CRC survivors to adhere to a healthy diet and to engage in regular physical activity. Future studies investigating lifestyle factors in relation to health outcomes in long-term (>5 years) survivors of CRC are warranted to further strengthen the evidence in order to develop specific lifestyle recommendations for long-term cancer survivors. The evaluation of HRQOL in CRC long-term survivors may enable the implementation of more targeted survivorship care programs.

7 Zusammenfassung

Das Kolorektale Karzinom (KRK) ist eine der häufigsten Krebserkrankungen weltweit. Aufgrund früherer Diagnosestellungen und effektiverer Therapieansätze steigt die Anzahl der KRK-Überlebenden kontinuierlich an. KRK-Überlebende haben ein großes Interesse an spezifischen Lebensstilempfehlungen, um ein erneutes Auftreten der Krebserkrankung zu verhindern und ihr Überleben zu verlängern. Darüber hinaus wird neben der Lebenszeitverlängerung auch die Lebensqualität von KRK-Überlebenden zu einem zunehmend relevanten Public Health-Thema. Die vorliegende Arbeit untersuchte die Assoziationen von definierten Ernährungsmustern, der körperlichen Aktivität und der Lebensqualität (je durchschnittlich 6 Jahre nach der Krebsdiagnose erhoben) mit der Gesamtmortalität von Langzeit-KRK-Überlebenden. Zudem wurden der Lebensqualitätsstatus und Korrelate der Lebensqualität von Langzeit-KRK-Überlebenden bestimmt.

Im Rahmen einer prospektiven Kohortenstudie mit anfänglich 2733 rekrutierten KRK-Überlebenden aus Norddeutschland wurden die Assoziationen zweier a priori-definierter Ernährungsmuster, der Mediterranen Ernährung und der gesunden nordischen Ernährung, mit der Gesamtmortalität mithilfe von Cox-Regressionen untersucht. Außerdem wurde die postdiagnostische körperliche Gesamtaktivität, verschiedene Arten der körperlichen Aktivität, die Schlafenszeit während des Tages und in der Nacht und die Zeit, die vor dem Fernseher verbracht wurde, im Zusammenhang mit der Gesamtmortalität analysiert. Darüber hinaus wurde der Lebensqualitätsstatus der Langzeit-KRK-Überlebenden ermittelt und soziodemographische und klinische Korrelate der Lebensqualität im Querschnittsdesign mithilfe von logistischen Regressionsanalysen identifiziert. Cox-Regressionsanalysen wurden eingesetzt, um die Assoziation zwischen der Lebensqualität und der Gesamtmortalität zu untersuchen.

Eine Ernährung, die sich stärker an der Mediterranen oder an der gesunden nordischen Ernährung orientierte, war mit einer geringeren Gesamtmortalität assoziiert. Ein höherer Umfang an körperlicher Gesamtaktivität und vor allem an Sport, Spazierengehen und Gartenarbeit zeigte ebenfalls eine Assoziation mit geringerer Gesamtmortalität. Längere Schlafenszeit am Tag und höherer Fernsehkonsum waren hingegen mit höherer Gesamtmortalität assoziiert. Die Lebensqualität der Langzeit-KRK-Überlebenden zeigte sich als relativ hoch. Geschlecht, Alter, Bildung, Tumorlokalisation, Metastasen, andere Krebserkrankungen, Therapieart und Stoma-Anlage wurden als statistisch signifikante Korrelate der Gesamt-Lebensqualität und verschiedener Lebensqualitätsbereiche identifiziert. Höhere Lebensqualität und bessere Funktionalität waren mit geringerer

Gesamtmortalität assoziiert, während stärkere Symptomatik mit höherer Gesamtmortalität assoziiert war.

Aufgrund der vorhandenen Evidenz ist es sinnvoll, KRK-Überlebende zu einer gesunden Ernährungsweise und regelmäßiger körperlicher Aktivität zu ermutigen. Zukünftige Studien sind notwendig, die Lebensstilfaktoren bei Langzeit-KRK-Überlebenden (>5 Jahre nach der Diagnose) in Zusammenhang mit dem Gesundheitszustand erforschen, um spezifische Lebensstilempfehlungen für Krebsüberlebende entwickeln zu können. Die Untersuchung der Lebensqualität von Langzeitkrebsüberlebenden könnte die Implementierung gezielter Gesundheitsprogramme für Krebsüberlebende ermöglichen.

8 Appendix

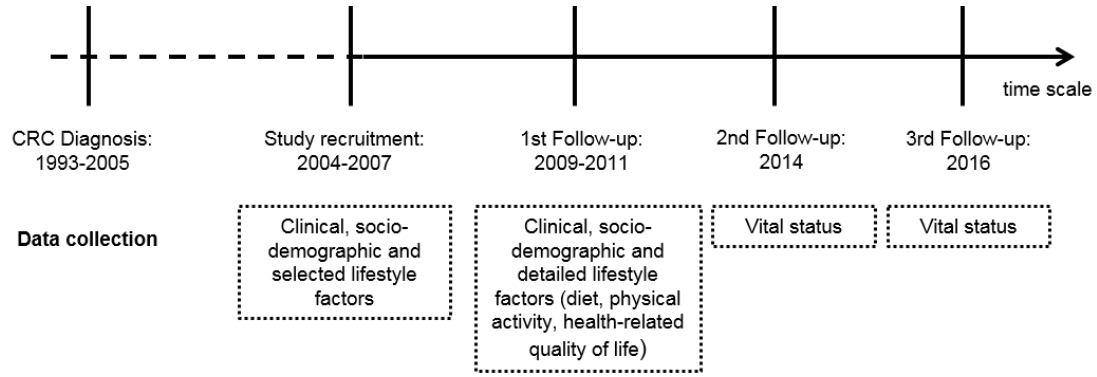

Figure 1. Study design of the PopGen colorectal cancer survivor cohort. Modified from [1].

1. Ratjen I, Schafmayer C, di Giuseppe R, Waniek S, Plachta-Danielzik S, Koch M, et al. *Postdiagnostic Mediterranean and Healthy Nordic Dietary Patterns Are Inversely Associated with All-Cause Mortality in Long-Term Colorectal Cancer Survivors*. J Nutr 2017;147(4):636-44.

Danksagung

In erster Linie bedanke ich mich bei meinem Doktorvater Herrn Prof. Dr. Wolfgang Lieb für die Möglichkeit am Institut für Epidemiologie zu promovieren, für die Zurverfügungstellung der Daten, die Betreuung der Arbeit, die gemeinsamen Projekte und das Vertrauen.

Ich bedanke mich bei Frau Prof. Dr. Ute Nöthlings, Herrn Prof. Dr. Clemens Schafmayer und Herrn Prof. Dr. Jochen Hampe für die Bereitstellung des Datensatzes und die Kooperationsbereitschaft.

Ich möchte mich darüber hinaus bei allen Kolleginnen und Kollegen aus dem Institut für Epidemiologie für die angenehme Arbeitsatmosphäre und den kollegialen Austausch bedanken. Insbesondere bedanke ich mich bei Lukas Tittmann und Kathrin Jaeger für die Vorarbeiten zum Mortalitäts-Follow-up und die Bemühungen bei allen Fragen rund ums Datenmanagement. Für konstruktive und belebende fachliche Diskussionen und Anregungen bedanke ich mich bei Sabrina Schlesinger, Romina di Giuseppe, Sandra Plachta-Danielzik, Manja Koch, Janna Enderle und Sabina Waniek. Ein besonderer Dank gilt Sabrina Schlesinger, die meine Promotionsarbeit mit vielen fachlichen und methodischen Hinweisen unterstützt hat. Ich bedanke mich zudem bei Sabina Waniek für den gemeinsamen Weg durch Höhen und Tiefen der Promotionszeit, den fachlichen wie privaten Austausch und die gemeinsamen Fahrten und Vorlesungsaufenthalte des Weiterbildungsmasters in Oldenburg. Bei Janna Enderle möchte ich mich ganz herzlich bedanken für die wertvollen Diskussionen und Gespräche, die emotionale Unterstützung vor allem auf der Zielgeraden der Promotionszeit und die erheiternden Momente im Büro.

Mein Dank gilt außerdem den Teilnehmern der PopGen-Kolorektalkarzinom-Studie, ohne deren Beitrag diese Forschungsarbeit nicht möglich gewesen wäre.

Ich bedanke mich ganz herzlich bei meiner Familie für die Begleitung durch die Zeit der Promotion. Ein ganz besonderer Dank gilt meinen Eltern für die ausnahmslose Unterstützung über all die Jahre. Ohne dies wäre vieles deutlich schwerer zu bewältigen gewesen und es hätten einige Situationen aussichtsloser ausgesehen. Ich bedanke mich vor allem für den emotionalen Beistand, die hilfreichen und konstruktiven Anregungen und die Geduld. Zudem bedanke ich mich ganz besonders bei Marvin, der mich während der Promotionszeit in jedem Gemütszustand und jeder Gefühlslage erlebte und dem mit sehr viel Verständnis begegnet ist. Außerdem danke ich ihm für die notwendige und wohltuende Ablenkung, die positiven Sichtweisen und die optimistischen Zusprüche.

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