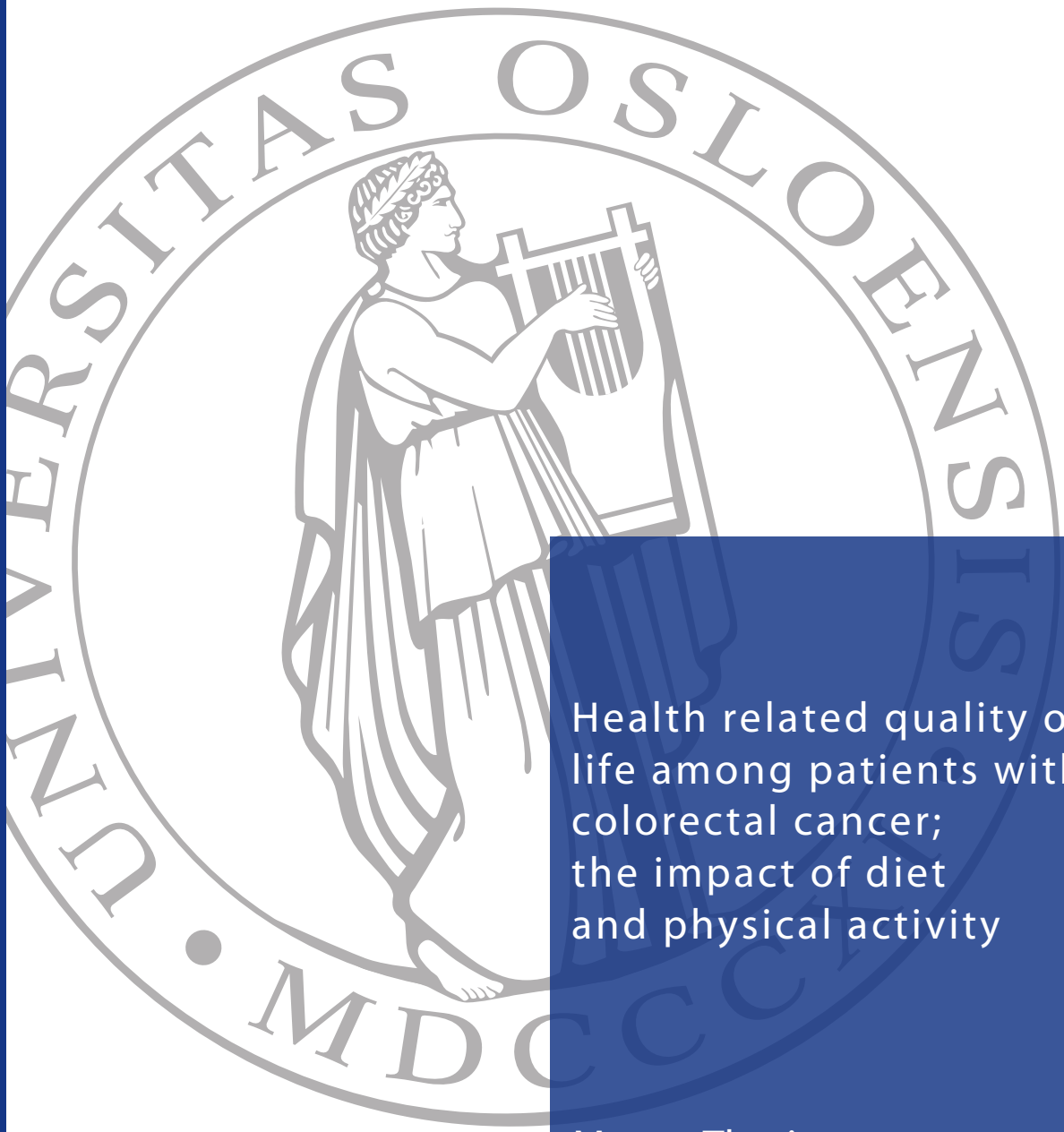

Health related quality of life among patients with colorectal cancer; the impact of diet and physical activity

Master Thesis

by

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May 2015

Health related quality of life in colorectal cancer patients; the impact of diet and physical activity

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Abstract

Objective: The main objectives of this thesis were to: (i) characterize the health related quality of life (HRQOL) in newly diagnosed colorectal cancer (CRC) patients in comparison with a reference population; (ii) investigate whether anthropometric measures, physical performance, diet and clinicopathological characteristics were associated with HRQOL; and (iii) investigate the effect of a six months diet and lifestyle intervention on HRQOL in CRC patients.

Subjects and methods: This master thesis reports on a subpopulation (n=137, aged 50-80 years) within 'The Norwegian Dietary Guidelines and Colorectal Cancer Survival Study', a randomized clinical intervention trial in surgically treated CRC patients. The patients were randomized into an intervention group (diet and physical activity) or a control group (physical activity). At time of analysis 89 patients had completed the 6-month follow-up visit. HRQOL was assessed in the CRC patients by the SF-36 questionnaire at baseline and at 6-month follow-up. Measures of anthropometry and physical performance, compliance questionnaire for dietary information and clinicopathological characteristics were also collected from the participants. The normal reference population, (n=880, aged 50-80 years) was selected from a general Norwegian population from 1995.

Results: The interim results from this study suggest that the CRC population have a poorer HRQOL at baseline compared to the 1995 Norwegian reference population. The CRC population had a 31 % lower score (i.e. worse HRQOL) in the 'role-physical' (Δ=19.8 points, p=<.001), 9 % lower score in 'vitality' (Δ=5.6 points, p=.007), and 9.2 % lower score in the 'social functioning' scales (Δ=7.7 points, p=.001) as well as 28 % lower score for the 'health transition' item (Δ=16 points, p=<0.001). Age and gender differences in HRQOL were less distinct in the CRC population as compared with the reference population. In the CRC patients, several clinicopathological variables were negatively associated with HRQOL, whilst increased muscle mass and improved physical performance was positively associated with HRQOL. Compared to the controls, the intervention group did not change any of the HRQOL scales over the 6 month intervention period. However, a statistically significant increase was found for all SF-36 scales for the entire subpopulation.

Conclusions: This study confirms that CRC patients have a lower HRQOL compared with the reference population and that HRQOL is associated with the severity of the disease, treatment, and measures of physical performance. The lack of intervention-effects on HRQOL might be due to the limited number of participants, a limited time frame of the intervention or differences in baseline characteristics between the groups. Normal reconstitution after treatment may also have masked an eventual effect of the diet intervention. Furthermore, it is possible that both groups have gained positive effects from the physical activity intervention.

List of abbreviations

AICR	American Institute for Cancer Research
AJCC	American Joint Committee on Cancer
BMI	Body mass index
COPD	Chronic obstructive pulmonary disease
CRC	Colorectal cancer
CRC-NORDIET	Norwegian Dietary Guidelines and Colorectal Cancer Survival Study
CVD	Cardiovascular disease
FFQ	Food frequency questionnaire
HRQOL	Health related quality of life
ICD	International classification of diseases
QOL	Quality of life
SF-36	Short form 36
TNM	Tumor node metastasis
WCRF	World Cancer Research fund
WHO	World Health Organization

List of tables

List of figures

Table of contents

1 Introduction

This master thesis is conducted within the "Norwegian Dietary Guidelines and Colorectal Cancer Survival Study" (CRC-NORDIET Study) which is a multicenter randomized controlled, parallel two-arm intervention trial. The primary aim of the CRC-NORDIET study is to investigate the effect of the Norwegian food-based dietary guidelines on overall mortality, cancer recurrence, relapse and comorbidities among patients radically treated for colorectal cancer (CRC).

1.1 Cancer – incidence and survival

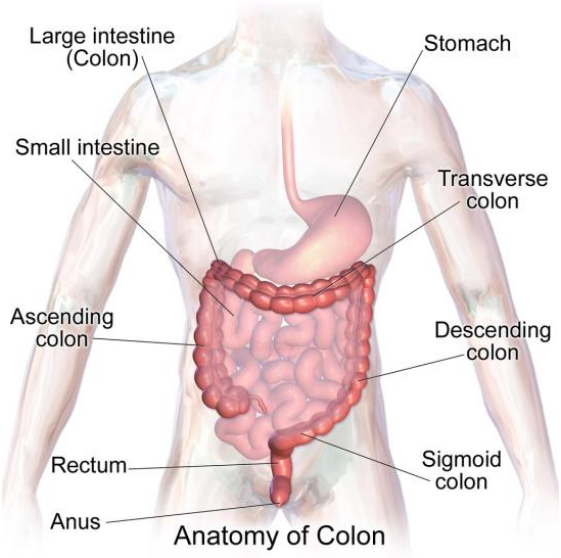
Worldwide, the overall burden of cancer continuous to increase. According to the World Health Organization (WHO) (1), estimates for 2011 indicate that cancer now causes more deaths than all coronary heart disease or all strokes. Lung, liver, stomach, breast and CRC accounts for the most cancer deaths each year (1). The continuous increase in cancer prevalence is due to several factors, including growth of the world population, aging, improved diagnostic routines and adoption of cancer-causing behaviors (2). It is estimated that 30 % of cancer deaths are due to the five leading behavioral and dietary risk factors; high body mass index (BMI), low fruit and vegetable intake, lack of physical activity, tobacco and alcohol use (1). Within the two next decades, it is expected that annual cases of cancer will rise from 14 million in 2012 to 22 million worldwide (1).

1.2 Colorectal cancer

1.2.1 Anatomy and functions of the large intestine

CRC is defined as cancer developing in the tissues of the colon or rectum. Together with the cecum and the anal canal, the colon and rectum constitute the large intestine (3) (**Figure 1**). The colon is the longest part of the large intestine and comprises four sections; the ascending colon, the transverse colon, the descending colon and the sigmoid colon. The ascending and transverse sections are collectively referred to as the proximal colon, while the descending and sigmoid colon are referred to as the distal colon (4). The main function of the colon is to absorb water and mineral nutrients from the food matter. The chyme is mixed with mucus and

bacteria from the colon before the waste (feces) left from this process passes into the rectum and is then expelled through the anal canal and anus (4).



Figur 1 Anatomy of the large intestine. The large intestine can be divided into four parts; the cecum, the colon, the rectum and the anal canal. The colon, the largest section of the large intestine, is further divided into the ascending, the transverse, the descending and the sigmoid colon. The picture is obtained from Wikipedia. Source: Wikiversity Journal of Medicine (Blausen Gallery 2014).

1.2.2 Incidence and survival

CRC is the fourth most common cause of death from cancer, and is fatal in just under half of all cases (5). Furthermore, CRC is the third most common cancer in the world, with approximately more than 1.3 million new cases each year (6). CRC is most prevalent in the western parts of the world; with many lifestyle-related risk factors proposed to contribute to the higher incidence (7). The highest incidence rates are found in Australia, New Zealand, Europe and North America, whereas the lowest rates are found in Africa and south-central Asia (8). It is more common in men than in women (9).

Incidence (age-standardized rate per 100.000) of CRC in Norway is among the highest in the world, particularly among women. In fact, Norwegian men and women have been on the top of the age-standardized incidence list among the Nordic countries for the last 20 years (6). In Norway, the average number of new cases of CRC between 2004 and 2008 were about 3500 cases per year, an increase in incidence of about 750 cases per year compared to the 5-year

period from 1989-1993 (10). In addition, there has been a substantial increase in the 5-year survival rate for CRC patients. The 5-year survival for CRC increased from 30 % to 60 % from the period of 1969-1973 to 2007-2011, with a slightly higher survival rate among women than in men (10). It is also estimated a doubling of CRC survivors by the year 2025 (11). Cancer survivors include all patients diagnosed with cancer, both those with active disease and those who have recovered (9). The increasing incidence combined with improved survival rate, contribute to the fast growing population of CRC survivors (10). However, the 5-year survival is still lower in Norway compared to many other countries like, Sweden, Australia and Canada (12).

1.2.3 Pathogenesis

About 95 % of CRC's are adenocarcinomas, cancers originating from the glandular tissue (9). These cancers most often arise from adenomatous polyps and can be further classified by histologic grade (see **Table 2**) (9). As for other cancers, CRC develops as a complex interplay between inherited and environmental factors through a multistep process of accumulated DNA damage and genetic imprinting's (9). Most CRCs develop slowly over years, but the age onset of CRC symptoms depend on both heritage and environmental factors. It is estimated that approximately 5-10 % of all CRCs are a consequence of known hereditary factors (9). Those with a family history of CRC have up to a threefold higher risk of developing the disease and the disease-onset is often at a young age (9, 13, 14). Inflammation is closely related to the pathogenesis of cancer and inflammatory bowel diseases, such as ulcerative colitis and Crohn's disease are known to predispose to CRC (15-17).

1.2.4 Environmental risk factors

Geographic variation in the incidence of CRC, as well as observations from migrant studies, indicates that several life style factors play an important role in the etiology of CRC. These include diet, physical activity, diabetes and obesity (18-22). See **Table 1** for an overview of the risk factors and their degree of evidence. According to the continuous update project report by World Cancer Research Fund/American Institute of Cancer Research (WCFR/AICR); 'Food, Nutrition, Physical Activity, and the Prevention of Colorectal Cancer' (2011) (23), there is convincing evidence that red and processed meat, body fatness, abdominal fatness, factors that lead to greater adult attained height and ethanol from alcoholic drinks by men, increases the risk of CRC. By women, there is a probable increased risk of

CRC from ethanol from alcoholic drinks. In the same report they also found that it is possible that eating cheese, foods containing iron, foods containing animal fats, and foods containing sugars may increase the risk, but evidence is limited. On the contrary, there is convincing evidence that dietary fiber and physical activity protects against bowel cancer. They also reported that garlic, milk, and calcium probably have a protective effect whilst non-starchy vegetables, fruits and dietary vitamin D may offer some reduction in bowel cancer risk, but concluded that evidence is limited. It remains unclear on current evidence whether fish, the glycemic index of foods, low-fat foods, folate, vitamin C, vitamin E, selenium and dietary pattern affect bowel cancer risk.

The WCFR/AICR further claim that 45 % of all CRC incidents could be prevented with a healthy lifestyle, which entails a healthy diet, physical activity and weight maintenance. Furthermore, they have estimated that overweight and obesity accounts for up to 23 % of the CRC incidence, physical activity up to 33 % of the CRC incidence, and fruit and/or vegetable intake up to 29 % of the CRC incidence (9). In a large prospective cohort Danish study involving 55,487 individuals aged 50–64, they found that adherence to national and international recommendations for five CRC risk factors could prevent about one quarter of CRC cases (24). These risk factors included physical activity, waist circumference, alcohol, smoking and diet. In addition to an increased risk of CRC from smoking (25), it has also been associated with worse outcome after the diagnosis of CRC, with an increased risk of mortality (26). Clearly, promoting healthy lifestyle behaviors is of great importance for the prevention of CRC.

Table 1 Overview of modifiable risk factors of CRC

Degree of evidence	Decreases risk	Increases risk
Convincing	Physical activity Foods containing dietary fiber	Red meat Processed meat Alcoholic drinks (men) Body fatness Abdominal fatness Adult attained height
Probable	Garlic Milk Calcium	Alcoholic drinks (women)
Limited – suggestive	Non-starchy vegetables Fruits Foods containing vitamin D	Foods containing iron Cheese Foods containing animal fats Foods containing sugars
Limited – no conclusion	Fish; Glycemic index; folate; vitamin C; vitamin E; selenium; low fat; dietary pattern	

Overview of modifiable risk factors of CRC based on the continuous update project report 'Food, Nutrition, Physical Activity and the Prevention of Colorectal Cancer' produced by WCRF/AICR, 2011 (23)

1.2.5 Diagnosis

CRC can be symptomatic or asymptomatic at presentation. Asymptomatic CRCs can be detected through screening and is often at an early stage. As the tumor grows, it obstructs the inner lining of the lumen, or filtrates the adjacent structure (27). This is often a manifestation of a relatively advanced tumor and symptoms may occur. Common symptoms include rectal bleeding; both hematochezia or melena, abdominal pain, nausea or vomiting, unexplained iron deficiency anemia, altered bowel habits, and involuntary weight loss (27, 28). Most CRCs are diagnosed after the onset of symptoms, although the increasing use of screening has resulted in more cases being diagnosed at an asymptomatic stage (27). Screening is evidently important to reduce the mortality of CRC. According to a recent randomized trial in the United Kingdom, a one-time flexible sigmoidoscopy screening between 55 and 64 years of age reduced CRC incidence by 33 % and mortality by 43 % (29). Colonoscopy is today the gold standard for a pathologic diagnosis of CRC as the method is capable to localize and biopsy lesions throughout the large intestine (27). Ultrasound, chest radiography, fecal occult blood test and imaging tests (MRI and CT) are examples of other tests that can be used if a

biopsy is not possible, if there is suspicion of metastasis or as an additional part of the diagnostic process (27, 30).

1.2.6 Classification

CRC is commonly grouped into four stages (with additional stage called stage 0 to denote carcinoma in situ) according to the tumor-node-metastasis (TNM) staging system published by the Union for International Cancer Control (UICC) (31). See **Table 2** for an overview of the different grades of tumor-node-metastases with description of level of involvement as well as CRC staging according to TNM. Stage is currently the strongest prognostic factor for patients with CRC as it describes the extent and severity of the cancer at time of diagnosis (32). In 2008, the 5-year relative survival for localized CRC (stage I-II) was around 90 %, around 70 % for involvement of regional lymph nodes (stage III), and for stage IV (metastasis to distant sites) only 10 % (10). The staging system describes how far the cancer has grown into the lumen of the intestine and whether it has reached nearby structures (T), the extent of metastasis to nearby lymph nodes (N) and whether or not the cancer has metastasized to other organs (M). The letters T, N, M are further supplied with more letters or numbers to provide more details of each stage. The numbers 0 to 4 indicates increasing severity. The stage (I-IV) describes to which extent the cancer has spread and can be further sub-grouped into A, B and C (30, 33).

Table 2 CRC staging according to tumor-node-metastasis (TNM)

Stage	TNM classification
Stage I	T1 N0 M0
Stage II	T2 N0 M0
Stage III	T3 N0 M0, or T1, T2, or T3 N1 M0
Stage IV:	
Stage IVA	T4a N0 or N1 M0, or T1, T2, T3 or T4a N2 M0
Stage IVB	Any T N3 M0, or T4b any N M0
Stage IVC	Any M1 lesion

T level indicates the size or the extent of the primary tumor. T1: Limited to mucosa and submucosa, T2: Extension into but not through muscularis propria, T3: Invasion of perirectal fat, T4: Invasion of adjacent structures.
N level indicates the extent of spread to nearby lymph nodes.
N0: No regional lymph node metastasis, N1: Fewer than four regional nodes involved, N2: More than four regional nodes involved, N3: Distant nodes involved
M level indicates whether or not the cancer has metastasized to other organs. M0: No distant metastasis, M1: Distant metastasis
Source: American Joint Commission on Cancer and Indian Journal of Radiology and Imaging

1.2.7 Treatment

Surgical resection is regarded as the cornerstone for curative treatment and a laparoscopic approach has become the standard technique for CRC treatment (34, 35). However, treatment of CRC also varies by tumor location and stage at diagnosis (36). Patients with stage II and III rectal cancers are often treated with neoadjuvant chemotherapy combined with radiation therapy prior to surgery. For stage III and some stage II cancers, surgery is followed by approximately 6 months of adjuvant chemotherapy aiming at reduction of cancer recurrence. For patients with advanced CRC, chemotherapy is the main treatment. Targeted drugs are also available in order to treat metastatic CRC (34). Commonly reported side effects of surgery and adjuvant treatment include nausea, vomiting, abdominal pain, irregular bowel movements, gas and flatulence, malabsorption and diarrhea (37). Patients may also experience long-term side effects due to the cancer treatment.

1.2.8 Comorbidities

Comorbidity, the presence of diseases or disorders in addition to the primary illness of treatment, is common among CRC patients (38, 39). Furthermore, comorbidity has shown to be an important impact on the management and prognosis of cancer patients (38, 40). Studies have for example shown that high levels of comorbidity are associated with poorer survival among CRC patients (41-44). Common comorbidities among CRC patients includes cardiovascular disease (CVD), chronic obstructive pulmonary disease (COPD), diabetes mellitus type 2 (DMT2), arthritis, hypertension and other cancer diseases (38, 40, 45). CRC share common risk factors with the majority of these diseases, including lack of physical activity, unhealthy diet, obesity and high age (46). Comorbid conditions are reported to be more common among the elderly population and patients with lower socioeconomic status (45).

1.3 Lifestyle interventions

A growing body of evidence suggests that diet and exercise interventions influence health-related outcomes after a cancer diagnosis with improvement in diet quality, nutrition-related biomarkers, physical performance and quality of life (47-51). Furthermore, lifestyle interventions have been shown to have a significant influence on cancer recurrence and survival (47). However, in relation to CRC, there is today a limited number of lifestyle interventions (52). There is particularly limited evidence with regards to the long-term effect of interventions, as well as the effect of a complex diet, as compared with single food components (47, 48, 52). Due to the large and increasing number of cancer survivors, more research that investigates the impact of lifestyle change on health-related outcomes in CRC patients is warranted (47).

Recommendations from the World Cancer Research Fund (WCRF) states that cancer survivors should follow the same cancer prevention guidelines as the general population; maintain a healthy weight, engage in physical activity, consume at least five portions of fruit and vegetables a day, limit alcohol consumption and avoid smoking (9).

Several studies have investigated health behaviors amongst cancer survivors. For CRC survivors, no more than a third met physical activity recommendations, although this is about the same as the population in general (53). With regards to diet, studies show that the intake of healthy foods is also under the recommended levels. A review by Demark-Wahnefried *et al*. (54), found that only 25 % to 42 % of cancer survivors consume adequate amounts of fruit and vegetables.

Oncologists may play an important role in health promotion amongst cancer survivors, as they have the opportunity to impact upon the patients in the “teachable moment” which is postulated to occur after having cancer (54, 55). Yet, it is estimated that only 20 % of patients receive such guidance (54). Interventions are therefore necessary in order to develop strategies that are found to effectively improve lifestyle behaviors and thereby the health of cancer survivors.

1.4 Health related quality of life and colorectal cancer

1.4.1 HRQOL definition

It is common among cancer patients to experience reduced quality of life (QOL) due to the cancer disease and/or side-effects of treatment (56). WHO (World Health Organization) (57) defines QOL as "an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns". It is a broad ranging concept affected in a complex way by the person's physical health, psychological state, level of independence, social relationships, personal beliefs and their relationship to salient features of their environment (57). In health care research, health related quality of life (HRQOL) is a multidimensional health-oriented concept to describe QOL related to symptoms, physical function, social functioning, psychological well-being, meaning and fulfilment (58). HRQOL is therefore a constriction of the concept of QOL and encompass those aspects of overall QOL that primarily concerns health (59). HRQOL may therefore be regarded as a subjective and multidimensional construct that includes physical, mental, and social domains which scientifically makes it possible to determine the impact of health on QOL.

1.4.2 HRQOL in CRC patients

A somewhat poorer HRQOL has been reported in CRC survivors compared to the normal population. According to Downing *et al.* (60), poorer HRQOL has been most distinct in the younger age groups. This finding has also been confirmed by other studies (61, 62). Furthermore, an impaired HRQOL seems to be more prevalent early after treatment (63, 64). When it comes to the long-term HRQOL amongst CRC patients, after recovery from treatment, studies report a HRQOL similar to the normal population (64, 65). However, a somewhat lower physical QOL has been shown (56). This accounts especially for those diagnosed with late-stage cancer in which bowel dysfunction is particularly common, and some patients must live with permanent colostomy (56). Over how long period of time HRQOL improves after diagnosis and whether it reaches to a level similar to that of the normal population have not been reported consistently (56).

1.4.3 Determinants of HRQOL in CRC patients

Lifestyle behaviors

Understanding the potential determinants on HRQOL in CRC patients is important in order to develop and adapt appropriate intervention strategies. A number of factors have been claimed to either improve or reduce HRQOL. With regards to the amendable determinants, there have been some studies investigating the effect of lifestyle behaviors, including diet and physical activity. Dietary habits (e.g. fruit and vegetable consumption) have been found to be significantly related to less psychological distress and depression in breast cancer survivors after treatment (66). It has been proposed that a quality diet (rich in fruit and vegetable and low in fat) may reduce bowel dysfunction and thereby improve HRQOL(53). A high alcohol intake and smoking has also been associated with reduced HRQOL (67).

Also, anthropometric measures, reflecting a good nutritional status, have been shown to be positively associated with HRQOL. A review by Gupta *et al.* (68), found that 24 studies concluded that better nutritional status was associated with better QOL, one study showed that better nutritional status was associated with better QOL only in high-risk patients, while one study concluded that there was no association between nutritional status and QOL. Decreased dietary intake due to the cancer, cancer treatment or side effects of treatment, and cancer cachexia (characterized by weight loss and muscle wasting), may contribute to cancer-related malnutrition and consequently reduced HRQOL (69). Furthermore, weight loss is typically present among patients with advanced cancer and is a known cause of morbidity and mortality (70). Weight loss also decreases patient tolerance to both radiotherapy and chemotherapy (71). Nutritional status might therefore be a strong predictor of HRQOL in cancer patients. However, a poor nutritional status during active disease or treatment is primarily caused by the cancer and the treatment rather than lifestyle behaviors.

With regards to physical activity, studies have shown that survivors who met the physical activity recommendation had significantly higher HRQOL compared with those who did not (72). Physical activity reduces symptoms such as fatigue, pain and insomnia and thereby affect HRQOL (53). Furthermore, it is found that multiple behavior changes have a better cumulative effect on HRQOL compared with single lifestyle modifications, although studies suggest that physical activity may be the key lifestyle behavior to include in multi-behavioral interventions aimed at improving HRQOL (53, 72).

It could therefore be argued that anthropometric measures, diet and physical performance would be significantly associated with HRQOL and that cancer survivors who practiced healthy lifestyle behaviors (i.e., adhered to national guidelines for diet and physical activity) would report better HRQOL.

Clinicopathological factors

There are also clinicopathological factors affecting CRC patients that might impact upon their HRQOL. Understanding the role of these factors in CRC patients is important in the interpretation of their HRQOL. Data show that cancer survivors are at increased risk of complications, morbidities and secondary cancers due to a complex interplay between cancer treatment, genetic predisposition, and/or common lifestyle factors (48, 73). Overall, these conditions can negatively affect the patients' HRQOL (56, 74). Also, HRQOL has shown to be dependent of the severity of the cancer. Patients with stage IV disease who received surgery and concurrent chemo-radiotherapy (CCRT) had the worst HRQOL (75).

Socio-demographic factors

Gender and age also impact upon HRQOL, yet to a less extent compared with behavioral and clinicopathological factors (67). Gender differences have been found for HRQOL, with a lower HRQOL among women (76, 77). However, the difference has shown to be less apparent in the presence of disease (78). Studies investigating associations between age and HRQOL have been inconclusive. Some report an increase in HRQOL with age (79), whilst others report a reduction (80). However, it appears that it is the physical domains that is lower for participants with greater ages as compared with the mental domains (65). Other socio-demographic factors may also affect HRQOL, such as ethnicity, income, education, marital status and social network (56).

Importance of HRQOL assessment in CRC patients

Developing a clearer understanding of the associations between HRQOL, lifestyle behaviors, medical, clinicopathological and demographic variables is an important step toward developing more targeted behavioral interventions for patients diagnosed with CRC (81). Furthermore, measuring HRQOL in CRC patients may enhance our understanding of how cancer and its treatment influence the patients, and assessing HRQOL across and within populations has been considered essential in order to make clinical interpretation more meaningful (77, 82). It may also be an effective tool in order to establish the effectiveness of interventions. HRQOL has shown to have a prognostic value in terms of long-term outcome

and longer survival, and in some groups of cancer patients, it has been claimed that HRQOL is a more accurate predictor of survival than some other clinical parameters, such as performance status (83-85). Assessment of HRQOL is therefore recommended as an independent endpoint in oncological research (82, 86).

1.4.4 Measuring HRQOL

HRQOL refers to subjective assessment of health and functioning and therefore differs from objective measures (82). Studies have furthermore shown that the concordance between the health professionals' and the patients' assessment of subjective health is relatively poor (87, 88). Patient-reported HRQOL is therefore considered the most reliable method. As a result, several types of questionnaires have been developed in attempts to capture the patient's perception of health. Since the 1980s, HRQOL has become a relevant tool for monitoring the overall health in CRC patients (89).

The HRQOL-measures are commonly divided into generic, disease-specific and domain-specific (90). The generic measures are not specific to any population or disease. They are therefore applicable for subjects with more than one condition, and they make comparisons across populations and conditions possible. The disease-specific measures are developed for specific groups of patients, such as the EORTC-QLQ-C30 to be used in cancer patients (91). Both the generic and disease-specific measures are multidimensional and generally include self-assessed functioning such as physical, role and social functioning and subjective appraisal of well-being (92). On the contrary, the domain-specific measures refer to specific domains of HRQOL of special relevance in specific populations, such as fatigue, anxiety or depression (93).

The SF-36 questionnaire is a generic, multi-purpose, short-form health survey which contains 35 items, plus one item measuring a self-evaluated change in health status during the last year. These 35 items generate eight scales for various domains within HRQOL (94). The eight health scales were selected from dozens in the Medical Outcomes Study (MOS). Furthermore, these scales represent the most frequently measured concepts shown to be affected by disease and treatment in health surveys used worldwide. Also, the survey provides a generic measure of health status instead of targeting specific groups (i.e. age, disease or treatment groups). The survey has therefore been appropriate in comparing general and specific populations (95). In clinical settings, the SF-36 has also been widely used and has been extensively validated with high reliability in diverse groups of cancer patients and cancer survivors (96, 97).

The SF-36 contains 36 items measuring health across eight different scales:

1. physical functioning (PF),
2. role-physical (limitation because of physical health) (RP),
3. social functioning (SF),
4. vitality (VT),
5. bodily pain (BP),
6. mental health (MH),
7. role-emotional (limitation because of emotional problems) (RE) and
8. general health (GH).

The eight scales produce two distinct higher-ordered clusters (summary scales) due to the mental and physical health variance they have in common. Also, factor analytic studies show that the three scales 'physical functioning', 'role-physical' and 'bodily pain' correlates most highly with the physical component and contribute most to the Physical Component Summary (PCS) measure. The scales 'mental health', 'role-emotional' and 'social functioning' correlates most highly with the mental component and contribute most to the Mental Component Summary (MCS) measure. The remaining scales, 'vitality' and 'general health', as well as 'social functioning', have noteworthy correlations with both components (98). In addition to the eight scales, there is a single item 'health transition item' which asks respondents the amount of change in their health in general over a 1-year period. This item provides valuable information of changed health status during the year prior to the administration of the SF-36 (99).

2 Study objectives

This master thesis is an interim study and a subproject within the CRC-NORDIET Study and will study the HRQOL among patients diagnosed with and surgically treated for CRC. The assessment period focused in this master thesis lasts from the time of diagnosis to 6-month follow-up (see **Figure 2**).

The main study objectives of this master thesis were as follow:

1. Characterize the CRC population at baseline.
    - Characterize and compare the CRC-NORDIET population with a national reference group with regards to HRQOL.
    - Test whether anthropometric measures and physical performance are associated with HRQOL.
    - Test whether CRC dietary risk factors and smoking are associated with HRQOL.
    - Test whether clinicopathological characteristics including comorbidities, stoma, treatment regimens, cancer localization and TNM staging are associated with HRQOL.

2. Determine whether a 6 month dietary intervention program (based on the Norwegian food-based dietary guidelines for 2011) affects HRQOL in the CRC-NORDIET population.
    - Investigate whether a change in HRQOL from baseline to 6 months is different between the intervention group and the control group.
    - Investigate whether change in anthropometric measures, physical performance and dietary risk factors are associated with the changes in HRQOL.

3 Subjects and methods

This master thesis was one out of two master theses involved in the Norwegian Dietary Guidelines and Colorectal Cancer Survival Study (CRC-NORDIET Study) in 2014/2015. Data for this thesis were primarily collected from baseline and the 6-month follow-up visit (see **Figure 2**).

3.1 Study design of the CRC-NORDIET Study

The CRC-NORDIET Study is a diet and lifestyle intervention for patients with CRC. The study design is a multicenter randomized controlled, parallel two-arm intervention trial (intervention group A and control group B). The CRC-NORDIET Study intervention will last for 12 months, with follow-up at 6 and 12 months and 1, 3, 5, 8, 10 and 15 years after baseline. The first subjects were recruited in February of 2012 and the last subject will be recruited by the end of 2016. All subjects will have completed the 1 year intervention by the end of 2017, and the final 15 year follow-up by the end of 2032. A schematic overview of the study design with corresponding tests and measurements is presented in **Figure 2**. The main objective of the CRC-NORDIET Study is to investigate whether a diet and lifestyle intervention will reduce the risk of morbidity and mortality in CRC patients. In addition, several other measures for adverse health events are included, such as anthropometric measures, physical performance, blood pressure and blood biomarkers. Several different questionnaires are also used to assess patient-reported outcomes. Among these is the SF-36 questionnaire that assesses HRQOL in 8 different health dimensions and is the main outcome in this master project.

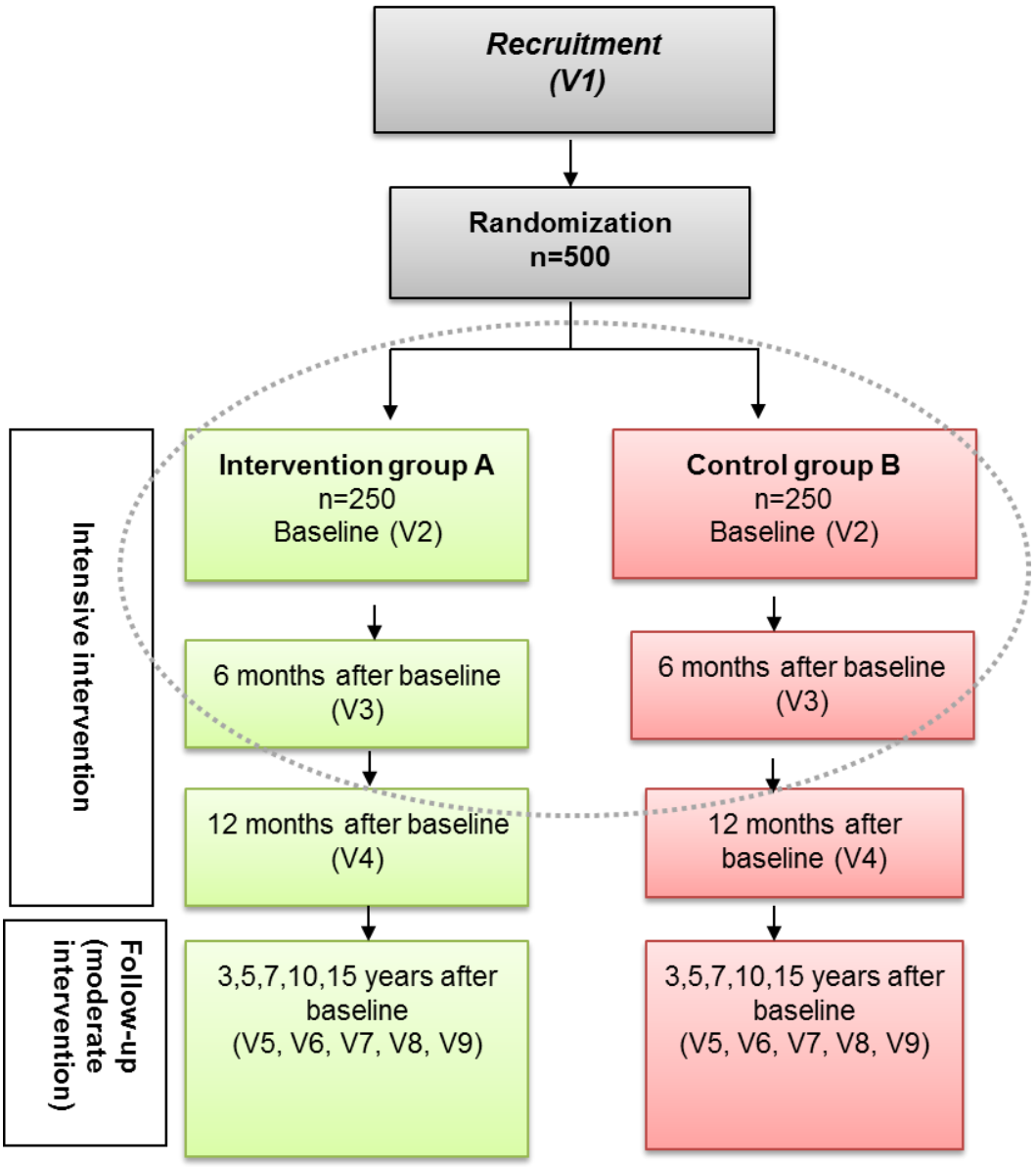


Figure 2 Overview of the study design including corresponding measurements and tests. The CRC-NORDIET Study is a randomized controlled trial with an intervention period lasting for one year. CRC patients are invited to the study prior to surgery. Then they are randomized into intervention group A (diet and physical activity) or group B (physical activity). Two to three months after surgery, patients are invited to the study center for their baseline visit. The participants are thereafter followed at 6 and 12 months, and after the intervention, at 3, 5, 7, 10 and 15 years. The assessment period relevant for this master thesis is circled. The figure is obtained from the CRC-NORDIET Study's project description with permission.

3.2 Subjects

Patients from the hospitals in the 'Helse Sør-Øst' region of Norway were invited to participate in this study. All patients were recruited at the regular hospital visit 1-2 weeks before surgery. The patients were then randomized into the intervention group or the control group. Men and women aged 50-80 years, treated for stage I-III CRC (according to the tumor-node-metastasis (TNM) staging system) were invited to participate in the study. Patients accomplishing baseline measures by January 2015 were included in this master thesis (*n*=137). Participants reaching the 6-month follow-up by January 2015 were included in order to measure the effect of the intervention (*n*=89). A flow chart of the recruitment and inclusion process, including relevant samples and tests are shown in **Figure 3.**

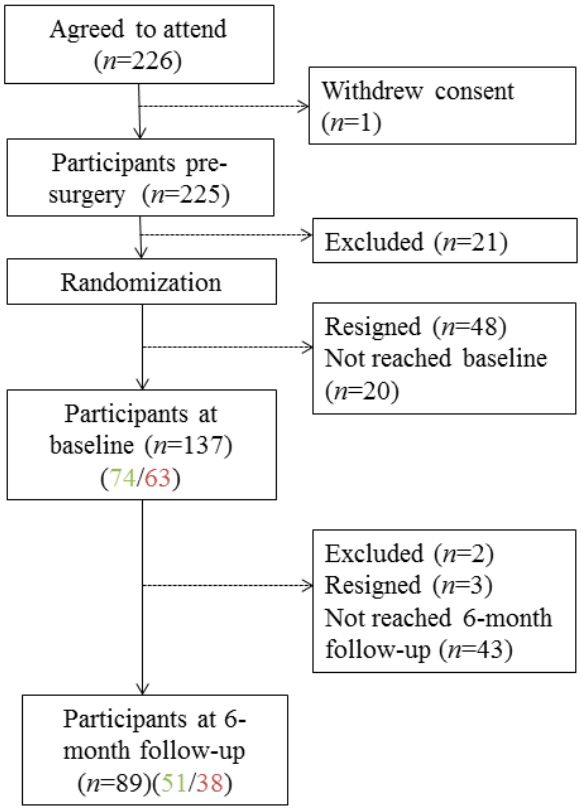


Figure 3 Flowchart of the recruitment and inclusion process, including distributions of relevant measures. By February 2015, 226 of the invited patients agreed to attend. One withdrew consent and patient material and written information was therefore destroyed. At the pre-surgery stage, the remaining study population consisted of 225 subjects. Out of these, 137 participants completed baseline, and 89 participants completed the follow-up visit after 6 months at February 2015. Numbers highlighted in green represents the intervention group, and numbers highlighted in red represents the control group.

In order to compare HRQOL of CRC patients with a normal reference population, a selection of normative data on the SF-36 from the general Norwegian population from 1995 was used. A sub-group of the reference population was selected for this thesis using the CRC-NORDIET Study inclusion criteria on age; 50-80 years. Out of 2,323 participants in the normative sample, a total of 880 (37, 9 %) were aged 50-80 years, and thus eligible for comparison with the CRC-NORDIET population (see **Figure 4**).

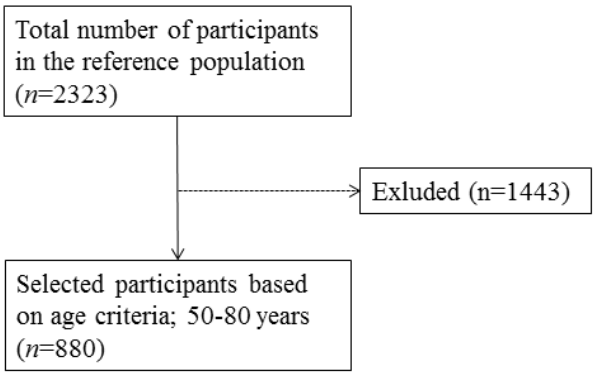


Figure 4 Flowchart of the inclusion process of participants in the reference population based on age criteria

3.3 Methods

3.3.1 Subject and clinicopathological characteristics

All measurements performed on the CRC-NORDIET Study group which were applicable for this master thesis are presented in detail in this chapter. The measurements are also outlined in **Table 3** which gives an overview of time point and source of data collection.

Subject characteristics

Data on age and gender were collected from medical records. Information on smoking status was collected from FFQs.

Anthropometric measures

In this master thesis, anthropometric measures encompass weight, height, BMI, waist and hip circumference, and body composition (muscle mass, fat mass and fat-free mass). Data on anthropometric measures were collected at baseline and at 6 months. All measurements were performed in the morning by trained dietitians or researchers. Weight and height were measured with light clothing, empty pockets and with shoes taken off. Weight was measured by using Marsden MS-4203 (Marsden, Henley-on-Thames, UK) digital portable scale. To compensate for clothing, a value of 0.5 kg was subtracted from weight measures. All measurements were recorded to the nearest 0.1 kg. Height was measured using a Kern MSF 200 (KERN & SOHN, Balingen, DE) mechanical height rod and all measurements were recorded to the nearest 0.1 cm. The measurements were performed with the participants standing firmly against the wall with a straight back and the head in a horizontal position. The measured height was used to calculate BMI.

BMI is an index of weight-for-height used to classify underweight, overweight and obesity in adults. It is defined as the weight in kilograms divided by the square of height in meters (kg/m^2) (100), and was calculated by using height and weight both measured at baseline and at 6 months.

Waist and hip circumference were measured using a stretch-resistant measuring tape (Clas Ohlson, Insjön, SE). Waist circumference was measured at the midpoint between the top of the iliac crest and the lower margin of the last palpable rib in the mid axillary line. Hip

circumference was measured at the largest circumference at the buttocks and hips, at the height of the hip socket. Measurements were recorded to the nearest 0.1 cm.

Body composition (muscle mass, fat-free mass and fat mass) was measured using bioimpedance analyzis (BIA), a single frequency AKERN 101 BIA (Akern Srl, Pontassieve, Italy) with an alternating electrical current at 50 kHz. The participants were asked to remove socks, watch, jewelry, belt and other items which may disturb the measurement. BIA was conducted with patients in horizontal position (lying on a mat), with legs apart and arms not touching the upper body. The participants rested for about two minutes to ensure a homogenous distribution of body fluids. Each of the two adhesive electrodes was placed on the dorsum side of the hand and foot on the dominant side of the body (four electrodes all together). The red electrode was placed distal and the black electrode was placed proximal about 5 cm. apart on the hand and the foot. Rx and Xc were measured in ohms and were used to calculate muscle mass, fat-free mass and fat mass in kilograms.

Physical performance

In this master thesis, physical performance encompasses measures of hand-grip-strength, the sit-to-stand test and physical activity in minutes per day. All physical performance tests were completed at baseline and at 6-month follow-up. Maximal voluntary hand-grip-strength was measured using a portable MAP handgrip dynamometer. The participants were asked to sit upright with the upper arm placed beside to body with the elbow flexed to approximately 90°. The participants were then asked to perform a maximal isometric contraction. Test of maximal strength were performed three times on each arm, switching arm between each measure. The average score of the three measures were used in the analysis and was calculated in IBM SPSS Statistics 20.0 (SPSS Inc., Chigaco, IL USA). Maximal hand-grip-strength was recorded to the nearest 0.1 kg.

For the sit-to-stand test, the participants were asked to sit upright on a chair without armrests. The chair should be approximately 44 cm, and the same chair was used for all measurements. The legs were placed parallel on the ground and the arms were crossed in front of the chest. The participant was instructed to stand and sit one time before the test in order to practice. When the participant was ready, the test was started with a stop-watch after the phrase “ready, set, go”. The participants stood upright as many times possible within 30 seconds. The total number of full stands within 30 seconds was registered.

Physical activity level was self-registered in a compliance questionnaire. The question asks how many times a week physical activity, both with moderate and high intensity, was performed as well as the duration of each workout (in minutes). For the analysis in this master thesis, physical activity was reported as total minutes per day.

Diet

Dietary intake was registered at baseline and at 6-month follow-up by a compliance questionnaire; a semi-quantitative FFQ (food frequency questionnaire) which also includes one question on physical activity. The amounts are based on portion sizes from the Norwegian food and nutrient database (KBS) and based on intake of vegetables, fruits, berries, nuts, wholegrain, dairy products, fish, meat, sweets/dessert, supplements and beverages (water, juice, milk, alcohol, coffee and tea). In this master thesis, the focus will be on red and processed meat, fruit and vegetables, whole-grain and alcohol, as there is convincing evidence (with the exception of fruit and vegetables, where evidence is limited) that these dietary components increases the risk of CRC. The questionnaire is developed in order to estimate the degree of compliance to the Norwegian dietary guidelines and measures food intake and level of physical activity in a typical week during the last 1-2 months. The compliance questionnaire for the first 20 participants included in the CRC-NORDIET Study was a previous version of the questionnaire used today. These were not comparable and were therefore excluded from the analysis of dietary factors and HRQOL.

Clinicopathological characteristics

As 'pathological' is defined as factors related to or caused by disease, the term 'clinicopathological' is used in this master thesis to encompass all factors registered in the clinic, related to or caused by CRC or other diseases. The clinicopathological characteristics include stoma, comorbidities, TNM staging, treatment and CRC localization. Data on comorbidities and presence of stoma were self-reported and collected at baseline using questionnaires developed in-house (**Table 3**). If data for comorbidities were not available at baseline, comorbidities at 6 or 12 months were used. The following comorbidities were included in the questionnaire; myocardial infarction, angina pectoris, heart failure, other heart disease, stroke, kidney disease, asthma, chronic obstructive pulmonary disease (COPD), diabetes (type I and II), psoriasis, hand eczema, other cancer disease, rheumatoid arthritis, bechterew's disease, osteoporosis, fibromyalgia, arthrosis.

The remaining clinicopathological characteristics; treatment, TNM stage and cancer localization, were collected from medical records. CRC localization from medical records was assessed using the International Classification of Diseases 10 (ICD-10) coding system. TNM stage assessed by the pathologist after surgery was used when available. In the remaining cases, stage was determined based on information recorded by the surgeon. With regards to radiation –and chemotherapy, it is common practice that the patient starts either before operation (neoadjuvant treatment) or about three weeks after operation (adjuvant treatment). Since the patients are invited to baseline visit 2-3 months after operation, they have either finished treatment (if neoadjuvant treatment) or are still being treated or just finished treatment (if adjuvant treatment).

Table 3 Subject and clinicopathological characteristics

Study variable	Specific variable	Source of collection
Anthropometric measures	Height, weight, BMI, waist and hip circumference, body composition; fat-free mass, fat mass, muscle mass	Data registered at baseline and 6 month visit
Physical performance	Hand-grip-strength, sit-to-stand test, physical activity (min/day)	Data registered at baseline and 6 month visit
Diet	Red and processed meat, fruit and vegetables, whole-grain, alcohol	Data registered at baseline and 6 month visit (from compliance questionnaire)
Smoking	Current smoker/non-smoker	Data registered at baseline, or alternatively at 6 month visit
Clinicopathological characteristics		
Stoma	Yes/no	Data registered at baseline and 6 month visit
Comorbidities	Myocardial infarction, angina pectoris, heart failure, other heart disease, stroke, kidney disease, asthma, COPD, diabetes, psoriasis, hand eczema, other cancer disease, rheumatoid arthritis, bechterew's disease, osteoporosis, fibromyalgia, arthrosis	Data registered at baseline and alternatively at 6 month visit
Treatment	Neoadjuvant chemoradiotherapy, adjuvant chemotherapy	Medical record
TNM stage	Stage I-IV	Medical record
Localization	Colon (specified), colon/rectum, rectum	Medical record

Abbreviations: BMI; body mass index, COPD; chronic obstructive pulmonary disease

3.3.2 Data from the reference population

In the data material from the reference population, information used for comparison with the CRC-NORDIET population, in addition to the SF-36 scores, included age, gender and comorbidities. Comorbidities for the reference population were self-reported. The categories of self-reported diseases were somewhat different from the CRC-NORDIET Study. To enable comparison between the studies the following assumptions were undertaken; 'heart problem' was assumed to equal 'angina pectoris and other heart disease'; 'chronic lung disease' assumed to equal 'COPD'; and 'chronic skin problem' was assumed to equal 'psoriasis and hand eczema'. In addition, several of the comorbidities or conditions registered in the reference population were not available for the CRC-NORDIET Study and were therefore not included in the comparisons.

3.3.3 The SF-36 questionnaire

In this subproject, data on HRQOL are assessed by the SF-36 questionnaire at baseline and at 6 months. **Figure 5** gives an overview of the eight scales together with a description of their belonging items.

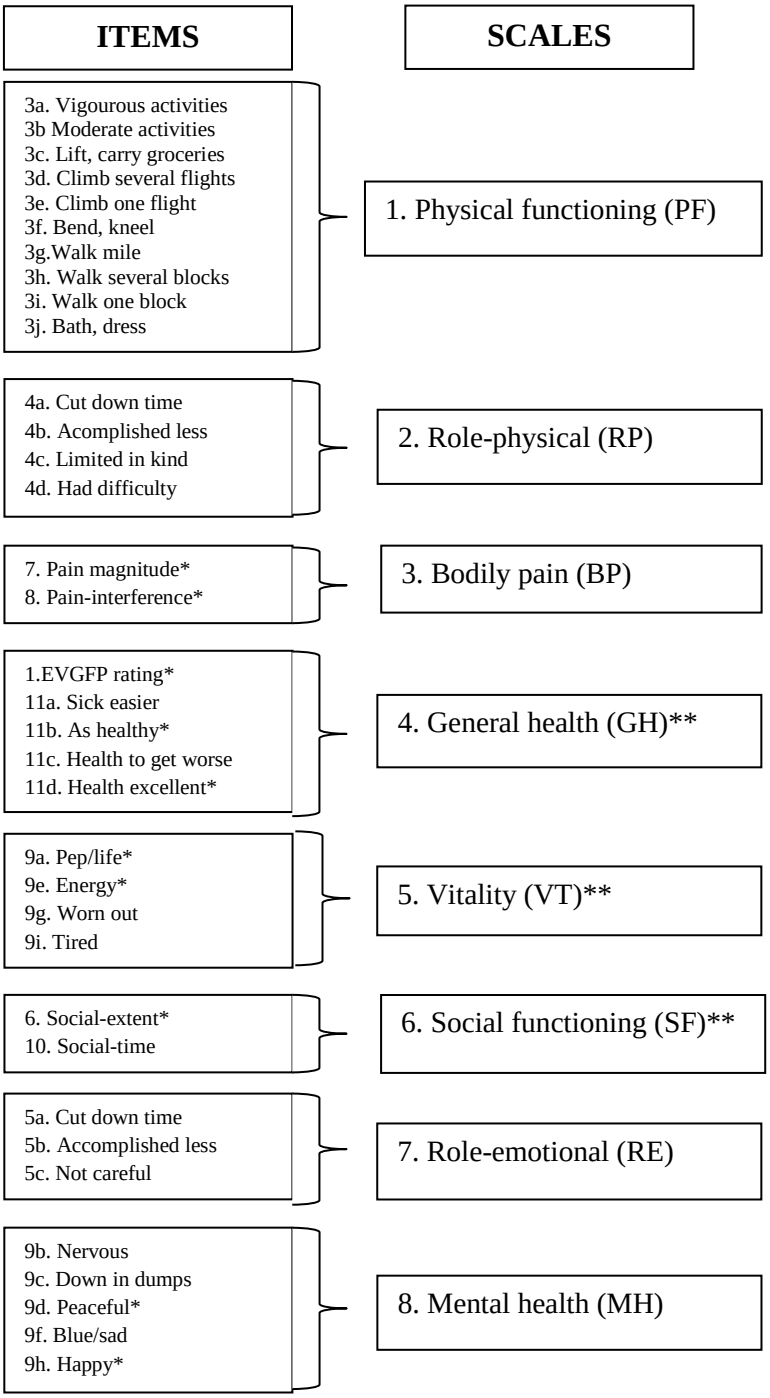


Figure 5 Item descriptions of HRQOL measures for the SF-36 questionnaire. * indicates the items that are recoded so that a higher score indicates better health. ** indicates significant correlation with other summary measure. The figure is inspired by the measurement model presented by the SF-36 community web-site (101).

3.3.4 Scoring the SF-36 questionnaire

The SF-36 includes eight multi-item scales containing two to ten items each, as well as a single-item measuring health transition during the last year. Standardization of content and scoring are essential to the interpretation of the SF-36 and in order to compare results across studies (99). The final scores for the SF-36 items should be interpreted so that a higher score indicates better health. In order to transform the items into the eight final scale scores, there is process of several steps which is described below (see **Figure 6**). Several of the items are scored in an inverse manner, where low values indicate good HRQOL and high values indicate low HRQOL. These items must therefore be recoded so that all of the 36 items are scored in the same direction, where a higher value indicates better health. A raw score was computed for each scale as an algebraic sum of responses for all items in that scale. Finally, the scores were transformed to a 0 to 100 range so that the lowest and highest possible scores are set at 0 and 100, respectively. **Figure 6** illustrates a flow chart for each step in scoring the SF-36. SPSS syntax specifically developed to calculate the SF-36 score for each of the participants were used. This syntax was developed by Jon Håvard Loge and is the same syntax used for the Norwegian reference population (77).

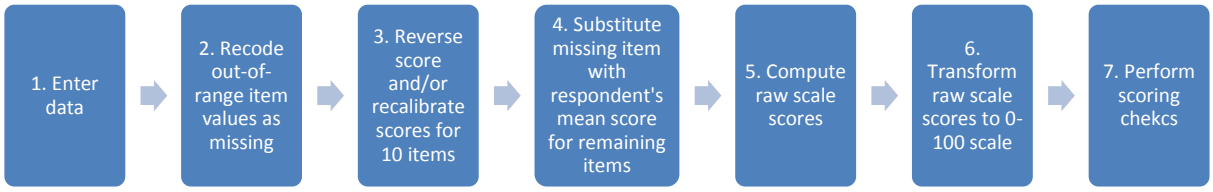


Figure 6 Flow chart for scoring the SF-36

1. Enter data. The first stage for scoring the SF-36 is data entry for every 36 items of the questionnaire, creating the raw-dataset. The precoded number marked by the subject was entered. 2. Recode out-of-range item values as missing. In the case of an unclear response, such as marking two responses, the item was coded as 'missing'.3. Reverse score and/or recalibrate scores for 10 items. The 10 items that were recoded in an inverse manner, where low values indicated good HRQOL and high values indicated low HRQOL (as indicated in **Figure 5**); were recoded so that a higher score indicates better health. 4. Missing items responses were substituted with the respondent's average score for the remaining items. 5. Raw scale scores were computed by adding the sum of items in the same scale; 6. The raw scale scores were then transformed to a 0-100 scale.

1. Item recoding

Item recoding is the process of deriving the item values that was used to calculate the scale scores and includes three steps; a) change out-of-range values to missing; b) recode values for 10 items; and c) substitute values for missing data.

a. Recode out-of-range values as missing

All items were checked for out-of-range values before the final item values were calculated. Out-of-range values include values that are lower or higher than an item's precoded minimum or maximum level, respectively. These values are usually caused by data-entry errors and were changed through verification of the originally questionnaire. If the questionnaire was not available, the value was recoded as missing data.

b. Recode and/or recalibrate values for 10 items

Seven items are reverse scored. These items are worded so that a higher precoded item value indicates poorer health, which is the opposite of the other scores. The score was reversed to ensure that a higher item value indicates better health on all SF-36 items. For 34 of the SF-36 items, there is good support for a linear relationship between item scores and the underlying health concept defined by their scales (99). However, for the scales 'general health' (GH) and 'bodily pain' (BP), empirical work has shown that recalibration is necessary in order to obtain such linearity (99).

'general health' scale

The 'general health' scale is based on five items in which item 1 has five response choices of which "very good" and "good" are recalibrated due to unequal intervals between the response choices (99). Item1 asks "In general, would you say your health is:" a) "Excellent" b) "Very good", c) "Good" d) "Fair", and e) "Poor". The interval between "Excellent" and "Very Good" is about half the size of the interval between "Fair" and "Good" (102). These items are therefore recalibrated to achieve a better linear fit with the 'general health' concept measured in that scale. The result was a very high 0.70 correlation with the sum of the additional four items in the GH scale (103).

'bodily pain' scale

The scoring instructions for the 'bodily pain' (BP) scale was based on three considerations:

1) The items offer both different number of response choices and different content of response choice, and; 2) administration of item 8 depended on the response to item 7.Their variance are therefore not equal and it is necessary to recode the items 8 so that it has 6 response choices, with roughly equal variance to the responses in item 7.

3) Empirical studies indicate that recalibration of Item 7 is necessary to achieve a linear fit with the scale score of 'bodily pain' as measures of pain departs significantly from a linear association (99). This finding has been confirmed using visual analogue scales measuring pain severity and categorical ratings of pain frequency and duration. By recalibrating item 7, it is possible to assume that the equal interval between the response choices are satisfied (103).

c. Recode missing item responses with a mean substitution

A scoring algorithm was used to estimate missing values. If the respondent answered at least 50 % of the items in a scale, the respondent's average score for the remaining items was used to estimate the missing value. If less than 50 % of the items were not answered, the score for that scale was set to missing. This scoring algorithm was used as items in the same scale have roughly equivalent relationships to the health concept being measured (99). In addition, no item is used in more than one scale and it is therefore not necessary to standardize or weight items.

2. Computing raw scale score

Following item recoding a raw score was computed for each scale as an algebraic sum of responses for all items in that scale. Recoded items values and imputed values were used where applicable.

3. Transformation of scale scores

The next step was transformation of scale scores where the responses to each question within each dimension were combined to generate a score from 0 to 100, where 100 indicate "good health". Thus, the SF-36 generates a profile of HRQOL outcomes on eight dimensions. This is required as each scale compromise a different range of scores. The score is generated using the formula shown below to each scale.

$$\text{Transformed scale} = \left[\frac{(\text{Actual raw score} - \text{lowest possible raw score})}{\text{Possible } raw\ score\ range}\right] \times 100$$

Transformation is highly recommended in order to compare scale scores with values derived from other studies using the same scoring rules (99).

4. Scoring checks

Scoring errors may occur whilst reproducing a form, entering data, programming or processing. Scoring checks were therefore performed in order to detect discrepancies which were further investigated for scoring errors. Scoring checks were performed according to the recommendations in the SF-36 Health Survey Manual & Interpretation Guide (99):

1. SF-36 scale scores were calculated by hand for several of the forms and compared with those produced by the scale-scoring computer software.
2. After the items have been recoded to their final values, the frequency distribution was tested in order to verify that the values were recoded correctly (checked for out-of-range values).
3. After item recoding and calculation of scale scores, the correlation between each scale and its component items was checked in order to verify that all correlations were in a positive direction and substantial in magnitude (0.30 or higher).
4. Correlation between the General Health scale and the other seven scales were tested in order to verify that all were positive. With rare exceptions, they should also be substantial in magnitude (0.30 or higher).
5. Principal factor or components analysis was used in order to inspect correlations between the eight scales and the first unrotated factor or component extracted from the correlations among those scales. The correlations should be positive and substantial in magnitude (0.30 or higher).

All scoring checks were satisfactory. This indicates that no major scoring errors were performed. See **Table 4** for internal consistency estimates for each scale and its component items.

Internal consistency estimates were tested in order to inspect the correlation for each scale and its component items. This is to verify that all correlations are positive in direction and substantial in magnitude. Cronbach's alpha exceeded 0.70 for all scales, indicating high internal consistency. This is expected as all items in a scale are measured for the same underlying health concept. **Table 4** shows that for the CRC-NORDIET population, estimates for internal consistency within each scale ranged from 0.76 ('general health' perception) to 0.89 ('vitality'), whilst for the reference population it ranged from 0.83 ('role-emotional' and 'mental health') to 0.91 ('physical functioning').

Within the CRC-NORDIET population, maximum scores were most pronounced in the 'role-emotional' scale, with over 50 % of the respondents scoring 100 points. For the reference population, maximum scores were most pronounced in the 'role-emotional' as well as the 'social functioning' scales. For both groups, minimum scores were most pronounced in the 'role-physical' and the 'role-emotional' scales.

Table 4 Internal consistency estimates (Cronbach's alpha) for the SF-36 scales

		Reference population		CRC-NORDIET population	
	No. of items	Cronbach's alpha	% min./max. SF36 score	Cronbach's alpha	% min./max. SF36 score
'physical functioning'	10	0.91	0.6/13.9	0.85	0.7/8.8
Role limitations, physical	4	0.90	21.0/46.3	0.88	38.2/29.4
Role limitations, emotional	3	0.83	10.9/59.2	0.91	19.1/65.4
'bodily pain'	2	0.87	1.5/31.0	0.82	0.7/35.3
'social functioning'	2	0.85	1.6/55.8	0.86	1.5/34.6
'mental health'	5	0.83	0.1/9.8	0.79	1.5/5.9
'vitality'	4	0.88	1.7/3.4	0.89	1.5/1.5
'general health' perception	5	0.85	0.2/5.0	0.76	0.7/0.7

The table presents the internal consistency estimates (Cronbach's alpha) for the reference population (n=880) and CRC-NORDIET population (n= 137) and the percentage of subjects with minimum/maximum scores (% min./max. SF-36 score).

3.4 Statistical analysis

The data was analyzed with the use of SPSS Statistics for Windows, version 20.0. Categorical variables are expressed as frequencies and percentages. Normally distributed variables are expressed as means with standard deviation (SD). Non-normally distributed variables are expressed as medians with quartiles. *P*-values below 0.05 were considered statistically significant and presented with three decimals.

For independent groups (such as the CRC group and the general population), differences were tested using T-tests or Mann-Whitney tests for continuous variables, and Chi-square tests with Yates Continuity Correction and Fisher's exact tests were used for categorical variables. Post Hoc test with Bonferroni correction was performed in order to correct for multiple testing. Differences in HRQOL between the CRC-NORDIET population and the reference population, and the intervention group and the control group were controlled for age and gender.

Linear regression analysis was used in order to establish whether there was a significant association between HRQOL and anthropometric measures, physical performance, diet and clinicopathological characteristics. For regression analysis of more than two categories, dummy variables were made for comparison analyses. For the regression analysis, only statistical significant associations are presented in this master thesis. Statistical significant associations were adjusted for age and gender. Data were checked for normality, linearity and homoscedasticity of residuals to ensure that assumptions were not violated. HRQOL were treated as dependent variable, whilst the variables mentioned above were treated as independent variables. The significant associations were presented with both unadjusted and adjusted regression coefficients (b) with corresponding 95 % confidence intervals (CIs) and *p*-values.

Changes in anthropometric measures and physical performance between the intervention group and the control group were analyzed by independent samples t-test and expressed as means with SD as they were normally distributed.

In order to detect a difference of 10 points between the reference population and the CRC-NORDIET population, which is regarded as a clinical relevant difference, the sample size needed was estimated to be 50 individuals in each group. The calculation was based on a delta between 80 and 70 points, SD=25, α=0.05 and power=0.8. The delta was based on the work

by Arndt *et al.* who reported that HRQOL scores for the relevant age group will be around 70-80.

In order to detect a significant improvement in HRQOL of 10 points with the assumptions as mentioned in the previous section, we would need 50 individuals in each group. An improvement of 5 points from 75 to 80 would imply a need for 197 individuals in each group.

However, the CRC-NORDIET study was not designed primarily to detect changes in HRQOL. Power calculations for the whole CRC-NORDIET population were based on primary and intermediate endpoints. According to power calculations with a two-sided significance level of 5 % and 80 % power, 218 patients are required per group (intervention group and control group), based on expected changes in primary endpoints after 10 years (reduced total mortality and mortality caused by inflammatory related diseases).With an expected 20 % drop-out during the study, about 250 patients was therefore calculated as the required sample size, i.e. 500 in total.

It is important to emphasize that this master thesis is an explorative study on interim data within the CRC-NORDIET Study and the results presented are therefore preliminary.

3.5 My contribution to the research project

As the CRC-NORDIET population is a large and complex randomized controlled trial, it requires a large number of staff including both researchers and technicians. Their coordination and participation are required for planning and preparation of the trial, recruitment and follow-up of patients, data sampling, and processing and analysis. As a master student within this project, I have contributed to several aspects within the CRC-NORDIET population. This has given me the opportunity to learn about the process of running a randomized controlled trial as well as it has provided me with relevant clinical experience. See **Table 5** for an overview of my contribution to the research project, “Master student” represents me.

Table 5 Overview of my contribution to the research project

Work assignment	Description	Responsibility
Recruiting patients	▪ Invite patients from hospital before operation	▪ Board of clinical trial ▪ Master student
Follow-up visits	▪ Preparing oral glucose tolerance tests ▪ Dietary consultations ▪ Measure blood pressure ▪ Admission and discharge of patients	▪ Board of clinical trial ▪ Master student
Data from SF-36	▪ Plot data from SF-36 forms from baseline and 6 months visit	▪ Master student
Screening of medical records	▪ Record information of clinicopathological characteristics including tumor localization, TNM stage, comorbidity and medication use	▪ Master student
Data from national reference group	▪ Determine appropriate variables for this master thesis	▪ Master student
Statistical analysis	▪ Analyze data with relevant statistical methods as discussed with the supervisors and the statistician involved in CRC-NORDIET	▪ Master student

At the time period this master thesis was conducted, the project group of the CRC-NORDIET Study consisted of Professor Rune Blomhoff, post doc Siv Kjølsrud Bøhn, post doc Ingvild Paur, Associate Professor Christine Henriksen, PhD student Hege Berg Henriksen, PhD student Hanna Ræder, PhD student Ane Sørlie Kværner, laboratory technician Siv Åshild Wiik, physiotherapist Katrine Rolid, the research assistant Anne Juul Skjetne and researcher Torgrim Langleite, and the master students Stine Fallingen Ødegaard and myself.

3.6 Ethics

The CRC-NORDIET Study is registered in ClinicalTrial.gov (ID no. NCT01570010), and approved by The National Committee for Medical and Health Research Ethics in Norway (REC no. 2011/836).

4 Results

4.1 Subject characteristics and SF-36 scores at baseline in comparison to the reference population

This master thesis is based on the first included patients constituting a sub-group consisting of 137 subjects. By February 2015, 226 patients diagnosed with CRC agreed to participate in the CRC-NORDIET Study. The exact number of patients invited to participate is not known, but the study has a participation rate between 60-70 %. A total of 137 participants had reached baseline and were included in the analysis of baseline characteristics and the comparison with the reference population. At the same time point, 89 participants had reached the 6-month follow-up visit, of which 84 had completed the SF-36 questionnaire, and were included in the analysis of the effect of the intervention. See **Figure 4** for an overview of the recruitment and inclusion process. The CRC-NORDIET Study is designed to include 500 subjects. The results presented are therefore preliminary and should be interpreted accordingly.

4.1.1 The CRC-NORDIET Study population

Subject characteristics of the CRC-NORDIET Study population at baseline are presented in **Table 6**. For the three age groups, 31 (22.6 %) subjects were in the age range 50-59 years, 65 (47.4 %) subjects were in the age range 60-69 years, and 40 (29.2 %) subjects were in the age range 70-80 years. The population consisted of 69 men (50.4 %) and 68 women (49.6 %). Information about cancer localization was available for 131 patients, where over half of the population, 74 (56.4 %) were diagnosed with colon cancer, 8 (6.1 %) were diagnosed with rectosigmoideum cancer and 49 (37.4 %) were diagnosed with rectum cancer. TNM stage was available for 126 patients. Stage II was the most common stage, with a total number of 62 (49.3 %), next was stage III, with a total number of 41 (32.3 %) and lastly, stage I, with a total number of 23 (18.3 %). Out of the 113 that had registered stoma status, 38 (33.6 %) had installed a stoma. Information on adjuvant treatment was available for all participants and a total of 46 patients received adjuvant treatment. Adjuvant chemotherapy was the most common treatment regime amongst the CRC patients (n=27, 58.7 %). The most common comorbidities included other cancer disease (n=25, 27.8 %), arthritis (n=23, 25.6 %) and diabetes (n=19, 21.1 %). Information on comorbidities was available for 135 participants, where 90 participants reported to have one or more comorbidities.

Table 6 Personal and clinicopathological characteristics at baseline of the CRC-NORDIET population

Subject characteristics	Frequency, n (%)
Age, years (n =137)	
50-59	31 (22.6)
60-69	65 (47.4)
70-80	40 (29.2)
Gender (n =137)	
Male	69 (50.4)
Female	68 (49.6)
Tumor localization (n = 131)	
Colon cancer	74 (56.4)
Rectosigmoid cancer	8 (6.1)
Rectum cancer	49 (37.4)
TNM stage (n = 126)	
Stage I	23 (18.3)
Stage II	62 (49.2)
Stage III	41 (32.5)
Stoma (n = 113)	
Yes	38 (33.6)
No	75 (66.4)
Adjuvant treatment (n = 46)	
Neoadjuvant chemoradiotherapy	19 (41.3)
Adjuvant chemotherapy	27 (58.7)
Comorbidities (n = 90)	
Myocardial infarction	9 (1.0)
Angina pectoris	2 (0.2)
Heart failure	3 (0.3)
Other heart disease	16 (17.7)
Stroke	3 (0.3)
Kidney disease	5 (0.5)
Asthma	14 (15.5)
COPD	8 (0.8)
Diabetes I + II	19 (21.1)
Psoriasis	9 (1.0)
Hand eczema	6 (0.6)
Other cancer disease	25 (27.8)
Rheumatoid arthritis	3 (0.3)
Bechterew's disease	1 (0.1)
Osteoporosis	10 (1.1)
Fibromyalgia	1 (0.1)
Arthrisis	23 (25.6)

Abbreviations: COPD; chronic obstructive pulmonary disease.

4.1.2 CRC-NORDIET population vs the reference population; comparison of baseline HRQOL

The first major aim of this master thesis was to compare HRQOL amongst the CRC-NORDIET population at baseline with a Norwegian reference population. **Table 7** presents the mean SF-36 scores for the CRC-NORDIET population and the reference population with the mean difference and p-values. Significant differences between the groups were found in 4 of the SF-36 scales as well as in 'the health transition' item. Compared with the reference population, the CRC patients had a 31 % lower score (i.e. worse HRQOL) in the 'role-physical' scale (Δ=19.8 points, p=<.001), a 9 % lower score in the 'vitality' scale (Δ=5.6 points, p=.007), and a 9.2 % lower score in the 'social functioning' scale (Δ=7.7 points, p=.001). The largest difference was therefore found in the 'role-physical' scales, with a mean difference of 19.8. In addition, the CRC patients reported a 28 % lower score for the health transition item (Δ=16.0 points, p=<0.001). On the contrary, there was a trend showing that the score for 'bodily pain' was higher in the CRC-NORDIET population compared with the reference population (p=.060), which indicates that the participants in the CRC-NORDIET population have less 'bodily pain'.

Overall, the CRC-NORDIET population reported a lower score in HRQOL (i.e. poorer HRQOL) compared with the reference population. Most of the significant differences in HRQOL are found for the scales within the mental domain.

Table 7 Comparison of SF-36 score between the CRC-NORDIET population at baseline and the reference Norwegian population

Mean SF-36 scale scores (SD)				
SF-36 scales	CRC-NORDIET population (*n*= 131-136)	Reference population (*n*= 776-858)	Δ (95 % CI)	p-value
Physical domain				
PF	79.1 (17.3) *n = 136*	77.9 (22.7) *n = 817*	1.2 (-5.2, 2.8)	.552
RP	44.6 (42.7) *n = 135*	64.4 (41.9) *n = 799*	19.8 (12.1, 27.5)	<.001*
BP	74 (72.0-84.0) [1] *n = 135*	72 (62.0-74.0) [1] *n = 858*	2 (-10.3, 6.3)[1]	.060
GH	69.2 (20.5) *n = 131*	69.2 (23.8) *n = 776*	0.1(-4.4, 4.3)	.978
Mental domain				
VT	54.2 (22.5) *n = 132*	59.9 (22.3) *n = 840*	5.6 (1.5, 9.7)	.007**
SF	76.1 (24.2) *n = 136*	83.8 (23.8) *n = 872*	7.7 (3.4, 12.0)	.001*
RE	72.6 (40.9) *n = 135*	77.6 (35.6) *n = 782*	5.1 (-1.6, 11.7)	.137
MH	76.6 (16.1) *n = 132*	79.6 (17.1) *n = 825*	3.0 (-0.1, 6.1)	.061
Reported health transition item	41.1 (27.9) *n = 133*	57.1 *(18.4) n = 865*	16 (12.4, 19.6)	<.001*

Independent-samples t-tests and Mann-Whitney tests were used to determine the difference in SF-36 score between the CRC-NORDIET population and the Norwegian Reference population. Values are presented as mean (SD) if not other specified. [1]Values presented as median (CI). *p-value <0.001, **p-value <0.05. Abbreviations: PF = 'physical functioning'; RP = 'role limitations', physical; RE = role limitations, emotional; BP = 'bodily pain'; SF = 'social functioning'; MH = 'mental health'; VT = 'vitality'; GH = 'general health' perceptions.

4.1.3 CRC-NORDIET population vs the reference population; comparison of baseline characteristics and comorbidities

In order to interpret the difference in HRQOL between the CRC-NORDIET population and the reference population, the subject and clinicopathological characteristics were compared between the populations (**Table 8)**.

There was a statistically significant difference in the proportion of participants representing the three age groups between the two study populations. In the reference population, the highest proportion were in the youngest age group (50-59 years, 41.3 %), whilst in the CRC-NORDIET population most of the participants were in the middle age range (60-69 years, 47.4 %). There was no statistically significant difference in distribution of gender between the groups.

In addition to the occurrence of cancer, which obviously is higher in the CRC-NORDIET population due to the inclusion criteria's (100 % vs 9.1 % respectively), there were also a statistical significant difference in the prevalence of diabetes. The CRC-NORDIET population had a prevalence of 14.1 %, compared with 4.8 % in the reference population (p=<0.001). The reference population has a 9.1 % occurrence of cancers (all types).

Table 8 Comparison of subject and clinicopathological characteristics between the CRC-NORDIET population and the reference population

Subject characteristics	CRC-NORDIET population (*n*=137)	Reference population (*n*= 880)	p-value
Age, years			<.001**
50-59	31 (22.6)	363 (41.3)	
60-69	65 (47.4)	283 (32.2)	
70-80	40 (29.2)	234 (26.6)	
Gender			.516
Male	69 (50.4)	423 (48.1)	
Female	68 (49.6)	457 (51.9)	
Comorbidities			
Myocardial infarction	9 (6.7)	61 (6.9)	.987
Heart problem	16 (11.9)	106 (12.0)	.981
Diabetes I + II	19 (14.1)	42 (4.8)	<.001**
Cancer	137 (100.0)	80 (9.1)	<.001**
Conditions			
Chronic allergy	NA	104 (11.8)	NA
Rheumatoid arthritis	3 (2.2)	52 (5.9)	.119
Sciatica/other back problems	NA	246 (28)	NA
Blindness/impaired vision	NA	79 (9)	NA
Chronic lung disease	8 (5.9)	68 (7.7)	.572
Chronic skin problem	14 (10.4)	55 (6.3)	.112
Deafness/hearing disorder	NA	121 (13.8)	NA
Impaired function in legs/arms	NA	169 (19.2)	NA
Other	NA	164 (18.6)	NA

Chi-square tests were used to determine the difference in age, gender, comorbidity and condition between the groups. * p-value <0.001, ** p-value <0.05. All results are listed as n (%). Abbreviations: NA = not applicable.

4.1.4 Baseline SF-36 score by age groups and gender for the CRC-NORDIET population

In order to investigate whether the differences in HRQOL between the populations could be explained by differences in age and gender, ANCOVA analysis was performed for each of the SF-36 scales. For all scales except 'mental health', the HRQOL varied with age. The scales 'social functioning' and 'vitality' remained significantly different between the populations after adjusting for age, age*population and gender (p<0.001), whilst 'physical functioning' became significantly different between the populations after adjustment (p<0.001). Because Levene's test for the assumption of equal variance was violated for several SF-36 scales; 'bodily pain', 'general health' and 'role physical', the effect of age was examined further by comparing the populations within the 3 different groups; 50-59, 60-69 and 70-80 years.

Table 9 shows the SF-36 score for the 8 different health scales for the 3 different age groups; 50-59, 60-69 and 70-80 years for both populations. For the age groups 50-59 years, the results were similar to that of the total populations where the reference population had better HRQOL compared to the CRC-NORDIET for 'vitality' (p=0.002), 'social functioning' (p=0.003), 'role physical' (p<0.01) and the 'health transition' item (p<0.01). However, the scores for 'physical functioning' were significantly lower in the CRC population for this age group (p=0.01). For the age groups 60-69 years there were only significant differences between the populations with regards to 'social functioning' (p=.001), 'role-physical' (p<.001) and the 'health transition' item (p<.01). In the oldest age groups, 70-80 years, unexpectedly, the CRC-NORDIET population reported significantly better HRQOL for the scales 'physical functioning', 'bodily pain' and 'general health'. 'Physical functioning' (p<.001) (CRC-NORDIET Study; 81.40, reference population; 65.35), 'bodily pain' (p<.001) (CRC-NORDIET Study; 84.25, reference population; 64.44), and 'general health' (p=.033) (CRC-NORDIET Study; 73.29, reference population; 65.02).

In the reference population, most SF-36 scores decreased with age while the 'mental health' score remained relatively constant. On the contrary, there are fewer differences between the age groups within the CRC-NORDIET population. For the scales 'physical functioning', 'role-physical', 'role-emotional', 'vitality' and 'general health', there are no significant differences between the age groups.

For 'bodily pain' there was a significant difference (p=.004) between all age groups, where the score increases with age (a higher score indicates less 'bodily pain'). For 'social

functioning' there is a significant difference between the age groups 60-69 years and 70-80 years, with the same trend as the 'bodily pain' scale, where the score increases with age. The same trend is found for three of the other scales ('role-physical', 'mental health' and 'vitality'); however, the difference was not significant ($p>.05$).

Within the CRC-NORDIET population and within the reference population several SF-36 scores also vary with gender. **Table 10** shows the SF-36 score for the 8 different health scales for men and women for the 3 different age groups; 50-59, 60-69 and 70-80 years.

In both the reference population and the CRC-NORDIET population there were no gender differences for HRQOL scales in the youngest age group. In the reference population the gender differences appear in the age group 60-69 years with significantly higher scores among men compared to women with regards to 'vitality' ($p=0.01$), 'bodily pain' ($p=0.01$), 'social functioning' ($p=0.02$), 'physical functioning' ($p<0.01$) and 'role-physical' ($p=0.01$). In the oldest age group (70-80 years), similar differences were found with the addition of 'mental health' which had a higher score for men compared with women ($p=0.02$).

In the CRC-NORDIET population, the differences between gender appeared only for 'vitality' in the age group 60-69 years and in the oldest age group with a higher score for men compared to women for 'mental health', 'vitality', 'social functioning', 'physical functioning' and 'role-emotional'.

Table 9 SF-36 score for the CRC-NORDIET population and the reference population according to age-groups

	CRC-NORDIET population				Reference population			
	50-59	60-69	70-80		50-59	60-69	70-80	
	n = 31	*n* = 64	*n* = 40	p-value	*n* = 335-362	*n* = 250-283	*n* = 187-227	p-value
PF	78.9 (14.4)[a]	77.7 (20.3)	81.4 (14.3)[b]	.574	86.4 (17.0)	76.8 (21.7)	65.4 (26.0)	<.010*
RP	38.9 (44.2)[a]	41.0 (41.4)[a]	55.6 (42.9)	.162	77.8 (36.0)	61.5 (41.5)	44.6 (44.0)	<.010*
RE	75.6 (41.0)	70.8 (41.4)	74.2 (41.0)	.851	85.9 (29.5)	76.5 (35.5)	64.5 (41.3)	<.010*
BP	67.0 (26.9)	70.6 (23.4)	84.3 (19.8)[b]	.004**	73.5 (26.3)	66.3 (27.1)	64.4 (28.7)	<.010*
SF	71.8 (24.8)[a]	73.1 (25.0)[a]	84.7 (20.9)	.029**	86.3 (22.7)	85.1 (21.9)	78.1 (26.7)	<.010*
MH	75.1 (16.2)	76.3 (15.1)	78.2 (17.8)	.722	79.6 (16.6)	79.4 (16.9)	79.7 (18.3)	.987
VT	49.9 (19.0)[a]	53.8 (22.9)	58.8 (24.4)	.256	62.2 (21.3)	59.8 (22.7)	56.1 (23.0)	.008*
GH	70.4 (18.7)	66.8 (22.8)[a]	73.3 (17.1)[b]	.291	74.4 (22.4)	65.3 (25.2)	65.0 (22.4)	<.010*

Oneway ANOVA was used to test whether there was a statistical significant difference in HRQOL score between the age groups. Values are presented as mean (SD). [a] Indicates lower score in the CRC-NORDIET population compared with the reference population. [b] Indicates higher score in the CRC-NORDIET population compared with the reference population. * p-value <0.05. Abbreviations: PF = 'physical functioning'; RP = 'role limitations'; RE = 'role emotional'; BP = 'bodily pain'; SF = 'social functioning'; MH = 'mental health'; VT = 'vitality'; GH = 'general health'; M = males; F = females.

Table 10 SF-36 score for the CRC-NORDIET population and the reference population according to age-groups and gender

CRC-NORDIET population

	50-59			60-69			70-80		
	M	F		M	F		M	F	
	n = 15	*n* = 16	p-value	*n* = 30	*n* = 34	p value	*n* = 23	*n* = 17	p-value
PF	81.2 (12.4)	76.7 (16.2)	.393	76.8 (20.5)	78.5 (20.5)	.583	84.8 (14.1)	76.8 (13.6)	.030*
RP	51.1 (40.3)	26.7 (45.8)	.132	45.0 (39.1)	37.5 (43.6)	.471	63.0 (42.6)	45.6 (42.6)	.209
RE	73.3 (42.2)	77.8 (41.1)	.772	67.8 (41.5)	73.5 (41.7)	.741	87.0 (31.4)	56.9 (46.8)	.030*
BP	68.8 (24.0)	65.3 (30.2)	.726	69.9 (22.6)	71.3 (24.4)	.822	86.5 (18.9)	81.2 (21.1)	.424
SF	70.0 (30.2)	73.4 (19.3)	.711	75.4 (22.9)	71.0 (27.0)	.477	94.0 (9.9)	72.1 (25.2)	<.010*
MH	73.9 (19.1)	76.3 (13.6)	.686	79.5 (12.6)	73.5 (16.7)	.118	85.3 (10.0)	69.4 (21.5)	.010*
VT	48.7 (19.2)	51.0 (19.4)	.735	60.1 (20.6)	48.3 (23.7)	.040*	68.1 (18.5)	47.4 (26.3)	.010*
GH	67.8 (19.9)	72.8 (17.8)	.469	66.8 (18.8)	66.7 (26.2)	.991	75.1 (14.2)	71.1 (20.3)	.505

Reference population

	50-59			60-69			70-80		
	M	F		M	F		M	F	
	n =	*n* =	p-value	*n* =	*n* =	p value	*n* =	*n* =	p-value
PF	87.2 (17.4)	85.6 (16.6)	.366	84.3 (16.9)	70.4 (23.3)	<0.01*	75.0 (19.8)	56.1 (27.8)	<.010*
RP	78.0 (35.9)	77.6 (36.2)	.921	68.2 (38.6)	55.3 (43.3)	.010*	52.5 (43.8)	37.0 (43.0)	.010*
RE	87.5 (28.0)	84.3 (30.9)	.316	78.6 (31.9)	74.5 (38.5)	.356	69.7 (37.6)	59.5 (44.2)	.086
BP	73.2 (25.5)	73.8 (27.1)	.828	70.6 (25.4)	62.6 (28.0)	.010*	69.4 (27.8)	60.0 (29.0)	.010*
SF	86.5 (24.1)	86.1 (21.3)	.840	89.3 (20.2)	81.5 (22.7)	.020*	82.3 (23.8)	74.2 (28.7)	.020*
MH	79.6 (16.0)	79.5 (17.3)	.936	81.2 (15.8)	77.9 (17.8)	.102	82.7 (16.9)	76.7 (19.3)	.020*
VT	62.4 (21.6)	62.0 (21.0)	.870	64.7 (21.6)	55.4 (22.8)	.010*	61.9 (21.8)	50.6 (22.9)	<.010*
GH	74.1 (22.5)	74.7 (22.4)	.789	68.0 (25.1)	63.1 (25.1)	.125	67.5 (22.6)	62.5 (22.1)	.125

Oneway ANOVA was used to test whether there was a statistical significant difference in HRQOL score between the genders for each of the three age-groups. Values are presented as mean (SD). *p-value < 0.05. Abbreviations: PF = 'physical functioning'; RP = 'role limitations'; RE = 'role emotional'; BP = 'bodily pain'; SF = 'social functioning'; MH = 'mental health'; VT = 'vitality'; GH = 'general health'; M = males; F = females.

4.1.5 Association between HRQOL and anthropometric measures, physical performance, diet, smoking and clinicopathological characteristics for the CRC-NORDIET at baseline

Regression analyses were used in order to test for associations between each of the eight different SF-36 scales and anthropometric measures (weight, BMI, fat-free mass, fat mass, muscle mass, waist circumference, hip circumference), physical performance (hand-grip-strength, sit-to-stand test), diet (red meat, whole grains, fruit and vegetables and alcohol), smoking and clinicopathological characteristics (stoma, comorbidity, hypertension, treatment, TNM stage and cancer localization). Only results with statistically significant associations are presented (see **Table 11**). For one unit increase/decrease for the different variables tested, the score of HRQOL increased/decreased according to the beta value (B). The unadjusted values are presented in the following section.

Anthropometric measures

For the anthropometric measures, a positive association were found between muscle mass and 'physical functioning' (B=0.45, *p*=.035). A positive trend was shown between muscle mass and 'vitality' (*p*=.072).

Physical performance

For the physical performance variables, a positive association were found between hand-grip-strength (left) and the SF-36 scales 'mental health' (B=0.41, *p*=.008) and 'vitality' (B=0.45, *p*=.038). A positive association were also found for hand-grip-strength (right) and 'mental health' (B=0.46, *p*=.001) and 'vitality' (B=0.57, *p*=.005). For the sit-to-stand test, a positive association was found for 'vitality' (B=1.30, *p*=.015) and 'bodily pain' (B=1.29, *p*=.022). With regards to physical activity (minutes/day), a positive association was found for 'vitality' (B=0.33, *p*=.000), 'bodily pain' (B=0.21, *p*=.027) and 'social functioning' (B=0.22, *p*=.021), in addition to a positive trend for the scale 'role-physical' (*p*=.062). A positive trend were also shown between hand-grip-strength (right) and 'social functioning' (*p*=.064).

Diet

In the regression analysis between HRQOL and diet (red meat, whole grains, fruit and vegetables and alcohol), a positive association were only shown between red meat and the SF-36 scale 'mental health' (B=0.08, *p*=.024).

Clinicopathological characteristics

Regression analysis between HRQOL and clinicopathological characteristics (adjuvant treatment, smoking, comorbidity, stoma, TNM stage and cancer localization) showed that several of these characteristics were significantly associated with the SF-36 scales in a negative direction. Adjuvant chemotherapy was found to be negatively associated with the scales 'general health' (B=-9.49, p=.035), 'social functioning' (B=-12.26, p=.018), 'vitality' (B=-18.90, p<.001), and 'physical functioning' (B= -8.9, p=.017). With regards to comorbidities, a negative association was found between stroke and 'physical functioning' (B=-27.9, p=.006), between kidney disease and 'bodily pain' (B=23.80, p=.030), between COPD and the scales 'social functioning' (B=-17.52, p=.048) and 'physical functioning' (B=21.90, p<.001). Compared with TNM stage I, TNM stage III was negatively associated with the SF-36 scales 'physical functioning' (B=-9.20, p=.041), 'general health' (B=-15.12, p=.006), 'vitality' (B=-18.40, p=.002) and 'social functioning' (B=-15.11, p=.013). No significant association was found when TNM stage II was compared with TNM stage I (data not shown). In addition, a negative trend was seen between smoking and 'general health' (p=.053). Also, there was a negative trend between stroke and 'bodily pain' (p=.062), between kidney disease and the scales 'vitality' (p=.054) and 'physical functioning' (p=.050), and between other cancer disease and 'mental health' (p=.064).

Significant associations were also found between the scales 'role-physical', 'role-emotional' and several of the variables; however, the residuals were not normally distribution (even not after log-transformation) and the results are therefore not presented. There were no significant associations between the presence of stoma, cancer localization, smoking and HRQOL (data not shown).

In summary, several clinicopathological variables were negatively associated with HRQOL, whilst increased muscle mass and improved physical performance was positively associated with HRQOL.

Table 11 Associations between HRQOL and anthropometric measures, physical performance, diet and clinicopathological characteristics in the CRC-NORDIET at baseline

	SF-36 scales			
	Unadjusted values		Adjusted values[1]	
	B	p-value	*B*	p-value
	‘physical functioning’			
Muscle mass (kg)	0.45 (0.03, 0.86)	.035	0.86 (0.16,1.56)	.017
Stroke	-27.90 (-47.50, -8.32)	.006	-28.64 (-48.40, -8.89)	.005
COPD	-21.90 (-33.90, -9.93)	.000	-22.42 (-34.52, -10.31)	.000
Adjuvant chemotherapy	-8.90 (-16.14, -1.60)	.017	-8.50 (-15.91, -1.08)	.025
TNM stage III[a]	-9.20 (-17.10, -0.39)	.041	-8.90 (-17.96, 0.23)	.056
	‘bodily pain’			
Sit-to-stand test[b]	1.29 (0.19, 2.38)	.022	1.58 (0.49, 2.69)	.005
Physical activity (min/day)	0.21 (0.03, 0.40)	.027	0.21 (0.03, 0.40)	.024
Kidney disease	-23.80 (-45.29, -2.31)	.030	-27.65 (-48.42, -6.88)	.009
	‘general health’			
Adjuvant chemotherapy	-9.49 (-18.32, -0.66)	.035	-9.40 (-18.35, -0.44)	.040
TNM stage III[a]	-15.12 (-25.83, -4.40)	.006	-15.77 (-26.84, -4.71)	.006
	‘vitality’			
Hand-grip strength (right) (kg)	0.57 (0.18, 0.96)	.005	0.58 (-0.02, 1.18)	.056
Hand-grip strength (left) (kg)	0.45 (0.03, 0.87)	.038	0.34 (-0.25, 0.93)	.253
Sit-to-stand test[b]	1.30 (0.26, 2.33)	.015	1.26 (0.21, 2.31)	.020
Physical activity (min/day)	0.33 (0.16, 0.50)	.000	0.31 (0.15, 0.48)	.000
Adjuvant chemotherapy	-18.90 (-28.10, -9.69)	.000	-16.72 (-25.77, -7.68)	.000
TNM stage III[a]	-18.40 (-30.00, -6.83)	.002	-15.35 (-26.92, -3.78)	.010
	‘social functioning’			
Physical activity (min/day)	0.22 (0.03, 0.41)	.021	0.21 (0.03, 0.40)	.025
COPD	-17.52 (-34.86, -0.18)	.048	-18.52 (-35.34, -1.69)	.031
Adjuvant chemotherapy	-12.26 (-22.42, -2.10)	.018	-10.23 (-20.25, -0.20)	.046
TNM stage III[a]	-15.11 (-27.04, -3.18)	.013	-13.62 (-25.50, -1.74)	.025
	‘mental health’			
Hand-grip strenght (right) (kg)	0.46 (0.18, 0.74)	.001	0.55 (0.12, 0.98)	.013
Hand-grip strenght (left) (kg)	0.41 (0.11,0.71)	.008	0.41 (-0.02, 0.84)	.059
Red meat	0.08 (0.01, 0.15)	.024	0.07 (-0.00, 0.14)	.062

All variables are analyzed by linear regression. The results are presented as B (beta) with 95 % CI. [1] Adjusted for age and gender. [a] Dummy variables; compared with TNM stage I. [b] Full stands within 30 seconds. Abbreviations: COPD; chronic obstructive pulmonary disease.

4.2 The CRC-NORDIET Study; effect of the intervention

At the time of analysis, 49 participants in the intervention group and 35 participants in the control group had completed the SF-36 questionnaire at the 6-month follow-up visit. In order to test the effect of the intervention on HRQOL, differences in the SF-36 scales from baseline to the 6-month follow-up visit were compared between the intervention group and the control group. Mean changes in the SF-36 scale scores and mean baseline scores for each scale are shown in **Table 12**.

All SF-36 scale scores increased (i.e. improved) in both groups during the intervention period. There was no statistically significant difference between the intervention group and the control group with regards to changes in mean SF-36 scales during six months of intervention. A t-test was also performed between the two groups at baseline. No statistical difference was found, which indicates a successful randomization with a random allocation of participants into the two different groups.

For the reported health transition item, there was a statistical significant difference between the groups (p=.010), with the control group showing a higher mean change in score compared with the intervention group. However, there was also a significant difference (p=.026) at baseline, where the intervention group had a 13.8 better score compared with the control group.

An intervention effect on HRQOL was not observed. Therefore the groups were investigated further by comparing clinicopathological characteristics at baseline **(Table 13)**. Anthropometry and physical performance were also compared between the groups at baseline as well as changes from baseline to the 6-month follow-up (**Table 14**).

Table 12 Comparison of changes in SF-36 score between the intervention group and the control group from baseline (V2) to six months (V3)

	Intervention group (n=49)		Control group (n= 35)		
SF-36 scales	Baseline	Mean change (SD)	Baseline	Mean change (SD)	p-value[1]
Physical domain					
PF	77.4 (18.9)	8.4 (15.4)	81.1 (15.3)	7.4 (11.8)	.752
RP	42.8 (44.6)	26.7 (47.2)	46.6 (40.8)	27.4 (39.5)	.945
BP	71.4 (25.2)	8.8 (28.7)	76.8 (22.3)	5.6 (25.2)	.593
GH	66.9 (21.8)	6.8 (18.8)	72.0 (18.7)	10.9 (23.8)	.383
Mental domain					
VT	54.6 (21.8)	8.4 (20.9)	53.8 (23.5)	9.5 (26.1)	.831
SF	74.0 (25.5)	11.5 (28.7)	78.6 (22.6)	14.3 (26.8)	.651
RE	74.4 (41.0)	12.9 (37.2)	70.4 (41.0)	5.7 (43.9)	.419
MH	76.1 (16.6)	6.2 (19.9)	77.1 (15.6)	6.1 (17.5)	.992
Reported health transition item	42.2 (29.3)	21.4 (41.0)	28.4 (23.2)	44.8 (37.0)	.010*

Independent-samples t-tests and Mann-Whitney tests were used to test whether the change in SF-36 score was different between the intervention group and the control group. Values are presented as mean (SD).[1] p-value for difference in mean change between the groups. * p-value <0.05.

There was a significant difference in the number of participants treated by adjuvant chemotherapy between the groups (*p*=.004) with a higher number treated in the control group (n=20) compared with the intervention group (n=9). On the contrary, a significant higher proportion in the intervention group (n=19) reported to have other cancer disease compared with the control group (n=6) (*p*=.015) **(Table 13)**.

Table 13 Comparison of clinicopathological characteristics between the intervention group and the control group

	Frequency, n (%)		
Clinicopathological variables	Intervention group	Control group	p-value
Tumor localization (n = 131)			.540
Colon cancer	37 (51.4)	37 (62.7)	
Rectosigmoid cancer	6 (8.3)	2 (3.4)	
Rectum cancer	29 (40.3)	20 (33.9)	
TNM stage (n = 126)			.127
Stage I	17 (13.5)	6 (4.8)	
Stage II	34 (27.0)	28 (22.2)	
Stage III	21 (16.7)	20 (15.9)	
Stoma (n = 38)	25 (65.8)	13 (34.2)	.054
Adjuvant treatment (n = 50)			
Neoadjucvant chemoradiotherapy	12 (24.0)	9 (18.0)	.805
Adjuvant chemotherapy	9 (18.0)	20 (40.0)	.004*
Comorbidities (n = 90)			
Myocardial infarction	3 (0.3)	6 (0.7)	.301
Angina pectoris	0 (0.0)	2 (0.2)	.209
Heart failure	1 (0.1)	2 (0.2)	.594
Other heart disease	9 (1.0)	6 (0.7)	.625
Stroke	3 (0.3)	0 (0.0)	.249
Kidney disease	2 (0.2)	3 (0.3)	.661
Asthma	7 (0.8)	7 (0.8)	.747
COPD	6 (0.7)	2 (0.2)	.288
Diabetes I + II	10 (1.1)	9 (1.0)	.892
Psoriasis	5 (5.6)	4 (0.4)	1.00
Hand eczema	3 (0.3)	3 (0.3)	1.00
Other cancer disease	19 (2.1)	6 (0.7)	.015*
Rheumatoid arthritis	3 (0.3)	0 (0.0)	.249
Bechterew's disease	1 (0.1)	0 (0.0)	1.00
Osteoporosis	7 (0.8)	3 (0.3)	.342
Fibromyalgia	0 (0.0)	1 (0.1)	.459
Arthrosis	12 (13.3)	11 (12.2)	.841

Chi-square test and Fisher's exact test were performed to determine the difference in clinicopathological characteristics between the groups. * p-value <0.05. Abbreviations: COPD; chronic obstructive pulmonary disease.

Changes in anthropometric measures and physical performance from baseline to the 6-month follow-up visit between the two groups are presented in **Table 14**. There was a statistically significant difference in changes of muscle mass (p=.023), where the intervention group had a 1.6 kg increase whilst the control group had a 0.2 kg decrease in muscle mass. A significant difference was also found for the sit-to-stand test (p=.041), where the intervention group had an improvement of 2.6 (full stands within 30 seconds), compared to 0.6 in the control group. There was no significant difference for the clinical characteristics between the intervention group and control group at baseline.

Table 14 Changes in anthropometric measures and physical performance from baseline to six months in the CRC-NORDIET population

Clinicopathological variables	Intervention group		Control group		p-value*
	Baseline	Change	Baseline	Change	
Age, years (n=137)					.202
50-59	20 (26.0 %)		12 (18.2 %)		
60-69	39 (50.6 %)		30 (45.5 %)		
70-80	18 (23.4 %)		24 (36.4 %)		
Gender (n=137)					.978
Male	40 (51.3 %)		34 (51.5 %)		
Female	38 (48.7 %)		32 (48.5 %)		
Anthropometry					
Height (cm)	172.2 ± 8.6		172.3 ± 7.6		
Weight (kg)	76.9 ± 17.0	1.1 ± 5.1	76.8 ± 14.3	1.5 ± 2.7	.681
Body mass index (kg/m$^{2)}$	25.8 ± 4.8	0.4 ± 1.6	25.8 ± 4.3	0.5 ± 0.9	.778
Fat free mass (kg)	50.8 ± 10.6	0.1 ± 4.1	50.9 ± 11.8	-0.4 ± 5.2	.205
Fat mass (kg)	25.1 ± 10.5	0.4 ± 4.1	24.8 ± 8.5	1.5 ± 4.1	.247
Muscle mass (kg)	30.5 ± 7.5	1.6 ± 2.5	31.4 ± 7.9	-0.2 ± 3.9	.023*
Waist circumference (cm)	93.0 ± 14.6	0.1 ± 5.7	93.1 ± 12.7	0.5 ± 4.5	.551
Hip circumference (cm)	100.7 ± 8.5	0.6 ± 4.1	100.7 ± 8.5	0.0 ± 2.5	.433
Physical performance					
Hand-grip strength (right)(kg)	31.0 ± 9.8	0.7 ± 3.3	29.8 ± 9.5	1.0 ± 4.4	.724
Hand-grip strength (left)(kg)	27.6 ± 9.4	1.5 ± 10.9	27.5 ± 8.9	0.8 ± 4.1	.724
Sit-to-stand test[1]	15.6 ± 5.4	2.6 ± 3.7	15.6 ± 4.0	0.6 ± 2.3	.041*
Physical act. (min/day)	27.7 ± 26.2	8.9 ± 28.5	24.2 ± 20.6	6.1 ± 21.0	.649

T-tests were performed for continuous variables; chi-square tests were performed for categorical variables (age groups and gender). Values are presented as mean ± SD if not other specified. *p-value for difference in mean change between the groups. [1]Full stands within 30 seconds.

4.2.2 Associations between changes in HRQOL and changes in anthropometric measures, physical performance and diet in the CRC-NORDIET population from baseline to the six months visit

Because both groups in the CRC-NORDIET population had an increase in HRQOL during the first 6 months after baseline, we investigated whether the changes in HRQOL were associated with changes in anthropometric measures, physical performance and diet in the whole CRC population. The data for the significant associations are not presented in a table, but described in detail in this section. Several anthropometric measures were significantly associated with 'social functioning'. A 1 kg weight increase was associated to a 1.7 points increase (B=1.7, *p*=.019), 1 cm increase in hip circumference was associated with 1.9 point increase (B=1.9, *p*=.033) and an increase in 1 BMI unit was associated with 5.1 points increase (B=5.1, *p*=.021) in 'social functioning'. A 1 kg increase in fat free mass was significantly positively associated with a 1 point increase in 'mental health' (B=, *p*=.035).

For the majority of diet-relevant measures there were no significant associations with the change in HRQOL scales. However, weak negative associations were found between 1 gram reduction in alcohol consumption and 'general health', 'mental health' (B= -0,02 for both, *p*=.020 and .030 respectively) and a weak positive association with changes in 'bodily pain' (B=0.03, *p*=.007). A 1 minute increase in physical activity per day was also found to be positively associated with 'vitality' (B=0.27, *p*=.017), 'bodily pain' (B=0.40, *p*=.003), 'role-physical' (B=0.65, *p*=.002), 'physical functioning' (B=0.21, *p*=.002) and a positive trend were shown for 'general health' (B=0.18, *p*= .078). I.e., significant associations were observed between difference in HRQOL and changes in several of the variables for both anthropometric measures and measures of physical performance. With the exception of weak associations for alcohol, no significant associations were found between differences in HRQOL and changes in other dietary variables.

5 Discussion

In this master thesis, I have investigated HRQOL in a CRC population and compared with data material from a Norwegian reference population to measure and estimate the relative burden of CRC. Furthermore, I have tested whether anthropometric measures, physical performance, diet and clinicopathological variables are associated with HRQOL in CRC patients and examined the effect of a six months diet and life-style intervention on HRQOL. It is important to note that this is an exploratory study reporting on a subpopulation as part of a larger randomized controlled trial. The results are therefore preliminary and must be interpreted with caution.

The results from this interim analysis confirm that CRC patients have a lower HRQOL compared with the reference population. Furthermore, HRQOL is associated with the severity of the disease, adjuvant treatment, improved measured of anthropometry and physical performance in the CRC population. However, no intervention effect was observed on HRQOL at the 6-month follow-up when comparing changes in HRQOL between the intervention group and the controls.

5.1 Methodological considerations

5.1.1 Study population and clinical characteristics

There are several limitations with regards to data collection in both the CRC-NORDIET population and the reference population. Data on comorbid conditions for both the CRC-NORDIET population and the reference population were collected from questionnaires and therefore self-reported. This may have increased the risk of information bias in both groups with an incorrect perception of their medical health status. There were also some challenges comparing the CRC-NORDIET population with the reference population due to the use of different design of the sampling methods in the studies. For example, the categories of self-reported diseases were different. To enable comparison some categories in the CRC-NORDIET were converted into the equivalents used to categorize comorbidities within the reference population: ‘heart problem’ was converted into ‘angina pectoris and other heart disease’; ‘chronic lung disease’ into ‘COPD’; and ‘chronic skin problem’ into ‘psoriasis and hand eczema’. However, it is important to take into consideration the different procedures in

reporting comorbidity when interpreting the results. In addition, some of the reported conditions in the reference population were not applicable for comparison with the CRC-NORDIET population. These included chronic allergy, sciatica/other back problems, blindness/impaired vision, deafness/hearing disorder, impaired function in legs/arms and other.

With the exception of diabetes, and of course cancer, there was no significant difference in comorbidities between the groups. In the reference population 4.8 % (*n*=42) reported to have diabetes compared to 14.1 % (*n*=19) in the CRC-NORDIET population.

Another limitation in comparing the CRC-NORDIET population with the reference population was that many of the variables used to look at associations and as explanatory factors for HRQOL in the CRC-NORDIET population, were not available for the reference population. It was therefore not possible to compare significant associations found in the CRC-NORDIET population with the reference group.

5.1.2 SF-36 questionnaire

There has been an increasing interest in HRQOL amongst different populations. However, due to various definitions and methods of measurements, comparisons between groups can be challenging. HRQOL is also a subjective perception of health, and can be defined differently by groups and individuals. Furthermore, the perception of well-being might change over the life-span. In addition, HRQOL may vary with research methods, including study design, sample selection (sample size and distribution of age and gender), the year the population was conducted and the method used for measuring HRQOL.

The short form SF-36 questionnaire, used in this master thesis, is based on eight scales which measures different dimensions of self-reported health. These scales represent the most frequently measured concepts shown to be affected by disease and treatment in health surveys used worldwide (102). Also, the survey provides a generic measure of health status instead of targeting specific groups (i.e. age, disease or treatment groups). The SF-36 was therefore considered a suitable tool in this master thesis as the main objective was to characterize and compare the CRC-NORDIET population with a national reference group with regards to HRQOL score and other variables. It gave the opportunity to measure and estimate the

relative burden of CRC. It must also be emphasized that the scales demonstrated high internal consistencies indicating appropriate measuring qualities of the SF-36.

The SF-36 questionnaire has some limitations. These limitations are mostly related to the time frame of the questions. For example, item 2 is formulated as follows; "Compared to one year ago, how would you rate your health in general now?" As this question is asked at baseline and at six months, the participants should in theory give about the same answer since it has not been a year from the last time they answered the question. Because most of the patients have not yet been diagnosed, had their surgery or started on treatment 1 year before baseline or 6 months visit, we expected the participants to be similarly affected. It is possible that the patients, when asked at 6 months after baseline, refer to the period of high disease burden, i.e. around diagnosis and/or surgery and not used the appropriate reference time point from 1 year ago. In addition, 20 of the items ask questions related to health for the last 4 weeks. Since the baseline visit is 2-3 months after operation, a possible reduction in HRQOL due to the CRC and its treatment may have improved, and the lowest point in HRQOL may not have been captured. The change in HRQOL may therefore have been different if the baseline measure was around the time of operation.

There are also factors among the CRC population which are not measured by the SF-36 and it might be questioned whether other questionnaires would be more appropriate, for example the EORTC-QLQ-CR29 developed specifically for CRC patients or the EORTC-QLQ-C30 developed specifically for cancer patients, or combining both. These questionnaires have item and symptom scales that covers commonly complications in CRC or cancer patients, for example dyspnea, loss of appetite, insomnia, constipation, vomiting, diarrhea, fatigue, pain and questions related to colostomy (90). However, many of these extra items and symptom scales are covered by other questionnaires or instruments within the CRC-NORDIET population, for example questionnaire on fatigue and the PG-SGA (Patient-Generated Subjective Global Assessment) assessing the nutritional status of the patients. If the EORTC-QLQ-CR29 or the EORTC-QLQ-C30 had been used, information might unnecessarily have been registered twice and the participants might have felt that they were repeating themselves. Furthermore, the timeframe for the assessment in the two questionnaires is at one week and it might, to a less extent, register HRQOL at its lowest (around the time of operation) as the baseline visit is 2-3 months after operation. The SF-36 also exists in an acute version with questions asking within a time-frame of one week, however the version of four weeks was chosen for the same reason, to capture HRQOL at its lowest and for comparison with the reference population. The four-week version

was also chosen due to the design of the study; with 6 months between each visit during the year of intervention. Also, since the SF-36 is a generic questionnaire, it makes the data comparable with the normal population. However, one limitation is that many of the studies on cancer patients and HRQOL have chosen EORTC-QLQ-C30, and comparison with these has consequently been challenging. Nevertheless, the SF-36 is also commonly used in cancer patients and a review by Jansen *et al.* (56), showed that the SF-36 questionnaire was the most commonly instrument used in the studies measuring HRQOL among CRC patients. In addition, the SF-36 has been extensively validated and proven high reliability among older adults and cancer survivors (96, 97), which makes it appropriate for the CRC-NORDIET population. As the CRC population will be followed for up to 15 years, it is likely that they over these years will normalize with regards to disease and treatment related symptoms and complications. Consequently, they will be more or less normalized compared with the normal population, and the generic SF-36 questionnaire would be more appropriate rather than a disease-specific questionnaire.

5.2 Discussion of results

5.2.1 Characteristics of the CRC-NORDIET population

Several comorbid conditions were registered in the CRC-NORDIET population. The most common comorbidities included other cancer disease (n=25, 18.2 %), arthritis (n=23, 16.8 %) and diabetes (n=19, 13.9 %). Also, when all the cardiovascular diseases (CVD) were grouped into one category; including myocardial infarction, angina pectoris, heart failure, other heart disease and stroke, CVD accounted for the most prevalent comorbidity within the CRC-NORDIET population with a prevalence of 24 %. This is, to some extent, supported by other studies. A study by van Leersum *et al.* (39), including 27 339 CRC patients, reported CVD (24 %) along with hypertension (29 %) to be the most prevalent comorbidities among CRC patients. Unfortunately, because we did not have access to information about medicine use from medical records, this master thesis did not include hypertension in the category for comorbidities. However, a study by De Marco *et al.* (40), including 3355 CRC patients, showed a prevalence of hypertension of 13.7 %. Although this percentage was lower, it was still one of the most frequently reported comorbidity within the study. It therefore seems to be an agreement that hypertension is one of the most common comorbidity amongst CRC patients; however the prevalence varies across studies. With regards to diabetes, other studies have reported prevalence similar to our findings. A study by van Leersum *et al.* (39), found that the prevalence of diabetes between 2007 and 2010 was at 13.8 % for males and 14.5 % for females. A discrepancy in the prevalence is, however, apparent as De Marco *et al.* (40) reported the prevalence of diabetes to be 8.2 %. When comparing the CRC-NORDIET population with the reference population, a significant difference were only found for diabetes ($p<0.001$), with a prevalence of 14.1 % and 4.8 %, respectively. It is however important to recognize that the data from this study is from 1995, and that the prevalence of comorbidities have increased during that time, as confirmed by the study of van Leersum *et al.* (39). As a cause of ageing, increased life expectancy, life style changes and improved screening, they found an increase in comorbidities in CRC patients from 1995 to 2010, in particular for nutritional diseases. The prevalence of diabetes in 1995-1998 was 6.7 % for males and 9.1 % for females, which are more in line with the prevalence rate in the reference population.

When comparing the prevalence of comorbidities between studies, it is also important to take into consideration the impact of age. As the prevalence of comorbidities increase with age, a

higher prevalence is expected in the CRC-NORDIET population, with the age range of 50-80 years of the included participants, when comparing with other studies with a broader age-span. This might explain the lower prevalence found in the study by De Marco *et al.* which investigated the prevalence of comorbidities regardless of age. In the study by van Lersum *et al.*, which were in line with our study, the mean age was 69.5 years at diagnosis, as compared with 64.8 years in the CRC-NORDIET population.

5.2.2 The CRC-NORDIET population had poorer HRQOL compared to the reference population

To our knowledge, there has until present been no assessment of HRQOL amongst the Norwegian CRC population. It was therefore unknown whether HRQOL among CRC patients differs from that of a normal population. Comparison between CRC or gastric cancer survivors and healthy controls show that the CRC survivors perceived their well-being as inferior to that of the healthy population (104). Therefore, it is interesting to see how the CRC patients rate their HRQOL in comparison with healthy subjects. In this master thesis, we therefore aimed to determine the HRQOL amongst the CRC-NORDIET population in comparison to a Norwegian reference population (reference population).

Compared with the reference population we found that the CRC population had poorer HRQOL with worse scores for 'role-physical', 'vitality', 'social functioning' and the 'health transition' item, where the difference was greatest for 'role-physical'.

A study by Arndt *et al.* (61), comparing QOL in CRC patients (n=439) with the general population, revealed a difference between the groups similar to our findings. However, it must be emphasized that this study is not optimal for comparison to our study as they have used a different method for assessing HRQOL; the EORTC-QLC30 questionnaire. Nevertheless, several of the scales are to a certain extent comparable to the SF-36 scales. For the 'social functioning' scale they reported the CRC population to have a lower score. This is in line with our study, with the CRC-NORDIET population reporting a significant lower score for the 'social functioning' scale.

A number of factors might contribute to the reduced HRQOL in CRC patients. We found that the severity of disease; TNM stage, treatment; adjuvant chemotherapy as well as comorbidities; COPD, stroke and kidney disease independently were significantly negatively

associated with both the physical and mental domains the SF-36 scales. This is in line with a study of Marventano *et al.* (67) suggesting that symptoms, surgical procedures and the number of comorbidity significantly affect QOL.

Arndt *et al.* found that fatigue, dyspnea, insomnia, constipation, diarrhea, and financial difficulties were the main factors reducing the QOL in CRC patients. Another factor which might hamper HRQOL in CRC patients is colostomy. In the whole CRC-NORDIET population, 33.6 % had installed a stoma. According to a review by Sprangers *et al.* (105), CRC patients with stoma reported more restrictions in their level of 'social functioning'. It therefore seems probable that colostomy is a contributing factor for the reduced HRQOL compared with the reference population. However, we did not find any significant associations between the presence of stoma and HRQOL in the CRC-NORDIET population. Furthermore, the distribution of comorbidities may indicate that the CRC-NORDIET population had a slightly poorer health compared to the reference population and hence explain the lower HRQOL. When comparing the CRC-NORDIET population with the reference population, a significant difference was found for diabetes, with a prevalence of 14.1 % and 4.8 % respectively. Although we did not find any associations between HRQOL and diabetes, several studies (106-109) have shown that both type I and type II diabetes, and especially diabetes accompanied with severe complications, is associated with worse HRQOL. However, we found no significant difference between the CRC population and the reference population with regards to other comorbidities, which indicates that differences with regards to HRQOL may not solely be explained by factors related to comorbidities.

When it comes to the remaining SF-36 scales 'physical functioning', 'general health', 'role-emotional' and 'mental health', the CRC patients and the reference groups showed almost identical scores. This may also be supported by the findings of Arndt *et al.* which showed that the CRC patients and the population controls reported similar mean scores of physical functioning and global health. These scales might be compared with 'physical functioning' and 'general health', respectively. In our study, both of these scales also showed a negligible difference between the populations.

On the contrary, there was a trend showing that the score for 'bodily pain' was higher (indicating less 'bodily pain') in the CRC-NORDIET population compared to the reference population. In addition, the score for this scale increased significantly with age, as opposed to the reference population, which showed the opposite trend (77). Less pain amongst CRC

patients compared with the general population were also reported by Arndt *et al.* which found a mean symptom score of pain at 20.4 for CRC patients compared with 23.3 for the general population.

A possible explanation for the better score in 'bodily pain' amongst CRC patients, as well as the minor difference between the groups for the scales 'physical functioning', 'general health', 'role-emotional' and 'mental health', might be that the patients experience a different perception of good health as a result of being diagnosed with, and treated for CRC, and may consequently report a better HRQOL. This is a known phenomenon which has been referred to as 'reframing' and has been found to be an integral part of CRC patients' adaptation to disease and treatment (110). Also, it might be speculated that it takes less time to improve the 'bodily pain' scale compared to 'vitality'. It may also be questioned whether cancer patients often take analgesics to relieve potentially symptoms.

HRQOL and the impact of age and gender

Because we had access to the participant's age, this enabled the selection of a reference population having the same age span as the CRC-NORDIET population. However, there was an unequal distribution of participants in the different age groups between the populations. In the reference population, the highest proportion were in the youngest age group (50-59 years, 41.3 %), whilst in the CRC-NORDIET population most of the participants were in the middle age group (60-69 years, 48.3 %). This inequality might affect the difference in HRQOL score between the groups. In order to investigate whether the differences in HRQOL between the populations could be explained by differences in age and gender, ANCOVA analysis was performed for each of the SF-36 scales. The differences between the populations with regards to 'social functioning' and 'vitality' could not be explained by differences in age and gender. The effect of age was examined further by comparing the populations within the three age-groups. For the age group 50-59 years the CRC patients had significantly lower HRQOL compared to the reference population. In the age-group 60-69 years there were fewer differences and, surprisingly, in the oldest age-group the CRC-NORDIET population had a better HRQOL for several of the SF-36 scales. In the reference population all scales except 'mental health' decreased with age. Interestingly, in the CRC population, none of the scales decreased with age. Furthermore, 'bodily pain' and 'social functioning' was higher in the oldest age group. This finding is both supported and contradicted by previous studies. Some report an increase in HRQOL with age (79), whilst others report a reduction (77, 80). However, it appears that it is the physical component summary score that is lower for

participants with greater ages as compared with the mental summary score (65). Arndt *et al.* (61) showed similar results with our study, where the role and social functioning tended to increase with older age. The findings of our results might be attributed to selection bias; that only the healthiest subjects agree to participate in the study and that the subjects with poorer health were more likely to withdraw from the CRC-NORDIET population. It may also be explained by a gate-keeping effect. That in those cases the staff from the CRC-NORDIET were not able to recruit, health professionals from the hospitals invited the patients, and they may have withheld the invitation for the very ill patients. This is a common phenomenon in clinical settings (111). However, in line with our results a study of breast cancer survivors found that young women reported worse HRQOL in the first year after radiotherapy compared to older subjects (112). Another explanation might therefore be that older participants have lower expectations, considering their age and experience less difference in limitations relevant for their HRQOL. This explanation fits well with the 'gap-theory' as proposed by Calman in 1984 (113), claiming there is an inverse relationship between an individual's expectations and the perception of the given situation; the larger gap between expectations and the perception, the lower QOL. Furthermore, the item responses are subjective measures of self-reported health, and each individual have their own reference of their health which might change over the life-span. The cancer disease and its treatment and complications might also increase the threshold of what the respondents consider as good HRQOL and they might have experienced a response shift. In addition, Bouvier *et al.* (63), documented that adjuvant chemotherapy for CRC patients had no long-term (12 months after initial diagnosis) negative effect on the HRQOL of elderly patients (>75 years). It has also been hypothesized that younger cancer patients are a more vulnerable group and view cancer as a greater threat to their lives (114, 115). Younger patients also seem to possess fewer strategies and resources in order to cope and manage a life-threatening disease than older, perhaps reflecting differences in expectations as well as experiences (116). Taking every aspect under consideration, it might be argued that the increase in HRQOL with older age is a valid and generable finding which is not attributed to selection bias. These findings imply that intervention strategies should take into account the socio-demographic background of the patients.

In both the reference population and the CRC-NORDIET population there were no gender differences for the HRQOL scales in the youngest age-group. However, for the middle- (60-69 years) and oldest age-groups (70-80 years), a difference between genders was observed

only in the reference population. In the reference population a better HRQOL was reported in men. This is also in line with other studies (76, 117). It can therefore be speculated that the CRC disease and its treatment equalize the HRQOL between age groups and gender. This can further be supported by a study by Jordhoy *et al.* (78), concluding that the impact of socio-demographic characteristics, including gender, seemed less important to HRQOL scores among advanced cancer patients than in general populations.

5.2.3 Is the reference population suitable as a reference group for the CRC-NORDIET population?

Data from the reference population presenting the HRQOL amongst the Norwegian population is chosen as the material used for comparison with the CRC-NORDIET population. It was considered an appropriate reference population as it uses the same SF-36 questionnaire as the CRC-NORDIET population. However, with the data being collected in 1995 this offers a number of limitations. With a time difference of 20 years there are many external factors which might influence HRQOL that are not possible to account for, e.g. change in lifestyle and socio-economic status. The HRQOL amongst the reference population may therefore not give a true reflection of the HRQOL of the normal Norwegian population today. Since 1995, it is likely that a reduction in physical activity and increased prevalence of obesity is two important lifestyle factors which negatively affect HRQOL. Another limitation is that the categories of self-reported diseases were different between the CRC-NORDIET population and the reference population and were for that reason difficult to compare. Nevertheless, the most prevalent comorbidities were accessible for the reference population and available for comparison. Also, a sample size of 880 subjects in the reference population is a substantial number which is regarded as a strength of the study.

5.2.4 Associations between HRQOL and anthropometric measures, physical performance, diet and clinicopathological characteristics in the CRC-NORDIET population

It could be argued that weight status, diet and physical performance would be significantly associated with HRQOL and that cancer survivors who practiced healthy lifestyle behaviors (i.e., adhered to national guidelines for diet and physical activity) would report better HRQOL.

We found a positive association between HRQOL and muscle mass and physical performance. However, no associations were found between smoking or the nutritional parameters and HRQOL except a positive association between red meat and 'mental health'. In line with our observations, Mosher and colleagues (118) reported that in long-term survivors of CRC, breast and prostate cancer, greater exercise were associated with better QOL outcomes (e.g., better 'vitality' and 'physical functioning'; ($p< 0.05$)), whereas greater BMI was associated with reduced physical quality of life ($p< 0.001$). However, in contrast to our findings, Mosher *et al.* found positive associations between diet quality and HRQOL. Similar results were found in a systematic review by Pekmezi and colleagues (47), were both dietary and physical activity interventions showed significant improvements in QOL among cancer survivors.

It is suggested that the relationship between poor nutritional parameters and HRQOL remain widely underestimated (51). However, it has been suggested that a healthy diet may improve symptoms and complications among CRC patients and hence improve HRQOL (67). A randomized controlled trial (RCT) by Ravasco *et al.* (119) found that both at the end and at three months after radiotherapy, dietary counseling ensuring adequate dietary intake and nutritional status, significantly improved HRQOL.

In our study, a significant association was only found between the dietary variable red meat and 'mental health'. However, it is not likely that there is a causal relationship between intake of red meat and QOL. We speculate that the associations are due to confounding factors, such as socioeconomic factors. An intake of red meat might also reflect a generally better health condition among CRC patients at baseline since red meat is not well tolerated among patients severely affected by the disease and/or treatment (based on personal communication with clinical nutritionist in the CRC-NORDIET study). It is also possible that intake of red meat is associated with the ability to socialize, e.g. social dinners, and thus have impact on mental domains. While these are only speculations, a higher mental health score has been associated with time spent in socializing activities (120) and introduction of social mealtimes is often included as a strategy to improve QOL in institutionalized populations (121). The lack of significant associations between the remaining, assumingly healthy nutritional variables, and HRQOL may be explained with similar arguments. Lower intake of fruit and vegetables may indicate poorer health status, for example gas problems or other digestive problems. The presence of stoma may for example hamper the ability for a high intake of fruits and

vegetables. Indeed we find significantly lower intake of fruits and vegetables among the patients that have a stoma compared to the patients that do not have a stoma (data not shown).

Even though associations are found between HRQOL and several of the measures for anthropometry and physical performance, it must be emphasized that multiple behavior changes are more likely to have a better cumulative effect on HRQOL compared with single lifestyle alterations (53).

The regression analysis showed that HRQOL were negatively associated with several of the clinicopathological characteristics of the participants. A negative association was found between HRQOL and TNM stage III but not for TNM stage II. This is in line with other studies, showing that patients with stage IV disease who also had surgery and chemoradiation therapy had the poorest HRQOL (75). In the CRC-NORDIET population, adjuvant chemotherapy was negatively associated with 4 of SF-36 scales. Adjuvant chemotherapy has also shown to have a negative impact on HRQOL in other studies (61). However, Anthony *et al.* (122), reported that there was no measurable lasting impact of CRC adjuvant therapy on HRQOL when compared with surgery alone. It may therefore be assumed that, also in the CRC-NORDIET population, adjuvant chemotherapy may only have a short-term effect. By measuring HRQOL at least 12 months after baseline, treatment related factors likely to affect HRQOL and mask a possible intervention effect, may not be apparent. Finally, our regression analysis showed that there was a negatively association between HRQOL and comorbidities. This is also supported by Smith *et al.* (123), which reported negative associations between comorbidities and cancer, especially in those with two or more comorbidities and in those diagnosed with cancer within the past year. The negatively association between clinicopathological characteristics and HRQOL, which clearly differs between individuals, implies that there is a need for individualized support and follow-up of this patient group.

Finally it should be noted that we did not adjust for multiple testing when testing subject characteristics with the different scales of HRQOL in regression analysis. Thus we cannot rule out that some of the associations are significant by chance without a causative relation.

5.2.5 Effects of the intervention

It has been suggested that a healthy diet may improve symptoms and complications among CRC patients and hence improve HRQOL (67). To our knowledge, this is the first randomized controlled trial in CRC survivors that has compared the effects of the combined impact of diet and physical activity to the isolated effect of physical activity on HRQOL. For all of the SF-36 scales there were no statistically significant differences in the changes from baseline to the 6-month follow-up visit between the control group and the intervention group.

The lack of an intervention effect on HRQOL may have several causes. Firstly, the intervention group may not have complied to the diet intervention. Interim analysis of the concurrent submitted master thesis by Ødegaard indicates that the intervention group significantly changes intake of whole grain. However, the increase in intake of fruits and vegetables was not significantly higher in the intervention group compared to the controls and there were no significant reduction in intake of red meat (Stine Fallingen Ødegaard, 2015). Lack of compliance to the intervention during the first 6 months after baseline may be due to disease related symptoms. The compliance to dietary advices may be more apparent at a later stage in the study with a possible concomitant association with HRQOL. Secondly, the study may be attributed to selection bias; that only the healthiest subjects were likely to participate or it might be due to a gate-keeping effect by hospital staff (explained in section 5.2.2). A healthy bias may not merely account for the absence of adverse treatment effect, comorbidities, complications, etc., but an overall healthy life-style behavior and good nutritional status. It can therefore be speculated that the participants with an already healthy diet were most likely to participate and less likely to gain advantage of the intervention. However, another master thesis (by Solheim Hustad, 2014) completed in the CRC-NORDIET population, found that 33.9 % had metabolic syndrome, a condition that reflect the nutritional status of an individual as it encompass dyslipidemia, hypertension, blood glucose and abdominal obesity. This indicates that, nonetheless, a large proportion of the study population are likely to gain advantage of the intervention and that a lack of effect may not solely be attributed to healthy bias.

The only relevant intervention studies on CRC survivors and HRQOL conducted so far, is the Australian CanChange study (50) and a randomized controlled trial (RCT) by Ravasco *et al.* (51). The Australian CanChange study found effects of a telephone-delivered multiple health behavior change intervention on health and behavioral outcomes in CRC survivors. The

control group was following usual care. Significant difference for cancer-specific QOL (physical well-being) was observed between the treatment groups at both 6 and 12 months. A randomized controlled trial (RCT) by Ravasco *et al.* found that both at the end and at three months after radiotherapy, dietary counselling ensuring adequate dietary intake and nutritional status, significantly improved HRQOL. Ravasco *et al.* compared QOL between three groups; group 1 received individualized nutritional counseling and education about regular foods, group 2 received dietary supplements and consumed their usual diet, and group 3 consumed their usual diet. Particularly, early nutritional counseling during radiotherapy was found to be effective in reducing acute radiotherapy toxicity and improving nutritional status and QOL. Also, in group 1 greater QOL dimensions were associated with the maintenance of adequate nutritional intake and status. The efficacy persisted for three months after the intervention.

Even though no preliminary intervention effect on HRQOL were observed in this interim study, it is likely that the impact of the treatment and time course of reconstitution on HRQOL have masked a potential effect of the intervention. We find that the study population as a whole significantly improved their HRQOL in several scales from baseline until the next assessment at 6 months. This is in line with other studies showing that HRQOL is reduced early after treatment before it gradually improves over time in the absence of cancer recurrence (64, 124). However, the time aspect for the improvement of HRQOL is not yet elucidated. Some studies have reported that even three to four years upon diagnosis there have been deficits in specific aspects of HRQOL (62, 125). At that time-point, late-effects can be of importance.

It is important to keep in mind that even though the intervention might improve HRQOL, the CRC-NORDIET Study is not specifically designed for this purpose. HRQOL was a secondary outcome. The intervention group received individualized advices for adhering to the Norwegian food-based dietary guidelines and advice on physical activity, whilst the control group received advice on physical activity only. A treatment as usual control group was therefore not available for this study. The purpose of this design was to isolate the effect of diet. As studies have shown that interventions on physical activity have been useful strategies to improve HRQOL (47, 118), it is likely that both groups have gained an advantage of the intervention and improved HRQOL. This is further supported by our results, which showed a statistically significant increase in all SF-36 scales for the entire CRC-NORDIET population from baseline to the 6-month follow-up visit (data not shown). In addition, significant associations were found between a higher HRQOL and improved physical performance,

which strengthens the interpretation that physical activity is an important determinant of HRQOL and might have affected upon both groups' HRQOL. The design of the study did not allow for exploring whether it is intervention on physical activity or diet that is of most importance. Nevertheless, it might be hypothesized that intervention on physical activity may have a more important impact on HRQOL compared to diet.

The lack of a differential effect between the groups might also be attributed to a skewed distribution of clinicopathological factors between the groups. The intervention group showed a higher prevalence of other cancer diseases compared with the control group, with a prevalence of 26 % vs. 9.7 % respectively. Also, there was a trend showing that stoma was more prevalent in the intervention group, with a prevalence of 41.7 % in the intervention group compared with 24.5 % in the control group. One might speculate that the higher disease burden will inhibit a lifestyle induced change in HRQOL. In the control group the number of participants treated with adjuvant chemotherapy was significantly higher than in the intervention group. Because adjuvant chemotherapy is associated with reduced HRQOL the control group is thus likely to experience a bigger change in HRQOL due to the effects of recovery after chemotherapy. The effects of recovery after chemotherapy might also partly explain why the control group had a statistical significant lower score in the reported health transition item at baseline compared to the intervention group, even though the question was asked as to encounter the health one year ago.

Another explanation for a lack of effect on HRQOL might be due to the limited number of participants having reached the 6-month follow-up visit. According to the power calculations a number of 50 participants were required in each group in order to detect a clinically significant difference of 10 points. At time of analysis only 49 in the intervention group and 35 in the control group had completed the SF-36 questionnaire at both baseline and 6 months.

A follow-up after 6 months may also be a too short duration of time to achieve effects of the diet intervention, and it might be suggested that a treatment-related increase in HRQOL amongst the whole CRC-NORDIET population may account for the lack of significant difference between the groups. This is also supported by the study of Hung *et al.* (75), which evaluated the changes in treatment outcomes in terms of HRQOL and symptom burden at zero, one, three, and six months after an initial diagnosis of CRC. The results showed that the patients' HRQOL, pain and symptoms were compromised at 1-month and 3-months (during treatment) but improved significantly 6-months after treatment. That HRQOL in patients

improves gradually over time due to recovery and the absence of disease or recurrence has also been confirmed by other studies (64, 124).

In contrast to the SF-36 scales we did find a statistical significant difference between the groups for the change in item 2, 'reported health transition'. This item is a measure of health relative to one year earlier. The controls increased significantly compared to the intervention group, implying that the controls had an increase in this relative measure. However, as mentioned in section 5.1.2, there are limitations using the SF-36 questionnaire with methodical issues regarding the time-line. Thus, it is necessary to interpret this result cautiously. It is also important to emphasize that there was a significant difference in the 'reported health transition' at baseline where the intervention group had a 13.8 better score compared with the control group. A 'regression to the mean' situation is therefore likely. Due to the inappropriate time-frame, there is also a possibility for a type 2 error, with a false-positive result in the measured item.

In conclusion, this interim analysis shows that for all the SF-36 scales there were no statistically significant differences in the changes from baseline to the 6-month follow-up visit between the control group and the intervention group. However, it is possible that a difference in HRQOL will appear with a longer timeframe and a larger study sample.

5.2.6 Associations between changes in HRQOL and changes in anthropometric measures, physical performance and diet in the CRC-NORDIET population from baseline to the six months visit

In this master thesis increases in anthropometric measures and physical performance from baseline to 6 months were found to be positively associated with both the physical and mental domains of HRQOL. However, no significant associations were found between changes in dietary variables and changes in HRQOL.

The evidence that physical activity is important for HRQOL is further strengthened by the finding that the changes in anthropometric measures and physical performance during the 6 months intervention period is associated with changes in HRQOL. The result also fits well with the findings on baseline associations, where significant associations were found between a higher HRQOL and improved muscle mass and physical performance. In addition, the whole study population increased HRQOL.

The lack of association between changes in dietary variables and changes in HRQOL is in accordance with the finding that there were no significant differences between the groups with regards to changes in HRQOL and that the intervention group did not significantly change intake of most dietary variables investigated. However, our results contradict other relevant studies as discussed in the previous section (50, 51).

It is likely that baseline measurements (post-surgery) is taken at a time-point where the patients experience the highest burden of disease and side-effects compared to pre-surgery (V1) and later time points. Therefore the increase in anthropometric measures, for this patient population, could be a positive indicator of restoration after surgery. In line with this argument, a previous master thesis on the CRC-NORDIET population reported that weight, BMI, waist and waist-to-hip ratio significantly decreased in the period from before surgery to baseline measurements (Kværner master thesis 2013).

It is possible that malnutrition and energy deficits are better indicators of nutritional status compared with the dietary CRC risk factors. It can therefore be argued that anthropometric measures such as weight and BMI, which reflect energy deficit, might be better predictors of HRQOL. This may be supported by the fact that alterations in physiological and psychological function as a cause of cancer and treatment induced changes in metabolism, might affect HRQOL by negatively influencing nutritional status (126).

6 Conclusions

To the best of our knowledge, this is the first study to assess HRQOL amongst CRC patients in Norway. The interim results from this master thesis suggest that the CRC patients have a poorer HRQOL in terms of 'role-physical', 'vitality', 'social functioning' and 'general health transition', compared with a Norwegian reference population. The CRC population also had less distinct age and gender differences in HRQOL. Furthermore, many of the clinicopathological variables (i.e. adjuvant treatment, comorbidity and TNM stage) were found to be negatively associated with HRQOL, whilst increased muscle mass and improved physical performance (hand-grip-strength, sit-to-stand test and physical activity (min/day)) were positively associated with HRQOL.

In the CRC-NORDIET population there were no statistically significant differences in the changes from baseline to the 6-month follow-up visit between the control group and the intervention group for any of the SF-36 scales. The lack of effect might be due to the limited number of participants having reached the 6-month follow-up at the time of analysis, a limited time frame of the intervention, differences in baseline characteristics between the groups in addition to lack of compliance to the diet intervention. It is also possible that the improvement due to normal recovery after treatment masks an eventual effect of diet. Indeed a statistically significant increase was found for all SF-36 scales for the entire CRC-NORDIET population from baseline to the 6-month follow-up visit. Furthermore, significant associations between a better HRQOL and improved measures of physical performance at baseline imply that both groups have gained an advantage of the physical activity intervention. Changes in HRQOL were also significantly associated with both changes in physical performance and anthropometric measures.

Even though no intervention effect was found in this interim analysis for HRQOL, it is an important message that most patients recover from this serious disease with an overall increase in HRQOL. Furthermore, our results show that HRQOL can be an indicator of disease burden, severity of disease and side-effects of treatment, which can be useful in order to optimize treatment strategies as part of a shared decision process with the patients. Measurements of HRQOL should therefore be an integrated part of clinical practice.

7 Future perspectives

The results of this master thesis raise several interesting issues that should be considered in future research. For the majority of the SF-36 scales, the reference population reported a better HRQOL compared to the CRC-NORDIET population. However, the material from the reference population was not optimal as a reference for HRQOL. Therefore we are currently preparing to parallelly recruit a reference group consisting of healthy subjects, representing the normal population, where all the appropriate measures will be comparable with the CRC patients. Future analysis using this reference group will provide a better foundation to establish whether subgroup differences are cancer-specific and how the CRC population differs from the general population, not only with regards to HRQOL but also for other important outcomes in the study. This is important in order to determine whether certain factors have a higher impact on CRC survivors compared with the general population.

The results from this master thesis do not show an effect of the intervention on HRQOL. However, caution should be made in the interpretation of these preliminary results due to the small and unequal sample size in the intervention group and the control group, as well as the presence of possible confounders. Future analysis on the total sample material (n=500) might show effects of the intervention on HRQOL after 6 months of intervention. Due to external factors, like cancer treatment, which might mask the effect of the intervention at the early stage; from baseline to six months, an effect might be apparent at a later stage in the intervention.

In order to fully interpret the HRQOL amongst CRC patients, it is necessary to establish all potential factors or determinants which might affect HRQOL. For future analysis, all socio-demographic factors (e.g. education, income, marital status, etc.) should therefore be considered. Also, the use of PG-SGA (Patient-Generated Subjective Global Assessment), which provides a more detailed description of the nutritional status, might be appropriate.

Furthermore, the results from the regression analysis can be used to generate hypotheses with regards to the associations found between HRQOL and measures of anthropometry and physical performance. However, these are exploratory findings and it remains to be tested whether these associations are causal or conclusive. Future analysis on the effect of the diet intervention should control for impact of physical performance, anthropometric measures, clinicopathological variables including treatment regimens and TNM stage. Because

nutritional interventions on HRQOL are more likely to be found in CRC patients with poorer health status, for example those receiving radiotherapy, it will be important to perform sub-group analysis. Such a strategy is essential in order to develop more targeted behavioral interventions for patients diagnosed with CRC.

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Appendixes

Appendix 1 The SF-36 questionnaire

SF - 36 SPØRRESKJEMA OM HELSE

INSTRUKSJON: Dette spørreskjemaet handler om hvordan du ser på din egen helse. Disse opplysningene vil hjelpe oss å få vite hvordan du har det og hvordan du er i stand til å utføre dine daglige gjøremål.

Hvert spørsmål besvares ved å sette ett kryss i den ruten som passer best for deg. Hvis du er usikker på hva du skal svare, vennligst svar så godt du kan.

1. Stort sett, vil du si at din helse er :

☐ 1. Utmerket
☐ 2. Meget god
☐ 3. God
☐ 4. Nokså god
☐ 5. Dårlig

2. Sammenlignet med for 1 år siden, hvordan vil du si at din helse stor sett er nå?

☐ 1. Mye bedre nå enn for 1 år siden
☐ 2. Litt bedre nå enn for 1 år siden
☐ 3. Omtrent det samme som for 1 år siden
☐ 4. Litt dårligere nå enn for 1 år siden
☐ 5. Mye dårligere nå enn for 1 år siden

De neste spørsmålene handler om aktiviteter som du kanskje utfører i løpet av en vanlig dag.
3. Er din helse slik at den begrenser deg i utførelsen av disse aktivitetene nå?
Hvis ja, hvor mye (sett kun ett kryss på hver linje)

AKTIVITETER	**Ja, begrenser meg mye**	**Ja, begrenser meg litt**	**Nei, begrenser meg ikke i det hele tatt**
a. Anstrengende aktiviteter som å løpe, løfte tunge gjenstander, delta i anstrengende idrett	☐ 1	☐ 2	☐ 3
b. Moderate aktiviteter som å flytte et bord, støvsuge, gå en tur eller drive hagearbeid	☐ 1	☐ 2	☐ 3
c. Løfte eller bære en handlekurv	☐ 1	☐ 2	☐ 3
d. Gå opp trappen flere etasjer	☐ 1	☐ 2	☐ 3
e. Gå opp trappen en etasje	☐ 1	☐ 2	☐ 3
f. Bøye deg eller sitte på huk	☐ 1	☐ 2	☐ 3
g. Gå mer enn to kilometer	☐ 1	☐ 2	☐ 3
h. Gå noen hundre meter	☐ 1	☐ 2	☐ 3
i. Gå hundre meter	☐ 1	☐ 2	☐ 3
j. Vaske deg eller kle på deg	☐ 1	☐ 2	☐ 3

4. I løpet av de siste 4 ukene, har du hatt noen av de følgende problemer i ditt arbeid eller i andre av dine daglige gjøremål på grunn av din fysiske helse?

(sett ett kryss på hver linje)

	Ja	Nei
a. Du har måttet redusere tiden du har brukt på arbeid eller på andre gjøremål	☐ 1	☐ 2
b. Du har utrettet mindre enn du hadde ønsket	☐ 1	☐ 2
c. Du har vært hindret i å utføre visse typer arbeid eller gjøremål	☐ 1	☐ 2
d. Du har hatt problemer med å gjennomføre arbeidet eller andre gjøremål (f.eks fordi det krevde ekstra anstrengelser)	☐ 1	☐ 2

5. I løpet av de siste 4 ukene, har du hatt noen av de følgende problemer i ditt arbeid eller i andre av dine daglige gjøremål på grunn av følelsesmessige problemer (som f.eks å være deprimert eller engstelig).

(sett ett kryss på hver linje)

	Ja	Nei
a. Du har måttet redusere tiden du har brukt på arbeid eller på andre gjøremål	☐ 1	☐ 2
b. Du har utrettet mindre enn du hadde ønsket	☐ 1	☐ 2
c. Du har utført arbeid eller andre gjøremål mindre grundig enn vanlig	☐ 1	☐ 2

6. I løpet av de siste 4 ukene, i hvilken grad har din fysiske helse eller følelsesmessige problemer hatt innvirkning på vanlig sosial omgang med familie, venner, naboer eller foreninger? (Sett ett kryss)

☐ 1. Ikke i det hele tatt ☐ 2. Litt ☐ 3. Endel ☐ 4. Mye ☐ 5. Svært mye

7. Hvor sterke kroppslige smerter har du hatt i løpet av de siste 4 ukene?

(Sett ett kryss)

☐ 1. Ingen ☐ 2. Meget svake ☐ 3. Svake ☐ 4. Moderate ☐ 5. Sterke ☐ 6. Meget sterke

8. I løpet av de siste 4 ukene, hvor mye har smerter påvirket ditt vanlige arbeid (gjelder både arbeid utenfor hjemmet og husarbeid)? (Sett ett kryss)

☐ 1. Ikke i det hele tatt ☐ 2. Litt ☐ 3. Endel ☐ 4. Mye ☐ 5. Svært mye

9. De neste spørsmålene handler om hvordan du har følt deg og hvordan du har hatt det de siste 4 ukene. For hvert spørsmål, vennligst velg det svaralternativet som best beskriver hvordan du har hatt det. Hvor ofte i løpet av de siste 4 ukene har du:

(sett ett kryss på hver linje)

	Hele tiden	Nesten hele tiden	Mye av tiden	Endel av tiden	Litt av tiden	Ikke i det hele tatt
a. Følt deg full av tiltakslyst?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
b. Følt deg veldig nervøs?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
c. Vært så langt nede at ingenting kunne muntre deg opp?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
d. Følt deg rolig og harmonisk?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
e. Hatt mye overskudd?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
f. Følt deg nedfor og trist	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
g. Følt deg sliten?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
h. Følt deg glad?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
i. Følt deg trett?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

10. I løpet av de siste 4 ukene, hvor mye av tiden har din fysiske helse eller følelsesmessige problemer påvirket din sosiale omgang (som det å besøke venner, slektninger osv.)?

☐ 1. Hele tiden ☐ 2. Nesten hele tiden ☐ 3. Endel av tiden ☐ 4. Litt av tiden ☐ 5. Ikke i det hele tatt

11. Hvor RIKTIG eller GAL er hver av de følgende påstander for deg?

(sett ett kryss på hver linje)

	Helt riktig	Delvis riktig	Vet ikke	Delvis gal	Helt gal
a. Det virker som om jeg blir syk litt lettere enn andre	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Jeg er like frisk som de fleste jeg kjenner	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. Jeg tror helsen min vil forverres	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. Jeg har utmerket helse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5