Lifestyle after colorectal cancer diagnosis

Observed changes and associations with recurrence and survival

Moniek van Zutphen

Propositions

1. It is necessary to take pre-diagnosis body weight into account when monitoring weight changes in colorectal cancer patients.
   (this thesis)

2. Cancer recurrence has to be included as a key outcome in survivorship studies.
   (this thesis)

3. A pitch is the most effective way to communicate science to non-experts.

4. In-person interactions with colleagues are essential for scientific achievements.

5. In the Netherlands, an environmentally sustainable diet includes beef.

6. Gynecologists must explore acceptance of a childfree life with their clients as alternative to fertility treatment.

7. A burn-out is a sign of perseverance.

Propositions belonging to the thesis, entitled

Lifestyle after colorectal cancer diagnosis:
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Moniek van Zutphen
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Moniek van Zutphen

Thesis committee

Promotors
Prof. Dr Ellen Kampman
Professor of Nutrition and Disease
Wageningen University & Research

Prof. Dr Hendriek C. Boshuizen
Special Professor, Biostatistical Modelling for Nutritional Research
Wageningen University & Research

Co-promotor
Dr Fränzel J.B. van Duijnhoven
Assistant Professor, Division of Human Nutrition and Health
Wageningen University & Research

Other members
Prof. Dr Lisette C.P.G.M. de Groot, Wageningen University & Research
Prof. Dr Anne M. May, UMC Utrecht
Dr Panagiota Mitrou, World Cancer Research Fund International, London, UK
Prof. Dr John C. Mathers, Newcastle University, UK

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Thesis

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CHAPTER 1

General introduction

One out of three people will get a cancer diagnosis (1). This means that everybody will be affected by cancer, either because you or somebody you love is diagnosed. After a cancer diagnosis many people wonder what they can do themselves, as can be seen by this remark from a cancer survivor, who was interviewed by World Cancer Research Fund NL:

> "*I was very motivated to take action myself. I didn't want to put my fate only in my doctor's hands, but I wanted to do something myself."*

Patients, as well as their loved ones, wonder how to improve their chances of becoming better again or at least of prolonging their survival. After successful treatment they wonder how to prevent the cancer coming back.

> *"Can I eat meat if I have or had cancer?"*
> *"Can I drink herbal tea without worries with cancer?"*
> *"What can I do to improve fitness?"*
> *"Is there an objection to drink alcohol?"*
> *"Do I have a higher risk the cancer comes back because I'm overweight?"*

These questions, taken from the website voeding&kankerinfo.nl, are just some examples of questions people have after a cancer diagnosis and illustrate peoples' needs for lifestyle guidance. The ultimate goal of this thesis is to empower cancer survivors by providing evidence-based lifestyle recommendations to alter their recurrence risk and to prolong their survival.

Lifestyle recommendations and cancer

Current lifestyle recommendations for cancer survivors are the same as those for the general public to decrease their risk of cancer. These recommendations include maintaining a healthy body weight, being physically active, eating a healthy diet, and limiting alcohol consumption (**Figure 1**) (2, 3). There is convincing evidence that diet, physical activity, smoking, alcohol, and body weight influence cancer risk (2, 4), but there is insufficient specific evidence for the role of these factors for those who have or had cancer. The vast majority of research relating diet, body fatness, and physical activity to aspects of cancer survivorship has been conducted in breast cancer survivors (5). However, even in this context, the evidence is insufficient to be considered strong and, consequently, specific recommendations cannot be justified. Currently, there is limited suggestive evidence that lifestyle behaviors after diagnosis, such as body fatness and physical activity, are associated with all-cause mortality among breast cancer survivors (5). The evidence that changing these factors after diagnosis will alter the clinical course of cancer is limited. However, following the cancer prevention recommendations is unlikely to be harmful to cancer survivors who have finished treatment.

Therefore, cancer survivors are advised by cancer research organizations to follow the general recommendations for cancer prevention.

Figure 1. World Cancer Research Fund / American Institute for Cancer Research cancer prevention recommendations (updated in 2018). These recommendations on body fatness, physical activity, diet, and alcohol intake are consistent with the American Cancer Society recommendations (updated in 2020). Cancer survivors are advised to follow the cancer prevention recommendations.

Several organizations provide guidance on nutrition and physical activity for cancer survivors, such as the World Cancer Research Fund / American Institute for Cancer Research (WCRF/AICR) (2) and the American Cancer Society (ACS) (6). All emphasize an optimal body weight, being physically active, eating a healthy diet, and limiting alcohol intake. An overview of recommendations for cancer survivors from different organizations is given in reference (5). As more studies on cancer risk were available over time, the cancer prevention recommendations were regularly updated. For example, WCRF/AICR updated their cancer prevention recommendations in 2018 (**Figure 1**) (2). While the 2018 recommendations remained consistent to the 2007 recommendations, there were some changes in the formulation of specific recommendations and a new recommendation on limiting consumption of fast foods was added.

One major change in cancer prevention recommendations over time has been a shift in emphasis to the importance of overall lifestyle. While following each individual recommendation offers benefit, most benefit is gained by treating all recommendations as an integrated pattern of behaviors related to diet, body fatness, physical activity, and alcohol intake. In two reviews, only few studies were identified that investigated whether an overall lifestyle consistent with cancer prevention guidelines (either before or after diagnosis) was associated with cancer mortality in cancer survivors (7, 8). Studies examining the recently updated guidelines need to further clarify such associations.

Lifestyle scores that measure adherence to lifestyle recommendations can be used to examine how overall lifestyle is associated with cancer-related outcomes across populations and countries. It would be an advantage if overall lifestyle could be measured with a standardized score. As no standard scoring approach was used to define adherence to the 2007 WCRF/AICR recommendations, each study derived their own version. To improve consistency and comparability of future studies, a standardized scoring system was developed by an international team of experts for assessing adherence to the 2018 WCRF/AICR recommendations (9). A higher score reflects greater adherence to the recommendations and therefore reflects a healthier overall lifestyle.

Colorectal cancer

It is well accepted that colorectal cancer risk is highly modifiable through diet and lifestyle, but it remains unclear if colorectal cancer outcomes are also modifiable through diet and lifestyle after diagnosis. Exposure to less than optimal levels of lifestyle behaviors is responsible for about 50% of colorectal cancers (10). There is strong evidence that a high intake of red and processed meat and alcoholic drinks and low intake of wholegrains, dietary fiber, and dairy increases the risk of colorectal cancer (2). In addition, body fatness increases the risk of colorectal cancer, while physical activity protects against colorectal cancer (2).

As the number of individuals living with and beyond colorectal cancer is expected to continue to increase (11), there is a need for effective strategies to improve the quality and duration of survivorship following colorectal cancer. Colorectal cancer is the third most common cancer type and the second leading cause of cancer-related death worldwide (12). In 2018, there were an estimated 1.8 million incident colorectal cancer cases worldwide and over 880,000 colorectal cancer deaths (12). In the Netherlands, there are about 9000 incident colorectal cancer cases and 5000 colorectal cancer deaths each year (13). If current trends continue, it is estimated that 2.4 million colorectal cancer cases will be diagnosed and 1.4 million will die of colorectal cancer annually worldwide by 2030 (12).

Rates of colorectal cancer survival are also increasing, with more people living with and beyond cancer (14-16). The increased number of colorectal cancer survivors is due to an

increasing incidence of colorectal cancer and higher survival rates, at least in part because of earlier detection and improved treatment (14, 16). Nowadays, there are more than 4.7 million colorectal survivors worldwide, of which more than 40000 in the Netherlands, who were diagnosed in the past five years (12). Therefore, colorectal cancer survivors are the largest group of cancer survivors involving both females and males.

Treatment for non-metastatic colorectal cancer (stage I-III) involves surgery, radiation therapy, and/or chemotherapy. Almost all (up to 98%) of these patients will receive surgery (11, 14). Administration of adjuvant chemotherapy is dependent on cancer stage and site. Approximately two-thirds of patients with stage III colon cancer receive chemotherapy after surgery (11, 14), while only a small proportion of patients with stage II colon cancer (8%) or stage II/III rectal cancer (10%) receive adjuvant chemotherapy (14). Radiation therapy is received by approximately two-thirds of patients with rectal cancer before surgery (neo-adjuvant treatment) (11, 14). Neo-adjuvant treatment consists either of radiotherapy or chemoradiation (14).

Lifestyle after colorectal cancer diagnosis could potentially modify short-term outcomes, such as recovery after surgery, and longer-term outcomes, such as risk of recurrence and mortality. Currently, less than half of colorectal cancer patients recover to pre-operative physical functioning five to six months after surgery (17, 18). Further, fear of recurrence is a common concern for colorectal cancer patients (19) and approximately 20% of colorectal cancer patients will experience a colorectal cancer recurrence (20, 21). The majority (60-80%) of colorectal cancer recurrences occur within the first two to three years after surgery (22, 23). The 5-year survival rate is currently 65% (11, 13). Evidence is emerging that modifiable lifestyle behaviors after colorectal cancer diagnosis could impact survival. It remains unclear if lifestyle after diagnosis could also impact recurrence risk, as data on colorectal cancer recurrence is not routinely collected.

Changes in body weight and lifestyle after colorectal cancer diagnosis

Although lifestyle recommendations for cancer survivors are available, only few colorectal cancer patients actually receive lifestyle advice after diagnosis (24-26). In the hospital, nutritional advice to cancer patients is mainly focused on treatment of unintentional weight loss, as weight loss is an important negative prognostic marker (27-30). Prevention of weight gain seems needed as previous studies have shown that >50% of colorectal cancer patients treated with adjuvant chemotherapy gain weight after diagnosis (29, 31) and this may affect long-term health (32-34). Therefore, prevention of weight gain has recently been incorporated in the Dutch oncological nutritional therapy guidelines for colorectal cancer with a focus on patients that undergo adjuvant chemotherapy (35). It is, however, unknown how changes in weight after diagnosis relate to weight before diagnosis and whether weight changes from pre-to-post diagnosis are restricted to chemotherapy treatment.

It has been suggested that a cancer diagnosis may be a window of opportunity for healthy changes in diet and other lifestyle behaviors (36, 37). Several, but not all, studies show that colorectal cancer survivors generally improve specific health behaviors after diagnosis, such as eating more healthy, decreasing alcohol intake, increasing physical activity, and quitting smoking (38-45). Only few studies tracked changes in health behaviors prospectively and it remains unknown how changes in specific health behaviors impact overall concordance with lifestyle recommendations.

Lifestyle and outcomes after colorectal cancer diagnosis

Lifestyle after colorectal cancer diagnosis might influence short-term outcomes, such as recovery after colorectal cancer surgery. Recovery after surgery might be best estimated with measures of functional status (46), such as physical functioning. Several studies consistently indicate that physically active CRC survivors (47-53) have higher physical functioning. However, the impact of physical activity on recovery of physical functioning after colorectal cancer surgery is unknown.

Lifestyle after colorectal cancer diagnosis might also influence longer-term outcomes. Some studies show that lifestyle, including diet, after CRC diagnosis might affect all-cause and CRC-specific mortality risk, while only few studies included colorectal cancer recurrence as outcome. The first large study that clearly showed an association between lifestyle after diagnosis and colorectal cancer outcomes was published in 2007 (54). It was shown that a higher intake of a Western dietary pattern after colorectal cancer diagnosis was associated with worse outcomes. Compared with patients in the lowest quintile of the Western dietary pattern, those in the highest quintile had a more than two times higher risk of colorectal cancer recurrence or death during the study period. The Western dietary pattern is generally regarded as an unhealthy diet and was characterized by high intakes of meat, fat, refined grains, and desserts. Since then, several other studies assessed associations on specific aspect of lifestyle and colorectal cancer outcomes. Several reviews and meta-analyses on observational studies summarized the available evidence on specific aspects of lifestyle, such as diet (55-57), physical activity (55, 56, 58-63), smoking (64, 65), and body composition (56, 61, 66-73), in relation to CRC outcomes. Based on mainly non-European studies, they concluded that being physically active or eating a healthy diet after diagnosis may improve overall survival. Less is known about the impact on recurrence risk as most studies did not include this outcome. None of these reviews included all the aforementioned lifestyle behaviors in one review or examined changes in lifestyle after colorectal cancer diagnosis and colorectal cancer outcomes.

The recommendations for cancer survivors emphasize the importance of adopting an overall healthy lifestyle, rather than focusing on single lifestyle behaviors, and little is known about the impact of an overall healthy lifestyle on colorectal cancer outcomes. Currently, only two

studies investigated whether an overall lifestyle consistent with cancer prevention guidelines was associated with all-cause mortality after colorectal cancer (74, 75). Inconsistent results were reported, although the guidelines used in both studies included the combination of the same four single lifestyle behaviors (an optimal body weight, being physically active, eating a healthy diet, and limiting alcohol intake).

Studies that assess overall lifestyle cannot identify the relative importance of different behaviors. Considering different lifestyle behaviors simultaneously, rather than combining all lifestyle behaviors, could provide a more comprehensive understanding of which aspects of lifestyle are most important for CRC prognosis. Currently no study identified which lifestyle behaviors are most important in relation to mortality or recurrence. Random survival forests analyses is a relatively new data-driven method which can be used to identify these lifestyle behaviors (76). Random survival forests are better suited than traditional Cox regression models to identify a subset of exposures that are related to the outcome of interest from a large set of potentially interesting exposures. Applying many Cox regression models to test associations for all available lifestyle behaviors and either recurrence or all-cause mortality, would result in multiple testing. Using random survival forests for exploratory analyses has the advantage that random survival forests do not rely on p-values and, more importantly, random survival forests use a subset of data not included in model building to identify important variables.

COLON and EnCoRe study

Two prospective cohort studies among colorectal cancer patients were initiated in the Netherlands to address the above-mentioned knowledge gaps. The COLON (Colorectal cancer: Longitudinal, Observational study on Nutritional and lifestyle factors that influence colorectal cancer tumor recurrence, survival and quality of life) study (77) was initiated by Wageningen University. The main aim of this study is to assess associations of diet and other lifestyle factors, with colorectal cancer recurrence, survival, and quality of life. In addition, the EnCoRe (Energy for life after ColoRectal Cancer) study (78) was initiated by Maastricht University Medical Center+. The main aim of the EnCoRe study is to determine how important lifestyle factors, such as diet and physical activity, affect the quality of life and overall well-being of colorectal cancer survivors after the end of initial treatment. Both studies can include colorectal cancer recurrence as an outcome, since information on recurrences was collected from medical records by trained registrars from the Dutch Cancer Registry.

The COLON study started in September 2010. Newly diagnosed patients with colon or rectal cancer were recruited in 11 hospitals in the Netherlands. Hospital staff invited eligible patients during a routine clinical visit before scheduled surgery. Patients were not eligible when they had a history of colorectal cancer, a previous (partial) bowel resection, known hereditary colorectal cancer, inflammatory bowel disease, dementia or another mental condition limiting their ability to fill out surveys, or were non-Dutch speaking. Data were

collected at baseline (shortly after diagnosis, before treatment started) and at six months, two and five years after diagnosis (**Figure 2**).

The EnCoRe study started in April 2012. In setting up the EnCoRe study, questionnaires and methodologies were chosen to largely overlap with those used in the COLON study to enable pooling of the data (**Figure 2**). Colorectal cancer patients with non-metastatic disease were recruited in three hospitals in the south of the Netherlands. Within this thesis, only EnCoRe data collected at six months after diagnosis is used.

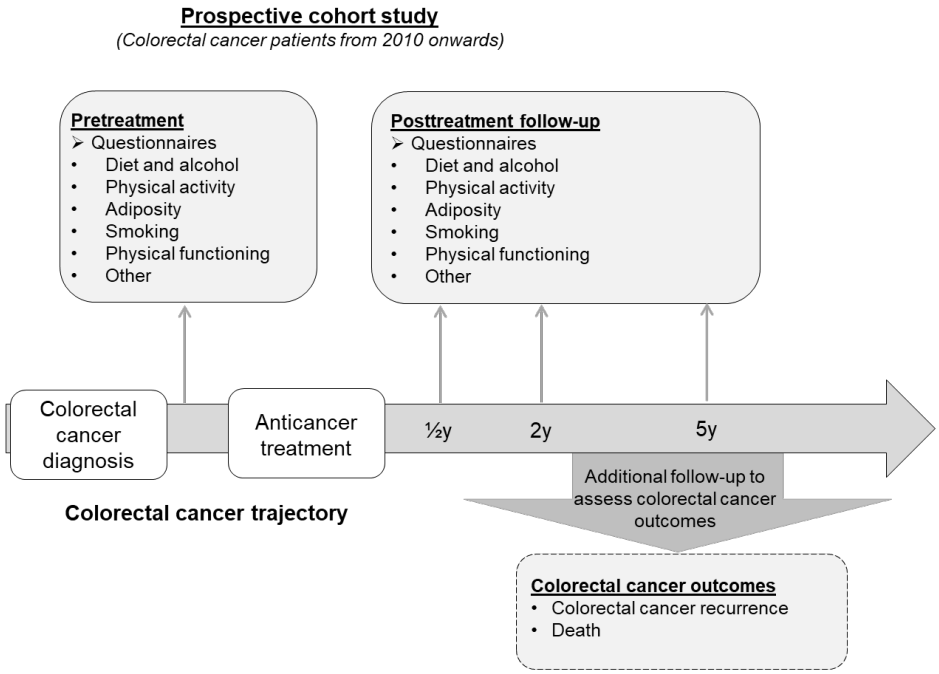

Figure 2. Study design of the COLON and EnCoRe study. y, year.

Aim of this thesis

The aims of this thesis are:

To assess

1. changes in lifestyle after diagnosis
2. associations between lifestyle and cancer outcomes

among colorectal cancer patients with stage I-III disease.

Insight into these associations will help to establish evidence-based lifestyle recommendations for colorectal cancer survivors.

To reach these aims we used data of a prospective cohort study with colorectal cancer survivors: the COLON study. In Chapter 6 we combined data of the COLON study with another prospective cohort study of colorectal cancer survivors, the EnCoRe study, to increase the power of the analyses.

Thesis outline

The first part of this thesis describes pre-to-post diagnosis changes in body weight and lifestyle behaviors. In **chapter 2** changes in body weight from pre-to-post diagnosis are examined and these weight trajectories are compared among colorectal cancer patients treated with and without adjuvant chemotherapy. **Chapter 3** presents changes in health behaviors and overall lifestyle in the first 2 years following colorectal cancer diagnosis and characterizes interrelationships between changes in health behaviors.

In the second part of this thesis, lifestyle in relation to outcomes after colorectal cancer diagnosis is evaluated. Chapter 4 focusses on a short-time outcome, recovery of physical functioning. Chapters 5-7 focus on longer-term outcomes: colorectal cancer recurrence (chapter 5-7), colorectal cancer specific mortality (chapter 5), and all-cause mortality (chapter 5-7). In **chapter 4** the association between physical activity and recovery of physical functioning is examined. In **chapter 5** the literature is reviewed to summarize the available evidence regarding diet, physical activity, smoking, and body composition after colorectal cancer diagnosis in relation to all-cause and colorectal cancer specific mortality and cancer recurrence. Additionally, we summarized the evidence regarding changes in lifestyle among colorectal cancer survivors and survival outcomes from either observational or intervention studies. In **chapter 6** it is explored if postdiagnosis overall lifestyle and change in overall lifestyle after colorectal cancer diagnosis are associated with recurrence and all-cause mortality in the COLON and EnCore studies. **Chapter 7** presents the relative importance of different lifestyle behaviors regarding recurrence and all-cause mortality.

In the general discussion (**chapter 8**), the main findings are summarized and placed into broader perspective. Furthermore, possible biological mechanisms and methodological considerations are addressed. Finally, implications for clinical practice and future research are described.

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CHAPTER 2

2

Pre-to-post diagnosis weight trajectories in colorectal cancer patients with non-metastatic disease

Moniek van Zutphen | Anouk Geelen | Hendriek C. Boshuizen | Renate M. Winkels | Anne J.M.R. Geijsen | Evertine Wesselink | Merel Snellen | Dieuwertje E. Kok | Johannes H.W. de Wilt | Paul C. van de Meeberg | Ewout A. Kouwenhoven | Henk K. van Halteren | Ernst J. Spillenaar Bilgen | Ellen Kampman | Fränzel J.B. van Duijnhoven

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Abstract

Purpose

Previous studies have shown that >50% of colorectal cancer (CRC) patients treated with adjuvant chemotherapy gain weight after diagnosis. This may affect long-term health. Therefore, prevention of weight gain has been incorporated in oncological guidelines for CRC with a focus on patients that undergo adjuvant chemotherapy treatment. It is, however, unknown how changes in weight after diagnosis relate to weight before diagnosis and whether weight changes from pre-to-post diagnosis are restricted to chemotherapy treatment. We therefore examined pre-to-post diagnosis weight trajectories and compared them between those treated with and without adjuvant chemotherapy.

Methods

We included 1184 patients diagnosed with stages I-III CRC between 2010 and 2015 from an ongoing observational prospective study. At diagnosis, patients reported current weight and usual weight two years before diagnosis. In the two years following diagnosis, weight was self-reported repeatedly. We used linear mixed models to analyse weight trajectories.

Results

Mean pre-to-post diagnosis weight change was -0.8 (95% CI -1.1, -0.4) kg. Post-diagnosis weight gain was +3.5 (95% CI 2.7, 4.3) kg in patients who had lost ≥5% weight before diagnosis, while on average clinically relevant weight gain after diagnosis was absent in the groups without pre-diagnosis weight loss. Pre-to-post diagnosis weight change was similar in patients treated with (-0.1 kg (95%CI -0.8, 0.6)) and without adjuvant chemotherapy (-0.9 kg (95%CI -1.4, -0.5)).

Conclusions

Overall, hardly any pre-to-post diagnosis weight change was observed among CRC patients, because post-diagnosis weight gain was mainly observed in patients who lost weight before diagnosis. This was observed independent of treatment with adjuvant chemotherapy.

Keywords

colorectal cancer, weight change, weight gain, chemotherapy

Introduction

Survival of colorectal cancer (CRC) has markedly improved over recent decades, which underlines the importance to study factors that can affect long-term health and quality of life of CRC survivors. One of the factors that may affect health and quality of life is body weight. Weight loss, either before diagnosis or during cancer treatment, is an important negative prognostic marker [1-4]. Therefore, in the hospital nutritional advice to cancer patients is mainly focused on prevention and/or treatment of unintentional weight loss. However, overweight and obesity are also affecting long-term health and quality of life among patients with non-metastatic disease. Therefore, prevention of weight gain after CRC diagnosis has recently been incorporated in the Dutch oncological nutritional therapy guidelines [5].

Many CRC patients are overweight or obese at diagnosis, as excess body weight is a risk factor for CRC [6]. Overweight/obese CRC survivors have an elevated risk of co-morbid disease, such as cardiovascular disease and diabetes, both at diagnosis and in the years following a diagnosis [7-9]. Weight gain after diagnosis might exacerbate existing co-morbid disease progression and further increase the risk of developing such diseases. Several studies reported that weight gain after diagnosis is common among CRC patients [1,10,2,3,11]. All these studies showed that weight gain after diagnosis was more common than weight loss after diagnosis [1,10,2,3,11]. The proportion of weight gain after diagnosis typically ranged from 25% to over 50% of patients [1,10,2,3,11]. In these studies weight gain was defined as either a weight gain of ≥5 kg [1,10] or ≥5% [2,3,11].

Although body weight may increase after CRC diagnosis, studies so far did not assess how body weight changed relative to usual body weight before diagnosis. Weight loss before CRC diagnosis is common [4,12] as unintended weight loss could be one of the reasons for patients to see a physician, leading to the diagnosis of CRC. Thus it is possible that patients catch up for this pre-diagnostic weight loss in the period during and after treatment. It is currently unknown if post-diagnosis weight change is different for patients with pre-diagnosis weight change compared to patients who were weight stable before diagnosis. Post-diagnosis weight gain might be more problematic in terms of long-term health if it results in overall weight gain compared to usual weight than when it reflects catching up for pre-diagnostic weight loss.

Weight gain is a common side-effect of chemotherapy in breast cancer patients [13], but weight gain is also common among non-metastatic CRC patients during and after chemotherapy. Two studies that both included >500 colon cancer patients with stage III disease treated with adjuvant chemotherapy reported that the majority (51-65%) of patients experienced weight gain [10,3]. Weight gain is observed both during and after

adjuvant chemotherapy [11]. Therefore, prevention of weight gain in oncological guidelines has a focus on patients treated with adjuvant chemotherapy [5]. However, there is only indirect evidence that weight gain after diagnosis is more prevalent among patients treated with adjuvant chemotherapy than among patients treated without adjuvant chemotherapy. Studies that included non-metastatic CRC patients irrespective of chemotherapy treatment reported lower proportions (28%) of weight gain [1,2] than studies among CRC patients treated with adjuvant chemotherapy (51-65%) [10,3]. There are no studies that directly compared weight changes between patients treated with or without adjuvant chemotherapy.

Weight trajectories should ideally include data on weight at multiple time points, both before and after diagnosis, to fully capture weight changes among CRC patients. This information is currently lacking and therefore it remains unclear whether post-diagnosis weight eventually surpasses usual pre-diagnosis weight. Our aim was to examine pre-to-post diagnosis weight trajectories in CRC patients with non-metastatic disease and to compare these weight trajectories among patients treated with and without adjuvant chemotherapy.

Methods

Study population

We used data of the COLON study, an ongoing prospective multicentre cohort study among CRC patients in the Netherlands [14]. Eligible participants with newly diagnosed colon or rectal cancer were invited by hospital staff to participate in the study during a routine clinical visit before scheduled surgery. Data were collected shortly after diagnosis, before treatment started, and at two or three time points in the first two years after diagnosis (see Assessment of body weight). Follow-up data were available until January 2018. All study participants provided written informed consent and the study was approved by the local review board.
This study was performed among all participants diagnosed with stage I-III CRC between 2010 and 2015 who had a surgical resection (n=1225). We excluded 70 participants who had information on weight available for <2 time points. Thus, data of 1152 participants remained for analyses. Of these participants, 16 (1%) had missing self-reported weight before diagnosis and 217 (19%) did not complete 2 years of follow-up. We chose to exclude patients with stage IV disease a priori, because survival for these patients is generally poor and weight loss and cachexia are common at the end of life.

Assessment of body weight

At diagnosis, participants completed a survey with questions on body weight 2 years prior to diagnosis, and current weight. Participants repetitively answered surveys about their current body weight at 6 months, 1 year (only for the subsample treated with adjuvant chemotherapy), and 2 years after diagnosis.

Assessment of covariates

We obtained information on clinical factors, including disease stage, tumour site, receipt of neo-adjuvant treatment, type of surgery, stoma placement after surgery, complications within 30 days after surgery, receipt of adjuvant chemotherapy, type of chemotherapy, and presence of comorbidities from the Dutch ColoRectal Audit [15]. At diagnosis, all participants completed a questionnaire on demographic and lifestyle information, including education, smoking behaviour, and height. Body Mass Index (BMI) at diagnosis was computed in kg/m^2.

Statistical analyses

We calculated pre-diagnosis, post-diagnosis, and pre-to-post diagnosis weight changes as weight at the end of the period minus weight at the start of the period, so negative differences indicate weight loss and positive differences indicate weight gain. Pre-diagnostic weight changes were grouped in three pre-defined categories: weight loss ≥5%, weight stable -5 to + 5%, and weight gain ≥5%. Characteristics of the study population were compared across pre-diagnosis weight change groups and across adjuvant chemotherapy treatment. Differences in categorical variables were assessed by using a chi-square test, and differences in means of continuous variables were tested by using analysis of variance or a t-test.

We fitted linear mixed models to examine weight trajectories over 4 years (two years pre-diagnosis to two years post-diagnosis). Linear mixed models take into account both the individual trajectories of change (random effects) and population averages (fixed effects) by using all available measurements and including participants with incomplete data [16]. Time was scaled in years (continuous) with the date of study enrolment (shortly after diagnosis) defined as time is zero. Time for each post-diagnosis weight was calculated as date of self-reported weight collection minus the date of study enrolment. Time for pre-diagnosis weight was set at -2 years for all subjects.

The final model included a random intercept, a random slope for time, and a random curvature for time (i.e. taking into account each participant's weight at diagnosis and the linear and quadratic slope). Using a step-up model building strategy, the random curvature model had much better fit than a random intercept model and a random slope model.

As fixed factors, we included baseline demographic determinants (sex, age, height, education, and smoking) and clinical factors (stage, tumour site, neo-adjuvant treatment, stoma, type of surgery, complications after surgery, and comorbidities). Age and height were centred to aid the interpretability of intercepts. The clinical factors neo-adjuvant treatment, stoma, and surgical complications were coded as not present before and at diagnosis. All fixed effects were included in the model as an interaction term with time. Only significant covariates and/or interactions were retained. Including additional interactions with time*time for the remaining covariates did not improve the model. The final model

used in all analyses included the following fixed factors: time, sex, age, height, education, smoking, complications, stoma, type of surgery, comorbidities, time*time, education*time, and complications*time. The coefficient for time represents average annual linear change and the coefficient for time*time captures additional quadratic (curvilinear) change in weight in kilograms.

Additionally, we performed several stratified weight trajectory analyses. First, we stratified by pre-diagnosis weight change category (≥5% loss, stable, ≥5% gain) to further explore if weight gain after diagnosis differed by pre-diagnosis weight change. Second, we stratified by receipt of chemotherapy to compare weight trajectories among those treated with and without adjuvant chemotherapy. Third, as an exploratory analysis, we stratified by BMI at diagnosis to compare weight trajectories among survivors with a healthy BMI (18.5-25 kg/m^2) and those with overweight or obesity (BMI ≥25 kg/m^2). Weight trajectories were depicted based on predicted values by using the average study population, except for type of surgery in which laparoscopic surgery served as reference category. Two sensitivity analyses were performed to reduce heterogeneity between patients in the analyses stratified by chemotherapy. First by excluding patients with other adjuvant chemotherapy regimens than capecitabine combined with oxaliplatin and second by excluding patients with rectal tumours from the analyses. In the Netherlands, rectal tumours are generally not treated with adjuvant chemotherapy, which is in line with the Dutch oncological guidelines.

In all analyses, a p-value <0.05 was considered statistically significant. Statistical analyses were performed in SAS 9.4 (SAS Institute, Cary NC).

Results

Characteristics of the study population according to pre-diagnosis weight change and adjuvant chemotherapy are shown in **Table 1**. Participants with ≥5% weight gain before diagnosis were on average slightly younger, more commonly female, obese at diagnosis (BMI ≥30 kg/m^2), and presenting with one or more comorbidities compared to those with either stable weight or ≥5% weight loss before diagnosis. Participants with ≥5% weight loss before diagnosis had more often a tumour located in the colon compared to those with stable weight or weight gain. Patients treated with adjuvant chemotherapy were slightly younger and had unfavourable clinical characteristics compared to patients not treated with chemotherapy; other characteristics, such as BMI, were similar between the two groups.

Compared to pre-diagnosis weight, mean weight change was -0.8 (95% CI -1.1, -0.4) kg over the four year period (**Table 2**). Over this total period, weight change was <5% for the majority of people (66%), while 14% of all patients experienced pre-to-post diagnosis weight gain of

≥5% and 20% experienced weight loss of ≥5%. When only the 2 years post-diagnosis were taken into account, mean weight change in the two years after diagnosis was +1.2 (95%CI 0.9, 1.5) kg.

The estimated 4-year weight trajectory in the entire cohort is presented in **Figure 1A**. The full model showed a clear positive quadratic relationship of weight changes in the entire cohort (p<0.001), but no linear effect was present (+0.04 kg annual weight gain, p=0.68). In other words, weight decreased before diagnosis while weight increased after diagnosis. Overall, weight 2 years after diagnosis was similar to weight 2 years before diagnosis.

To explore if post-diagnosis weight trajectories differed by pre-diagnosis weight change, we stratified the weight trajectory analyses by pre-diagnosis weight change. A mean gain in body weight after diagnosis was most prominent in the group that had lost weight before diagnosis **(Figure 1B**; **Table 2**). In this group, 42% gained weight after diagnosis and this proportion was much larger than that seen for the pre-diagnosis weight stable and weight gain groups (14% and 19%, respectively; Table 2). In absolute numbers, post-diagnosis weight gain was on average +3.5 (95%CI 2.7, 4.3) kg in the group that had lost weight pre-diagnosis. However, taking the two years before diagnosis into account, mean weight change was -4.8 (95%CI -5.7, -3.9) kg in this group. On average, clinically relevant weight change after diagnosis absent when pre-diagnosis weight was stable or when pre-diagnosis weight gain ≥5% was present.

Weight trajectories were similar for those treated with and without adjuvant chemotherapy (**Figure 1C**; **Table 2**). In both groups overall weight 2 years after diagnosis was similar to overall weight 2 years before diagnosis. Sensitivity analyses excluding patients with other adjuvant chemotherapy regimens than capecitabine combined with oxaliplatin or excluding patients with rectal tumours did not change the results (data not shown). Weight trajectories were similar for those with a BMI of 18.5-25 kg/m^2 and a BMI ≥25 kg/m^2 at diagnosis (data not shown).

Table 1. Clinical and personal characteristics of 1152 non-metastatic colorectal cancer patients according to pre-diagnosis weight change and adjuvant chemotherapy[1].

		Weight change in the 2 years before diagnosis				Adjuvant chemotherapy		
	Overall[2]	Loss (≥5%)	Stable (-5% to 5%)	Gain (≥5%)	P-value weight change group	No	Yes	P-value chemo therapy
N (%)	1152 (100%)	279 (25%)	788 (69%)	69 (6%)		844 (75%)	282 (25%)	
Sex					<0.001			0.21
Men	737 (64%)	179 (64%)	527 (67%)	19 (28%)		547 (65%)	171 (61%)	
Age at diagnosis (mean ± SD), years	66 ± 9	66 ± 9	66 ± 8	63 ± 11	0.029	67 ± 9	63 ± 8	<0.001
BMI at diagnosis (mean ± SD), kg/m^2	26.5 ± 4.0	26.0 ± 4.0	26.5 ± 3.9	29.2 ± 4.1	<0.001	26.5 ± 3.9	26.6 ± 4.3	0.66
BMI at diagnosis, kg/m^2					<0.001			0.64
<18.5	10 (1%)	3 (1%)	6 (1%)	0 (0%)		6 (1%)	4 (1%)	
18.5-25	447 (39%)	130 (47%)	301 (38%)	13 (19%)		331 (39%)	107 (38%)	
25-30	497 (43%)	110 (39%)	352 (45%)	27 (39%)		362 (43%)	122 (43%)	
30-35	161 (14%)	27 (10%)	107 (14%)	23 (33%)		120 (14%)	37 (13%)	
>35	37 (3%)	9 (3%)	22 (3%)	6 (9%)		25 (3%)	12 (4%)	
Education level					0.061			0.37
low	505 (44%)	133 (48%)	330 (42%)	36 (52%)		383 (45%)	115 (41%)	
medium	277 (24%)	58 (21%)	198 (25%)	20 (29%)		195 (23%)	72 (26%)	
high	365 (32%)	87 (31%)	260 (33%)	13 (19%)		262 (31%)	95 (34%)	
Smoking at diagnosis					0.005			0.27
yes	133 (11%)	47 (17%)	73 (9%)	11 (16%)		102 (12%)	25 (9%)	
former	682 (59%)	166 (60%)	468 (59%)	40 (58%)		498 (59%)	168 (59%)	
never	334 (29%)	67 (24%)	247 (32%)	18 (26%)		240 (28%)	89 (32%)	
Tumor stage					0.26			<0.001
I	299 (26%)	60 (22%)	218 (28%)	19 (28%)		297 (35%)	-	
II	350 (30%)	96 (34%)	229 (29%)	19 (28%)		311 (37%)	27 (10%)	
III	503 (44%)	123 (44%)	341 (43%)	31 (45%)		236 (28%)	255 (90%)	
Tumor location					0.038			<0.001

colon	778 (68%)	206 (74%)	517 (66%)	45 (65%)		499 (59%)	259 (92%)	
rectum	374 (32%)	73 (26%)	271 (34%)	24 (35%)		345 (41%)	23 (8%)	
Adjuvant chemotherapy					0.18			-
yes	282 (24%)	80 (29%)	184 (23%)	16 (23%)		-	282 (100%)	
no	844 (73%)	192 (69%)	587 (74%)	52 (75%)		844 (100%)	-	
Adjuvant chemotherapy regimen					0.94			-
capecitabine + oxaliplatin	214 (19%)	61 (22%)	140 (18%)	12 (17%)		-	214 (76%)	
capecitabine	37 (3%)	12 (4%)	22 (3%)	2 (3%)		-	37 (13%)	
other	7 (1%)	2 (1%)	5 (1%)	0 (0%)		-	7 (2%)	
Neo-adjuvant treatment					0.34			<0.001
yes	270 (23%)	57 (20%)	189 (24%)	19 (28%)		250 (30%)	15 (5%)	
no	882 (77%)	222 (79%)	599 (76%)	50 (72%)		594 (70%)	267 (95%)	
Stoma					0.061			<0.001
yes	340 (30%)	67 (24%)	245 (31%)	22 (32%)		309 (37%)	25 (9%)	
no	783 (68%)	207 (74%)	521 (66%)	46 (67%)		508 (60%)	255 (90%)	
Surgery					0.054			0.67
laparoscopic	725 (63%)	162 (58%)	512 (65%)	38 (55%)		538 (64%)	177 (62%)	
conversion	73 (6%)	18 (6%)	46 (6%)	9 (13%)		51 (6%)	21 (7%)	
open	303 (26%)	84 (30%)	198 (25%)	19 (28%)		213 (25%)	76 (27%)	
Complications after surgery								
yes	323 (28%)	96 (35%)	195 (25%)	26 (37%)	<0.001	257 (30%)	55 (20%)	<0.001
no	787 (68%)	170 (61%)	569 (72%)	40 (58%)		553 (66%)	220 (78%)	
Comorbidity								
yes	773 (67%)	182 (65%)	524 (67%)	56 (81%)	0.023	581 (69%)	173 (61%)	0.018
no	370 (32%)	97 (35%)	256 (32%)	12 (17%)		256 (30%)	107 (38%)	

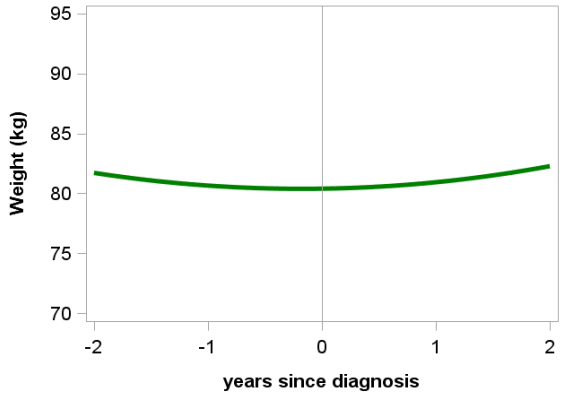
[1]Some counts do not add to totals because of missing data.
[2]Includes 16 participants with missing pre-diagnosis weight and 26 with missing chemotherapy status.

Table 2. Two year post-diagnosis and four year pre-to-post diagnosis weight changes by pre-diagnosis weight change groups and by adjuvant chemotherapy[1]

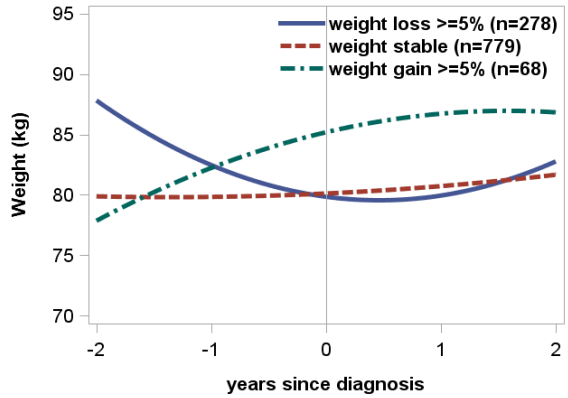
		Weight change during 2y before diagnosis			Adjuvant chemotherapy	
	Overall	Loss (≥5%)	Stable (-5% to 5%)	Gain (≥5%)	No	Yes
N (%)	922 (100%)	221 (24%)	644 (70%)	57 (6%)	687 (75%)	215 (23%)
pre-diagnosis weight change (mean (95%CI)), kg	-1.9 (-2.3, -1.6)	-8.3 (-9.1, -7,5)	-0.5 (-0.6, -0.3)	+6.2 (5.5, 6.8)	-1.9 (-2.2, -1.5)	-2.2 (-2.8, -1.5)
Pre-to-post diagnosis weight change (4y)						
absolute weight change (mean (95%CI)), kg	-0.8 (-1.1, -0.4)	-4.8 (-5.7, -3.9)	+0.0 (-0.3, 0.4)	+6.1 (4.5, 7.6)	-0.9 (-1.4, -0.5)	-0.1 (-0.8, 0.6)
weight loss (%)	20	48	11	4	21	16
weight stable (%)	66	47	76	30	65	69
weight gain (%)	14	5	12	67	14	15
Post-diagnosis weight change (2y)						
absolute weight change (mean (95%CI)), kg	+1.2 (0.9, 1.5)	+3.5 (2.7, 4.3)	+0.5 (0.2, 0.8)	-0.1 (-1.7, 1.5)	+0.9 (0.5, 1.3)	+2.1 (1.5, 2.7)
weight loss (%)	9	5	9	26	10	6
weight stable (%)	70	54	77	55	71	67
weight gain (%)	21	42	14	19	19	27

[1]230 participants with pre-diagnosis weight and/or 2 year post-diagnosis weight information missing omitted from table (n=16 and n=217, respectively)

A. Total group (n=1137)



B. By pre-diagnosis weight change group (n=1125)



C. By adjuvant chemotherapy treatment status (n=1112)

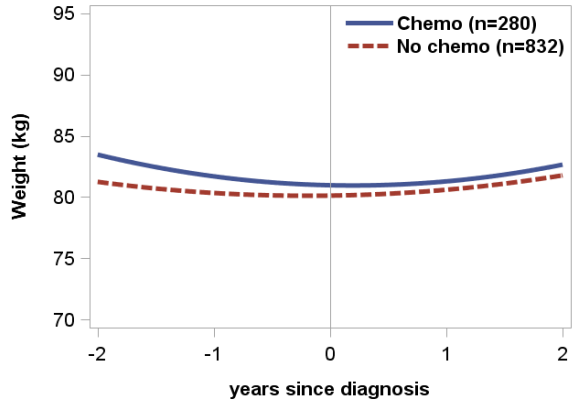


Figure 1. Weight trajectories from 2 years before diagnosis to 2 years after diagnosis in colorectal cancer patients (Weight trajectories were based on predicted values from mixed models adjusted for sex, age, height, education, education*time, smoking, complications, complications*time, stoma, type of surgery, and comorbidities).

Discussion

We examined pre-to-post diagnosis weight trajectories among patients with non-metastatic CRC. Overall, hardly any pre-to-post diagnosis weight change was observed among CRC patients, because post-diagnosis weight gain was mainly observed in patients who lost weight before diagnosis. This was observed independent of treatment with adjuvant chemotherapy.

This was the first study that examined pre-to-post diagnosis weight changes in CRC patients, therefore we can only compare our results on post-diagnosis weight changes with previous studies. All previous studies on post-diagnosis weight change in CRC patients with non-metastatic disease showed that weight gain was more common than weight loss [1,10,3,11,2,17], which is in line with our study. We found that 21% of patients with non-metastatic CRC experienced ≥5% weight gain in the first two years after diagnosis, which is slightly lower than the 28% reported in previous studies [1,2]. Among patients treated with adjuvant chemotherapy, 27% of patients experienced ≥5% weight gain in our study. Although the proportion of patients treated with chemotherapy who experienced weight gain in the current study was lower compared with other studies (36-65%) [10,3,11], the mean post-diagnosis weight gain of +2.1 kg in patients treated with chemotherapy was similar to the mean weight gain of +2.0 kg reported in a previous study based on body weights retrieved from medical records [11]. Weight gain was seen both during and after adjuvant chemotherapy [11], although in this study we were not able to make this distinction. While previous studies focussed on post-diagnosis weight changes, the current study also included usual weight pre-diagnosis into the analysis of weight changes. Our analyses revealed that post-diagnosis weight gain was most prominent in patients who lost ≥5% weight before diagnosis and therefore mean pre-to-post diagnosis weight gain was absent in the overall population.

The current study was the first that compared weight changes between CRC patients treated with and without adjuvant chemotherapy. By including weight data at multiple time points during the course of the disease, both before and after diagnosis, we showed that weight trajectories were similar for those treated with and without chemotherapy. In both groups weight two years post-diagnosis diagnosis did on average not surpass usual pre-diagnosis weight. However, in both groups about 15% experienced pre-to-post diagnosis weight gain of ≥5%. It was unexpected that weight trajectories over the course of CRC were independent of adjuvant chemotherapy treatment. Previous studies showed that post-diagnosis weight gain was more common in studies among patients treated with adjuvant therapy than in studies that included patients irrespective of adjuvant chemotherapy (36-65% versus 28%, respectively) [1,2,10,3,11]. Our results imply that weight gain is not a common side-effect of adjuvant chemotherapy in CRC patients with non-metastatic disease.

A limitation of this study is that body weight was self-reported at each time point, perhaps leading to measurement error with regard to weight change. Cross-sectional data show that self-reported weight values are typically slightly lower than directly measured values [18], although bias may differ by weight status and gender [18,19]. However, good-to-excellent agreement was reported for self-reported and directly measured values of body weight in studies with similar demographic characteristics to this study [20,21]. Participants are also likely to have internal consistency in their reporting, such that the degree of underreporting will be similar each time [19]. Therefore, changes in weight may be less prone to such bias than individual weight measurements. In our study weight two years prior to diagnosis was recalled while post-diagnosis weights were collected prospectively, which may decrease internal consistency. However, good-to-excellent agreement was also reported for pre-diagnosis weight recalled shortly after diagnosis and directly measured values of pre-diagnosis body weight [22]. We assume that weight two years before CRC diagnosis reflects usual pre-diagnosis weight, since the median time from onset of symptoms (such as weight loss) until the start of treatment is usually 4 to 5 months [23,24]. Another limitation is that we did not have information on changes in body composition. Even when pre-to-post diagnosis weight gain is not present, post-diagnosis weight gain may still lead to an increase in fat mass with a loss in muscle mass. Future research should be done to determine how post-diagnosis weight gain affects body composition.

This study has several strengths. First, the COLON study provided an opportunity to explore weight trajectories over the course of the disease in a large group of CRC patients, since we prospectively collected weight several times after diagnosis and also had pre-diagnosis weight available. We used mixed models to examine weight trajectories over four years. An advantage of mixed models is that participants with incomplete weight data were still included in the analyses. Second, we had detailed treatment information available so we were able to compare weight trajectories between those treated with and without adjuvant chemotherapy. Third, we were able to adjust for many covariates that could potentially affect weight change. Although other factors, such as physical activity and physical functioning, not included in the multivariate analyses could also affect weight change. However, both the adjusted weight trajectories (Figure 1) and the crude weight changes (Table 2) showed similar results. Lastly, the study population was representative of the total population of Dutch stage I-III CRC survivors with respect to stage of disease and location of the tumour (colon or rectum), but the proportion of females and the mean age were slightly lower as compared to the total population of CRC survivors [25,26]. Although not perfectly comparable, we believe our findings are generalizable to the total Dutch population of stage I-III CRC survivors, but they cannot be generalised to stage IV CRC survivors.

In clinical practice, not only weight loss, but also weight gain should receive attention as is stated in the Dutch Dieticians Oncology Group guidelines for bowel cancer therapy [5]. Based

on our results, weight changes should be monitored over the course of the disease in all patients, taking pre-diagnosis weight change into account. A previous study suggested that pre-to-post diagnosis weight change, weight loss as well as weight gain, may be associated with a higher mortality risk among CRC patients with non-metastatic disease [1]. In contrast, post-diagnosis weight gain did not seem to be associated with mortality risk [1,2,10]. Our results, together with these other studies [1,2,10], emphasise the importance of taking pre-diagnosis weight into account when examining weight changes in CRC patients. Our study showed that 14% of all patients experienced pre-to-post diagnosis weight gain and pre-to-post diagnosis weight gain was equally prevalent among patients treated with and without adjuvant chemotherapy. Therefore weight gain prevention should not only be targeted at patients receiving adjuvant chemotherapy, but at all CRC patients with non-metastatic disease.

In conclusion, pre-to-post diagnosis weight change was largely absent among CRC patients with non-metastatic disease, because post-diagnosis weight gain was mainly observed in patients who lost weight before diagnosis. This was observed independent of treatment with adjuvant chemotherapy. Future studies are needed to confirm our findings and to assess how weight change relates to survival and the development of co-morbidities to provide a solid basis for future recommendations directed towards managing weight during the course of CRC.

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Conflict of interest

The authors declare that they have no conflict of interest. P.C. van de Meeberg is also affiliated to the Dutch Obesity Clinic as a paid advisor. We have full control of all primary data and we agree to allow the journal to review our data if requested.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

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CHAPTER 3

3

Colorectal cancer survivors only marginally change their overall lifestyle in the first two years following diagnosis

Moniek van Zutphen | Hendriek C. Boshuizen | Dieuwertje E. Kok | Harm van Baar | Anne J.M.R. Geijsen | Evertine Wesselink | Renate M. Winkels | Henk K. van Halteren | Johannes H.W. de Wilt | Ellen Kampman | Fränzel J.B. van Duijnhoven

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Abstract

Purpose

A healthy lifestyle after colorectal cancer (CRC) diagnosis may improve prognosis. Data related to lifestyle change in CRC survivors are inconsistent and potential interrelated changes are unknown.

Methods

We assessed dietary intake, physical activity, body mass index (BMI), waist circumference, and smoking among 1072 patients diagnosed with stages I-III CRC at diagnosis, six months and two years post-diagnosis. An overall lifestyle score was constructed based on the 2018 World Cancer Research Fund/American Institute of Cancer Research recommendations (range 0-7). We used linear mixed models to analyze changes in lifestyle over time.

Results

Participants had a mean (±SD) age of 65 ± 9 years and 43% had stage III disease. In the two years following CRC diagnosis, largest changes were noted for sugary drinks (-45 g/day) and red and processed meat intake (-62 g/week). BMI (+0.4 kg/m^2), waist circumference (+2 cm), and dietary fiber intake (-1 g/day) changed slightly. CRC survivors did not statistically significant change their mean intake of fruits and vegetables, alcohol, or ultra-processed foods, nor did they change their physical activity or smoking behavior. Half of participants made simultaneous changes that resulted in improved concordance with one component as well as deteriorated concordance with another component of the lifestyle score. Overall lifestyle score changed from a mean 3.4 ± 0.9 at diagnosis to 3.5 ± 0.9 two years post-diagnosis.

Conclusions

CRC survivors hardly improve their overall lifestyle after diagnosis. **Implications for Cancer survivors** Given the importance of a healthy lifestyle, strategies to effectively support behaviour changes in CRC survivors need to be identified.

Keywords

colorectal cancer, survivorship, lifestyle changes, dietary changes, lifestyle recommendations

Introduction

Rates of cancer survival are increasing, with more people living with and beyond cancer, especially colorectal cancer [1]. Lifestyle recommendations for cancer survivors are largely extrapolated from recommendations for cancer prevention [2]. Cancer survivors who adhere to these recommendations may improve their prognosis. In colorectal cancer (CRC) survivors, for instance, emerging evidence suggests that being physically active or eating a healthy diet after diagnosis may improve survival [3]. However, many CRC survivors show low concordance with these lifestyle recommendations [4-6] and only few receive lifestyle advice [7, 8].

Several, but not all, studies suggest that CRC survivors generally improve specific health behaviors after diagnosis. Retrospective studies suggest these include eating more healthy [9-12], increasing physical activity [11], and quitting smoking [11]. Also some prospective studies report changes in concordance with lifestyle recommendations after CRC diagnosis, including an increase in vegetable consumption [13-15], an increase in physical activity [13], a decrease in alcohol intake [14], and quitting smoking [15]. In contrast, some prospective studies did not report notable changes in health behaviors after CRC diagnosis—including physical activity [15], alcohol intake [15], or body mass index (BMI) [13]—or even reported changes not in concordance with lifestyle recommendations, such as a decrease in physical activity [16].

Although several studies reported on changes in health behaviors after CRC diagnosis, no studies have examined how these changes are interrelated and few studies tracked behaviors over a 2-year period. Cancer survivors may be inclined to make changes in more than one health behavior [13], but it is unknown whether these changes are correlated with each other. Furthermore, it remains unknown how changes in specific health behaviors impact overall concordance with lifestyle recommendations. The present prospective study aimed to assess changes in health behaviors and overall lifestyle in the first two years following CRC diagnosis. We analyzed changes in overall lifestyle by assessing concordance with the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) recommendations. Furthermore, we characterized interrelationships between changes in health behaviors.

Methods

Study design and population

We used data from the COLON study, an ongoing prospective multicenter cohort study among CRC patients [17]. From 2010 onwards, newly diagnosed patients with colon or rectal cancer were recruited in 11 hospitals in the Netherlands. Hospital staff invited eligible patients during a routine clinical visit before scheduled surgery. Patients were not eligible when they had a history of CRC, a previous (partial) bowel resection, known hereditary CRC, inflammatory bowel disease, dementia or another mental condition limiting their ability to fill out surveys, or were non-Dutch speaking. Data were collected at baseline (shortly after diagnosis, before treatment started) and at six months and two years after diagnosis. All study participants provided written informed consent and the study was approved by the local review board.

This study was performed using data of all participants diagnosed with stage I-III CRC between 2010 and 2015 (n=1241). Participants were excluded when information on lifestyle was available for <2 time points (n=169). Thus, data of 1,072 participants remained for analyses. Patients with stage IV disease were excluded a priori, because survival for these patients is generally poor and changes in diet and lifestyle may reflect poor health.

Data collection

Habitual dietary intake was assessed with a 204-item semi-quantitative food frequency questionnaire (FFQ) at baseline and six months and two years after CRC diagnosis. The FFQ was developed by the Division of Human Nutrition and Health, Wageningen University & Research, the Netherlands. The reference period for the FFQ was the month before diagnosis at baseline, and the previous month during follow-up. To assess amounts of food intake, we combined frequencies of intake with standard portion sizes and household measures [18]. The FFQ was previously validated [19] and slightly adapted to be able to distinguish meat intake with respect to red, processed, and white meat. Self-reported dietary intake data from the FFQ were converted into fiber and alcohol intake based on the 2011 Dutch food composition Table [20]. Items of interest included fruits, vegetables, dietary fiber, ultra-processed foods, red and processed meat, sugary drinks, and alcohol.

In addition to the FFQ, participants filled out other lifestyle questionnaires. These questionnaires included questions on weight, waist circumference, physical activity, and smoking status. Patients reported weight at diagnosis and at six months and two years after diagnosis, while height was only reported at diagnosis. BMI was computed in kg/m^2. Waist circumference (midway between the lowest rib and the iliac crest) was measured with a tape sent to participants. Moderate-to-vigorous physical activity was self-reported by the validated SQUASH questionnaire [21-23]. Moderate-to-vigorous physical activity included

all activities (walking, cycling, gardening, odd-jobs, sports, household activities, and work) with a metabolic equivalent value ≥3 [24]. To ensure quality of the data, we checked each questionnaire after completion and contacted participants by telephone for clarification if needed.

Information was obtained on demographics, side-effects of treatment, and clinical factors. Demographic information, including level of education and living situation, was self-reported at diagnosis. Furthermore, participants reported if they changed their diet before diagnosis due to bowel complaints and if they experienced side-effects of treatment at six months and two years after diagnosis. Clinical factors were retrieved from the Dutch ColoRectal Audit [25], and included disease stage, tumor site, receipt of neo-adjuvant treatment, stoma placement after surgery, receipt of adjuvant chemotherapy, and presence of co-morbidities. Recurrence data (loco-regional or distant recurrence) were retrieved from the medical records by the Netherlands Cancer Registry.

WCRF/AICR lifestyle score

We quantified the degree of concordance between participants' lifestyles and the 2018 WCRF/AICR recommendations for cancer prevention using the standard WCRF/AICR score developed by Shams-White *et al.* [26] as measure of overall lifestyle. The score included 7 recommendations (**Table 1**), as the recommendation on breastfeeding was not applicable to our study population. The recommendations about dietary supplement use and cancer survivors were not included, since they were not operationalized in the standard WCRF/AICR score (Shams-White *et al*., submitted for publication). We assigned, for each component, 1 point when the recommendation was met (full concordance), 0.5 points when it was partially met (moderate concordance), and 0 points otherwise (low concordance). Quantitative criteria were used as cut-off points, except for the recommendation on ultra-processed foods where cut-offs were based on tertiles calculated as percentage of total energy intake from ultra-processed foods. Two recommendations (healthy weight and diet rich in wholegrains, vegetables, fruit and beans) included sub-recommendations. For these recommendations the recommendation score was the sum of each sub-recommendation score (meaning that plausible scores were 0, 0.25, 0.5, 0.75, and 1). The overall score ranged from 0 to 7, with higher scores indicating greater concordance with the 2018 WCRF/AICR recommendations.

Statistical analyses

To describe the study population we used descriptive analyses of demographic, clinical and lifestyle characteristics of the participants. Furthermore, we calculated concordance with the 7 WCRF/AICR recommendations at diagnosis and six months and two years after diagnosis.

Table 1. Description of the standardized WCRF/AICR score based on the 2018 WCRF/AICR recommendations for cancer prevention[a]

WCRF/AICR recommendations	Goal	Operationalization[b]	Scoring
1) Be a healthy weight.[c]	1a) Ensure that body weight during childhood and adolescence projects towards the lower end of the healthy adult BMI range	Not operationalized.	-
	1b) Keep your weight as low as you can within the healthy range throughout life	BMI (in kg/m^2): 18.5-24.9 BMI: 25 to <30 BMI: <18.5 or ≥30	0.5 0.25 0
	1c) Avoid weight gain (measured as body weight or waist circumference) throughout adulthood	WC men: <94 cm WC women: <80 cm WC men: 94 to <102 cm WC women: 80 to <88 cm WC men: ≥102 cm WC women: ≥88 cm	0.5 0.25 0
2) Be physically activity.	2a) Be at least moderately physically active, and follow or exceed national guidelines	MVPA: ≥150 min/week MVPA: 75 to <150 min/week MVPA: <75 min/week	1 0.5 0
	2b) Limit sedentary habits	Not operationalized.	-
3) Eat a diet rich in wholegrains, vegetables, fruit and beans.[c]	3a) Consume a diet that provides at least 30 grams per day of fiber from food sources	Dietary fiber intake: ≥30 g/d Dietary fiber intake: 15 to <30 g/d Dietary fiber intake: <15 g/d	0.5 0.25 0
	3b) Include in most meals foods containing wholegrains, non-starchy vegetables, fruit and pulses (legumes) such as beans and lentils.	Not operationalized.	-
	3c) Eat a diet high in all types of plant foods including ≥ 5 portions/ servings (≥400 g) of a variety of non-starchy vegetables and of fruit every day	F&V intake: ≥400 g/d F&V intake: 200 to <400 g/d F&V intake: <200 g/d	0.5 0.25 0
	3d) If you eat starchy roots and tubers as staples, eat non-starchy vegetables, fruit and pulses (legumes) regularly too if possible	Not operationalized.	-
4) Limit consumption of 'fast foods' and other processed foods high in fat, starches or sugars.	4a) Limit consumption of processed foods high in fat, starches or sugars – including 'fast foods'; many pre-prepared dishes, snacks, bakery foods and desserts; and confectionary (candy)	Ultra-processed foods: T1 (≤23.7 en%) Ultra-processed foods: T2 (23.7 to ≤32.0 en%) Ultra-processed foods: T3 (>32.0 en%)	1 0.5 0

Table 1. Continued

5) Limit consumption of red and processed meat.	5a) If you eat red meat, limit consumption to no more than about three portions per week. Three portions is equivalent to about 350 to 500 grams cooked weight of red meat. Consume very little, if any, processed meat	Red meat ≤500 g/wk and processed meat intake <21 g/wk Red meat ≤500 g/wk and processed meat intake 21 to <100 g/wk Red meat and processed meat >500 g/wk or processed meat intake ≥100 g/wk	1 0.5 0
6) Limit consumption of sugar sweetened drinks.	6a) Do not consume sugar sweetened drinks	Sugary drink intake: 0 g/d Sugary drink intake: ≤250 g/d Sugary drink intake: >250 g/d	1 0.5 0
7) Limit alcohol consumption.	7a) For cancer prevention, it's best not to drink alcohol	Alcohol intake: 0 g/d Alcohol intake men: ≤20 g/d (2 drinks) Alcohol intake women: ≤10 g/d (1 drink) Alcohol intake men: >20 g/d (2 drinks) Alcohol intake women: >10 g/d (1 drink)	1 0.5 0
8) Do not use supplements for cancer prevention.	8a) High-dose dietary supplements are not recommended for cancer prevention - aim to meet nutritional needs through diet alone	Not operationalized.	-
9) For mothers: breastfeed your baby, if you can.	9) This recommendation aligns with the advice of the World Health Organization, which recommends infants are exclusively breastfed for 6 months, and then up to 2 years of age or beyond alongside appropriate complementary foods	Not applicable to this population	-
10) After a cancer diagnosis: follow our recommendations, if you can.	10a) All cancer survivors should receive nutritional care and guidance on physical activity from trained professionals.	Not operationalized.	-
	10b) Unless otherwise advised, and if you can, all cancer survivors are advised to follow the Cancer Prevention Recommendations as far as possible after the acute stage of treatment.	Not operationalized.	-

[a] BMI, body mass index; en%, energy percentage; F&V, fruit and vegetables; MVPA, moderate-to-vigorous physical activity; T, tertile; WC, waist circumference; WCRF/AICR, World Cancer Research Fund / American Institute for Cancer Research

[b] Ultra-processed foods included French fries, crisps, pastry and biscuits, savory snacks, sugar and candy, sauces, pizza, pancake, sandwich fillings high in sugar or fat, refined grain products, and sweet dairy desserts. Not included were yoghurt and cheese, nuts, oils and fats, sugary drinks, processed meat, and diet soft drinks. Calculated as energy intake from ultra-processed foods of total energy intake. Sugary drinks included sugar-sweetened soft drinks, sugar-sweetened dairy drinks, and fruit juices.

[c] The score for recommendations 1 and 3 was the result of summing the scores of each sub recommendation

To describe changes over time in health behaviors in the first two years after CRC diagnosis, we used linear mixed models. Linear mixed models take into account both the individual trajectories of change and population averages by using all available measurements and including participants with incomplete data [27]. Each health behavior was modelled separately by using the 3 repeated measurements of that dependent variable. Time was scaled in years (continuous) and calculated as date of survey completion minus the date of study enrolment (i.e. shortly after diagnosis). All models included a random intercept, while a random slope was only included when this resulted in a better fit of the model (i.e. for BMI and ultra-processed foods). Inclusion of a random slope in the model means that the change over time can vary between participants. Changes were considered to be in concordance with lifestyle recommendations when the changes were as follows: an increase in physical activity, dietary fiber, fruit and vegetable intake or a decrease in BMI, waist circumference, red and processed meat, ultra-processed foods, sugary drinks, or alcohol intake.

To assess if multiple changes in different health behaviors led to a change in overall lifestyle, we modelled the 3 repeated measures of the WCRF/AICR lifestyle score as dependent variable in a linear mixed model with random slope (in the same way as described above). To assess if changes in overall lifestyle varied between subgroups, we included a grouping factor and its interaction term with time in the mixed models. As grouping factors, baseline demographic determinants (sex, age, education, and living situation), clinical characteristics (stage, tumor site, stoma, neo-adjuvant treatment, adjuvant chemotherapy, and comorbidities) and self-reported side-effects of treatment were included, each in a separate model.

To further assess the interrelatedness between changes in multiple health behaviors, we assessed change in concordance to the 7 components of the WCRF/AICR lifestyle score. We assessed the proportion of participants who did change concordance to ≥1 component(s), who only improved or only deteriorated concordance to ≥1 component(s), and who both improved and decreased concordance to components of the lifestyle score. Furthermore, we assessed Pearson correlations between changes in health behaviors.

By using two separate sensitivity analyses, we evaluated the robustness of our reported changes in lifestyle. The potential influence of recurrent CRC or pre-diagnosis illness on changes in lifestyle were determined by excluding participants diagnosed with a recurrence within two years of follow-up (n=98) and by excluding those who reported pre-diagnosis changes in diet due to bowel complaints (n=129), respectively. All statistical analyses were conducted using SAS 9.4 software (SAS Institute, Cary NC). A p-value <0.05 was considered statistically significant.

Results

Study population

Participants had a mean ± SD age of 65 ± 9 years, 63% was male, 67% had colon cancer, and 11% was a current smoker at diagnosis (**Table 2**). Stage III disease was more common (43%) than stage II (30%) or stage I disease (26%).

Table 2. Baseline demographic, clinical and lifestyle characteristics.

	Total
N	1072
Age at diagnosis (mean ± SD), years	65 ± 9
Men (%)	680 (63%)
Education level[a]	
low	463 (43%)
medium	263 (25%)
high	342 (32%)
Living with partner[a]	903 (84%)
Tumor stage	
I	284 (26%)
II	325 (30%)
III	463 (43%)
Tumor site	
colon	719 (67%)
rectum	353 (33%)
Neo-adjuvant therapy (%)	258 (24%)
Adjuvant chemotherapy (%)[b]	258 (24%)
Stoma (%)[2]	312 (29%)
Experienced side-effects of treatment (6 mo. after diagnosis)[a]	689 (65%)
Experienced side-effects of treatment (2y after diagnosis)[c]	500 (53%)
Co-morbidity at diagnosis (%)[a]	709 (66%)
Current smoker at diagnosis (%)[a]	116 (11%)
BMI (kg/m^2)	
<18.5	8 (1%)
18.5-25	411 (38%)
25-30	469 (44%)
30-35	150 (14%)
>35	34 (3%)

Education level: low, primary and pre-vocational; medium, secondary and vocational; high, university.
[a] Data of 3 to 10 participants were missing/unknown
[b] Data of 23 to 29 participants were missing/unknown
[c] Data of 124 participants were missing/unknown;

Concordance with lifestyle recommendations

Participants showed large variation in their concordance with the WCRF/AICR lifestyle recommendations (**Figure 1**). Upon CRC diagnosis, few participants reported full concordance with the dietary recommendations. Lowest concordance was observed for the recommendation to limit intake of red and processed meat (8%) and highest concordance was observed for the recommendation to limit intake of ultra-processed foods (33%). In contrast, the majority of patients (90%) adhered to the physical activity recommendation at CRC diagnosis. Furthermore, 38% of patients had a BMI within the healthy range and 24% had a healthy waist circumference.

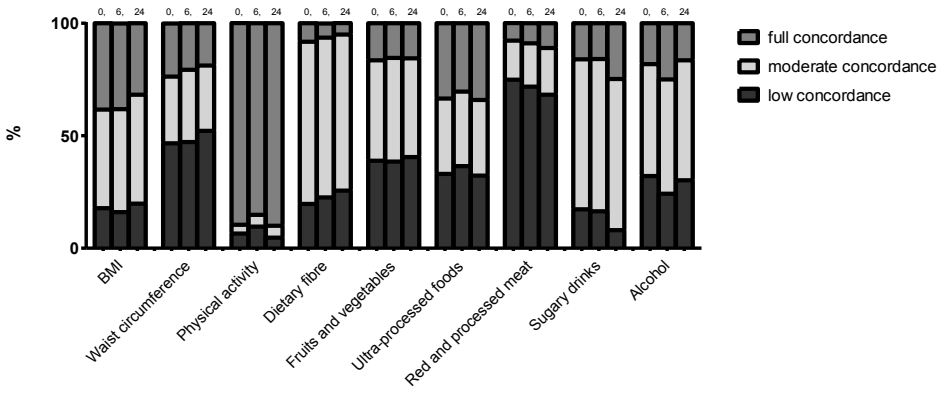

Figure 1. Concordance with the 2018 World Cancer Research Fund/American Institute for Cancer Research lifestyle recommendations at 0, 6 and 24 months after colorectal cancer diagnosis.

Change in health behaviors

Some changes in concordance with the WCRF/AICR lifestyle recommendations were seen in the first two years after diagnosis for specific health behaviors (**Table 3**). Most improvement was noted for sugary drinks (-45 g/day) and red and processed meat intake (-62 g/week). Changes not in concordance with the recommendations were the decrease in fiber intake (1 g/day) and the increase in BMI (0.4 kg/m^2) and waist circumference (2 cm). On average, participants did not change their intake of fruit and vegetables, ultra-processed foods, nor did they change their smoking behavior ($p>0.05$). Participants initially decreased their intake of alcohol and their physical activity level in the first six months after diagnosis. Although alcohol intake and physical activity levels were still lower two years after diagnosis compared to diagnosis, these decreases were not statistically significant.

Table 3. Changes in lifestyle in the first 2 years after colorectal cancer diagnosis, sorted by effect size (n=1072).

	Baseline[a]	6 months after diagnosis	2 years after diagnosis	Change from diagnosis to 2 years after diagnosis[b]	Effect size[c]	P-trend[d]
n	1066	1056	931			
WCRF/AICR score	3.4 ± 0.9	3.4 ± 0.9	3.5 ± 0.9	0.1	0.10	<0.001
Sugary drinks (g/day)[e]	128 ± 165	127 ± 161	83 ± 120	-45	-0.30	<0.001
Red & processed meat (g/week)	485 ± 263	455 ± 257	423 ± 255	-62	-0.24	<0.001
Dietary fiber (g/day)	20 ± 7	20 ± 6	19 ± 6	-1	-0.15	<0.001
Physical activity (min/week)	852 ± 723	621 ± 566	766 ± 650	-86	-0.13	0.16
Waist circumference (cm)	96 ± 12	96 ± 12	98 ± 12	2	0.11	<0.001
BMI (kg/m^2)	26.5 ± 4.0	26.4 ± 3.8	26.9 ± 4.0	0.4	0.09	<0.001
Alcohol (g/day)	14 ± 17	11 ± 14	13 ± 14	-1	-0.08	0.06
Fruit & vegetables (g/day)	261 ± 147	258 ± 142	258 ± 145	-3	-0.03	0.38
Ultra-processed foods (en%)[f]	28.4 ± 10.4	28.9 ± 10.1	28.2 ± 10.5	-0.2	-0.02	0.10
Current smoker (%)	11%	8%	9%	-2	-0.09	0.19

[a] Mean ± SD (all such values).
[b] Year 2 – baseline
[c] Effect size = 2y change / pooled SD;
[d] P-trend values were based on linear mixed models that included the three repeated measurements. For smoking a logistic mixed model was used.
[e] Sugary drinks included sugar-sweetened soft drinks, sugar-sweetened dairy drinks, and fruit juices.
[f] Ultra-processed foods included French fries, crisps, pastry and biscuits, savory snacks, sugar and candy, sauces, pizza, pancake, sandwich fillings high in sugar or fat, refined grain products, and sweet dairy desserts. Not included were yoghurt and cheese, nuts, oils and fats, sugary drinks, processed meat, and diet soft drinks. Intake of ultra-processed foods was shown in energy percentage (energy intake ultra-processed foods / total energy intake * 100%).

Interrelationships between changes

Although participants changed some health behaviors, overall lifestyle improved only marginally. Overall lifestyle changed from a mean (±SD) 3.4 ± 0.9 at diagnosis to 3.5 ± 0.9 two years later ($p<0.001$) (Table 3). Two year changes in overall lifestyle did not statistically significant differ between subgroups based on demographics (sex, age, education), clinical characteristics (stage, tumor site, treatment, comorbidities), or self-reported side effects of treatment (data not shown). The only difference between subgroups was noted for living situation. Participants living without partner had a better 2-year improvement in overall lifestyle (+0.2) than participants living with their partner (+0.1, $p_{interaction}=0.04$), while overall lifestyle was similar at diagnosis.

Almost all participants (92%) changed concordance with at least 1 of the 7 WCRF/AICR lifestyle recommendations in the first two years after CRC diagnosis. Seventy percent of participants improved concordance with at least 1 recommendation. About half (51%) of participants made simultaneous changes that resulted in both improved concordance with ≥1 component as well as deteriorated concordance with another component of the lifestyle score. Furthermore, 20% of participants only improved their concordance and 24% only decreased their concordance.

Although many participants made simultaneous changes, participants did not show a clear pattern of changes in health behaviors (**Figure 2**). Correlations between 2-year changes in health behaviors ranged from r=-0.11 to r=0.14. An exception was seen for the correlation between changes in dietary fiber and fruits and vegetable intake (r=0.56).

Sensitivity analyses

No differences in effect sizes were observed after excluding participants who reported to have made pre-diagnosis changes in diet due to bowel complaints (n=129), although the decrease in physical activity and alcohol intake became statistically significant (p=0.05 and p=0.04, respectively; data not shown). The effect sizes also did not differ when we excluded participants diagnosed with a recurrence within two years after diagnosis (n=98), although the decrease in ultra-processed foods became statistically significant (p=0.05).

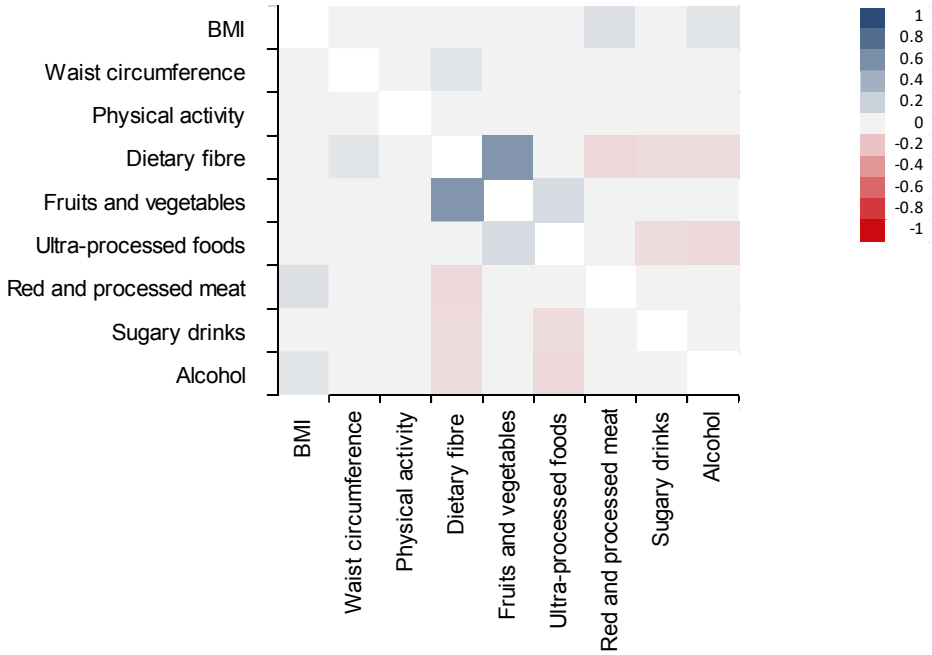

Figure 2. Pairwise correlations for changes in health behaviors included in the 2018 World Cancer Research Fund/ American Institute for Cancer Research score in the first 2 years following a colorectal cancer diagnosis. A blue square represents a positive correlation in which both changes go in the same direction. A red square represents an inverse correlation in which one change is in line with the recommendations and the other is not. The darker the color, the stronger the correlation. A grey square represents a non-significant correlation (p>0.05).

Discussion

In this prospective observational study, CRC survivors with stage I-III disease only marginally changed their overall lifestyle in the first two years after CRC diagnosis. Lifestyle was not in concordance with many of the WCRF/AICR lifestyle recommendations for cancer prevention during that period. Largest changes were noted for sugary drinks and red and processed meat intake. These improvements did not necessarily lead to a higher overall lifestyle score, as half of participants made simultaneous changes that resulted in both improved concordance with one component as well as deteriorated concordance with another component of the lifestyle score.

The current study was the first that characterized interrelationships between health behavior changes after CRC diagnosis. Overall lifestyle, as reflected by the 2018 WCRF/AICR score, only changed marginally from 3.4 at diagnosis to 3.5 two years after diagnosis. No differences in lifestyle changes were observed by clinical characteristics -such as stage, tumor site, treatment, or presences of comorbidities-, demographics, or self-reported side-effects

of treatment. The only difference between subgroups was that participants living without partner made slightly larger improvements to their overall lifestyle compared to those living with their partner. The overall improvement of 0.1 on the 7-point scale is probably not relevant, as it is an improvement of only 1%. Although almost all participants (92%) changed concordance with at least one WCRF/AICR lifestyle recommendation, participants did not show a clear pattern of simultaneous changes in health behaviors.

As this was the first study that examined changes in overall lifestyle in CRC patients, we can only compare our results on changes in specific health behaviors with previous studies in CRC patients. The largest observed change in our study was a decrease in sugary drink intake by 45 g/day, equivalent to a decrease of 2 servings (2x 150g) per week. Ours was the first study that assessed changes in sugary drink intake after CRC diagnosis. The second largest observed change was a decrease in red and processed meat intake by 62 g/wk. This is equivalent to, for example, a combined decrease of 0.3 serving (0.3x 100g) of red meat per week and 2 servings of processed meat (2x 16g as sandwich filling) per week and is in line with previous prospective studies [14, 15].

Changes not in line with the lifestyle recommendations were the slight decrease in fiber intake (1 g/day) and the slight increase in BMI (0.4 kg/m^2) and waist circumference (2 cm). Also several other studies have reported that weight gain after diagnosis is common among CRC patients [15, 28-32]. However, we previously concluded that post-diagnosis weight gain was mainly observed in individuals who lost weight before CRC diagnosis and post-diagnosis weight was similar to pre-diagnosis weight in this study population [33]. Participants did not change their intake of ultra-processed foods or fruit and vegetables, while the intake of alcohol and levels of physical activity tended to decline, especially in the first 6 months after diagnosis. Although previous prospective studies have shown an increase in vegetable intake after CRC diagnosis [13-15], results for changes in other health behaviors are inconsistent between studies [13-16, 34]. Together, these results suggest that CRC survivors improve some health behaviors after diagnosis, but other health behaviors may worsen after CRC diagnosis.

Overall, our findings provide little evidence that a CRC diagnosis triggers desirable lifestyle changes over and above lifestyle trends in the general adult population. Participants showed encouraging trends over time in sugary drinks and red and processed meat intake, in line with general health and nutrition advice. However, these trends have also been noted in the general Dutch adult population [35]; the intake of sugary drinks decreased with 49 g/day and the intake of red and processed meat decreased with 42 g/wk in the period between 2012 and 2016. Furthermore, two previous studies have concluded that changes in health behaviors did not differ between CRC survivors and people without a cancer diagnosis [13,

15]. Together these results suggest that changes in lifestyle after a cancer diagnosis may not be particularly related to the cancer diagnosis.

Both the lack of improvement in overall lifestyle and the discrepancy between lifestyle guidelines and the practiced lifestyle behaviors indicate that lifestyle support is needed after CRC diagnosis. Previous studies [4-6, 36] also reported only moderate concordance with lifestyle recommendations at cancer diagnosis and thereafter, leaving room for improvement in different lifestyle behaviors. Although there is growing evidence that healthier lifestyles after diagnosis are important for CRC outcomes, the evidence that changing these behaviors would alter the clinical course of CRC is limited [2, 3]. However, the current understanding of cancer and its relations with diet and physical activity support the idea that cancer survivors should change their behavior in concordance to the WCRF/AICR lifestyle recommendations to improve their long-term outcomes [2]. Therefore, support and guidance for a healthy diet and physical activity should be included as part of cancer survivorship care [2, 37]. Few of our participants received guidance on a healthy lifestyle, as is currently the case for most cancer survivors [7, 8]. Research is needed to evaluate the most effective support and to define the benefits of lifestyle changes in cancer survivors.

Given the probable improvement in prognosis with a healthy lifestyle, it is important that healthcare providers discuss lifestyle behaviors with their cancer patients. Three actions appear to be key steps in interventions to support a healthy lifestyle: asking, advising, and arranging, especially for the oncologist [38]. For example, the oncologist could ask how many minutes per week do you do exercise. If the answer is 150 or more, the oncologist can provide positive reinforcement; if not, the oncologist can advise to strive to do so and arrange referral to a trained exercise professional when needed. Using this approach, the oncologist can initiate and reinforce behaviour change, but a trained professional should oversee and support the process of behaviour change.

Potential limitations of our study should be considered. Diet and lifestyle were self-reported at each time point, thus only people who were motivated to fill out such questionnaires were included. This could potentially limit generalizability of the results. However, ranges of dietary intakes, physical activity, and BMI were broad and overlapped with national estimates [39-41] and CRC survivors not interested to participate in the study are unlikely to make more or larger improvements in lifestyle. Furthermore, self-reporting might lead to measurement error with regard to lifestyle changes. Generally, systematic errors are present in self-reported lifestyle data; some people underreport, while others overreport. However, participants are likely to have internal consistency in their reporting [42]. Therefore, changes in lifestyle may be less prone to such bias than single lifestyle measurements. Second, a large part of our study population (90%) was active at or over the recommended 150 min/week. This is slightly higher than the general Dutch population aged 65-80 years, in

which 76% meets the physical activity recommendation [43]. However, this activity level was similar to the 91% concordance to the physical activity guideline that was found in another study among Dutch CRC survivors [10]. The lack of increase in physical activity might be due to our active study population, since an increase in physical activity has been observed before in CRC survivors in the United States [13], where the proportion meeting the activity recommendation is much lower. Similarly, our study population contained few current smokers at diagnosis (11%), which might explain a lack of decrease in smoking. Third, we assumed that diet and lifestyle at diagnosis represents usual pre-diagnosis diet and lifestyle although these might have been altered because of illness. However, no differences in changes in overall lifestyle and specific health behaviors were observed after excluding participants who reported to have made pre-diagnosis changes in diet due to bowel complaints. Fourth, disease recurrence may influence lifestyle. However, when we excluded participants diagnosed with a recurrence within two years after diagnosis, our results did not change. Another limitation might be the potential influence of side-effects of treatment on lifestyle. Those side-effects are more likely to impact lifestyle at six months after diagnosis than two years after diagnosis, as chemotherapy is usually not completed within six months after diagnosis and also recovery from surgery might not be complete yet. Therefore, we focused our analyses on two year changes, while still taking six month changes into account. Two year changes represent relatively long-term changes that are sustained over prolonged time. These long-term changes are more likely to impact cancer outcomes than short-term changes and are therefore considered as the most relevant changes.

This study has several strengths. First, the COLON study provided an opportunity to prospectively study changes in multiple health behaviors and overall lifestyle in the first 2 years after diagnosis. We used mixed models to examine these changes after CRC diagnosis. An advantage of mixed models is that participants with incomplete lifestyle data during follow-up were still included in the analyses. Second, we had detailed clinical information available and we were thus able to compare lifestyle changes between different subgroups. No differences in lifestyle changes were observed by clinical characteristics, such as stage or tumor site.

In conclusion, our results show that overall lifestyle only marginally changed in the two years following CRC diagnosis. Future studies are needed to confirm our findings and to assess how post-diagnosis changes in lifestyle relate to recurrence, survival, and the development of co-morbidities. The growing evidence that healthier lifestyles are important for long-term cancer outcomes [3] highlights the need for strategies to effectively support health behavior change in CRC survivors.

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Author contributions
Conceptualization: Moniek van Zutphen, Hendriek C. Boshuizen, Ellen Kampman, Fränzel J.B. van Duijnhoven; Formal analysis: Moniek van Zutphen; Writing – original draft: Moniek van Zutphen; Writing – review & editing: Moniek van Zutphen, Hendriek C. Boshuizen, Dieuwertje E. Kok, Harm van Baar, Anne J.M.R. Geijsen, Evertine Wesselink, Renate M. Winkels, Henk K. van Halteren, Johannes H.W. de Wilt, Ellen Kampman, Fränzel J.B. van Duijnhoven; Funding acquisition: Fränzel J.B. van Duijnhoven, Ellen Kampman, Moniek van Zutphen; Investigation: Moniek van Zutphen, Harm van Baar, Anne J.M.R. Geijsen, Evertine Wesselink; Resources: Henk K. van Halteren, Johannes H.W. de Wilt; Supervision: Ellen Kampman, Fränzel J.B. van Duijnhoven, Hendriek C. Boshuizen; Data curation: Moniek van Zutphen.

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Data availability
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Compliance with ethical standards
Conflict of interest
The authors declare that they have no conflict of interest.

Ethical approval
All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (Commissie Mensgebonden Onderzoek - CMO, region Arnhem-Nijmegen (The Netherlands), CMO

number 2009/347, ABR number NL30446.091.09) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included in the study.

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CHAPTER 4

An increase in physical activity after colorectal cancer surgery is associated with improved recovery of physical functioning: a prospective cohort study

Moniek van Zutphen | Renate M. Winkels | Fränzel J.B. van Duijnhoven | A. Suzanne van Harten-Gerritsen | Dieuwertje E.G. Kok | Peter van Duijvendijk | Henk K. van Halteren | Bibi M.E. Hansson | Flip M. Kruyt | Ernst J. Spillenaar Bilgen | Johannes H.W. de Wilt | Jaap J. Dronkers | Ellen Kampman

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Abstract

Background

The influence of physical activity on patient-reported recovery of physical functioning after colorectal cancer (CRC) surgery is unknown. Therefore, we studied recovery of physical functioning after hospital discharge by (a) a relative increase in physical activity level and (b) absolute activity levels before and after surgery.

Methods

We included 327 incident CRC patients (stages I-III) from a prospective observational study. Patients completed questionnaires that assessed physical functioning and moderate-to-vigorous physical activity shortly after diagnosis and 6 months later. Cox regression models were used to calculate prevalence ratios (PRs) of no recovery of physical functioning. All PRs were adjusted for age, sex, physical functioning before surgery, stage of disease, ostomy and body mass index.

Results

At six months post-diagnosis 54% of CRC patients had not recovered to pre-operative physical functioning. Patients who increased their activity by at least 60 min/week were 43% more likely to recover physical function (adjusted PR 0.57 95%CI 0.39-0.82), compared with those with stable activity levels. Higher post-surgery levels of physical activity were also positively associated with recovery (P for trend=0.01). In contrast, activity level before surgery was not associated with recovery (P for trend=0.24).

Conclusions

At six month post-diagnosis, about half of CRC patients had not recovered to preoperative functioning. An increase in moderate-to-vigorous physical activity after CRC surgery was associated with enhanced recovery of physical functioning. This benefit was seen regardless of physical activity level before surgery. These associations provide evidence to further explore connections between physical activity and recovery from CRC surgery after discharge from the hospital.

Keywords

recovery of function, colorectal surgery, colorectal cancer, physical activity, rehabilitation, epidemiology

Background

Surgery for colorectal cancer (CRC) is followed by a period of recovery which begins in hospital and continues after discharge [1, 2]. Postoperative recovery is a complex process encompassing physical, psychological, and social elements [1]. Clinicians have mainly focused their interest on assessing the in-hospital phases of recovery [1-3], but from a patient's perspective recovery is only complete when the patient returns to normal function in day-to-day life [1, 2, 4]. Therefore, recovery might be best estimated with measures of functional status [1].

Functional status is often evaluated with patient-reported outcomes, for example with physical functioning [5, 6] or activities of daily living [7]. Low physical functioning is associated with disability and a loss of independence [8]. Following a rapid decline after CRC surgery [1, 9, 10], patient physical function scores return to pre-operative values [9, 10]. However, not all individual CRC patients recover to their pre-operative level of physical functioning. In a study among patients over 60 years of age undergoing major abdominal surgery for mixed reasons, less than 50% of patients recovered to baseline levels of functional status at 6 months after surgery [11]. Furthermore, 10% of patients were still unable to perform basic activities of daily living [11]. Recovery depends on clinical factors such as location of the tumor, presence of an ostomy, and patient characteristics (age and physical functioning before surgery) [12, 13].

Apart from patient and clinical factors, recovery of physical functioning could also be influenced by physical activity. Several studies consistently indicate that physically active older adults [14, 15] and physically active CRC survivors [6, 16-21] have higher physical functioning. The influence of physical activity on recovery of physical functioning after CRC surgery is unknown. Therefore, the aims of the present study are first to assess the proportion of CRC patients without patient-reported recovery of physical functioning at six months post-diagnosis. Second, we examine the association between patient-reported recovery of physical functioning and (a) an increase in moderate-to-vigorous physical activity from pre-to-post surgery and (b) absolute activity levels before and after surgery.

Methods

Study population

This study is embedded in the COLON-study [22]. In this prospective cohort study, data were collected from newly diagnosed CRC patients in any stage of the disease. Patients were excluded when they had a history of colorectal cancer or (partial) bowel resection, chronic inflammatory bowel disease, a known hereditary colorectal cancer syndrome, dementia or another mental condition, or were non-Dutch speaking. Eligible participants were invited by hospital staff to participate in the study during a routine clinical visit before scheduled surgery. Response rates varied from 35% to 70% in the four hospitals that reported non-responders; overall response rate was estimated to be 50%. Approval for the study was obtained from the Committee on Research involving Human Subjects, region Arnhem-Nijmegen (The Netherlands) and all participants provided written informed consent.

Participants were asked to fill out several mailed questionnaires shortly after diagnosis, but before start of clinical treatment, and 6 months later. Individuals in the current analysis included all COLON-study participants that were recruited between August 2010 and November 2013. Follow-up data collection was completed in May 2014.

Physical functioning

Physical functioning was assessed using the validated European Organization for Research and Treatment of Cancer quality-of-life questionnaire (EORTC QLQ-C30), translated in Dutch [23]. The physical functioning scale contained five questions (trouble with strenuous activities / long walk / short walk / need to stay in bed or chair during the day / basic activities of daily living). The answers ranged from 'not at all' to 'very much'. A summary score that ranged from 0 (worst) to 100 (best) was calculated according to the EORTC scoring manual [24]. At six months post-diagnosis patients were considered to be either recovered or not recovered. No recovery of physical functioning was predefined as a physical functioning score at 6 months post-diagnosis that was at least five points lower than before surgery. This decrease is considered a clinically relevant change [25].

Physical activity

Physical activity was assessed using the validated Short QUestionnaire to ASsess Health enhancing physical activity (SQUASH) [26-28]. Participants were asked to report their average time (days per week, hours and minutes per day) spent in walking, cycling, gardening, odd-jobs, sports, household activities and work. Based on the self-reported intensity level of each activity a metabolic equivalent (MET) value was assigned [29]. We used 3.3 MET as the lower cut-off for moderate activity [15]. However, in accordance with the SQUASH manual and the Dutch physical activity guideline, 4.0 MET was used as a cut-off value for those aged <55y. The change in physical activity from pre-to-post surgery was classified into three

pre-defined groups (stable, increase and decrease). When pre-to-post surgery moderate-to-vigorous physical activity changed less than 60 min/wk, this was considered a stable activity level; otherwise it was classified as a decrease or increase in activity. CRC surgery might result in a prolonged low physical functioning and therefore a reduced ability to be physically active. A decreased post-operative physical activity level might thus be the result of not being recovered. Therefore, we made the a priori decision to focus our analysis on the group that had the ability to be active at pre-surgery level six months after diagnosis.

Covariates

Socio-demographic characteristics, smoking, body mass index (BMI) and presence of comorbidities were assessed with a self-administered questionnaire shortly after diagnosis. Clinical characteristics (such as tumor location, stage of disease and treatment) were retrieved from medical record abstraction.

Statistical analyses

Descriptive statistics were used to assess the proportion of CRC patients not recovered at six months post-diagnosis and to describe participant characteristics by recovery of physical functioning. Cox regression models (with robust error variance and constant risk period assigned to all participants) were used to calculate adjusted prevalence ratios (PRs) of no recovery of physical functioning at six months post-diagnosis. This method was chosen instead of logistic regression, because it is a better alternative for the analysis of binary outcomes [30]. A PR>1.0 means that the proportion of people without recovery is greater in those with the exposure. A PR<1.0 means there is a lower prevalence of people without recovery; in other words, more people with the exposure of interest are recovered when the PR<1.0. The primary exposure of interest was an increase in physical activity from pre-to-post surgery. In addition, we examined the absolute level of physical activity before and after surgery in relation to recovery. Next, we stratified our main analysis on pre-surgery physical activity level, to explore if the magnitude of benefit was dependent on the starting level of physical activity. Age (years), sex, and physical functioning before surgery (score) were predefined covariates. Furthermore, stage of disease (I, II, and III), ostomy (yes, no), and BMI (kg/m^2) were covariates in all models because they yielded a >10% change in the PR estimate. In addition to the main covariates described above, other potential confounders were evaluated for inclusion in the Cox regression models. However, none of the variables tested [living with a partner (yes, no), smoker before surgery (yes, no), cancer site (colon, rectum), neo-adjuvant therapy (yes, no), adjuvant chemotherapy (yes, no), ostomy reversal (yes, no), length of hospital stay >10 days (yes, no), and having one or more comorbidity (yes, no)] yielded an important change (<10%) in the PR estimate and were therefore not included. The P-value for the linear trend test across categories of physical activity was calculated by using the median value of each category as a continuous variable. All analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC).

Results

Participant characteristics

A total of 515 CRC patients were included in the COLON study. Patients were excluded from analysis when they had stage IV disease or an unknown disease stage (n=63), did not undergo tumor resection (n=7), had long course neo-adjuvant therapy (n=45) or when post-surgery physical functioning was assessed within 8 weeks after tumor resection (n=2). Furthermore, 71 patients were excluded from analyses since they did not provide any information on physical activity and/or physical functioning before surgery (n=31) or 6 months post-diagnosis (n=40). Therefore, a total of 327 participants were available for analyses.

At six months post-diagnosis (164 ± 25 days after tumor resection) 54% (n=178) of CRC patients had not recovered to pre-operative physical functioning. Socio-demographic characteristics such as age, sex and education level were similar between the two groups (**Table 1**). Patients who had not recovered were more often smokers and had a BMI≥30 kg/m^2 compared with patients who had recovered. Furthermore, we observed that patients who had not recovered were more often rectal cancer patients and received additional treatment following surgery compared to patients who had recovered.

Participants who did not provide information on physical activity and/or physical functioning (n=71) were on average slightly older (69 y vs 65 y), female (51% vs 39%), rectal cancer patients (34% vs 28%), and of more advanced disease stage (stage III disease (44% vs 36%)), than the included subjects (n=327).

Increase in physical activity after surgery

About 25% (n=81) of patients were able to increase their level of physical activity from diagnosis to six months post-diagnosis. Those patients were 43% more likely to be recovered (adjusted PR 0.57; 95%CI 0.39-0.82) compared with patients who had a stable activity level (n=42) (Table 2). When the increase in physical activity was split into two groups, both an increase of 60-240 min/wk (adjusted PR 0.53; 95%CI 0.32-0.87) and an increase of ≥240 min/wk (adjusted PR 0.60; 95%CI 0.38-0.95) showed similar associations with recovery (**Figure 1A**).

A sensitivity analyses was conducted whereby we repeated our analysis in the subsample of patients treated with surgery only (n=168). This sensitivity analyses showed that patients who increased their activity level were 50% more likely to be recovered (adjusted PR 0.50; 95%CI 0.24-1.01) compared with patients who had a stable activity level.

Table 1. Characteristics of colorectal cancer patients, overall and by patient-reported recovery of physical functioning at six months after surgery.

		Recovery of physical functioning	
	Total	**Yes**	**No**
		46%	54%
	(n=327)	(n=149)	(n=178)
Socio-demographic characteristics[1]			
Age (y)[2]	65 ± 10	66 ± 9	65 ± 10
Male	198 (61%)	87 (58%)	111 (62%)
Education level			
Low	155 (47%)	69 (46%)	86 (48%)
Middle	66 (20%)	31 (21%)	35 (20%)
High	106 (32%)	49 (33%)	57 (32%)
Living with partner	263 (80%)	119 (80%)	144 (81%)
Lifestyle characteristics			
Smoking status			
Never	99 (30%)	50 (34%)	49 (28%)
Former	188 (58%)	85 (58%)	103 (58%)
Current smoker before surgery	38 (12%)	12 (8%)	26 (15%)
Body mass index before surgery (kg/m^2)			
<20	13 (4%)	9 (6%)	4 (2%)
≥20-25	134 (41%)	63 (42%)	71 (40%)
≥25-30	141 (43%)	68 (46%)	73 (41%)
≥30	39 (12%)	9 (6%)	30 (17%)
≥ 150 min/wk physical activity before surgery	281 (86%)	126 (85%)	155 (87%)
Physical activity before surgery (h/wk)	9.0 (4.5-17.8)	8.5 (4.0-17.8)	9.8 (4.9-17.3)
Physical activity at six months post-diagnosis (h/wk)	6.0 (2.0-11.5)	8.0 (4.0-14.1)	4.1 (0.8-8.3)
Physical activity difference (h/wk)	-2.5 (-8.0-0.7)	-1.0 (-5.0-3.0)	-4.0 (-12.0--0.3)
Increase of ≥60 min/wk of physical activity	81 (25%)	55 (37%)	26 (15%)
Clinical characteristics			
Colon cancer	233 (71%)	116 (78%)	117 (66%)
Rectal cancer	92 (28%)	32 (21%)	60 (34%)
Disease stage (pTNM)			
Stage I	96 (29%)	41 (28%)	55 (31%)
Stage II	112 (34%)	70 (47%)	42 (24%)
Stage III	119 (36%)	38 (26%)	81 (46%)
Neo-adjuvant therapy	73 (22%)	25 (17%)	48 (27%)
Adjuvant chemotherapy	91 (28%)	28 (19%)	63 (35%)
Ostomy	103 (32%)	35 (23%)	68 (38%)
Ostomy reversal	32 (10%)	14 (9%)	18 (10%)

Table 1. Continued

Length of hospital stay > 10 days	82 (25%)	35 (23%)	47 (27%)
Days after surgery[2]	164 ± 25	167 ± 24	162 ± 25
Health status characteristics			
Comorbidity before surgery[3]	142 (43%)	57 (40%)	85 (60%)
Physical functioning before surgery	93.3 (86.7-100)	93.3 (80.0-100)	93.3 (86.7-100)
Physical functioning at six months post-diagnosis	86.7 (73.3-93.3)	93.3 (86.7-100)	73.3 (60.0-86.7)
Change in physical functioning	-6.7 (-13.3-0.0)	0.0 (0.0-6.7)	-13.3 (-26.7--6.7)

[1] All data are presented as n (%) or median (25th, 75th percentile), unless otherwise indicated. [2] mean ± SD; [3] One or more of the following comorbidities: diabetes mellitus, chronic respiratory disease, and cardiovascular disease (excluding determinants of cardiovascular disease like high blood pressure)

Physical activity after surgery

Higher post-surgery physical activity was positively associated with recovery among the subset of patients that either increased their activity level or had a stable activity level from pre-to-post diagnosis (P for trend=0.01; **Figure 1B**). Compared with patients who reported no moderate-to-vigorous activity per week, those reporting 510 or more minutes per week (8.5 h/wk) were 52% more often recovered to their pre-operative level of physical functioning (adjusted PR 0.48; 95%CI 0.28-0.82).

Physical activity before surgery

Pre-surgery physical activity was not associated with recovery of physical functioning among the subset of patients that either increased their activity level or had a stable activity level from pre-to-post diagnosis (P for trend=0.24; **Figure 1C**). Also within the total group of patients (n=327) there was no association between physical activity level before surgery and recovery (P for trend=0.55; results not shown).

Increase in physical activity stratified by physical activity before surgery

We further subdivided patient groups of stable activity and increased activity, to assess whether the magnitude of benefit was dependent on physical activity level before surgery. For patients with stable activity, we divided participants into those engaging in <150 min/wk (inactive with stable activity) and ≥150 min/wk (active with stable activity). For patients with increased activity, we also defined two groups based on their pre-surgery activity level with a cut-off value of 150 min/wk (inactive with increased activity and active with increased activity) (Table 2). Both groups of patients who increased their activity (irrespective of pre-surgery activity) were 45% more likely to be recovered to their pre-operative physical functioning (**Table 2**) compared to patients that were inactive before surgery and remained inactive. In contrast, patients who were active before surgery with stable activity after surgery were not more often recovered (adjusted PR 0.91; 95%CI 0.65-1.26).

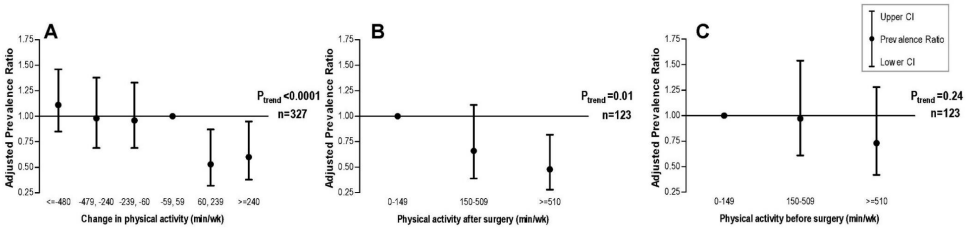

Figure 1. Prevalence ratio and 95% confidence intervals (CI) of the association between no recovery of physical functioning at six months post colorectal cancer diagnosis and (**A**) *change* in moderate-to-vigorous physical activity from pre-to-post surgery (n=327), n=87, 47, 70, 42, 41, 40 patients; or (**B**) absolute level of moderate-to-vigorous physical activity *after* surgery among the subset of patients that either increased their activity level or had a stable activity level from pre-to-post surgery (n=123), n=21, 41, 61 patients; or (**C**) absolute level of moderate-to-vigorous physical activity *before* surgery among the subset of patients that either increased their activity level or had a stable activity level from pre-to-post surgery (n=123), n=39, 47, 37 patients. Models adjusted for age, sex, physical functioning before surgery, stage of disease, ostomy, and body mass index.

Table 2. The association between no recovery of physical functioning after CRC surgery and stable or increased activity from pre-to-post surgery stratified by activity level before surgery.

Moderate-to-vigorous activity level	**No. events/ at risk**	**Adjusted PR (95% CI)**	**Adjusted PR (95% CI)**
Stable activity	25/42	1.00	
Inactive[1] with stable activity	12/20		1.00
Active[2] with stable activity	13/22		0.91 (0.65-1.26)
Increased activity	26/81	0.57 (0.39-0.82)	
Inactive with increasing activity	6/19		0.53 (0.29-0.97)
Active with increasing activity	20/62		0.55 (0.39-0.78)

Adjusted for age, sex, physical functioning before surgery, stage of disease, ostomy, and body mass index.[1]
Inactive is defined as a pre-surgery activity level <150 min/wk
[2] Active is defined as a pre-surgery activity level >150 min/wk

Discussion

The present study found that at six months post-diagnosis about half of CRC patients had not recovered to their pre-operative physical functioning. CRC patients who increased their activity from their levels before surgery were significantly more likely to be recovered compared to patients who had a stable activity level. Furthermore, patients who were physically active after CRC surgery were more likely to recover their physical functioning. In contrast, level of activity before surgery was not associated with recovery of physical functioning.

Few studies have assessed the association between physical activity and recovery of physical functioning after colorectal cancer surgery. Since recovery is defined as return to baseline function, quantification of recovery requires measurement both at baseline and after discharge from the hospital. Those data are not commonly reported. Several studies assessed in-hospital recovery [3], return to work [31], or assessed physical functioning only after surgery [9, 10, 32, 33]. We found that 54% of CRC patients had not recovered their pre-surgery physical functioning at six-months post-diagnosis. Along with a previous study [11], these data suggest that a substantial proportion of patients have not recovered to preoperative functioning by five to six months post-surgery.

The main finding in the present study was that CRC patients who increased their physical activity levels above baseline levels were more often recovered from surgery. The magnitude of benefit of increasing activity was similar in patients who had either a high or moderate increase in activity and was independent of pre-surgery physical activity level. Our analyses also demonstrate that CRC patients who were consistently active (at least 150 min/wk), but did not increase their activity, did not experience improved recovery. These results are in line with a previous study among cancer survivors, which concluded that it was the change in physical activity since cancer diagnosis that was associated with current physical functioning, rather than the absolute amount of physical activity [19]. However, a possible explanation for this finding is that an increase in physical activity level might be needed in order to regain muscle mass, aerobic capacity, and coordination [34]. Nonetheless, because this is the first study that assessed the impact of absolute levels and relative increases in activity on recovery after CRC surgery, these findings need to be confirmed. Future studies should preferably include multiple assessments of physical activity and physical functioning after surgery to better follow the recovery trajectory.

Furthermore, our results showed that pre-surgery activity was not associated with recovery. Several other studies have examined the effect of pre-surgery activity on recovery of physical functioning among CRC patients. In contrast to our result, one study concluded that a higher pre-operative physical activity level was associated with a faster self-reported recovery after surgery [35]. However, that study measured recovery at 3 and 6 weeks after surgery and

only used the single question "to what extent do you feel physically recovered?" to measure recovery among 115 CRC patients. Our results are in line with a recent systematic review that concluded there is no evidence that pre-operative physical activity improves post-operative outcomes such as recovery in CRC patients [36].

The current study has some limitations that need to be taken into consideration when interpreting the results. First, our measurements were taken at six months post-diagnosis and not at six months post-surgery. However, the number of days since surgery was similar for those patients that did recover versus patients that did not recover at six months post-diagnosis. Furthermore, our results did not seem to be influenced by additional cancer treatment. In sensitivity analyses, in which we included patients treated with only surgical resection, we found a similar association between an increase in physical activity and recovery as in the total study population.

Another limitation is that recovery of physical functioning was measured using questionnaires based on self-report. Generally, the ceiling effect of the physical functioning scale is considered a limitation [37]. Many patients score the maximum of 100 on physical functioning before surgery. As a consequence, patients with the highest possible score cannot be distinguished from each other, while differences in physical functioning are present. Therefore, patients who score the maximum both before and months after surgery (n=65, 20%) could still have experienced an overall decline in physical functioning, although we were not able to measure this decline. However, for this study we focused on a clinically relevant decline in physical functioning that resulted in a deterioration of the ability to cope independently [25], i.e. patients were considered not recovered from surgery. Ideally, both objective and self-reported measures should have been included to fully capture multiple domains of physical functioning. In a study among older patients undergoing major abdominal surgery, the proportion not recovered indeed varied across different measures [11]. In that study the proportion of patients without recovery was consistently greater with performance-based instruments than with self-reported measures of physical functioning [11]. We found that about half of patients were not recovered to their pre-surgery capacity to perform physical and daily routine activities. We do not expect that more patients would be considered to be recovered if we would have used objective measures of physical functioning.

Physical activity level was measured with self-reported questionnaires. Objective measures, such as accelerometers, are complementary to, rather than a replacement for, self-reported methods in epidemiologic studies. Accelerometers capture short-term measures of physical activity, while questionnaire are designed to give a representative view of habitual long-term physical activity. Physical activity levels of patients around the time of diagnosis may deviate significantly from their regular physical activity behaviour, e.g. because of frequent visits to the hospital. Therefore, accelerometers may be inappropriate to capture habitual physical activity before treatment, while questionnaires are.

Lastly, the response rate of 50% and missing data of some patients on exposure and/or outcome may limit the generalizability of our results. In addition, our study population was quite active; 86% of patients were active at or over the recommended 150 min/wk. This is slightly higher than the general Dutch population aged 55+, in which 72% meets the physical activity guideline. However, this activity level was similar to the 91% adherence to the physical activity guideline that was found in another study among Dutch CRC survivors [38]. In contrast, the proportion of CRC patients meeting the activity recommendation in North-America and Australia are generally much lower [16, 18]. The high level of physical activity in our study population might limit the generalizability of our results to other populations of CRC patients. However, our results suggest that the benefit of an increase in physical activity is independent from the pre-surgery level of activity (<150 min/wk vs. ≥150 min/wk).

This study has several strengths. First, we were able to adjust for many covariates that could potentially confound our associations. Although no data was available about complications that occurred, length of hospital stay was used as an indicator of major complications after surgery. Second, the COLON study provided a unique opportunity to explore recovery after CRC surgery, since we measured physical functioning both before surgery and after discharge from the hospital. Third, we compared CRC patients who increased their activity levels after surgery with patients who had a stable activity level. No comparison was made with regard to patients who decreased their activity levels after CRC surgery, since CRC surgery might result in a prolonged low physical functioning and therefore a reduced ability to be physically active.

Conclusions

Our results suggest that an increase in moderate-to-vigorous physical activity after CRC surgery is associated with enhanced recovery of physical functioning, independent of physical activity level before surgery. This benefit was seen regardless of age, stage of disease, BMI, or physical functioning before surgery. Furthermore, our results suggest that pre-surgery activity is not associated with recovery. The design of this study precludes any causal inference. The effects of pre-operative and post-operative physical activity on recovery should be further studied. Future prospective studies that investigate functional recovery are needed and should include more time points during follow-up to better follow the recovery trajectory. Moreover, randomized trials are needed to study if pre-operative and/or post-operative physical activity programs will enhance recovery. Randomized trials that examine the effects of post-operative physical activity programs should include pre-operative measures of both physical activity and functional status to be able to test the level of physical activity needed to enhance recovery.

Abbreviations

BMI: Body mass index; CRC: Colorectal cancer; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer quality-of-life questionnaire; MET: metabolic equivalent; PR: Prevalence ratio; SQUASH: Short QUestionnaire to ASsess Health enhancing physical activity.

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Availability of data and materials

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

MvZ contributed to data collection, was involved with the conception and design of the study and analyses, performed the statistical analyses and drafted the manuscript. RMW and EK were involved with the conception and design of the cohort as well as with the study and helped to design the analyses. ASvH, PD, HKvH, BMEH, FMK, EJSB, JHWdW, FJBvD, DEGK, RMW, and JJD contributed to data collection. All authors critically read and revised the manuscript and were involved in interpretation of the data. All authors approved the final version of the manuscript.

Competing interests

The authors have no conflicts of interest to report.

Consent to publish

Not applicable.

Ethics approval and consent to participate

Ethical approval for the study was obtained from the Committee on Research involving Human Subjects, (Commissie Mensgebonden Onderzoek – CMO, region Arnhem-Nijmegen (The Netherlands)), CMO number 2009/349, ABR nr NL30446.091.09. All participants provided a written informed consent.

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CHAPTER 5

5

Lifestyle after colorectal cancer diagnosis in relation to survival and recurrence: a review of the literature

Moniek van Zutphen | Ellen Kampman | Edward L. Giovannucci | Fränzel J.B. van Duijnhoven

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Abstract

Purpose of review

This review summarizes the evidence regarding diet, physical activity, smoking, and body composition after colorectal cancer (CRC) diagnosis in relation to all-cause and CRC-specific mortality and disease recurrence and gives suggestions for future research directions.

Findings

Overall, this review suggests that some, albeit not all, of the well-known modifiable risk factors for cancer incidence might also be associated with CRC survival. CRC prognosis appears to be worse with increased physical inactivity, smoking or being underweight after CRC diagnosis. Emerging evidence suggests that diets associated with a positive energy-balance, e.g. high consumption of sugar-sweetened beverages, may negatively impact survival in CRC survivors. In contrast, there is currently little evidence to support the recommendation to limit red and processed meat or alcohol intake after CRC diagnosis. Whether being overweight and obese after CRC diagnosis improves or worsens CRC prognosis remains controversial and may depend on the measure used to assess body fatness.

Summary

Further research on post-diagnosis lifestyle patterns is needed to understand the multifactorial influence on CRC prognosis. Disease recurrence and the development of comorbidities should be included as key outcomes in future studies and lifestyle should preferably be repeatedly measured.

Keywords

Colorectal cancer; Survival; Lifestyle; Diet; Alcohol; Physical activity; Sedentary behavior; Smoking; Body composition; Body Mass Index

Introduction

Diet, physical activity, smoking, alcohol, and body weight are associated with risk (incidence) of colorectal cancer (CRC) [1, 2]. In contrast, far fewer studies have examined the influence of these lifestyle factors on survival after CRC diagnosis. Currently, cancer survivors are advised to follow the recommendations formulated for cancer prevention [3]. However, it is currently unclear if making lifestyle changes after diagnosis would impact disease progression and survival.

Emerging evidence shows that lifestyle, including diet, after CRC diagnosis might affect all-cause and CRC-specific mortality risk. Several recent reviews and meta-analyses on observational studies summarized the available evidence on specific aspects of lifestyle, such as diet [4-6], physical activity [4, 5, 7-12], smoking [13, 14], and body composition [5, 10, 15-22], in relation to CRC outcomes. However, none of these reviews included all the aforementioned lifestyle factors in one review. Furthermore, results might differ due to the timing of lifestyle assessment (e.g., pre-diagnosis vs. post-diagnosis) [8, 10, 15] and characteristics of the included study population [15].

To better understand the association between lifestyle and CRC outcomes, we summarized the evidence regarding diet, physical activity, smoking, and body composition after CRC diagnosis across different groups of cancer survivors. Moreover, we also included observational studies, not included in previous reviews [23-39]. We identified three study design categories based on the selection of the included study population: 1) population-based studies including all incident CRC cases, 2) studies in the adjuvant setting limited to survivors treated with adjuvant therapy, and 3) studies in the metastatic setting limited to patients with metastatic disease (**Figure 1**). We chose to focus on post-diagnosis lifestyle factors, because this is the period during which CRC survivors could be counselled to alter their behavior. Therefore, we only included studies that examined the association between lifestyle at or after CRC diagnosis and all-cause mortality, CRC-specific mortality, or cancer recurrence. Additionally, we summarized the evidence regarding changes in lifestyle, i.e., from pre to post-diagnosis or changes made after diagnosis, among CRC survivors and survival outcomes from either observational or intervention studies. We did not include papers that examined lifestyle and CRC survival separately by molecular subtypes. These publications will be reviewed in future issue of this journal. Finally, we conclude with suggestions for future research directions.

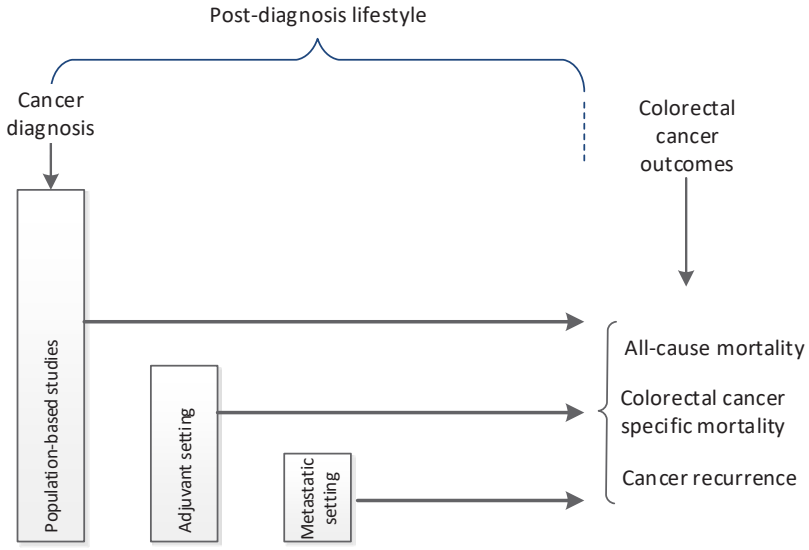

Figure 1. Schematic diagram of identification of three study categories based on the characteristics of the included study population. Based on the study population, studies were categorized into 1) population-based studies including all incident colorectal cancer cases, 2) studies in the adjuvant setting limited to survivors treated with adjuvant therapy, and 3) studies in the metastatic setting limited to metastatic patients. In each study category we identified studies with lifestyle information available at or after colorectal cancer diagnosis. Studies with lifestyle information limited to the period before colorectal cancer diagnosis, either collected prospectively before diagnosis or retrospectively after diagnosis, were not taken into account.

Overview of included studies

We excluded all studies that did not assess lifestyle at or after CRC diagnosis (e.g., those that assessed only pre-diagnosis factors) or did not adjust for critical confounders (e.g., age, stage). Furthermore, we excluded all studies that dichotomized body mass index (BMI) when examining the association between BMI and mortality or recurrence. Dichotomized BMI is considered a crude classification of BMI by combining diverse categories of body mass and body composition. Thus dichotomized BMI may not account for potential differential associations between sub-categories of BMI (e.g., by combining overweight and obese in one category) [15].

We included 57 relevant articles (based on 84 different observational studies) that reported on post-diagnosis diet, physical activity, smoking, or body fatness/body composition in CRC survivors in relation to all-cause mortality, CRC-specific mortality or cancer recurrence. An overview of the number of included articles according to exposure and type of study population is shown in **Figure 2**. Additionally, we included 13 relevant articles (one intervention study and 11 different observational studies) that reported on changes

in lifestyle among CRC survivors in relation to survival outcomes. In total, 61 articles are discussed in more detail in this review.

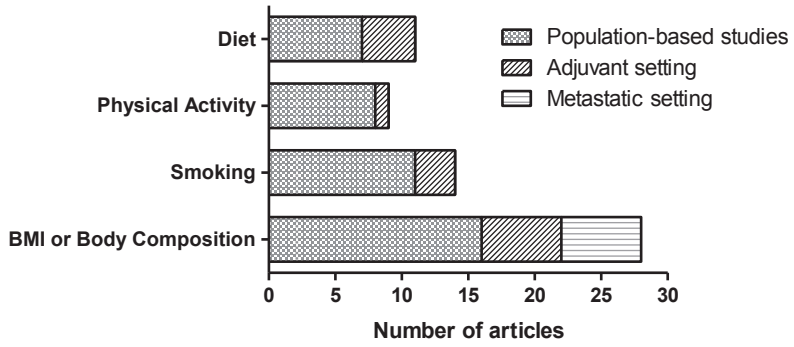

Figure 2. Overview of the number of included relevant articles on diet, physical activity, smoking and body mass index (BMI) or body composition at or after colorectal cancer diagnosis in relation to all-cause mortality, cancer-specific mortality, or disease recurrence by type of included study population. In total 57 articles were included: 54 articles reported on one exposure, two articles reported on both physical activity and BMI, and one article reported on all four exposures.

Diet after CRC diagnosis

Five population-based studies and one study in the adjuvant setting provided results on diet and CRC outcomes in 10 publications [23-27, 40-44] (**Table 1**). Three US cohorts assessed post-diagnosis diet in population-based cohorts with >1000 CRC patients: Nurses' Health Study I (NHS) [23, 44], Health Professional Follow-Up Study (HPFS) [44], and Cancer Prevention Study (CPS) II Nutrition Cohort [27, 40, 41]. All three cohorts consist of participants diagnosed with CRC during follow-up and have updated dietary assessment after diagnosis. Usually questionnaires that were completed after treatment was finished were utilized in the analyses. In contrast, two non-US cohorts (the German cohort PopGen [24] and BioBank Japan [26]) recruited >1000 CRC patients after CRC diagnosis. The study in the adjuvant setting, CALGB (Cancer and Leukemia Group B) 89803 Diet and Lifestyle Companion study [25, 42, 43], was embedded in a randomized trial of adjuvant chemotherapy among ~1000 patients with stage III colon cancer. Additionally, three articles, two from the CPS II Nutrition Cohort [27, 40] and one report on a small randomized dietary intervention trial reported on dietary changes among CRC survivors in relation to mortality [27, 40, 45].

In this review, we summarized the available evidence for dietary patterns, red and processed meat, sugar-sweetened beverages, alcohol consumption, other foods and beverages and CRC survival.

Dietary patterns

Two observational studies, the NHS I [23] and a German cohort of CRC survivors [24], assessed post-diagnosis dietary patterns in a population-based setting [23], while CALGB 89803 [42] reported results in the adjuvant setting (**Table 1**). Data-driven dietary patterns were assessed within NHS I [23] and CALGB 89803 [42]. Both studies observed patterns that were given the labels a 'Western' and a 'Prudent' dietary pattern. The Western dietary pattern was characterized by high- and low-fat dairy, refined grains, red and processed meats, desserts, and potatoes, while the Prudent dietary pattern was characterized by high intakes of fruits, vegetables, whole grains, and poultry.

For the Western dietary pattern, both studies reported an increased all-cause mortality risk [23, 42]. However, the association was statistically significant only in the adjuvant setting (CALBG: Q5 vs Q1: HR 2.32; 95%CI 1.36-3.96; P-trend <0.001) [42], and not in the population-based study (NHS I: Q5 vs Q1: HR 1.32 (0.89-1.97); P-trend=0.23) [23]. Similarly, a statistically significant increased risk of colon cancer recurrence was reported in the adjuvant setting [42], while a non-significant positive association was reported for CRC-mortality in the population-based study [23] (**Table 1**). For the Prudent dietary pattern, both studies reported statistically non-significant associations for all-cause mortality [23, 42], CRC-specific mortality [23] or colon cancer recurrence [42].
Furthermore, several a priori-defined dietary patterns were studied in the two population-based studies [23, 24] (**Table 1**). Of the a priori-defined dietary patterns, none has been studied in more than one cohort. Some a priori-defined dietary patterns were associated with lower risk of all-cause mortality, but not all [23, 24].

Only one small (n=111) randomized dietary intervention trial among CRC survivors assessed associations with survival [45]. Throughout the 1.5 months of neo-adjuvant radiotherapy patients with rectal cancer randomized to the intervention group received 6 weekly individualized nutrition counselling and education sessions using regular foods, while the control group maintained their usual diet. Overall, the main goal of the intervention was to enable every patient to achieve his or her calculated energy and protein requirements. After long-term follow up (median follow-up 6.5 (range: 4.9-8.1) years), CRC-specific survival was significantly longer in the intervention group after adjustment for age and disease stage (median survival 7.3 years versus 4.9 years).

Red and processed meats

Both NHS I [23] and CPS II Nutrition Cohort [40] reported on post-diagnosis red and processed meat intake, although the NHS I paper focused on dietary patterns (**Table 1**). The CPS II Nutrition Cohort also provided information regarding pre- to post-diagnosis change in red and processed meat consumption [40] (**Table 2**).

These two studies did not observe an association between red and processed meat intake and both all-cause mortality and CRC-specific mortality [23, 40]. Furthermore, changing meat intake from high (median or higher) before CRC diagnosis to low (below median) after diagnosis was not associated with lower mortality when compared to survivors with a consistently high intake [40].

Sugar-sweetened beverages

Both the NHS I [23] and CALGB 89803 [43] reported on post-diagnosis sugar-sweetened beverage intake and CRC outcomes (**Table 1**).

Both studies [23, 43] reported increased all-cause mortality risk for sugar-sweetened beverage consumption after CRC diagnosis, of which the association in the NHS I was statistically significant [23]. Each additional serving of sugar-sweetened beverages (including fruit juices) after CRC diagnosis was associated with an 11% increased risk for all-cause mortality (HR 1.11; 95%CI 1.01-1.23) [23]. A similar relative risk was reported for CRC-specific mortality, although it was not statistically significant [23]. For colon cancer recurrence, CALGB 89803 reported a statistically significant increased recurrence risk for patients consuming ≥ 2 servings of sugar-sweetened beverages per day (HR 1.75; 95%CI 1.04-2.94) compared to those consuming <2 servings per month (P-trend=0.04) [43].

Alcohol

Four population-based studies, NHS I [23, 44], HPFS [44], CPS II Nutrition cohort [27], and a Japanese cohort of CRC survivors [26], reported on post-diagnosis alcohol consumption and CRC outcomes (**Table 1**).

In the NHS I moderate drinking was used as the reference group and abstaining from alcohol consumption was associated with a statistically significant increased all-cause mortality risk (HR 1.30; 1.05-1.61) compared to women consuming 5-15 g of alcohol per day [23]. Drinking >15 g/day (approximately 1.5 drinks) was not statistically significantly associated with increased mortality risk. Similarly, abstainers had a higher mortality risk than drinkers in the Japanese cohort [26] and after combining both NHS I and HPFS cohort data [44]. However, the CPS II Nutrition cohort reported that drinking alcohol after diagnosis was not associated with all-cause mortality [27]. For CRC-specific mortality similar results were reported as for all-cause mortality (**Table 1**).

The CPS II Nutrition cohort also provided information regarding pre- to post-diagnosis change in alcohol consumption (**Table 2**). Participants who reported drinking before CRC diagnosis but stopped drinking alcohol after diagnosis had a statistically non-significant increased risk of all-cause and CRC-specific mortality compared to participants who continued to drink alcohol [27].

Other foods, beverages and nutrients

The intake of some foods, beverages and nutrients were only reported in one study each (**Table 1**). Higher nut consumption was associated with lower risk of CRC-mortality (HR per serving/day 0.69; 95%CI 0.49-0.97) in the NHS I, while no statistically significant association was reported for all-cause mortality [23]. Furthermore, no associations were observed within the NHS I with either all-cause mortality or CRC-specific mortality for vegetables, fruits or whole grains [23]. However, in the Japanese study lower green leafy vegetable intake after CRC diagnosis was associated with an increased all-cause mortality risk [26].

Higher milk intake was statistically significantly associated with lower all-cause mortality risk (Q4 vs Q1: HR 0.72; 95%CI 0.55-0.94; P-trend=0.02) in the CPS II Nutrition Cohort [41]. A similar risk was reported for overall dairy consumption, although associations did not reach statistical significance [41]. Additionally, higher coffee intake was statistically significantly associated with lower all-cause mortality (≥4 vs 0 cups/day: HR 0.66; 95%CI 0.37-1.18; P-trend=0.01) within CALGB 89803 [25]. No significant associations were reported for non-herbal tea intake [25].

Higher dietary glycemic load and total carbohydrate intake were statistically significant associated with an increased risk of mortality and recurrence in CALGB 89803 [46]. Higher total calcium intake was statistically significantly associated with both lower all-cause mortality and CRC-specific mortality in the CPS II Nutrition Cohort, while no significant associations were reported for vitamin D [41]. Also no significant associations were reported for intake of one-carbon nutrients (folate, vitamin B6 and B12) in NHS I [44].

Diet: Key points

One small randomized intervention trial which provided individualized nutritional counselling and education about regular foods suggest that making dietary changes may improve cancer-specific survival. No dietary pattern or food has been studied in more than two observational cohorts, with cancer recurrence only studied in one cohort in the adjuvant setting embedded in a randomized chemotherapy trial. While alcohol consumption has been studied more frequently, these studies often used abstainers as comparison group. Abstainers are probably an inappropriate reference group, as this group may, at least in part, include people who stopped drinking because of comorbidities or cancer related symptoms. Overall, emerging evidence shows that diet after CRC diagnosis might affect survival, but

further research is needed to clarify what aspects of diet are important and which dietary changes could affect survival.

Physical activity after CRC diagnosis

Seven population-based studies [26, 47-52] and one study in the adjuvant setting [53] provided results on physical activity after CRC diagnosis and mortality outcomes (**Table 1**). Five large US cohorts assessed post-diagnosis physical activity in population-based cohorts with >500 CRC patients: NHS I [47], HPFS [48], Cancer Prevention Study (CPS) II Nutrition Cohort [51], Women's Health Initiative [50], and National Institutes of Health-AARP Diet and Health Study [52]. All five cohorts consist of participants diagnosed with CRC during follow-up and have updated physical activity assessment after diagnosis, usually when treatment was completed. In contrast, two non-US cohorts (an Australian cohort [49] and BioBank Japan [26]) recruited >1500 CRC patients after CRC diagnosis. All studies reported on leisure time physical activity.

Physical activity

For all-cause mortality, seven studies [26, 47-53] were included in previous meta-analyses [7-10]. These meta-analyses have found highest versus lowest post-diagnostic physical activity to be associated with 40% lower all-cause mortality risk [7-10]. Five studies that were included in a dose-response meta-analysis showed a 28% lower risk of all-cause mortality (HR 0.72; 95%CI 0.65-0.80) for every 10 metabolic equivalent task-hour per week (MET-hours/week) increase in post-diagnosis physical activity [9], which is equivalent to current recommendations of 150 min/week of at least moderate intensity activity. For CRC-specific mortality, similar risk reductions were reported comparing high versus low physical activity after CRC diagnosis (HR 0.62; 95%CI 0.45-0.86) [11] and for every 10 MET-hours/week increase in post-diagnosis physical activity (HR 0.75; 95%CI 0.65-0.85) [9].

Changes in physical activity

The Australian cohort [49] and NHS I [47] also provided results on changes in physical activity and mortality outcomes in CRC patients (**Table 2**). An increase of physical activity >2 hours/week between 5 and 12 months post-diagnosis was statistically significantly associated with lower all-cause (HR 0.69; 95%CI 0.50-0.94) and CRC-specific mortality (HR 0.64; 95%CI 0.44-0.93) among Australian CRC survivors [49]. A pre- to post-diagnosis increase in physical activity showed a statistically significant lower all-cause and CRC-specific mortality risk in the NHS I [47], but no association was reported among Australian CRC survivors [49] (**Table 2**). The first randomized controlled trial designed primarily to assess the impact of physical activity on survival among colon cancer survivors is ongoing [54]. As of April 2017, the trial

has enrolled 536 of its planned 972 participants [55] and only one year feasibility results have been published so far [56].

Sedentary behavior

Three of the population-based studies, CPS II Nutrition Cohort [51], National Institutes of Health-AARP Diet and Health [52], and HPFS [57] also reported on post-diagnosis sedentary behavior and all-cause as well as CRC-specific mortality (**Table 1**). CPS II reported on leisure time spent sitting [51], whereas the other two studies assessed TV viewing [52, 57]. All three studies [51, 52, 57] reported no statistically significant associations between sedentary behavior and all-cause mortality. With regard to CRC-specific mortality, only one study, the CPS II Nutrition Cohort showed a statistically significant positive association between sedentary behavior and CRC-specific mortality (≥6 h/day vs <3 h/day sitting time: HR 1.62; 95%CI 1.07-2.44) [51].

Physical activity: Key points

Evidence from prospective observational studies has consistently suggested that higher physical activity after CRC diagnosis is associated with a lower risk of CRC-specific and all-cause mortality, but whether physical activity is causally related to CRC mortality remains unclear. A randomized controlled trial is currently ongoing to address whether aerobic physical activity after complement of adjuvant therapy improves survival. Based on few studies, there is some evidence suggesting that excessive sedentary behavior after CRC diagnosis might be associated with increased CRC-specific mortality, but findings are less consistent than for leisure time physical activity.

Smoking after CRC diagnosis

Eleven population-based studies [14, 26, 28-31, 58-62] and three studies in the adjuvant setting [63-65] reported on smoking at or after CRC diagnosis and mortality outcomes (**Table 1**). Four population-based studies used data from a cancer registry [14, 30, 31, 59], three were from single-institution hospital cohorts [58, 60, 61], three were non-US cohorts (Shanghai Cohort Study [28], the German cohort DACHS [62], and BioBank Japan [26]) and lastly the CPS II Nutrition cohort [29]. Two studies in the adjuvant setting were embedded in an adjuvant chemotherapy trial, CALGB 89803 [64] and N0147 [65], while the third study included patients referred to a single-institution for consideration of adjuvant treatment [63]. Six studies [28, 31, 58, 61-63] compared current smokers with non-smokers, while eight studies [14, 26, 29, 30, 59, 60, 64, 65] compared current smokers with never smokers.

Smoking

For all-cause mortality, eight out of nine population-based studies [26, 28, 29, 31, 58-61] reported increased all-cause mortality risk for smoking, of which six [26, 28, 29, 58, 59, 61] were statistically significant. Furthermore, the study in the adjuvant setting also reported a statistically significant increased all-cause mortality risk for smoking [65].

For CRC-specific mortality, five population-based studies [14, 29, 30, 61, 62] reported increased CRC-specific mortality risk for smoking, of which three [14, 29, 30] were statistically significant (**Table 1**). However, one study that reported results separately for men and women reported a statistically non-significant positive association among women for post-diagnosis smoking, while among men a statistically non-significant inverse association was reported [60]. Furthermore, one study in the adjuvant setting also reported a statistically significant increased CRC-specific mortality risk for smoking [63].

For colon cancer recurrence, one study embedded in the trial N0147 [65] reported a statistically significant increased cancer recurrence risk for smoking, while CALGB 89803 [64] reported no association with smoking among stage III colon cancer patients treated with adjuvant chemotherapy.

Smoking cessation

Four population-based studies provided results on smoking cessation and mortality outcomes in CRC patients (**Table 2**). People who continued smoking after CRC diagnosis had a more than 3-fold increased risk of all-cause mortality (HR 3.46; 95%CI 1.69-7.10) compared to people who quit smoking after diagnosis [28]. Pre- to post-diagnosis smoking cessation was not statistically significantly associated with all-cause or CRC-specific mortality risk [29, 62, 66], although one of these studies reported lower mortality risk for those who quit smoking compared to those who continued to smoke [29].

Smoking: Key points

Overall, evidence from observational studies has consistently suggested that smoking after CRC diagnosis increases the risk of CRC-specific and all-cause mortality. It seems plausible that smoking cessation would improve survival outcomes in CRC survivors, although direct evidence is limited.

Body fatness and body composition after CRC diagnosis

This review first focusses on studies that assessed BMI at or after CRC diagnosis. Next, we discuss weight changes and lastly, we describe the results of studies which quantified visceral adipose tissue or skeletal muscle mass from CT images.

Body Mass Index

Eleven population-based studies [16, 26, 32, 33, 49, 50, 67-71], two studies from adjuvant chemotherapy trials [72, 73], and one study among metastatic patients [34] assessed the association of BMI at or after CRC diagnosis and CRC outcomes (**Table 1**). Furthermore, 21 additional studies in the adjuvant setting were included in a pooled analyses of patients enrolled in trials of adjuvant chemotherapy [74]. Moreover, an additional article with pooled analyses in the metastatic setting included data of 25 treatment trials [75].

For underweight (either BMI <18.5 or 20 kg/m^2), all population-based studies [16, 26, 32, 33, 49, 67, 68, 70, 71], the pooled analysis of studies in the adjuvant setting [74], and both publications in the metastatic setting [34, 75] reported higher all-cause mortality risk compared to normal weight individuals. The majority of these studies [26, 32, 34, 49, 67, 71, 74, 75] reported statistically significant results (**Table 1**). In the largest population-based study, ~3400 men and women diagnosed with stage I to III CRC from the Kaiser Permanente Northern California population, underweight at diagnosis was associated with a 3-fold increased all-cause mortality risk (HR 3.01; 95%CI 1.88-4.83) compared to normal weight [32]. However, most other studies report a 1.5 to 2-fold increased risk (Table 1). Generally, similar results were reported for CRC-specific mortality and cancer recurrence (Table 1).
For overweight (defined as BMI 25.0-24.9 kg/m^2), all population-based studies [16, 26, 32, 33, 49, 50, 67-69, 71] reported lower all-cause mortality risk compared to normal weight individuals, of which three were statistically significant [49, 50, 67]. However, studies in the adjuvant setting of a chemotherapy trial reported that overweight individuals had a similar all-cause mortality risk as normal weight individuals (**Table 1**). For metastatic patients participating in treatment trials all-cause mortality risk was lowest at BMI 28 kg/m^2 [75], while overweight was associated with an increased all-cause mortality risk among a general population of patients diagnosed with metastatic disease (HR 1.23; 95%CI 1.03-1.46) [34]. Generally, similar results were reported for CRC-specific mortality and cancer recurrence (Table 1).

For obesity (BMI ≥30 kg/m^2), none of the population-based studies [16, 26, 32, 33, 49, 50, 67-69, 71] reported statistically significant associations with all-cause mortality. Nevertheless, the only study (Kaiser Permanente Northern California cohort) that reported on a separate group with class II or III obesity (BMI ≥35 kg/m^2) reported a statistically significant increased all-cause mortality risk [32]. Within the adjuvant setting pooled analyses showed a modest

increased all-cause mortality risk (HR 1.10; 95%CI 1.04-1.17) compared with normal weight [74]. Within the metastatic setting both publications showed that obese individuals had a somewhat similar, or lower, all-cause mortality risk as normal weight individuals [34, 75]. Generally, similar results were reported for CRC-specific mortality and cancer recurrence (**Table 1**).

Changes in weight

Four studies [49, 76-78] reported on weight changes (**Table 2**). Two studies were population-based studies, a cohort from the Kaiser Permanente Northern California population [76] and an Australian cohort [49], and two studies were in the adjuvant setting, CALGB 89803 [78] and a cohort from the British Columbia Cancer Agency [77].

Large post-diagnosis weight loss (>5 kg or ≥10%) was associated with a 3-fold increased all-cause and CRC-mortality risk compared with stable weight in both population-based studies [49, 76]. Modest weight loss (2-4.9 kg or 5-9.9%) was also associated with increased all-cause and CRC mortality risk [49, 76], although only statistically significant in the Kaiser Permanente Northern California cohort [76]. In fact, the association between weight loss and mortality was present regardless of at-diagnosis BMI [76]. Large weight loss during adjuvant chemotherapy was associated with increased all-cause mortality and recurrence risk in a cohort from the British Columbia Cancer Agency [77], but not in CALGB 89803 [78].

Post-diagnosis weight gain was not associated with increased all-cause or CRC-specific mortality risk [49, 76, 78] or colon cancer recurrence [77, 78]. Furthermore, pre- to post-diagnosis weight loss or weight gain of >5kg were both associated with a statistically significant 60% higher all-cause risk compared to stable weight [49].

Visceral adipose tissue

Three population-based studies [35, 39, 79], two studies in the adjuvant setting [80, 81], and one study among metastatic patients [82] reported on post-diagnosis visceral adipose tissue and all-cause mortality (**Table 1**). Most of these studies were small (n=62 to 339), except the population-based cohort from the Kaiser Permanente Northern California population (n~3200) [39].

For all-cause mortality, all population-based studies [35, 39, 79] reported statistically non-significant associations with visceral adipose tissue (**Table 1**). Both studies among patients treated with chemotherapy [80, 81] reported an increased all-cause mortality risk with high visceral adipose tissue, of which one was statistically significant [80]. The study among metastatic CRC patients [82] reported a statistically significant increased all-cause mortality risk for high visceral adipose tissue among patients treated with chemotherapy plus the

angiogenesis inhibitor bevacizumab, but not among patients treated with chemotherapy only.

Skeletal muscle mass

Four population-based studies [35, 38, 39, 83], one study in the adjuvant setting [37] and three studies among patients with metastatic disease [36, 84, 85] reported on all-cause mortality (**Table 1**). Most of these studies were small (n=67 to 339), except two population-based cohorts, from the Kaiser Permanente Northern California population (n~3200) [39] and from a single-institution hospital cohort that included stage I-IV patients [38].

Seven out of eight studies [36-39, 83-85] reported increased all-cause mortality risk for low skeletal muscle mass, of which five were statistically significant [37-39, 83, 84] (**Table 1**). A meta-analysis, based on three small studies [83-85], concluded that a low muscle mass was statistically significantly associated with a more than 2-fold increased all-cause mortality risk (HR 2.25; 95%CI 1.63-3.09) [20]. The only large population-based cohort with non-metastatic patients, from Kaiser Permanente Northern California, showed an almost 30% increased risk of overall mortality and 50% increased risk of CRC-specific mortality [39].

One study among metastatic patients reported on loss of muscle mass during chemotherapy [36]. This study showed that ≥9% loss of muscle mass during chemotherapy was associated with a more than 4-fold increased all-cause mortality risk (HR 4.47; 95%CI 2.21-9.05) [36].

Body fatness and body composition: Key Points

Body fatness was studied most often by assessment of body mass index, while only few studies assessed other measures of body composition. Altogether, the results of studies across the three study categories (population-based, adjuvant, and metastatic setting) suggest a J- or L-shaped association between BMI and all-cause mortality or CRC-specific mortality risk. The risk of death was highest among patients who were underweight, while lowest risk was seen in patients with a BMI between 25 and <30 kg/m^2. If obesity confers an additional mortality risk compared to normal weight or overweight patients remains uncertain. Nevertheless, the most recent meta-analysis of post-diagnosis BMI concluded that obesity was statistically significantly associated with a modest 8% increased all-cause mortality risk (HR 1.08; 95%CI 1.03-1.13) compared to normal weight, while no association was found between obesity and CRC-specific mortality [17]. Weight loss in the first two years after diagnosis was consistently associated with increased mortality risk and this association was independent of BMI at CRC diagnosis. Currently, there are no intentional weight loss trials among CRC survivors that assessed mortality risk [86] and no study that assessed the effect of weight loss after treatment was succesfully completed. That being overweight, and in some studies even obese states, seem to be associated with improved survival compared to normal weight is called the ‘obesity paradox’. The obesity paradox could be explained by

several methodological issues, including the crudeness of BMI as a measure of body fatness, especially in a cancer patient population where loss of weight and lean body mass is a strong adverse factor [87].

Other measures used to study the association between body composition and CRC outcomes were visceral adipose tissue and muscle mass quantified from CT images; studies with other measures, such as waist circumference, are currently lacking. There is only limited evidence that visceral adiposity increased mortality risk. Across study categories, studies had mixed results. Only in the adjuvant setting, two small studies consistently showed increased all-cause mortality risk with higher visceral adipose tissue. Even though quantification of adipose tissue from CT scans is regarded as a more precise measure of adiposity than BMI, the usefulness of single-slice analysis might be limited [88]. On the other hand, evidence consistently shows that low muscle mass is associated with reduced survival, although each study used other cut points to define low muscle mass. The notion that the association between overweight and lower mortality is due solely to methodologic biases is refuted by results from the only large population-based study among non-metastatic CRC patients with available data for both BMI and body compositon [39]. Within the overweight BMI range between 25 and <30 kg/m^2, body composition appeared to explain why a BMI higher than normal is associated with the lowest mortality. The majority (78%) of patients in the overweight group had adequate muscle mass, while less than half (43%) of the patients with a normal BMI had adequate muscle mass. Furthermore, the obesity paradox could also be explained by clinical issues [87], such as metabolic health. One study at Kaiser Permanente investigated the combination of obesity and metabolic health and concluded that mortality risk was statistically significant increased in obese patients with the metabolic syndrome, but not in metabolically healthy obese patients, compared with metabolically healthy non-obese patients [89].

Conclusions and future directions

In conclusion, this review suggests that some, albeit not all, modifiable risk factors for cancer incidence might also be associated with mortality risk after CRC diagnosis. CRC prognosis appears to be worse with increased physical inactivity, smoking or being underweight after CRC diagnosis. Emerging evidence suggests that diets associated with a positive energy-balance, e.g. high consumption of sugar-sweetened beverages, may negatively impact survival in CRC survivors. Nonetheless, data relating post-diagnosis diet to CRC prognosis are scarce; with less than three observational studies that have examined associations for each dietary pattern or individual food after CRC diagnosis. In contrast, high red and processed meat or alcohol intake, established risk factors for incident CRC, do not appear to be associated with mortality after CRC diagnosis. Whether overweight and obesity after

CRC diagnosis might confer an additional mortality risk compared to normal weight is still controversial and might depend on how body fatness is assessed and whether muscle mass was accounted for.

Since the first review on lifestyle factors in CRC survivors in 2010 [90], many new studies in this evolving area of research were published and summarized in subsequent reviews and meta-analyses. This is the first paper to comprehensively review post-diagnosis diet, physical activity, smoking and body composition together in one review. Our findings were generally consistent with previous work, regarding diet [4], physical activity [7-11], smoking [13], and underweight [16, 17, 19], although we included new publications. Overweight, assessed by BMI, was consistently associated with lowest mortality risk, although discussion remains about the causal claims regarding the effects of BMI on post-diagnosis mortality for CRC survivors. The only large population-based study among non-metastatic CRC patients concluded that body composition, i.e. muscle mass, appeared to explain why a BMI higher than normal is associated with the lowest mortality risk [39]. Moreover, low muscle mass was consistently associated with increased mortality risk. Besides observational data, there were no reported randomized controlled trials in smoking or alcohol cessation/reduction, while physical activity and/or dietary/excess weight interventions only reported on short-term outcomes [86]. Only one small randomized trial assessed long-term follow-up among CRC survivors, finding significantly improved cancer-specific survival after dietary counseling [45].

As people do not have isolated behaviors, a multidimensional lifestyle approach would be most informative for exploring mortality risk and cancer recurrence, as well as for translating these findings into meaningful strategies to improve disease prognosis. Some randomized controlled trials with both dietary and physical activity components have included CRC survivors, but they usually did not test the impact of comprehensive lifestyle interventions on risk of cancer recurrence or survival [86]. Furthermore, only one observational study evaluated the association of post-diagnosis comprehensive lifestyle patterns and CRC outcomes [91]. That study concluded that adherence to the WCRF recommendations on diet, physical activity and body fatness was not statistically significantly associated with mortality [91]. However, lifestyle was assessed on average 9 years after diagnosis and survivors were therefore at low risk to die from CRC during subsequent follow-up. Further research on post-diagnosis lifestyle patterns is needed to understand the multifactorial nature of risk of mortality and cancer recurrence and, furthermore, to avoid overemphasis of single lifestyle factors.

The existing studies have several limitations. Few observational studies have reported on the association between post-diagnostic lifestyle and CRC outcomes adjusting for pre-diagnostic lifestyle; thus, it is unknown whether the observed associations between post-

diagnostic lifestyle and survival are independent of pre-diagnosis lifestyle. Furthermore, only few studies assessed changes in lifestyle over time in relation to CRC outcomes, with weight change and smoking cessation studied most often. Large prospective cohort studies, such as NHS I, HPFS, the COLON study [92], and others [93, 94] provide further opportunities to examine post-diagnosis lifestyle changes in relation to CRC prognosis during different phases of the cancer trajectory.

Studies evaluating lifestyle factors and CRC outcomes mainly focused on mortality, while cancer recurrence and comorbidities are other important outcomes. Disease recurrence was usually reported by studies in the adjuvant setting, but is not commonly reported by population-based studies. Furthermore, definitions of recurrence were inconsistent between studies. Using the standard definitions proposed by Punt *et al.* [95] may add to the cross-comparability of future studies. In addition, few studies among CRC survivors studied incidence and progression of comorbidities, although some studies included cardiovascular-mortality as an endpoint. Only one study assessed the incidence of comorbidities after CRC diagnosis [96]. This study observed that BMI and sedentary behavior at five months post-diagnosis were associated with the development of comorbid cardiovascular disease in the first three years after CRC diagnosis.

More research is needed on the mechanisms underlying the impact of lifestyle after CRC diagnosis on prognosis. A lifestyle contributing to a positive energy balance and hyperinsulinemia has been suggested to be implicated in the prognosis of CRC [5, 97]. For instance, determinants of hyperinsulinemia, such as physical inactivity, excessive sedentary behaviour, and several aspects of diet, are associated with increased mortality risk. The dietary factors included in this review that might be linked to insulin-related pathways, a Western dietary pattern [23, 42], sugar-sweetenend beverages [23, 43], low coffee consumption [25], and higher dietary glycemic load [46] all showed increased mortality risk. Also, a high-insulinogenic diet [98] has been associated with increased mortality risk. However, these studies were almost all conducted in the same cohort embedded in a trial of adjuvant chemotherapy (CALGB 89803) [25, 42, 43, 46].

Overall, evidence is emerging that modifiable lifestyle factors after CRC diagnosis, such as physical activity, smoking, body compositon, and diet could impact survival. Although, not all modifiable risk factors for cancer presention seem relevant for cancer survivors. With increasing CRC survivorship, however, CRC recurrence should be studied as a key outcome within population-based studies of CRC survivors. Additionally, studies are needed that evaluate the development and progression of comorbidites after CRC diagnosis. Studying lifestyle patterns over time, by including multiple lifestyle factors simultaneously at different timepoints during the cancer trajectory, would lead to a greater understanding of the multifactorial influence on CRC prognosis. Additional data from prospective observational

studies and randomized controlled trials are urgently needed and, ultimately, will allow for lifestyle recommendations that are specifically tailored to cancer survivors.

Compliance with Ethical Standards

Conflict of interest

Moniek van Zutphen has received research support through a grant from the Dutch Cancer Society. Ellen Kampman declares that she has no conflict of interest. Edward L. Giovannucci declares that he has no conflict of interest. Fränzel J.B. van Duijnhoven declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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Annotated references:

Papers of particular interest, published recently, have been highlighted as:

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** Of major importance

4. ** Van Blarigan EL, Meyerhardt JA. Role of Physical Activity and Diet After Colorectal Cancer Diagnosis. Journal of Clinical Oncology. 2015. doi:10.1200/jco.2014.59.7799.

This review summarizes the evidence regarding physical activity and diet after CRC diagnosis in relation to quality of life, disease recurrence, and survival.

11. ** Friedenreich CM, Neilson HK, Farris MS, Courneya KS. Physical Activity and Cancer Outcomes: A Precision Medicine Approach. Clinical cancer research : an official journal of the American Association for Cancer Research. 2016;22(19):4766-75. doi:10.1158/1078-0432.ccr-16-0067.

This review summarizes the epidemiologic literature relating postdiagnosis physical activity to cancer outcomes overall and by molecular/genetic subgroups.

13. ** Walter V, Jansen L, Hoffmeister M, Brenner H. Smoking and survival of colorectal cancer patients: systematic review and meta-analysis. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO. 2014;25(8):1517-25. doi:10.1093/annonc/mdu040.
This systematic review and meta-analysis provides a summary of the epidemiologic literature between smoking and survival of CRC patients, including all-cause mortality, CRC-specific mortality, disease-free survival, and recurrence-free survival.

17. ** Lee J, Meyerhardt JA, Giovannucci E, Jeon JY. Association between Body Mass Index and Prognosis of Colorectal Cancer: A Meta-Analysis of Prospective Cohort Studies. PloS one. 2015;10(3):e0120706. doi:10.1371/journal.pone.0120706.
This meta-analysis of prospective studies summarized the association of pre- and post-diagnostic BMI with CRC-specific mortality and all-cause mortality in patients with CRC.

39. ** Caan BJ, Meyerhardt JA, Kroenke CH, Alexeeff S, Xiao J, Weltzien E et al. Explaining the Obesity Paradox: The Association between Body Composition and Colorectal Cancer Survival (C-SCANS Study). Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2017. doi:10.1158/1055-9965.EPI-17-0200.
This study among non-metastatic CRC patients concluded that body composition appeared to explain why a BMI higher than normal is associated with the lowest mortality risk and therefore they refute the notion that the association between overweight and lower mortality is solely due to methodologic biases.

86. ** Moug SJ, Bryce A, Mutrie N, Anderson AS. Lifestyle interventions are feasible in patients with colorectal cancer with potential short-term health benefits: a systematic review. International journal of colorectal disease. 2017:1-11. doi:10.1007/s00384-017-2797-5.
This systematic review assessed the evidence for the feasibility of performing lifestyle interventions in CRC patients and evaluated any short- and long-term health benefits.

Table 1. Cohort studies among individuals with colon or rectal cancer examining lifestyle factors after diagnosis in relation to all-cause mortality, colorectal cancer-specific mortality or recurrence

First author, year, name of cohort, country	Study population	Time of post-diagnosis exposure assessment	Outcomes assessed	Year of CRC diagnosis and follow-up	Lifestyle factor	All-cause mortality HR (95%CI)	Colorectal cancer-specific mortality HR (95%CI)	Covariates
Dietary patterns – population-based studies								
Fung, 2014, Nurses' Health Study I, USA [23]	n=1201 W only CRC Stage I-III	≥6 months after CRC diagnosis (mean 21.0 months)	All-cause mortality (n=435); CRC-specific mortality (n=162)	Diagnosis: 1986-2008; Median FU: 11.2 years	Western dietary pattern			Age, PA, BMI, weight change, tumor grade, chemotherapy, smoking, energy intake, tumor site, stage, date of CRC diagnosis
					Q1	1.0	1.0	
					Q2	1.15 (0.83-1.58)	1.48 (0.87-2.54)	
					Q3	1.02 (0.72-1.43)	1.00 (0.55-1.83)	
					Q4	1.37 (0.97-1.94)	1.50 (0.84-2.70)	
					Q5	1.32 (0.89-1.97)	1.66 (0.85-3.23)	
					P-trend	0.23	0.09	
					Prudent dietary pattern			
					Q1	1.0	1.0	
					Q2	0.84 (0.62-1.13)	0.67 (0.40-1.12)	
					Q3	0.91 (0.67-1.25)	0.62 (0.37-1.05)	
					Q4	1.02 (0.73-1.42)	0.91 (0.53-1.55)	
					Q5	0.93 (0.65-1.34)	0.67 (0.37-1.22)	
					P-trend	0.80	0.16	
					Alternate Healthy Eating Index (AHEI)			
					Q1	1.0	1.0	
					Q2	0.84 (0.63-1.10)	0.69 (0.42-1.12)	
					Q3	0.71 (0.53-0.94)	0.73 (0.45-1.17)	
					Q4	0.71 (0.52-0.96)	0.76 (0.47-1.23)	
					Q5	0.71 (0.52-0.98)	0.72 (0.43-1.21)	
					P-trend	0.01	0.07	
					Alternate Mediterranean Diet (aMED) score			
					Q1	1.0	1.0	
					Q2	1.14 (0.85-1.52)	1.18 (0.73-1.91)	
					Q3	1.01 (0.75-1.37)	0.96 (0.58-1.56)	
					Q4	0.92 (0.66-1.27)	0.73 (0.42-1.20)	
					Q5	0.87 (0.63-1.21)	0.84 (0.50-1.42)	
					P-trend	0.31	0.19	
					Dietary Approaches to Stop Hypertension (DASH) score			
					Q1	1.0	1.0	
					Q2	0.92 (0.68-1.24)	0.84 (0.52-1.34)	
					Q3	0.96 (0.69-1.32)	0.70 (0.41-1.22)	
					Q4	0.87 (0.65-1.18)	0.72 (0.43-1.20)	
					Q5	0.98 (0.71-1.35)	0.87 (0.52-1.45)	
					P-trend	0.66	0.35	

Table 1. Continued

First author, year, name of cohort, country	Study population	Time of post-diagnosis exposure assessment	Outcomes assessed	Year of CRC diagnosis and follow-up	Lifestyle factor	All-cause mortality HR (95%CI)	Colorectal cancer-specific mortality HR (95%CI)	Covariates
Ratjen, 2017, PopGen, Germany [24]	n=1404 M and W CRC Stage I-IV	6 years after diagnosis (median)	All-cause mortality (n=204)	Diagnosis: 1993-2005; Median FU: 7 years	Modified Mediterranean Diet Score Q1 Q2 Q3 Q4 P-trend Per 1-point increment Healthy Nordic Food Index Q1 Q2 Q3 Q4 P-trend Per 1-point increment	 1.0 0.92 (0.64-1.34) 0.85 (0.59-1.23) 0.48 (0.32-0.74) 0.001 0.88 (0.81-0.96) 1.0 0.87 (0.59-1.27) 0.77 (0.49-1.22) 0.63 (0.39-1.04) 0.06 0.90 (0.82-0.99)		Sex, age, BMI, PA, survival time from CRC diagnosis until diet assessment, tumor site, metastases, other cancer, chemotherapy, smoking, total energy intake, and time-varying age, BMI, and metastases.
Dietary patterns – studies in the adjuvant setting								
Meyerhardt, 2007, CALGB 89803, USA [42]	n=1009 M and W Colon Stage III	Midway through adjuvant therapy and 6 months after completion of adjuvant therapy	All-cause mortality (n=251); Recurrence-free survival (n=324); Disease free survival (n=352)	Diagnosis: 1999-2001; Median FU: 5.3 years	Western dietary pattern Q1 Q2 Q3 Q4 Q5 P-trend Prudent dietary pattern Q1 Q2 Q3 Q4 Q5 P-trend	 1.0 0.74 (0.48-1.17) 1.38 (0.90-2.11) 1.66 (1.04-2.65) 2.32 (1.36-3.96) <0.001 1.0 1.18 (0.81-1.71) 0.94 (0.62-1.43) 0.72 (0.46-1.13) 1.32 (0.86-2.04) 0.54	† 1.0 0.92 (0.63-1.36) 1.42 (0.98-2.07) 1.44 (0.94-2.19) 2.85 (1.75-4.63) <0.001 † 1.0 1.07 (0.76-1.51) 1.05 (0.74-1.51) 0.83 (0.57-1.23) 1.13 (0.77-1.67) 0.84	Sex, age, depth of invasion through bowel wall, number of positive lymph nodes, presence of clinical perforation at time of surgery, presence of bowel obstruction at time of surgery, baseline performance status, treatment group, weight change between first and second questionnaire, and time-varying body mass index, PA level, and total calories.

First author, year, name of cohort, country	Study population	Time of post-diagnosis exposure assessment	Outcomes assessed	Year of CRC diagnosis and follow-up	Lifestyle factor	All-cause mortality HR (95%CI)	Colorectal cancer-specific mortality HR (95%CI)	Covariates
Red and processed meats – population-based studies								
McCullough, 2013, CPS II Nutrition Cohort, USA [40]	n=1186 M and W CRC Stage I-III	3 years after diagnosis (mean)	All-cause mortality (n=472); CRC-mortality (n=146); CVD-mortality (n=110); other-mortality (n=216)	Diagnosis: 1992-2009 Mean FU: 7.6 years (SD 3.4 years)	Red and processed meat intake Q1 Q2 Q3 Q4 P-trend	 1.0 1.17 (0.89-1.55) 1.13 (0.84-1.52) 0.94 (0.68-1.30) 0.36	 1.0 1.28 (0.76-2.15) 0.93 (0.53-1.64) 1.10 (0.61-1.91) 0.91	Age, sex, stage, energy intake, weight change between 1992 pre-diagnostic and post-diagnostic questionnaires, and 1992 pre-diagnostic meat intake.
Fung, 2014, Nurses' Health Study I, USA [23]	n=1201 W only CRC Stage I-III	≥6 months after diagnosis (mean 21.0 months)	All-cause mortality (n=435); CRC-specific mortality (n=162)	Diagnosis: 1986-2008; Median FU: 11.2 years	Red/processed meat per serving/d (secondary analyses)	1.07 (0.87-1.30)	1.22 (0.90-1.67)	Age, PA, BMI, weight change, tumor grade, chemotherapy, smoking, energy intake, tumor site, stage, date of CRC diagnosis
Sugar-sweetened beverages – population-based studies								
Fung, 2014, Nurses' Health Study I, USA [23]	n=1201 W only CRC Stage I-III	≥6 months after diagnosis (mean 21.0 months)	All-cause mortality (n=435); CRC-specific mortality (n=162)	Diagnosis: 1986-2008; Median FU: 11.2 years	Sugar-sweetened beverages + juices per serving/d (secondary analyses)	1.11 (1.01-1.23)	1.16 (0.99-1.35)	Age, PA, BMI, weight change, tumor grade, chemotherapy, smoking, energy intake, tumor site, stage, date of CRC diagnosis

Table 1. Continued

First author, year, name of cohort, country	Study population	Time of post-diagnosis exposure assessment	Outcomes assessed	Year of CRC diagnosis and follow-up	Lifestyle factor	All-cause mortality HR (95%CI)	Colorectal cancer-specific mortality HR (95%CI)	Covariates
Sugar-sweetened beverages – studies in the adjuvant setting								
Fuchs, 2014, CALGB 89803, USA [43]	n=1011 M and W Colon Stage III	Midway through adjuvant therapy and 6 months after completion of adjuvant therapy	All-cause mortality (n=305); Recurrence-free survival (n=343); Disease free survival (n=386)	Diagnosis: 1999-2001; Median FU: 7.3 years	Sugar-sweetened beverages intake <2/mo 2/mo to 2/wk 3 to 6/wk 1 to <2/d ≥2/d P-trend	 1.0 0.74 (0.53-1.04) 1.07 (0.75-1.53) 0.70 (0.43-1.15) 1.41 (0.79-2.50) 0.21	† 1.0 0.98 (0.72-1.34) 1.34 (0.97-1.87) 1.07 (0.70-1.65) 1.75 (1.04-2.94) 0.04	Age, sex, depth of invasion through bowel wall, number of positive lymph nodes, baseline performance status, treatment group, and the following time-varying covariates total energy intake, BMI, PA level, Wester dietary pattern, prudent dietary pattern, and glycemic load.
Alcohol – population-based studies								
Fung, 2014, Nurses' Health Study, USA [23]	n=1201 W only Colon and rectum Stage I-III	≥6 months after diagnosis (mean 21.0 months)	All-cause mortality (n=435); CRC-specific mortality (n=162)	Diagnosis: 1986-2008; Median FU: 11.2 years	No alcohol intake 5-15 g/day >15 g/day (secondary analyses)	1.30 (1.05-1.61) 1.0 1.22 (0.85-1.76)	1.32 (0.93-1.87) 1.0 0.97 (0.50-1.87)	Age, PA, BMI, weight change, tumor grade, chemotherapy, smoking, energy intake, tumor site, stage, date of CRC diagnosis
Lochhead, 2015, Nurses' Health Study I + Health Professional Follow-Up Study, USA [44]	n=1550 M and W CRC Stage I-III	≥1 year but ≤4 year after CRC diagnosis (median 29.5 months)	All-cause mortality (n=641); CRC-specific mortality (n=176)	Diagnosis: up to 2006; Median FU: 14.9 years	Alcohol intake g/d 0 0.1-14.9 ≥15 P-trend	 1.0 0.83 (0.70-0.99) 0.91 (0.72-1.16) 0.41	 1.0 0.51 (0.34-0.76) 0.53 (0.28-0.98) 0.33	Prediagnostic alcohol consumption, age, year of diagnosis, BMI, family history of CRC, aspirin use, multivitamin use, smoking, PA, folate, vitamin B-12, methionine, and vitamin B-6 intake, tumor site, tumor differentiation, time from diagnosis to questionnaire return, and stage- and sex-stratified

First author, year, name of cohort, country	Study population	Time of post-diagnosis exposure assessment	Outcomes assessed	Year of CRC diagnosis and follow-up	Lifestyle factor	All-cause mortality HR (95%CI)	Colorectal cancer-specific mortality HR (95%CI)	Covariates
Yang, 2017, CPS II Nutrition Cohort, USA [27]	n=1599 M and W CRC Stage I-III	1.9 years after CRC diagnosis (mean)	All-cause mortality (n=732); CRC-specific mortality (n=235); CVD-mortality (n=172); other mortality (n=325)	Diagnosis: 1992-2011; Mean FU: 8.2 years (SD 4.7 years)	Alcohol drinking Never Former-former Current-former Current <2 drinks/day Current ≥2 drinks/day	 1.0 1.09 (0.81-1.48) 1.21 (0.92-1.60) 0.94 (0.77-1.16) 0.92 (0.66-1.26)	 1.0 1.28 (0.73-2.23) 1.81 (1.13-2.91) 1.27 (0.87-1.86) 1.44 (0.80-2.60)	Age, six, tumor stage, smoking status, BMI, PA, education, and pre-existing diseases in 1982/1992.
Tamakoshi, 2017, BioBank Japan, Japan [26]	n=1598 M and W CRC Stage I-IV	Within 90 days after CRC diagnosis	All-cause mortality (n=521)	Diagnosis: 2003-2008; Median FU: 7.4 years	Never drinker Ex drinker 0-15 g/d 15-30 g/d ≥30 g/d	1.0 1.26 (0.98-1.63) 0.73 (0.56-0.97) 0.79 (0.57-1.11) 0.73 (0.56-0.96)		Stratified by sex and institutions and adjusted for age and entry year.

Table 1. Continued

First author, year, name of cohort, country	Study population	Time of post-diagnosis exposure assessment	Outcomes assessed	Year of CRC diagnosis and follow-up	Lifestyle factor	All-cause mortality HR (95%CI)	Colorectal cancer-specific mortality HR (95%CI)	Covariates
Other food groups and nutrients – population-based studies								
Yang, 2014, CPS II Nutrition cohort, USA [41]	n=1111 M and W CRC Stage I-III	2.6 years after CRC diagnosis (mean)	All-cause mortality (n=429); CRC-specific mortality (n=143);	Diagnosis: 1992-2009; Mean FU: 7.6 years (SD 3.4)	Total dairy intake			Age, sex, stage, energy intake, post-diagnostic energy intake, and total folate intakes.
					Q1	1.0	1.0	
					Q2	0.91 (0.69-1.21)	0.73 (0.44-1.23)	
					Q3	0.73 (0.54-0.98)	0.92 (0.56-1.52)	
					Q4	0.75 (0.56-1.01)	0.73 (0.44-1.23)	
					P-trend	0.05	0.32	
					Milk intake			
					Q1	1.0	1.0	
					Q2	0.85 (0.64-1.13)	0.90 (0.54-1.49)	
					Q3	0.76 (0.52-1.12)	0.85 (0.44-1.67)	
					Q4	0.72 (0.55-0.94)	0.93 (0.59-1.49)	
					P-trend	0.02	0.81	
					Total calcium intake			
					Q1	1.0	1.0	
					Q2	0.89 (0.67-1.18)	1.15 (0.71-1.86)	
					Q3	0.72 (0.53-0.98)	0.81 (0.48-1.38)	
					Q4	0.72 (0.53-0.98)	0.59 (0.33-1.05)	
					P-trend	0.02	0.01	
					Dietary calcium intake			
					Q1	1.0	1.0	
					Q2	0.84 (0.63-1.11)	0.85 (0.51-1.41)	
					Q3	0.69 (0.51-0.93)	0.98 (0.59-1.62)	
					Q4	0.86 (0.65-1.14)	1.00 (0.61-1.63)	
					P-trend	0.21	0.83	
					Supplemental calcium intake			
					C1	1.0	1.0	
					C2	0.95 (0.72-1.27)	1.04 (0.65-1.69)	
					C3	0.98 (0.73-1.31)	0.65 (0.38-1.11)	
					P-trend	0.55	0.13	
					Total vitamin D			
					Q1	1.0	1.0	
					Q2	0.81 (0.59-1.10)	0.99 (0.59-1.66)	
					Q3	0.97 (0.67-1.40)	1.31 (0.66-2.58)	
					Q4	0.88 (0.57-1.35)	1.74 (0.80-3.77)	
					P-trend	0.35	0.52	
					Dietary vitamin D intake			
					Q1	1.0	1.0	
					Q2	0.99 (0.75-1.31)	0.78 (0.46-1.32)	
					Q3	0.95 (0.71-1.27)	1.11 (0.67-1.85)	
					Q4	0.90 (0.67-1.21)	1.28 (0.77-2.10)	
					P-trend	0.33	0.19	

First author, year, name of cohort, country	Study population	Time of post-diagnosis exposure assessment	Outcomes assessed	Year of CRC diagnosis and follow-up	Lifestyle factor	All-cause mortality HR (95%CI)	Colorectal cancer-specific mortality HR (95%CI)	Covariates
Fung, 2014, Nurses' Health Study, USA [23]	n=1201 W only CRC Stage I-III	≥6 months after diagnosis (mean 21.0 months)	Overall mortality (n=435); CRC-specific mortality (n=162)	Diagnosis: 1986-2008; Median FU: 11.2 years	Per serving/day Whole fruits Vegetables Nuts Whole grains (all secondary analyses)	 1.08 (0.98-1.20) 1.0 (0.94-1.06) 0.98 (0.82-1.17) 0.98 (0.95-1.01)	 1.03 (0.87-1.21) 0.94 (0.84-1.04) 0.69 (0.49-0.97) 0.97 (0.93-1.02)	Age, PA, BMI, weight change, tumor grade, chemotherapy, smoking, energy intake, tumor site, stage, date of CRC diagnosis
Lochhead, 2015, Nurses' Health Study I + Health Professional Follow-Up Study, USA [44]	n=1550 M and W CRC Stage I-III	≥1 year but ≤4 year after CRC diagnosis (median 29.5 months)	All-cause mortality (n=641); CRC-specific mortality (n=176)	Diagnosis: up to 2006; Median FU: 14.9 years	Folate intake Q1 Q2 Q3 Q4 Q5 P-trend Vitamin B-6 intake Q1 Q2 Q3 Q4 Q5 P-trend Vitamin B-12 intake Q1 Q2 Q3 Q4 Q5 P-trend Methionine Q1 Q2 Q3 Q4 Q5 P-trend	 1.0 1.03 (0.81-1.31) 1.17 (0.92-1.49) 0.86 (0.66-1.13) 0.87 (0.65-1.16) 0.13 1.0 0.87 (0.69-1.11) 0.80 (0.62-1.03) 0.94 (0.73-1.22) 0.78 (0.59-1.03) 0.18 1. 0 1.19 (0.93-1.52) 0.96 (0.74-1.23) 0.94 (0.72-1.22) 1.11 (0.82-1.50) 0.71 1.0 0.82 (0.63-1.05) 0.92 (0.71-1.19) 1.02 (0.79-1.31) 1.17 (0.92-1.49) 0.053	 1.0 1.17 (0.74-1.88) 1.63 (1.04-2.56) 0.76 (0.43-1.35) 1.04 (0.60-1.82) 0.21 1.0 0.95 (0.59-1.51) 1.08 (0.67-1.74) 0.94 (0.57-1.55) 0.93 (0.58-1.49) 0.66 1.0 1.23 (0.77-1.95) 0.70 (0.43-1.14) 0.88 (0.55-1.42) 1.04 (0.62-1.74) 0.99 1.0 0.57 (0.34-0.95) 0.82 (0.51-1.32) 0.79 (0.50-1.27) 0.90 (0.57-1.41) 0.91	Alcohol consumption, age, year of diagnosis, BMI, family history of CRC, aspirin use, multivitamin use, smoking, PA, folate, vitamin B-12, methionine, and vitamin B-6 intake, tumor site, tumor differentiation, time from diagnosis to questionnaire return, and stage- and sex-stratified

Table 1. Continuedt

First author, year, name of cohort, country	Study population	Time of post-diagnosis exposure assessment	Outcomes assessed	Year of CRC diagnosis and follow-up	Lifestyle factor	All-cause mortality HR (95%CI)	Colorectal cancer-specific mortality HR (95%CI)	Covariates
Tamakoshi, 2017, BioBank Japan, Japan [26]	n=1598 M and W CRC Stage I-IV	Within 90 days after CRC diagnosis	All-cause mortality (n=521)	Diagnosis: 2003-2008 Median FU: 7.4 years	Green leafy vegetable consumption Almost everyday 3-4 days/week 1-2 days/week Almost never Meat consumption Almost everyday 3-4 days/week 1-2 days/week Almost never	 1.0 1.27 (0.99-1.62) 1.61 (1.18-2.20) 1.87 (1.22-2.88) 1.0 1.04 (0.76-1.41) 1.06 (0.78-1.43) 1.21 (0.85-1.71)		Stratified by sex and institutions and adjusted for age and entry year
Other food groups and nutrients – studies in the adjuvant setting								
Meyerhardt, 2012, CALGB 89803, USA [46]	n=1011 M and W Colon Stage III	Midway through adjuvant therapy and 6 months after completion of adjuvant therapy	All-cause mortality (n=305); Recurrence-free survival (n=343); Disease free survival (n=386);	Diagnosis: 1999-2001; Median FU: 7.3 years	Glycemic load Q1 Q2 Q3 Q4 Q5 P-trend Glycemic index Q1 Q2 Q3 Q4 Q5 P-trend Fructose Q1 Q2 Q3 Q4 Q5 P-trend Carbohydrate intake Q1 Q2 Q3 Q4 Q5 P-trend	 1.0 0.83 (0.55-1.23) 1.05 (0.72-1.54) 1.50 (1.04-2.17) 1.74 (1.20-2.51) <0.001 1.0 0.94 (0.64-1.37) 1.22 (0.84-1.77) 1.09 (0.74-1.61) 1.23 (0.83-1.82) 0.22 1.0 0.82 (0.57-1.18) 0.74 (0.51-1.08) 0.92 (0.64-1.32) 1.11 (0.79-1.58) 0.40 1.0 1.00 (0.68-1.49) 1.11 (0.76-1.63) 1.60 (1.11-2.32) 1.80 (1.25-2.60) <0.001	† 1.0 1.01 (0.70-1.47) 1.07 (0.74-1.56) 1.70 (1.18-2.40) 1.97 (1.39-2.79) <0.001 1.0 0.99 (0.69-1.43) 1.21 (0.85-1.73) 1.21 (0.84-1.73) 1.24 (0.85-1.81) 0.14 1.0 0.82 (0.58-1.17) 0.95 (0.67-1.33) 1.04 (0.74-1.47) 1.43 (1.04-1.98) 0.01 1.0 1.07 (0.73-1.56) 1.20 (0.83-1.73) 1.76 (1.24-2.50) 2.06 (1.45-2.91) <0.001	Sex, age, depth of invasion through bowel wall, number of positive lymph nodes, baseline performance status, treatment group, time-varying BMI, time-varying PA, time-varying cereal fiber, and time-varying dietary pattern

First author, year, name of cohort, country	Study population	Time of post-diagnosis exposure assessment	Outcomes assessed	Year of CRC diagnosis and follow-up	Lifestyle factor	All-cause mortality HR (95%CI)	Colorectal cancer-specific mortality HR (95%CI)	Covariates
Guercio, 2015, CALGB 89803, USA [25]	n=953 M and W Colon Stage III	Midway through adjuvant therapy and 6 months after completion of adjuvant therapy	All-cause mortality (n=324); Recurrence-free survival (n=329); Disease free survival (n=365);	Diagnosis: 1999-2001; Median FU: 7.3 years	Total coffee cups/d 0 <1 1 2-3 ≥4 P-trend Non-herbal tea cups/d 0 <1 1 2-3 ≥4 P-trend	 1.0 0.97 (0.66-1.44) 0.97 (0.66-1.42) 0.69 (0.47-1.01) 0.66 (0.37-1.18) 0.01 1.0 1.08 (0.81-1.44) 0.87 (0.58-1.30) 0.95 (0.60-1.50) 0.82 (0.40-1.67) 0.36	† 1.0 0.98 (0.68-1.43) 0.97 (0.66-1.42) 0.80 (0.56-1.14) 0.71 (0.41-1.23) 0.07 † 1.0 1.09 (0.83-1.43) 0.89 (0.61-1.30) 1.03 (0.67-1.57) 0.86 (0.44-1.68) 0.51	Age, sex, depth of invasion through bowel wall, number of positive lymph nodes, baseline performance status, treatment group, smoking history, multivitamin, and the following time-varying covariates total energy intake, alcohol consumption, BMI, PA level, Wester dietary pattern, prudent dietary pattern, sugar-sweetened beverage intake and dietary glycemic load.
Physical activity – population-based studies								
Meyerhardt, 2006, Nurses' Health Study I, USA [47]	n=554 W only CRC Stage I-III	≥1 year but ≤4 year after CRC diagnosis (median 22 months)	All-cause mortality (n=121); CRC-specific mortality (n=72)	Diagnosis: 1986-2002; Median FU: 9.6 years	Total MET-h activity/wk <3 3-8.9 9-17.9 ≥18 P-trend	 1.0 0.77 (0.48-1.23) 0.50 (0.28-0.90) 0.43 (0.25-0.74) 0.003	 1.0 0.92 (0.50-1.69) 0.57 (0.27-1.20) 0.39 (0.18-0.82) 0.008	Age, year of diagnosis, BMI, stage, tumor grade, tumor site, chemotherapy, time from diagnosis to PA measurement, change in BMI before and after diagnosis, and smoking.

Table 1. Continuedt

First author, year, name of cohort, country	Study population	Time of post-diagnosis exposure assessment	Outcomes assessed	Year of CRC diagnosis and follow-up	Lifestyle factor	All-cause mortality HR (95%CI)	Colorectal cancer-specific mortality HR (95%CI)	Covariates
Meyerhardt, 2009, Health Professional Follow-Up Study , USA [48]	n=661 M only CRC Stage I-III	≥6 months but ≤4 years after CRC diagnosis (median 15 months)	All-cause mortality (n=258); CRC-specific mortality (n=88)	Diagnosis: 1986-2004; Median FU: 8.6 years	Total MET-h activity/wk ≤3 3.1-9 9.1-18 18.1-27 ≥27 P-trend	 1.0 1.00 (0.68-1.48) 1.12 (0.74-1.70) 0.74 (0.46-1.20) 0.59 (0.41-0.86) <0.001	 1.0 1.06 (0.55-2.08) 1.30 (0.65-2.59) 0.76 (0.33-1.77) 0.47 (0.24-0.92) 0.002	Age, stage, tumor grade, tumor site, diagnosis year, BMI at diagnosis, time from diagnosis to PA measurement, change in BMI before and after diagnosis, and smoking.
Baade, 2011, Queensland, Australia [49]	n=1825 M and W CRC Stage I-III	5 months after CRC diagnosis	All-cause mortality (n=462); CRC-specific mortality (n=345)	Diagnosis 2003-2004; Median FU: 4.9 years (range 4.0-6.0)	PA min/wk 0 1-149 ≥150 P-trend	 1.0 0.72 (0.57-0.91) 0.75 (0.60-0.94) 0.007	 1.0 0.90 (0.69-1.17) 0.88 (0.68-1.15) 0.585	NR
Kuiper, 2012, Women's Health Initiative, USA [50]	n=606 W only CRC Stage I-III	1.5 year after CRC diagnosis (median)	All-cause mortality (n=108); CRC-specific mortality (n=51)	Diagnosis ≥ 1993; Median FU 11.9 years (IQR 10.9-12.9)	Total MET-h activity /wk 0 >0-2.9 3.0-8.9 9.0-17.9 ≥18 P-trend	 1.0 0.71 (0.40-1.30) 0.42 (0.23-0.77) 0.57 (0.31-1.07) 0.41 (0.21-0.81) 0.005	 1.0 0.49 (0.21-1.14) 0.30 (0.12-0.73) 0.53 (0.22-1.25) 0.29 (0.11-0.77) 0.02	Age, study arm, stage, ethnicity, education, alcohol, smoking, and hormone therapy use, pre-diagnostic BMI, time between baseline measurement and diagnosis.
Campbell, 2013, CPS II Nutrition Cohort, USA [51]	n=1800 M and W CRC Stage I-III	1.4 years after CRC diagnosis (median)	All-cause mortality (n=588); CRC-specific mortality (n=226); CVD-mortality (n=127); Mortality from other causes (n=235)	Diagnosis: 1994-2007; Mean FU: 6.8 years	Total MET-h activity/wk <3.5 3.5-8.74 ≥8.75	 1.0 0.78 (0.60-1.00) 0.58 (0.47-0.71)	 1.0 1.00 (0.64-1.56) 0. 87 (0.61-1.24)	Age, sex, smoking, BMI, red meat intake, stage, leisure-time spent sitting and education
Arem, 2015, National Institutes of Health-AARP, USA [52]	n=1759 M and W CRC Stage I-III	4.2 years after CRC diagnosis (median)	All-cause mortality (n=412); CRC-specific mortality (n=128); CVD-specific mortality (n=82)	Diagnosis 1996-2006; Median FU: 7.1 years	PA h/wk 0 <1 1-3.9 4-6.9 ≥7 P-trend	 1.0 1.00 (0.72-1.39) 0.88 (0.65-1.19) 0.66 (0.46-0.94) 0.69 (0.49-0.98) 0.006	 1.0 0.98 (0.53-1.81) 0.96 (0.57-1.62) 0.69 (0.36-1.29) 0.53 (0.27-1.03) 0.041	Sex, tumor site, tumor grade, stage, surgery, radiation, chemotherapy, time watching TV, smoking, BMI, self-reported health status, pre- and post-diagnosis PA (age is time metric in model).

First author, year, name of cohort, country	Study population	Time of post-diagnosis exposure assessment	Outcomes assessed	Year of CRC diagnosis and follow-up	Lifestyle factor	All-cause mortality HR (95%CI)	Colorectal cancer-specific mortality HR (95%CI)	Covariates
Tamakoshi, 2017, BioBank Japan, Japan [26]	n=1598 M and W CRC Stage I-IV	Within 90 days after diagnosis	All-cause mortality (n=521)	Diagnosis: 2003-2008 Median FU: 7.4 years	Physical exercise ≥3 times/wk 1-2 times/wk No habit	 1.0 0.60 (0.33-1.08) 1.33 (1.05-1.68)		Stratified by sex and institutions and adjusted for age and entry year.
Physical activity – studies in the adjuvant setting								
Meyerhardt, 2006, CALGB 89803, USA [53]	n=832 M and W Colon Stage III	7.1 months after completion of adjuvant treatment (median)	All-cause mortality (n=84); Recurrence-free survival (n=159); Disease-free survival (n=172)	Inclusion: 999-2001; Median FU: 2.7 years	Total MET-h activity/wk <3 3-8.9 9-17.9 18-26.9 ≥27 P-trend	 1.0 0.85 (0.49-1.49) 0.71 (0.36-1.41) 0.71 (0.32-1.59) 0.37 (0.16-0.82) 0.01	† 1.0 0.86 (0.57-1.30) 0.89 (0.55-1.42) 0.51 (0.26-1.01) 0.60 (0.36-1.01) 0.03	Age, sex, depth of invasion through bowel wall, no. of positive lymph nodes, clinical perforation at time of surgery, baseline CEA, tumor, baseline performance status, treatment arm, weight change between first and second questionnaire, BMI at time of second questionnaire, time between study entry and completion of second questionnaire
Sedentary behavior – population-based studies								
Campbell, 2013, CPS II Nutrition Cohort, USA [51]	n=1656 M and W CRC Stage I-III	1.9 years after CRC diagnosis (median)	All-cause mortality (n=477); CRC-specific mortality (n=169); CVD-mortality (n=110); Mortality from other causes (n=198)	Diagnosis: 1994-2007; Mean FU: 6.8 years	Leisure time spent sitting <3 h/d 3-<6 ≥6 h/d	 1.0 1.13 (0.91-1.40) 1.27 (0.99-1.64)	 1.0 1.23 (0.84-1.78) 1.62 (1.07-2.44)	Age, sex, smoking, BMI, red meat intake, stage, PA, and education

Table 1. Continuedt

First author, year, name of cohort, country	Study population	Time of post-diagnosis exposure assessment	Outcomes assessed	Year of CRC diagnosis and follow-up	Lifestyle factor	All-cause mortality HR (95%CI)	Colorectal cancer-specific mortality HR (95%CI)	Covariates
Arem, 2015, National Institutes of Health-AARP, USA [52]	n=1759 M and W CRC Stage I-III	4.2 years after diagnosis (median)	All-cause mortality (n=412); CRC-specific mortality (n=128); CVD-specific mortality (n=82)	Diagnosis 1996-2006; Median FU: 7.1 years	TV viewing 0-2 h/d 3-4 h/d ≥5 h/d P-trend	 1.0 0.98 (0.75-1.27) 1.25 (0.93-1.67) 0.126	 1.0 0.90 (0.56-1.46) 1.45 (0.85-2.47) 0.156	Age as time metric. Sex, tumor site, tumor grade, stage, chemotherapy, PA, smoking, BMI, self-reported health and pre-diagnosis TV viewing
Cao, 2015, Health Professional Follow-Up Study, USA [57]	n=714 M only CRC Stage I-III	≥6 months but ≤ 3 years after CRC diagnosis	All-cause mortality (n=325); CRC-specific mortality (n=72); Mortality from other causes (n=253);	Diagnosis: 1986-2010; FU until end 2011	Sitting watching TV 0-6 h/w 7-13 h/w 14-20 h/w ≥21 h/w P-trend	 1.0 0.98 (0.70-1.37) 1.01 (0.72-1.42) 1.16 (0.80-1.68) 0.66	 1.0 0.62 (0.27-1.41) 0.68 (0.30-1.54) 1.45 (0.73-2.87) 0.27	Age, year of diagnosis, stage, tumor grade, tumor site, smoking, PA, BMI, AHEI, and pre-diagnosis TV viewing
Smoking – population based studies								
Jadallah, 1999, Dunedin hospital, New Zealand [58]	n=241 M and W CRC Stage I-III	Hospital record	All-cause mortality (n=81);	Diagnosis: 1990-1992; FU: 5 years	Non-smoker Smoking	1.0 2.26 (1.31-3.90)		Blood transfusion, stage
Ali, 2011, Irish National Cancer Registry, Ireland [59]	n=22335 M and W CRC Stage I-IV	Cancer registry	All-cause mortality (n=11400);	Diagnosis: 1994-2005; Max FU: 15 years	Former smoker Current smoker Never smoker Current smoker	1.0 1.15 (1.07-1.23) 1.0 1.20 (1.13-1.28)		Age, tumor grade, stage
Warren, 2013, Roswell Park Cancer Institute, USA [60]	n=359 M and W CRC Stage I-IV	Within 1 month after CRC diagnosis	All-cause mortality (n=NR); CRC-specific mortality (n=NR):	Diagnosis: 1982-1998 FU:12-27.7 years	Men Former smoker Current smoker Never smoker Current smoker Women Former smoker Current smoker Never smoker Current smoker	 1.0 1.07 (0.64-1.81) 1.0 1.05 (0.62-1.78) 1.0 0.89 (0.39-2.06) 1.0 1.70 (0.87-3.31)	 1.0 1.14 (0.56-2.27) 1.0 0.70 (0.36-1.36) 1.0 1.18 (0.34-4.05) 1.0 1.85 (0.85-4.02)	Disease site, sex, age, stage, race, date of diagnosis, BMI, total pack-years of smoking

First author, year, name of cohort, country	Study population	Time of post-diagnosis exposure assessment	Outcomes assessed	Year of CRC diagnosis and follow-up	Lifestyle factor	All-cause mortality HR (95%CI)	Colorectal cancer-specific mortality HR (95%CI)	Covariates
Tao, 2013, Shanghai Cohort Study, China [28]	n=248 M only CRC Stage NR	At diagnosis and yearly thereafter	All-cause mortality (n=152)	Diagnosis: 1986-2010; Mean FU: 5.3 (±4.8) years	Non-smoking Smoking (time-dependent)	1.0 1.65 (1.14-2.38)		Age, education, pack-years of smoking before diagnosis, treatment, and cancer site
Amri, 2015, Massachusetts General Hospital, USA [61]	n=1071 M and W CRC Stage I-IV	At pre-operative assessment	All-cause mortality (n=NR); CRC-specific mortality (n=NR); Metastatic recurrence (n=NR)	Diagnosis: 2004-2011; FU: NR	Non-smoking Current smoking P-trend	1.0 1.44 (1.07-1.94) 0.017	1.0 1.21 (0.80-1.83) 0.36	Age, stage, BMI, comorbidities
Walter, 2015, DACHS study, Germany [62]	n=3130 M and W CRC Stage I-IV	24 days after CRC diagnosis (median)	All-cause mortality (n=889); CRC-specific mortality (n=644); Recurrence-free survival (n=828); Disease-free survival (n=1024); Non-CRC related mortality (n=232)	Diagnosis: 2003-2010; Median FU: 4.9 years (IQR 2.9-5.1)	Non-smoking <15 cigarettes/d ≥15 cigarettes/d	1.0 1.10 (0.85-1.43) 0.99 (0.73-1.32)	1.0 1.08 (0.83-1.41) 1.14 (0.87-1.51)	Age, sex, BMI, stage, alcohol consumption, red meat consumption, family history of CRC, use of statins, use of NSAIDs, use of beta blockers, diabetes mellitus, history of heart failure, myocardial infarction, angina pectoris or stroke, history of nonCRC cancer; additional adjustment for age*log(time) and cancer*log(time)
Yang, 2015, CPS II Nutrition Cohort, USA [29]	n=2256 M and W CRC Stage I-III	1.4 years after CRC diagnosis (mean)	All-cause mortality (n=865); CRC-specific mortality (n=324)	Diagnosis: 1992-2009; Mean FU: 7.5 years (SD 4.6 years)	Never smoking Former smoking Current smoking	1.0 1.21 (1.03-1.42) 2.22 (1.58-3.13)	1.0 0.91 (0.71-1.18) 1.92 (1.15-3.21)	Age, sex, stage, alcohol consumption, BMI, and PA
Sharp, 2017, National Cancer Registry Ireland, Ireland [14]	n=18166 M and W Colon Stage I-IV	At diagnosis	CRC-specific mortality (n=7488)	Diagnosis: 1994-2012; FU: 5 years	Never smoker Ex-smoker Current smoker P-trend		1.0 1.00 (0.94-1.07) 1.14 (1.07-1.22) <0.01	Sex, marital status, deprivation category, period of diagnosis, grade, tumor site. With stage and age fitted as stratification factors.

Table 1. Continuedt

First author, year, name of cohort, country	Study population	Time of post-diagnosis exposure assessment	Outcomes assessed	Year of CRC diagnosis and follow-up	Lifestyle factor	All-cause mortality HR (95%CI)	Colorectal cancer-specific mortality HR (95%CI)	Covariates
Sharp, 2017, National Cancer Registry Ireland, Ireland [30]	n=10,794 M and W Rectum Stage I-IV	At diagnosis	CRC-specific mortality (n=4491)	Diagnosis: 1994-2012; FU: 5 years	Never smoker Ex-smoker Current smoker P-trend		1.0 1.02 (0.93-1.11) 1.15 (1.06-1.24) <0.01	Sex, marital status, deprivation category, period of diagnosis, grade. With stage and age fitted as stratification factors.
Rasouli, 2017, Kurdistan's Cancer Registry, Iran [31]	n=335 M and W CRC Stage II-III	Medical record	All-cause mortality (n=164)	Diagnosis: 2009-2014; Median FU: 42.6 ± 2.8 months	Non-smoking Smoking	1.0 1.34 (0.92-1.95)		Age, residence, marital status, occupation, education, socioeconomic status, comorbidity, stage, tumor grade
Tamakoshi, 2017, BioBank Japan, Japan [26]	n=1598 M and W CRC Stage I-IV	Within 90 days after CRC diagnosis	All-cause mortality (n=521)	Diagnosis: 2003-2008; Median FU: 7.4 years	Never smoker Ex-smoker Current smoker	1.0 1.27 (1.02-1.59) 1.38 (1.06-1.81)		Stratified by sex and institutions and adjusted for age and entry year.
Smoking – studies in the adjuvant setting								
Munro, 2006, Tayside Cancer Centre, UK [63]	n=284 M and W CRC Stage NR	At the first assessment in the oncology department, usually around 4 weeks after surgery	CRC-specific mortality (n=83)	Diagnosis: 1997-1999; Median FU: 56 months (range 20-83)	Non-smoker Current smoker		1.0 2.24 (1.25-4.01)	Number of positive nodes, deprivation, co-morbidity, T-stage
McCleary, 2010, CALGB 89803, USA [64]	n=1045 M and W Colon Stage III	4 months after surgery	All-cause mortality (n=257); Recurrence-free survival (n=332); Disease-free survival (n=363);	Diagnosis: 1999-2001; Median FU: 5.3 years	Never smoker Former smoker Current smoker	1.0 1.17 (0.87-1.57) 1.38 (0.87-2.18)	† 1.0 1.15 (0.89-1.48) 0.90 (0.58-1.41)	Age, sex, number of positive lymph nodes, extent of invasion through bowel wall, tumor differentiation, BMI, and clinical bowel obstruction at diagnosis.

First author, year, name of cohort, country	Study population	Time of post-diagnosis exposure assessment	Outcomes assessed	Year of CRC diagnosis and follow-up	Lifestyle factor	All-cause mortality HR (95%CI)	Colorectal cancer-specific mortality HR (95%CI)	Covariates
Phipps, 2013, North Central Cancer Treatment Group N0147, USA [65]	n=1968 M and W Colon Stage III	Within 56 days after surgery	Time-to-recurrence (n=NR); Disease-free survival (n=NR)	Diagnosis: 2004-2009; Median FU: 3.5 years	 Never smoker Former smoker Current smoker		† 1.0 1.19 (0.97-1.46) 1.47 (1.03-2.11)	Tumor site, number of involved lymph nodes, T stage, mismatch repair status, performance score, PA, BMI, alcohol consumption, age, and sex
BMI – population based studies								
Asghari-Jafarabadi, 2009, Shahid Beheshti Medical University, Iran [67]	n=1219 M and W CRC Stage I-IV	Hospital record	All-cause mortality (n=NR)	Diagnosis: NR Mean FU: 2.1 years	BMI <18.5 18.5-24.9 25.0-29.9 ≥30	 2.74 (1.17-6.45) 1.0 0.32 (0.14-0.73) 0.71 (0.25-2.03)		Age, alcohol history, inflammatory bowel disease, tumor grade, stage.
Hines, 2009, University of Alabama at Birmingham Hospital, USA [70]	n=496 M and W Colon Stage I-IV	At time of surgery	All-cause mortality (n=333)	Diagnosis: 1981-2002 FU: until 2008	BMI <18.5 18.5-24.9 ≥25	 1.54 (0.96-2.45) 1.0 0.77 (0.61-0.97)		Age, ethnicity, comorbidity, stage, tumor grade, bowel obstruction.
Baade, 2011, Queensland, Australia [49]	n=1825 M and W CRC Stage I-III	5 months after diagnosis	All-cause mortality (n=462); CRC-specific mortality (n=345)	Diagnosis: 2003-2004; Median FU: 4.9 years (range 4.0-6.0)	BMI <18.5 18.5-24.9 25.0-29.9 ≥30	 2.29 (1.47-3.59) 1.0 0.75 (0.61-0.94) 0.78 (0.59-1.03)	 1.74 (1.00-3.04) 1.0 0.75 (0.59-0.97) 0.70 (0.51-0.97)	NR
Campbell, 2012, CPS II Nutrition Cohort, USA [68]	n=1957 M and W Colon Stage I-III	18 months after diagnosis	All-cause mortality (n=815); CRC-specific mortality (n=380); CVD-specific mortality (n=153)	Diagnosis: 1994-2007; Median FU: 6.4 years (range 2 days-16.1 years)	BMI <18.5 18.5-24.9 25.0-29.9 ≥30	 1.30 (0.82-2.06) 1.0 0.83 (0.70-1.00) 0.93 (0.75-1.17)	 0.64 (0.25-1.60) 1.0 0.87 (0.65-1.17) 1.14 (0.81-1.60)	Age, smoking, PA, red meat intake, stage
Chin, 2012, Taiwan [71]	n=2135 M and W Colon Stage I-III	NR	All-cause mortality (n=NR); CRC-specific mortality (n=NR); Disease-free survival (n=NR)	Diagnosis: 1995-2003; FU: at least 5 years or until death	BMI <18.5 18.5-24.9 25.0-29.9 ≥30	 1.58 (1.23-2.05) 1.0 0.83 (0.68-1.01) 0.94 (0.74-1.18)	 1.33 (0.94-1.87) 1.0 0.96 (0.76-1.22) 1.06 (0.80-1.41)	Stage, age, sex, comorbidities, CEA, hemoglobin, albumin, timing of surgery, postoperative morbidity, tumor site, histolic type, tumor grade

Table 1. Continuedt

First author, year, name of cohort, country	Study population	Time of post-diagnosis exposure assessment	Outcomes assessed	Year of CRC diagnosis and follow-up	Lifestyle factor	All-cause mortality HR (95%CI)	Colorectal cancer-specific mortality HR (95%CI)	Covariates
Kuiper, 2012, Women's Health Initiative, USA [50]	n=587 W only CRC Stage I-III	0.8 (IQR 0.4-1.7) years after diagnosis (median)	All-cause mortality (n=108); CRC-specific mortality (n=51)	Diagnosis: ≥1993 Median FU: 11.9 years (IQR 10.9-12.9)	BMI 18.5-25.0 25.0-30.0 ≥30	 1.0 0.77 (0.47-1.27) 1.09 (0.65-1.83)	 1.0 0.45 (0.22-0.92) 0.95 (0.49-1.85)	Age, study arm, stage, ethnicity, education, alcohol, smoking, and hormone therapy use, pre-diagnostic BMI, time between baseline measurement and diagnosis
Alipour, 2013, British Columbia Cancer Agency, Canada [69]	n=913 M and W Colon Stage II-III	Recorded at initial consultation	All-cause mortality (n=NR); CRC-specific mortality (n=NR); Relapse-free survival (n=NR)	Diagnosis: 2001-2005; Median FU: 6.9 (IQR 5.2-8.5) years	BMI 18.5-25.0 25.0-30.0 ≥30	 1.0 0.89 (0.71-1.11) 1.02 (0.78-1.33)	 1.0 0.80 (0.61-1.05) 1.05 (0.77-1.42)	Age, gender, stage, number of lymph nodes retrieved, and systemic therapy
Schlesinger, 2014, PopGen, Germany [16]	n=2143 M and W CRC Stage I-IV	4 years after diagnosis (mean)	All-cause mortality (n=349);	Diagnosis: 2002-2005; Mean FU: 3.5 years	BMI <18.5 18.5-24.9 25.0-29.9 ≥30 P-trend	 1.65 (0.79-3.46) 1.0 0.80 (0.62-1.02) 0.84 (0.62-1.14) 0.09		Age, sex, alcohol, smoking, tumor site, family history of CRC, metastases and other cancer
Kroenke, 2016, Kaiser Permanente Northern California, USA [32]	n=3408 M and W CRC Stage I-III	At diagnosis and 15 months after diagnosis	All-cause mortality (n=617); CRC-specific mortality (n=411)	Diagnosis: 2006-2011; Median FU: 3.5 (range 0.0-7.9) years	BMI at diagnosis <18.5 18.5-24.9 25.0-29.9 30-34.9 ≥35 BMI after diagnosis <18.5 18.5-22.9 23-24.9 25.0-27.9 28-29.9 30-34.9 ≥35	 3.01 (1.88-4.83) 1.0 0.81 (0.64-1.03) 1.03 (0.77-1.38) 1.63 (1.13-2.33) 3.38 (2.19-5.20) 1.0 0.72 (0.52-1.02) 0.56 (0.41-0.77) 0.39 (0.26-0.58) 0.51 (0.35-0.73) 0.85 (0.56-1.30)	 3.35 (1.92-5.87) 1.0 0.77 (0.57-1.03) 1.06 (0.75-1.50) 1.47 (0.96-2.27) 3.21 (1.88-5.47) 1.0 0.69 (0.46-1.05) 0.50 (0.34-0.75) 0.42 (0.26-0.67) 0.56 (0.36-0.85) 0.84 (0.51-1.37)	Sociodemographics, disease severity, treatment, and pre-diagnosis BMI

First author, year, name of cohort, country	Study population	Time of post-diagnosis exposure assessment	Outcomes assessed	Year of CRC diagnosis and follow-up	Lifestyle factor	All-cause mortality HR (95%CI)	Colorectal cancer-specific mortality HR (95%CI)	Covariates
Walter, 2016, DACHS, Germany [33]	n=3130 M and W CRC Stage I-IV	At diagnosis	All-cause mortality (n=896); CRC-specific mortality (n=649); Recurrence-free survival (n=828); Disease-free survival (n=1024)	Diagnosis: 2003-2010; Median FU: 4.9 years	BMI <20 20-24.9 25.0-29.9 ≥30	 1.21 (0.89-1.66) 1.0 0.82 (0.70-0.95) 0.80 (0.66-0.98)	 0.95 (0.65-1.41) 1.0 0.84 (0.71-1.01) 0.78 (0.62-0.99)	Age, sex, tumor site, stage, alcohol, smoking, use of statins, use of NSAIDs, use of beta-blockers, hyperlipidemia, diabetes mellitus, history of heart failure, myocardial infarction, angina pectoris or stroke, history of other cancer, age x log(time) and history of other cancer x log(time)
Tamakoshi, 2017, BioBank Japan, Japan [26]	n=1598 M and W CRC Stage I-IV	Within 90 days after diagnosis	All-cause mortality (n=521)	Diagnosis: 2003-2008 Median FU: 7.4 years	BMI <18.5 18.5-24.9 25.0-29.9 ≥30	 1.40 (1.12-1.76) 1.0 0.80 (0.62-1.05) 1.54 (0.86-2.76)		Stratified by sex and institutions and adjusted for age and entry year
BMI – studies in the adjuvant setting								
Meyerhardt, 2003, Intergroup Trial 0089, USA [72]	n=3438 M and W Colon Stage II-III	Day 1 of chemotherapy	All-cause mortality (n=NR); Recurrence-free survival (n=NR); Disease-free survival (n=NR)	Diagnosis: 1988-1992; Median FU: 9.4 years (max 12.7)	BMI <21 21.0-24.9 25.0-27.49 27.5-29.9 ≥30 P-trend	 1.15 (0.98-1.35 1.0 1.10 (0.95-1.26) 1.05 (0.90-1.24) 1.11 (0.96-1.29) 0.20	† 1.06 (0.88-1.27) 1.0 1.06 (0.88-1.27) 1.12 (0.94-1.33) 1.11 (0.94-1.30) 0.17	Age, sex, race, performance status, bowel obstruction, bowel perforation, stage, peritoneal implants, predominant macroscopic pathologic feature, completion of chemotherapy
Meyerhardt, 2004, Intergroup Trial 0114, USA [73]	n=1688 M and W Rectum Stage II-III	Day 1 of chemotherapy	All-cause mortality (n=NR); Recurrence-free survival (n=NR); Disease-free survival (n=NR)	Diagnosis: 1990-1992; Median FU: 9.9 years (max 11.8)	BMI <20 20.0-24.9 25-26.9 27-29.9 ≥30 P-trend	 1.43 (1.08-1.89) 1.0 0.97 (0.80-1.17) 0.95 (0.78-1.15) 1.09 (0.90-1.33) 0.5	† 1.16 (0.85-1.58) 1.0 1.01 (0.81-1.24) 0.88 (0.71-1.09) 1.08 (0.87-1.33) 0.8	Age, sex, race, performance status, bowel obstruction, extent of bowel wall invasion, number of positive lymph nodes

Table 1. Continuedt

First author, year, name of cohort, country	Study population	Time of post-diagnosis exposure assessment	Outcomes assessed	Year of CRC diagnosis and follow-up	Lifestyle factor	All-cause mortality HR (95%CI)	Colorectal cancer-specific mortality HR (95%CI)	Covariates
Sinicrope, 2013, pooled analyses ACCENT database (21 studies), USA [74]	n=25291 M and W CRC Stage II-III	At study enrolment	All-cause mortality (n=7973); Time to Recurrence (n=7973); Disease-free survival (n=15946);	Diagnosis: NR; Median FU: 7.8 years	BMI <20 20-24.9 25.0-29.9 ≥30 30-34.9 ≥35 P-trend	 1.21 (1.11-1.32) 1.0 0.99 (0.94-1.04) 1.10 (1.04-1.17) 1.10 (1.02-1.18) 1.11 (1.00-1.23) <0.0001	† 1.13 (1.04-1.24) 1.0 0.99 (0.94-1.04) 1.06 (1.00-1.13) 1.05 (0.98-1.20) 1.08 (0.98-1.20) 0.007	Age, stage, treatment, sex
BMI – studies in the metastatic setting								
Patel, 2015, South Australia Clinical registry for metastatic CRC, Australia [34]	n=1174 M and W CRC Stage IV	At first diagnosis of metastatic CRC, prior to treatment with chemotherapy	All-cause mortality (n=NR)	Diagnosis: ≥2006; Median FU: 24 months	BMI <18.5 18.5-24.9 25.0-29.9 30.0-34.9 ≥35	 2.21 (1.53-3.19) 1.0 1.23 (1.03-1.46) 1.20 (0.94-1.51) 0.89 (0.64-1.23)		Age, sex, synchronous disease, >1 met site, number of lines of chemotherapy and number of lines of antibody
Renfro, 2016, ARCAD database (25 studies) [75]	n=21149 M and W CRC Stage IV	Baseline BMI	All-cause mortality (n=NR); Progression-free survival (n=NR)	Diagnosis: 1997-2012; Median FU: 18.9 months.	Continuous BMI	P<0.001 with an L-shaped pattern; highest risk for patients with the lowest BMI, it decreased until a BMI of approximately 28 kg/m^2, and remained similar for patients with higher BMI		Age, sex, performance score, cancer site, number of metastatic sites; previous chemotherapy usage; presence of liver, lung and lymph node metastases
Visceral adipose tissue – population-based studies								
Rickles, 2013, University of Rochester Medical Center, USA [79]	n=219 M and W CRC Stage I-III	CT, preoperative visceral fat volume	All-cause mortality (n=NR); Recurrence-free survival (n=34); Disease-free survival (n=NR)	Diagnosis: 2003-2010; Max FU: 96 months	Visceral fat volume Stage I <median >median Stage II <median >median Stage III <median >median	 1.0 0.67 (0.18-2.59) 1.0 1.97 (0.78-5.02) 1.0 0.43 (0.17-1.07)	† insufficient number of events † 1.0 3.76 (1.12-12.57) † 1.0 0.39 (0.16-0.99)	Major complication, intraoperative blood transfusion, laparoscopic approach, smoking history, gender, age, use of adjuvant or neoadjuvant chemotherapy, and tumor size

First author, year, name of cohort, country	Study population	Time of post-diagnosis exposure assessment	Outcomes assessed	Year of CRC diagnosis and follow-up	Lifestyle factor	All-cause mortality HR (95%CI)	Colorectal cancer-specific mortality HR (95%CI)	Covariates
Black, 2017, Aberdeen Royal Infirmary, UK [35]	n=339 M and W CRC Stage I-III	CT, preoperative visceral fat index	All-cause mortality (n=213)	Diagnosis: 2006-2014; Median FU: 62 months (range 3-105)	Visceral fat index High Medium Low	 1.00 (0.80-1.26)		Age, sex, stage, neoadjuvant therapy, adjuvant therapy, lymphovascular invasion, neutrophil count, subcutaneous fat index, skeletal muscle index
Caan, 2017, Kaiser Permanente Northern California, USA [39]	n=3262 M and W CRC Stage I-III	CT, within 4 months of diagnosis and before chemotherapy or radiation, visceral fat area	All-cause mortality (n=788); CRC-specific mortality (n=433)	Diagnosis: 2006-2011; Median FU: 5.8 years (range 0.0-9.9)	Body composition Normal High visceral adiposity and normal muscle High visceral adiposity and low muscle	 1.0 1.22 (0.99-1.49) 1.40 (1.05-1.87)		Age, sex, race, stage, chemotherapy, radiation, tumor site, partitioned BMI, subcutaneous adiposity
Visceral adipose tissue – studies in the adjuvant setting								
Clark, 2013, Moffit Cancer Center, USA [80]	n=96 M and W Rectum Stage II-III	CT, diagnostic visceral fat area to subcutaneous fat area ratio and perinephric fat thickness	All-cause mortality (n=NR); Disease-free survival (n=26)	Diagnosis: 1998-2010; max FU: 7 years	Visceral fat area to subcutaneous fat area ratio <0.4 ≥0.4 Perinephric fat thickness, mm	 1.0 2.03 (0.57-7.20) 1.04 (0.99-1.09)		Grade and pathologic response
Lee, 2015, St. Vincent's University Hospital, Ireland [81]	n=62 M and W CRC Stage I-III	CT, preoperative visceral fat area	All-cause mortality (n=NR); Disease-free survival (n=NR)	Diagnosis: 2006-2009; Median FU: 62.5 months	Visceral fat area <130 cm^2 >130 cm^2	 1.0 7.0 (2.0-24.6)		T stage, N stage
Visceral adipose tissue – studies in the metastatic setting								
Guiu, 2010, Georges-François Leclerc Cancer Centre, France [82]	n=120 M and W CRC Stage IV	CT, pre-treatment visceral fat area	All-cause mortality (n=22); Disease progression (n=92)	Diagnosis: 2002-2008; Mean FU: 24 months	Visceral fat area Bevacizumab group <117.88 ≥117.58 P Chemotherapy group <117.88 ≥117.58 P	 1.0 2.88 0.027 NS		Performance status, CEA, high subcutaneous fat area

Table 1. Continuedt

First author, year, name of cohort, country	Study population	Time of post-diagnosis exposure assessment	Outcomes assessed	Year of CRC diagnosis and follow-up	Lifestyle factor	All-cause mortality HR (95%CI)	Colorectal cancer-specific mortality HR (95%CI)	Covariates
Muscle mass – population-based studies								
Miyamoto, 2015, Kumamoto University Hospital, Japan [83]	n=220 M and W CRC Stage I-III	CT, preoperative skeletal muscle index	All-cause mortality (n=37); Recurrence-free survival (n=85)	Diagnosis: 2005-2010; Median FU: 41.4 months	Skeletal muscle index Q1-3 Q4	 1.0 2.27 (1.15-4.49)	† 1.0 2.18 (1.20-3.94)	Sex, performance score, tumor site, histological findings, preoperative serum CEA level
Malietzis, 2016, St Mark's Hospital, UK [38]	n=805 M and W CRC Stage I-IV	CT, preoperative skeletal muscle index	All-cause mortality (n=156); Disease-free survival (n=101)	Diagnosis: 2006-2011; Median FU: 47 months (IQR 24.9-65.6)	Skeletal muscle index Normal Low	 1.0 1.70 (1.25-2.31)		Age, ASA score, surgical approach, stage, tumor grade, lymphovascular invasion, adjuvant chemotherapy
Black, 2017, Aberdeen Royal Infirmary, UK [35]	n=339 M and W CRC Stage I-III	CT, preoperative skeletal muscle index	All-cause mortality (n=213)	Diagnosis: 2006-2014; Median FU: 62 months (range 3-105)	Skeletal muscle index Normal Low	 1.0 0.76 (0.35-1.65)		Age, sex, stage, neoadjuvant therapy, adjuvant therapy, lymphovascular invasion, neutrophil count, subcutaneous fat index, visceral fat index
Caan, 2017, Kaiser Permanente Northern California, USA [39]	n=3262 M and W CRC Stage I-III	CT, within 4 months of diagnosis and before chemotherapy or radiation, skeletal muscle index and muscle cross-sectional area	All-cause mortality (n=788); CRC-specific mortality (n=433)	Diagnosis: 2006-2011; Median FU: 5.8 years (range 0.0-9.9)	Skeletal muscle index Normal Low Muscle, cm^2 Low tertile 1 Middle tertile 2 High tertile 3 P-trend	 1.0 1.27 (1.09-1.48) 1.32 (1.07-1.64) 1.13 (0.93-1.37) 1.0 0.01	 1.0 1.46 (1.19-1.79) 1.54 (1.16-2.05) 1.19 (0.92-1.55) 1.0 0.003	Age, sex, race, stage, chemotherapy, radiation, tumor site, partitioned BMI, total adiposity
Muscle mass – studies in the adjuvant setting								
Jung, 2015, Seoul National University Bundag Hospital, South Korea [37]	n=229 M and W Colon Stage III	CT, preoperative psoas muscle cross-sectional area	All-cause mortality (n=30); Disease-free survival (n=NR)	Diagnosis: 2003-2010; Median FU: 61.3 months (IQR 49.7-72.0)	1 SD decrement in the psoas index	1.85 (1.10-3.13)		Age, sex, T stage, N stage, chemotherapy dose intensity, comorbidities, and BMI

First author, year, name of cohort, country	Study population	Time of post-diagnosis exposure assessment	Outcomes assessed	Year of CRC diagnosis and follow-up	Lifestyle factor	All-cause mortality HR (95%CI)	Colorectal cancer-specific mortality HR (95%CI)	Covariates
Muscle mass – studies in the metastatic setting								
van Vledder, 2012, Erasmus Medical Center, the Netherlands [84]	n=196 M and W CRC Stage IV	CT, perioperative skeletal muscle mass	All-cause mortality (n=84); Disease-free survival (n=NR)	Diagnosis: 2001-2009; Median FU: 29 (1-97) months	Skeletal muscle mass Normal Low	1.0 2.69 (1.67-4.32)		No. of metastases, radiofrequency ablation, resection margin.
Thoresen, 2013, St. Olav's University Hospital/Cross Cancer Institute, Norway/ Canada [85]	n=71 M and W CRC Stage IV	CT, skeletal muscle mass cross-sectional area	All-cause mortality (n=60)	Diagnosis: 2004-2006; Median FU: 15.8 / 20.6 months	Skeletal muscle mass Normal Low	1.0 1.74 (0.99-3.03)		Nation, age, and gender
Blauwhoff-Buskermolen, 2016, Vrije Universiteit Medical Center, the Netherlands [36]	n=67 M and W CRC Stage IV	CT, skeletal muscle area	Overall mortality (n=NR)	Diagnosis: 2011-2014; Median FU: 17.5 months (95%CI 13.3-21.7) for patients receiving first-line chemotherapy and 8.5 months (95%CI 4.4-12.6) for patients receiving second-line chemotherapy or beyond.	Muscle mass Normal Low	1.0 1.65 (0.85-3.18)		Sex, age, lactate dehydrogenase concentration, comorbidity, metastases, chemotherapy line

Abbreviations: CRC, colorectal cancer; HR, hazard ratio; 95%CI, 95% confidence interval; SD, standard deviation; IQR, interquartile range; M, men; W, women; NR, not reported; NS, non-significant; Q, quintile or quartile; C, category; BMI, body mass index; PA, physical activity; MET-h, metabolic equivalent task-hour; CT, computed tomography; CEA, Carcinoembryonic Antigen; MSI, microsatellite instability; CALGB, Cancer and Leukemia Group B; CPS II, Cancer Prevention Study II; DACHS, German: Darmkrebs: Chancen der Verhutüng durch Screening, English: chances for prevention through screening; ACCENT, Adjuvant Colon Cancer Endpoints; ARCAD, Aide et Recherche en Cancérologie Digistive.

†Results are for disease recurrence.

Table 2. Cohort studies among individuals with colon or rectal cancer examining change in lifestyle factors in relation to all-cause mortality, colorectal cancer-specific mortality or recurrence; changes could be changes from pre- to post-diagnosis or changes made after diagnosis

First author, year, name of cohort, country	Study population	Time of post-diagnosis exposure assessment	Outcomes assessed	Year of CRC diagnosis and follow-up	Lifestyle factor	All-cause mortality HR (95%CI)	Colorectal cancer-specific mortality HR (95%CI)	Covariates
Change in diet – population-based studies								
McCullough, 2013, CPS II Nutrition Cohort, USA [40]	n=1186 Both genders Colon and rectum Stage I-III	Red and processed meat 9 years before CRC diagnosis (mean) and 3 years after diagnosis (mean)	All-cause mortality (n=472); CRC-specific mortality (n=146); CVD-mortality (n=110); other-mortality (n=216)	Diagnosis: 1992-2009; Mean 7.6 years (SD 3.4 years)	Remained low meat Remained high meat Low to high meat High to low meat	1.0 1.28 (0.98-1.67) 1.25 (0.93-1.67) 1.37 (1.02-1.85)	1.0 1.79 (1.11-2.89) 0.96 (0.55-1.66) 1.43 (0.80-2.57)	Age, sex, stage, 1992 pre-diagnostic energy intake, and post-diagnostic energy intake.
Yang, 2017, CPS II Nutrition Cohort, USA [27]	n=1599 M and W CRC Stage I-III	Alcohol 3.2 years before CRC diagnosis (mean) and 1.9 years after diagnosis (mean)	All-cause mortality (n=732); CRC-specific mortality (n=235); CVD-mortality (n=172); other mortality (n=325)	Diagnosis: 1992 -2011; Mean FU: 8.2 years (SD 4.7 years)	Never drinker Former-former Current-former Current<2 drinks/d Current≥2 drink/d	1.0 1.09 (0.81-1.48) 1.21 (0.92-1.60) 0.94 (0.77-1.16) 0.92 (0.66-1.28)	1.0 1.28 (0.73-2.23) 1.81 (1.13-2.91) 1.27 (0.87-1.86) 1.44 (0.80-2.60)	Age, sex, tumor stage, smoking, BMI, PA, education, and pre-existing diseases in 1982/1992 (COPD, liver disease, kidney disease)
Change in physical activity – population-based studies								
Meyerhardt, 2006, Nurses' Health Study I, USA [47]	n=573 W only CRC Stage I-III	6 months before CRC diagnosis (mean) and 22 months after diagnosis (mean)	All-cause mortality (n=132); CRC-specific mortality (n=80)	Diagnosed: 1986-2004; Median FU: 9.6 years	Decreased PA No change in PA Increased PA MET-hours/week Stable activity <9 Stable activity ≥9 Increase activity Pre-diagnosis activity <9 Pre-diagnosis activity ≥9	1.23 (0.79-2.34) 1.0 0.51 (0.30-0.85) 1.0 0.33 (0.11-0.97) 0.26 (0.10-0.66) 0.35 (0.11-1.13)	1.32 (0.74-2.34) 1.0 0.48 (0.24-0.97) 1.0 0.27 (0.09-0.80) 0.36 (0.19-0.67) 0.62 (0.28-1.34)	BMI, stage, differentiation grade, tumor location, age, year of diagnosis, chemotherapy, time from diagnosis to PA measurement, change in BMI, smoking
Baade, 2011, Queensland, Australia [49]	n=1825 M and W CRC Stage I-III	Pre-diagnosis physical activity was recalled after CRC diagnosis and assessed 5 months after diagnosis	All-cause mortality (n=462); CRC-specific mortality (n=345);	Diagnosis: 2003-2004 Mean FU: 4.9 years (range 4.0-6.0)	Pre-diagnosis to 5 months post-diagnosis No change or decreased Increased ≤2 h/wk Increased >2 h/wk P-trend	 1.0 1.27 (0.88-1.83) 1.06 (0.65-1.71) 0.449	 1.0 1.32 (0.89-1.98) 1.03 (0.59-1.80) 0.389	5 months post-diagnosis PA level, age, stage, smoking status, tumor location, treatment, sex and comorbidities.

First author, year, name of cohort, country	Study population	Time of post-diagnosis exposure assessment	Outcomes assessed	Year of CRC diagnosis and follow-up	Lifestyle factor	All-cause mortality HR (95%CI)	Colorectal cancer-specific mortality HR (95%CI)	Covariates
	n=1554 M and W CRC Stage I-III	5 months and 12 months after CRC diagnosis			5 to 12 months post-diagnosis No change or decreased Increased ≤2 h/wk Increased >2 h/wk P-trend	 1.0 0.79 (0.59-1.04) 0.69 (0.50-0.94) 0.030	 1.0 0.68 (0.48-0.97) 0.64 (0.44-0.93) 0.015	
Smoking cessation – population-based studies								
Phipps, 2011, Seattle Colon Cancer Family Registry, USA, [66]	n=2264 M and W CRC Stage I-IV	2 years before CRC diagnosis and 8.0 months after diagnosis (mean)	All-cause mortality (n=831); CRC-specific mortality (n=562)	Diagnosis: 1998-2007; FU: up to 2010	Remained never smoker Remained former smoker Continued smoking Quit smoking	1.0 1.26 (1.07-1.48) 1.50 (1.14-1.97) 1.52 (1.21-1.90)	1.0 1.14 (0.93-1.38) 1.47 (1.07-2.03) 1.32 (1.00-1.74)	Age, time from diagnosis to interview, history of preventive screening, sex, and education level.
Tao, 2013, Shanghai Cohort Study, China [28]	n=114 M only CRC Stage NR	Yearly assessments of smoking cessation after diagnosis among smokers at diagnosis	All-cause mortality (n=73)	Diagnosis: 1986-2010; Mean FU: 5.3 ±4.8 years	Quit smoking Intermittent smoking Continued smoking Time-dependent smoking	1.0 1.35 (0.68-2.67) 3.46 (1.69-7.10) 2.31 (1.40-3.81)		Age, education, pack-years of smoking before diagnosis, treatment, and cancer site
Walter, 2015, DACHS study, Germany [62]	n=3130 M and W CRC Stage I-IV	Smoking cessation in the year of diagnosis.	All-cause mortality (n=889), CRC-specific mortality (n=828), non-CRC related mortality (n=644), recurrence-free survival (n=1024), disease-free survival (n=232)	Diagnosis: 2003-2010; Median FU: 4.9 years.	Nonsmokers Recent quitters Continued smokers	1.0 0.97 (0.70-1.33) 1.10 (0.86-1.41)	1.0 0.87 (0.60-1.25) 1.10 (0.83-1.45)	Age, sex, BMI, stage, alcohol consumption, red meat consumption, family history of CRC, use of statins, use of NSAIDs, use of beta-blockers, diabetes mellitus, history of heart failure, myocardial infarction, angina pectoris or stroke, history of non-CRC cancer; additional adjustment for age*log(time) to account for time-dependent effects

Table 2. Continued

First author, year, name of cohort, country	Study population	Time of post-diagnosis exposure assessment	Outcomes assessed	Year of CRC diagnosis and follow-up	Lifestyle factor	All-cause mortality HR (95%CI)	Colorectal cancer-specific mortality HR (95%CI)	Covariates
Yang, 2015, CPS II Nutrition Cohort, USA [29]	n=2256 M and W CRC Stage I-III	2.3 years before CRC diagnosis (mean) and 1.4 years after diagnosis (mean)	All-cause mortality (n=859); CRC-specific mortality (n=323)	Diagnosis:1 992-2009; Mean FU: 7.5 years SD 4.6 years)	Remained never smoker Remained former smoker Continued smoking Quit smoking	1.0 1.18 (1.00-1.39) 2.33 (1.62-3.34) 1.94 (1.29-2.91)	1.0 0.86 (0.66-1.11) 2.20 (1.29-3.76) 1.85 (1.02-3.35)	Age, sex, stage, alcohol consumption, BMI, and PA
Weight change – population-based studies								
Baade, 2011, Queensland, Australia [49]	n=1763 M and W CRC Stage I-III	Pre-diagnosis weight was recalled after CRC diagnosis and assessed 5 months after diagnosis	All-cause mortality (n=462); CRC-specific mortality (n=345);	Diagnosis: 2003-2004 Mean FU: 4.9 yea rs (range 4.0-6.0)	Pre-diagnosis to 5 months post-diagnosis >5 kg loss 2-4.9 kg loss ± 2 kg 2-4.9 kg gain >5 kg gain P-trend	 1.63 (1.29-2.06) 1.10 (0.83-1.46) 1.0 1.12 (0.60-2.09) 1.63 (1.02-2.61) <0.001	 1.64 (1.24-2.15) 1.02 (0.73-1.42) 1.0 0.90 (0.41-1.96) 1.46 (0.84-2.53) 0.001	5 months post-diagnosis weight, height, PA level, stage, smoking status, tumor site, treatment, sex and comorbidities.
	n=1503 M and W CRC Stage I-III	5 months and 12 months after CRC diagnosis			5 to 12 months post-diagnosis >5 kg loss 2-4.9 kg loss ± 2 kg 2-4.9 kg gain >5 kg gain P-trend	 2.92 (1.89-4.49) 1.68 (1.10-2.59) 1.0 0.95 (0.68-1.32) 0.91 (0.69-1.20) <0.001	 3.21 (1.95-5.31) 1.59 (0.95-2.68) 1.0 1.02 (0.69-1.50) 0.89 (0.64-1.25) <0.001	
Meyerhardt, 2016, Kaiser Permanente Northern Carolina, USA [76]	n=2781 M and W CRC Stage I-III	Within 3 months after CRC diagnosis (prior to surgery) and approximately 18 months after diagnosis (range 15-21)	All-cause mortality (n=549); CRC-specific mortality (n=311)	Diagnosis: 2006-2011; Median FU: 4.2 years (range 0.1-8.1 years)	% Weight change ≥10% loss 5-9.9% loss ±4.9% 5-9.9% gain ≥10% gain P-trend loss P-trend gain	 3.27 (2.56-4.18) 1.74 (1.34-2.25) 1.0 0.86 (0.65-1.14) 1.20 (0.91-1.58) <0.0001 0.27	 3.20 (2.33-4.39) 1.58 (1.12-2.23) 1.0 0.84 (0.58-1.22) 0.93 (0.63-1.37) <0.0001 0.54	Age, weight at diagnosis, gender, race/ethnicity, stage, grade, chemotherapy, and tumor site

First author, year, name of cohort, country	Study population	Time of post-diagnosis exposure assessment	Outcomes assessed	Year of CRC diagnosis and follow-up	Lifestyle factor	All-cause mortality HR (95%CI)	Colorectal cancer-specific mortality HR (95%CI)	Covariates
Weight change – studies in the adjuvant setting								
Meyerhardt, 2008, CALGB 89803, USA [78]	n=1053 M and W Colon Stage III	During and 6 months after adjuvant chemotherapy	All-cause mortality (n=261); Recurrence-free survival (n=338); Disease-free survival (n=369)	Diagnosis: 1999-2001; Median FU: 5.3 years	Weight change (kg) >5 loss 2.1-5 loss ± 2 2-4.9 gain ≥5 gain	 1.13 (0.44-2.93) 0.89 (0.31-2.57) 1.0 0.97 (0.43-2.18) 1.23 (0.65-2.31)	† 1.35 (0.64-2.81) 1.04 (0.46-2.35) 1.0 1.00 (0.52-1.95) 1.17 (0.70-1.96)	Sex, age, T stage, number of positive lymph nodes, presence of clinical perforation at time of surgery, presence of bowel obstruction at time of surgery, performance status, treatment arm, time between questionnaire one and questionnaire two, time-varying BMI, smoking status at time of questionnaire two, PA level
Vergidis, 2016, British Columbia Cancer Agency, Canada [77]	n=539 M and W Colon Stage III	At initial oncology consultation visit before the receipt of any systemic therapy and follow-up weights were serially reported at each subsequent clinic visit throughout the entire course of their adjuvant treatment or until 9 months after their first clinic visit, whichever came later. The peak and nadir weights were used to calculate weight change	All-cause mortality (n=NR); Recurrence-free survival (n=NR)	Diagnosis: 2008-2010; FU: 3-5 years	Weight gain <5% ≥5% <10% ≥10% Weight loss <5% ≥5% <10% ≥10% Weight change <5% ≥5% <10% ≥10%	 1.0 0.80 (0.39-1.66) 1.0 0.52 (0.24-1.20) 1.0 1.92 (1.00-3.70) 1.0 2.63 (1.04-6.67) 1.0 1.02 (0.54-1.95) 1.0 1.15 (0.59-2.22)	† 1.0 0.84 (0.46-1.53) 1.0 0.81 (0.40-1.65) † 1.0 1.56 (0.88-2.28) 1.0 2.94 (1.39-6.25) † 1.0 1.44 (0.79-2.64) 1.0 1.10 (0.64-1.83)	Age, sex, comorbidities, performance status, tumor site, stage, grade, receipt of systemic therapy, type of regimen received

Table 2. Continued

First author, year, name of cohort, country	Study population	Time of post-diagnosis exposure assessment	Outcomes assessed	Year of CRC diagnosis and follow-up	Lifestyle factor	All-cause mortality HR (95%CI)	Colorectal cancer-specific mortality HR (95%CI)	Covariates
Muscle loss – studies in the metastatic setting								
Blauwhoff-Buskermolen, 2016, Vrije Universiteit Medical Center, the Netherlands [36]	n=67 M and W CRC Stage IV	Skeletal muscle area was measured using CT scans conducted before start of chemotherapy and during chemotherapy	Overall mortality (n=NR)	Diagnosis: 2011-2014; Median FU: 17.5 months (95%CI 13.3-21.7) for patients receiving first-line chemotherapy and 8.5 months (95%CI 4.4-12.6) for patients receiving second-line chemotherapy or beyond.	Muscle loss <9% ≥9%	 1.0 4.47 (2.21-9.05)		Sex, age, lactate dehydrogenase concentration, comorbidity, metastases, chemotherapy line, tumor progression at first evaluation by CT scan

Abbreviations: CRC, colorectal cancer; HR, hazard ratio; 95%CI, 95% confidence interval; M, men; W, women; NR, not reported; BMI, body mass index; PA, physical activity; MET-h, metabolic equivalent task-hour; CT, computed tomography; CPS II, Cancer Prevention Study II; CALGB, Cancer and Leukemia Group B; DACHS, German: Darmkrebs: Chancen der Verhutüng durch Screening, English: chances for prevention through screening.
†Results are for disease recurrence.

CHAPTER 6

6

Lifestyle after colorectal cancer diagnosis in relation to recurrence and all-cause mortality

Moniek van Zutphen | Hendriek C. Boshuizen | Marlou-Floor Kenkhuis | Evertine Wesselink | Anne J.M.R. Geijsen | Johannes H.W. de Wilt | Henk K. van Halteren | Ernst Jan Spillenaar Bilgen | Eric T.P. Keulen | Maryska L.G. Janssen-Heijnen | Stéphanie O. Breukink | Martijn J.L. Bours | Dieuwertje E. Kok | Renate M. Winkels | Matty P. Weijenberg | Ellen Kampman | Fränzel J.B. van Duijnhoven

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Abstract

Background

An unhealthy lifestyle is associated with colorectal cancer (CRC) incidence, but it is unclear whether overall lifestyle after CRC diagnosis is associated with recurrence and mortality.

Objective

To examine associations of postdiagnosis lifestyle and change in lifestyle after CRC diagnosis with recurrence and all-cause mortality.

Design

The study population included 1425 newly diagnosed stage I-III CRC patients from two prospective cohort studies enrolled between 2010 and 2016. Lifestyle, including body mass index (BMI), physical activity, diet, and alcohol intake, was assessed at diagnosis and six months postdiagnosis. We assigned lifestyle scores based on concordance with two sets of cancer prevention guidelines – from the World Cancer Research Fund / American Institute for Cancer Research (WCRF/AICR) and the American Cancer Society (ACS) – and national disease prevention guidelines. Higher scores indicate healthier lifestyles. We computed adjusted hazard ratios (HRs) and 95% confidence intervals (95%CIs) using Cox regression.

Results

We observed 164 recurrences during 2.8-year median follow-up and 171 deaths during 4.4-year median follow-up. No associations were observed for CRC recurrence. A lifestyle more consistent with the ACS recommendations was associated with lower all-cause mortality risk (HR per +1 SD: 0.85, 95%CI 0.73, 0.995). The same tendency was observed for higher WCRF/AICR (HR 0.92, 95%CI 0.78, 1.08) and national (HR 0.90 (95%CI 0.77, 1.05) lifestyle scores, although statistically nonsignificant. Generally, no statistically significant associations were observed for BMI, physical activity, diet, or alcohol. Improving lifestyle after diagnosis (+1 SD) was associated with a lower all-cause mortality risk for the ACS (HR 0.80, 95%CI 0.67, 0.96) and national (HR 0.84, 95%CI 0.70, 0.999) scores, yet was statistically nonsignificant for the WCRF/AICR score (HR 0.94, 95%CI 0.78, 1.13).

Conclusions

A healthy lifestyle after CRC diagnosis and improvement therein were not associated with recurrence, but were associated with a decreased all-cause mortality risk.

Keywords

colorectal cancer, survival, recurrence, lifestyle, body mass index, physical activity, diet, alcohol

Introduction

Rates of cancer survival are increasing, with more people living with and beyond cancer, including colorectal cancer (CRC) (1, 2). Current lifestyle recommendations for cancer survivors are largely extrapolated from recommendations for cancer prevention (3, 4). Cancer survivors who adhere to lifestyle recommendations may improve their prognosis. In CRC survivors, for instance, several reviews concluded that being physically active or eating a healthy diet after diagnosis may improve overall survival (5-7). However, the recommendations emphasize the importance of adopting an overall healthy lifestyle pattern, rather than focusing on single lifestyle behaviors, and little is known about the impact of an overall healthy lifestyle on CRC prognosis.

Currently, only two studies investigated whether an overall lifestyle consistent with cancer prevention guidelines was associated with all-cause mortality after CRC (8, 9). Inconsistent results were reported, although the guidelines used in both studies included the combination of the same four single lifestyle behaviors (an optimal body weight, being physically active, eating a healthy diet, and limiting alcohol intake). Concordance with the World Cancer Research Fund / American Institute for Cancer Research (WCRF/AICR) recommendations for cancer prevention was not associated with a lower all-cause mortality risk among 380 older female CRC survivors (8). In contrast, a lifestyle more consistent with the American Cancer Society (ACS) guidelines for cancer prevention was associated with a lower risk of both recurrence and all-cause mortality among 992 stage III colon cancer survivors (9). These inconsistent results might be explained by differences in timing of lifestyle assessment after diagnosis, differences between study populations, and/or differences between lifestyle scores (number of included dietary components and scoring).

More research is needed to examine if a healthy overall lifestyle after CRC diagnosis lowers risk of recurrence and all-cause mortality. Using pooled data of two prospective cohort studies, we examined the association of overall lifestyle after CRC diagnosis with risk of CRC recurrence and all-cause mortality. Overall lifestyle was assessed with three lifestyle scores that reflected concordance with either the WCRF/AICR, ACS, or national guidelines. The first two scores incorporate cancer prevention guidelines, while the national guidelines aim to prevent common diseases (including cancer and cardiovascular disease). We hypothesized that the three lifestyle scores would show similar associations with outcomes, as they all reflect a healthy overall lifestyle by emphasizing an optimal body weight, being physical active, eating a healthy diet, and limiting alcohol intake. Furthermore, we examined if a change in concordance with these guidelines after diagnosis is associated with CRC recurrence and all-cause mortality.

Subjects and Methods

Study design and population

We used pooled data from two ongoing prospective cohort studies from the Netherlands that enrolled CRC patients: the COLON study (NCT03191110; ClinicalTrials.gov) and the EnCoRe study (NL6904; trialregister.nl). Detailed descriptions of the cohorts are provided elsewhere (10, 11). Briefly, patients diagnosed with colon or rectal cancer were recruited at diagnosis in 14 hospitals in the Netherlands from 2010 (2012 for EnCoRe) onwards. All patients with a newly diagnosed primary stage I-IV colorectal tumor were eligible for the COLON study, but patients with stage IV disease were not eligible for the EnCoRe study. Patients were not eligible when they had a previous (partial) bowel resection, hereditary CRC, inflammatory bowel disease, dementia or another mental condition limiting their ability to fill out surveys, or when they were non-Dutch speaking. Data were collected at diagnosis (before start of treatment) to reflect prediagnosis lifestyle and up to four times in the five years following diagnosis. All participants provided written informed consent. The COLON study was approved by the Committee on Research involving Human Subjects, region Arnhem-Nijmegen, the Netherlands. The EnCoRe study was approved by the Medical Ethics Committee of the University Hospital Maastricht and Maastricht University, the Netherlands.

In total, recurrence data were available for 1922 participants diagnosed between 2010 and 2016 (**Figure 1**). Exclusions were made for the following reasons: missing stage (n=73), distant metastatic disease (stage IV) at diagnosis (n=132), a BMI <18.5 kg/m^2 at diagnosis (n=13), or CRC recurrence before postdiagnosis lifestyle assessment (n=18). Furthermore, we excluded 261 participants who had missing lifestyle data 6 months after diagnosis. The final sample size for the postdiagnosis analyses was 1425, 86% of all eligible participants. For the change after diagnosis analyses, all participants (n=247) from the EnCoRe study were excluded, as dietary assessment methods differed between diagnosis (FFQ) and follow-up (dietary records) (11). From the COLON study, 16 participants with missing lifestyle data at diagnosis were excluded for these analyses. The final sample size for the change after diagnosis analyses was 1162.

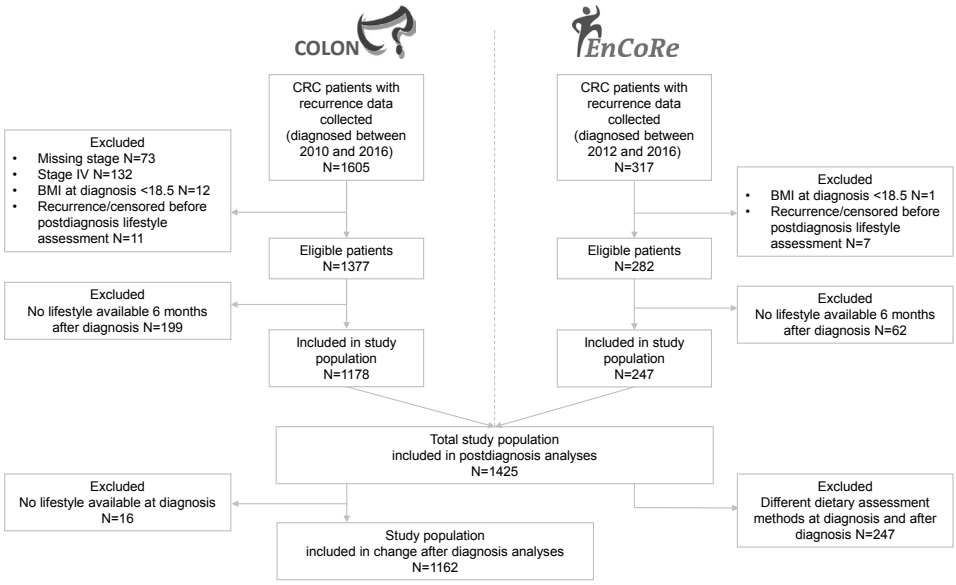

Figure 1. Flowchart representing patient selection for the current study. COLON, Colorectal cancer: Longitudinal, Observational study on Nutritional and lifestyle factors that may influence colorectal tumor recurrence, survival, and quality of life; EnCoRe, Energy for life after ColoRectal cancer; CRC, colorectal cancer

Lifestyle assessment

We used data collected at 6 months after diagnosis (COLON) or 6 months after end of treatment (EnCoRe) to calculate postdiagnosis lifestyle scores. Data collected at diagnosis, before the start of treatment, were used to calculate pretreatment lifestyle scores (COLON only). Patients completed a food frequency questionnaire (FFQ) that queried intake of 204 items at both time points (COLON) or a 7-day dietary record 6 months after treatment (EnCoRe), as previously described (10-12). The reference period for the FFQ was the month before diagnosis or the previous month during follow-up. Intake of dietary fiber and alcohol (alcoholic drinks only) were calculated based on the 2011 Dutch Food Composition Database (13). Moderate-to-vigorous intensity physical activity was self-reported by the validated SQUASH questionnaire (14-16) for both cohorts. Moderate-to-vigorous physical activity included all activities (walking, cycling, gardening, odd-jobs, sports, household activities, and work) with a metabolic equivalent value ≥3 (17). At diagnosis, the reference period was a normal week in the 2 months before diagnosis. BMI was calculated from body weight (assessed at diagnosis and during follow-up) and height (only assessed at diagnosis). Weight, height, and waist circumference were self-reported (COLON) or measured by trained research dieticians during a home visit (EnCoRe). To ensure quality of the data, completed questionnaires and dietary records were thoroughly checked and participants were contacted for clarification if needed.

Lifestyle scores

Two sets of evidence-based cancer prevention recommendations (WCRF/AICR and ACS) and one set of disease prevention guidelines (national guidelines from the Netherlands) were used to calculate overall lifestyle scores. All three included body weight, physical activity, diet, and alcohol intake, but differed on the dietary components included and scoring criteria (**Table 1**). The national score includes the most dietary components (n=12), as it also takes into account foods that impact cardiovascular disease risk, while the ACS score includes the lowest number of dietary components (n=3).

The WCRF/AICR score, developed by Shams-White et al. (18), is based on quantitative cut-off points for BMI and waist circumference, physical activity, fiber and fruits/vegetables, red and processed meat, sugary drinks, and alcohol intake. The cut-off points for fast foods were based on cohort-specific tertile rankings of ultra-processed foods. Both the ACS score, developed by McCullough et al. (19), and the national score are based on quantitative cut-offs for BMI, physical activity, and alcohol intake. The dietary component of the ACS score is based on the sex- and cohort-specific intake of fruits and vegetables, proportion of whole grains out of total grains consumed, and intake of red and processed meat. The dietary component of the national score, adapted from Looman et al. (20), is based on sex- and cohort-specific tertile rankings of intake of vegetables, fruits, whole grains, legumes, nuts, dairy, fish, tea, fats and oils, red meat, processed meat, and sugary drinks. Scoring criteria for the three lifestyle scores are listed in Table 1. Higher scores indicated that one's lifestyle was more consistent with the recommendations. The WCRF/AICR score ranged from 0 to 7 to represent seven recommendations (1x weight, 1x physical activity, 4x diet, 1x alcohol intake). Each recommendation was assigned 1 point when the recommendation was met, 0.5 point when it was partially met, and 0 points otherwise. Two recommendations included sub-recommendations and possible scores for these two recommendations included 0, 0.25, 0.5, 0.75, and 1. The ACS score ranged from 0 to 8. Each of the four recommendations was assigned 2 points when the recommendation was met, 1 point when it was partially met, and 0 points otherwise. The national score ranged from 0 to 4. Each of the four recommendations was assigned 1 point when the recommendation was met, 0.5 point when it was partially met, and 0 points otherwise.

Table 1. Description of the WCRF/AICR and ACS score based on cancer prevention recommendations, and the national score based on disease prevention recommendations from the Netherlands[1]

2018 WCRF/AICR score	Points	ACS score	Points	National score	Points
		1. Body weight			
BMI (kg/m²)		**BMI (kg/m²)**		**BMI (kg/m²)**	
18.5-24.9	0.5	18.5-24.9	2	18.5-24.9	1
25 to <30	0.25	25 to <30	1	25 to <30	0.5
<18.5 or ≥30	0	≥30	0	<18.5 or ≥30	0
Waist circumference (cm)					
<94 M and <80 F	0.5				
94 to <102 M and 80 to <88 F	0.25				
≥102 M and ≥88 F	0				
		2. Physical activity (PA)			
Moderate-to-vigorous PA (min/wk)		**Moderate-to-vigorous PA (min/wk)**		**Moderate-to-vigorous PA (min/wk)**	
≥150	1	≥300	2	≥150	1
75-150	0.5	150-300	1	75-150	0.5
<75	0	<150	0	<75	0
		3. Diet			
Dietary fiber (g/d):		**Diet sub-score**		**Diet sub-score**	
≥30	0.5	Diet sub-score 7-9 points	2	Sex-specific tertile 3	1
15 to <30	0.25	Diet sub-score 3-6 points	1	Sex-specific tertile 2	0.5
<15	0	Diet sub-score 0-2 points	0	Sex-specific tertile 1	0

Table 1. Continued

Fruits and vegetables (g/d):			
≥400	0.5	**Fruits and vegetables (g/d)**	**Dutch Healthy Diet index 2015**[2]
200 to <400	0.25	1: ≥400, 0: <400 1 or 2 points for being in the 2nd or 3rd sex-specific tertile of number of unique fruits and vegetables eaten per month	**Vegetables (g/d)** 10: ≥200, 0: 0
<200	0		**Fruit (g/d)** 10: ≥200, 0: 0
Percent of total kcal from ultra-processed foods[3]**:**		**Ratio of wholegrains to refined grains** 0-3 points corresponding to sex-specific quartiles of proportion of grains that are whole	**Wholegrains (g/d)** 5: ≥90, 0: 0
Tertile 1	1		Ratio of wholegrains to refined grains 5: ≥11, 0: ≤0-7
Tertile 2	0.5	**Red and processed meat (g/wk)** 0-3 points corresponding to sex-specific quartiles of red and processed meat intake, reverse scored	**Legumes (g/d)** 10: ≥10, 0: 0
Tertile 3	0		**Nuts (g/d)** 10: ≥15, 0: 0
Red meat and processed meat (g/wk):			**Dairy (g/d)** 10: 300-450, 0: 0 or ≥750
Red meat ≤500 and processed meat intake <21	1		**Fish (g/d)** 10: ≥15, 0: 0
Red meat ≤500 and processed meat intake 21 to <100	0.5		**Tea (g/d)** 10: ≥450, 0: 0
Red meat >500 or processed meat intake ≥100	0		**Ratio of liquid fats to solid fats** 10: ≥13, 0: ≤0-6
Sugary drinks[4] **(g/d):**			**Red meat (g/d)** 10: ≤45, 0: ≥100
0	1		**Processed meat (g/d)** 10: 0, 0: ≥50
>0 to ≤250	0.5		**Sugary drinks**[4] **(g/d)** 10: 0, 0: ≥250
>250	0		

4. Alcohol					
Ethanol (g/d)		**Ethanol (g/d)**		**Ethanol (g/d)**[5]	
0	1	>0 to ≤20 M and ≤10 F	2	≤10 (1 drink)	1
>0 to ≤20 M and ≤10 F	0.5	0	1	>10 to <30 M and >10 to <20 F	0.5
>20 M and >10 F	0	>20 M and >10 F	0	≥30 M and ≥20 F	0
WCRF/AICR score range	0-7	**ACS score range**	0-8	**National score range**	0-4

[1] Quartiles and tertiles were calculated in both cohorts separately. WCRF/AICR, World Cancer Research Fund/American Institute of Cancer Research; ACS, American Cancer Society; PA, physical activity

[2] Dutch Healthy Diet index 2015 (20) without salt and type of coffee components (data not available). The alcohol component is excluded from the dietary score, as this is a separate component in the national score. Cut-off values represent the minimum and maximum required amount of consumption awarded with 0 and 10 points. Intakes between the cut-off values are scored proportionally. The total possible score range is 0-120.

[3] Ultra-processed foods included French fries, crisps, pastry and biscuits, savory snacks, sugar and candy, sauces, pizza, pancake, sandwich fillings high in sugar or fat, refined grain products, sweet dairy desserts, and diet soft drinks. Not included were yoghurt and cheese, nuts, oils and fats, sugary drinks, and processed meat. Calculated as energy intake from ultra-processed foods of total energy intake.

[4] Sugary drinks included sugar-sweetened soft drinks, sugar-sweetened dairy drinks, and fruit juices.

[5] Scoring taking from the alcohol component of the Dutch Healthy Diet index 2015 (20).

Outcome assessment

Both CRC recurrence and all-cause mortality were considered primary outcomes. We defined CRC recurrence as time from postdiagnosis lifestyle assessment to locoregional recurrence or distant metastasis. Patients who died without CRC recurrence or who experienced another type of cancer with metastasis were censored in analyses with CRC recurrence as the outcome. Information on recurrences was collected from medical records by trained registrars from the Dutch Cancer Registry through February/March 2018 for both cohorts. We defined all-cause mortality as time from postdiagnosis lifestyle assessment to death. Vital status and date of death were determined through linkage to the Municipal Personal Record Database of the Netherlands through May (EnCoRe) or December (COLON) 2019.

Covariate assessment

Information was obtained on demographics, health-related factors, and clinical factors. Demographic information was self-reported at diagnosis. We used cigarette smoking status and daily use of nonsteroidal anti-inflammatory drugs self-reported at postdiagnosis lifestyle assessment in our analyses. Clinical data, such as CRC stage, tumor site, administration of neo-adjuvant treatment and adjuvant chemotherapy, and presence of co-morbidities were retrieved from the Dutch ColoRectal Audit. The Dutch ColoRectal Audit is a nationwide audit initiated by the Association of Surgeons from the Netherlands to monitor, evaluate, and improve CRC care (21).

Statistical analyses

Demographic and lifestyle characteristics of the CRC patients are shown for the total study population and by lifestyle score group. Cox proportional hazards regression models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs). For continuous models, a 1-standard deviation (SD) increase in each lifestyle score was calculated to allow comparability between the scores. Furthermore, the WCRF/AICR and ACS scores were categorized into four groups according to predefined cut-offs based on sufficient participants in each group. The national score was categorized into three groups as we combined patients with scores of 0 to 2, because few participants had low scores. Groups with the lowest scores, indicating a lifestyle least consistent with the recommendations, were the referent for all analyses. To test for linear trends, the median score of each category was assigned to all participants within that category and entered as a continuous exposure in Cox models. Multivariable models included age at diagnosis, CRC stage, sex, adjuvant chemotherapy, education level, smoking status, and cohort. Total energy intake, tumor site, neo-adjuvant therapy, nonsteroidal anti-inflammatory drug use, and co-morbidities at diagnosis were also evaluated as potential confounders, but these made minimal differences (<5%) to the results and were therefore not included in the final models. We used the Assess statement in SAS to check proportional hazards assumptions. As the proportional hazard assumption did not hold for CRC stage, we ran the models for all-cause mortality with stage as stratifying

variable (in the strata statement). This allows each stratum to have its own baseline hazard function, while the hazard ratios are assumed to be the same across all strata. Furthermore, we ran all postdiagnosis models with cohort as stratifying variable to account for differences in lifestyle assessment between cohorts. To examine effect modification, subgroup analyses were performed by age at diagnosis (<70 years, ≥70 years), sex (male, female), cancer site (colon, rectum), and stage (I, II, III).

Additionally, we also performed analyses for each lifestyle score component (body weight, physical activity, diet, alcohol intake) separately, to get a better understanding on which individual behaviors contribute to the association between the lifestyle score and CRC outcomes. For these analyses, we used the sub-scores of body weight, physical activity, diet, and alcohol, while mutually adjusting for the other components.

For the change after diagnosis analyses, we calculated the difference between the postdiagnosis and pretreatment lifestyle scores. For continuous models, a 1 SD increase in each lifestyle change score was calculated. The group with a change in lifestyle score of zero served as the referent in the categorical models. Change models were adjusted for the same covariates as the postdiagnosis models, with addition of pretreatment lifestyle scores. To satisfy the proportional hazards assumption, we ran the change models using adjuvant chemotherapy as stratifying variable in all models; for the all-cause mortality models we additionally used stage as stratifying variable.

We evaluated the robustness of our findings with sensitivity analyses. Participants usually completed adjuvant chemotherapy treatment about 6-7 months after diagnosis. Within the COLON study acute treatment effects might have influenced lifestyle at 6 months postdiagnosis. In sensitivity analyses of both the postdiagnosis and change analyses, we therefore excluded all participants from the COLON study treated with adjuvant chemotherapy (as date of end of chemotherapy was not available). Furthermore, we performed the postdiagnosis analyses after excluding all participants from the EnCoRe study, as these were also excluded from the change analyses, and after excluding current smokers. We did not perform stratified analyses among participants of the EnCoRe study, because of the small sample size (n=247) and low number of events (recurrence n=17; death n=19). Additionally, we also assessed the associations between lifestyle scores measured at diagnosis with recurrence and all-cause mortality. All statistical analyses were conducted using SAS 9.4 software (SAS Institute, Cary, NC). A p-value <0.05 was considered statistically significant.

Results

In total, 1425 non-metastatic CRC patients were included in the postdiagnosis analyses (Figure 1): 1178 (83%) from the COLON study and 247 (17%) from the EnCoRe study. Baseline characteristics of the study population are listed in **Table 2**. Mean age at CRC diagnosis was 66 years and 66% of the tumors were located in the colon. Stage III disease (44%) was more common than stage II (29%) or stage I disease (27%). Overall, lifestyle at 6 months postdiagnosis was suboptimal. Although physical activity levels were generally high and only 7% smoked, adherence to dietary guidelines was low and 64% was overweight or obese. As expected, participants whose lifestyle was most consistent with the WCRF/AICR, ACS, or national recommendations had healthier behaviors for many aspects of their lifestyle than those participants of whom lifestyle was least consistent with the guidelines. Characteristics for each cohort separately are listed in **Supplemental Table 1.** We observed 164 recurrences during 2.6-year (IQR 1.7-3.6) median follow-up. A total of 171 patients died during 4.4-year (IQR 3.5-5.5) median follow-up; 55% of people with a recurrence died during follow-up (n=91).

Postdiagnosis lifestyle

Postdiagnosis lifestyle scores were not associated with CRC recurrence (**Table 3**). However, our results suggest that these associations with recurrence might differ by stage of disease (**Figure 2A**). Among patients with stage I or stage III disease, we consistently observed a HR<1 with each SD higher lifestyle score, although 5 out of 6 associations were statistically non-significant. In contrast, among patients with stage II disease we unexpectedly observed an increased recurrence risk with each SD higher lifestyle score, which was statistically significant for the WCRF/AICR and national score. There was no evidence of effect modification by age, sex, and cancer site in the total study population regarding recurrence (**Figure 2B-D**).

A lifestyle more consistent with the ACS recommendations was associated with lower all-cause mortality risk (HR per 1 SD increase: 0.85, 95%CI 0.73, 0.995). Despite statistical insignificance, likely due to a small number of deaths, the same tendency was observed for higher concordance with the WCRF/AICR (HR 0.92, 95%CI 0.78, 1.08) and national (HR 0.90 (95%CI 0.77, 1.05) recommendations. There was no evidence for effect modification by stage, age, sex, and cancer site regarding all-cause mortality (**Supplemental Figure 1A-D**).

Change in lifestyle after diagnosis

Change in lifestyle scores after diagnosis was not associated with CRC recurrence (**Table 4**). A lower risk of all-cause mortality was observed for each SD increase in the ACS (HR 0.80, 95%CI 0.67, 0.96) and national (HR 0.84, 95%CI 0.70, 0.999) score, while this association was statistically non-significant for the WCRF/AICR score (HR 0.94, 95%CI 0.78, 1.13).

Postdiagnosis lifestyle score components

Body weight, physical activity, dietary, and alcohol sub-scores were generally not associated with CRC recurrence and all-cause mortality when highest concordance was compared with lowest concordance within the specific lifestyle component (**Supplemental Table 2**). One exception was noted, the dietary component of the national score was associated with a 22% lower mortality risk for each SD higher score (HR 0.78, 95%CI 0.64, 0.94).

Lifestyle at diagnosis

Lifestyle scores measured at diagnosis were not associated with CRC recurrence and all-cause mortality (**Supplemental Table 3**).

Sensitivity analyses

Similar to our main analyses in the total study population, postdiagnosis lifestyle scores were not associated with CRC recurrence when we excluded participants possibly treated with chemotherapy during postdiagnosis lifestyle assessment (n=283 from COLON study) (**Supplemental Table 4**), excluded all participants from the EnCoRe study (n=247) (**Supplemental Table 5**), or excluded current smokers (n=99) (**Supplemental Table 6**). However, for all-cause mortality associations on a continuous scale were no longer statistically significant and HRs were attenuated in these three sensitivity analyses. For the change analyses, HRs of all continuous models did not meaningfully change when we excluded people who received adjuvant chemotherapy (n=283) (results not shown). However, the association between change in the national score and all-cause mortality was no longer statistically significant (HR per SD increase 0.89, 95%CI 0.72, 1.10).

Table 2. Demographic, clinical, and lifestyle characteristics of colorectal cancer survivors at six months postdiagnosis by lifestyle score group[1]

Characteristic	Total population	Lifestyle score			
		WCRF/AICR score			
		0-2.5	2.75-3.25	3.5-4.25	4.5-7
	(n=1425)	(n=268)	(n=448)	(n=511)	(n=198)
Age at diagnosis, y	66 (61-71)	65 (59-70)	66 (60-71)	66 (62-72)	65 (60-70)
Men (%)	914 (64%)	173 (65%)	315 (70%)	317 (62%)	109 (55%)
Education (%)[2]					
Low	544 (38%)	117 (44%)	162 (36%)	190 (37%)	75 (38%)
Medium	409 (29%)	82 (31%)	145 (33%)	136 (27%)	46 (23%)
High	462 (33%)	64 (24%)	139 (31%)	182 (36%)	77 (39%)
Tumor stage (%)					
I	390 (27%)	73 (27%)	120 (27%)	139 (27%)	58 (29%)
II	407 (29%)	82 (31%)	118 (26%)	151 (30%)	56 (28%)
III	628 (44%)	113 (42%)	210 (47%)	221 (43%)	84 (42%)
Tumor site (%)					
Colon	947 (66%)	171 (64%)	286 (64%)	341 (67%)	149 (75%)
Rectum	478 (34%)	97 (36%)	162 (36%)	170 (33%)	49 (25%)
Neo-adjuvant treatment (%)	336 (24%)	69 (26%)	113 (25%)	117 (23%)	37 (19%)
Adjuvant chemotherapy (%)[3]	359 (25%)	58 (22%)	114 (25%)	131 (26%)	55 (28%)
Co-morbidity at diagnosis (%)[4]	975 (68%)	199 (74%)	319 (71%)	337 (66%)	120 (61%)
Current smoker (%)[5]	99 (7%)	29 (11%)	23 (5%)	40 (8%)	7 (4%)
Daily NSAID use (%)	111 (8%)	20 (7%)	39 (9%)	33 (6%)	19 (10%)
WCRF/AICR score (mean, SD)	3.4 (0.9)	2.2 (0.4)	3.0 (0.2)	3.8 (0.3)	4.9 (0.5)
ACS score (mean, SD)[6]	4.9 (1.5)	3.6 (1.4)	4.7 (1.3)	5.3 (1.2)	6.1 (1.2)
National score (mean, SD)[7]	2.7 (0.8)	1.9 (0.6)	2.6 (0.6)	3.0 (0.6)	3.5 (0.5)
BMI, kg/m^2	26.2 (24.1-29.0)	28.9 (26.3-32.0)	27.1 (24.9-29.4)	25.2 (23.7-27.7)	24.0 (22.4-26.4)

Waist circumference, cm	97 (89-105)	104 (96-110)	100 (93-107)	94 (87-100)	90 (84-97)
Physical activity,[8] min/wk	480 (240-840)	265 (60-630)	493 (258-870)	540 (300-900)	585 (345-870)
Dietary components (g/day)					
Fruits and vegetables	244 (147-347)	161 (102-231)	222 (135-318)	274 (170-371)	362 (265-453)
No. of unique fruits and vegetables consumed per month	11 (8-13)	10 (7-13)	11 (9-13)	11 (9-13)	12 (9-14)
Dietary fiber	19 (16-24)	16 (13-20)	19 (15-22)	21 (16-25)	23 (19-27)
Total grains that are whole (%)	72 (56-86)	61 (42-75)	69 (53-81)	77 (63-89)	82 (69-92)
Processed foods, en%	28 (22-35)	34 (29-40)	31 (25-37)	26 (20-32)	21 (17-27)
Red and processed meat	69 (43-98)	78 (57-109)	74 (52-103)	67 (40-95)	36 (10-62)
Legumes	0 (0-11)	0 (0-11)	0 (0-11)	2 (0-15)	7 (0-18)
Nuts	1 (0-4)	0 (0-2)	1 (0-4)	1 (0-4)	3 (0-7)
Dairy	262 (155-376)	247 (149-366)	254 (159-386)	272 (145-382)	287 (170-372)
Fish	9 (4-14)	6 (3-11)	9 (4-14)	9 (4-14)	11 (6-17)
Tea	116 (0-233)	77 (0-230)	115 (0-232)	116 (0-250)	156 (18-311)
Sugary drinks	69 (14-170)	128 (41-288)	85 (25-176)	54 (9-142)	16 (0-96)
Alcohol intake					
Nondrinker (%)	371 (26%)	45 (17%)	90 (20%)	151 (30%)	85 (43%)
Amount (g/d) among drinkers	10 (4-22)	12 (4-25)	12 (4-23)	10 (3-21)	8 (3-14)
Amount (g/d) among all	5 (0-17)	7 (1-22)	7 (1-20)	4 (0-15)	1 (0-9)
Total energy intake, kcal/day	1813 (1503-2153)	1843 (1525-2135)	1852 (1539-2177)	1776 (1476-2139)	1716 (1430-2129)

[1] Values are median (IQR), except where indicated otherwise. NSAID, non-steroidal anti-inflammatory drugs; WCRF/AICR, World Cancer Research Fund/American Institute of Cancer Research; ACS, American Cancer Society
[2] Data of 10 participants were missing/unknown
[3] Data of 23 participants were missing/unknown
[4] Data of 5 participants were missing/unknown
[5] Data of 2 participants were missing/unknown
[6] Data of 9 participants were missing/unknown
[7] Data of 7 participants were missing/unknown
[8] Moderate-to-vigorous physical activity included all activities with a metabolic equivalent value ≥3

Table 2 continued.

Characteristic	Lifestyle score						
	ACS score				National score		
	0-3 (n=253)	4 (n=295)	5 (n=344)	6-8 (n=524)	0-2 (n=369)	2.5-3 (n=691)	3.5-4 (n=358)
Age at diagnosis, y	67 (60-72)	66 (61-71)	65 (61-72)	65 (61-71)	66 (61-71)	66 (61-72)	65 (60-70)
Men (%)	143 (57%)	197 (67%)	227 (66%)	342 (65%)	249 (67%)	459 (66%)	157 (44%)
Education (%)[2]							
Low	113 (45%)	115 (39%)	127 (37%)	187 (36%)	146 (40%)	275 (40%)	121 (34%)
Medium	77 (31%)	83 (28%)	106 (31%)	142 (27%)	129 (35%)	190 (28%)	89 (25%)
High	62 (25%)	95 (32%)	108 (32%)	194 (37%)	91 (25%)	224 (33%)	146 (41%)
Tumor stage (%)							
I	68 (27%)	73 (25%)	95 (28%)	153 (29%)	102 (28%)	186 (27%)	101 (28%)
II	77 (30%)	87 (29%)	99 (29%)	140 (27%)	112 (30%)	193 (28%)	98 (27%)
III	108 (43%)	135 (46%)	150 (44%)	231 (44%)	155 (42%)	312 (45%)	159 (44%)
Tumor site (%)							
Colon	169 (67%)	197 (67%)	221 (64%)	354 (68%)	246 (67%)	438 (63%)	258 (72%)
Rectum	84 (33%)	98 (33%)	123 (36%)	170 (32%)	123 (33%)	253 (37%)	100 (28%)
Neo-adjuvant treatment (%)	58 (23%)	74 (25%)	86 (25%)	116 (22%)	84 (23%)	184 (27%)	67 (19%)
Adjuvant chemotherapy (%)[3]	54 (21%)	78 (26%)	86 (25%)	138 (26%)	76 (21%)	173 (25%)	108 (30%)
Co-morbidity at diagnosis (%)[4]	205 (81%)	209 (71%)	230 (67%)	328 (63%)	285 (77%)	472 (68%)	215 (60%)
Current smoker (%)[5]	21 (8%)	29 (10%)	22 (6%)	26 (5%)	38 (10%)	47 (7%)	14 (4%)
Daily NSAID use (%)	23 (9%)	22 (7%)	29 (8%)	36 (7%)	31 (8%)	57 (8%)	23 (6%)
WCRF/AICR score (mean, SD)	2.6 (0.7)	3.1 (0.7)	3.5 (0.8)	3.9 (0.8)	2.7 (0.7)	3.4 (0.7)	4.2 (0.8)
ACS score (mean, SD)[6]	2.6 (0.7)	4.0 (0)	5.0 (0)	6.4 (0.6)	3.4 (1.2)	5.0 (1.1)	6.3 (0.9)
National score (mean, SD)[7]	1.8 (0.6)	2.4 (0.5)	2.8 (0.5)	3.3 (0.5)	1.7 (0.4)	2.8 (0.2)	3.7 (0.2)
BMI, kg/m^2	30.0 (26.8-32.4)	27.3 (25.4-29.3)	25.8 (23.8-29.0)	24.8 (23.1-26.8)	29.3 (26.3-32.2)	26.2(24.3-28.7)	24.2 (22.7-26.0)

Waist circumference, cm	105 (97-112)	99 (92-107)	97 (89-105)	93 (86-100)	105 (96-111)	97 (90-104)	91 (84-97)
Physical activity,[8] min/wk	150 (60-390)	420 (185-780)	480 (270-823)	690 (430-1073)	290 (60-630)	540 (280-885)	585 (360-960)
Dietary components (g/day)							
Fruits and vegetables	199 (115-288)	226 (134-333)	234 (135-346)	288 (181-387)	168 (110-261)	239 (145-339)	331 (250-424)
No. of unique fruits and vegetables consumed per month	10 (7-12)	11 (8-13)	11 (8-13)	12 (10-14)	10 (7-12)	11 (9-13)	12 (10-14)
Dietary fiber	17 (14-21)	18 (15-23)	19 (16-23)	22 (17-26)	17 (13-20)	19 (15-24)	22 (19-27)
Total grains that are whole (%)	66 (47-78)	67 (51-83)	70 (56-87)	78 (64-89)	66 (49-81)	72 (56-86)	78 (63-91)
Processed foods, en%	29 (22-36)	29 (21-35)	28 (21-36)	28 (22-35)	29 (21-36)	29 (22-36)	27 (21-35)
Red and processed meat	85 (63-121)	73 (53-100)	68 (43-101)	57 (34-87)	81 (55-122)	71 (45-99)	52 (27-80)
Legumes	0 (0-11)	0 (0-11)	2 (0-16)	4 (0-16)	0 (0-5)	0 (0-11)	8 (0-18)
Nuts	0 (0-2)	0 (0-3)	1 (0-3)	2 (0-6)	0 (0-1)	1 (0-4)	3 (0-7)
Dairy	215 (126-356)	244 (146-380)	255 (157-377)	287 (176-395)	212 (126-351)	262 (154-386)	296 (202-385)
Fish	6 (2-12)	8 (4-13)	9 (4-14)	10 (4-15)	6 (2-11)	9 (4-13)	11 (7-17)
Tea	54 (0-230)	80 (0-232)	116 (0-234)	156 (18-279)	36 (0-156)	116 (0-233)	190 (77-345)
Sugary drinks	54 (11-160)	75 (12-158)	75 (19-176)	64 (13-171)	90 (21-193)	79 (21-189)	51 (5-138)
Alcohol intake							
Nondrinker (%)	96 (38%)	88 (30%)	97 (28%)	88 (17%)	81 (22%)	189 (27%)	101 (28%)
Amount (g/d) among drinkers	24 (14-35)	21 (5-29)	12 (4-25)	6 (2-12)	20 (8-22)	12 (4-22)	4 (2-9)
Amount (g/d) among all	12 (0-27)	4 (1-10)	4 (0-19)	4 (1-10)	14 (1-31)	6 (0-17)	2 (0-7)
Total energy intake, kcal/day	1761 (1470-2069)	1844 (1529-2134)	1770 (1508-2093)	1847 (1514-2220)	1789 (1470-2088)	1836 (1519-2162)	1813 (1520-2175)

Table 3. Hazard ratios (HRs) for the association of postdiagnosis concordance with lifestyle guidelines (including body weight, physical activity, diet, and alcohol intake) with risk of colorectal cancer recurrence and all-cause mortality[1]

		CRC recurrence		Death from any cause	
Lifestyle score	**n**	**No. of events/ Person-years**	**HR (95%CI)**	**No. of events/ Person-years**	**HR (95%CI)**
WCRF/AICR score					
0-2.5	259	32 / 686	1.00 (ref)	39 / 1129	1.00 (ref)
2.75-3.25	444	46 / 1249	0.74 (0.47, 1.16)	45 / 2042	0.61 (0.40, 0.94)
3.5-4.25	498	59 / 1420	0.89 (0.58, 1.38)	60 / 2304	0.70 (0.47, 1.06)
4.5-7	190	21 / 545	0.85 (0.48, 1.48)	21 / 885	0.75 (0.44, 1.29)
P_{trend}			0.85		0.38
Continuous[2]			0.99 (0.84, 1.17)		0.92 (0.78, 1.08)
ACS score					
0-3	248	27 / 681	1.00 (ref)	35 / 1095	1.00 (ref)
4	287	39 / 793	1.23 (0.75, 2.02)	41 / 1281	1.03 (0.65, 1.62)
5	339	39 / 951	1.01 (0.62, 1.65)	36 / 1543	0.74 (0.46, 1.19)
6-8	511	53 / 1457	0.92 (0.57, 1.47)	52 / 2413	0.69 (0.44, 1.06)
P_{trend}			0.41		0.03
Continuous[2]			0.94 (0.81, 1.11)		0.85 (0.73, 0.995)
National score					
0-2	360	43 / 975	1.00 (ref)	50 / 1583	1.00 (ref)
2.5-3	681	71 / 1946	0.82 (0.56, 1.21)	77 / 3135	0.78 (0.54, 1.11)
3.5-4	346	44 / 969	1.03 (0.67, 1.59)	37 / 1625	0.80 (0.52, 1.23)
P_{trend}			0.89		0.18
Continuous[2]			1.00 (0.86, 1.18)		0.90 (0.77, 1.05)

[1] Cox proportional hazards model adjusted for age at diagnosis, stage of disease, sex, adjuvant chemotherapy, education, smoking and cohort. P_{trend} values were calculated by entering the median lifestyle scores within each category as continuous variables in the models. The study population varied slightly for each score because of missing data (WCRF/AICR, n=1391; ACS, n=1385, National, n=1387). CRC, colorectal cancer; WCRF/AICR, World Cancer Research Fund/American Institute of Cancer Research; ACS, American Cancer Society.

[2] Continuous HRs were calculated for a 1-standard deviation increment in the score. Higher scores represent higher concordance with the respective guidelines.

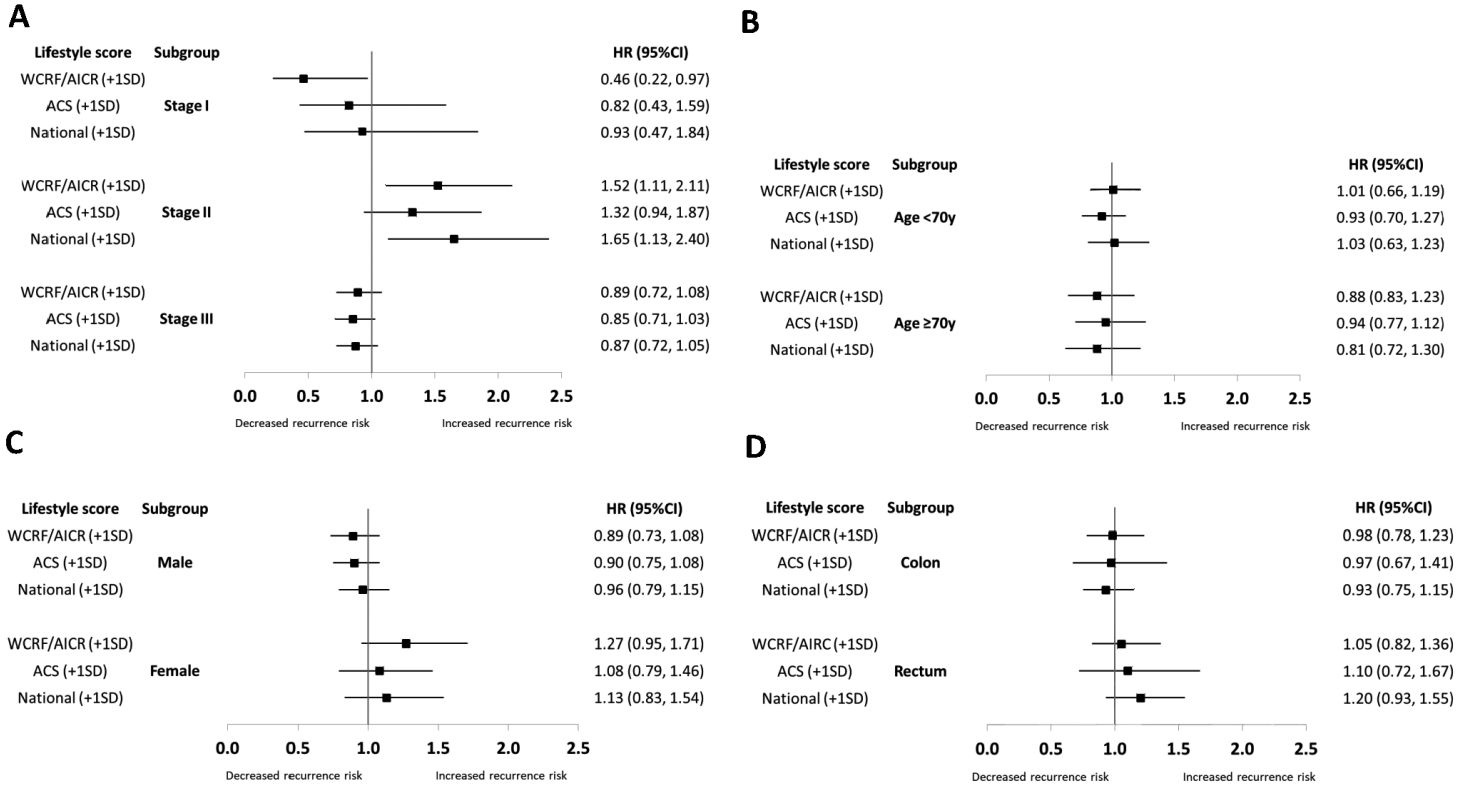

Figure 2. Subgroup analyses of the association between postdiagnosis lifestyle and colorectal cancer recurrence by (A) CRC stage, (B) age, (C) sex, and (D) tumor location. The squares indicate HRs and the width of the horizontal lines indicates the 95% CIs. Continuous (+1 SD) Cox proportional hazards models were adjusted for age at diagnosis, stage of disease, sex, adjuvant chemotherapy, education, smoking and cohort. WCRF/AICR, World Cancer Research Fund/American Institute of Cancer Research; ACS, American Cancer Society. Number of recurrences/total: stage I 9/388, II 40/390, III 109/613, <70y 110/960, >70y 48/431, male 112/889, female 46/502, colon 87/924, rectum 71/467.

Table 4. Hazard ratios (HRs) for the association of change in lifestyle scores after CRC diagnosis with risk of CRC recurrence and all-cause mortality[1]

		CRC recurrence		Death from any cause	
Change in lifestyle score	**n**	**No. of events/ Person-years**	**HR (95%CI)**	**No. of events/ Person-years**	**HR (95%CI)**
WCRF/AICR-score					
<-0.5	204	26 / 603	0.94 (0.52, 1.68)	28 / 998	1.81 (0.92, 3.56)
-0.5 to -0.25	266	35 / 812	1.01 (0.56, 1.82)	42 / 1307	2.24 (1.20, 4.20)
0	178	22 / 506	1.00 (ref)	13 / 863	1.00 (ref)
0.25 to 0.5	282	31 / 823	0.88 (0.51, 1.52)	34 / 1358	1.63 (0.86, 3.10)
>0.5	206	24 / 595	1.01 (0.56, 1.82)	26 / 973	1.90 (0.96, 3.74)
P_{trend}			0.99		0.85
Continuous[2]			0.95 (0.79, 1.14)		0.94 (0.78, 1.13)
ACS score					
<-1	142	29 / 423	1.57 (0.98, 2.52)	25 / 691	1.56 (0.95, 2.58)
-1	212	20 / 658	0.75 (0.44, 1.27)	35 / 1032	1.51 (0.97, 2.36)
0	422	49 / 1223	1.00 (ref)	45 / 2020	1.00 (ref)
1	214	26 / 620	1.11 (0.69, 1.81)	26 / 1033	1.12 (0.69, 1.84)
>1	141	11 / 399	0.97 (0.51, 1.83)	14 / 680	0.75 (0.37, 1.50)
P_{trend}			0.42		0.03
Continuous[2]			0.89 (0.74, 1.08)		0.80 (0.67, 0.96)
National score					
<-0.5	108	16 / 321	1.20 (0.68, 2.10)	19 / 521	1.30 (0.77, 2.20)
-0.5	206	29 / 611	1.17 (0.74, 1.85)	29 / 988	1.10 (0.70, 1.73)
0	433	52 / 1298	1.00 (ref)	58 / 2106	1.00 (ref)
0.5	261	31 / 734	1.12 (0.71, 1.77)	23 / 1241	0.74 (0.45, 1.22)
>0.5	125	10 / 367	0.73 (0.36, 1.48)	13 / 610	0.84 (0.45, 1.57)
P_{trend}			0.32		0.09
Continuous[2]			0.90 (0.75, 1.08)		0.84 (0.70, 0.999)

[1] Cox proportional hazards model adjusted for age at diagnosis, stage of disease, sex, adjuvant chemotherapy, education, smoking, and pretreatment lifestyle score. P_{trend} values were calculated by entering the median lifestyle scores within each category as continuous variables in the models. The study population varied slightly for each score because of missing data (WCRF/AICR, n=1136; ACS, n=1133, National, n=1133). CRC, colorectal cancer; WCRF/AICR, World Cancer Research Fund/American Institute of Cancer Research; ACS, American Cancer Society.

[2] Continuous HRs were calculated for a 1-standard deviation increase in the score.

Discussion

In this prospective study among 1425 people diagnosed with stage I-III CRC, overall lifestyle (including body weight, physical activity, diet, and alcohol intake) after diagnosis was not associated with CRC recurrence, while it was inversely associated with all-cause mortality. A lifestyle more consistent with the ACS recommendations was associated with lower all-cause mortality risk. The same tendency was observed for higher WCRF/AICR and national lifestyle scores, although statistically nonsignificant. Regarding change in lifestyle after diagnosis, our results suggest that improving concordance with the ACS or national recommendations after CRC diagnosis was not associated with recurrence, while it was associated with a lower all-cause mortality risk.

Only one previous study examined the association between an overall healthy lifestyle after CRC diagnosis and recurrence and only few examined single lifestyle behaviors in relation to recurrence. A lifestyle most consistent with the ACS guidelines after CRC diagnosis was associated with a 36% lower recurrence risk ($HR_{high\ vs\ low}$ 0.64; 95%CI 0.44, 0.94) among 992 stage III colon cancer survivors (9). In contrast, we report null associations between overall lifestyle after CRC diagnosis and recurrence. Our study suggests that associations with CRC recurrence might differ by stage of disease, which we cannot explain. This effect modification should be interpreted with caution as follow-up time was limited (3 years) and it was based on relatively few recurrences (n=164). Previous studies, all in the same cohort of stage III colon cancer patients, have observed an increased risk of recurrence in association with low levels of physical activity (22), a Western dietary pattern (23), and high intake of sugary sweetened drinks (24). Our dietary subscores were not associated with recurrence. Additional large population-based studies should include CRC recurrence as a key outcome when examining lifestyle after diagnosis, as fear of recurrence is a common concern for CRC patients (25) and because there are several proposed mechanisms relating an unhealthy lifestyle after diagnosis to CRC recurrence (26).

Data supporting a relation of an overall healthy lifestyle after a CRC diagnosis with all-cause mortality, as we provide here, is scarce. Among 380 women with CRC, no association was previously observed between a lifestyle more consistent with the WCRF/AICR cancer prevention recommendations and all-cause mortality ($HR_{high\ vs\ low}$ 1.19; 95%CI 0.59, 2.43) (8). One possible explanation for this lack of association in that study is that lifestyle was assessed among long-term survivors. In contrast, a lifestyle more consistent with the ACS guidelines was associated with a 51% lower all-cause mortality risk (HR 0.49; 95%CI 0.32, -0.76) among 992 stage III colon cancer survivors (9). In that study, lifestyle was an average of lifestyle assessed during chemotherapy and 6 months after chemotherapy, which is in line with the timing of lifestyle assessment in our study.

We expected and observed inverse associations between all three lifestyle scores and all-cause mortality, as they all reflect a healthy overall lifestyle by emphasizing an optimal body weight, being physical active, eating a healthy diet, and limiting alcohol intake. Subtle differences in scoring and number of dietary components included in the score, might explain the observed differences in statistical significance. Our results are in line with a meta-analysis in the general population, which showed that an overall healthy lifestyle was consistently associated with lower all-cause mortality, despite heterogeneous definitions of an overall healthy lifestyle (27). The single lifestyle behaviors included in the lifestyle scores (weight, physical activity, diet, and alcohol intake) were generally not statistically significantly associated with all-cause mortality in our study. Therefore, the associations between the lifestyle scores and reduced all-cause mortality risk could not be attributed to one lifestyle behavior. This further emphasizes the importance of adopting an overall healthy lifestyle pattern rather than focusing on a single lifestyle behavior.

For CRC patients it is important to know if changing lifestyle after diagnosis can lower risk of recurrence and can improve survival. In our study, change in overall lifestyle after diagnosis was not associated with CRC recurrence. An improvement in ACS and national score after diagnosis was statistically significantly associated with a lower all-cause mortality risk, independent of pretreatment lifestyle score. Our all-cause mortality results are in line with two previous observational studies that assessed either changes in the ACS score from midway chemotherapy to six months after chemotherapy or pre- to postdiagnosis changes in diet quality (9, 28). No previous study assessed these associations with CRC recurrence. Additional studies are needed to further examine if changing lifestyle after CRC diagnosis impacts recurrence risk.

Potential limitations of our study should be considered. We could not explore cause-specific mortality, as we do not have access to these data. This would have been of interest as we observed an inverse association for all-cause mortality, but not for CRC recurrence. A healthy lifestyle after CRC diagnosis might therefore specifically be related to the cardiovascular risk profile, but not with CRC-specific mortality. Second, we had limited power, as we observed relatively few events (n=164 for recurrence; n=171 for mortality), even after combining data of two cohorts. Nonetheless, we observed similar associations for all three lifestyle scores, making our results more robust. Third, for some patients postdiagnosis lifestyle was assessed before chemotherapy was completed. As a sensitivity analysis we excluded all participants for who this might have been the case (as date of end of chemotherapy was not available). This did not change our conclusions from the postdiagnosis analyses and the change analyses with regard to recurrence. However, the inverse associations between postdiagnosis lifestyle and all-cause mortality were attenuated and no longer statistically significant. Fourth, postdiagnosis lifestyle was assessed six months after diagnosis or six months after treatment. Lifestyle assessed at these times might not reflect lifestyle later

during the CRC trajectory. However, 60-80% of CRC recurrences occur within the first two years after resection (29) and therefore recurrence risk will be minimally affected by lifestyle later during the CRC trajectory. Furthermore, reported associations did not change when we used time-varying analyses in which we updated lifestyle scores based on each repeated postdiagnosis lifestyle assessment (up to four in the first five years after diagnosis) (results comparable to those presented in Supplemental Table 5). Fifth, results of this study can only be generalized to Western populations of CRC survivors. Finally, as with all observational studies, we cannot completely eliminate the possibility of reverse causation and/or residual confounding. However, our results do not indicate that survivors without comorbidities, who are likely to have healthier lifestyles, had better outcomes, as lifestyle measured at diagnosis was not associated with mortality. Furthermore, associations with all-cause mortality were similar across cancer stages.

Strengths of the current study include its prospective design and availability of CRC recurrence data. A unique feature was the ability to evaluate change in lifestyle after diagnosis, due to the repeated lifestyle measurements starting at diagnosis. In addition, we had detailed lifestyle data that allowed us to compute different lifestyle scores to assess potential associations between concordance with healthy lifestyle recommendations and outcomes.

In conclusion, a healthy lifestyle after CRC diagnosis was not associated with CRC recurrence among patients with stage I-III CRC, but tended to be associated with a decreased all-cause mortality risk. This suggests that CRC patients could be advised to follow healthy lifestyle recommendations that emphasize a healthy body weight, being physically active, eating a healthy diet, and limited alcohol intake after CRC diagnosis to prolong survival. More research needs to be done to understand if and how lifestyle after diagnosis could influence CRC recurrence.

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Abbreviations used
ACS, American Cancer Society; CRC, colorectal cancer; COLON, Colorectal cancer: Longitudinal, Observational study on Nutritional and lifestyle factors that may influence colorectal tumor recurrence, survival, and quality of life; EnCoRe, Energy for life after ColoRectal cancer; IQR, interquartile range; WCRF/AICR , World Cancer Research Fund / American Institute for Cancer Research.

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Author responsibilities
MvZ, HCB, EK, MPW, and FJBvD designed research; MvZ, AJMRG, EW, and M-FK conducted research; MvZ analysed data, wrote draft paper, and had primary responsibility for final content; HKvH, EJSB, SOB, ETPK, MLGJH and JHWdW contributed to the recruitment of participants. All authors critically read and revised the draft manuscript and read and approved the final manuscript.). MFK is supported by a grant from Wereld Kanker Onderzoek Fonds (WKOF) 2017/1619 (to MJLB). All the other authors report no conflicts of interest.

Data availability

Because the data consist of identifying cohort information, some access restrictions apply, and therefore they cannot be made publicly available. Requests for data of the COLON study can be sent to Dr. Fränzel van Duijnhoven, Division of Human Nutrition and Health, Wageningen University & Research, the Netherlands (e-mail:franzel.vanduijnhoven@wur.nl). Requests for data of the EnCoRe study can be sent to Dr. Martijn Bours, Department of Epidemiology, GROW-School for Oncology and Developmental Biology, Maastricht University, the Netherlands (e-mail: m.bours@maastrichtuniversity.nl.

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Supplementary material

Supplemental Table 1. Demographic, clinical, and lifestyle characteristics of 1425 colorectal cancer survivors at six months postdiagnosis[1]

Characteristic	COLON (n=1178)	EnCoRe (n=247)
Age at diagnosis, y	66 (61-71)	67 (60-73)
Men (%)	746 (63%)	170 (67%)
Education (%)		
Low	481 (41%)	63 (25%)
Medium	313 (27%)	99 (39%)
High	375 (32%)	89 (35%)
Unknown	9	1
Tumor stage (%)		
I	307 (26%)	83 (33%)
II	354 (30%)	56 (22%)
III	517 (44%)	113 (45%)
Tumor site (%)		
Colon	792 (67%)	159 (63%)
Rectum	386 (33%)	93 (37%)
Neo-adjuvant treatment (%)	274 (23%)	63 (25%)
Adjuvant chemotherapy (%)	283 (24%)	76 (30%)
Unknown	23	0
Co-morbidity at diagnosis (%)	777 (66%)	203 (81%)
Unknown	5	0
Current smoker (%)	80 (7%)	19 (8%)
Unknown	2	0
Daily NSAID use (%)	99 (8%)	12 (5%)
Time between enrolment and postdiagnosis lifestyle assessment, y	0.5 (0.5-0.5)	0.6 (0.6-1.0)
WCRF/AICR-score, (mean, SD)	3.4 (0.9)	3.3 (0.8)
ACS score, (mean, SD)	5.0 (1.5)	4.5 (1.5)
Unknown	8	1
National lifestyle score, (mean, SD)	2.8 (0.8)	2.5 (0.7)
Unknown	6	1
BMI, kg/m^2	25.9 (23.9-28.5)	27.5 (24.9-30.9)
Unknown	6	1
Physical activity,[2] min/wk	480 (240-840)	560 (300-960)
Fruits and vegetables, g/day	248 (146-350)	225 (148-339)
Red and processed meat, g/day	63 (38-85)	127 (89-175)
Alcohol, g/day	5 (0-16)	7 (0-22)
Total energy intake, kcal/day	1765 (1472-2112)	2023 (1673-2349)

[1] Values are median (IQR), except where indicated otherwise. NSAID, non-steroidal anti-inflammatory drugs; WCRF/AICR, World Cancer Research Fund/American Institute of Cancer Research; ACS, American Cancer Society
[2] Moderate-to-vigorous physical activity included all activities with a metabolic equivalent value ≥3

Supplemental Table 2. Mutually adjusted hazard ratio's (HRs) for the association of postdiagnosis components of the WCRF/AICR, ACS, and national score with risk of colorectal cancer recurrence or death[1]

Score component	n	Cancer recurrence		Death from any cause	
		No. of events/ Person-years	HR (95%CI)	No. of events/ Person-years	HR (95%CI)
Weight sub-score					
WCRF/AICR sub-score (BMI + waist circumference)[2]					
0	252	26 / 645	1.00 (ref)	33 / 1065	1.00 (ref)
0.25	363	39 / 1045	0.91 (0.55, 1.50)	42 / 1681	0.75 (0.47, 1.20)
0.5	308	34 / 876	0.93 (0.56, 1.56)	38 / 1425	0.76 (0.47, 1.22)
0.75	244	28 / 717	0.99 (0.57, 1.70)	23 / 1162	0.62 (0.36, 1.07)
1	224	31 / 618	1.09 (0.64, 1.85)	29 / 1027	0.84 (0.50, 1.41)
P_{trend}			0.65		0.39
ACS subscore (BMI, kg/m^2)					
≥30	258	27 / 663	1.00 (ref)	32 / 1098	1.00 (ref)
25 to <30	628	69 / 1796	0.92 (0.59, 1.44)	73 / 2895	0.82 (0.54, 1.25)
18.5-24.9	499	62 / 1422	1.07 (0.67, 1.69)	59 / 2339	0.86 (0.55, 1.34)
P_{trend}			0.65		0.61
National subscore (BMI, kg/m^2)					
<18.5 or ≥30	261	27 / 674	1.00 (ref)	32 / 1114	1.00 (ref)
25 to <30	628	69 / 1796	0.92 (0.59, 1.45)	73 / 2895	0.82 (0.54, 1.25)
18.5-24.9	499	62 / 1422	1.06 (0.67, 1.69)	59 / 2339	0.86 (0.55, 1.34)
P_{trend}			0.65		0.60
Physical activity sub-score					
WCRF/AICR subscore (min/wk)					
<75	126	21 / 369	1.00 (ref)	22 / 586	1.00 (ref)
75-150	73	5 / 204	0.43 (0.16, 1.14)	9 / 331	0.79 (0.36, 1.73)
≥150	1192	132 / 3327	0.75 (0.47, 1.21)	134 / 5443	0.79 (0.50, 1.26)
P_{trend}			0.45		0.35

ACS subscore (min/wk)					
<150	199	26 / 573	1.00 (ref)	31 / 917	1.00 (ref)
150-300	213	35 / 608	1.34 (0.80, 2.23)	33 / 988	1.16 (0.70-1.90)
≥300	973	97 / 2701	0.86 (0.55, 1.34)	100 / 4427	0.80 (0.52-1.21)
P_{trend}			0.22		0.15
National subscore (min/wk)					
<75	126	21 / 369	1.00 (ref)	22 / 586	1.00 (ref)
75-150	73	5 / 204	0.42 (0.16, 1.11)	9 / 331	0.80 (0.37-1.76)
≥150	1189	132 / 3319	0.74 (0.46, 1.18)	133 / 5431	0.80 (0.50-1.27)
P_{trend}			0.40		0.31
Diet sub-score					
WCRF/AICR sub-score (Fruit and vegetables + dietary fibre, processed foods, red and processed meat, sugary drinks)[2]					
0-1	409	51 / 1122	1.00 (ref)	49 / 1849	1.00 (ref)
1.25-2	724	75 / 2051	0.78 (0.54, 1.13)	86 / 3334	0.87 (0.61-1.24)
2.25-4	258	32 / 727	1.16 (0.74, 1.82)	30 / 1179	1.07 (0.67-1.70)
P_{trend}			0.64		0.85
Continuous[3]			1.01 (0.86, 1.20)		0.91 (0.77-1.08)
ACS sub-score (Fruits and vegetables + variety, whole grains, red and processed meat)[2]					
0-2	244	29 / 666	1.00 (ref)	37 / 1077	1.00 (ref)
3-6	985	109 / 2822	0.92 (0.61, 1.40)	113 / 4583	0.75 (0.51-1.10)
7-9	156	20 / 393	1.32 (0.74, 2.37)	14 /673	0.85 (0.45-1.60)
P_{trend}			0.37		0.42
Continuous[3]			1.12 (0.95, 1.32)		0.98 (0.83-1.15)
National sub-score (Fruit, vegetables, whole grains, legumes, nuts, dairy, fish, tea, fats and oils, red meat, processed meat, and sugary drinks)[2]					
Q1	342	42 / 953	1.00 (ref)	56 / 1537	1.00 (ref)
Q2	351	38 / 992	1.02 (0.65, 1.58)	43 / 1600	0.85 (0.57, 1.27)

Supplemental Table 2. Continued

Q3	351	40 / 999	1.01 (0.65, 1.58)	33 / 1636	0.60 (0.39, 0.94)
Q4	344	38 / 948	1.16 (0.73, 1.83)	32 / 1575	0.74 (0.47, 1.16)
P_{trend}			0.55		0.07
Continuous[3]			1.08 (0.91, 1.28)		0.78 (0.64, 0.94)
Alcohol sub-score					
WCRF/AICR sub score (ethanol, g/day)					
>20 M and >10 F	362	40 / 978	1.00 (ref)	37 / 1598	1.00 (ref)
>0 to ≤20 M and ≤10 F	666	72 / 1903	0.86 (0.58, 1.27)	74 / 3129	0.89 (0.58, 1.32)
0	363	46 / 1019	0.96 (0.61, 1.49)	54 / 1633	1.22 (0.79, 1.91)
P_{trend}			0.87		0.32
ACS sub score (ethanol, g/day)					
>20 M and >10 F	361	40 / 975	1.00 (ref)	37 / 1594	1.00 (ref)
0	361	46 / 1012	0.94 (0.61, 1.47)	54 / 1622	1.25 (0.81, 1.94)
>0 to ≤20 M and ≤10 F	663	72 / 1895	0.87 (0.59, 1.29)	73 / 3116	0.90 (0.61, 1.35)
P_{trend}			0.46		0.40
National sub score (ethanol, g/day)					
≥30 M and ≥20 F	184	22 / 496	1.00 (ref)	18 / 811	1.00 (ref)
>10 to <30 M and >10 to <20 F	347	33 / 944	0.70 (0.40, 1.21)	32 / 1557	0.86 (0.48, 1.55)
≤10	857	103 / 2452	0.80 (0.50, 1.30)	114 / 3981	1.14 (0.68, 1.91)
P_{trend}			0.62		0.34

[1] Cox proportional hazards model adjusted for age at diagnosis, stage of disease, sex, adjuvant chemotherapy, education, smoking, and cohort. All components were mutually adjusted for each other. P_{trend} values were calculated by modelling the sub-score of each component (median dietary sub-score) as continuous variable. WCRF/AICR, World Cancer Research Fund/American Institute of Cancer Research; ACS, American Cancer Society

[2] Scoring is explained in Table 1.

[3] Continuous HRs were calculated for a 1-standard deviation increase in the dietary scores.

Supplemental Table 3. Hazard ratios (HR) for the association of prediagnosis concordance with lifestyle guidelines (including body weight, physical activity, diet, and alcohol intake) with risk of colorectal cancer recurrence and all-cause mortality among participants from the COLON study[1]

		CRC recurrence		Death from any cause	
Lifestyle score	n	No. of events/ Person-years	HR (95%CI)	No. of events/ Person-years	HR (95%CI)
WCRF/AICR-score					
0-2.5	226	28 / 732	1.00 (ref)	35 / 1141	1.00 (ref)
2.75-3.25	383	50 / 1239	1.12 (0.70, 1.78)	59 / 1953	0.93 (0.61, 1.41)
3.4-4.25	416	63 / 1636	1.09 (0.70, 1.70)	74 / 2537	0.90 (0.60, 1.35)
4.5-7	141	22 / 520	1.20 (0.69, 2.11)	20 / 821	0.82 (0.47, 1.42)
P_{trend}			0.59		0.47
Continuous[2]			1.05 (0.90, 1.23)		0.97 (0.84, 1.13)
ACS guidelines score					
0-3	208	25 / 682	1.00 (ref)	29 / 1063	1.00 (ref)
4	259	42 / 848	1.10 (0.65, 1.86)	34 / 1322	1.18 (0.73, 1.90)
5	297	28 / 996	0.77 (0.44, 1.33)	35 / 1540	0.86 (0.52, 1.41)
6-8	490	76 / 1599	1.40 (0.88, 2.22)	82 / 2528	1.26 (0.82, 1.94)
P_{trend}			0.13		0.38
Continuous[2]			1.15 (0.98, 1.35)		1.07 (0.92, 1.24)
National score					
0-2	334	38 / 1090	1.00 (ref)	53 / 1687	1.00 (ref)
2.5-3	612	83 / 2021	1.21 (0.82, 1.77)	89 / 3176	0.89 (0.64, 1.26)
3.5-4	308	42 / 1016	1.31 (0.84, 2.05)	46 / 1589	1.01 (0.68, 1.51)
P_{trend}			0.21		0.85
Continuous[2]			1.14 (0.97, 1.33)		1.01 (0.87, 1.17)

[1] Cox proportional hazards model adjusted for age at diagnosis, stage of disease, sex, adjuvant chemotherapy, smoking at diagnosis, and education. P_{trend} values were calculated by entering the median lifestyle scores within each category as continuous variables in the models. CRC, colorectal cancer; WCRF/AICR, World Cancer Research Fund/American Institute of Cancer Research; ACS, American Cancer Society.

[2] Continuous HRs were calculated for a 1-standard deviation increment in the score. Higher scores represent higher concordance with the respective guidelines.

Supplemental Table 4. Hazard ratios (HR) for the association of postdiagnosis concordance with lifestyle guidelines (including body weight, physical activity, diet, and alcohol intake) with risk of colorectal cancer recurrence and all-cause mortality, excluding participants from the COLON study who possibly did not complete adjuvant chemotherapy yet[1]

Lifestyle score	n	CRC recurrence		Death from any cause	
		No. of events/ Person-years	HR (95%CI)	No. of events/ Person-years	HR (95%CI)
WCRF/AICR score					
0-2.5	215	23 / 559	1.00 (ref)	30 / 922	1.00 (ref)
2.75-3.25	353	29 / 1000	0.68 (0.39, 1.18)	32 / 1618	0.57 (0.35, 0.95)
3.5-4.25	399	41 / 1139	0.90 (0.53, 1.50)	45 / 1837	0.68 (0.43, 1.09)
4.5-7	142	15 / 407	1.04 (0.54, 2.01)	16 / 657	0.87 (0.47, 1.61)
P_{trend}			0.66		0.68
Continuous[2]			1.07 (0.88, 1.31)		0.98 (0.81, 1.19)
ACS score					
0-3	207	16 / 551	1.00 (ref)	29 / 882	1.00 (ref)
4	227	27 / 619	1.57 (0.84, 2.92)	28 / 1001	0.86 (0.51, 1.46)
5	275	27 / 774	1.24 (0.67, 2.32)	26 / 1248	0.63 (0.37, 1.08)
6-8	395	38 / 1143	1.28 (0.71, 2.30)	39 / 1878	0.66 (0.40, 1.08)
P_{trend}			0.76		0.06
Continuous[2]			1.06 (0.88, 1.29)		0.88 (0.73, 1.05)
National score					
0-2	299	27 / 798	1.00 (ref)	36 / 1296	1.00 (ref)
2.5-3	552	52 / 1575	1.00 (0.63, 1.60)	60 / 2525	0.85 (0.56, 1.29)
3.5-4	254	29 / 720	1.35 (0.79, 2.29)	26 / 1196	0.94 (0.56, 1.56)
P_{trend}			0.37		0.56
Continuous[2]			1.14 (0.94, 1.39)		0.95 (0.79, 1.14)

[1] Cox proportional hazards model adjusted for age at diagnosis, stage of disease, sex, adjuvant chemotherapy, education, smoking, and cohort. P_{trend} values were calculated by entering the median lifestyle scores within each category as continuous variables in the models. CRC, colorectal cancer; WCRF/AICR, World Cancer Research Fund/ American Institute of Cancer Research; ACS, American Cancer Society.

[2] Continuous HRs were calculated for a 1-standard deviation increment in the score. Higher scores represent higher concordance with the respective guidelines.

Supplemental Table 5. Hazard ratios (HR) for the association of postdiagnosis concordance with lifestyle guidelines (including body weight, physical activity, diet, and alcohol intake) with risk of colorectal cancer recurrence and all-cause mortality, excluding participants from the EnCoRe study[1]

		CRC recurrence		Death from any cause	
Lifestyle score	**n**	**No. of events/ Person-years**	**HR (95%CI)**	**No. of events/ Person-years**	**HR (95%CI)**
WCRF/AICR score					
0-2.5	213	28 / 590	1.00 (ref)	34 / 975	1.00 (ref)
2.75-3.25	353	41 / 1041	0.77 (0.47, 1.25)	37 / 1722	0.58 (0.37, 0.94)
3.5-4.25	406	52 / 1219	0.93 (0.59, 1.49)	54 / 1990	0.76 (0.49, 1.17)
4.5-7	173	20 / 507	0.90 (0.50, 1.60)	21 / 824	0.86 (0.49, 1.49)
P_{trend}			1.00		0.83
Continuous[2]			1.02 (0.85, 1.21)		0.97 (0.81, 1.16)
ACS score					
0-3	189	21 / 557	1.00 (ref)	26 / 898	1.00 (ref)
4	230	34 / 664	1.42 (0.82, 2.45)	35 / 1087	1.15 (0.69, 1.92)
5	269	34 / 797	1.16 (0.67, 2.01)	34 / 1298	0.91 (0.54, 1.52)
6-8	452	52 / 1322	1.11 (0.67, 1.86)	50 / 2205	0.80 (0.50, 1.29)
P_{trend}			0.90		0.17
Continuous[2]			1.00 (0.88, 1.13)		0.93 (0.83, 1.05)
National score					
0-2	280	36 / 794	1.00 (ref)	39 / 1309	1.00 (ref)
2.5-3	552	64 / 1667	0.88 (0.59, 1.33)	70 / 2695	0.89 (0.60, 1.32)
3.5-4	310	41 / 887	1.09 (0.69, 1.72)	36 / 1494	0.94 (0.59, 1.48)
P_{trend}			0.85		0.60
Continuous[2]			1.03 (0.87, 1.23)		0.95 (0.80, 1.12)

[1] Cox proportional hazards model adjusted for age at diagnosis, stage of disease, sex, adjuvant chemotherapy, education, smoking, and cohort. P_{trend} values were calculated by entering the median lifestyle scores within each category as continuous variables in the models. CRC, colorectal cancer; WCRF/AICR, World Cancer Research Fund/ American Institute of Cancer Research; ACS, American Cancer Society.

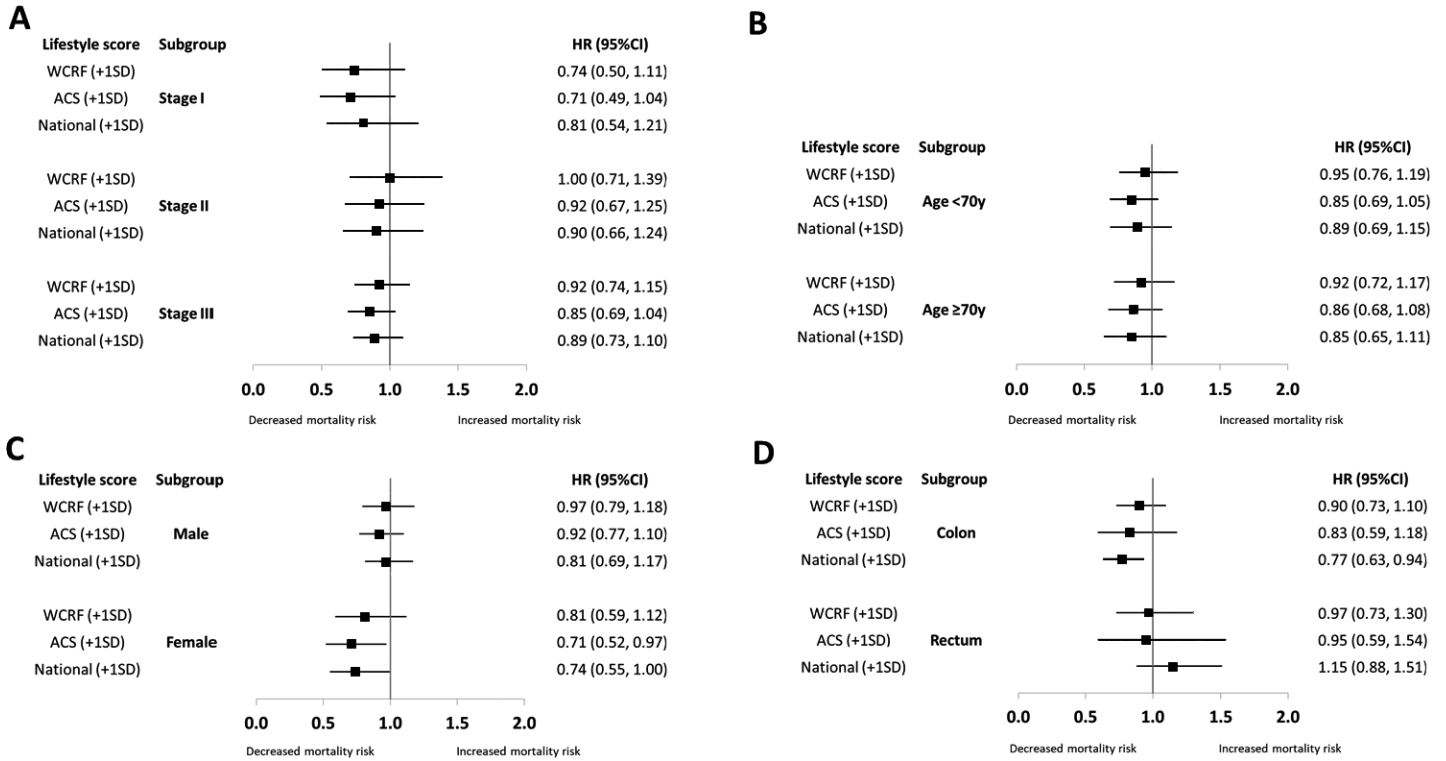
[2] Continuous HRs were calculated for a 1-standard deviation increment in the score. Higher scores represent higher concordance with the respective guidelines.

Supplemental Table 6. Hazard ratios (HR) for the association of postdiagnosis concordance with lifestyle guidelines (including body weight, physical activity, diet, and alcohol intake) with risk of colorectal cancer recurrence and all-cause mortality among non-smokers[1]

Lifestyle score	n	CRC recurrence		Death from any cause	
		No. of events/ Person-years	HR (95%CI)	No. of events/ Person-years	HR (95%CI)
WCRF/AICR-score					
0-2.5	234	30 / 614	1.00 (ref)	31 / 1024	1.00 (ref)
2.75-3.25	424	44 / 1174	0.72 (0.45, 1.14)	42 / 1921	0.67 (0.42, 1.06)
3.4-4.25	459	56 / 1318	0.88 (0.56, 1.37)	57 / 2123	0.81 (0.52, 1.26)
4.5-7	183	20 / 529	0.80 (0.45, 1.42)	21 / 856	0.86 (0.49, 1.50)
P_{trend}			0.75		0.86
Continuous[2]			0.99 (0.83, 1.17)		0.99 (0.83, 1.18)
ACS guidelines score					
0-3	229	25 / 633	1.00 (ref)	30 / 1016	1.00 (ref)
4	259	35 / 717	1.21 (0.72, 2.03)	36 / 1157	1.08 (0.66, 1.76)
5	319	38 / 893	1.03 (0.62, 1.71)	34 / 1457	0.78 (0.48, 1.28)
6-8	485	52 / 1378	0.96 (0.59, 1.55)	50 / 2274	0.76 (0.48, 1.21)
P_{trend}			0.58		0.11
Continuous[2]			0.96 (0.81, 1.13)		0.87 (0.74, 1.03)
National score					
0-2	325	39 / 880	1.00 (ref)	40 / 1434	1.00 (ref)
2.5-3	635	68 / 1811	0.85 (0.57, 1.26)	74 / 2915	0.91 (0.62, 1.35)
3.5-4	333	43 / 931	1.07 (0.69, 1.66)	36 / 1559	0.94 (0.60, 1.49)
P_{trend}			0.96		0.65
Continuous[2]			1.02 (0.86, 1.20)		0.93 (0.79, 1.10)

[1] Cox proportional hazards model adjusted for age at diagnosis, stage of disease, sex, adjuvant chemotherapy, and education. P_{trend} values were calculated by entering the median lifestyle scores within each category as continuous variables in the models. CRC, colorectal cancer; WCRF/AICR, World Cancer Research Fund/American Institute of Cancer Research; ACS, American Cancer Society.

[2] Continuous HRs were calculated for a 1-standard deviation increment in the score. Higher scores represent higher concordance with the respective guidelines.



Supplemental figure 1. Subgroup analyses of the association between postdiagnosis lifestyle and all-cause mortality by (A) stage, (B) age, (C) sex, and (D) tumor location. The squares indicate HRs and the width of the horizontal lines indicates the 95% CIs. Continuous (+1 SD) Cox proportional hazards models were adjusted for age at diagnosis, stage of disease, sex, adjuvant chemotherapy, education, smoking, and cohort. WCRF/AICR, World Cancer Research Fund/American Institute of Cancer Research; ACS, American Cancer Society. Number of deaths/total: stage I 29/388, II 45/390, III 91/613, <70y 88/960, >70y 77/431, male 117/889, female 48/502, colon 105/924, rectum 60/467.

CHAPTER 7

Identification of lifestyle behaviors associated with recurrence and survival in colorectal cancer patients using random survival forests

Moniek van Zutphen | Fränzel J.B. van Duijnhoven | Evertine Wesselink | Ruud W.M. Schrauwen | Ewout A. Kouwenhoven | Henk K. van Halteren | Johannes H.W. de Wilt | Renate M. Winkels | Dieuwertje E. Kok | Hendriek C. Boshuizen

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Simple summary

Current lifestyle recommendations for cancer survivors are the same as those for the general public to decrease their risk of cancer. However, it is unclear which lifestyle behaviors are important for prognosis after a cancer diagnosis. In an observational study among 1180 colorectal cancer patients, we aimed to identify which lifestyle behaviors were most important regarding cancer recurrence and all-cause mortality. We simultaneously evaluated lifestyle 55 behaviors, related to diet, physical activity, adiposity, alcohol use, and smoking. Higher intakes of sugary drinks were associated with increased recurrence risk. For all-cause mortality, fruit and vegetable, liquid fat and oil, and animal protein intake were identified as important lifestyle behaviors. Our exploratory findings identified several lifestyle behaviors related to prognosis after colorectal cancer. These findings should be confirmed in other observational studies before they can be translated into clinical practice.

Abstract

Current lifestyle recommendations for cancer survivors are the same as those for the general public to decrease their risk of cancer. However, it is unclear which lifestyle behaviors are most important for prognosis. We aimed to identify which lifestyle behaviors were most important regarding colorectal cancer (CRC) recurrence and all-cause mortality with a data-driven method. The study consisted of 1180 newly diagnosed stage I-III CRC patients from a prospective cohort study. Lifestyle behaviors included in the current recommendations, as well as additional lifestyle behaviors related to diet, physical activity, adiposity, alcohol use, and smoking, were assessed six months after diagnosis. These behaviors were simultaneously analyzed as potential predictors of recurrence or all-cause mortality with Random Survival Forests (RSFs). We observed 148 recurrences during 2.6-year median follow-up and 152 deaths during 4.8-year median follow-up. Higher intakes of sugary drinks were associated with increased recurrence risk. For all-cause mortality, fruit & vegetable, liquid fat & oil, and animal protein intake were identified as most important lifestyle behaviors. These behaviors showed non-linear associations with all-cause mortality. Our exploratory RSF findings give new ideas on potential associations between certain lifestyle behaviors and CRC prognosis that still need to be confirmed in other cohorts of CRC survivors.

Keywords
colorectal cancer; survival; recurrence; lifestyle; random survival forests.

Introduction

Rates of cancer survival are increasing, with more people living with and beyond cancer, including colorectal cancer (CRC) [1,2]. Current lifestyle recommendations for cancer survivors are the same as those for the general public to decrease their risk of cancer [3,4]. The current guidelines are to (1) achieve and maintain a healthy body weight; (2) engage in regular physical activity; and (3) achieve a dietary pattern high in vegetables, fruits, and whole grains while limiting fast foods, red and processed meat, sugary drinks, and alcohol consumption.

Cancer patients with a healthy lifestyle after CRC diagnosis may have a better prognosis. Several meta-analyses concluded that higher levels of physical activity after CRC diagnosis were associated with lower mortality [5-9]. Additionally, several studies showed that body mass index (BMI) after CRC diagnosis seems associated with mortality. The risk of death was highest among patients who were underweight, while lowest risk was seen in patients with a BMI between 25 and <30 kg/m^2 [10-13]. Although the number of studies that assessed the association between diet after CRC diagnosis and mortality is limited, it seems that healthier diets are associated with lower mortality [10]. Higher intake of fruit and vegetables [14-16] and wholegrains [15,17,18] were generally associated with lower mortality, although not in all studies. An unhealthy ("Western") dietary pattern [15,19,20] or higher intake of sugary drinks [15,21] were generally associated with higher mortality, In contrast, there is currently little evidence to support the recommendation to limit red and processed meat intake after CRC diagnosis [14,15,22]. Because of the limited number of studies, it remains unclear if lifestyle after CRC diagnosis is associated with recurrence risk [10]. A limitation of many of these studies is that they examine the importance of single lifestyle behaviors. However, lifestyle is multidimensional, with behaviors representing dietary habits, alcohol use, physical activity, adiposity, and smoking. Considering different lifestyle behaviors simultaneously, rather than a series of separate characteristics, could provide a more comprehensive understanding of which aspects of lifestyle are most important in relation to CRC prognosis.

Efforts to quantify overall lifestyle in CRC survivors have been limited to assessing adherence to lifestyle recommendations [14,23,24]. Previous studies among CRC survivors showed that an overall healthy lifestyle after CRC diagnosis was associated with improved survival [14,24], but not among long-term survivors [23]. Results regarding CRC recurrence were inconsistent [14,24]. Our group reported that post-diagnosis lifestyle might be more important than lifestyle before diagnosis, as the summary lifestyle score before CRC diagnosis was not associated with all-cause mortality [24]. No study has identified which post-diagnosis lifestyle behaviors are most important in relation to mortality or recurrence.

To date, researchers have used multivariable Cox proportional hazard regression models to test hypotheses that a certain lifestyle behavior (or lifestyle score) is associated with CRC outcomes. With exploratory analyses, to identify variables of interest, Cox regression models can also be used. However, exploratory analysis of a dataset containing many correlated variables has statistical challenges, including correction for multiple testing and handling of multicollinearity. Random survival forests (RSF) [25] are a robust alternative for Cox regression models in the case of exploratory analyses. RSF seeks a model that best explains the data, thus before building the model there is no need to select a limited number of variables of interest or to know the relationship (i.e. linear, nonlinear) of a variable with the outcome. Furthermore, RSF can handle many variables, take complex interactions between variables into account, and does not rely on P-values. RSF has been successfully applied to identify risk factors of different diseases and disease outcomes [26-31], but has not been used to identify important lifestyle behaviors with regard to cancer prognosis.

We aimed to identify which lifestyle behaviors were most important regarding colorectal cancer (CRC) recurrence and all-cause mortality among CRC survivors with stage I-III disease with RSF. We evaluated lifestyle behaviors currently included in cancer prevention recommendations, as well as other lifestyle behaviors that might need to be included in future recommendations for cancer survivors.

Methods

Study population

We used data from the COLON study, a prospective multicenter cohort study among CRC patients (NCT03191110; ClinicalTrials.gov) [32]. From 2010 onwards, newly diagnosed patients with colon or rectal cancer were recruited in 11 hospitals in the Netherlands. Hospital staff invited eligible patients during a routine clinical visit before start of treatment. Patients were not eligible when they had a history of CRC, a previous (partial) bowel resection, known hereditary CRC, inflammatory bowel disease, dementia or another mental condition limiting their ability to fill out surveys, or were non-Dutch speaking. All study participants provided written informed consent and the study was approved by the Committee on Research involving Human Subjects, region Arnhem-Nijmegen, the Netherlands.

Recurrence data were available for 1605 participants diagnosed between 2010 and 2016. Exclusions were made for the following reasons: missing stage (n=73), stage IV disease (n=132), ASA physical status classification IV (severe systemic disease that is a constant threat to life) (n=3), BMI <18.5 kg/m^2 (n=8), or CRC recurrence before lifestyle assessment (n=11). Furthermore, we excluded 198 participants who had missing lifestyle data six months after diagnosis. The final sample size for the analyses was 1180.

Lifestyle assessment

Lifestyle data were collected six months after diagnosis. Habitual dietary intake was assessed with a 204-item semi-quantitative food frequency questionnaire (FFQ). The reference period for the FFQ was the previous month. To assess amounts of food intake, we combined frequencies of intake with standard portion sizes and household measures [33]. The FFQ was previously validated [34] and slightly adapted to be able to distinguish meat intake with respect to red, processed, and white meat. Self-reported dietary intake data from the FFQ were converted into energy, macronutrient, fiber, and alcohol intake based on the 2011 Dutch food composition table [35]. In our RSF models, we included all dietary components (food groups and dietary fiber) present in either the cancer prevention recommendations (American Cancer Society (ACS) [4] or the World Cancer Research Fund / American Institute for Cancer Research (WCRF/AICR) [3]) or national dietary guidelines from the Netherlands [36,37]. Furthermore, we included additional food groups not included in these recommendations (for example, coffee intake) and macronutrients. In total, 44 dietary variables were included in the RSF models (**Supplementary Table S1**).

In addition to the FFQ, participants filled out other lifestyle questionnaires assessing self-reported weight, height, and physical activity, and current smoking (including number of cigarettes smoked per day). Waist (midway between the lowest rib and the iliac crest) and hip circumference were measured with a tape sent to participants. Waist-hip-ratio and BMI (kg/m^2) were computed. Waist circumference and waist-hip-ratio were standardized to relative values that express excess adiposity directly. Standardizing was done by subtracting the sex-specific cut-offs that determine excess adiposity from the measured values (**Supplementary Table S1**). Moderate-to-vigorous physical activity was self-reported by the validated SQUASH questionnaire [38-40]. Moderate-to-vigorous physical activity included all activities (walking, cycling, gardening, odd-jobs, sports, household activities, and work) with a metabolic equivalent value ≥3 [41]. To ensure quality of the data, we checked each questionnaire after completion and contacted participants by telephone for clarification if needed. In total, 6 physical activity, 3 adiposity, and 2 smoking variables were included in the RSF models (**Supplementary Table S1**).

Assessment of background variables

Information was obtained on socio-demographic and clinical factors. Socio-demographic information and daily use of nonsteroidal anti-inflammatory drugs (NSAIDs). Clinical data, such as CRC stage, tumor site, administration of neo-adjuvant treatment, adjuvant chemotherapy, and ASA physical status classification were retrieved from the Dutch ColoRectal Audit. The Dutch ColoRectal Audit is a nationwide audit initiated by the Association of Surgeons from the Netherlands to monitor, evaluate, and improve CRC care [42]. Self-reported smoking status at diagnosis (never, former, smoking at diagnosis) was also included as background variable, instead as lifestyle variable, because smoking status is a potential confounder but

smoking behavior at diagnosis does not differ between former and never smokers. In total, 11 background variables were included in the RSF models (**Table 1**).

Outcome assessment

We defined CRC recurrence as time from postdiagnosis lifestyle assessment to locoregional recurrence or distant metastasis. Patients who died without CRC recurrence or who experienced another type of cancer with metastasis were censored in analyses with CRC recurrence as the outcome. Information on recurrences was collected from medical records by trained registrars from the Dutch Cancer Registry from January through March 2018. We defined all-cause mortality as time from postdiagnosis lifestyle assessment to death. Vital status and date of death were determined through linkage to the Municipal Personal Record Database of the Netherlands through December 2019.

Random Survival Forests

Random survival forest (RSF) analysis is an ensemble tree method for the analysis of right censored survival data [25]. Trees in a survival forest are grown randomly using a two-step randomization process (**Figure 1**). First, each tree is grown using a randomly drawn bootstrap sample (training set), that includes on average two thirds of the original data. Second, random variable selection is used when growing the tree. At each split, a new random subset of candidate variables is selected. The bootstrap sample, including for each tree a random subset of the study population, can be seen as the root of the tree. During the tree-growing process, the root is split into two branches. The branch is split using the variable, from the randomly selected subset of candidate variables, that indicates the largest survival difference between daughter branches. Averaging over trees in combination with the randomization used in growing a tree, creates an ensemble of independent trees that form the RSF.

Once an RSF model is computed, prediction accuracy and variable importance can be assessed. Prediction accuracy for RSF was assessed using data that were not included in the tree-growing process (i.e. the remaining one third of the original data) [25]. These data are called out-of-bag (OOB) data (i.e. test set). The RSF prediction error rate has values between 0 and 1, where a lower RSF prediction error rate corresponds to an RSF model with more precise prediction accuracy.

Variable importance (VIMP) was determined by applying the RSF model on the OOB data (i.e. test set) [25]. VIMP is calculated as follows: i) in the OOB cases for a tree, all values of a certain variable are randomly permuted; ii) this new variable is put down the tree and a new internal error rate is computed; iii) the amount this new error rate exceeds the original OOB error is defined as the importance of that variable for the tree; iv) averaging over the forest yields VIMP. High positive VIMP values indicate that a variable is important in predicting the outcome of interest.

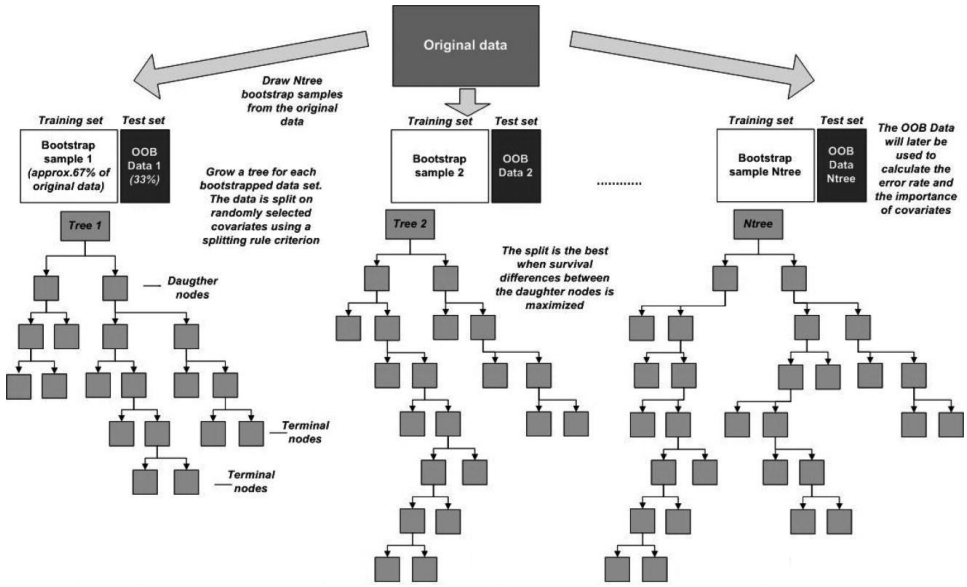

Figure 1. Graphical presentation of the Random Survival Forest (RSF) algorithm. Adapted from Datema et al., 2012 [26]. OOB, out-of-bag data.

Statistical analysis

To identify important lifestyle behaviors for recurrence or all-cause mortality, we generated RSF models. The full RSF models were applied on the data of all participants, consisting of all lifestyle and background variables. The important variables regarding either recurrence or all-cause mortality were determined as those with positive VIMP values that exceeded the amplitude of the largest negative value (i.e. the dashed line in Figure 2) [43]. However, as the random process involved in building the trees might influence the VIMP observed, we computed 10 repetitions for each RSF model. For each model repetition, we identified which variables were predictive of the outcome based on the VIMP values. Only those lifestyle variables that were identified in ≥7 out of 10 model repetitions were considered important regarding the outcome and were selected for the final model. The final RSF models contained all 11 pre-defined background variables (see Table 1) plus the subset of identified lifestyle variables to account for possible confounding. Additionally, the analyses were repeated in two subsets of the data based on tumor location (colon or rectum).

Final RSF models were used to derive partial (dependence) plots of selected lifestyle variables. Partial plots represent the effect of each lifestyle behavior on predicted (recurrence-free) survival after accounting for the average effects of all variables in the model and can be used to graphically assess the direction and non-linearity of associations [44]. Thus, partial plots are adjusted for all variables in the final model, similar to multivariable Cox regression

models that include confounders. The y-axis of the plot shows the risk of (recurrence-free) survival at different levels of dietary intake (x-axis). So for example, a value of 0.80 should be interpreted as 80% chance of recurrence-free survival (i.e. no recurrence) or, similarly, 20% chance of recurrence. We choose 3- and 5-years' time curves to be shown in the partial plot. These time points are clinically relevant and in line with the available follow-up time.

To evaluate prediction accuracy, we computed three additional RSF models next to the full and final models described above. These models contained: (i) only background variables; (ii) only lifestyle variables; and (iii) only randomly generated noise variables. This last model was used to benchmark the prediction error. This model can be seen as a 'control' model and did not include any of the original background or lifestyle variables. The noise variables consist of randomly generated values that follow a normal distribution (mean=0, SD=1). Eleven noise variables were included in the benchmark (i.e. 'control') models, as the models with only background variables also included 11 variables. For each RSF model, 10 repetitions were generated and used to calculate means and standard errors (SE) of prediction error rates of the respective RSF models.

The analyses were conducted with the statistical software R (version 3.6.1), the R-package RandomForestSRC (version 2.9.3) and SAS version 9.4. In preliminary analyses, we did a grid search to determine model parameters (numbers of trees grown in the forest, number of randomly selected candidate variables, and number of unique cases in terminal branches) with optimal predictive power. The results indicated that the default values were adequate, although ≥1000 trees were needed. Therefore, we generated RSF models with 2000 trees. We used the following default values: i) log-rank splitting rule = 10 splits per variable; ii) number of candidate variables = the square root of the total number of exposure variables; iii) number of unique cases in terminal branches = 15. We dealt with missing data by using the imputation option within the RandomForestSRC package [25].

Results

Our cohort consisted of 1180 people diagnosed with CRC. Median age at CRC diagnosis was 66 years and 67% of the tumors were located in the colon (**Table 1**). Stage III disease (44%) was more common than stage II (30%) and stage I disease (26%). We observed 148 recurrences during 2.6-year (IQR 1.7-3.9) median follow-up. A total of 152 patients died during 4.8-year (IQR 3.7-5.8) median follow-up; 55% of people with a recurrence died during follow-up (n=81).

Figure 2 plots the variable importance (VIMP) of all 66 variables (55 lifestyle and 11 background variables) of the full model. The dashed horizontal line separates the predictive variables from the remaining non-predictive variables. Stage of disease is easily seen to be

the most predictive variable for recurrence, while this is age for all-cause mortality. However, some variables were inconsistently identified as predictive variables over the 10 repetitions of the RSF models (**Table 2**).

For recurrence, sugary drink intake was consistently identified as most predictive lifestyle variable. Saturated fat intake was identified as predictive lifestyle variable in 8 out of 10 models. The background variables stage, tumor location, adjuvant chemotherapy, and neo-adjuvant therapy were consistently identified as the top 4 most predictive variables. Separate analyses by tumor location showed that sugary drink intake was identified as important variable among people with colon cancer, but not among people with rectal cancer (**Supplementary Table S1**). Saturated fat intake was identified as important variable in both groups.

For all-cause mortality, 3 lifestyle variables were consistently identified as predictive in all model repetitions: liquid fat & oil, fruit & vegetable, and animal protein intake. Fruit, polyunsaturated fat, potato, and processed meat intake were identified as predictive lifestyle variables in ≥7 out of 10 models. The background variables age and stage were consistently identified as the top 2 most predictive variables, while ASA-classification was predictive in 7 out of 10 models. Separate analyses by tumor location showed that fruit, liquid fat & oil, and fruit & vegetable intake were only identified as important variables among people with colon cancer (**Supplementary Table S1**). In contrast, animal protein, processed meat, and polyunsaturated fat intake were only identified as important variables among people with rectal cancer.

Final RSF models included the subset of identified lifestyle behaviors (recurrence: sugary drink and saturated fat intake; all-cause mortality: liquid fat & oil, fruit & vegetable, animal protein, fruit, polyunsaturated fat, potato, and processed meat intake) together with the 11 pre-defined background variables that were included as potential confounders. Final RSF models had the smallest mean prediction error rates for both recurrence (0.3376) and all-cause mortality (0.3452) of all constructed models (**Table 3**). This indicates that adding identified lifestyle variables to an RSF model with background variables reduced prediction error. However, adding all available lifestyle variables to the model worsened prediction error.

Direction and non-linearity between identified lifestyle variables and predicted 3 and 5-year recurrence-free survival (**Figure 3**) or survival (**Figure 4**) was assessed visually in partial plots. From the plots in figure 2 we can see that the association between sugary drink intake and recurrence appears to be approximately linear, with higher intakes being associated with lower recurrence-free survival and thus a higher recurrence risk. From the plots in figure 3 we can see that the associations between the continuous dietary behaviors and survival appear to be non-linear. For example, a non-linear inverse association was observed for fruit intake, with most of the risk reduction observed when increasing intake up to about 100 g/day.

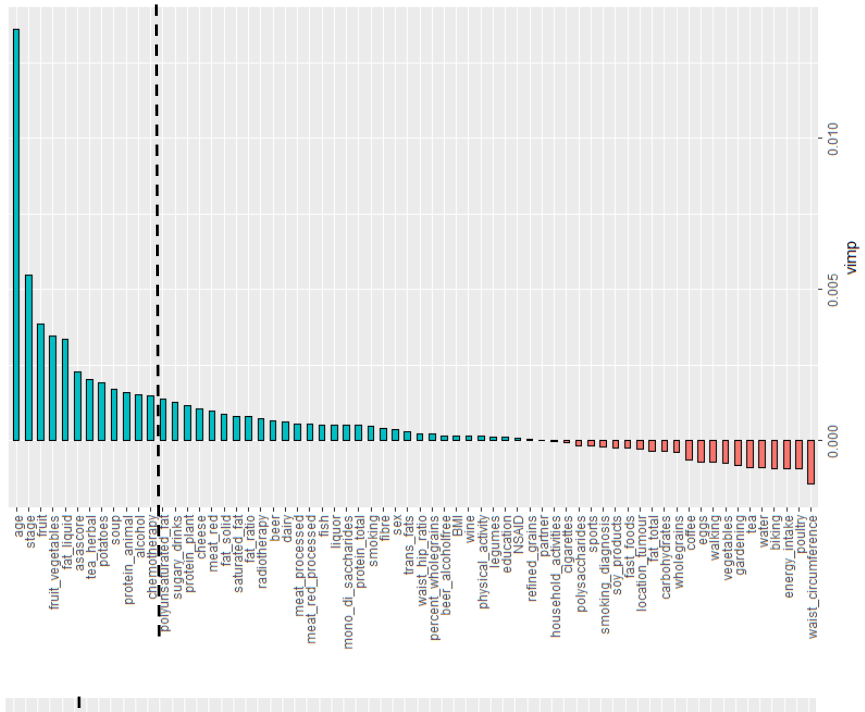

Figure 2. Variable importance (VIMP) from random survival forest analysis for (A) colorectal cancer recurrence and (B) all-cause mortality for one model repetition. The dashed horizontal line is the threshold for filtering variables: all variable above the line are identified as predictive variables. VIMP values are shown for 1 out of 10 model repetitions. Of note: some variations in VIMP values were noted over the 10 repetitions of the RSF models.

Table 1. Characteristics of the study population at colorectal cancer diagnosis and lifestyle characteristics six months after diagnosis

Background variables, n(%) or median (IQR)	n=1180
Age at diagnosis, y	66 (61-71)
Men	747 (63%)
Education, *missing n=9*	
Low	482 (41%)
Medium	314 (27%)
High	375 (32%)
Living with partner, *missing n=7*	988 (84%)
Tumor stage	
I	307 (26%)
II	356 (30%)
III	517 (44%)
Tumor site	
Colon	796 (67%)
Rectum	384 (33%)
Neo-adjuvant treatment	272 (23%)
Adjuvant chemotherapy	284 (24%)
ASA physical performance classification, *missing n=51*	
I	354 (30%)
II	653 (55%)
III	122 (10%)
Daily NSAID use	102 (9%)
Smoking at diagnosis, *missing n=8*	
Yes	119 (10%)
Former	694 (59%)
Never	359 (31%)
Lifestyle six months post-diagnosis, n(%) or median (IQR)	
Body Mass Index, kg/m2, *missing n=6*	25.9 (23.9-28.5)
Physical activity[1], min/wk.	480 (240-840)
Diet	
Fruits and vegetables, g/day	248 (147-350)
Red and processed meat, g/day	63 (38-85)
Sugary drinks, g/day	70 (13-176)
Dietary fiber, g/day	19 (15-24)
Energy intake, kcal/day	1765 (1472-2112)
Alcohol intake	
Non-drinker[2]	293 (25%)
Amount (g/d) among drinkers	9 (3-21)
Amount (g/d) among all	5 (0-16)
Current smoker, *missing n=2*	80 (7%)

[1]Moderate-to-vigorous physical activity included all activities with a metabolic equivalent value ≥3
[2]No alcohol intake in past month

Table 2. Variables predictive of recurrence or all-cause mortality based on variable importance.

Variables predictive of recurrence	**Number of times selected as predictive variable in 10 repetitions of RSF model**
Stage	10
Tumor location	10
Adjuvant chemotherapy	10
Neo-adjuvant therapy	10
Sugary drinks	10
Saturated fat	8
Fruit	6
Total fat	4
Trans-fats	3
Eggs	3
Polyunsaturated fat	3
Carbohydrates	3
Fiber	2
Liquor	2
Energy intake	2
Variables predictive of all-cause mortality	
Age	10
Stage	10
Liquid fat & oils	10
Fruit & vegetables	10
Animal protein	10
Fruit	9
Polyunsaturated fat	9
Potato	8
Processed meat	8
ASA classification	7
Herbal tea	6
Sugary drinks	6
Soup	6
Adjuvant chemotherapy	6
Alcohol	5
BMI	4
Beer	4
Education	4
Plant protein	4
Neo-adjuvant therapy	2
Dietary fiber	2

Variables printed in *italics* are background variables, all other variables are lifestyle variables. Variables were selected as predictive based on their VIMP values. Only variables selected in ≥2 model repetitions are included in this table.

Table 3. RSF-derived error rates for the prediction of recurrence and all-cause mortality in different RSF models based on 10 model repetitions.

RSF model	Prediction error rate[1] (mean ± SE)	
	Recurrence	**All-cause mortality**
Final model (background and identified lifestyle variables)	0.3376 ± 0.0005	0.3452 ± 0.0006
Only background variables	0.3570 ± 0.0005	0.3483 ± 0.0004
Full model (background and lifestyle variables)	0.3777 ± 0.0006	0.3964 ± 0.0009
Only lifestyle variables	0.4858 ± 0.0014	0.4309 ± 0.0007
Only noise (benchmark model)	0.5706 ± 0.0014	0.4886 ± 0.0011

Background variables included age, sex, education, living with partner, stage of disease, neo-adjuvant treatment, adjuvant chemotherapy, tumor location, smoking status at diagnosis, use of non-steroidal anti-inflammatory drugs at diagnosis, and ASA classification.
[1]Standard error (SE) represents randomness based on 10 repetitions of the RSF model within the same dataset.

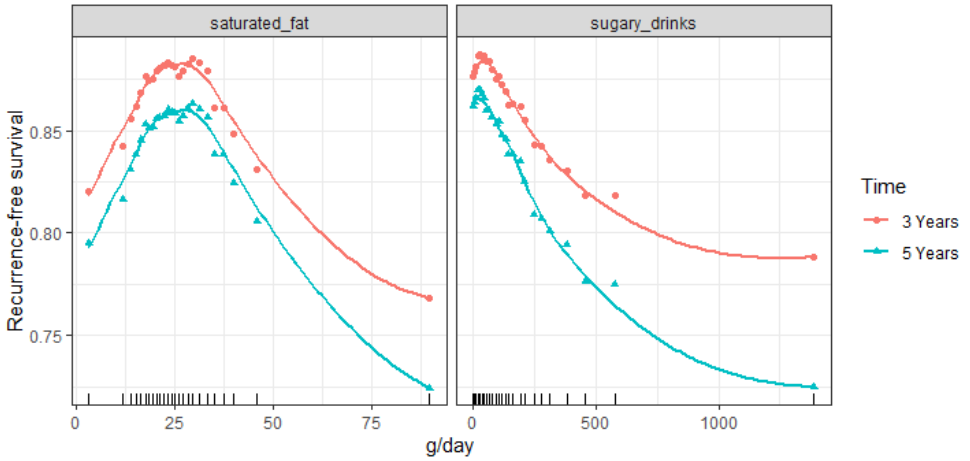

Figure 3. Partial plots of identified lifestyle variables for recurrence. Values on the vertical axis represent predicted three-year and five-year recurrence-free survival for a given variable after adjusting for all other variables (background and shown lifestyle variables). Dietary intakes in grams per day are on the horizontal axis. A lower predicted recurrence-free survival means a higher risk to develop a local or distant recurrence within three or five years of follow-up. The rug plots on the x-axis show the distribution of intake data observed in the cohort; about 90% of observations occurs between the second and second-last rug.

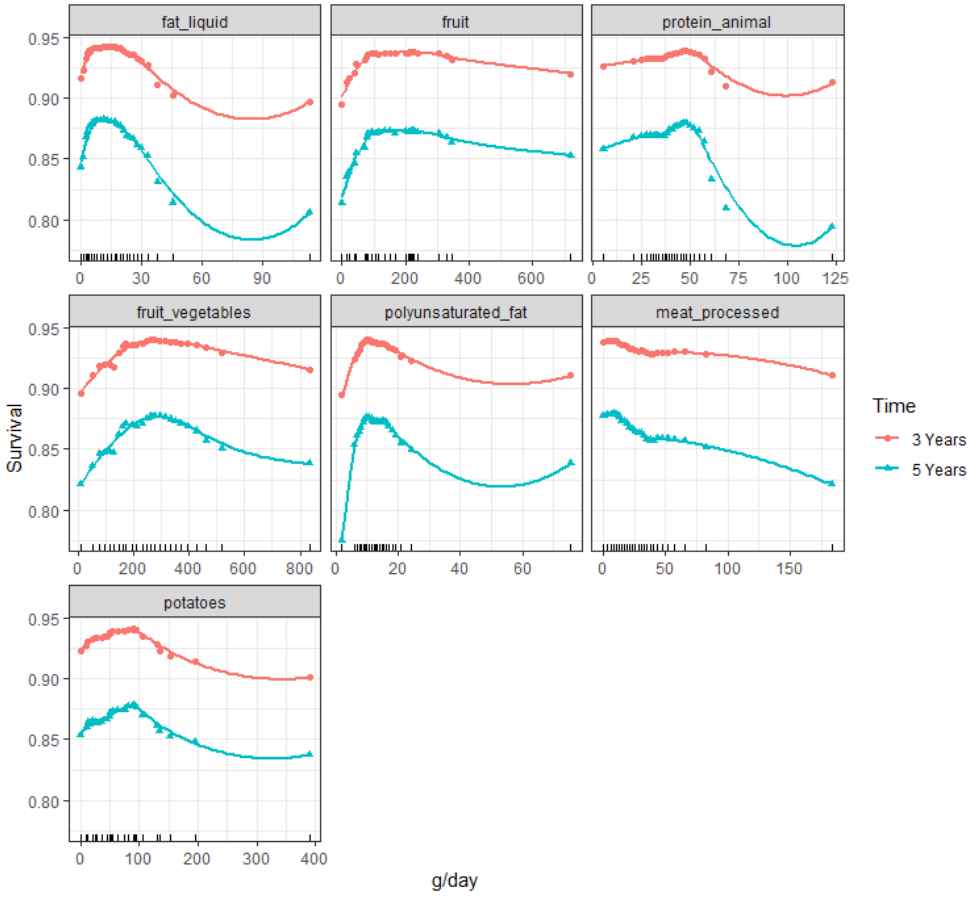

Figure 4. Partial plots of identified lifestyle variables for all-cause mortality. Values on the vertical axis represent predicted three-year and five-year survival for a given variable after adjusting for all other variables (background and shown lifestyle variables). Dietary intakes in grams per day are on the horizontal axis. The rug plots on the x-axis show the distribution of intake data observed in the cohort; about 90% of observations occurs between the second and second-last rug.

Discussion

Random survival forests (RSF) identified sugary drink intake as most important lifestyle behavior after colorectal cancer diagnosis related to recurrence in our cohort of 1180 patients with stage I-III CRC. Higher intakes of sugary drinks were associated with increased recurrence risk. For all-cause mortality, fruit & vegetable, liquid fat & oil, and animal protein intake were consistently identified as most predictive lifestyle variables. These lifestyle variables showed non-linear associations with all-cause mortality. Predictive power improved by adding these identified lifestyle variables to RSF models that only included 11 pre-defined background (socio-demographic and clinical) variables.

This was the first study that identified lifestyle behaviors important for recurrence and all-cause mortality in cancer survivors with a data-driven method. Therefore, we can only compare our results with prospective cohort studies which assessed associations between post-diagnosis lifestyle behaviors and CRC outcomes with traditional Cox regression models. Our RSF models identified higher sugary drink intake after CRC diagnosis as an important risk factor for recurrence, which is in line with the only previous study which assessed this association among colon cancer survivors [21]. However, sugary drink intake might not be related to recurrence risk among rectal cancer survivors (Supplementary Table S2). Further analyses in other cohorts of CRC survivors are needed to support (or refute) the potential role of sugary drink intake in CRC recurrence.

Our RSF model identified three dietary behaviors - fruit & vegetable, liquid fat & oil, and animal protein intake - as important lifestyle behaviors regarding all-cause mortality. These dietary behaviors were selected from a set of 55 lifestyle variables, which included well-known risk factors for cancer incidence –which are potentially also linked to CRC survival–, as well as lifestyle variables not previously linked to CRC survival. In line with our findings, two previous studies also reported that lower fruit & vegetable intake after CRC diagnosis was associated with higher all-cause mortality [14,16], while no associations were reported for either fruit or vegetable intake in another study [15]. Our partial plots suggest that particularly low fruit & vegetables intake is associated with higher all-cause mortality. Although this is comparable to the inverse non-linear association observed for CRC risk [45], this has not been observed for CRC survival before. Two previous studies in which the association between fat intake and all-cause mortality among CRC survivors was assessed reported mixed findings [46,47]. Although both did not report on liquid fat & oil intake, one concluded that neither total nor major types of dietary fat were associated with disease-free survival [46]. The other study concluded that replacing carbohydrates with plant or polyunsaturated fat was associated with lower all-cause mortality [47]. Previous studies that assessed the association between animal protein intake and all-cause mortality among CRC survivors also reported mixed findings. Replacing carbohydrates with animal protein was associated with a higher all-cause mortality [47]. Instead of animal protein intake, other studies investigated red and processed meat or dairy intake. Red and processed meat intake was not associated with all-cause mortality [15,22], while another study reported higher all-cause mortality with lower red and processed meat intake [14]. Higher all-cause mortality was also reported for lower milk intake [48]. A low animal protein intake could result in loss of muscle mass which could worsen clinical outcomes and increase mortality risk [49,50]. Taken together, emerging evidence seems to indicate low fruit & vegetable intake is associated with higher all-cause mortality, especially among colon cancer survivors. Further research is needed to assess the potentially non-linear associations between liquid fat & oils or animal protein intake and all-cause mortality. Such studies should also assess if these

associations differ by tumor location, as our additional analyses identified different lifestyle behaviors among subgroups with colon or rectal cancer.

RSFs are better suited than traditional Cox regression models to identify a subset of exposures that are related to the outcome of interest from a large set of potentially interesting exposures. Researchers can use RSF to consider many lifestyle behaviors simultaneously and to identify which of these modifiable behaviors are most important for CRC recurrence and all-cause mortality. Applying many Cox regression models to test all these associations with either recurrence or all-cause mortality, would result in multiple testing. There are two advantages for using RSFs in this situation. First, RSFs do not rely on p-values and, more importantly, RSF uses a subset of data not included in model building (i.e. out-of-bag data) to identify important variables. Second, RSF takes complex interactions between variables into account. Cox regression models are a suitable method to test hypothesis on exposure-outcome associations with a limited number of exposures of interest. Cox models are, therefore, complementary to RSF models. Future research, in external cohorts, could use Cox regression models to further study the associations between our identified dietary behaviors and CRC progression.

Several studies have now compared RSF to other methods, including Cox regression models, and these have shown that the predictive accuracy of RSF was consistently better than, or at least as good as, competing methods [25-28,51]. In our study, predictive accuracy was best in models that included identified lifestyle behaviors on top of background variables, although performance was only slightly better than our models with only background variables. A similar pattern was observed in a previous study which identified modifiable lifestyle behaviors related to CRC risk in the EPIC-cohort [52]. Their final model, including both age and identified modifiable lifestyle behaviors, also performed only slightly better than a model with age only. However, they showed that lifestyle information in addition to age was important for absolute risk assessment. The reported prediction error rates of our final models are similar to those reported in the EPIC-cohort [52] and several other RSF models [27,51]. However, models which included all 55 lifestyle behaviors performed worse than models with only background variables. We assume that many of these lifestyle behaviors are not impacting CRC prognosis and therefore add ‘noise’ to the model, which decreases predictive accuracy.

Potential limitations of our study should be considered. A first limitation of our study is that we have not validated our RSF models with an external cohort of CRC survivors. Although RSF does validate the model by testing prediction on the “out-of-bag” sample, that is, individuals that were not used to create the particular tree, the ensemble of trees are still derived from the entire original dataset. This study needs to be repeated in an external cohort to see if the same variables will be identified. This is not different from studies

which use Cox regression models, as multiple studies are always needed to strengthen the evidence. Another limitation is that we noted some variations in the identified predictive variables over the 10 repetitions of the RSF models. This variation is likely explained by the conservative approach used to identify important lifestyle variables. All variables below the threshold are clearly not important, while values above the threshold may (or may not) be predictive [43]. To limit this variation, we created larger RSFs with 2000 trees and limited our identified lifestyle variables to those consistently identified in 10 out of 10 model repetitions. Although variable importance values differed slightly between repetitions, our partial plots were robust as we observed no clear differences between partial plots based on slightly different models (results not shown). Furthermore, we could not explore cause-specific mortality, as we do not have access to these data. This would have been of interest as we identified three dietary behaviors (fruit & vegetable, liquid fat & oil, and animal protein intake) related to all-cause mortality, which were not important for CRC recurrence. These dietary behaviors might therefore specifically be related to other causes of death (e.g. cardiovascular mortality or mortality associated with loss of muscle mass), but not with CRC-specific mortality. Lastly, we did not include information on muscle mass, as this information is only available at diagnosis for a subset of our population. Our group previously showed that muscle mass tended to increase with increasing BMI among stage I-III CRC patients [53]. Thus, lower BMIs might serve as a proxy for low muscle mass in the current analyses. However, BMI was not identified as an important variable for all-cause mortality.

Strengths of the current study include the availability of both CRC recurrence data and a large number of post-diagnosis lifestyle behaviors related to diet, physical activity, alcohol use, adiposity, and smoking, which allowed us to simultaneously identify which of these behaviors are related to CRC outcomes. This was the first study that considered many modifiable lifestyle behaviors simultaneously to identify modifiable risk factor for CRC recurrence and survival. Results of this study indicate the relative importance of different lifestyle behaviors and show that lifestyle behaviors currently not included in the recommendations could also impact CRC prognosis.

Conclusions

This study among CRC patients with non-metastatic disease identified different lifestyle behaviors for recurrence risk and all-cause mortality. For recurrence, higher intakes of sugary drinks were associated with increased recurrence risk. For all-cause mortality, fruit & vegetable, liquid fat & oil, and animal protein intake were identified as most important lifestyle behaviors. These latter behaviors showed non-linear associations with all-cause mortality. Identified behaviors comprised a few known factors included in cancer prevention recommendations, but also some additional lifestyle behaviors. Our exploratory RSF

findings give new ideas on potential associations between certain lifestyle behaviors and CRC prognosis that still need to be confirmed in other cohorts of CRC survivors.

Supplementary Materials

The following are available: Table S1: Overview of all post-diagnosis lifestyle variables included in the Random Survival Forest models. Table S2: Variables predictive of recurrence or all-cause mortality, based on variable importance, by tumor location.

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Author contributions:

Author contributions

Conceptualization, Moniek van Zutphen and Hendriek Boshuizen; Data curation, Moniek van Zutphen; Formal analysis, Moniek van Zutphen; Funding acquisition, Moniek van Zutphen, Fränzel van Duijnhoven, Renate Winkels and Dieuwertje Kok; Investigation, Moniek van Zutphen and Evertine Wesselink; Methodology, Moniek van Zutphen and Hendriek Boshuizen; Project administration, Moniek van Zutphen and Evertine Wesselink; Resources, Ruud Schrauwen, Ewout Kouwenhoven, Henk van Halteren and Johannes de Wilt; Supervision, Fränzel van Duijnhoven and Hendriek Boshuizen; Validation, Moniek van Zutphen; Visualization, Moniek van Zutphen; Writing – original draft, Moniek van Zutphen; Writing – review & editing, Moniek van Zutphen, Fränzel van Duijnhoven, Evertine Wesselink, Ruud Schrauwen, Ewout Kouwenhoven, Henk van Halteren, Johannes de Wilt, Renate Winkels, Dieuwertje Kok and Hendriek Boshuizen. All authors have read and agreed to the submitted version of this manuscript.

Institutional Review Board Statement

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Committee on Research involving Human Subjects, region Arnhem-Nijmegen, the Netherlands (protocol code 2009/349, date of approval: 27 April 2010).

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

Data availability Statement

Because the data consist of identifying cohort information, some access restrictions apply, and therefore they cannot be made publicly available. Requests for data of the COLON study can be sent to Dr. Fränzel van Duijnhoven, Division of Human Nutrition and Health, Wageningen University & Research, the Netherlands (e-mail:franzel.vanduijnhoven@wur.nl).

Conflicts of interest

The authors declare no conflict of interest. The funders had no role in the design, execution, interpretation, or writing of the study.

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Abdominal Skeletal Muscle Mass, Fat Mass, and Mortality among Men and Women with Stage I-III Colorectal Cancer. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology* **2020**, *29*, 956-965, doi:10.1158/1055-9965.epi-19-1134.

Supplementary material

Supplementary Table S1. Overview of all post-diagnosis lifestyle variables included in the Random Survival Forest models.

Lifestyle variables	Description
Diet (g/day)	
Fruits & vegetables	Any type of fruits and vegetables
Fruits	Any type of fruits
Vegetables	Any type of vegetables
Legumes	Any type of legumes
Ratio of wholegrains to refined grains	
Wholegrains	Brown and wholemeal bread, rye bread, oats, wholemeal pasta, brown rice
Refined grains	White bread, croissant, cornflakes, muesli, white pasta, white rice
Fast foods, snacks, and sweets	French fries, crisps, pastry and biscuits, savoury snacks, candy, sauces, pizza, pancakes, sandwich fillings high in sugar of fat, refined grains, sweet dairy desserts, and diet soft drinks
Red and processed meat	Any type of red and processed meat
Red meat	Steak, organ meat, beef roll, pork tenderloin, minced meat
Processed meat	Sausages, bacon, ribs, ham, cold cuts
Poultry	Any type of poultry
Fish	Any type of fish, with a maximum of 4g lean fish[1]
Eggs	Boiled and fried eggs
Soy products	Soy, bean curd, soy milk, soy drink, soy yoghurt
Dairy	Milk, yoghurt, quark, sweet dairy desserts, sweetened dairy drinks, coffee creamer, and a maximum of 40g cheese[1]
Cheese	Any type of cheese
Sugary drinks	Any type of sugary drinks including fruit juice and sweetened dairy
Tea	Any type of tea
Herbal tea	Any type of herbal tea
Coffee	Any type of coffee
Mineral water	Any type of mineral water
Alcohol-free beer	Any type of alcohol-free beer
Ethanol from alcoholic drinks	Ethanol from beer, wine, liquor
Beer	Any type of alcoholic beers
Wine	Any type of wines
Liquor	Any type of liquor
Ratio of liquid fats to solid fats	
Solid cooking fats	Butter, low-fat butter, hard margarine, solid backing/frying fat, lard
Liquid fats & oils	Soft margarine, low fat spreads, liquid cooking fats, olive oil
Potatoes	Boiled or baked potatoes
Soups	Any type of soups
Energy intake (kcal/day)	Total intake based on all FFQ items

Supplementary Table S1. Continued

Dietary fiber	Total intake based on all FFQ items
Protein	Total intake based on all FFQ items
Plant protein	Total intake based on all FFQ items
Animal protein	Total intake based on all FFQ items
Total fat	Total intake based on all FFQ items
Saturated fat	Total intake based on all FFQ items
Monounsaturated fat	Total intake based on all FFQ items
Polyunsaturated fat	Total intake based on all FFQ items
Trans fat	Total intake based on all FFQ items
Carbohydrates	Total intake based on all FFQ items
Mono- and disaccharides	Total intake based on all FFQ items
Polysaccharides	Total intake based on all FFQ items
Physical activity (min/week)	
Moderate-to-vigorous activities	All activities ≥3 MET
Walking	Leisure time and commuting
Biking	Leisure time and commuting
Gardening	≥3 MET
Sports	All sports ≥3 MET
Vigorous household activities and odd jobs	≥3 MET
Adiposity	
Body mass index (kg/m^2)	Based on self-reported height and weight
Waist circumference (cm)	Difference from 94cm (M) or 80cm (F)
Waist hip ratio (cm)	Difference from 0.95 (M) or 0.80 (F)
Smoking	
Current smoker (yes/no)	
Number smoked per day	

[1] Based on the Dutch Healthy diet index {Looman, 2017 #3527}
Abbreviations: MET, metabolic metabolic equivalent value; M, male; F, female.

Supplementary Table S2. Variables predictive of recurrence or all-cause mortality, based on variable importance, by tumor location.

Variables predictive of recurrence	**Colon** Number of times selected as predictive variable in 10 repetitions of RSF model	**Rectum** Number of times selected as predictive variable in 10 repetitions of RSF model
Stage	10	10
Adjuvant chemotherapy	10	10
Sugary drinks	10	0
Alcohol-free beer	10	5
Liquor	9	0
Trans-fats	8	1
Saturated fat	8	10
Fast foods	7	0
Soy products	0	10
Total fat	1	10
Wholegrains (percentage)	0	8
Dairy	6	0
Polyunsaturated fat	4	0
Alcohol	2	0
Physical activity	2	0
Tea	0	6
Age	0	5
Plant protein	0	3
Mono- and disaccharides	0	3
Household activities	0	2
Variables predictive of all-cause mortality		
Age	10	10
Stage	10	0
ASA classification	10	0
Fruit	10	0
Liquid fat & oil	10	0
Soup	0	10
Sugary drinks	0	10
Red meat	0	10
Processed meat	0	10
Animal protein	0	10
Chemotherapy	1	9
Fruit & vegetables	9	0
Polyunsaturated fat	2	7
Fish	0	5
Coffee	4	0
Liquor	4	0
Saturated fat	0	3

Supplementary Table S2. Continued

Potatoes	1	3
Dairy	3	0
Herbal tea	2	0
Plant protein	0	2
Beer	0	2
Education	0	2

Variables printed in *italics* are background variables, all other variables are lifestyle variables. Variables were selected as predictive based on their VIMP values. Only variables selected in ≥2 model repetitions are included in this table.

CHAPTER 8

General discussion

Table 1. Overview of the studies and main findings presented in this thesis.

Ch	Type of study	Study population	Exposure	Outcome	Main findings
			Changes		
2	Prospective cohort *COLON study*	1184 patients with stage I-III CRC	-	Change in body weight from 2y before diagnosis to 2y after diagnosis	Post-diagnosis weight gain was more common than post-diagnosis weight loss. However, hardly any pre-to-post diagnosis weight gain was observed, as post-diagnosis weight gain was mainly observed in patients who lost weight before diagnosis. Pre-to-post diagnosis weight change was similar in patients treated with and without adjuvant chemotherapy.
3	Prospective cohort *COLON study*	1072 patients with stage I-III CRC	-	Change in lifestyle in the 2y following diagnosis	Although almost everybody changed concordance with ≥1 WCRF/AICR lifestyle recommendation after diagnosis, overall lifestyle hardly changed.
			Associations		
4	Prospective cohort *COLON study*	327 patients with stage I-III CRC	Increase in physical activity	Recovery of physical functioning at 6mo after diagnosis	An increase in physical activity after CRC surgery was associated with improved recovery of physical functioning, independent of physical activity level before surgery.
5	Review of the literature	CRC patients	Lifestyle after diagnosis *(57 papers were included that reported on one or more lifestyle behavior(s))*	• All-cause mortality • CRC-specific mortality • CRC recurrence	Some, but not all, of the well-known modifiable risk factors for cancer incidence might also be associated with mortality. Only one cohort assessed recurrence. Physical inactivity, smoking, or being underweight were associated with higher mortality. Emerging evidence suggests that diets increasing energy intake may also be associated with higher mortality.
6	Prospective cohort *COLON and EnCoRe study*	1425 patients with stage I-III CRC	Overall lifestyle after diagnosis	• All-cause mortality • CRC recurrence	A healthy lifestyle (i.e. higher adherence to healthy lifestyle recommendations) after CRC diagnosis and improvement therein were not associated with recurrence, but were associated with a decreased all-cause mortality risk.
7	Prospective cohort *COLON study*	1180 patients with stage I-III CRC	55 post-diagnosis lifestyle behaviors	• All-cause mortality • CRC recurrence	Random survival forests identified sugary drinks intake as most important lifestyle behavior for recurrence. For all-cause mortality, liquid fat, fruit & vegetable, and animal protein intake were identified as most important lifestyle behaviors.

Many cancer patients question whether making lifestyle changes can improve their prognosis. However, so far it was unclear if and how people change their lifestyle after a cancer diagnosis and if a lifestyle consistent with general healthy lifestyle recommendations impacts recurrence risk and survival. Therefore, the aims of this thesis were to assess 1) changes in lifestyle after diagnosis and 2) associations between lifestyle and cancer outcomes, among colorectal cancer patients with stage I-III disease.

The main findings of this thesis are summarized in **Table 1**. First, we investigated changes in lifestyle after CRC diagnosis within the COLON study (**chapter 2-3**). With regard to changes in body weight, we noted that post-diagnosis weight gain was more common than post-diagnosis weight loss. However, hardly any pre-to-post diagnosis weight gain was observed, as post-diagnosis weight gain was mainly observed in patients who lost weight before diagnosis (**chapter 2**). Pre-to-post diagnosis weight change was similar in patients treated with and without adjuvant chemotherapy (**chapter 2**). Regarding changes in overall lifestyle, defined by the World Cancer Research Fund / American Institute for Cancer Research (WCRF/AICR) score, overall lifestyle hardly changed after CRC diagnosis (**chapter 3**). Second, we investigated associations between lifestyle after CRC diagnosis and cancer outcomes (**chapter 4-7**). An increase in physical activity after CRC surgery was associated with improved recovery of physical functioning, independent of physical activity level before surgery (**chapter 4**). In **chapter 5** we gave an overview of the available literature regarding lifestyle after CRC diagnosis in relation to all-cause and CRC-specific mortality and recurrence risk. Our review revealed that some, but not all, of the well-known modifiable risk factors for cancer incidence might also be associated with mortality after CRC diagnosis. Our review also revealed that only one cohort assessed CRC recurrence risk. We were able to assess recurrence risk as both the COLON and EnCoRe study collected data on CRC recurrences. Based on both studies, we concluded that a healthy lifestyle after CRC diagnosis and improvement therein were not associated with recurrence, but were associated with a decreased all-cause mortality risk (**chapter 6**). With a data-driven method, random survival forests, we identified several lifestyle behaviors related to either recurrence –sugary drinks- or all-cause mortality -fruit & vegetables, liquid fats & oils, and animal protein (**chapter 7**).

Below the main findings regarding associations between lifestyle and recurrence and all-cause mortality are summarized and placed into broader perspective to give an overview of all the available evidence. Subsequently, possible biologic mechanisms linking lifestyle and all-cause mortality or recurrence are described. In **chapters 2-7**, methodological considerations specific for the respective chapters have been addressed. Therefore, these issues will not be discussed in detail in this chapter. Methodological considerations are addressed to judge the strength of the available evidence regarding lifestyle and outcomes after CRC. Finally, implications for clinical practice and future research are described.

Overview of available evidence

Figures 1-3 summarize all published studies to date that assessed either overall lifestyle (**Figure 1**), dietary patterns (**Figure 2**), or foods and food groups (**Figure 3**) regarding CRC recurrence and survival, together with our findings from **chapter 6-7**. The inner ring shows the exposure, while the outer ring indicates the results of each study with the given exposure. The results regarding CRC recurrence and all-cause mortality are shown separately. I also shortly summarize the latest evidence regarding physical activity and body weight, together with our finding from chapter 6-7.

Note on the outcome recurrence: CRC recurrence was defined differently among studies. In some studies, the events included in the definition of recurrence are local, regional and/or distant recurrence (metastasis). Other studies included second primary cancer, CRC-mortality, any cause of death, or any combination of these events under recurrence. In this thesis, studies that included death as event under recurrence were excluded regarding the recurrence outcome.

Overall lifestyle

Overall lifestyle is defined with several scores that reflect adherence to healthy lifestyle recommendations of different organizations (**Figure 1**). Lifestyle scores were assigned based on concordance with two sets of cancer prevention guidelines–from the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) and the American Cancer Society (ACS)–and national disease prevention guidelines (1-3). We concluded that a healthy lifestyle after CRC diagnosis was not associated with recurrence risk (**chapter 6**). In contrast, the only other study that examined this association concluded that a lifestyle most consistent with the ACS guidelines after CRC diagnosis was associated with a lower recurrence risk (4).

For all-cause mortality, we concluded that an overall healthy lifestyle after CRC diagnosis was associated with lower all-cause mortality (**chapter 6**). A lifestyle more consistent with the ACS recommendations was associated with a lower all-cause mortality risk. The same tendency was observed for higher WCRF/AICR and national lifestyle scores, although these associations were statistically nonsignificant. In line with these results, a previous study among 992 stage III colon cancer patients also observed an association between higher ACS scores and lower all-cause mortality (4). Higher WCRF/AICR scores were not associated with lower all-cause mortality among 380 female long-term survivors (5).

Figure 1. Observed associations between lifestyle after colorectal cancer diagnosis and recurrence or all-cause mortality in previous prospective cohort studies and this thesis.[a]

[a] The outer ring shows the observed association within a specific cohort with the exposure shown in the inner ring. Observed associations were categorized as protective (green), null association (grey), or harmful (red). Categorization of the association was based on adjusted hazard ratios and statistical significance. Statistically significant associations are depicted in bright colors (■) and statistical nonsignificant protective (■) or harmful associations (■) are depicted in muted colors. Abbreviations: ACS, American Cancer Society; WCRF/AICR, World Cancer Research Fund/American Institute for Cancer Research; CALGB89803, Cancer and Leukemia Group B 89803; IWHS, Iowa Women's Health Study.

Dietary patterns

There are two approaches to define dietary patterns: i) scores that reflect adherence to dietary recommendations and ii) data-driven methods to derive empirical dietary patterns, which are often labeled as Prudent (i.e. 'healthy') and Western (i.e. 'unhealthy') (**Figure 2**). Both approaches generally reveal a similar healthy and unhealthy pattern regarding the included food groups (6). A healthy dietary pattern is often characterized by high intakes of fruits, vegetables, whole grains, and poultry (6). The 'unhealthy' dietary pattern is often characterized by high intakes of refined grains, red and processed meats, desserts, and potatoes (6).

In **chapter 6**, we used scores that reflected adherence to the Dutch dietary recommendations (DHD-15 index (3)) and to the dietary recommendations included in the WCRF/AICR or ACS cancer prevention guidelines. We concluded that a higher adherence to dietary recommendations after CRC diagnosis was not associated with recurrence (**chapter 6**). No other study assessed the association between adherence to dietary recommendations after CRC diagnosis and recurrence. One study assessed this association for data-driven dietary patterns (7). Also, this study found no association between a 'healthy' dietary pattern and CRC recurrence. In contrast, the 'unhealthy' dietary pattern was associated with higher risk of recurrence.

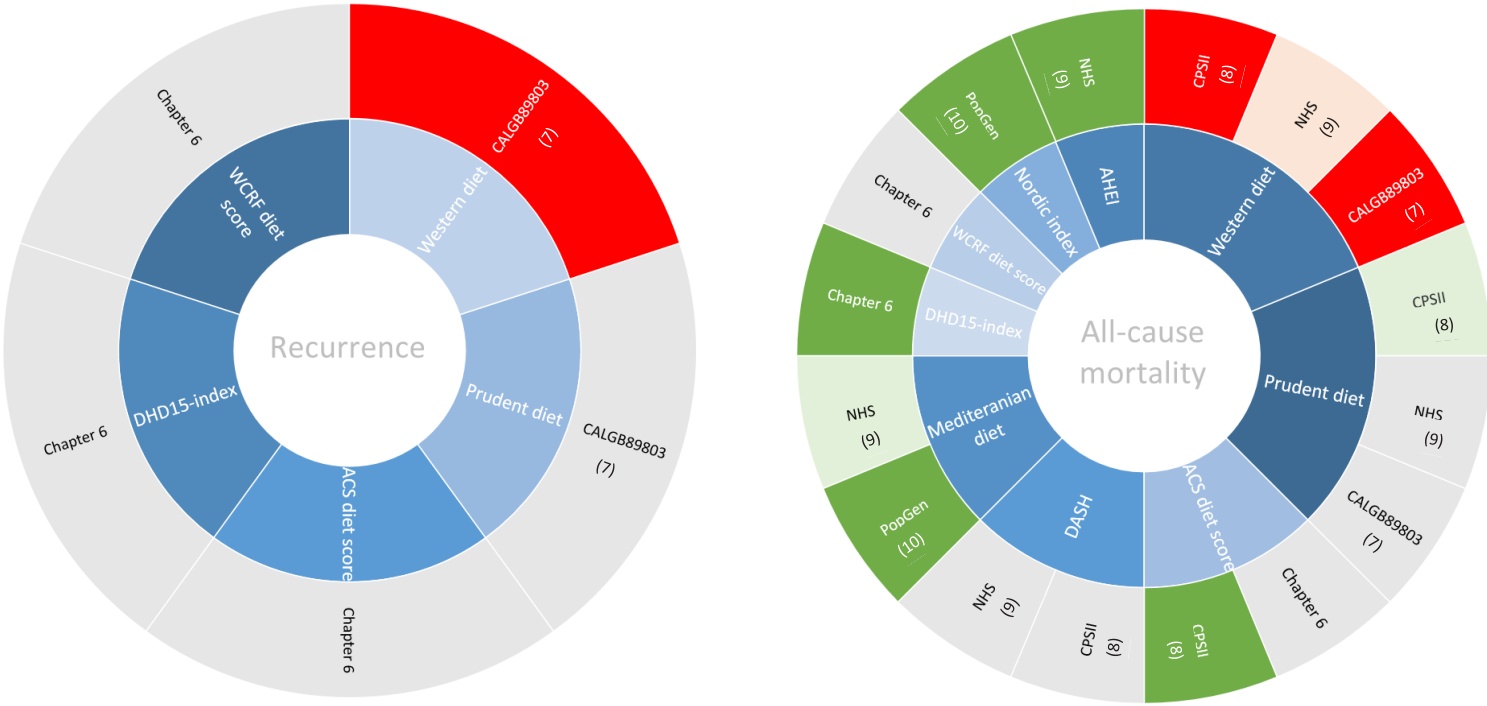

Figure 2. Observed associations between dietary patterns after colorectal cancer diagnosis and recurrence or all-cause mortality in previous prospective cohort studies and this thesis.[a]

[a]The outer ring shows the observed association within a specific cohort with the exposure shown in the inner ring. Observed associations were categorized as protective (green), null association (grey), or harmful (red). Categorization of the association was based on adjusted hazard ratios and statistical significance. Statistically significant associations are depicted in bright colors (or) and statistical nonsignificant protective ( ) or harmful associations ( ) are depicted in muted colors. Abbreviations: ACS, American Cancer Society; DHD, Dutch Healthy Diet; WCRF, World Cancer Research Fund/American Institute for Cancer Research; DASH, Dietary Approaches to Stop Hypertension; AHEI, Alternate Healthy Eating Index; CALGB89803, Cancer and Leukemia Group B 89803; CPSII, Cancer Prevention Study II Nutrition Cohort; NHS, Nurses' Health Study.

For all-cause mortality, we also observed no association with adherence to dietary recommendations after CRC diagnosis (**chapter 6**). We noted one exception, in which higher adherence to the Dutch dietary recommendations was associated with lower all-cause mortality. Previous studies reported that higher adherence to dietary recommendations after CRC diagnosis, including the ACS diet score, Mediterranean diet, Nordic index, and healthy eating index, was generally associated with lower all-cause mortality (8-10), but this association was not observed for the dietary approaches to stop hypertension meal plan (DASH) (8, 9). The data-driven 'healthy' dietary pattern, showed no associations with all-cause mortality (7-9). In contrast, the data-driven 'unhealthy' dietary patterns was generally associated with higher all-cause mortality (7-9).

Foods and drinks

In **chapter 7**, we used a data-driven method for exploratory identification of post-diagnosis lifestyle behaviors important for CRC prognosis. Sugary drink intake was the most important lifestyle variable for recurrence. Higher intakes were associated with increased recurrence risk (**Figure 3A**). The only previous study that assessed this association also showed an increased risk of recurrence with higher intakes of sugary drinks among 1011 stage III colon cancer patients (11). In the same cohort, also a higher intake of refined grains after CRC diagnosis has been associated with increased recurrence risk (12). In contrast, higher intakes of fish and diet drinks after CRC diagnosis have been associated with a lower recurrence risk in this cohort (13, 14). No statistically significant associations with recurrence were observed for intake of wholegrains (12), coffee (15), tea (15), or nuts (16).

For all-cause mortality, we identified fruit & vegetables, liquid fat & oil, and animal protein intake as most predictive lifestyle behaviors (**chapter 7**). These food groups showed non-linear associations with all-cause mortality. Previous studies generally showed lower all-cause mortality with higher intakes of fruits & vegetables (4, 9, 17), wholegrains (9, 12, 18), or coffee (15, 19) after CRC diagnosis (**Figure 3B**). A recent meta-analyses for all-cause mortality indeed revealed post-diagnosis wholegrain (HR 0.83; 95%CI 0.69-0.99) and coffee (HR 0.69; 95%CI 0.55-0.98) intake as protective factors for all-cause mortality in CRC survivors (20). An increased risk all-cause mortality risk has been observed for higher intake of sugary drinks after CRC diagnosis (9, 11). No associations with all-cause mortality have been observed for red & processed meat (4, 9, 21) and fish intake (13, 22, 23), while mixed findings have been observed for nut intake (9, 16). Some foods and drinks were only included once as exposure. A higher intake of refined grains (12) was associated with higher all-cause mortality and a higher intake of diet drinks (14) or dairy (24) with lower all-cause mortality. No associations with all-cause mortality were observed for fat (25) or tea (15) intake after CRC diagnosis.

Figure 3A. Observed associations between food or drink intake after colorectal cancer diagnosis and recurrence in previous prospective cohort studies and this thesis.a

[a] The outer ring shows the observed association within a specific cohort with the exposure shown in the inner ring. Observed associations were categorized as protective (green), null association (grey), or harmful (red). Categorization of the association was based on adjusted hazard ratios and statistical significance. Statistically significant associations are depicted in bright colors (■ or ■) and statistical nonsignificant protective (■) or harmful associations (■) are depicted in muted colors. Abbreviations: CALGB89803, Cancer and Leukemia Group B 89803.

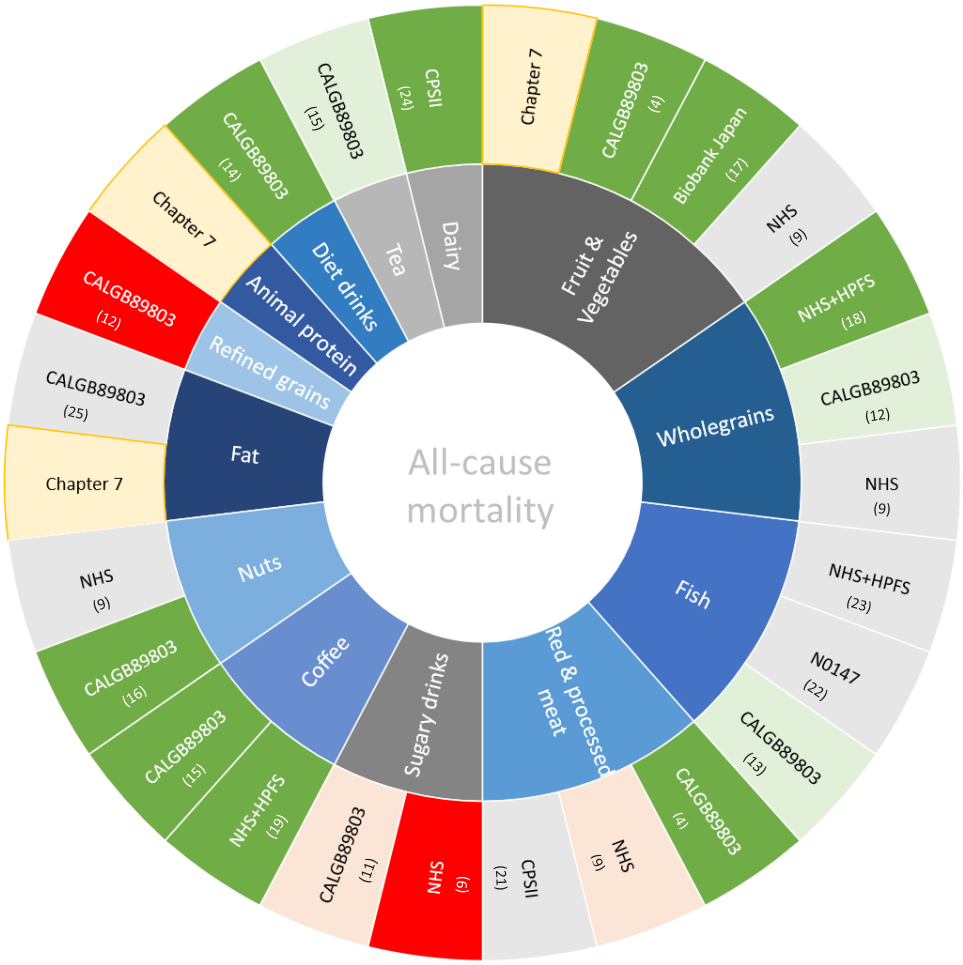

Figure 3B. Observed associations between food or drink intake after colorectal cancer diagnosis and all-cause mortality in previous prospective cohort studies and this thesis.[a]

[a] The outer ring shows the observed association within a specific cohort with the exposure shown in the inner ring. Observed associations were categorized as protective (green), null association (grey), or harmful (red). Categorization of the association was based on adjusted hazard ratios and statistical significance. Statistically significant associations are depicted in bright colors (■ or ■) and statistical nonsignificant protective (■) or harmful associations (■) are depicted in muted colors. Foods identified as import regarding all-cause mortality by random survival forests are depicted in yellow. Abbreviations: CALGB89803, Cancer and Leukemia Group B 89803; NHS, Nurses' Health Study; HPFS, Health Professional Follow-Up study; CPSII, Cancer Prevention Study II Nutrition Cohort.

Physical activity

As previously described in **chapter 5**, several meta-analyses found an inverse association between highest versus lowest amounts of physical activity after diagnosis and all-cause mortality and CRC-mortality in CRC survivors based on seven prospective cohort studies (26-29). This finding was confirmed in a more recent meta-analysis based on ten prospective cohort studies (30). Only one study included recurrence as outcome and showed that higher levels of physical activity were associated with lower recurrence risk (31). In line with these findings, we showed that concordance with the physical activity recommendations was associated with lower all-cause mortality and recurrence, although these associations were not statistically significant (**chapter 6**). In contrast, physical activity was not identified as an important behavior related to all-cause mortality or recurrence when we evaluated different lifestyle behaviors simultaneously (**chapter 7**).

Body weight

As previously described in **chapter 5**, studies suggest a J- or L-shaped association between post-diagnosis body mass index (BMI) and all-cause mortality or CRC-mortality. The risk of death was lowest among patients with a BMI between 25 and <30 kg/m^2. If obesity confers an additional mortality risk compared to normal weight or overweight patients remains uncertain. Nevertheless, a 2015 meta-analysis of post-diagnosis BMI concluded that obesity was associated with a modest 8% (HR 1.08; 95% CI 1.03-1.13) increased all-cause mortality compared to normal weight (32). We did not observe statistically significant associations between post-diagnosis obesity and all-cause mortality or recurrence risk (**chapter 6**). BMI was not identified as an important behavior related to all-cause mortality or recurrence when we evaluated different lifestyle behaviors simultaneously (**chapter 7**).

Conclusion

It is noteworthy that all previous studies which included recurrence as outcome are based on the same cohort of stage III colon cancer patients who were initially enrolled in the Cancer and Leukemia Group B (CALGB) 89803 study, a randomized controlled trial of adjuvant chemotherapy. Because of the limited number of studies, it remains unclear if lifestyle after CRC diagnosis is associated with recurrence risk. Sugary drink intake is the only dietary behavior that is included in more than one study that assessed recurrence. Sugary drink intake after CRC diagnosis was consistently associated with higher recurrence risk.

The number of studies that assessed the association between overall lifestyle or diet after CRC diagnosis and all-cause mortality is limited. For most of these exposures, only one to three studies are available. Although the number of studies is limited, it seems that higher adherence to healthy lifestyle or dietary recommendations is associated with improved survival. A healthy diet consists, at least partially, of a high fruit & vegetable and wholegrain intake. These food groups indeed generally showed lower all-cause mortality with higher

intakes. In line with these findings, a Western (i.e. 'unhealthy') dietary pattern after CRC diagnosis was generally associated with decreased survival.

In contrast, a larger number of prospective observational studies is available for physical activity and BMI, which allowed meta-analyses to be carried out for the outcomes all-cause mortality and CRC-mortality. For physical activity, it was concluded that higher levels of physical activity after CRC diagnosis were associated with lower mortality. For BMI, studies suggest a J- or L-shaped association with mortality.

Whether the observed associations are likely causal or not needs judgement, which is often based on (modified) Bradford Hill criteria (33-35). Important criteria are temporality, strength of the association, consistency, dose-response relationship, and biological plausibility (33). Therefore, I will first discuss possible biological mechanisms linking lifestyle and all-cause mortality or recurrence. Second, I will discuss if the current evidence is strong enough to support causality between lifestyle after CRC diagnosis and recurrence and all-cause mortality in the light of methodological considerations.

Biologic mechanisms

Biological plausibility is essential for making strong inferences from epidemiologic evidence. Therefore, I will discuss some of the possible biologic mechanisms relating lifestyle and all-cause mortality or recurrence.

All-cause mortality includes all causes of death and is, therefore, not a cancer-specific outcome in CRC patients. Many CRC patients will die of other diseases than their cancer, mainly cardiovascular diseases (36). Literature suggests that the mechanisms by which lifestyle lowers risk of mortality in the general population might also apply to cancer survivors (37-39). Those mechanisms include factors that relate to body composition (i.e. body fat and skeletal muscle), bioavailable sex hormones, insulin sensitivity, chronic low-grade inflammation, and immunosurveillance. If a healthy lifestyle after CRC diagnosis lowers all-cause mortality, this does not necessarily mean that it also lowers recurrence risk. Indeed, in **chapter 6** we concluded that a healthy lifestyle after CRC diagnosis was associated with decreased all-mortality risk, but not with recurrence. It is therefore relevant to question if there are plausible mechanisms linking lifestyle after a cancer diagnosis and recurrence risk.

The majority (60-80%) of CRC recurrences appear within the first two to three years after surgical resection (40, 41). Based on this relatively short time span, it is assumed that micrometastases or pre-cancerous lesions are already present before curative treatment. The presence of circulating tumor DNA (ctDNA) likely reflects the presence of micrometastases

(42). In CRC patients who have undergone curative resection, postoperative detection of ctDNA ranges from 10-15% of patients with stage II disease to nearly 50% in those with stage IV disease (42). Whether or not micrometastases can be fully cleared by adjuvant chemotherapy remains unclear, it is also possible the ctDNA levels are lowered below the detectable limit (42). ctDNA has emerged as a sensitive marker of recurrence. For example, after completion of adjuvant chemotherapy, ctDNA-positive patients were 17 times more likely to have a recurrence than ctDNA-negative patients with stage I-III CRC (43).

Lifestyle behaviors may impact the release and growth of micrometastases into recurrent cancer. Data from in vitro and rodent studies suggest that physical activity may regulate the release of cancer cells from the tumor and can reduce the ability of cancer cells to form metastases (44). Furthermore, several interrelated mechanisms are presumed to influence cell growth, although this is currently not fully understood. The interrelated mechanisms most often studied in relation to lifestyle and cancer recurrence include insulin sensitivity and chronic low-grade inflammation (see box for mechanisms).

Insulin sensitivity
Insulin is a growth factor and major regulator of cell metabolism, and its effects in target cells are mediated by the insulin receptor (45). Evidence suggests that in many cancer cells, the insulin receptor is overexpressed (45). Therefore, malignant cells are overstimulated by insulin which provides a selective growth advantage to cancer cells when exposed to insulin. Therefore, all conditions of hyperinsulinemia, both endogenous (e.g., type 2 diabetes, metabolic syndrome, obesity) and exogenous (e.g. hyperinsulinemic diets, low levels of physical activity; which also influence some of the endogenous conditions) may affect risk of recurrence. Indeed, diabetic patients have been shown to be at increased risk of CRC recurrence (46).

Chronic low-grade inflammation
Cancer patients often have an irregular balance between pro-inflammatory and anti-inflammatory mechanisms, leading to chronic low-grade inflammation (47). Cytokines, such as tumor necrosis factor (TNF)α, Interleukin (IL)6, and IL8, may play a role in tumor progression by producing an optimal environment for tumor growth, reducing cell death, and promoting angiogenesis. Therefore, cytokines might contribute to survival and growth of residual micrometastases.

Besides these mechanisms, lifestyle might also have potential additive or synergistic effects on cancer treatments, including chemotherapy (38, 44). This has mainly been studied for physical activity and current insights stem for a large part from rodent studies. Physical

activity may have direct cancer-specific effects through promotion of treatment efficacy, enhanced drug tolerance, and amelioration of adverse effects (44). For example, physical activity immediately prior to radiotherapy may enhance treatment response as it affects blood circulation and oxygen delivery to tissues (44). Radiotherapy requires sufficient oxygen delivery to tumors, which is essential for promoting the generation of reactive oxidative species that facilitate the therapeutic effect (44). Physical activity might also improve chemotherapy tolerance (38, 44). Receipt of the full chemotherapy dose according to the planned treatment schedule predicts disease recurrence and a relative dose intensity < 85% is a commonly accepted clinically threshold whereby adjuvant chemotherapy effectiveness significantly worsens (48, 49). However, a systematic review of exercise and chemotherapy completion rate concluded that, although promising, the evidence for an exercise benefit to chemotherapy tolerance in cancer patients is insufficient (48).

Conclusion

In conclusion, there are some plausible biological mechanisms linking lifestyle to mortality and CRC recurrence. Most of the mechanisms by which lifestyle lowers risk of mortality or cancer incidence in the general population might also apply to all-cause mortality and recurrence risk in cancer survivors. Furthermore, lifestyle may have potential additive or synergistic effects on cancer treatments which are likely to impact recurrence risk.

Methodological considerations

There is no perfect way to establish whether observed associations between lifestyle exposures and disease outcomes are causal. Prospective cohort studies are generally characterized by large populations and longer follow-up periods. Although RCTs have the power to test cause and effect rigorously, lifestyle and diet are complex and difficult to manipulate in experimental studies. RCTs generally include selected populations with short follow-up periods. Thus, both types of prospective studies have advantages, but also disadvantages, when assessing relationships between lifestyle and long-term outcomes.

In the case of cancer survivorship studies, as well as cancer prevention studies, the available evidence is mainly based on prospective observational studies. When interpreting epidemiological evidence from observational studies one needs to decide if the evidence is strong enough to support causality. Judgements regarding causality are based on the number of studies, consistency of results between studies (based on meta-analyses), quality of the studies (i.e. factors limiting interpretation), and biological plausibility (i.e. biological mechanisms) (34, 35). The large number of cancer prevention studies generally showed consistent results without substantial unexplained heterogeneity. These studies were well-designed, and the results were reinforced by studies that investigated mechanisms linking

lifestyle and cancer incidence. Furthermore, associations were generally also consistent for different types of cancer (50).

Here, I will discuss if the current evidence is strong enough to support causality between lifestyle after CRC diagnosis and recurrence and all-cause mortality. First, I will discuss the number of studies and consistency of results. Second, I will discuss several factors further limiting interpretation of the available evidence that are specific for cancer survivorship studies: lack of specific outcome of interest, reverse causality, confounding by treatment, and timing of exposure assessment. I will conclude with judging the available evidence.

Number of studies and consistency of results

As mentioned before, the number of studies that assessed the association between overall lifestyle or diet after CRC diagnosis is limited. For most of these exposures, only one to three studies are available. As only few studies are available for CRC survivors, it is hard to evaluate consistency of results.

In contrast, a larger number of prospective observational studies is available for physical activity after CRC diagnosis, which allowed meta-analyses to be carried out. In high versus low physical activity analyses, 9 out of 10 studies showed an inverse association with all-cause mortality, of which 7 were statistically significant (30). Highest versus lowest post-diagnosis physical activity showed a 37% reduced all-cause mortality (HR 0.63; 95%CI 0.54-0.74). The dose-response meta-analysis (based on seven studies) showed that each ten metabolic equivalent task-hour per week (MET-hour/week) increase in post-diagnosis physical activity was related to a 21% (HR 0.79; 95%CI 0.69-0.90) lower risk of all-cause mortality (30). Results for CRC-mortality were virtually identical.

The number of available studies also allowed a meta-analyses of BMI after CRC diagnosis. In obese versus normal weight analyses, 8 out of 13 studies showed an increased risk of all-cause mortality, of which 2 were statistically significant (32, 51). Obesity was associated with a modest 8% (HR 1.08; 95% CI 1.03-1.13) increased all-cause mortality compared to normal weight (32).

Overall, there is currently not enough evidence to support a judgement of a causal relationship between overall lifestyle or diet and all-cause mortality or recurrence risk. The evidence in CRC survivors seems to be quite consistent for physical activity, at least regarding the direction of the association, but not for high BMI.

Lack of a specific outcome of interest

Besides consistency of results, there are several factors further limiting interpretation of the available evidence. First, there is a lack of a specific outcome of interest. The outcome

is clearly defined in cancer prevention studies (i.e. cancer incidence), but there is variety in the outcomes in cancer survivorship studies. Cancer survivorship studies usually include all-cause mortality as outcome (**chapter 5**). Although all-cause mortality is a clearly defined outcome, all-cause mortality cannot be considered as a specific cancer outcome. As survival rates of CRC are relatively good, many CRC patients will die of other diseases, mainly cardiovascular diseases (36). Another commonly included outcome is CRC-mortality (**chapter 5**). Cancer mortality is subject to the accuracy of death certification, which can be challenging, especially in older adults representing the majority of CRC cases (52, 53). In contrast to cancer incidence data derived from cancer registry data, which are subject to strict quality control procedures, death certificates are very rarely validated against any pathological or clinical information (52). Another key outcome in cancer survivorship studies is cancer recurrence (54). As information about recurrence is not routinely collected in cancer registries or other population-based data sources, and is only available in medical records, this outcome is rarely included in cancer survivorship studies (**chapter 5**). Our results presented in **chapter 6 and 7** suggest that lifestyle behaviors may impact differently on recurrence and all-cause mortality. Thus, the available evidence should be judged for each outcome separately. Also other, more short-term, outcomes are relevant to CRC patients, such as physical functioning, cancer-related fatigue, and health related quality of life (55). There is strong evidence that physical activity after a cancer diagnosis can improve these health outcomes (55), but this is unclear for other lifestyle behaviors.

Reverse causality

A limitation of cancer survivorship studies is that they are prone to be biased by reverse causality, especially studies investigating physical activity or underweight (i.e. CRC progression leading to less physical activity and/or underweight). Reverse causality is more likely with short follow-up, as people who will die within several years because of illness might already have lowered physical activity levels at exposure assessment. Reverse causality cannot be ruled out in observational survivorship studies and judgement is needed how severely this bias can affect the results. To assess the impact of reverse causality, different lag times (between physical activity assessment and time at risk) were applied among healthy women participating in the Nurses' Health Study (56). Physical activity with no or short lag-time showed the strongest association with mortality, and application of a two year lag between physical activity assessment and period of risk attenuated the magnitude of the association, while longer time lags greater than two years only minimally further attenuated the association. Thus, reverse causation may amplify the magnitude of the association, but generally does not seem to alter the direction of the association. The observed association between physical activity after CRC diagnosis and mortality is, therefore, unlikely fully explained by reverse causation.

To limit reverse causality in **chapter 4**, we compared CRC patient who increased their activity levels after surgery with patients who had a stable activity level. No comparison was made regarding patients who decreased their activity levels after CRC surgery, since reverse causality is more likely among people who decreased their physical activity levels after CRC surgery. We were unable to use this strategy in **chapter 6**, as it is unpredictable how overall lifestyle is influenced by reverse causality. For example, weight loss might result in an improved lifestyle score and lower physical activity might result in a deteriorated lifestyle score. To limit reverse causality bias, some studies included a lag time between exposure assessment and time at risk, either as a sensitivity analyses or in the main analyses. We did not use this approach in **chapter 6**, because of the limited number of events. We did perform stratified analyses by cancer stage to explore reverse causation by disease severity. However, associations with all-cause mortality were similar across cancer stages (**chapter 6**).

Confounding by treatment

Furthermore, survivorship studies could be confounded by treatment. Treatments are likely to have stronger effects on the outcome than lifestyle behaviors. Treatment and lifestyle behaviors might also be associated, as socio-economic status may influence access to care, although this will differ between countries. Treatment differences due to socio-economic status are apparent in the United States, while in the Netherlands access to care is not dependent on socio-economic status. It is known that a lower socio-economic status is associated with unhealthier behavior (for example smoking and/or unhealthier dietary pattern) (57). Not all survivorship studies are adjusted for treatment. In the case of physical activity, 7 out of 10 studies adjusted for treatment, but this did not seem to explain heterogeneity of results (30). In our studies, we were able to adjust for treatment (i.e. neo-adjuvant treatment or adjuvant chemotherapy), although it did not meaningfully change our results (**chapter 6**, data not shown). Moreover, most data from previous studies comes from the Nurses' Health Study, Health Professional Follow-up Study, and CALGB89803. The participants of these studies had likely equal access to care as they were all health professionals (i.e. homogenous socio-economic status) or were randomized to strictly controlled chemotherapy regimens. It seems unlikely that confounding by treatment can fully explain observed associations between lifestyle after CRC diagnosis and all-cause mortality.

None of the studies reviewed in **chapter 5** adjusted for amount of chemotherapy received, which could potentially also lead to confounding by treatment. Clinical evidence suggests that optimal outcomes are achieved with standard chemotherapy regimens, and chemotherapy dose delays and dose reductions result in poorer outcomes (49). Intensity of treatment may also be associated with lifestyle behaviors, such as physical activity. It is possible that physical activity influences tolerance and efficacy of chemotherapy treatment (38, 44, 48). Therefore, intensity of treatment could be an intermediate between exposure and mortality (or recurrence). In this case, adjustment would remove part of the association.

Thus, it seems unlikely that potential residual confounding by treatment has a large impact on observed associations in CRC survivorship studies.

Timing of exposure assessment

Another limitation of survivorship studies is that it is not clear what the best timing of exposure assessment (i.e. pre- versus post-diagnosis) is. We focused on post-diagnosis lifestyle as this is the period in which cancer survivors can make changes to their lifestyle (**chapter 5-7**). Results from studies that relied on pre-diagnosis lifestyle cannot directly be translated into lifestyle recommendations, as patients cannot change their past behavior. However, best timing of exposure is related to the etiologic period and thus to the mechanisms through which the exposure impacts the outcome. As mentioned before, physical activity may regulate the release of cancer cells from the tumor (44). In this case, pre-diagnosis exposure might be more important than post-diagnosis exposure as in most cases the tumor is surgically removed a few weeks after diagnosis. Physical activity may also have additive or synergistic effects on anti-cancer treatment (38, 44). In this case, post-diagnosis exposure might be most relevant. General health benefits of physical activity are likely to occur both pre- and post-diagnosis, as mechanisms are likely similar in cancer survivors and the general population. Examining pre-diagnostic exposure could be complementary to examining post-diagnosis exposure, as pre-diagnosis lifestyle is less likely affected by reverse causality or treatment, but at the same time it is unclear if observed associations are independent of post-diagnosis exposure. However, in the case of CRC, lifestyle in the period before diagnosis may change. About 10% of our study population recalled pre-diagnosis changes in diet due to bowel complaints (**chapter 3**).

In **chapter 6**, we assessed associations with either pre- and post-diagnosis overall lifestyle and recurrence or all-cause mortality. Overall lifestyle, measured either at pre- or post-diagnosis, was not associated with recurrence risk. A healthier post-diagnosis lifestyle was associated with lower all-cause mortality, while no association (HR~1) was observed for pre-diagnosis lifestyle. We also assessed associations between changes in lifestyle and all-cause mortality. An improvement in overall lifestyle after CRC diagnosis was associated with a lower all-cause mortality risk compared with a stable lifestyle score, independent of pretreatment lifestyle score. The difference in observed associations between pre- and post-diagnosis lifestyle and all-cause mortality may be explained by changes in lifestyle behaviors. In **chapter 3**, we concluded that overall lifestyle hardly changed in the first two years after diagnosis and changes in overall lifestyle did not differ between subgroups based on demographic or clinical characteristics. However, almost all participants changed concordance with at least one recommendation and half of participants made simultaneous changes that resulted in both improved concordance with ≥1 recommendations and deteriorated concordance with another recommendation. These changes in lifestyle behaviors within individuals might

explain the difference in observed associations between pre- and post-diagnosis lifestyle and all-cause mortality in **chapter 6**.

Judging the evidence

In conclusion, there is currently not sufficient evidence to enable conclusions regarding overall lifestyle or diet after CRC diagnosis, because of the limited number of studies. Although more studies are available for BMI, the results are inconsistent, limiting a conclusion regarding high BMI. Furthermore, the strength of the association between obesity and mortality is weak, making it harder to eliminate study limitations as a possible explanation for the apparent effect.

For physical activity consistent results have been reported, showing that higher levels of physical activity after CRC diagnosis are associated with 37% lower all-cause mortality. The observed association is unlikely fully explained by reverse causation or confounding. Furthermore, there are some plausible biological mechanisms linking physical activity to mortality and recurrence as described earlier, although much less is known than for cancer incidence. However, expert opinions differ regarding the causal relation between physical activity and all-cause mortality. The Physical Activity Guidelines Advisory Committee of the U.S. Department of Health and Human Services judged the strength of evidence to be moderate or lower, because of the considerable probability of reverse causation (58). In contrast, the American College of Sports Medicine judged the strength of evidence to be strong (59). Generally, a judgement of strong evidence is needed to allow formulation of lifestyle recommendations for cancer survivors. Formulation of recommendations regarding overall lifestyle or dietary behaviors specific for CRC survivors is currently not warranted.

Implications for clinical practice and (future) patients

Based on the results described in this thesis, I have three recommendations for clinical practice regarding physical activity, diet, and body weight, that can potentially benefit (future) CRC patients.

Physical activity

As mentioned before, there is consistent observational evidence that engaging in physical activity after a CRC diagnosis reduces the risk of all-cause mortality for individuals diagnosed with non-metastatic CRC. Furthermore, there is strong evidence from RCTs that physical activity after a cancer diagnosis improves short-term outcomes, such as physical functioning, fatigue, and quality of life (55). This evidence is often disproportionately based on trials among breast cancer survivors, but the results are assumed to generalize across cancer types (55). Current recommendations of the American College of Sports Medicine

advise cancer survivors to avoid inactivity (55). To improve general health, cancer patients should aim to achieve the current physical activity guidelines for health (i.e. 150 min/week aerobic exercise and 2x/week strength training). More specific recommendations (including frequency, intensity, time, and type of activity) are available to improve short-term outcomes (55).

Exercise is generally safe for cancer survivors (55). Ideally, cancer survivors should receive an assessment of physical fitness before starting to exercise. However, this would create unnecessary barriers to starting activity. For this reason, no physical fitness assessments are required to start low-intensity aerobic training (i.e., walking or cycling), resistance training with gradual progression, or a flexibility program. Specific guidance for the indications of medical clearance before exercise testing and/or training, as well as adaptations for cancer survivors, have been described elsewhere (55).

As a first practical clinical intervention to support physical activity, oncologists could "Assess, Advise, and Refer" (55, 60). The oncologist could assess how many minutes per week a patient is physically active. If the answer is 150 or more, the oncologist can provide positive reinforcement; if not, the oncologist can advise to strive to do so and arrange referral to a trained exercise professional when needed. Using this approach, the oncologist can initiate and reinforce behavior change, but a trained professional should oversee and support the process of behavior change. This approach of minimal intervention has been demonstrated to be effective and well accepted by physicians for smoking cessation (60). There is some evidence that this approach also works well to improve physical activity among cancer survivors (60).

In the future, exercise could be prescribed as part of standard cancer care. Physical activity is associated with numerous health benefits, also for cancer survivors (55). The evidence-based foundation for prescribing exercise as medicine has already been described for several chronic diseases, such as cardiovascular disease (61). Likewise, physical activity may protect cancer patients from comorbidities. In addition to the general health benefits (i.e. all-cause mortality), physical activity might also have cancer-specific effects as previously mentioned (e.g. recurrence, treatment efficacy, side-effects of treatment) (44). If physical activity does indeed drive such direct anti-cancer effects, it seems logical to incorporate exercise training into standard treatment for cancer patients.

Diet

As mentioned before, there is currently not sufficient evidence to enable specific dietary recommendations after CRC diagnosis, because of the limited number of studies. However, following general lifestyle recommendations likely helps to prevent other diseases (e.g. cardiovascular disease), as well as helps to control existing comorbidities, which can

improve survival. Our results in **chapter 6** suggest that patients could either follow the national recommendations for disease prevention or cancer prevention recommendations to lower all-cause mortality. Cancer survivors are likely to benefit from healthy changes to their lifestyle, as studies among older adults without cancer have shown that adhering to a healthy diet prevents chronic diseases and lowers cardiovascular and all-cause mortality (62, 63). As a first practical intervention to support a healthy diet, oncologists could "Assess, Advise, and Refer" (55, 60) or at least make reference to websites where patients can find reliable information (e.g. voeding&kankerinfo.nl). As many patients have a sub-optimal diet and do not seem to improve their overall lifestyle after CRC diagnosis (**chapter 3**), a minimal intervention can positively impact dietary behaviors of CRC survivors (60).

Body weight

In clinical practice, not only weight loss, but also weight gain should receive attention as is stated in the Dutch Dieticians Oncology Group guidelines for bowel cancer therapy (64). Prevention of weight gain in oncological guidelines is currently focused on CRC patients treated with adjuvant chemotherapy and does not take pre-diagnosis weight change into account. Based on our results described in **chapter 2**, changes in body weight should be evaluated based on pre-diagnosis weight change and should not be limited to patients receiving adjuvant chemotherapy. Our study showed that post-diagnosis weight gain was mainly observed in patients who lost weight before diagnosis. Our results also imply that weight gain is not a common side-effect of adjuvant chemotherapy in CRC patients with non-metastatic disease, as weight trajectories were similar in patients treated with and without adjuvant chemotherapy.

CRC patients who are overweight or obese should not be advised to lose weight during active treatment. Weight loss might result in loss of muscle mass, which might worsen outcomes. Furthermore, intentional weight loss could mask involuntary weight loss, which is an important prognostic marker of poor prognosis. Moreover, formulation of recommendations regarding body weight specific for CRC survivors is not warranted based on the current evidence described in this thesis.

Implications for future research

In this thesis, associations between lifestyle after CRC diagnosis and prognosis have been evaluated. Generally, a judgement of strong evidence is needed to translate findings of prospective observational studies to evidence-based lifestyle recommendations. Such recommendations could potentially help cancer survivors to do something themselves to lower recurrence risk and to prolong survival. Based on the available studies, CRC survivors could be advised to be physically active. However, formulation of recommendations

regarding overall lifestyle or dietary behaviors specific for CRC survivors is currently not warranted. Furthermore, it remains unknown if lifestyle after CRC diagnosis can impact recurrence risk. Therefore, some suggestions for future research are given.

Recurrence should be included as key outcome in survivorship studies

Only 2% of cancer publications in the last five years deal specifically with cancer recurrence (65). Also, CRC survivorship studies usually have not included recurrence as outcome (**chapter 5**). Cancer recurrence worsens the prognosis of patients, is a factor that contributes significantly to mortality, and approximately 20% of colorectal cancer patients will experience a colorectal cancer recurrence (66, 67). Cancer recurrence is one of the greatest concerns for patients with cancer (68, 69). Furthermore, several mechanisms are proposed that relate lifestyle to CRC recurrence. Together, this warrants further research on what patients can do themselves to alter their recurrence risk.

To include recurrence as outcome in population-based cancer survivorship studies, accurate and easily available cancer recurrence data is needed. Yet information about recurrence is not routinely collected in cancer registries or other population-based data sources. Recurrence data needs to be gathered from medical records, which is labor intensive. Registries are not funded to undertake patient follow-up (other than obtaining information about vital status by linking to existing data). If data collection of cancer registries, of both cancer incidence and cancer recurrence, could be (partly) automated, it would be possible to collect recurrence data within current budget constraints. This would also result in a more standardized reporting of recurrence. Electronic pathology reporting might be used as resource needed to automatically collect information about cancer recurrences, although they do not contain the totality of information needed as not all recurrences are sent to the pathology lab (54).

Many studies used CRC-specific mortality as outcome, instead of CRC recurrence (**chapter 5**). Unfortunately, we did not have access to causes of death within the COLON and EnCoRe studies. Otherwise, we would have included both recurrence and CRC-mortality in the studies described in this thesis. If CRC-mortality data would have been available, we could have compared both outcomes and assessed if observed associations would differ between outcomes. As treatments are advancing and recurrences might be treated with curative intend (66), CRC-mortality might not be an appropriate proxy for CRC recurrence. For example, in our study population 55% of people with a recurrence died during follow-up (**chapter 6 and 7**); median follow-up time after recurrence among survivors was 3.2 year (IQR 2.6-4.5). To be able to compare recurrence and CRC-mortality associations in future studies, concrete and specific language in the informed consent should be used to get access to these data.

Prospective observational studies

As mentioned before, there are several factors that limit interpretation of prospective observational studies. The main limitation in judging the evidence for diet and CRC outcomes is the limited number of studies that is available. More studies with dietary exposures are thus needed. Other limitations include: a lack of specific outcome of interest, reverse causality, confounding by treatment, and timing of exposure assessment. These limitations cannot be easily solved. For example, longer follow-up times would be needed to limit reverse causation bias. Although this is possible regarding all-cause mortality, feasibility is limited for the outcome recurrence as most occur within 2-3 years after diagnosis (40, 41). Furthermore, biological plausibility is essential for making strong inferences from epidemiologic evidence. There are some plausible biological mechanisms linking physical activity to mortality and CRC recurrence as described earlier, although much less is known than for cancer incidence. Even less is known on biological mechanisms linking diet to cancer recurrence.

Randomized controlled trials

As mentioned before, both prospective observational studies and RCTs have advantages, but also disadvantages. Because lifestyle interventions cannot be blinded, randomized trials are also hampered by methodological challenges such as drop out if participants are not allocated to the intervention they had hoped for or contamination of the control arm as they make changes to the lifestyle behavior(s) under study. To overcome these challenges, the 'cohort multiple randomized controlled trial' design–also known as the trials within cohorts design–was proposed (70). On cohort entry, patients provide informed consent for longitudinal data collection in the context of a cohort study. Patients may give additional broad consent for randomization to future interventions (71). Patients are informed that providing broad consent for randomization entails the possibility of unknowingly serving as a control. After randomization, at a later stage, a second informed consent is only obtained from those allocated to the intervention arm. Participants in the control group are unaware of the intervention, which may limit the potential of contamination of the control arm to some extent. This staged informed consent procedure has been applied to three cohorts enrolling cancer patients. So far, participation rates of trials within these cohorts and longitudinal patient-reported outcomes return rates have been high in all three cohorts (72). Furthermore, patients participating in ongoing cohort multiple randomized controlled trials accept that their data are being used to serve as control without further notice (72). Whether the cohort multiple randomized controlled trial design is more efficient compared with traditional RCTs depends on the amount and nature of non-compliance in the intervention group (73).

Currently, there are several intervention studies developed that aim to improve adherence with the WCRF/AICR cancer prevention recommendations after a cancer diagnosis. The SoFit

trial is an example of such an trial (74). These trials will have short-term outcomes, such as fatigue. These trials do not include recurrence as outcome, as the number of participants would be too small to find effects on recurrence risk. However, these trials could gather information about recurrence later point if participants give permission in the informed consent and if interventions start relatively shortly after diagnosis. As many (relatively small) trials have interventions with the same goal (improving adherence to the WCRF/AICR guidelines) and if permission to collect recurrence data is given, these trials can ultimately be pooled to assess the effect of a healthier overall lifestyle on CRC recurrence.

Currently, two RCTs are ongoing that assess long-term outcomes among CRC survivors: one is designed to assess the impact of physical activity after adjuvant chemotherapy on disease-free survival in colon cancer survivors (75); the other is designed to assess the impact of adherence to the Norwegian food-based dietary guidelines after curative surgery on disease-free survival in colorectal cancer patients, with a major focus on long-term disease-free living and secondary prevention (76). An advantage of these RCTs is that they measure biomarkers at different time-points during the intervention. These data can be used to further explore the mechanism(s) through which lifestyle might impact cancer recurrence.

Overall conclusion

Our findings, together with previous studies, suggest that lifestyle after colorectal cancer diagnosis is associated with all-cause mortality. It remains unknown if lifestyle after CRC diagnosis is associated with recurrence risk, because only few studies included this outcome. Generally, a judgement of strong evidence is needed to translate findings of prospective observational studies to evidence-based lifestyle recommendations. Based on the available studies, CRC survivors could be advised to be physically active to improve physical functioning and prolong survival. However, it is too early to formulate specific dietary recommendations for colorectal cancer survivors, as the number of studies is limited and there are several factors that limit interpretation of the available studies.

Our findings provide little evidence that a colorectal cancer diagnosis triggers desirable lifestyle changes over and above lifestyle trends in the general adult population. To support an active lifestyle, oncologists should “Assess, Advise, and Refer”. This approach can initiate and reinforce behavior change, but a trained professional should oversee and support the process of behavior change. Furthermore, general lifestyle recommendations, that emphasize a healthy lifestyle and diet, seem appropriate for CRC survivors to lower all-cause mortality. Our results imply that weight gain after colorectal cancer diagnosis is only common after pre-diagnosis weight loss, and does not depend on adjuvant chemotherapy. Monitoring of changes in body weight should, therefore, not only be targeted at patients

receiving adjuvant chemotherapy and these changes should be evaluated based on pre-diagnosis weight change. In future research, recurrence should be included as key outcome to assess if cancer patients can alter recurrence risk themselves with their lifestyle and diet. Overall, I encourage CRC patients to be physically active and/or improve adherence to general healthy lifestyle recommendations to prolong survival.

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Summary

Summary

Colorectal cancer (CRC) is one of the most prevalent cancers worldwide. It is well accepted that CRC risk is highly modifiable through diet and lifestyle, but it is unclear whether diet and lifestyle after CRC diagnosis can impact prognosis. Current lifestyle recommendations for cancer survivors are the same as those for the general public to decrease their risk of cancer. They are freely available on the internet, but are not implemented in standard care. Thus, most CRC patients do not receive lifestyle advice after diagnosis. Little is known on how CRC patients change their body weight, diet, and physical activity after diagnosis. The aims of this thesis were to assess changes in lifestyle after diagnosis and to assess associations between lifestyle and cancer outcomes among CRC patients with stage I-III disease. The analyses are based on prospective cohort studies among CRC patients.

The first part of this thesis described pre-to-post diagnosis changes in body weight and lifestyle behaviors. In **chapter 2**, we examined pre-to-post diagnosis changes in body weight and compared them between those treated with and without adjuvant chemotherapy. We used data of 1184 participants of the COLON study. Body weight was repeatedly self-reported in the two years following diagnosis. At diagnosis, participants also reported usual weight two years before diagnosis. Post-diagnosis weight gain (21%) was more common than weight loss (9%). However, post-diagnosis weight gain was only common among patients who lost ≥5% weight before diagnosis. Clinically relevant weight gain after CRC diagnosis was, on average, absent in the participants without pre-diagnosis weight loss. Overall, hardly any pre-to-post diagnosis weight change was observed. Pre-to-post diagnosis weight change was similar in CRC patients treated with and without adjuvant chemotherapy (-0.1 kg, 95%CI -0.8, 0.6 versus -0.9 kg, 95%CI -1.4, -0.5).

In **chapter 3**, we assessed changes in lifestyle behaviors and overall lifestyle in the first two years following CRC diagnosis. We analyzed changes in overall lifestyle by assessing concordance with the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) recommendations among 1072 participants from the COLON study. In the two years following CRC diagnosis largest changes were noted for sugary drinks (-45 g/day) and red & processed meat intake (-62 g/week). BMI (+0.4 kg/m^2), waist circumference (+2 cm), and dietary fiber intake (-1 g/day) changed slightly. Half of participants made simultaneous changes that resulted in both improved concordance with one component and deteriorated concordance with another component of the lifestyle score. Overall lifestyle hardly changed from a mean 3.4 ± 0.9 at diagnosis to 3.5 ± 0.9 two years after diagnosis. Our findings provided little evidence that a CRC diagnosis triggers lifestyle changes over and above lifestyle trends in the general adult population.

In the second part of this thesis, we described associations between lifestyle after CRC diagnosis and outcomes. We first focused on the short-term outcome recovery of physical functioning. The association between physical activity and recovery of physical functioning after CRC surgery was assessed among 327 participants of the COLON study (**chapter 4**). Both physical activity and physical functioning were self-reported shortly after diagnosis and six months later. Higher post-surgery levels of physical activity were associated with improved recovery of physical function (P_{trend}=0.01). In contrast, activity levels before surgery were not associated with recovery (P_{trend}=0.24). An increase in physical activity after CRC surgery was associated with improved recovery of physical functioning (PR 0.57, 95%CI 0.39-0.82) compared with stable activity levels. This benefit was seen regardless of physical activity level before surgery.

Next, we focused on longer-term outcomes. The review presented in **chapter 5** summarizes the literature regarding diet, physical activity, smoking, and body composition after CRC diagnosis in relation to all-cause mortality, CRC-mortality, and recurrence. Some, but not all, of the well-known modifiable risk factors for cancer incidence might also be associated with mortality. Survival appears to be worse with increased physical inactivity, smoking, or being underweight. Diets associated with a positive energy balance may negatively impact survival. There is currently little evidence that limiting red and processed meat or alcohol intake may improve survival. Nonetheless, data relating post-diagnosis diet to colorectal cancer survival are scarce; with less than three observational studies that have examined associations for each dietary pattern or individual food after colorectal cancer diagnosis. Whether being overweight and obese after colorectal cancer diagnosis improves or worsens survival remains controversial and may depend on the measure used to assess body fatness. As only one cohort assessed CRC recurrence, it remains unknown if lifestyle impacts CRC recurrence.

In **chapter 6**, we examined associations of post-diagnosis lifestyle and change in lifestyle after CRC diagnosis with recurrence and all-cause mortality. We used data of 1425 participants from the COLON and EnCoRe study. Lifestyle was assessed at diagnosis and six months post-diagnosis. We assigned lifestyle scores based on concordance with two sets of cancer prevention guidelines – from WCRF/AICR and the American Cancer Society (ACS) – and national disease prevention guidelines. Higher scores indicate healthier lifestyles. No associations were observed for CRC recurrence. A post-diagnosis lifestyle more consistent with the ACS recommendations was associated with lower all-cause mortality risk (HR per +1 SD: 0.85, 95%CI 0.73, 0.995). The same tendency was observed for higher WCRF/AICR (HR +1 SD 0.92, 95%CI 0.78, 1.08) and national (HR +1 SD 0.90 (95%CI 0.77, 1.05) lifestyle scores, although these associations were statistically nonsignificant. Improving one's lifestyle after diagnosis (+1 SD) was associated with a lower all-cause mortality risk for the ACS (HR 0.80,

95%CI 0.67, 0.96) and national (HR 0.84, 95%CI 0.70, 0.999) scores, yet was statistically nonsignificant for the WCRF/AICR score (HR 0.94, 95%CI 0.78, 1.13).

In **chapter 7**, we identified the relative importance of various lifestyle behaviors, either included in healthy lifestyle recommendations or not, for CRC recurrence and all-cause mortality. Lifestyle behaviors were assessed six months after CRC diagnosis. These behaviors were simultaneously analyzed with Random Survival Forests (RSFs), a data-driven method, for 1180 participants of the COLON study. RSF identified sugary drink intake as most important lifestyle behavior regarding recurrence. Higher intakes were associated with increased recurrence risk. For all-cause mortality, fruit & vegetable, liquid fat & oil, and animal protein intake were identified as most important lifestyle behaviors. These behaviors showed non-linear associations with all-cause mortality.

In conclusion, our findings together with previous studies, suggest that lifestyle after colorectal cancer diagnosis is associated with all-cause mortality. It remains unknown if lifestyle after CRC diagnosis is associated with recurrence risk, because only few studies included this outcome. Generally, a judgement of strong evidence is needed to translate findings of prospective observational studies to evidence-based lifestyle recommendations. Based on the available studies, CRC survivors could be advised to be physically active to improve physical functioning and prolong survival. However, it is too early to formulate specific dietary recommendations for colorectal cancer survivors as the number of studies is limited and there are several factors that limit interpretation of the available studies. These limitations include: lack of a specific outcome of interest, reverse causality, confounding by treatment, timing of exposure assessment, and biological plausibility linking lifestyle with CRC prognosis.

The results described in this thesis have several implications for clinical practice and future research. Our findings provide little evidence that a colorectal cancer diagnosis triggers desirable lifestyle changes. To support an active lifestyle oncologists should “Assess, Advise, and Refer”. This approach can initiate and reinforce behavior change, but a trained professional should oversee and support the process of behavior change. Furthermore, general lifestyle recommendations, that emphasize a healthy lifestyle and diet, seem appropriate for CRC survivors to prolong survival. Our results imply that weight gain after colorectal cancer diagnosis is only common after pre-diagnosis weight loss, and does not depend on adjuvant chemotherapy. Monitoring of changes in body weight should, therefore, not only be targeted at patients receiving adjuvant chemotherapy and these changes should be evaluated based on pre-diagnosis weight change. In future research, recurrence should be included as key outcome to assess if cancer patients can alter recurrence risk themselves with their lifestyle and diet. Overall, I encourage CRC patients to be physically active and/or improve adherence to general healthy lifestyle recommendations to prolong survival.

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About the author

About the author

Moniek van Zutphen was born on the 28th of November 1981 in Wormerveer, the Netherlands. In 2000, she completed secondary school at 'Saenredam College' in Zaandijk, and started studying Nutrition and Health at Wageningen University. Three years later, Moniek obtained her Bachelor's degree and continued with a two-year Master's Nutrition and Health with a specialisation in Epidemiology and Public Health. As part of her study, she conducted two Master projects. The first one at the division of Human Nutrition and Health, about the effect of supplementation with cobalamin (vitamin B12) on cobalamin status in mildly cobalamin-deficient elderly, which resulted in a paper published in 'The American Journal of Clinical Nutrition'. The second one at the Public Health Service of Mid-Netherlands, about trends in the prevalence of overweight in the adult population. After that Moniek performed her Master's internship at the WHO Collaborating Centre for Obesity Prevention at Deakin University in Geelong, Australia. This 5-month internship resulted in a first-authored paper on the association between the family environment and television viewing with childhood obesity.

After obtaining her Master's degree in 2005, Moniek worked as a junior researcher at the Centre for Prevention and Health Care research within the National Institute of Public Health. She worked on several projects, mainly focused on modifiable lifestyle factors and obesity, which resulted in several publications. In 2011, she returned to the department of Human Nutrition and Health and worked as the study coordinator of the COLON study. She worked together with the research team on setting up and conducting efficient data collection and data management. Being involved in all aspects of this epidemiological study motivated her to start her PhD research within the COLON study. In 2015, Moniek prepared a grant proposal entitled: 'Lifestyle patterns after colorectal cancer diagnosis: role in cancer recurrence, comorbidities, and survival', that was funded by the Dutch Cancer Society and resulted in Moniek's PhD project.

In February 2017, Moniek started her PhD research of which the results are described in this thesis. Her project focused on lifestyle after colorectal cancer diagnosis. She joined the educational program of the graduate school VLAG, and attended several (international) conferences to present her results. In 2016, she won the poster prize at the WEON conference. Furthermore, Moniek was involved in teaching and supervising MSc thesis students and was part of the organizing committee of the PhD tour to East Canada in 2019. In April 2021, Moniek started as a postdoctoral researcher at Radboud University, Nijmegen, where she focusses on lifestyle after early stage bladder cancer diagnosis.

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Oral presentations and poster presentations

Occasion	Title	Type	Year
WEON 2016, Wageningen	Colorectal cancer patients who increase their activity after surgery are more often recovered	poster	2016
Hot topic conference: Life Course Influences and Mechanisms: Obesity, Physical Activity &Cancer, London (UK)	Colorectal cancer patients who increase their activity after surgery are more often recovered	poster	2016
Nutritional Science Days, Heeze	Weight changes in colorectal cancer patients	oral	2017
PhD tour 2017, Cambridge (UK)	Lifestyle after colorectal cancer diagnosis	oral	2017
Winter Conference 2017: Diet, nutrition and the changing face of cancer survivorship, London (UK)	Changes in body weight among colorectal cancer survivors treated with and without chemotherapy	oral	2017
Masterclass: Energy metabolism and body composition in nutrition and health research, Wageningen	Changes in body weight among colorectal cancer patients	oral	2018
WEON 2018, Bilthoven	Will I get fat? Pre-to-post diagnosis weight trajectories in colorectal cancer patients with non-metastatic disease	oral	2018
Nutritional Science Days, Heeze	Lifestyle trends in colorectal cancer survivors	oral	2018
Winter Conference 2018: Optimal diet and lifestyle strategies for the management of cardio-metabolic risk, London (UK)	Lifestyle trends in colorectal cancer survivors	poster	2018
Masterclass: Nutrition and Cancer: from Bench to Bed to Behaviour, Wageningen	Is a cancer diagnosis a trigger for health behaviour change?	poster	2019
Meeting KWF working group cancer epidemiology, Utrecht	Lifestyle patterns after colorectal cancer diagnosis	oral	2019
Famelab 2019 Wageningen heat, Wageningen	Diet after a cancer diagnosis may impact prognosis	oral	2019
Lunch lecture Hospital Gelderse Vallei, Ede	Voeding en leefstijl na diagnose van dikkedarmkanker	oral	2019
AICR 2019 Research Conference: Beyond the Blueprint - Diet, obesity, physical acitivity & cancer, Chapel Hill (USA)	Is a cancer diagnosis a trigger for health behaviour change?	poster	2019
COLON participant day, Wageningen	Beweging, gewicht en voeding na darmkanker	oral	2019
Course Nutrition and Cancer - Hot topics III: frontiers in research, Wageningen	Physical activity, weight and diet after colorectal cancer	oral	2019
PhD tour 2019, Canada	Lifestyle after colorectal cancer diagnosis	oral	2019
Course Nutrition and Cancer - Hot topics, Wageningen	Lifestyle after colorectal cancer diagnosis	oral	2020

Overview of completed training activities

Discipline specific courses and activities	Organiser and location	Year
Courses		
Energy metabolism and body composition in nutrition and health research	VLAG, Wageningen, NL	2018
Exposure Assessment in Nutrition Research	VLAG, Wageningen, NL	2018
Masterclass: Nutrition and Cancer: from Bench to Bed to Behaviour	VLAG, Wageningen, NL	2019
Famelab 2019 Wageningen heat	WUR, Wageningen, NL	2019
Conferences and meetings		
WEON	VvE, Wageningen, NL	2016 & 2018
Hot topic conference: Life Course Influences and Mechanisms: Obesity, Physical Activity & Cancer	WCRF/World Obesity Federation, London, UK	2016
Nutritional Science Days	NAV, Heeze, NL	2017 & 2018
18e Food for Thought	Alliantie Voeding en Gezondheid, Ede, NL	2017
Winter Conference 2017: Diet, nutrition and the changing face of cancer survivorship	London, UK	2017
NAV publiekslezing 2018	NAV, Driebergen, NL	2018
Publiekslezing Voeding, sport en bewegen	WUR, Wageningen, NL	2018
Presentation third Export Report WCRF	WCRF, Amsterdam, NL	2018
International Early Career Nutrition Research Championship	Nutrition Society, London, UK	2018
Winter Conference 2018: Optimal diet and lifestyle strategies for the management of cardio-metabolic risk	Nutrition Society, London, UK	2018
Bijeenkomst KWF werkgemeenschap kanker epidemiologie	IKNL/KWF, Utrecht, NL	2019
AICR 2019 Research Conference: Beyond the Blueprint - Diet, obesity, physical acitivity & cancer	AICR, Chapel Hill, USA	2019
Symposium - Pioneering Nutrition	WUR, Wageningen, NL	2019
Symposium Towards healthy and sustainable diets for European consumers	TiFN/WUR, Wageningen, NL	2020
Interpretation of observational studies: the good, the bad and the sensational	Nutrition Society, Online	2021
AICR's Lifestyle & Cancer Symposium: Evidence Matters	AICR, Online	2021
General courses and activities		
Chemometrics	VLAG, Wageningen, NL	2016
Workshops networking	WUR/YoungWUR, Wageningen, NL	2017
Symposium 'Publish for Impact'	WGS/Library, Wageningen, NL	2017
Masterclass Mixed Models	VLAG, Wageningen, NL	2017
Symposium 'Go your own way, carrièreperspectief voor junior epidemiologen'	VvE, Utrecht, NL	2017
Lezingen working in industry / carriereperspectief	VLAG/YoungWUR, Wageningen, NL	2017 & 2018

PhD workshop carousel	WGS, Wageningen, NL	2017 & 2018
Symposium 'Keep calm and be a responsible junior epidemiologist'	VvE, Nijmegen, NL	2017
Workshop 'How to manage your work life energy'	YoungWUR, Wageningen, NL	2018
Reviewing a Scientific Paper	WGS, Wageningen, NL	2018
Workshop 'How to 'own the room' without words'	YoungWUR, Wageningen, NL	2018
Symposium "Your Epidemiological Career, Your Future"	VvE, Amsterdam, NL	2018
Nutritional Leadership Workshop: To discourage or to encourage, how to balance?	NAV/ENLP, 's Hertogenbosch, NL	2018
Workshop 'Beyond Connection"	YoungWUR, Wageningen, NL	2018
Effective behaviour in your professional surroundings	WGS, Wageningen, NL	2018
Scientific Writing	WGS/Wageningen in'to language, Wageningen, NL	2018
Famelab presentation workshop	WUR, Wageningen, NL	2019
Pitch training	WUR, Wageningen, NL	2019
Workshop Lifesciences with Industry	Lorentz Center, Leiden, NL	2019
Career Orientation	WGS, Online	2020
Other activities		
Preparation of PhD research proposal	WUR, Wageningen, NL	2017
PhD study tour to UK	WUR, UK	2017
Staff seminars & Chair group meetings	WUR, Wageningen, NL	2017-2021
NAD paperclub	WUR, Wageningen, NL	2017-2021
ECS_65800 Intuitive Intelligence	WUR, Wageningen, NL	2017
PhD study tour to Canada (treasurer)	WUR, Canada	2018-2019

Colophon

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