# Prevention of colorectal cancer development and mortality: from epidemiology to endoscopy

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Prevention of colorectal cancer development and mortality: from epidemiology to endoscopy.

Thesis with a summary in Dutch, University of Utrecht.

ISBN/EAN: 978-94-6169-657-1
Lay-out and printing: Optima Grafische Communicatie, Rotterdam, The Netherlands

The printing of this thesis was financially supported by:
Afdeling Maag-, Darm- en Leverziekten UMC Utrecht; Nederlandse Vereniging voor Gastroenterologie; EndoAid Ltd.; Cobra Medical BV; Tramedico BV; Dr. Falk Pharma Benelux BV; ChipSoft BV; Kenniscentrum Koffie en Gezondheid.

# Prevention of colorectal cancer development and mortality: from epidemiology to endoscopy

Preventie van het ontwikkelen van en sterfte aan colorectaal carcinoom: van epidemiologie tot endoscopie

*(met samenvatting in het Nederlands)*

**Proefschrift**

ter verkrijging van de graad van doctor aan de Universiteit Utrecht
op gezag van de rector magnificus, prof. dr. G.J van der Zwaan,
ingevolge het besluit van het college voor promoties in het openbaar
te verdedigen op 28 mei 2015 des middags te 4.15 uur

door

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geboren op 2 januari 1986 te Heerhugowaard

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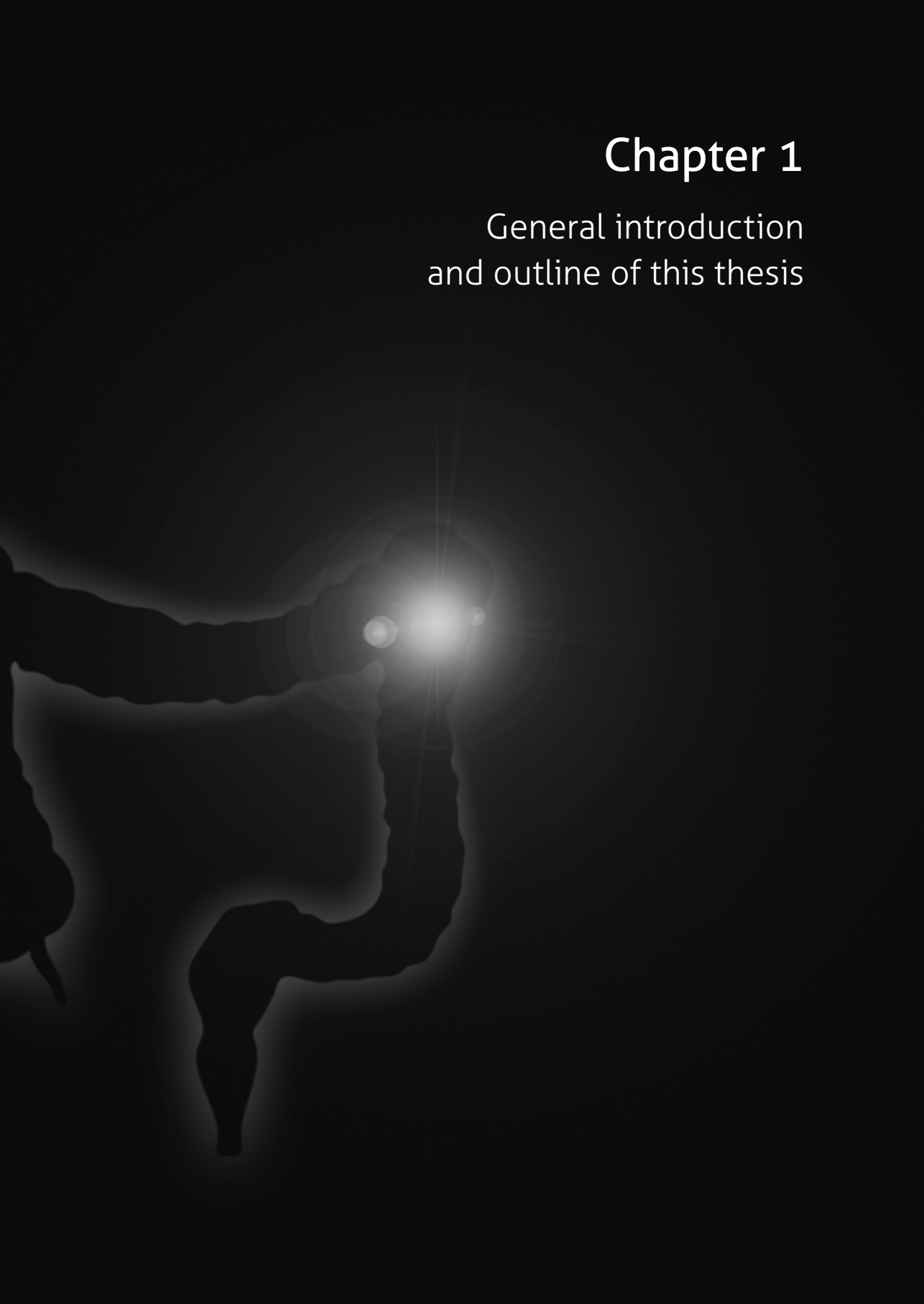
# Chapter 1

## General introduction and outline of this thesis



Globally, colorectal cancer is the third most common cancer and the fourth most common cancer related cause of death, accounting for approximately 1.2 million new patients and over 600 thousand deaths annually.[1] In the Netherlands, approximately thirteen thousand persons are diagnosed with colorectal cancer each year.[2] The majority of colorectal cancers develop from precursor lesions that can roughly be classified in conventional adenomas and serrated adenomas. The onset and progression from precursor lesions to cancer is caused by the accumulation of genetic and epigenetic mutations[3-5] and takes on average ten years, but only occurs in an estimated 5% of adenomas.[6] Apart from changing personal risk factors, this relatively slow transition gives the opportunity to screen, detect and remove adenomas before becoming malignant.

## PART 1. STRATEGIES TO IMPROVE THE DETECTION OF COLORECTAL ADENOMAS

### Quality of colonoscopy and adenoma detection

The gold standard for the detection and removal of neoplastic lesions is colonoscopy.[7-10] Convincing evidence has shown that the removal of adenomas by colonoscopy reduces colorectal cancer incidence and mortality by 48%-67% and 65%-81%, respectively.[11-15] Despite being the most sensitive method to date, there has been an increasing concern about the effectiveness of colonoscopy for the detection of adenomas and early-stage colorectal cancer, especially in the proximal colon.[16-19] This concern is driven by the significant polyp and adenoma miss rates of 20%-25% reported in back-to-back colonoscopy studies with standard colonoscopes[20] and the observation in population-based studies that 3%-8% of patients with colorectal cancer had a colonoscopy within 3-5 years prior to their diagnosis.[19,21-24] It is not exactly clear why colonoscopy is not as effective in protecting against proximally located cancers as in protecting against distally located cancers, but several studies have shown that proximal advanced adenomas are more often diminutive in size or non-polypoid in appearance compared to advanced adenomas in the distal colon and may therefore be more easily overlooked.[20,25,26] In addition, serrated precursor lesions, which are typically located in the proximal colon, are easier to be missed due to their flat morphology and similar color as the surrounding mucosa.[27,28] Second, approximately 5%-10% of colonoscopies are incomplete, leading to proximal lesions being missed.[29] Other factors that are responsible for missing lesions include poor bowel preparation[30-33] and the relative difficulty to visualize polyps at the proximal side of haustral folds and internal curves of flexures.[34,35] Besides, considerable variation has been observed between endoscopists with regard to adenoma detection rates and the mean number of adenomas being detected per colonoscopy.[36-39]

With the aging population and the introduction of nationwide colorectal cancer screening programs in many Western countries, a steep increase in the number of colonoscopies are expected. However, as outlined above, colonoscopy quality is still from being perfect and various improvements are required, including: 1) improving bowel cleansing rates, 2) technological improvements that allow visualization of the complete colonic surface while maintaining optimal washing, suction and therapeutic capabilities and keeping the procedural time and costs as low as possible, and 3) new developments that help monitoring, training and optimizing colon inspection of individual endoscopists. The first part of this thesis focuses on all three of these aspects and aims to investigate new modalities that may aid in increasing the detection of adenomas and early colorectal cancers.

### Bowel preparation

Poor bowel preparation is associated with incomplete colonoscopy, lower adenoma detection rates, higher adenoma miss rates, increased procedure times and need to repeat the procedure.[30-33,40] For example, in a study by Froehlich *et al.*[30] subjects with inadequate bowel preparation more frequently had an incomplete colonoscopy (28.9% vs. 9.6%), had on average a 6 minutes longer total procedure time and had a lower polyp detection rate (23.9% vs. 29.4%). Lebwohl *et al.*[32] found miss rates of 42% for all adenomas and 27% for advanced adenomas in inadequately prepared colons. Thus, bowel cleansing is critical for successful colonoscopy, but is complex and requires a low-fiber intake several days before colonoscopy, a well timed start of bowel cleansing and a split-dose bowel preparation, as is recommended by both the European Society of Gastrointestinal Endoscopy and the U.S. Multi-Society Task Force on Colorectal Cancer.[41,42] Nonetheless, recent studies still report inadequate bowel preparation in 10%-30% of colonoscopies, even with split-dose bowel preparation.[32,33,43-46] This is probably partly due to non-adherence to the bowel preparation regimens but is also caused by several medical conditions, such as chronic constipation, previous intra-abdominal or pelvic surgery, medication use, and factors related to immobilization such as older age, physical condition, obesity, neurological disease and hospitalization.[30,44,45,47-51] Identifying subjects at risk for inadequate bowel preparation due to these factors may be helpful to increase the number of successful colonoscopies as this allows taking precautions in this specific group. In **chapter 2** we use data of a multicenter cohort study including more than two thousand colonoscopies to develop a prediction score that can be used to identify subjects at risk for inadequate bowel preparation who may benefit from an intensified bowel cleansing regimen.

### Visualization of the colonic surface

An important limitation of the current standard colonoscopes is that the proximal side of haustral folds and internal curves of flexures are relatively difficult to inspect. This is illustrated by the observation that standard 140 and 170 degrees colonoscopes are able to visualize at best 87% to 92% of the mucosal surface in a clean colon.[52] As a result, premalignant lesions can be missed and it has been found that two-thirds of non-rectal ≥6 mm lesions that are missed during colonoscopy are located at the proximal side of folds.[35] Simple solutions like cap-assisted colonoscopy have been tried to improve visualization behind folds, but more recent devices such as the Third-Eye Retroscope® seem also promising. The latter is a flexible single-use catheter with a camera and diode light source at the tip that can be advanced through the working channel of a colonoscope providing a 135 degrees retrograde view of the colon. In a study by Leufkens *et al.*, evaluating the Third-Eye Retroscope, a net additional detection rate of 29.8% for polyps and 23.2% for adenomas was found.[53] In an earlier study in simulated colonoscopies using CT-colonography software, it was shown that a retroscope improves visualization of the colonic surface area from 87% with standard 140 degrees view colonoscopes to 99% when combined with a retroscope.[52] However, a drawback of this technique is that the device needs to be removed from the working channel in case of polypectomy and is therefore more time consuming. In an effort to better recognize subtle and flat lesions, high definition endoscopy[54] and several virtual chromoendoscopy techniques[55] were introduced. These modalities have improved the quality of the video images but the overall improvement of adenoma detection seems limited to approximately 5%.

Taken together, the high adenoma miss rates and the rates of interval cancers reported in literature demonstrate that new technologies are warranted. In **chapter 3** we summarize various endoscopic innovations and their diagnostic yield that have been developed in the past years. In **chapter 4 and 5** the diagnostic yield of two novel technologies, Fuse colonoscopy and EndoRings colonoscopy, are compared with standard colonoscopy in multicenter, randomized, back-to-back tandem colonoscopy studies.

### Withdrawal time and inspection of the colonic surface

Another important aspect concerning the quality of colonoscopy is that considerable inter-endoscopist variability exists with regard to adenoma detection, withdrawal technique and withdrawal time.[36,37,56] Because a higher adenoma detection rate is associated with a lower risk of interval cancers[12,57] and longer withdrawal times correlate with higher adenoma detection rates,[37,56,58-60] both adenoma detection rate and withdrawal time are regarded as standard objective quality indicators for colonoscopy.[29] However, a proper inspection of the colonic surface, characterized by careful examination of the proximal sides of folds and flexures, takes a longer time and may be a better quality indicator than withdrawal time itself.[37,61] In **chapter 6** we evaluate the feasibility of eye

tracking technology for measuring colon inspection during real-time, self-performed colonoscopies. Such a technique may be helpful to distinguish inspection strategies with a high diagnostic yield from those with lower yields.

## PART 2. FACTORS ASSOCIATED WITH COLORECTAL CANCER DEVELOPMENT AND SURVIVAL

### Risk factors for colorectal cancer development

In the past few decades, a large number of epidemiological studies has led to the identification of lifestyle and dietary risk factors for the development of colorectal cancer. Important factors associated with colorectal cancer risk include smoking, alcohol consumption, limited physical activity, obesity and a Western diet characterized by a high intake of animal fat and red and processed meat, and low intake of dietary fibers.[62,63] A meta-analysis performed by the World Cancer Research Fund (Continuous Update Project Report, Food, Nutrition, Physical Activity, and the Prevention of Colorectal Cancer, 2011) showed that the highest consumers of red and processed meat have a 20% increased colorectal cancer risk when compared with the lowest consumers, whereas no association with poultry was found.[63] A recent meta-analysis found that fish consumption reduced the risk of colorectal cancer by 12%.[64] The evidence for an inverse association between fruit and vegetables is less evident; previous studies have shown small, but non-significant risk reductions for highest consumers, when compared to lowest consumers.[65-67] Inverse associations have also been found for the intake of dairy products with an estimated 17% lower colorectal cancer risk for every 400 grams increase per day.[63]

Colorectal cancer is one of the most common types of cancer and fewer than 60% of patients survive more than 5 years.[68,69] The WCRF/AICR expert panel concluded in its second report that research into the effects of food, nutrition and physical activity in cancer survivors is only in its early stages.[63] Furthermore, studies investigating the role of socioeconomic status in relation to surgical treatment and short-term survival are relatively scarce. Cancer survivors now rely on the personal view of the treating physicians regarding the usefulness of tertiary prevention. Epidemiological studies that investigate the exact impact of diet, lifestyle and socioeconomic status on colorectal cancer survival are required in order to study, promote and incorporate tertiary prevention measures and improve colorectal cancer survival in general.

The aim of the second part of this thesis is to provide more insight in factors that are possibly associated with colorectal cancer development and survival. We first focus on the use of antibiotics and on the consumption of coffee and tea and their association with colorectal cancer risk. Second, we investigate the possible association between the

intake of dairy products and colorectal cancer survival and the effect of socioeconomic status on surgical treatment and short-term survival in patients with colorectal cancer.

### Microbiota and colorectal cancer risk

In the past few years an increasing interest has focused on the role of the gut microbiota in the development of colorectal cancer. The human microbiota consists of approximately $10^{14}$ bacteria of 500-1000 different species. It is important for the defense against pathogens, the metabolization of polysaccharides, the production of certain vitamins and plays a key role in maintaining a healthy immune system.[70] Furthermore, the colonic microbiota ferments undigested carbohydrates from fibers into short-chain fatty acids including butyrate, acetate and propionate,[71,72] which are the preferred energy source of the colon mucosa and possess anti-inflammatory, anti-proliferative and anti-carcinogenic properties.[73-80] High intakes of meat and animal fat increase the bacterial production of genotoxic hydrogen sulfide and the secretion of bile acids which are metabolized into carcinogenic secondary bile acids by 7α-dehydroxylating bacteria.[81,82]

Only a few epidemiological studies have investigated whether an association exists between the colonic microbiota and colorectal cancer development. These studies have shown differences in the composition of the colon microbiota between a low and a high colorectal cancer risk based on diet. A reduced content of short-chain fatty acid producing bacteria[81] and an increase in secondary bile acid producing species have been reported in populations that consume a diet that is linked to a higher risk of colorectal cancer.[83,84] Furthermore, short-chain fatty acid producing bacteria have been found to be depleted in colorectal cancer patients compared to healthy controls.[85,86] These findings suggest a role for the gut microbiota in the development of colorectal cancer and it may therefore be that other factors, besides diet, known to induce a disturbed balance of the gut microbiota are associated with colorectal cancer risk. In this perspective, (frequent) use of antibiotics is of interest since this may affect the diversity of the colonic microbiota. Epidemiological data are scarce, but two cohort studies[87,88] have suggested a positive association between the use of antibiotics, while another case-control study has not.[89] In **chapter 7** the association between the use of antibiotics and colorectal cancer development is investigated using data of a large Dutch health insurance company.

### Coffee and tea consumption and colorectal cancer risk

Coffee and tea are among the most widespread and most consumed beverages in the world. Both contain a mixture of components of which some have been shown to have potential anticarcinogenic effects in animal models and human cell cultures and may play a protective role against colorectal cancer.[90-93] These components include phenolic compounds, chlorogenic acid and diterpenes (cafestol and kahweol) in coffee and catechins and polyphenols in tea.[94,95] In addition, cafestol and kahweol may lower colorectal

cancer risk by reducing bile acid synthesis and secretion, while caffeine inhibits colon cancer cell growth and may lower carcinogen exposure of colonic epithelial cells by increasing colonic motility.[95-98]

Epidemiological studies are inconsistent regarding the association between coffee and tea consumption and colorectal cancer risk. A recent meta-analysis has reported a reduced colon cancer risk for high versus non/low coffee consumers (OR 0.79, 95%-CI 0.67-0.95) in case-control studies but not in cohort studies (OR 0.93, 95%-CI 0.86-1.01).[99] Similarly, in a pooled analysis of cohort studies, high tea consumption was found to be slightly positively associated with colon cancer risk,[100] while others have reported an inverse or no association.[101,102] Due to a limited number of colorectal cancer cases in most previous studies, separate analyses by localization of the cancer (proximal colon, distal colon and rectal cancer) are scarce. Since considerable differences may exist for subsite colorectal cancers with regard to particular risk factors,[66] subsite analyses on the association between coffee and tea consumption and colorectal cancer risk are required. Furthermore, there are no epidemiological studies that have investigated potential effect modification by caffeine metabolization rate. Caffeine is almost completely hydroxylated in the liver by the cytochrome *P450* isoform *CYP1A2* and acetylated by N-acetyltransferase (*NAT)2*.[103,104] *CYP1A2* and *NAT2* activity varies widely between subjects and depend on genetic background (single nucleotide polymorphisms; SNPs) and environmental factors such as diet and certain medication.[105,106] If caffeine as one of the major coffee and tea component lowers colorectal cancer risk, then the association between coffee and tea consumption and colorectal cancer risk may be modified by the *CYP1A2* and *NAT2* depended metabolization of caffeine. In **chapter 8** we use data of the European Investigation into Cancer and Nutrition (EPIC) cohort to investigate the association between coffee and tea consumption and colorectal cancer risk and to study potential effect modification by *CYP1A2* and *NAT2* genotypes.

### Factors associated with colorectal cancer survival

Survival after colorectal cancer diagnosis strongly depends on local tumor extent, lymph node involvement and the presence of distant metastases. Pathological TNM-stage at the time of diagnosis is one of the strongest predictors of colorectal cancer survival.[107] Nonetheless, a great variability remains in colorectal cancer survival. A combination of histological features, genomic profile, lifestyle and environmental factors, and clinical factors influence colorectal cancer prognosis independent from tumor stage.[108-114] In contrast to the large number of studies that have investigated the association between lifestyle and diet on the one hand and colorectal cancer risk on the other hand, studies that have examined an association of these factors with colorectal cancer survival are scarce. Besides, they were often small, retrospective, heterogeneous in study design

and have not resulted in definitive conclusions.[63,115] Many of these studies are ecologic studies, meaning that the results cannot directly be translated to individual patients.

A prospective US study with 1,009 stage III colon cancer patients showed a reduced survival for patients with a Western dietary pattern compared to those with a prudent dietary pattern.[111] Individual foods were not investigated, but a Western diet was characterized by high intakes of meat, fat, grains and desserts, whereas a prudent diet was characterized by high intakes of fruit, vegetables, poultry and fish. Concerning individual food items, high meat consumption was found to be associated with an increased risk of death after colorectal cancer diagnosis (high vs. low consumers: HR 2.24, 95%-CI 1.25-4.03) in one prospective cohort study.[116] In a relatively small French case-control study including 148 colorectal cancer patients who underwent a resection of the tumor, high energy intake was associated with a better 5-year survival, but no significant associations were found for specific foods.[117] There is some evidence that a higher level of non occupational physical activity improves colorectal cancer survival,[118] but this could not be confirmed by other prospective studies.[110,119] However, several prospective cohort studies in stage II and III colorectal cancer patients have shown that highly physically active patients and patients who become more physically active after diagnosis have a lower risk of death compared to patients who are less physical active after diagnosis.[110,119-121] Further, a substantial number of studies have shown that a pre-diagnostic high body mass index (BMI) is associated with an increased colorectal cancer-specific[122-125] and overall mortality risk.[122-128] In addition, an increasing percentage body fat and large waist circumference were found to be associated with an increased risk of death.[118,123] Finally, a recent meta-analysis of prospective cohort studies and nested case-control studies reported a dose-dependent increased risk of colorectal cancer-specific death for current smokers (RR 1.27, 95%-CI 1.05-1.53) and former smokers (RR 1.20, 95%-CI 0.98-1.49). In **chapter 9** data of the EPIC cohort is used to study the association between the pre-diagnostic intake of dairy products and dietary calcium and subsequent colorectal cancer survival.

Another factor that has been found to be associated with colorectal cancer survival, particularly short-term survival, is socioeconomic status.[69,108,129,130] Factors responsible for inequalities in survival between subjects with high and low socioeconomic status have been suggested to include lifestyle, BMI, access to and use of medical care, stage at diagnosis and presence of comorbidities.[131-135] Besides, differences in the administration and adequate dosing of (neo)adjuvant treatment in relation to socioeconomic status have been reported and may affect prognosis in different subgroups of patients.[136-139] Several studies have indicated that socioeconomic status may also be associated with postsurgical mortality.[140-142] In general, patients with non-metastatic colorectal cancer are advised to undergo treatment with curative intent, including resection of the primary tumor. Apart from older age and the presence of serious comorbidities, factors associated with

a poor prognosis after surgical treatment include a low number of examined lymph nodes, residual tumor after surgery, small circumferential resection margin, surgical complications and emergency surgery.[143-145] Few studies have however focused on socioeconomic status-specific disparities regarding surgical treatment characteristics and complications, and their association with short-term outcome after surgery in patients with colorectal cancer.[141,146,147] In **chapter 10** we investigate whether socioeconomic status is associated with differences in surgical treatment and postsurgical mortality in patients with colorectal cancer using data of the Eindhoven Cancer Registry.

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# Part 1

## Strategies to improve the detection of colorectal adenomas

# Chapter 2

## Predicting inadequate bowel preparation for colonoscopy in participants receiving split-dose bowel preparation: development and validation of a prediction score

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*Gastrointestinal Endoscopy 2015 Jan 16. [Epub ahead of print]*

## ABSTRACT

### Background

Adequate bowel preparation is important for optimal colonoscopy. It is important to identify patients at risk for inadequate bowel preparation as this allows taking precautions in this specific group.

### Objective

To develop a prediction score to identify patients at risk for inadequate bowel preparation that may benefit from an intensified bowel cleansing regimen.

### Design

Patient and colonoscopy data were prospectively collected, while clinical data were retrospectively collected for 1,996 colonoscopies in subjects that received split-dose bowel preparation. Multivariable logistic regression analyses were conducted in a random two-thirds of the cohort to develop a prediction model. Validation and evaluation of the discriminative power of the prediction model was performed within the remaining one-third of the cohort.

### Settings

Consecutive colonoscopies in November and December 2012 in four centers.

### Main outcome measurement

Inadequate bowel preparation defined as Boston Bowel Preparation Scale (BBPS) score <6.

### Results

A total of 1,331 colonoscopies were included in the development cohort, of which 172 (12.9%) had an inadequate bowel preparation. Independent factors included in the prediction model were ASA-score ≥3, use of tricyclic antidepressants or opioids, diabetes, chronic constipation, history of abdominal and/or pelvic surgery, history of inadequate bowel preparation and current hospitalization. The discriminative ability of the score was good with an AUC of 0.77 in the validation cohort.

### Limitations

Study design partially retrospective, no data on patient's adherence.

### Conclusion

We developed a validated, easy-to-use prediction score that can be used to identify subjects with an increased risk of inadequate bowel preparation with good accuracy.

## INTRODUCTION

Colonoscopy is currently the predominant method for detecting mucosal abnormalities in the colorectum. Adequate bowel preparation is essential for the efficacy of colonoscopy as inadequate bowel preparation is associated with incomplete colonoscopy, lower adenoma detection rates, increased procedure times and need to repeat the procedure.[1-5] Despite its importance, recent studies still report inadequate bowel preparation in 10%-30% of colonoscopies, even with split-dose bowel preparation.[4-9] The addition of laxatives such as bisacodyl or sennosides to standard bowel cleansing regimens have been shown to improve the quality of bowel preparation.[10,11] Furthermore, some data suggest that it is possible to achieve higher cleansing rates with intensified regimens in patients with previous inadequate bowel preparation.[12] Identification of patients at an increased risk for inadequate bowel preparation may therefore enable physicians to intensify the bowel preparation regimen in order to prevent unnecessary repeat endoscopies and the risk of missing neoplastic lesions.

Risk factors that have been found to negatively affect quality of bowel preparation through inhibition of bowel motility include chronic constipation, liver cirrhosis, diabetes, previous intra-abdominal or pelvic surgery, polypharmacy, use of opioids or tricyclic antidepressants, and factors related to immobilization such as older age, physical condition, obesity, neurological disease and hospitalization.[1,7,8,13-17] An increasing number of these baseline risk factors has been found to be associated with a higher risk of inadequate bowel preparation.[13] Hassan *et al.* developed a prediction model to identify patients at increased risk for inadequate bowel preparation.[8] It was found that this model had a fair accuracy (area-under-curve; AUC 0.63). This study did however also include subjects that were non-compliant with the bowel preparation regimen. Moreover, only 12% of subjects took split-dose bowel preparation which is nowadays recommended as optimal bowel preparation by the European Society of Gastrointestinal Endoscopy.[18]

The aim of the present study was to develop a validated, easy-to-use prediction score to identify patients at risk for inadequate bowel preparation that may benefit from an intensified bowel cleansing regimen.

## METHODS

### Study population and data collection

Centers participating in this study were three medium to large size non-academic and one academic center located in three different regions in the Netherlands. For this observational cohort study we enrolled consecutive colonoscopies that were performed from November 1st to December 31st 2012. Bowel preparation regimens that were applied

in the four centers included 4L Polyethylene glycol (PEG) in two centers and 2L PEG + ascorbic acid in another center. In a fourth center sodium picosulfate + magnesium citrate was used as standard bowel preparation with sodium phosphate used in a selected group of young subjects without comorbidities, and 4L PEG in case of hospitalization.

Patient and procedure related factors were prospectively collected for quality auditing purposes. Data on comorbidities and medication use were collected from the hospital's electronic medical charts.

### Study variables

The primary outcome of this study was inadequate bowel preparation, defined as a Boston Bowel Preparation Scale (BBPS) score below six.[19;20] The BBPS score was assigned by the endoscopist directly after the colonoscopy. Factors possibly associated with the quality of bowel preparation that were collected for this study were based on the available literature[1,7,8,13-17] and included age, body mass index (BMI), the American Society of Anesthesiologists (ASA) physical status classification score, number of non-topical medications, tricyclic antidepressant use, opioid use, diabetes, liver cirrhosis, chronic constipation, history of neurological disease (stroke, spina bifida, dementia, paraplegia or Parkinson disease), history of intra-abdominal/ -pelvic surgery, current hospitalization, previous colonoscopies and history of inadequate bowel preparation. Male sex was not included because its association with inadequate bowel preparation has previously been found to be related to non-adherence to the bowel preparation regimen.[21] Other procedural factors that were collected included indication for colonoscopy (screening/ surveillance, abdominal symptoms/ blood loss/ anemia, inflammatory bowel disease or other), cecal intubation and cause of cecal intubation failure, procedure time (morning or afternoon), inpatient bowel preparation and whether the bowel preparation was taken.

### Statistical analyses

Standard descriptive statistics were used to assess the distribution of study variables. A two-thirds random sample of the total cohort was used for the development cohort to identify risk factors for inadequate bowel preparation and to develop a prediction score. Randomization was done using computer-defined randomization. Data of the remaining one-third of the cohort were used for the validation of the prediction score. Differences between colonoscopies with adequate and inadequate bowel preparation in the development cohort were tested with the Pearson's chi-square test. Study variables that were statistically significantly associated with inadequate bowel preparation were included in a multivariable binary logistic regression analysis in which a selection procedure was performed based on a backward stepwise elimination using likelihood ratio statistics. The regression coefficients of the remaining predictive factors were used to assign inte-

ger points for the prediction score. The discriminative power of the prediction score was assessed by calculating the AUC of the receiver operating characteristics curves (ROC's) in both the development and validation cohort. The sensitivity, specificity, positive (PPV) and negative predictive values (NPV) of different cut-off points were determined in the validation cohort. All statistical analyses were conducted with IBM SPSS Statistics 20.0 (IBM Corp., Armonk, NY, USA). Two-sided p-values <0.05 were considered statistically significant.

## RESULTS

After the exclusion of colonoscopies with unknown bowel preparation score (n=29), absence of clinical data (n=98), incomplete colonoscopy caused otherwise than inadequate bowel preparation (n=76), patients who did not take the bowel preparation (n=8) and patients who were hospitalized for inpatient bowel preparation due to previous inadequate bowel preparation (n=74), a total of 1,996 colonoscopies remained for the analyses (see Figure 1). Indications for colonoscopy were screening/ surveillance (n=542, 27%), abdominal symptoms/ blood loss/ anemia (n=1,194, 60%), inflammatory bowel disease (n=177, 9%) and others (n=83, 4%). All patients took a split-dose bowel preparation according to the standard protocols of the participating centers with 4L Polyethylene glycol (PEG) (n=922, 46%), 2L PEG + ascorbic acid (n=798, 40%), sodium picosulfate + magnesium citrate (n=236, 12%) or sodium phosphate (n=40, 2%).

Mean ± SD BBPS scores were 7.3 ± 1.8 in the development cohort and 7.4 ± 1.9 in the validation cohort (p=0.25). Inadequate bowel preparation was found in 172 (12.9%) cases in the development cohort and in 77 (11.6%) cases in the validation cohort (p=0.39). Mean age (p=0.38) and male/female distribution (p=0.27) were similar in the development cohort (57.5 ± 15.9 years, 44.9% male) and validation cohort (56.8 ± 16.0 years, 47.5% male). There were no statistically significant differences between the

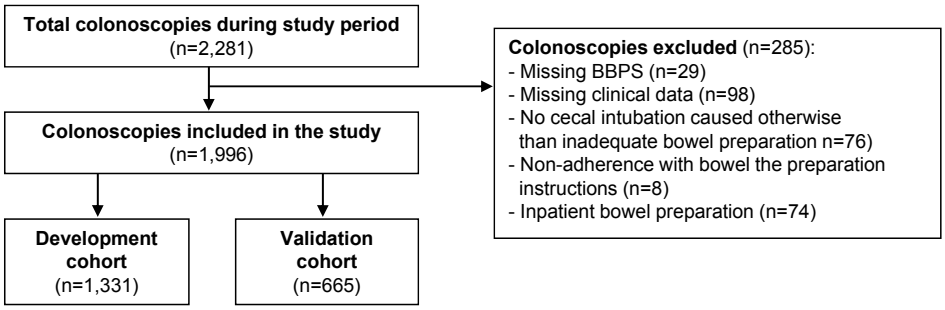


**Figure 1.** Study flow-chart.

**Table 1.** Distribution and multivariable binary logistic regression analyses for patient, clinical and procedural factors in association with inadequate bowel preparation in the development cohort.

| Risk factors | Adequate bowel prep (n=1,159) | Inadequate bowel prep (n=172) | P-value[1] | Adjusted OR (95%-CI) |
|---|---|---|---|---|
| **Age (years), n (%)** | | | | |
| < 50 | 337 (29.1) | 42 (24.4) | 0.50 | |
| 50 - 59 | 244 (21.0) | 34 (19.8) | | |
| 60 - 69 | 302 (26.1) | 49 (28.5) | | |
| ≥ 70 | 276 (23.8) | 47 (27.3) | | |
| **Sex** | | | | |
| Male | 506 (43.7) | 92 (53.5) | 0.02 | |
| Female | 653 (56.3) | 80 (46.5) | | |
| **BMI (kg/m$^2$), n (%)** | | | | |
| < 25 | 198 (17.1) | 26 (15.1) | 0.66 | |
| 25 - 29 | 181 (15.6) | 25 (14.5) | | |
| ≥ 30 | 110 (9.5) | 21 (12.2) | | |
| Missing | 670 (57.8) | 100 (58.1) | | |
| **ASA-score, n (%)** | | | | |
| 1 | 735 (63.4) | 73 (42.4) | | ref. |
| 2 | 365 (31.5) | 69 (40.1) | < 0.001 | 1.3 (0.9 - 2.0) |
| ≥ 3 | 59 (5.1) | 30 (17.5) | | 2.5 (1.3 - 4.6) |
| **Number of medications, n (%)** | | | | |
| 0 - 3 | 736 (63.5) | 77 (44.8) | | ref. |
| 4 - 6 | 240 (20.7) | 42 (24.4) | < 0.001 | 1.2 (0.8 - 1.8) |
| 7 - 9 | 106 (9.1) | 24 (14.0) | | 0.8 (0.4 - 1.5) |
| ≥ 10 | 77 (6.7) | 29 (16.9) | | 1.0 (0.5 - 1.8) |
| **Medication use, n (%)** | | | | |
| Tricyclic antidepressants | 15 (1.3) | 11 (6.4) | < 0.001 | 5.3 (2.3 - 12.5) |
| Opioids | 51 (4.4) | 23 (13.4) | < 0.001 | 1.9 (1.0 - 3.6) |
| **Comorbidities, n (%)** | | | | |
| Diabetes | 114 (9.8) | 39 (22.7) | < 0.001 | 2.1 (1.3 - 3.4) |
| Liver cirrhosis | 4 (0.3) | 2 (1.2) | 0.14 | |
| Chronic constipation | 120 (10.4) | 39 (22.7) | < 0.001 | 2.7 (1.7 - 4.3) |
| Neurological disease | 31 (2.7) | 13 (7.6) | < 0.01 | 1.8 (0.8 - 4.0) |
| **History of intra-abdominal/ -pelvic surgery, n (%)** | 399 (34.4) | 84 (48.8) | < 0.001 | 1.8 (1.3 - 2.6) |
| **Current hospitalization, n (%)** | 66 (5.7) | 27 (15.7) | < 0.001 | 1.8 (1.0 - 3.1) |
| **Previous colonoscopy, n (%)** | 408 (35.2) | 58 (33.7) | 0.70 | |
| **History of inadequate bowel preparation, n (%)** | 81 (7.0) | 27 (15.7) | < 0.001 | 1.8 (1.1 - 3.0) |
| **Indication of colonoscopy, n (%)** | | | | |
| Abdominal symptoms/ blood loss/ anemia | 673 (58.1) | 114 (66.3) | 0.04 | |
| Screening/ surveillance | 327 (28.2) | 36 (20.9) | | |
| Inflammatory bowel disease | 105 (9.1) | 19 (11.1) | | |
| Other | 54 (4.6) | 3 (1.7) | | |
| **Procedural time, n (%)** | | | | |
| Morning | 595 (51.3) | 79 (45.9) | 0.19 | |
| Afternoon | 564 (48.7) | 93 (54.1) | | |

1. Pearson chi-square.

OR = odds ratio, 95%-CI = 95% confidence interval, BMI = body mass index, ASA-score = American Society of Anesthesiologists score.

development cohort and the validation cohort with respect to clinical and procedural characteristics (data not shown).



### Univariable and multivariable analyses

Results of univariable and multivariable analyses in the development cohort are shown in Table 1. Factors that were univariable associated with inadequate bowel preparation were increasing ASA-score, increasing number of medications, use of tricyclic antidepressants and opioids, a history of diabetes, chronic constipation, neurologic disease, intra-abdominal/ -pelvic surgery and inadequate bowel preparation, and current hospitalization. After multivariable logistic regression analysis with backward stepwise elimination, ASA-score ≥ 3, tricyclic antidepressants, opioids, a history of diabetes, chronic constipation, intra-abdominal/ -pelvic surgery and inadequate bowel preparation, and current hospitalization remained independently associated with inadequate bowel preparation and were included for the development of the prediction score. Male sex (univariable OR 1.48, 95%-CI 1.08-2.05) and screening/surveillance colonoscopy versus other indications (univariable OR 0.67, 95%-CI 0.46-0.99) were associated with inadequate bowel preparation but not included in the prediction model.

### Prediction score for inadequate bowel preparation

We assigned points for each predictive factor based on the regression coefficients as displayed in Table 2. The total prediction score may range between 0 - 12 and higher risk scores are associated with an increasing risk of inadequate bowel preparation (see Figure 2). The ROC's of the development and validation cohorts are shown in Figure 3. The prediction score had an AUC of 0.72 (95%-CI 0.68-0.76) in the development cohort and 0.77 (95%-CI 0.71-0.83) in de validation cohort. In the validation cohort, a prediction

**Table 2.** Independent predictive factors for inadequate bowel preparation and derivation of a prediction score.

| Predictive factors | Regression Coefficient | Score |
|---|---|---|
| ASA-score ≥ 3 | 0.993 | 2 |
| Tricyclic antidepressants | 1.653 | 3 |
| Opioids | 0.535 | 1 |
| Diabetes | 0.748 | 1 |
| Chronic constipation | 0.935 | 2 |
| History of intra-abdominal/ -pelvic surgery | 0.490 | 1 |
| Current hospitalization | 0.617 | 1 |
| History of inadequate bowel preparation | 0.673 | 1 |
| ***Total score*** | | ***12*** |

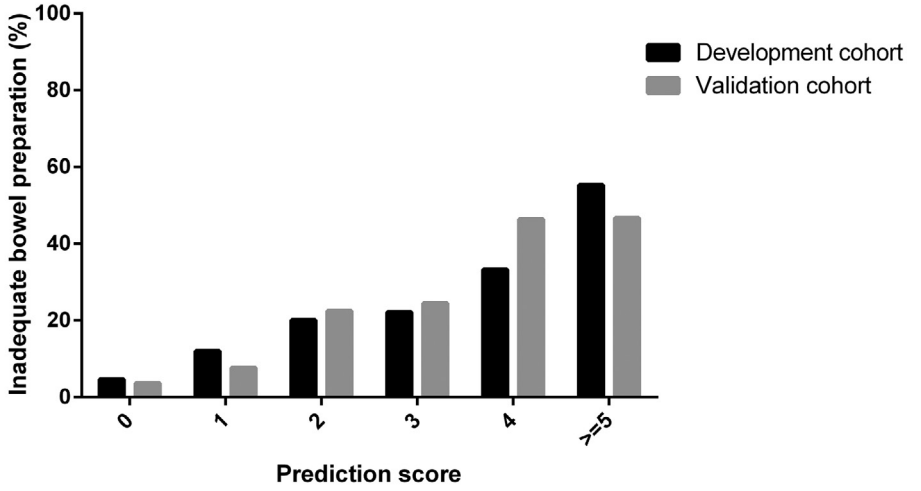


**Figure 2.** Frequencies of patients with inadequate bowel preparation depending on prediction scores.

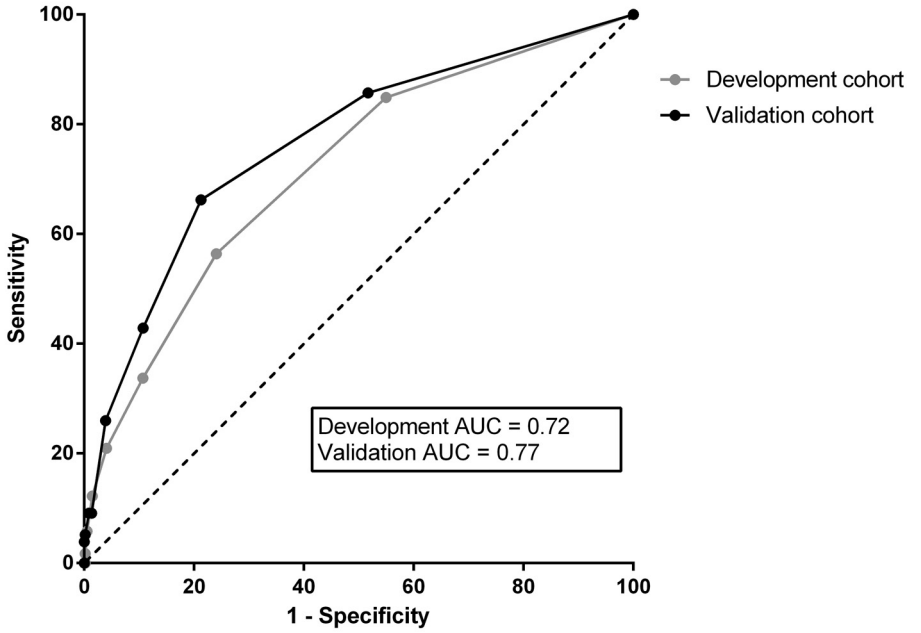


**Figure 3.** Receiver operating characteristics curves of the prediction model in the development cohort and validation cohort.

score of ≥ 2 was found in 26% of the subjects and resulted in a 66% sensitivity, 79% specificity, 29% PPV and 95% NPV. A prediction score of ≥ 3 was found in 14% of the subjects and resulted in a 43% sensitivity, 90% specificity, 34% PPV and 93% NPV.

## DISCUSSION

For an optimal colonoscopy it is indispensable to achieve an adequate level of bowel preparation. This study shows that the clinical factors ASA-score ≥ 3, use of tricyclic antidepressants and opioids, diabetes, chronic constipation, abdominal and/or pelvic surgery, hospitalization and a history of inadequate bowel preparation are independent risk factors for inadequate bowel preparation. Based on these risk factors we were able to design a validated and easy-to-use prediction score that allows identifying patients at risk for inadequate bowel preparation. To our knowledge, the present study is the first that describes a prediction model with this level of discrimination. Moreover, we developed this prediction score in a well-defined and representative population undergoing colonoscopy.

Several previous studies have reported independent risk factors for inadequate bowel preparation. A distinction can be made between factors associated with poor bowel cleansing through a biological effect, i.e. by inhibiting bowel motility, and factors associated with non-adherence to the bowel preparation regimen such as health awareness, educational level, illiteracy, marital status, appointment waiting time, indication of colonoscopy and male sex.[14,16,17,22] As we intended to develop a prediction model for the identification of subjects that may potentially benefit from an intensified bowel preparation regimen, we did not include factors associated with non-adherence in the model. Factors that were included in our final prediction score have all been reported previously.[1,7,8,13-17] However, some of these risk factors, such as increasing age, polypharmacy, overweight and liver cirrhosis were not independently associated with inadequate bowel preparation in our study. In the case of liver cirrhosis this is probably due to a lower number of subjects with this condition in our study population. BMI was missing in more than half of the patients and is likely to be not statistically significant due to insufficient sample size. ASA-score was found to be an independent risk factor for inadequate bowel preparation, which as to our knowledge has not been reported previously. The ASA-score reflects the clinical condition of a patient and serves as a surrogate marker for patient's age, physical condition, obesity, medication use and comorbidities, all factors that have been shown to be associated with poor bowel preparation.

Although it is difficult to directly compare results between different studies, we were able to develop a prediction model with a better discriminative power than a previous model reported by Hassan *et al.* [8] An important factor that may have contributed to this discrepancy is the case-mix of the study populations. This is reflected by the remarkable difference in inadequate bowel preparation rates of 32.9% reported by Hassan *et al.* and only 12.5% in our study. This may have been caused by the fact that our population was routinely prescribed split-dose bowel preparation whereas this was taken by only 12.3% of the subjects in the study by Hassan *et al.* Furthermore, we excluded subjects

that did not adhere to the bowel preparation regimen or were admitted to the hospital for inpatient bowel preparation. Most importantly is however the differences in risk factors that were included in both prediction models. Apart from diabetes and previous colorectal surgeries, none of the clinical factors included in our model were included by Hassan *et al.* On the other hand, these colleagues included non-adherence to the bowel preparation instructions, factors associated with non-adherence and procedural factors such as split-dose preparation and time between preparation and colonoscopy to predict inadequate bowel preparation.

The strengths of our study include the large study population from four different centers in the Netherlands and the prospectively collected data on BBPS score, demographic characteristics, ASA-score and procedural variables. Furthermore, to improve the generalizability and applicability of our prediction score we only included risk factors that can be modified using an intensified bowel cleansing and excluded factors that relate to non-adherence. Finally, we excluded all patients who underwent inpatient bowel preparation because in those cases the treating physician already anticipated on an increased risk of poor bowel cleansing. Nonetheless, there are also some limitations. First, data on BMI, medication use and comorbidities were retrospectively collected from electronic medical charts and were incomplete in 98 (4.3%) cases, as were data on BBPS scores in 29 (1.3%) cases. The potentially important factor BMI was not registered in more than half of the subjects and could therefore not be included in our prediction model. Second, only 12.5% of the total study population had an inadequate bowel preparation, which is on the lower end of the range reported in literature, with inadequate bowel preparation rates varying between 10 and 44% in subjects taking split-dose bowel preparation.[4-9] Patients in our cohort may have been more adherent to the bowel preparation instructions compared to populations from previous studies. This is supported by the fact that in three of the four participating centers patients were actively informed about the importance of bowel preparation quality during pre-colonoscopy screening visits. Furthermore, we found that only eight patients did not take any bowel preparation at all. On the other hand, endoscopists may have systematically rated the quality of the bowel preparation too high in patients who actually had a poorer bowel preparation, leading to an underestimation of the association between predictive factors and the study outcome. Although we did not test this in the present study, we believe this is unlikely because the inter- and intra-rater reliability has reported to be high for the BBPS.[19,23] Third, although we know of eight patients that did not take the bowel preparation at all, we do not have data on how many patients were only partially adherent to the dietary instructions and prescribed bowel preparation. Fourth, we did not exclude repeat colonoscopies, meaning that in cases where a patient underwent two colonoscopies in the study period he/she was included twice. The reason that we did not exclude these repeat colonoscopies was that we a-priori hypothesized that a

history of inadequate bowel preparation is a risk factor for future bowel preparation. Finally, although we randomly divided the study population in a development cohort and validation cohort, we did not validate our findings in a new cohort. Nonetheless, we validated our prediction score in a separate cohort and this showed that our score is likely reproducible. Moreover, we included four centers from different regions in the country, which also contributes to the generalizability of the results.

Our findings have several important implications for clinical practice. First, we confirmed that various clinical risk factors are associated with inadequate bowel preparation. Second, our prediction score is only based on clinical factors that interfere with bowel motility and is able to identify patients at risk for inadequate bowel preparation with sufficient accuracy. This means that it is possible to identify high-risk patients who could benefit from an intensified bowel preparation regimen. Such an approach requires a prediction score with good sensitivity to identify high-risk patients but with sufficient specificity to prevent that patients undergo unnecessary interventions to the improve bowel cleansing. When using a cut-off point of ≥2 to define an increased risk, 66% of subjects with poor bowel preparation were identified in our cohort. However, 21% of patients with adequate bowel preparation were wrongly classified as subjects with an increased risk. A cut-off point of ≥3 would remarkably improve the specificity, resulting in only 10% of low-risk subjects mistakenly being classified as high-risk patients, but this lowers the sensitivity to 43%. A cut-off value of ≥2 therefore gives the most optimal sensitivity, but depending on the intensiveness of intervention that is prescribed to patients to improve the quality of bowel cleansing in the high risk group, a cut-off of ≥3 may be more suitable if unnecessary measures should be as low as possible. Nonetheless, by applying this prediction score, the quality of colonoscopy may well be improved through better visualization and preventing unnecessary repeat colonoscopies.

In conclusion, in this study some important independent clinical risk factors for inadequate bowel preparation were identified and a validated, easy-to-use prediction score with good discriminative power was developed. By applying this prediction score, a considerable number of subjects with poor bowel preparation that are potentially eligible for intensified bowel preparation can be identified with only a small subgroup of subjects being wrongly classified as having an increased risk of poor bowel preparation.

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# Chapter 3

## Endoscopic innovations to increase the adenoma detection rate during colonoscopy

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*World Journal of Gastroenterology. 2014 Mar 7;20(9):2200-11.*

## ABSTRACT

Up to a quarter of polyps and adenomas are missed during colonoscopy due to poor visualization behind folds and the inner curves of flexures, and the presence of flat lesions that are difficult to detect. These numbers may however be conservative because they mainly come from back-to-back studies performed with standard colonoscopes, which are unable to visualize the entire mucosal surface. In the past several years, new endoscopic techniques have been introduced to improve the detection of polyps and adenomas. The introduction of high definition colonoscopes and visual image enhancement technologies have been suggested to lead to better recognition of flat and small lesions, but the absolute increase in diagnostic yield seems limited. Cap assisted colonoscopy and water-exchange colonoscopy are methods to facilitate cecal intubation and increase patients comfort, but show only a marginal or no benefit on polyp and adenoma detection. Retroflexion is routinely used in the rectum for the inspection of the dentate line, but withdrawal in retroflexion in the colon is in general not recommended due to the risk of perforation. In contrast, colonoscopy with the Third-Eye Retroscope® may result in considerable lower miss rates compared to standard colonoscopy, but this technique is not practical in case of polypectomy and is more time consuming. The recently introduced Full Spectrum Endoscopy™ colonoscopes maintain the technical capabilities of standard colonoscopes and provides a much wider view of 330 degrees compared to the 170 degrees with standard colonoscopes. Remarkable lower adenoma miss rates with this new technique were recently demonstrated in the first randomized study. Nonetheless, more studies are required to determine the exact additional diagnostic yield in clinical practice. Optimizing the efficacy of colorectal cancer screening and surveillance requires high definition colonoscopes with improved virtual chromoendoscopy technology that visualize the whole colon mucosa while maintaining optimal washing, suction and therapeutic capabilities, and keeping the procedural time as low and patient discomfort as optimal as possible.

## INTRODUCTION

Colonoscopy is considered the gold standard for the detection and removal of polyps and adenomas in the colorectum. There is strong evidence that the removal of polyps and adenomas by colonoscopy lowers colorectal cancer incidence and mortality.[1,2] However, in recent years there has been an increasing concern about the effectiveness of colonoscopy for the detection of adenomas and early-stage colorectal cancer, and especially right-sided cancers.[3] Population-based studies have reported that 3%-8% of patients with colorectal cancer had a colonoscopy within 3-5 years prior to colorectal cancer diagnosis.[4-6] Retrospective studies revealed that these so-called interval or post-colonoscopy cancers can mainly be attributed to missed lesions or inadequate examination.[5] Indeed, a considerable proportion of polyps and adenomas are being missed with colonoscopy, with overall polyp and adenoma miss rates being estimated between 20%-25% in most back-to-back colonoscopy studies.[7]

The main factors thought to be responsible for missing lesions, besides endoscopist dependent factors, include the relative difficulty to visualize polyps at the proximal side of haustral folds and internal curves of flexures,[8,9] the presence of flat lesions[10] and poor bowel preparation.[11] In addition, especially right-sided advanced adenomas are more often diminutive in size or non-polypoid in appearance compared to left-sided advanced adenomas and may therefore be more easily overlooked.[10,12] Surface visualization with standard 140 and 170 degrees colonoscopes is approximately between 87% and 92% in a clean colon, which illustrates the limitation of standard colonoscopes to adequately visualize the entire mucosa.[13] As a result, premalignant lesions can be missed and it has been shown that two-thirds of the non-rectal ≥ 6 mm lesions that are missed during colonoscopy are located on the proximal side of folds.[9]

In the recent years, new endoscopic technologies aimed to increase polyp detection rates (PDR) and adenoma detection rate (ADR) have been developed. In this review we will discuss these endoscopic innovations and their potential to improve the detection of premalignant lesions during colonoscopy (Table 1).

## HIGH-DEFINITION COLONOSCOPY

High definition colonoscopy uses a high definition monitor that enables more images per second to be shown. Moreover, the images have a higher resolution as compared to standard definition colonoscopy. Although high definition colonoscopy provides much better imaging, studies evaluating polyp detection with high definition as compared to standard definition colonoscopes are scarce and show conflicting results.[14] Two randomized trials[15,16] found no significant differences in ADR and PDR between both techniques.

**Table 1.** Endoscopic innovations to improve the adenoma detection during colonoscopy

| Technique | Colonoscopy technology |
|---|---|
| *High definition* | High definition monitor with more images per second and high resolution. |
| *Narrow Band Imaging (NBI)* | Narrow band filters increase blue (415 nm) and green (540 nm) wavelengths and enhance the visualization of mucosal blood vessels. |
| *Fujinon Intelligent Color Enhancement (FICE)* | Computed spectral estimation technology enhances the visibility of mucosal and vascular details by narrowing the bandwidth of light. |
| *Auto Fluorescence Imaging (AFI)* | Tissue is exposured to light of short wavelength, which leads to the excitation of endogenous substances and the emission of autofluorescent light. |
| *Water-immersion colonoscopy* | Infusion of water, combinated with air-insufflation, during insertion of the colonoscope. Water and remaining fecal content are removed during withdrawal. |
| *Water-exchange colonoscopy* | Water containing residual feces is removed and "exchanged" for clean water during insertion in lieu of air-insufflation. |
| *Cap-assisted colonoscopy* | Can be used to depress colonic folds to improve the visualization of proximal aspects of these folds. |
| *Retroflexion* | Withdrawal in retroflexion is possible in the proximal colon due to the large diameter of this segment and may improve the visualization of the proximal aspects of folds. |
| *Third-Eye Retroscope* | The retroscope is retroflexed 180 degrees after being advanced through the working channel and enhances the visualization behind folds. |
| *Full Spectrum Endoscopy (FUSE)* | Three imagers positioned at the front and both sides of the tip provide a 330 degrees view, which improve the visualization of the internal lining of flexures and proximal aspects of folds. |

In contrast, one randomized study reported a higher PDR (64% *vs.* 53%, p = 0.03) and mean number of small hyperplastic polyps per subject (0.10 *vs.* 0.25, p = 0.003) with high definition colonoscopy,[17] while in another randomized multicenter study[18] high definition colonoscopy yielded more adenomas per subject (1.12 *vs.* 0.69, P = 0.02) and especially flat adenomas and right-sided adenomas (both p < 0.01). Furthermore, East *et al.*[19] reported in a prospective non-randomized study more diminutive (< 6 mm), non-flat adenomas with high definition colonoscopy, although no significant differences in ADR and PDR could be demonstrated. Similar results were found in a retrospective study by Buchner *et al.*[20] including 1226 patients undergoing standard definition colonoscopy and 1204 patients undergoing high definition colonoscopy. Both ADR (28.8% *vs.* 24.3%)

| Diagnostic yield | Clinical applicability |
|---|---|
| Marginal increase in number of polyps and adenomas, mostly small, flat, right-sided lesions. ~3.5% increase in ADR. | High quality images with reduced artifacts and more natural appearance. |
| Small increase in flat and small serrated lesions, but higher detection rates when combined with high definition. | Possibly improving the detection of subtle lesions, but insufficient brightness and dark appearing bile and stool prohibit optimal pan-colonic use. |
| Very few randomized studies but polyp and adenoma detection seems similar compared to white light colonoscopy. | Like with NBI, images are too dark to advice routine pan-colonic use. |
| AFI has lower adenoma miss rates (absolute difference of ~20%) when compared to white light colonoscopy, especially for flat and depressed lesions. | Not advised for routine practice in colonoscopy due to low resolution images, few images per second and artifacts due to residual fecal fluids. |
| No difference in ADR between water-immersion and air-insufflated colonoscopy. | Reduces pain scores, need for sedation and general intolerability, but only studied in highly experienced hands. |
| ADR is reported to be ~10% higher with water-exchange colonoscopy compared to standard air-insufflated colonoscopy. | Provides extra cleansing of the mucosa but is more time consuming and is thus far only studied in highly experienced hands. |
| Contradicting results with ~10% higher detection rates for small polyps and adenomas in some studies, but no beneficial results in others. | Easy to use, can assist during mucosectomies and facilitates introduction of the colonoscope, but probably has a limited effect on diagnostic yield. |
| No additional diagnostic yield in the proximal colon and questionable in the rectum. | Routine withdrawal in retroflexion is not recommended but may facilitate the removal of large sessile polyps. |
| Limited number of studies, but polyp and adenoma detection are reported to be 15%-25% higher compared to standard colonoscopy. | Increases diagnostic yield, but reduces suctioning capacity when in position and needs to be removed from working channel in case of polypectomy. |
| One randomized tandem study thus far, which showed considerably lower miss rates for polyps (9.7% vs. 43.%) and adenomas (7.5% vs. 40.8%) compared to standard colonoscopy. | Provides a comprehensive view while maintaining technical capabilities of standard colonoscopes. Requires little training. |

and PDR (42.2% *vs.* 37.8%) were statistically significantly higher with high definition colonoscopy but this mainly concerned smaller lesions.

Hence, the use of high definition colonoscopy leads to high quality images and a marginal increase in ADR and PDR compared to standard definition colonoscopy. The absolute increase in ADR is however small and is estimated to be approximately 3.5% according to a meta-analysis with pooled data of five studies in 4422 patients.[21] The additional value of high definition colonoscopy seems mainly limited to small lesions and, according to one study, flat lesions in the right colon. However, caution is required when interpreting the results because marked heterogeneity exists with differences in study design and the type of population included.

## VIRTUAL CHROMOENDOSCOPY

Virtual chromoendoscopy uses a narrow spectrum of wavelengths with a decreased penetration depth to enhance visualization of the colon mucosa and has been developed as an alternative to dye assisted chromoendoscopy. Light of short wavelengths increases the vascular contrast of the mucosa, allowing improved visualization of the colonic mucosal surface. Manufactures have developed multiple techniques including Narrow Band Imaging (NBI), Fuji Intelligent Color Enhancement (FICE) and Auto Fluorescence Imaging (AFI), which can easily be switched on during colonoscopy. These techniques have been suggested to improve the detection of (subtle) mucosal lesions.[22-24]

### Narrow band imaging

NBI (Figure 1) is one of the most widely used and extensively studied image enhancement technologies and is aimed to improve adenoma detection and differentiation. Narrow band filters placed behind the light source eliminate red light and increase the contribution of blue (415 nm) and green (540 nm) wavelengths. The 415 nm light enhances the visualization of superficial mucosal capillaries while the 540 nm light increases the visibility of submucosal and deeper mucosal vessels.

Studies investigating the additional yield of pan-colonic NBI are somewhat conflicting. A meta-analysis including six randomized trials with a total of 2,284 patients[23] reported no significant differences between high definition NBI and high definition white light colonoscopy for the detection of total, flat and < 10 mm adenomas or polyps. Furthermore, no differences in adenoma or polyp miss rates were observed between both techniques. These findings were recently confirmed in a large randomized study by Chung *et al*.[25] In contrast, studies in which high definition NBI was compared to standard

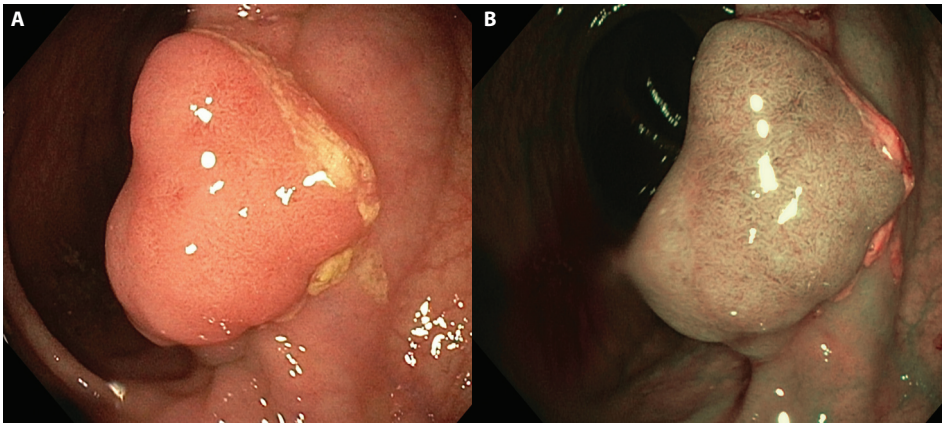


**Figure 1.** Adenomatous polyp with white light (A) and Narrow Band Imaging (B).

definition colonoscopy have shown differences in detection and miss rates of polyps and adenomas.[18,26,27] In a randomized back-to-back study by Gross *et al.*[27] comparing high definition NBI and standard definition colonoscopy, significant lower miss rates for polyps (31% *vs.* 57%, P = 0.005) and adenomas (27% *vs.* 49%, P = 0.036) were observed. However, the same group reported similar results in a retrospective study comparing high definition white light to standard definition white light colonoscopy, which suggests that the additional yield obtained with high definition NBI may be related to the high definition component and not to the use of NBI.[20] This is further supported by a study of Rastogi *et al.*[18] in which more adenomas per subjects were found with high definition NBI (1.13) compared to standard definition white light (0.69, P = 0.01) but not to high definition white light colonoscopy (1.12). In the latter study, high definition NBI detected significantly more flat and right sided lesions compared to standard definition colonoscopy but a similar number compared to high definition colonoscopy. A back-to-back study including patients with hyperplastic polyposis syndrome also reported a lower polyp miss rate, in particular for flat polyps and sessile serrated adenomas, when high resolution NBI colonoscopy was compared to white light colonoscopy.[28] Two randomized studies that compared high definition NBI with high definition white light colonoscopy[29,30] reported no difference in adenoma detection, but high definition NBI yielded more flat adenomas[29,30] and hyperplastic polyps.[29]

In summary, polyp and adenoma detection seem to be higher with high definition NBI compared to standard definition white light colonoscopy, but the additional value of high definition NBI over high definition white light colonoscopy may be limited to the detection of subtle lesions such as small serrated lesions and flat adenomas. It has been suggested that the limited value of high definition NBI over high definition white light colonoscopy may be related to the potential learning effect that is induced by NBI during colonoscopy, i.e. the introduction of NBI may have improved the recognition of polyps and adenomas with white light colonoscopy.[23] In this regard, it is of interest that East *et al.*[31-33] showed that the improvement in adenoma detection rate by high definition NBI colonoscopy over high definition white light colonoscopy declined from 61% in the first 52 patients to 45% and only 8% in a second and third group of 91 and 214 patients. A similar effect was observed in a study by Adler *et al.*[34] with consecutive groups of 100 patients undergoing white light colonoscopy; the ADR of 8% in the first group increased to 26% in the last group of patients, compared to an ADR of 25% with NBI which remained unchanged during the course of the study.

### Fuji Intelligent Color Enhancement

FICE is a computed spectral estimation technology that enhances the visibility of mucosal and vascular details by narrowing the bandwidth of light. FICE enables the endoscopist to choose between different wavelengths for optimal examination of the

colon mucosa.[24] Only a limited number of studies have evaluated FICE colonoscopy for its proposed increased capability to detect of adenomas and polyps. In the reported randomized back-to-back studies that compared FICE with white light colonoscopy[25,35] or NBI[36] no significant benefit of FICE was demonstrated. Furthermore, in an earlier randomized study[37] the ADR and mean number of adenomas were similar with FICE compared to targeted indigocarmine chromoendoscopy.

**Auto Fluorescence Imaging**

Real-time pseudo-color images produced with AFI are created by a rotating filter producing a short wavelength light. The exposure of tissue to this specific light leads to the excitation of some endogenous substances and subsequently the emission of fluorescent light. The autofluorescent image produced with AFI is created by a green filter, which exposes the tissue to the remaining blue and red light. The reflected blue light is blocked by a second filter while the reflected red light and the emitted green auto fluorescence from the tissue are used to obtain a pseudo-color image.[22,38] AFI colonoscopy colors neoplastic lesions red-purple while non-neoplastic mucosa appears green.

Three back-to-back studies reported lower adenoma miss rates with AFI colonoscopy compared to white light colonoscopy with an absolute difference of approximately 20%.[39-41] In one of these studies,[39] the location, size, macroscopic appearance and histopathology of the lesions detected with AFI and white light colonoscopy were not different, but the lesions that were histologically graded as dysplastic were less frequently missed with AFI (30% *vs.* 49%, P = 0.01). Another study by Moriichi *et al.*[40] compared AFI with high resolution white light colonoscopy and reported a higher ADR (26.1% *vs.* 18.2%, $p < 0.05$) and more specifically a higher detection rate of flat and depressed adenomas (9.1% *vs.* 3.4%, $p < 0.05$). In the same study, an increased ADR with AFI was only observed when used by less experienced endoscopists. One study investigated the diagnostic yield of high resolution colonoscopy using Endoscopic Trimodal Imaging technology.[42] These colonoscopes have both AFI and NBI technology incorporated in the endoscope. The high resolution and AFI technology in these colonoscopes can be used to detect lesions ("red flag"), whereas NBI can be used to differentiate between different types of lesions. The study was performed in six non-academic centers and showed no differences in ADR or adenoma miss rate compared to standard white light colonoscopy.

In summary, the effect of pan-colonic virtual chromoendoscopy on adenoma and polyp detection seems limited and virtual chromoendoscopy probably only has a minor benefit on the detection of small and flat lesions. These somewhat disappointing results are most likely due to technical issues inherent to virtual chromoendoscopy, in that the brightness of the virtual image with high-definition technology remains insufficient to

allow optimal visualization of the colonic mucosa in a large diameter colon lumen. In addition, a good inspection of the colon mucosa with virtual chromoendoscopy is only possible in a colon that is really optimally prepared because remaining bile fluid and stool appear red and dark in virtual images, hindering an optimal view of the mucosa.[43] In our opinion, virtual chromoendoscopy is most optimally used as an add-on technology to differentiate between neoplastic and non-neoplastic lesions. This could allow a "resect-and-discard" or "leave-in-situ" approach to reduce the risk of complications and costs associated with unnecessary removal of polyps. However, accuracy rates should exceed well above 90% to consider such an approach. In experienced hands, high accuracy rates for a "resect-and-discard" policy have been reported for NBI,[44-46] FICE[47,48] and AFI,[49] ranging between 85%-92% when used with high magnification, but these rates are lower when used by non-experts.[42,44,50] Good training may improve the detection and differentiation of lesions, but before the routine use of pan-colonic virtual chromoendoscopy can be justified, new generation devices with higher light intensity are required.



## WATER-INFUSION TECHNIQUES

Colonoscopy techniques combining or replacing air-insufflation with water infusion were initially designed to facilitate cecal intubation, reduce colonic spasms, lower patient discomfort and need for sedation.[51,52] The infusion of water during the insertion of the colonoscope causes the colon to distend and can be combined with air-insufflation (water-immersion method) or be performed without air-insufflation (water-exchange method).[53,54] Similarly to standard air-insufflated colonoscopy, air is also insufflated during withdrawal of the colonoscope irrespective of the type of water infusion technique used. The water-immersion technique allows the water to flow in the direction of the lumen which may aid in finding the correct direction for intubation. The infused water and remaining fecal contents are mainly removed during withdrawal of the colonoscope.

This method has been shown to reduce pain scores,[55-61] need for sedation[55,59,62] and general intolerability in most studies,[55,59,60] but concerns have been raised about an impaired ability to detect lesions due to contaminated water impairing visibility. A recent systematic review[53] in which the results of six studies were combined, reported no differences in ADR between water-immersion and air-insufflated colonoscopy. In contrast, the recently developed water-exchange method was reported to increase ADR compared to air-insufflation colonoscopy in the first observational study (water-exchange 36.5% *vs.* air 25.8%, P = 0.18).[63] in a subsequent retrospective cohort study (water-exchange 34.9% *vs.* air 26.9%, P = 0.003)[64] and in a head-to-head comparison study (water-exchange 57.1% *vs.* air 46.1%, P = 0.04).[65] In two randomized controlled trials.[62,66] ADR was higher

with the water-exchange method but this difference was not statistically significant. The water-exchange method is a technique in which water containing residual feces is removed and "exchanged" for clean water in lieu of air-insufflation. The exchange of large volumes of water during the insertion of the colonoscope results in additional cleansing of the mucosa, which has been proposed to improve the detection of adenomas.[53] An alternative hypothesis is that the improved cleansing during colonoscope insertion allows more time for inspection during withdrawal since less time needs to be spent on colonic cleansing. Nonetheless, several attempts have been made to improve the efficacy of water-exchange colonoscopy. In a group of 50 consecutive US veterans undergoing water-exchange colonoscopy, indigocarmine was added to the infused water (concentration 0.008%).[67] The ADR was significantly higher in the indigocarmine group in comparison with a historical cohort of patients who had undergone standard water-exchange colonoscopy (62% *vs.* 40%, $p < 0.05$) or air-insufflation colonoscopy (62% *vs.* 36%, $p < 0.05$). In a pilot study by Yen *et al.*,[68] the water-exchange method was combined with cap assisted colonoscopy in 50 consecutive patients. The results were compared to a control group of 101 consecutive patients undergoing air-insufflation colonoscopy. It was demonstrated that the mean number of adenomas was higher with the water-exchange cap assisted colonoscopy method compared to air-insufflated colonoscopy (3.08 *vs.* 1.50, $P = 0.002$), although the ADR was not statistically significantly higher (70.0% *vs.* 59.4%, $P = 0.22$).

Although water-exchange colonoscopy improves the detection of adenomas, the benefit of water-infusion colonoscopy methods seems particularly be due to improving patient comfort. In addition, the majority of studies published so far were performed by endoscopists that were highly experienced with water-infusion colonoscopy. This raises the question whether the same results can be achieved when performed by less experienced endoscopists. Especially when considering the prolonged insertion time due to the time consuming suction and exchange of water, it remains to be further elucidated whether water-exchange colonoscopy will indeed be one of the preferred techniques in daily clinical colonoscopy practice.

## CAP-ASSISTED COLONOSCOPY

Transparent caps attached to the distal tip of the colonoscope were first designed to assist during endoscopic mucosal resection but they have also been suggested to be of help in depressing colonic folds to improve visualization of their proximal aspects. A potential disadvantage of cap-assisted colonoscopy is that fecal debris may accumulate in the cap, requiring removal by water irrigation and drainage through the side holes present in some cap models. Several studies have reported reduced cecal intubation

times[69-71] and improved cecal intubation rates for trainees using cap-assisted colonoscopy.[70] The same accounted for procedures in patients in whom cecal intubation initially failed with standard colonoscopy.[72,73] Randomized controlled trials that evaluated the additional diagnostic yield of cap-assisted colonoscopy were mostly performed in Asian countries and have in general shown mixed results.[74]

In a study by Kondo *et al.*,[70] 684 subjects were randomized to colonoscopy with a 4-mm transparent cap or a 2-mm rubber cap or to colonoscopy without a cap. PDR for colonoscopies with the transparent cap, rubber cap and no cap were 49.3%, 44.7% and 39.1%, respectively, with only the difference between the transparent 4-mm cap and no cap being statistically significant. In a recent study reporting on 2502 procedures performed by trainees,[75] a statistically significant higher overall PDR was found for cap-assisted colonoscopy compared to standard colonoscopy (47.0% *vs.* 42.6%). Subgroup analyses showed that this difference was particularly due to an improved detection of small (≤ 5 mm) polyps. In a randomized controlled trial by Rastogi *et al.*[71] ADR was 13% higher with cap-assisted colonoscopy compared to standard colonoscopy, but similarly to the previous study, this was only observed for small (≤ 5 mm) adenomas. Horiuchi *et al.*[76] studied a retractable transparent device that can be extended up to a maximum length of 7 mm by injection of air. The mean number of adenomas detected was statistically significantly higher with the retractable extension device compared to standard colonoscopy (0.48 *vs.* 0.36, P = 0.04) while the ADR was comparable between both groups. In contrast, in the single largest randomized trial[73] published thus far (1000 patients included), a lower ADR (30.5% *vs.* 37.5%) and mean number of adenomas per subject was reported with cap-assisted colonoscopy compared to standard colonoscopy. Furthermore, three later studies, including the largest published multicenter trial thus far,[69] reported no higher overall and small polyp detection rates with cap-assisted colonoscopy. [69,77,78]

Taken together, cap-assisted colonoscopy may be of benefit in reducing cecal intubation time, but has limited or no benefit on polyp detection, which is confirmed by the results of a recent meta-analysis including 16 randomized controlled trials.[74] In this study, a marginally higher proportion of subjects with polyps was found with cap-assisted colonoscopy (RR = 1.08, 95%CI: 1.00-1.17) while no statistically significant difference in ADR was found. Of note, subgroup analysis showed that both expert and trainee endoscopists had reduced cecal intubation times and improved polyp detection rate, highlighting that it is unlikely that especially trainees should benefit from cap-assisted colonoscopy.

## RETROFLEXION

Retroflexion is commonly used in the rectum for the inspection of the dentate line, though the additional diagnostic yield is questionable.[79] Due to its relatively large diameter, the retroflexion technique has also been suggested to be useful in the proximal colon to improve the visualization on the proximal aspects of folds and to facilitate the removal of proximally located large sessile polyps. This was shown in a retrospective observational study in 59 patients.[80]

Harrison *et al.*[81] performed a randomized study in 100 patients who underwent standard forward colonoscopy from the cecum to the splenic flexure with removal of polyps. The cecum was then reintubated and patients were randomized to undergo a second exam of the proximal colon in retroflexion or in forward view. Retroflexion was successfully performed in the ascending and transverse colon in almost all patients. No statistically significant differences were observed between forward view and retroflexion with regard to the detection of additional polyps and adenomas. A more recent observational study in a cohort of 1000 consecutive patients reported an adenoma miss rate of 9.8% in patients first undergoing careful inspection of the proximal colon in forward view and a second inspection in retroflexion.[82] Although this was an observational study, the adenoma miss rate was thought to be comparable to that expected when a second inspection would have been done with forward viewing colonoscopy.

Based on the relatively limited number of studies which demonstrated no clear extra additional polyps being detected, in combination with a possibly increased risk of perforation when withdrawing the colonoscope in retroflexion, we currently do not recommend this technique in routine colonoscopy practice.

## THIRD-EYE RETROSCOPE

A device specifically designed to enhance the visualization behind the proximal aspects of colonic folds is the Third-Eye Retroscope® (Avantis Medical Systems, Inc) (Figure 2). This device consists of a video processor, a single-use polarizing filter cap for the colonoscope light source, and a 3.5 mm flexible single-use catheter with a camera and diode light source at the tip. The retroscope is retroflexed 180 degrees after being advanced through the working channel of the colonoscope and provides a 135 degrees retrograde view of the colon. In simulated colonoscopies using CT-colonography software, it was shown that the Third-Eye Retroscope improves the visualization of the colonic surface area from 87% with standard 140 degrees view colonoscopes to 99%.[13]

The efficacy of the Third-Eye Retroscope was initially studied in three colon models with simulated polyps.[83] Standard colonoscopy detected 12% of the polyps located on

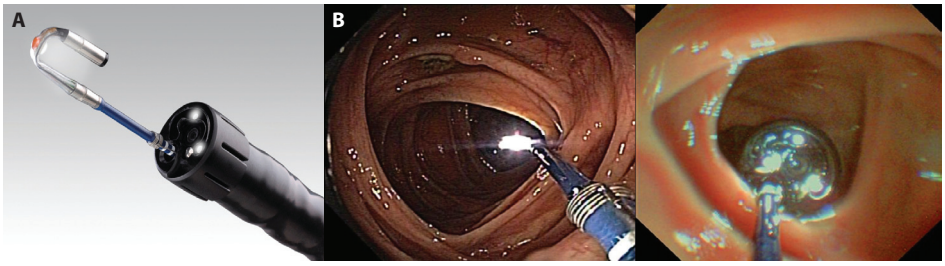


**Figure 2.** Third-Eye Retroscope (A) and colonoscopy view with Third-Eye Retroscope (B).



the proximal aspects of folds, while 81% of these polyps were detected with the Third-Eye Retroscope. The first pilot study[84] in 24 patients resulted in an 11.8% increase in diagnostic yield, with 34 polyps detected in the antegrade view and 4 additional polyps in the retrograde view. In two non-randomized studies,[85,86] the additional diagnostic yield of the Third-Eye Retroscope was investigated by evaluating whether polyps detected with the Third-Eye Retroscope could also been seen with the antegrade view of the colonoscope alone. In the first study, 182 polyps in 298 subjects were found with the antegrade view and 27 additional polyps were found with the Third-Eye Retroscope, resulting in a 14.8% increase in polyp detection and a 16.0% increase in adenoma detection.[85] The second study reported a similar result with a 13.2% increase in polyp detection and a 11.0% increase in adenoma detection.[86] Until now, one randomized back-to-back study has been performed, the TERRACE study.[87] In this multicenter study including 349 patients, a net additional detection rate with the Third-Eye Retroscope of 29.8% for polyps and 23.2% for adenomas was reported. This study was criticized by the fact that the mean withdrawal time was almost two min longer with the Third-Eye Retroscope compared to standard colonoscopy as this may have resulted in some bias in this study. In a post-hoc analysis of the TERRACE study,[88] withdrawal time was not significantly associated with the risk of missing adenomas. Interestingly, the Third-Eye Retroscope was shown to be particularly beneficial in patients undergoing colonoscopy for surveillance or diagnostic work-up and not in those undergoing screening colonoscopy.

Studies that investigated the Third-Eye Retroscope have shown a significant additional diagnostic yield when using this technique, but there are some limitations inherent to this device. First, thorough suctioning of colonic debris must be done during insertion of the colonoscope due to a 50% reduced suctioning capacity when the retroscope is in position. A second disadvantage is that the Third-Eye Retroscope needs to be removed from the working channel in case an accessory device is required, such as a biopsy forces or a polypectomy snare, which is bothersome and increases the procedural time.

## FULL SPECTRUM ENDOSCOPY

The recently developed Full Spectrum Endoscopy™ (Fuse; EndoChoice®, Alpharetta, Georgia, US) (Figure 3) colonoscope allows a high resolution 330 degrees "full spectrum" viewing of the colonic lumen while maintaining the standard colonoscope technical features and capabilities of a standard 140 and 170 degrees colonoscope. The Fuse system consists of a main control unit and a video colonoscope with three imagers and LED groups located at the front and both sides of the flexible tip. The video images transmitted from the three cameras on the left-side, front and right-side of the colonoscope are displayed on three contiguous monitors corresponding with each individual camera. The two additional side cameras incorporated in the Fuse colonoscope provide a better and comprehensive view of the total colonic lumen. The frequently encountered blind spots, such as the internal lining of flexures and proximal aspects of folds, should be easily visualized with this system.

The first published study was performed with an anatomical model of the colon with simulated polyps in a non-randomized setting.[89] Thirty-seven endoscopists performed colonoscopy by using the forward-viewing camera only (160 degrees), followed by a colonoscopy with all three cameras, which increases the field of view to 330 degrees. In total, 85.7% of the polyps were detected with the three cameras compared to 52.9% with only forward-viewing colonoscopy ($p < 0.001$). Particularly polyps that were "hidden" behind flexures and folds were more frequently detected with Fuse colonoscopy than with forward-viewing colonoscopy (81.9% *vs.* 31.9%). An additional pilot study including 50 patients showed that Fuse colonoscopy was indeed safe and feasible with a 100% cecal intubation rate and a mean cecal intubation time of 3.1 ± 1.5 min. Preliminary results of a randomized, multicenter, back-to-back study presented at the Digestive Disease Week 2013 are promising. Same-day colonoscopies with Fuse and standard colonoscopes were performed in 185 randomized subjects. In 88 subjects undergoing standard colonoscopy first, 50 polyps including 28 adenomas were detected while Fuse yielded 39 additional polyps including 20 adenomas, corresponding with an increase in polyps and adenomas detection of 78.0% and 71.4%, respectively. In 97 subjects

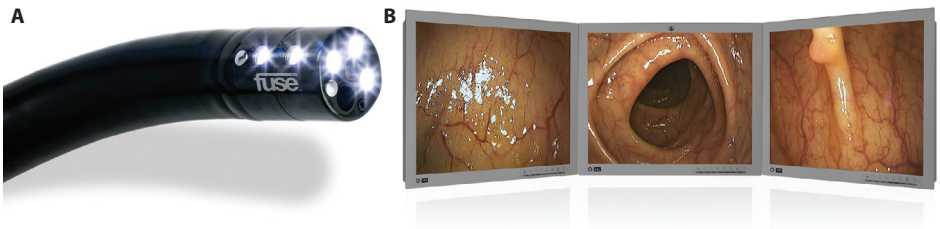


**Figure 3.** Full Spectrum Endoscopy colonoscope (A) with three side-by-side monitors (B).

undergoing Fuse first, 102 polyps including 61 adenomas were detected while standard colonoscopy yielded 11 additional polyps including 5 adenomas, corresponding with an increase in polyps and adenomas of 10.8% and 8.2%, respectively (Fuse *vs.* standard $p < 0.01$). The adenoma miss rate with Fuse was found to be considerably lower than with standard colonoscopy (7.5% *vs.* 40.8%, $p < 0.0001$). However, the median withdrawal time was approximately half a minute longer with Fuse colonoscopy (5.6 *vs.* 6.2 min, $p < 0.01$) and may have caused some bias in the results. More studies will be required before definitive conclusions can be made, but the first results definitely show that Fuse colonoscopy may be an important advancement to improve adenoma detection.



## CONCLUSION

A considerable proportion of polyps and adenomas are missed during colonoscopy due to poor visualization behind folds and the inner curves of flexures, and the presence of flat lesions that are known to be difficult to detect. Based on the findings of back-to-back studies with standard colonoscopes, adenoma and polyp miss rates are estimated to be approximately 20% to 25%. However, some recent studies that evaluated new endoscopic technologies have reported even higher miss rates (up to 40%) with standard colonoscopy than previously reported, which suggests that the miss rates with standard colonoscopy may have been previously underestimated.

The introduction of high-definition technology has considerably improved the quality of images during colonoscopy and is likely to stay the standard in the field of endoscopy. Visual image enhancement technologies such as NBI, FICE and AFI have possibly resulted in an increased recognition of flat and small lesions, but the absolute increase in terms of adenomas is probably limited. Besides, the quality of the images produced with virtual chromoendoscopy technologies requires further improvement before the general application of such technologies can be fully recommended. Cap-assisted colonoscopy and water-exchange colonoscopy were originally designed to facilitate cecal intubation and increase patient comfort, but studies have generally shown a marginal or no benefit at all on polyp and adenoma detection. Furthermore, the applicability of water-infusion methods has only been studied in highly experienced hands and is more time consuming compared to standard colonoscopy. Retroflexion is commonly used in the rectum for the inspection of the dentate line, but its use in the proximal colon has not clearly been demonstrated to improve ADR and may be associated with an increased risk of perforation. Studies evaluating colonoscopy with the Third-Eye Retroscope have shown considerable lower miss rates compared to standard colonoscopy, but this device is inconvenient in case of polypectomy, it impacts suction capabilities and it adds to total colonoscopy time. The recently introduced Fuse colonoscope maintains the technical

capabilities of standard colonoscopes and provides a much wider view of 330 degrees compared to 170 degrees with standard colonoscopes. A recent randomized back-to-back study using Fuse colonoscopy has shown remarkable lower adenoma miss rates with this technique. Although the results look promising, more studies investigating the diagnostic yield and the use of three monitors are needed before this device can be recommended for routine practice.

Hence, the majority of the endoscopic innovations that have been introduced in the past few years have only shown little additional diagnostic yield, are more time consuming or are not practical in use. In order to increase the efficacy of screening and surveillance colonoscopies, colonoscopy techniques will be needed that provide an optimal view of the whole colonic mucosa while maintaining optimal washing, suction and therapeutic capabilities and without increasing the procedural time or impairing patients comfort. In this perspective, a combination of high-definition and improved virtual enhancement technologies incorporated in ultra-wide colonoscopes may be the most obvious way to enhance the diagnostic yield of colonoscopy in the next few years.

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# Chapter 4

## Standard forward-viewing colonoscopy versus full-spectrum endoscopy: an international, multicenter, randomized, tandem colonoscopy trial

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*Lancet Oncology. 2014 Mar;15(3):353-60.*

## ABSTRACT

### Background

Although colonoscopy is the accepted standard for detection of colorectal adenomas and cancers, many adenomas and some cancers are missed. To avoid interval colorectal cancer, the adenoma miss rate of colonoscopy needs to be reduced by improvement of colonoscopy technique and imaging capability. We aimed to compare the adenoma miss rates of full-spectrum endoscopy colonoscopy with those of standard forward-viewing colonoscopy.

### Method

We did an international, multicentre, randomized trial at three sites in Israel, one site in the Netherlands, and two sites in the USA between Feb 1, 2012, and March 31, 2013. Patients aged 18-70 years referred for colorectal cancer screening, polyp surveillance, or diagnostic assessment underwent same-day, back-to-back tandem colonoscopy with standard forward-viewing colonoscope and the full-spectrum endoscopy colonoscope. The patients were randomly assigned (1:1), via computer-generated randomization with block size of 20, to which procedure was done first. The endoscopist was masked to group allocation until immediately before the start of colonoscopy examinations; patients were not masked. The primary endpoint was adenoma miss rates. We did per-protocol analyses. This trial is registered with ClinicalTrials.gov, number NCT01549535.

### Findings

197 participants were enrolled. 185 participants were included in the per-protocol analyses: 88 (48%) were randomly assigned to receive standard forward-viewing colonoscopy first, and 97 (52%) to receive full-spectrum endoscopy colonoscopy first. By per-lesion analysis, the adenoma miss rate was significantly lower in patients in the full-spectrum endoscopy group than in those in the standard forward-viewing procedure group: five (7%) of 67 *vs.* 20 (41%) of 49 adenomas were missed ($p < 0.0001$). Standard forward-viewing colonoscopy missed 20 adenomas in 15 patients; of those, three (15%) were advanced adenomas. Full-spectrum endoscopy missed five adenomas in five patients in whom an adenoma had already been detected with first-pass standard forward-viewing colonoscopy; none of these missed adenomas were advanced. One patient was admitted to hospital for colitis detected at colonoscopy, whereas five minor adverse events were reported including vomiting, diarrhea, cystitis, gastroenteritis, and bleeding.

### Interpretation

Full-spectrum endoscopy represents a technology advancement for colonoscopy and could improve the efficacy of colorectal cancer screening and surveillance.

## INTRODUCTION

Colonoscopy and polypectomy prevent incident cases of colorectal cancer by detection at an early and curable stage, and by identification and removal of colorectal adenomas – the precursor lesions of most colorectal cancers.[1-11] However, this protection is imperfect and is less effective in the proximal than the distal colon,[12-16] largely resulting from missed cancers and precancerous lesions (e.g. adenomas) during colonoscopic examinations.[17] Adenoma miss rates during colonoscopy have become widely acknowledged,[18-24] which has spawned an extensive effort within the gastroenterology community to improve the quality of colonoscopy examinations by measurement of quality indicators.[25-28] Additionally, new colonoscope technologies have been tested for their ability to better detect flat or subtle lesions, or to improve visualization of the mucosa behind colonic folds (e.g. with cap-fitted or retroscopic colonoscopes) where adenomas might be hidden. Until now, these technological changes have been minimally effective or impractical for improvement of adenoma detection.[29,30]



Nowadays, standard forward-viewing colonoscopes visualize the colon from the flexible tip of the instrument, with an angle of view up to 170°. The full-spectrum endoscopy colonoscope (Fuse, EndoChoice, GA, USA) is a new endoscopic platform that has imagers on not only the forward tip of the colonoscope, but also on both sides of the tip.[31,32] Together three imagers provide a 330° angle of view of the colon displayed to the endoscopist on three side-by-side, contiguous video monitors. In preliminary testing, the full-spectrum endoscopy colonoscope provided far better detection of all polyps and of hidden polyps in an in-vitro colon model than the standard forward-viewing colonoscopies.[31] Moreover, in the first ever pilot and feasibility study of the full-spectrum colonoscope in 50 participants, the device had a 100% cecal intubation rate and provided high evaluation scores from patients and endoscopists, with no adverse events.[32]

We postulated that full-spectrum endoscopy would have a significantly lower adenoma miss rate than the standard forward-viewing procedure.

## METHODS

### Study design and patients

We did this international, multicentre, randomized, tandem colonoscopy trial at three sites in Israel, one site in the Netherlands, and two sites in the USA between February 1, 2012, and March 31, 2013. We enrolled patients aged 18-70 years who had been referred for colorectal cancer screening, polyp surveillance, or diagnostic assessment. We excluded individuals with a history of colonic resection; inflammatory bowel disease; polyposis syndrome; lower gastrointestinal bleeding; colonic stricture; acute diver-

ticulitis or toxic megacolon; or a history of radiation therapy to the abdomen or pelvis. Institutional review board or medical ethics committee approval was obtained at each site. Informed written consent was obtained from all participants. This trial is registered with ClinicalTrials.gov, number NCT01549535.

### Randomization and masking

Patients were randomly assigned (1:1), by computer-generated randomization with block design (20 patients per block), to receive same-day, back-to-back tandem colonoscopy with either full-spectrum colonoscopy or standard forward-viewing colonoscopy, followed immediately by the other procedure. Immediately before start of the colonoscopy examinations, the site study coordinator opened the concealed allocation card to reveal group allocation. Until that moment, the endoscopist was masked to group assignment; patients were not masked.

### Procedures

We used same-day, back-to-back tandem colonoscopy to assess adenoma miss rates. Each participant had both colonoscopy examinations done by the same gastroenterologist. All polyps were removed as they were identified, other than diminutive (1-2 mm) rectal polyps thought by the gastroenterologist to be hyperplastic in nature, and therefore would not falsely increase polyp detection. The Fuse full-spectrum endoscopy platform comprises a video colonoscope and a processor. The full-spectrum colonoscope is a standard adult (168 cm working length, 12.8 mm scope outer diameter), flexible, reusable, reprocessable colonoscope intended for repeated clinical use (diagnostic visualization and therapeutic interventions). The device provides a high-resolution, 330° field of view while maintaining standard colonoscope capabilities and maneuverability, including full tip deflection (scope up or down 180° and left or right 160°), working channel (3.8 mm), air or CO2 insufflation options, suction, and forward water jet irrigation - identical technical features to the present industry standard, forward-viewing colonoscopes. Full-spectrum endoscopy is achieved by use of three imagers and light-emitting diode (LED) groups positioned at the front and on the sides of the distal tip of the colonoscope. Figure 1 shows the field of view of the standard forward-viewing and full-spectrum colonoscope displayed on three contiguous video monitors. The left, centre, and right video monitors correspond with the colonic images transmitted from the left-facing, forward-facing, and right-facing lenses, respectively.

All patients underwent preparation for standard colonoscopy with either a polyethylene glycol-based solution or a sodium picosulfate preparation, both of which are commercially available and approved for use as colonoscopy preparations. The choice of colon preparation was at the discretion of the gastroenterologist. We measured the level of bowel cleanliness at the time of colonoscopy with the Ottawa Bowel Preparation

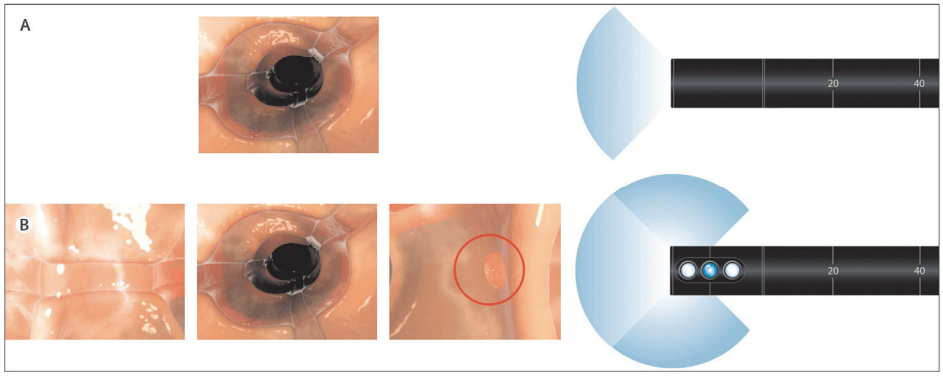


**Figure 1.** Standard forward-viewing colonoscopy (A) versus full-spectrum endoscopy (B).



Scale.[33] Conscious sedation was delivered by the gastroenterologist or anesthesiologist and included midazolam, fentanyl, propofol, or a combination thereof during both colonoscopy examinations. Standard forward-viewing colonoscopy was done with Olympus (Evis Exera II 160 and 180 series) or Pentax (Pentax EPKi) adult colonoscopes. All colonoscopy exams were done with white light only with no other electronic imaging technologies. On colonoscope withdrawal, the endoscopist was instructed to use their usual colonoscope withdrawal technique and asked to spend a minimum of 6 min withdrawing and examining the colon.[34] Water-jet irrigation was used to wash residual fluids and liquid stool to improve visualization. Insertion time to the cecum, withdrawal time, and total procedure time were all recorded with a stopwatch during each colonoscopy procedure. The stopwatch was paused during polypectomy or diagnostic biopsy, then restarted after completion of these interventions. The endoscopist estimated polyp size with the open biopsy forceps technique. A polyp found proximal to the splenic flexure was a priori defined as located in the right colon; all other more distal polyps were regarded as being located in the left colon.[20,22,23] Retroflexion of the colonoscope in the rectum was requested in each patient. The time between the tandem back-to-back colonoscopy examinations was less than 5 minutes and both examinations were done in the same endoscopy suite.

All polyps detected during first-pass colonoscopy were completely removed. Any additional polyps detected on second-pass colonoscopy were also completely removed. All removed polyps were sent to the pathology department at each study site. Histology results were reported to the attending gastroenterologist and to the study coordinator. Polyps were categorized as adenomatous, hyperplastic, or other. If a polyp was reported to be adenomatous on the basis of pathology, then the adenoma subtype was also recorded - i.e. tubular, tubulovillous, villous, or serrated. We also used histological analysis to detect the presence of low-grade and high-grade dysplasia within adenomas.

### Outcomes

The primary endpoint was adenoma miss rates. Secondary endpoints included polyp miss rates, advanced adenoma miss rates, time to cecal intubation, colonoscope withdrawal time, total procedure time, and adverse events. We defined advanced adenomas as any adenoma of 10 mm or greater in size, containing villous histology, or with high-grade dysplasia.[6,9]

### Statistical analysis

We prospectively designed this study to allow for 80% power or more to detect a 20% difference (35% *vs.* 15%) in adenoma miss rates, per lesion analysis, between colonoscopy procedures with a two group $\chi^2$ test with a two-sided $\alpha$ level of 0.05. A sample size of 178 participants was needed; therefore, the overall participant enrolment goal was 196 to allow for potential exclusions or dropouts, with each participant undergoing same day, back-to-back colonoscopy (356 tandem colonoscopies in total). Descriptive statistics were calculated for all measured variables and derived parameters. For continuous variables, time to reach the cecum, colonoscope withdrawal time, and total procedure time, we calculated means, medians, IQRs, SDs, and minimums and maximums. For categorical variables, summary statistics were counts and percentages. Because each participant was his or her own control in this study, we used paired t tests to compare continuous variables. For categorical variables, we used Fisher's exact test or $\chi^2$ test to compare detection rates between groups. For estimates of proportions, we calculated 95% exact binomial CIs. All tests applied were two-tailed. We analyzed data with SAS (version 9.1).

## RESULTS

Figure 2 shows the trial profile. One-hundred-ninety-seven participants were randomly assigned to the forward-viewing first group (n=96) or the full-spectrum first group (n=101), of whom 88 (92%) versus 97 (96%) completed the study and were included in the per-protocol analysis (Figure 2). Excluded participants did not differ significantly from the included individuals in terms of age, sex, indication for colonoscopy, and randomization group, but did differ on the Ottawa Bowel Preparation Scale (data not shown). The number of procedures done by each endoscopist is shown in Table 1. Baseline and demographic characteristics were similar between groups (Table 2).

### Adenoma miss rate

In patients who had standard forward-viewing colonoscopy first, 29 adenomas were identified on first-pass examination in 25 patients; full-spectrum colonoscopy detected

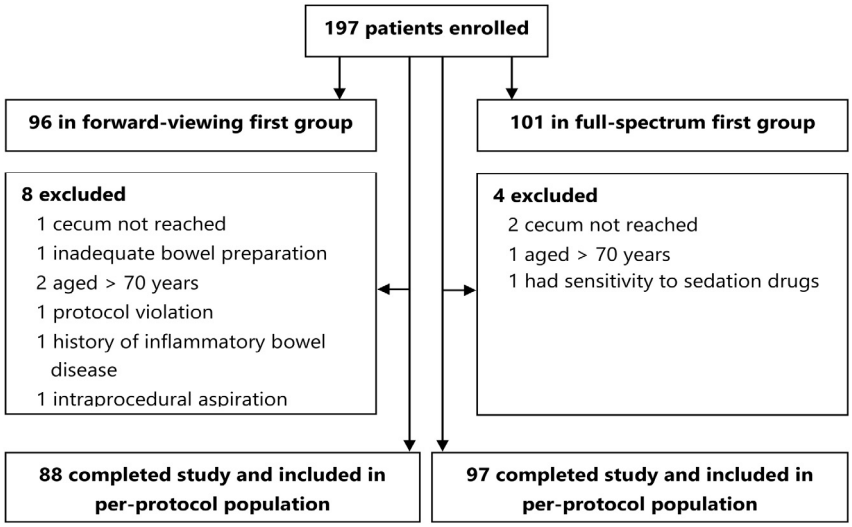


**Figure 2.** Study flow-chart.

**Table 1.** Number of endoscopists and patients completing analysis at each study site.

| Site | Patients (n=185) | Endoscopists per study site | Number of procedures per endoscopist |
|---|---|---|---|
| Site 1 (Elisha Hospital, Haifa, Israel) | 53 (29%) | 2 | Endoscopist 1 = 38<br>Endoscopist 2 = 15 |
| Site 2 (North Shore Gastroenterology Associates, Great Neck, NY, USA) | 30 (16%) | 5 | Endoscopist 1 = 11<br>Endoscopist 2 = 9<br>Endoscopist 3 = 5<br>Endoscopist 4 = 2<br>Endoscopist 5 = 3 |
| Site 3 (South Shore Gastroenterology, Cedarhurst, NY, USA) | 3 (2%) | 1 | Endoscopist 1 = 3 |
| Site 4 (University Medical Center Utrecht, Utrecht, the Netherlands) | 43 (23%) | 3 | Endoscopist 1 = 18<br>Endoscopist 2 = 16<br>Endoscopist 3 = 9 |
| Site 5 (Lady Davis Carmel Medical Center, Haifa, Israel) | 6 (3%) | 1 | Endoscopist 1 = 6 |
| Site 6 (Tel Aviv Sourasky Medical Center, Tel Aviv, Israel) | 50 (27%) | 3 | Endoscopist 1 = 32<br>Endoscopist 2 = 16<br>Endoscopist 3 = 2 |

20 additional adenomas in 15 patients on second-pass examination (a 69% increase; Table 3). In the full-spectrum colonoscopy first group, 60 adenomas and two cancers in 33 patients were identified initially. On second pass with standard forward-viewing colonoscopy, five additional adenomas were detected. The proportion of missed adenomas was significantly lower with full-spectrum colonoscopy (Table 3).

**Table 2.** Baseline and demographic characteristics of randomized groups completing tandem colonoscopy examinations.

| Characteristics | Standard forward-viewing colonoscopy first (n=88) | Full-spectrum colonoscopy first (n=97) |
|---|---|---|
| Age (years) | 56 (22-70) | 57 (21-70) |
| Sex (female) | 46 (52%) | 55 (57%) |
| Ottawa bowel preparation scale | 3 (2-5) | 3 (0-5) |
| Indication | | |
| Screening | 53 (60%) | 50 (52%) |
| Surveillance | 16 (18%) | 20 (21%) |
| Diagnostic assessment | 19 (22%) | 27 (28%) |
| Total adenoma detection | 30 (34%) | 34 (35%) |

Data are median (inter quartile range) or n (%).

**Table 3.** Adenomas detected and missed with standard forward-viewing and full-spectrum colonoscopy.

| Study group | Adenomas detected with standard forward-viewing colonoscopy | Adenomas detected with full-spectrum colonoscopy | Total number of adenomas identified | Adenoma miss rate with standard-forward viewing colonoscopy* | Adenoma miss rate with full-spectrum colonoscopy* |
|---|---|---|---|---|---|
| Standard forward-viewing colonoscopy first (n=88) | 29 | 20† | 49 | 20/49 (41%; 27.0%-56.0%) | - |
| Full-spectrum colonoscopy first (n=97) | 5 | 62‡ | 67 | - | 5/67 (7%; 2.5%-16.6%) |

Data are n or n/N(%) with 95% confidence intervals. * Full spectrum colonoscopy versus standard forward-viewing colonoscopy adenomas miss, $p < 0.0001$.
† includes three advanced adenomas (two adenomas with villous histology and one adenoma ≥ 10 mm in size. ‡ includes two cancers.

## Adenoma detection rate

The proportion of patients with at least one adenoma detected at colonoscopy was lower in the standard forward-viewing first group than in the full-spectrum first group ($p = 0.41$; Table 4). Five (6%) patients in the standard forward-viewing first group had no adenomas detected at first-pass examination, then had adenomas detected by full-spectrum endoscopy (Table 4). By contrast, no patients in the full-spectrum endoscopy first group had additional adenomas detected by standard forward-viewing colonoscopy (Table 4). Although this study was not a priori powered towards per-participant analyses, we assessed false-negative detection at the time of initial colonoscopy examination. Full-spectrum colonoscopy led to significantly fewer false-negative examinations than did standard forward-viewing colonoscopy ($p = 0.02$; Table 4). Furthermore, we assessed

**Table 4.** Adenomas detected and missed per patient.

| Study group | Patients with adenomas detected by standard forward-viewing colonoscopy | Patient with adenomas detected by full-spectrum colonoscopy | Unique patients with adenomas detected with second colonoscopy | Total patients with adenomas | Patients with false-negative first colonoscopy* | Patient miss rate (adenomas) with false-negative first colonoscopy† |
|---|---|---|---|---|---|---|
| Standard forward-viewing colonoscopy first (n=88) | 25 (28%) | 15 (17%) | 5 (6%) | 30 (34%) | 5/88 (6%; 1.9%-12.8%) | 5/30 (17%; 5.6%-34.7%) |
| Full-spectrum colonoscopy first (n=97) | 5 (5%) | 33 (34%) | 0 (0%) | 33 (34%) | 0/97 (0%; 0%-3.7%) | 0/33 (0%; 0%-10.6%) |

Data are n (%) or n/N(%) with 95% confidence intervals. A per-patient analysis, * p = 0.02 Fisher's exact test, † p = 0.02 Fisher's exact test.
† includes three advanced adenomas (two adenomas with villous histology and one adenoma ≥ 10 mm in size. ‡ includes two cancers.

**Table 5.** Polyp detected and missed.

| Study group | Polyps detected with standard forward-viewing colonoscopy | Polyps detected with full-spectrum colonoscopy | Total polyps identified | Incremental polyps detected with full-spectrum colonoscopy* | Incremental polyps detected with standard forward-viewing colonoscopy | Polyp miss rate with standard forward-viewing colonoscopy | Polyp miss rate with full-spectrum colonoscopy† |
|---|---|---|---|---|---|---|---|
| Standard forward-viewing colonoscopy first (n=88) | 50 | 38 | 88 | 38/50 (76%; 61.8%-86.9%) | - | 38/88 (43%; 32.7%-54.2%) | - |
| Full-spectrum colonoscopy first (n=97) | 11 | 102 | 113 | - | 11/102 (11%; 5.5%-18.5%) | - | 11/113 (10%; 5.0%-16.8%) |

Data are n (%) or n/N(%) with 95% confidence intervals. * Full spectrum colonoscopy versus standard forward-viewing colonoscopy additional polyps detected, p < 0.0001. † Full spectrum colonoscopy versus standard forward-viewing colonoscopy polyps missed, p < 0.0001.

patients with false-negative colonoscopy examinations as a proportion of all patients with adenomas detected, thereby providing an assessment of sensitivity. Thirty patients assigned to receive standard forward-viewing colonoscopy followed by full-spectrum colonoscopy had adenomas detected. From this cohort, 25 (83%) patients had adenomas detected by standard forward viewing and five (17%) had adenomas detected by full-spectrum endoscopy. 33 patients assigned to receive full-spectrum endoscopy first had adenomas detected. From this cohort, 33 (100%) patients had adenoma detected by full-spectrum endoscopy; no additional unique patients with adenomas were detected by second-pass standard forward-viewing colonoscopy ($p = 0.02$).

### Polyp miss rate

Standard forward-viewing colonoscopy identified 50 polyps on first-pass examination; on second-pass examination with full-spectrum endoscopy, 38 additional polyps were detected (a 76% increase; Table 5). Full-spectrum endoscopy identified 102 polyps and, on second-pass colonoscopy with standard forward viewing, 11 additional polyps were detected (Table 5). The overall polyp miss rate was significantly lower with full-spectrum colonoscopy than with the standard forward-viewing technique ($p < 0{\cdot}0001$; Table 5).

### Characteristics of missed adenomas

Of the 20 adenomas missed by standard forward-viewing colonoscopy, 18 (90%) were sessile and two (10%) pedunculated; 14 (70%) were 1-5 mm in size, five (25%) were 6-9 mm, and one (5%) was 10 mm or larger; 18 (90%) were tubular, one (5%) was tubulovillous, and one (5%) was villous adenoma. Thus, three (15%) of the 20 adenomas missed with standard forward-viewing colonoscopy were regarded as advanced.[6,9] 14 (70%) of the missed adenomas were in the right colon and six (30%) were in the left colon. Of the five adenomas missed by full-spectrum colonoscopy, all were sessile, 1-5 mm in size, tubular adenomas without high-grade dysplasia, thus none of the missed tumors were advanced. Two missed adenomas were in the right colon and three were in the left colon.

### Time endpoints

The median time to the cecum did not significantly differ between the procedures ($p = 0.84$; Table 6). Median time for colonoscope withdrawal and total procedure duration were significantly shorter with standard forward-viewing colonoscopy (both $p < 0.0001$; Table 6).

**Table 6.** Time to cecum, withdrawal time and total procedure time.

| Study group | Time to cecum (min.) | Withdrawal time (min.) | Total procedure time (min.) |
|---|---|---|---|
| Standard forward-viewing colonoscopy first (n=88) | 5.1 (3.2-7.6) | 5.6 (4.1-6.8) | 12.2 (9.2-16.5) |
| Full-spectrum colonoscopy first (n=97) | 4.8 (3.1-8.0) | 6.2 (5.1-8.3) | 14.5 (10.8-20.2) |
| P-value* | 0.84 | < 0.001 | < 0.001 |

Data are median (inter quartile range). * Wilcoxon signed-rank test.

### Adverse events

One patient from the forward-viewing colonoscopy group was admitted to hospital for colitis detected at colonoscopy. We recorded five minor adverse events: vomiting, cystitis, bleeding, and gastroenteritis in the full-spectrum colonoscopy followed by standard forward-viewing colonoscopy group, and diarrhea in the forward-viewing colonoscopy first group.



## DISCUSSION

Our findings show that compared with standard forward-viewing colonoscopy, full-spectrum colonoscopy had a significantly lower adenoma miss rate (panel). Because significantly more adenomas were detected with full-spectrum colonoscopy than with the standard forward-view procedure, changes were made in patient management, with alterations to surveillance colonoscopy recommendations. In patients with adenomas missed by standard forward-viewing colonoscopy, the adenomas subsequently detected led to a shortening of the recommended post-polypectomy surveillance interval for eight patients on the basis of present US (American Gastroenterological Association Institute, American Society for Gastro intestinal Endoscopy, and American College of Gastroenterology) and five patients on the basis of European (European Society of Gastrointestinal Endoscopy) guidelines.[9-11]

When full-spectrum colonoscopy was used first, five adenomas were missed in five patients, although each of these patients had other adenomas detected during full-spectrum colonoscopy. The five adenomas missed by full-spectrum colonoscopy were not advanced adenomas. Two adenomas missed by full-spectrum colonoscopy were in the right colon and three were in the left colon; none of the adenomas missed by full-spectrum colonoscopy would have altered the post-polypectomy surveillance colonoscopy recommendations by US or ESGE guidelines.[9,11] On the basis of European guidelines, one patient was reclassified into the high-risk category because they went from four to five to total small (<10 mm) adenomas detected after second-pass standard forward-viewing colonoscopy.[10]

Seventy per cent of the adenomas missed by standard forward-viewing colonoscopy, and which were subsequently detected by full-spectrum colonoscopy, were in the right colon. This finding might have clinical significance in view of the known reduced protective effect of colonoscopy for proximal, compared with distal, colon cancers.[12-16] Moreover, although this trial was not statistically powered for per-patient analyses, we noted that full-spectrum colonoscopy yielded significantly fewer false-negative examinations than did standard forward-viewing colonoscopy. However, because of the small sample size of the study, the adenoma detection rate was non-significant for standard forward-viewing versus full-spectrum colonoscopy.

One of the main solutions to significantly reduce the adenoma miss rate of standard forward-viewing colonoscopy is to improve on present colonoscope technology with more advanced optics and wider-angle visualization combined with a user-friendly, intuitive platform interface.[29] Findings from several studies in diverse patient populations have shown that adenomas are missed with present standard forward-viewing colonoscopy.[18-24] Many previous developments have had no, or only a small, effect on adenoma miss rates, including colonic dye spraying (chromoendoscopy), virtual chromoendoscopy, autofluorescence, and cap-fitted colonoscopy.[29,30] Although the individual adenomas missed in this study were mostly diminutive, in clinical practice, the detection of more adenomas of all sizes is strongly correlated with clinically important endpoints, including detection of large adenomas and of more patients with more than one adenoma.[34,35] This point suggests that techniques and emerging technologies that detect more adenomas overall, will also detect more large adenomas. Furthermore, improved detection of several small adenomas in individual patients results in improved recognition of this well-known risk factor for subsequent advanced lesions, and might result in shorter and more protective surveillance intervals.[9-11]

The most recent technological advancement in colonoscopy is the Third-Eye Retroscope (Avantis Medical Systems, CA, USA).[36,37] This device is an auxiliary, through-the-scope, optical technology intended to detect polyps located on the proximal side of colonic folds and at the anatomic flexures of the colon. In an international, multicentre, randomized trial of 349 participants, Leufkens and colleagues reported reductions in the proportion of missed adenomas, albeit more modest than those described here for full-spectrum colonoscopy.[23] Furthermore, the retroscope technology is probe based, requiring the accessory channel of the colonoscope, thus increasing the time needed for scope withdrawal, biopsies, and polypectomies. By contrast, the full-spectrum colonoscope platform does not interfere with any of the standard operating features of colonoscopes.

We recorded that the time to reach the cecum with full-spectrum colonoscopy was less than 5 minutes. This time efficiency might have been aided by the improved driveability of the colonoscope on insertion because blind corners and angles within the

colon lumen were largely eliminated by the greatly increased field of view provided by the three imagers. The first colonoscopy done, with either procedure, took longer (total procedure time) than did the second procedure. This finding might be partly explained by the straightening and shortening of the colon that happens during the first-pass examination thereby easing scope passage during the second examination. Moreover, although full-spectrum colonoscopy was significantly slower on both colonoscope withdrawal and total procedure times, these time differences are not likely to be clinically meaningful or relevant in daily endoscopy practice. Despite the recorded 30 seconds longer withdrawal time for full-spectrum colonoscopy (an estimated 10% longer than for standard forward-viewing colonoscopy), we do not believe this slight time differential explains the significantly higher proportion of adenomas detected.



Our study has some limitations. First, the endoscopist could not be masked to which colonoscope they were using and one endoscopist did both back-to-back colonoscopy examinations. Additionally, one endoscopist might not have used the same effort when trying to detect adenomas in both examinations and might have favored the new technology. Although use of one endoscopist might create bias, this methodology has been the standard one used in most tandem, back-to-back colonoscopy trials.[19,21,23,35,36] Use of the same endoscopist for both examinations has some advantages because they act as their own control with use of an identical withdrawal technique and baseline adenoma detection rate. Second, the study was statistically powered to be a per-lesion and not a per-patient analysis. However, published scientific literature about polyp and adenoma miss rates with tandem colonoscopy design have all used per-lesion analyses.[18-23] Third, we did not restrict the study population to screening only participants. Nevertheless, in the patients who were specifically referred for screening colonoscopy, the study findings remained consistent. Fourth, we did not force colonoscopy withdrawal times to be equal in the two study groups. Despite this, withdrawal times and total procedure times using the two colonoscope types were similar. Fifth, we recorded protocol violations and exclusions that led to the withdrawal of patients.

In conclusion, these data suggest that full-spectrum colonoscopy improves visualization of the colonic mucosa during colonoscopy and could improve the efficacy of screening of colorectal cancer and surveillance colonoscopy.

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# Chapter 5

## Multicenter, randomized, tandem evaluation of EndoRings colonoscopy – results of the CLEVER study

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*Submitted*.

## ABSTRACT

### Background

Adenoma miss rate during colonoscopy has become widely acknowledged as a proxy measure for post-colonoscopy colorectal cancer. Amongst others, this is due to inadequate visualization of the proximal aspects of colonic folds and flexures. EndoRings (EndoAid Ltd., Caesarea, Israel) is a silicone rubber device that is fitted onto the distal end of the colonoscope. Its flexible circular rings engage and mechanically stretch colonic folds during withdrawal. The primary aim of this study was to compare adenoma miss rates between standard colonoscopy and colonoscopy using EndoRings.

### Methods

In this multicenter, randomized, tandem colonoscopy study, we performed same-day, back-to-back colonoscopies with EndoRings followed by standard colonoscopy or vice versa.

### Results

We enrolled 126 subjects. After excluding 10 subjects due to protocol violations, 116 subjects (38.8% female, mean age 58.7 years) remained for analysis. Adenoma miss rate (7/67, 10.4%) of EndoRings colonoscopy was significantly ($p<0.001$) lower compared to standard colonoscopy (28/58, 48.3%). Similar results were found for polyp miss rates, i.e. 9.1% for EndoRings and 52.8% for standard colonoscopy ($p<0.001$). Mean cecal intubation times (9.3 vs. 8.4 min., $p=0.142$) and withdrawal times (7.4 vs. 7.2 min., $p=0.286$) were not significantly different between EndoRings and standard colonoscopy respectively. Mean total procedure time was longer with EndoRings compared to standard colonoscopy (21.6 vs. 18.5 min., $p=0.001$) due to removal of more polyps.

### Conclusions

This study demonstrates that colonoscopy with EndoRings has lower adenoma and polyp miss rates compared to standard colonoscopy and this may particularly improve the efficacy of screening and surveillance colonoscopies.

## INTRODUCTION

Colonoscopy is the standard method for the detection and removal of colorectal adenomas, the precursor lesions of most colorectal cancers.[1-4] Despite being the most sensitive, colonoscopy does not fully protect a person from developing future colorectal cancer.[5-10] This imperfection is for a major part caused by missed precancerous lesions due to inadequate bowel preparation, the presence of flat lesions that are difficult to detect,[8,9,11] and the relative difficulty to visualize lesions at the proximal side of haustral folds and internal curves of flexures.[12,13] The latter may at least partly be caused by the fact that standard 140 and 170 degrees colonoscopes are only able to visualize approximately 90% of the colonic surface.[14] Moreover, it has been shown that up to two-thirds of missed lesions are located on the proximal side of folds.[13] Miss rates with colonoscopy have become widely acknowledged with back-to-back colonoscopy studies showing polyp and adenoma miss rates of approximately 20 to 25% in older studies[15] and up to 40% in more recent studies[16,17] evaluating novel technologies developed to improve visualization behind folds. Besides the implementation of measuring quality indicators,[1,18] technologies such as cap-assisted colonoscopy, virtual chromoendoscopy, Third Eye colonoscopy and Full Spectrum Endoscopy (Fuse) colonoscopy have been developed to improve adenoma detection.[16,17,19,20] Some of these techniques have been shown to only marginally increase the detection of adenomas, while others are less practical in use or demand high investments with a change in endoscopy platform.[21,22]

In order to optimize the efficacy of colonoscopy, easy-to-use technological developments aiming to improve colonic visualization are required while maintaining standard colonoscopic capabilities and keeping the procedural time and associated costs at a minimum. One such device is the EndoRings (EndoAid Ltd., Caesarea, Israel), which is a silicone rubber device that is fitted onto the distal end of the colonoscope (Figure 1). Its flexible circular rings allow cecal intubation while they mechanically stretch the colonic folds during withdrawal and keep the tip of the colonoscope centered within the colonic

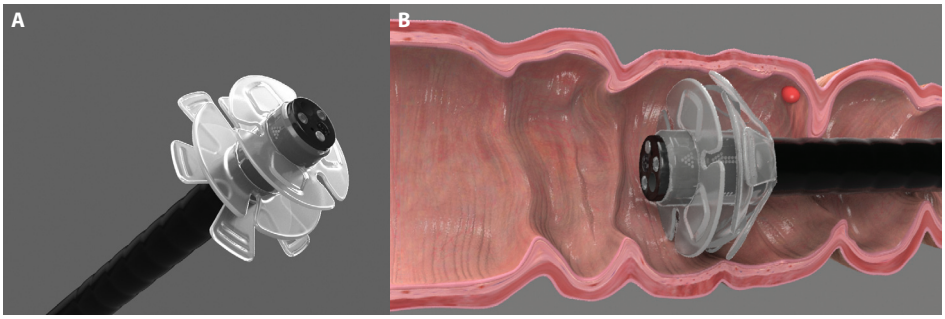


**Figure 1. A** The EndoRings device attached to the distal end of the colonoscope. **B** The EndoRings device during withdrawal of the colonoscope.

lumen. In this study we aimed to investigate the diagnostic yield of colonoscopy with EndoRings as compared to standard colonoscopy by comparing adenoma and polyp miss rates of both techniques. We further compared adenoma and polyp detection rates, impact on colonoscopy surveillance intervals, cecal intubation, withdrawal and total procedure time, and adverse events.

## METHODS

### Study design

For this randomized, multicenter tandem colonoscopy study we enrolled subjects between 40 and 75 years old that were referred for screening, surveillance or diagnostic colonoscopy. Exclusion criteria were a history of colonic resection, radiation therapy to the abdomen or pelvis, colonic stricture, inflammatory bowel disease, polyposis syndrome, acute diverticulitis, lower gastrointestinal bleeding or toxic megacolon. Subjects were included in one center in the Netherlands, one center in Israel and one center in the United States between July 2013 and June 2014. Six experienced gastroenterologists performed colonoscopies for this study. Study approval was obtained from the institutional review board or medical ethics committee at each participating center. This study was performed in compliance with the Declaration of Helsinki. Written informed consent was obtained from all participants. This trial is registered with ClinicalTrials.gov, number NCT01955122. All authors had access to the study data and reviewed and approved the final manuscript.

Bowel preparation was done according to the standard protocols of the individual centers with 4 L split-dose polyethylene glycol-based solution or picosulphate solution. The quality of bowel preparation was assessed during colonoscopy using the Boston Bowel Preparation Scale (BBPS).[23,24] Conscious sedation was delivered by the gastroenterologist or an anesthesiologist and included a combination of midazolam and fentanyl with or without propofol.

### Randomization

Randomization was done using computer-generated randomization blocks (1:1) with eight subjects per block. The study site coordinator revealed the group randomly assigned allocation up until the start of the colonoscopy. Until that moment, subjects and endoscopists were blinded for the allocation.

### Procedures

Patients underwent same-day, back-to-back tandem colonoscopy examination performed by the same endoscopist. Depending on randomization, patients underwent EndoRings colonoscopy immediately followed by standard colonoscopy or standard

colonoscopy immediately followed by EndoRings colonoscopy. All colonoscopies were performed with Olympus Evis Exera II 180 and 190 series or Pentax 3890 series colonoscopes. In case of colonoscopy with the EndoRings, the device was attached to the distal tip of the same colonoscope as was used for the standard colonoscopy procedure. The colonoscope with the EndoRings was advanced to the cecum using standard colonoscopic insertion technique.

Endoscopists were instructed to adhere to their usual withdrawal technique and to spend a minimum of six minutes withdrawing and examining the colon mucosa. Cecal intubation time, withdrawal time, total procedure time and time for pauses for performing polypectomies and biopsies were recorded by a research assistant using a stopwatch. Polyps detected during the first procedure were immediately removed and sent for histology, as were polyps detected during the second colonoscopy. Diminutive (1-2 mm in size), rectal polyps with hyperplastic appearance were not removed and not included in the analysis. Upon polyp detection, the estimated size and morphological appearance of the polyp were reported by the endoscopist. Polyps located proximally to the splenic flexure were defined as located in the proximal colon; polyps located more distally were defined as distally located polyps. Based on histological examination, polyps were categorized into adenomatous, hyperplastic or other. Adenomatous polyps were further categorized into tubular or (tubulo)villous lesions, with or without high-grade dysplasia. Subjects were followed-up by telephone for adverse events at 24 hours and at one week after the colonoscopy.



### Outcomes

The primary endpoint of this study was the adenoma miss rate, which was defined as the number of adenomas detected during the second colonoscopy divided by the total number of adenomas detected during the first and second colonoscopy. Secondary outcomes included polyp miss rate, advanced adenoma miss rate, adenoma detection rate, false negative first colonoscopy, impact on the recommended surveillance interval (according to the United States guidelines for colonoscopy surveillance after screening and polypectomy[3] and the European Union guidelines for quality assurance in colorectal cancer screening and diagnosis[1]), cecal intubation time, withdrawal time, total procedure time and adverse events.

### Sample size calculation

The required study sample size was calculated using a two-group chi-square test with 80% power and 0.05 two-sided significance level and was based on an expected adenoma miss rate of 35% with standard colonoscopy and 10% with EndoRings colonoscopy. This estimation was based on recent studies with techniques that improve the visualization behind folds en flexures.[16,17] With an estimated mean number of adenomas

per subject of 0.75 and a 10% dropout rate, the calculated total sample size required was 126 subjects.

### Statistical analysis

Descriptive statistics were calculated for all measured variables. For continuous variables, mean values and standard deviations were calculated. Counts and percentages were calculated for categorical variables. Two-sample t-tests were used to compare age and BBPS between study groups. Because subjects acted as their own controls, paired t-tests were used to compare cecal intubation time, withdrawal time, time for polypectomies and total procedure time between standard colonoscopy and colonoscopy with EndoRings. Pearson Chi-square and Fisher's Exact tests were used to compare categorical variables, miss rates (per lesion analysis) and detection rates (per subject analysis) between study groups. Two-sided p-values below 0.05 were considered statistically significant. All statistical analyses were performed with IBM SPSS 22 (IBM Corp., Armonk, NY, USA).

## RESULTS

### Baseline characteristics

A total of 126 subjects were enrolled in this study and randomly assigned to undergo EndoRings colonoscopy followed by standard colonoscopy (n=62) or standard colonoscopy followed by colonoscopy with EndoRings (n=64), of whom 116 (92.1%) were included in the per-protocol analysis (see Figure 2 for study flow-chart). Number of tandem procedures per center and endoscopist are shown in Table 1. Of the tandem

**Table 1.** Tandem procedures per center and endoscopist.

| Center | Procedures | Endoscopist | Procedures per endoscopist |
|---|---|---|---|
| **Center A** | 38 | 1 | 17 |
| GI Endoscopy Unit, Elisha Hospital, Haifa, Israel | | 2 | 8 |
| | | 3 | 13 |
| **Center B** | 70 | 4 | 64 |
| Department of Gastroenterology and Hepatology, University Medical Center Utrecht, Utrecht, The Netherlands | | 5 | 4 |
| | | 6 | 2 |
| **Center C** | 8 | 6 | 8 |
| Department of Medicine, Division of and Hepatology, Indiana University Hospital, Indianapolis, IN, United States | | | |

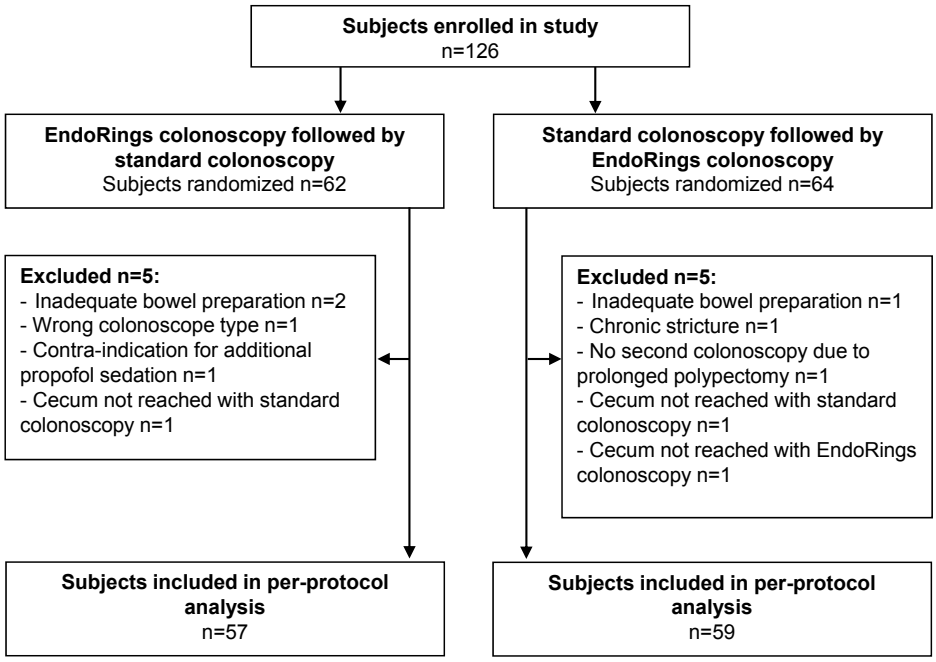


**Figure 2.** Study flow-chart.

**Table 2.** Baseline characteristics of per-protocol study population.

| Characteristics | Total | EndoRings colonoscopy first | Standard colonoscopy first | P-value[1] |
|---|---|---|---|---|
| **Subjects** | 116 | 57 | 59 | - |
| **Age (years), mean ± SD** | 58.7 ± 9.2 | 57.9 ± 9.1 | 59.6 ± 9.3 | 0.322 |
| **Female sex, n (%)** | 45 (38.8%) | 16 (28.1) | 29 (49.2) | 0.020 |
| **BBPS, mean ± SD** | 7.8 ± 1.1 | 7.8 ± 1.1 | 7.8 ± 1.1 | 0.838 |
| **Indication, n (%)** | | | | |
| Screening | 34 (29.3%) | 17 (29.8) | 17 (28.8) | 0.800 |
| Surveillance | 40 (34.5%) | 21 (36.9) | 19 (32.2) | |
| Diagnostic | 42 (36.2%) | 19 (33.3) | 23 (39.0) | |
| **Center** | | | | |
| 1 | 38 (32.8) | 36 (63.2) | 20 (33.9) | |
| 2 | 70 (60.3) | 18 (31.5) | 34 (57.6) | 0.730 |
| 3 | 8 (6.9) | 3 (5.3) | 5 (8.5) | |

1. Continuous variables tested with students t-test and categorical variables tested with Pearson's chi-square test.
SD = standard deviation, BBPS = Boston Bowel Preparation Scale.

colonoscopy procedures, 38 (32.8%) were performed in center A, 70 (60.3%) in center B and 8 (6.9%) in center C. One endoscopist (6) performed procedures in both Center B and C. Mean age was 58.7 ± 9.2 years, 38.8% were female and indications for colonoscopy were screening (n=34; 29.3%), surveillance (n=40; 34.5%) and diagnostic evaluation (n=42; 36.2%). Mean age (p=0.322) and BBPS scores (p=0.838) were not statistically significantly different between study groups (Table 2). The group that underwent standard colonoscopy first included significantly (p=0.020) more female subjects compared to the group that underwent EndoRings colonoscopy first.

**Table 3.** Adenomas[1] detected and missed with EndoRings and standard colonoscopy.

| Adenoma endpoints | EndoRings colonoscopy first | Standard colonoscopy first | P-value[2] |
|---|---|---|---|
| **Adenomas detected** | | | |
| First procedure | 60 | 30 | |
| Second procedure[3] | 7 | 28 | |
| Total | 67 | 58 | |
| **Adenoma miss rate first procedure** | 10.4% | 48.3% | < 0.001 |
| **Adenoma miss rates by characteristics, n (%)** | | | |
| Proximal | 5 (10.6%) | 18 (58.1%) | < 0.001 |
| Distal | 2 (10.0%) | 10 (37.0%) | 0.047 |
| 1-5 mm | 7 (13.5%) | 26 (54.2%) | < 0.001 |
| 6-9 mm | 0 (0.0%) | 2 (33.3%) | 0.125 |
| ≥10 mm | 0 (0.0%) | 0 (0.0%) | - |
| Pedunculated | 1 (5.3%) | 1 (14.3%) | 0.474 |
| Sessile | 6 (12.8%) | 22 (50.0%) | < 0.001 |
| Flat | 0 (0.0%) | 5 (71.4%) | 0.375 |
| Tubular | 7 (11.1%) | 28 (50.9%) | < 0.001 |
| (Tubulo)villous | 0 (0.0%) | 0 (0.0%) | - |
| Low grade dysplasia[4] | 7 (10.8%) | 27 (50.0%) | < 0.001 |
| High grade dysplasia | 0 (0.0%) | 0 (0.0%) | - |
| **Subjects with at least one adenoma detected** | | | |
| First procedure | 28/57 | 17/59 | |
| Second procedure[3] | 4/57 | 17/59 | |
| Total | 28/57 | 27/59 | |
| **Adenoma detection rate first procedure** | 49.1% | 28.8% | 0.025 |
| **False negative first procedure** | 0.0% | 16.9% | 0.001 |

1. Including tubular adenomas and (tubulo)villous adenomas.
2. Tested with Pearson's chi-square test.
3. Cross-over design with removal of lesions during the first procedure.
4. Grade of dysplasia unknown in five of the adenomas detected during the first procedure and in one detected during the second procedure.

### Adenoma miss rate

In subjects who underwent EndoRings colonoscopy first, 60 adenomas in 28 subjects were detected, while during the second-pass standard colonoscopy an additional 7 adenomas in 4 subjects were found (Table 3). In subjects who underwent standard colonoscopy first, 30 adenomas in 17 subjects were detected with standard colonoscopy while the second-pass colonoscopy with EndoRings identified 28 additional adenomas in 17 subjects. Therefore, the adenoma miss rate was significantly ($p<0.001$) lower with EndoRings colonoscopy (10.4%) compared to standard colonoscopy (48.3%). Adenoma miss rates per center are shown in Supplemental Table 1. In center B adenoma miss rates with standard and EndoRings colonoscopy were 31.8% versus 14.9% respectively ($p=0.103$), while in both center A and C adenoma miss rates were 58.3% versus 0.0% respectively.



### Polyp miss rate

EndoRings colonoscopy identified 110 polyps in 39 subjects during first-pass examinations. With second-pass standard colonoscopy, an additional 11 polyps in 7 subjects were found (Table 4). In subjects who underwent standard colonoscopy first, 50 polyps in 24 subjects were found during the first-pass examinations while during the second-pass colonoscopies using EndoRings an additional 56 polyps in 32 subjects were found. Thus, the polyp miss rate was significantly ($p<0.001$) lower with EndoRings colonoscopy (9.1%) compared to standard colonoscopy (52.8%).

### Adenoma and polyp detection rate

Adenoma detection rate of the first-pass colonoscopy was higher ($p=0.025$) with EndoRings (28 of 57 subjects, 49.1%) than with standard colonoscopy (17 of 59 subjects, 28.8%). Moreover, in the group that underwent standard colonoscopy first, 10 subjects had no adenomas detected during first-pass colonoscopy but were found to have adenomas during the second-pass colonoscopy with EndoRings, resulting in a false negative colonoscopy rate for adenomas of 16.9%. In contrast, the false negative colonoscopy rate of EndoRings colonoscopy was 0% ($p=0.001$). Furthermore, polyp detection rate with EndoRings was significantly ($p=0.003$) higher (68.4%) compared to standard colonoscopy (40.7%).

### Characteristics of missed adenomas

The miss rate of proximally located adenomas was significantly ($p<0.001$) lower with EndoRings (5 of 47; 10.6%) compared to standard colonoscopy (18 of 31; 58.1%). Most of the missed adenomas were 1-5 mm in size (100% for EndoRings and 92.9% for standard colonoscopy) and these small adenomas were less frequently ($p<0.001$) missed with EndoRings (7 of 52; 13.5%) compared to standard colonoscopy (26 of 48; 54.2%). Miss

**Table 4.** Polyps[1] detected and missed with EndoRings and standard colonoscopy.

| Polyp endpoints | EndoRings colonoscopy first | Standard colonoscopy first | P-value[2] |
|---|---|---|---|
| **Polyps detected** | | | |
| First procedure | 110 | 50 | |
| Second procedure[3] | 11 | 56 | |
| Total | 121 | 106 | |
| **Polyp miss rate first procedure** | 9.1% | 52.8% | < 0.001 |
| **Polyp miss rates by characteristics, n (%)** | | | |
| Proximal | 7 (10.8%) | 28 (62.2%) | < 0.001 |
| Distal | 4 (7.1%) | 28 (45.9%) | < 0.001 |
| 1-5 mm | 11 (10.7%) | 53 (57.6%) | < 0.001 |
| 6-9 mm | 0 (0.0%) | 3 (33.3%) | 0.074 |
| ≥10 mm | 0 (0.0%) | 0 (0.0%) | - |
| Pedunculated | 2 (6.9%) | 5 (33.3%) | 0.036 |
| Sessile | 9 (10.6%) | 41 (52.6%) | < 0.001 |
| Flat | 0 (0.0%) | 10 (76.9%) | 0.003 |
| Hyperplastic | 4 (8.0%) | 28 (59.6%) | < 0.001 |
| Adenoma | 7 (10.4%) | 28 (48.3) | < 0.001 |
| Serrated | 0 (0.0%) | 0 (0.0%) | - |
| Other | 0 (0.0%) | 0 (0.0%) | - |
| **Subjects with at least one polyp detected** | | | |
| First procedure | 39/57 | 24/59 | |
| Second procedure[3] | 7/57 | 32/59 | |
| Total | 39/57 | 39/59 | |
| **Polyp detection rate first procedure** | 68.4% | 40.7% | 0.003 |
| **False negative first procedure** | 0.0% | 25.4% | < 0.001 |

1. Including hyperplastic polyps, tubular adenomas, (tubulo)villous adenomas, serrated polyps, lipomas, leiomyomas and inflammatory polyps.
2. Tested with Pearson's chi-square test.
3. Cross-over design with removal of lesions during the first procedure.

rates of 6-9 mm (p=0.125), pedunculated (p=0.474) and flat (p=0.375) adenomas were not different. However, the miss rate of sessile adenomas was significantly (p<0.001) lower with EndoRings (6 of 47, 12.8%) compared to standard colonoscopy (22 of 44, 50.0%). All adenomas missed with standard or EndoRings colonoscopy were tubular adenomas smaller than 10 mm and none showed histological evidence of high-grade dysplasia, meaning that no advanced adenomas were missed with EndoRings or standard colonoscopy. There were no serrated polyps missed with EndoRings or standard colonoscopy.

### Impact on surveillance intervals

The impact of the second-pass colonoscopy using EndoRings and standard colonoscopes is shown in Supplemental Table 2. Of the 59 subjects who underwent standard colonoscopy first, in 8 subjects (13.6%) the recommended surveillance interval according to current US guidelines changed from ten to five years and in 3 (5.1%) the recommended surveillance interval changed from five to three years after the second-pass colonoscopy with EndoRings. In contrast, only in 2 of 57 subjects (3.5%) that underwent EndoRings colonoscopy first, the recommended surveillance interval was shortened after second-pass standard colonoscopy. This difference was significant (p=0.013). When applying the European guidelines, the recommend surveillance interval was shortened in 3 (5.3%) subjects that underwent EndoRings colonoscopy first and in 5 (8.5%) subjects that underwent standard colonoscopy first (p=0.617).



### Time endpoints

Mean cecal intubation time, withdrawal time and total procedure time are shown in Table 5. Mean ± SD cecal intubation time was shorter with standard colonoscopy (8.4 ± 5.6 min.) compared to EndoRings colonoscopy (9.3 ± 7.3 min.) but this difference was not statistically significant (p=0.142). Mean ± SD withdrawal time was comparable (p=0.286) between standard (7.2 ± 2.2 min.) and EndoRings colonoscopy (7.4 ± 1.9 min.), also when this was limited to the first-pass colonoscopies (7.0 ± 2.1 vs. 7.8 ± 2.1 min., p=0.055). Total procedure time was approximately three minutes longer with EndoRings colonoscopy (21.6 ± 8.9 min.) compared to standard colonoscopy (18.5 ± 8.2 min.), which was due to more time required for additional polypectomies (3.5 ± 4.3 min. vs. 1.8 ± 4.5 min., p=0.001). The time per polypectomy was similar with EndoRings and standard colonoscopy (3.0 ± 2.5 min. vs. 2.8 ± 2.1 min., p=0.697).

**Table 5.** Procedural time endpoints of EndoRings and standard colonoscopy.

| Time endpoints | EndoRings colonoscopy | Standard colonoscopy | P-value[1] |
|---|---|---|---|
| **Cecum intubation time (min.), mean ± SD** | 9.3 ± 7.3 | 8.4 ± 5.6 | 0.142 |
| **Withdrawal time (min.), mean ± SD** | 7.4 ± 1.9 | 7.2 ± 2.2 | 0.286 |
| **Time for polypectomies, mean ± SD** | 3.5 ± 4.3 | 1.8 ± 4.5 | 0.001 |
| **Time per polypectomy, mean ± SD** | 3.0 ± 2.5 | 2.8 ± 2.1 | 0.697 |
| **Total procedure time (min.), mean ± SD** | 21.6 ± 8.9 | 18.5 ± 8.2 | 0.001 |

1. Tested with paired t-test.
SD = standard deviation.

### Adverse events

No adverse events related to the EndoRings device occurred during the conduct of this study. However, in one subject the cecum could not be intubated with EndoRings colonoscopy and in two other subjects the cecum was not intubated with standard colonoscopy. In a fourth subject, a second procedure with the EndoRings was not performed due to a prolonged polypectomy with the placement of multiple clips during the first procedure with a standard colonoscope.

## DISCUSSION

Although colonoscopy is currently the preferred method to detect (pre)cancerous lesions in the colorectum,[1-4] it is increasingly being recognized as an imperfect examination method due to its inability to visualize the entire mucosal surface, particularly the proximal aspects of folds and flexures.[12,13] In the present randomized tandem colonoscopy study we showed that significantly fewer adenomas and polyps are missed with EndoRings colonoscopy and that both the adenoma and polyp detection rates are significantly higher as compared to standard colonoscopy. Although we were unable to demonstrate a statically significantly difference in missed advanced adenomas, a substantial number of flat and proximally located lesions were missed with standard colonoscopy while such lesions were less frequently missed with EndoRings colonoscopy. Furthermore, the recommended colonoscopy surveillance interval was more frequently shortened after the second procedure with EndoRings than with a standard colonoscope due to additional adenomas being detected.

The improved detection of polyps and adenomas with the EndoRings is provided by three circular rows of flexible, silicone-rubber rings that engage and mechanically straighten the colonic folds during withdrawal. The EndoRings additionally improves visualization of the total colonic surface area by keeping the distal tip of the colonoscope centered in the colonic lumen. Colonoscopy with the EndoRings has no interference with the standard washing, suctioning and therapeutic capabilities of the colonoscope and does not block parts of the camera view as some other devices may do.[25]

Although it is difficult to make direct comparisons between studies, the results of the present study indicate that the effect of the EndoRings on polyp and adenoma miss rates is in the upper range of other devices or techniques designed to improve visualization of the colonic mucosa, such as cap-assisted colonoscopy,[26,27] virtual chromoendoscopy,[20] and Third Eye Retroscope colonoscopy.[17] The recently developed Endocuff seems to have comparable features compared to the EndoRings: both are add-on devices that are designed to flatten the mucosal folds during withdrawal.[28] In a recent randomized controlled trial, the Endocuff was shown to significantly improve both polyp (56% vs. 42%)

and adenoma detection rate (36% vs. 28%) as compared to standard colonoscopy.[29] Another recently introduced technology is FUSE colonoscopy. This novel colonoscope has three cameras incorporated in the tip that enlarge the field of view up to 330 degrees compared to the 170 degrees of a conventional standard colonoscope. The advantage of the FUSE colonoscope has recently been demonstrated in the FUSE study, a randomized, back-to-back tandem study in which significantly lower adenoma miss rates were found when using FUSE colonoscopy compared to standard colonoscopy (7% vs. 41%, $p<0.0001$).[16] These results closely resemble the findings of our study. Although the maneuverability may be expected to be easier with the FUSE colonoscope, the advantage of the EndoRings is that it is compatible with the currently used standard colonoscopes, making it a cheaper alternative that can be easily applied in health care systems with constraints on the budget. Nonetheless, insertion of the colonoscope when using EndoRings may be more challenging in cases with strictures, previous bowel surgery or severe diverticulosis because the flexible rings of the EndoRings may cause some resistance during advancement of the colonoscope. This is probably why we found a slightly but not significantly longer cecal intubation time with EndoRings colonoscopy. Cecal intubation took however less than a minute longer thus this difference is not likely to be clinically relevant. The total procedure time was three minutes longer with EndoRings colonoscopy compared to standard colonoscopy, which was due to the extra time required for polypectomies. The time per polypectomy was similar with EndoRings as compared to standard colonoscopy. The tip control during polypectomy was not reported as a limitation by the performing endoscopists. In contrast, some reported they benefitted from the EndoRings because it stabilized the tip of the colonoscope in the lumen. Nonetheless, the longer total procedure time and shortened surveillance interval should be balanced against the additional diagnostic yield with EndoRings colonoscopy. In our view, the latter is preferable if the aim of colonoscopy is to reduce the risk of developing colorectal cancer.



The higher number of adenomas that were removed significantly affects the recommended colonoscopy surveillance interval as was demonstrated in this study. The clinical relevance may be argued since this was for the most part because more small, sessile adenomas were found. However, we also demonstrated that the miss rate of proximally located adenomas was significantly lower and no flat adenomas were missed with EndoRings colonoscopy. This is highly relevant when considering that colonoscopy is especially less effective in preventing colorectal cancer in the proximal colon,[30-33] largely resulting from missed (pre)cancerous lesions with often a flat morphology.[8,9]

Our study has some limitations. First, the study was powered to perform a per-lesion analysis and not to detect a difference in adenoma or polyp detection rates (per-subject analysis). Nevertheless and importantly, significantly higher adenoma and polyp detection rates were found with EndoRings colonoscopy. Second, the study was not powered

to detect differences between groups with an indication for screening, surveillance or diagnostic colonoscopy. This may be important since some subgroups of patients might benefit more from add-on devices or technologies than others. Third, the same endoscopist performed both procedures and was therefore not blinded to the findings of the first-pass procedures and may not have used the same effort during both colonoscopy procedures when trying to detect adenomas. This may to some extent have favored EndoRings colonoscopy. However, investigator bias may also not be fully prevented when two different endoscopists perform the back-to-back colonoscopies. Moreover, choosing one endoscopist for both procedures has the advantage of preventing bias due to differences in withdrawal technique and overall adenoma detection rates between endoscopists. In other words, the single endoscopist acts as his/her own control. Fourth, procedures were not evenly distributed among the study centers with most (60.3%) procedures being performed in center B. In this center adenoma miss rate with standard colonoscopy was lower while miss rate with EndoRings colonoscopy were higher as compared to the other two centers that included significantly fewer participants. This finding may imply a type I error in the two centers that included fewer participants. The total adenoma miss rates that we found should therefore be interpreted with caution and may in reality be around the miss rates found in center B. This is also supported by the findings of previous back-to-back colonoscopy studies in which adenoma miss rates of standard colonoscopy were lower. Fifth, the endoscopists in this study were instructed to apply a minimal withdrawal time of six minutes but no restrictions were given for a maximal withdrawal time. Yet, the mean withdrawal times were similar for standard and EndoRings colonoscopy. Finally, ten subjects were not included in the analysis because of protocol violations. In two subjects undergoing standard colonoscopy first, the advancement of the colonoscope (in one case with standard and in another with EndoRings colonoscopy) was not possible due to a narrow sigmoid as a consequence of diverticulosis. Furthermore, in one subject it was decided not to perform a second colonoscopy with the EndoRings due to a colonic stricture. In contrast, in another subject the cecum was not intubated with standard colonoscopy while the cecum was successfully intubated with the EndoRings. It should be noted that the manufacturer recently developed an EndoRings that fits onto a pediatric colonoscope for cases with a narrow colon. No adverse events related to the EndoRings occurred during the conduct of this study.

In conclusion, the results of this multicenter, randomized, back-to-back tandem colonoscopy study demonstrate that as compared to standard colonoscopy, colonoscopy with EndoRings significantly reduces adenoma and polyp miss rates. The simple and easy-to-use design and the minimal impact on cecal intubation time of this add-on device may help to improve the efficacy of screening and surveillance colonoscopies. A next step to evaluate this device would be to investigate adenoma detection rates in

a parallel randomized controlled trial including more endoscopists and study subjects, and to investigate what type of adenomas are more frequently found with EndoRings colonoscopy.

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## SUPPLEMENTAL TABLES

**Supplemental Table 1.** Adenomas[1] detected and missed with EndoRings and standard colonoscopy per center.

| Adenoma endpoints | EndoRings colonoscopy first | Standard colonoscopy first | P-value[2] |
|---|---|---|---|
| **Center A (38 procedures, 32.8%)** | | | |
| First procedure | 13 | 10 | |
| Second procedure | 0 | 14 | |
| Total | 13 | 24 | |
| **Adenoma miss rate first procedure** | 0.0% | 58.3% | < 0.001 |
| **Center B (70 procedures, 60.3%)** | | | |
| First procedure | 40 | 15 | |
| Second procedure | 7 | 7 | |
| Total | 47 | 22 | |
| **Adenoma miss rate first procedure** | 14.9% | 31.8% | 0.103 |
| **Center C (8 procedures, 6.9%)** | | | |
| First procedure | 9 | 5 | |
| Second procedure | 0 | 7 | |
| Total | 9 | 12 | |
| **Adenoma miss rate first procedure** | 0.0% | 58.3% | 0.005 |

1. Including tubular adenomas and (tubulo)villous adenomas.
2. Tested with Pearson's chi-square test.

**Supplemental Table 2.** Impact of second colonoscopy on the recommended surveillance interval.

| Change in surveillance interval | EndoRings colonoscopy first | Standard colonoscopy first | P-value[1] |
|---|---|---|---|
| **US guidelines[2]** | | | |
| No change, n (%) | 55 (96.5) | 48 (81.4) | |
| Interval changed from 10 years to 5 years, n (%) | 0 (0.0) | 8 (13.6) | 0.013 |
| Interval changed from 5 years to 3 years, n (%) | 2 (3.5) | 3 (5.1) | |
| **European guidelines[3]** | | | |
| No change, n (%) | 54 (94.7) | 54 (91.5) | |
| Interval changed from regular screening to 3 years, n (%) | 2 (3.5) | 2 (3.4) | 0.617 |
| Interval changed from 3 years to 1 year, n (%) | 1 (1.8) | 3 (5.1) | |

1. Tested with paired t-test.
2. According to the American Gastroenterological Association guidelines for colonoscopy surveillance. (Lieberman DA *et al*. Guidelines for colonoscopy surveillance after screening and polypectomy: a consensus update by the US multi-society task force on colorectal cancer. Gastroenterology 2012; 143:844-57).[3]
3. According to the European Union guidelines for quality assurance in colorectal cancer screening and diagnosis. First edition. (Atkin WS *et al*. Colonoscopic surveillance following adenoma removal. Endoscopy 2012; 44:SE151-SE163).[1]

# Chapter 6

## Measuring gaze patterns during colonoscopy: a useful tool to evaluate colon inspection?

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*Submitted.*

## ABSTRACT

### Background and study aim

Considerable variation in adenoma detection has been shown between endoscopists, which may be explained by differences in colon inspection. Eye tracking technology is an objective tool that detects differences in viewing patterns. In this pilot study we investigated the feasibility of eye tracking technology during real-time, self-performed colonoscopies.

### Methods

Ten endoscopists performed each two procedures. A Tobii mobile eye tracking system to register the right eye position was used to determine the gaze across four areas of interest (AOI's) of the endoscopy monitor (upper, lower, left and right quadrant). The measured gaze across the endoscopy monitor was correlated with the gaze across the endoscopically visualized colonic surface. Furthermore, we investigated whether these parameters depended on level of colonoscopy experience.

### Results

Gaze patterns were successfully measured in 18 of 20 procedures. Significant differences in time spent per AOI were observed between endoscopists. The measured total gaze time per AOI strongly correlated with the time spent on the corresponding area of the colonic surface (Pearson correlation coefficients ranging between 0.91 and 0.97). Endoscopists with more years of colonoscopy experience tended to have higher mean gaze times ($r=0.52$, $p=0.06$) and demonstrated significantly higher percentages of overlap between the measured gaze position in the different AOI and the actual inspected area of the colonic surface ($r=0.65$, $p=0.02$).

### Conclusion

Eye tracking technology to measure gaze patterns of endoscopists during real-time, self-performed colonoscopies is feasible and can be used to evaluate and compare viewing behavior across the colonic surface of endoscopists.

## INTRODUCTION

Colonoscopy is the current gold standard for the detection and removal of polyps and adenomas in the colorectum and reduces CRC incidence and mortality.[1,2] Significant polyp and adenoma miss rates have been reported in back-to-back colonoscopy studies[3] which has resulted in an increasing awareness among gastroenterologists to improve the detection of neoplastic lesions. Several measures have been proposed to achieve this, e.g. by optimizing pre-procedural bowel cleansing, improving basic colonoscopy skills or using new technologies to improve visualization.[4-6] However, even when all these factors are optimal, the detection of neoplastic lesions remains dependent on the eyes of the endoscopist.

Observational studies have shown considerable differences between endoscopists with regard to adenoma detection, withdrawal technique and withdrawal time.[7-9] Adenoma detection rate is associated with withdrawal time[7,9-12] and are both regarded as standard objective quality indicators for colonoscopy.[6] Although it seems reasonable that a longer withdrawal time implies a better inspection of the colonic mucosa, it is criticized for its role of being a good quality indicator.[7,13-15] The opponents state that it is not a longer withdrawal time but rather a careful and complete inspection of the total mucosal surface that improves adenoma detection rate. This is supported by the observation that an increasing compliance to a minimal withdrawal time of seven minutes does not necessarily lead to an increase in polyp detection.[15]

One potential tool to more objectively assess the quality of colon inspection and to quantify viewing behavior of endoscopists may be eye tracking technology. This technique enables to study differences in gaze patterns between endoscopists and may be helpful in distinguishing gaze patterns associated with lower adenoma detection from those with higher adenoma detection. Furthermore, it could be used for monitoring and training purposes. Until now little is known about gaze patterns of endoscopists. In a study by Almansa *et al.* it was demonstrated that endoscopists that tend to focus on the central part of the endoscopy monitor have higher adenoma detection rates compared to those that move more broadly across the screen.[16] This study also showed that more experienced endoscopists spent less time focusing on the center of the monitor. An important limitation of this study was however that endoscopists' gaze patterns were measured while watching recorded colonoscopy videos, which may not reflect viewing behavior during real-time and self-performed colonoscopies. This is illustrated by findings of a study comparing gaze patterns of surgeons during real-time laparoscopic cholecystectomies and later self-watching videos, in which only 55% overlap was found.[17] Furthermore, it may well be that other factors such as patient restlessness, procedural difficulties and colonoscopy skills influence viewing behavior of endoscopists and that the impact of such factors differs according to the level of experience.

Several issues need to be considered before introducing eye tracking technology in the endoscopy unit. First of all the technology should provide reliable and good quality data while intervening with the viewing behavior as little as possible. Second, it must be relatively easy to implement and install the technology in an endoscopy room without interfering with the provided care. Finally, it is important to realize that the endoscopist is watching a dynamic stimulus (the colonoscopy images) on a static area of interest (the endoscopy monitor) and that eye tracking technology only provides data on the gaze across the endoscopy monitor. As it is not possible to keep the colonic lumen centrally visualized during the complete withdrawal, the measured coordinates of the eye on the endoscopy monitor will not always correspond one-to-one with the area of the colonic surface that is inspected. For example, in cases when an endoscopist inspects the right-sided area of the colonic surface it may well be that this area is visualized in the lower part of the endoscopy monitor, depending on the position of the camera. It is obvious that before eye tracking technology is used in future studies, it must be elucidated whether the eye gaze across the endoscopy monitor is a reliable measure for colon inspection.

In this pilot study, we investigated the feasibility of eye tracking technology for measuring colon inspection, using a mobile eye tracking device during real-time, self-performed colonoscopies. Our aims were to investigate the data quality and completeness of gaze measurements in endoscopists performing colonoscopy, to investigate potential differences in gaze patterns between endoscopists, to study whether the gaze across the endoscopy monitor is a reliable measure for the gaze across the colonic surface and to study whether such differences are associated with level of experience.

## METHODS

### Endoscopists

For this study we invited fifteen endoscopists. Five endoscopists were not eligible for the study because they were unable to perform colonoscopies without wearing their own glasses. A total of ten endoscopists, including five fellows and five staff physicians, participated in this study. Median age of the endoscopists was 35 years (range 29 – 54 years), three (30%) were female, median years of colonoscopy experience was 3 years (range 2 – 4 years) in fellows and 12 years (range 5 – 20 years) in staff physicians and the number of lifetime colonoscopies was below 750 in four (40%), between 750 and 1500 in three (30%), more than 1,500 in three (30%) endoscopists.

## Eye tracking measurements

We used a Tobii mobile eye tracking system (Figure 1), consisting of light-weight eye tracking glasses (A), a pocket-sized recording assistant (B) and infrared markers (C). The eye tracking glasses have a 640x480 pixels scene camera incorporated on the right side of the glasses to capture where the subject is looking at, an infrared sensor communicating with the infrared markers positioned in the surrounding area, and an eye tracking sensor registering the reflection of the right pupil. The eye tracking sensor registers the right eye position at a sampling rate of 30 Hz. The infrared markers were placed on the outskirt of the endoscopy monitor (Figure 2). Tobii glasses measure gaze coordinates in the coordinate system of the glasses, i.e. a coordinate system that moves with the head. The infrared markers are used to transform the head centered gaze coordinates into real-world centered coordinates, which are in this case the coordinates of the endoscopy monitor. Real-world centered coordinates allow defining areas of interest (AOI's) for automated AOI analysis and were used to determine the gaze coordinates across the endoscopy monitor.

Each endoscopist performed two colonoscopies with the mobile eye tracking system. The eye tracking glasses were tightly positioned on the head of the endoscopist before the start of the procedure. Calibration was done shortly before the colonoscopy and the endoscopists were instructed not to touch the eye tracking glasses after calibration to prevent moving of the glasses and subsequent incorrect gaze data. The eye tracking system was turned on after cecal intubation. To test whether the gaze was measured accurately in relation to the infrared markers and to verify whether the position of the eye tracking glasses had not changed during the colonoscopy, the endoscopists were instructed to carefully fixate at each infrared marker at the start and the end of the eye tracking measurements (infrared marker checks). The distance between the endoscopist and the endoscopy monitor ranged from 100 to 145 cm. Depending on the distance, the viewing angle of the monitor (600 x 360 mm) ranged from 33.4° x 20.4° (100 cm distance) to 23.4° x 14.2° (145 cm distance). The viewing angle of the Tobii glasses is large enough to have a complete overview of the endoscopy monitor without the frame



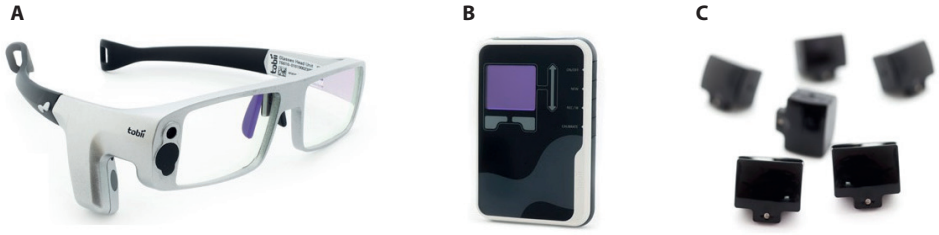


**Figure 1.** Tobii mobile eye tracking system consisting of light-weight eye tracking glasses (A), a pocket-sized recording assistant (B) and infrared markers (C).

of the glasses blocking the view. The endoscopy room was dimly illuminated and did not contain interfering infrared light sources.

### Data analysis

Data of the eye tracking measurements were manually divided with the Tobii Studio eye tracking software into segments consisting of infrared marker checks, colonoscope withdrawal and other activities such as biopsies, polypectomies and suctioning. Data of infrared marker checks and colonoscope withdrawal segments were exported for additional off-line calibration and further analyzed using self-written software. Off-line calibration was done to improve the gaze data quality using data of the infrared marker checks.

For data analysis we defined four AOI on the endoscopy monitor, i.e. the upper, lower, left and right area of the colonoscopy video (Figure 2). It was also registered when the measured gaze was outside one of these areas. From the gaze data we automatically calculated the total gaze time and relative total gaze time per AOI, the total number and relative number of visits per AOI (transitions), the mean gaze time per AOI visit and the number of transitions per second between AOI's.

The quality of the individual gaze measurements was assessed in two ways. First, the measured gaze positions at the start (infrared marker check 1) and end of the colonoscopy (infrared marker check 2) were plotted on a snapshot of the endoscopy monitor to evaluate the precision of the measured gaze positions and to verify whether the glasses had moved during the colonoscopy. Second, we calculated the percentage of invalid gaze samples, i.e. samples with missing eye position coordinates.

To study whether the gaze across the endoscopy monitor is a good measure for the gaze across the colonic surface, a random 30 seconds withdrawal video was taken from each gaze measurement. These videos were manually and frame-by-frame reviewed using Tobii Studio software and scored for the particular area of the colonic surface that the endoscopist looked at (upper, lower, left, right area of the colonic surface or outside


**Figure 2.** Endoscopy monitor with eight infrared markers on the outskirt of the endoscopy monitor and the four areas of interest.

the endoscopy monitor). These scorings were linked to the corresponding measured gaze positions in the four AOI's and the outside of the endoscopy monitor to evaluate the exact overlap and to determine the correlation between the relative total gaze time per AOI and per area of the colonic surface.

### Statistical analyses

Standard descriptive statistics were used to calculate medians, ranges, numbers and frequencies where applicable. A Cohen's weighted kappa was calculated to evaluate the exact overlap between the measured gaze position on the endoscopy monitor and the gaze position in colonic lumen. Furthermore, a correlation coefficient (r) was calculated using Pearson's correlation test to evaluate the correlation between relative total gaze time per area on the endoscopy monitor and the relative total gaze time per area of the colonic lumen. Pearson's correlation test was also used to evaluate the association between years of colonoscopy experience, mean gaze time per visit and the overlap between eye position in the AOI's and the areas of the colonic lumen. All statistical analyses were performed with SAS 9.2 (SAS Institute Inc, Cary, USA).



## RESULTS

### Data quality

Gaze measurements were performed during twenty colonoscopies: two measurements per endoscopists. Both the first infrared marker check and the second infrared marker check were plotted on a snapshot of the endoscopy monitor as illustrated in Figure 3a and 3b. In eighteen of the twenty procedures (90%), the first and second infrared marker check nicely overlapped and the measured gaze position were accurately plotted on the infrared markers (e.g. Figure 3a). In two procedures (10%) in different endoscopists, the first and second infrared marker check did not overlap (Figure 3b), indicating that the position of the eye tracking glasses had moved during the colonoscopy. These two procedures were excluded from further analyses.

Eye position was measured with a rate of 30 samples per second. The mean percentage of samples with missing coordinates was 3.9% (range, 0.8%-10.0%). We estimated precision (variable error) in the eye tracker signal by determining root mean square (RMS) noise.[18] The precision was 1.27° ± 0.47° (25 ± 8 mm on the endoscopy monitor), which means that it is 5 to 10 times higher than the precision of earth based eye trackers. However, this set up is precise enough to measure gaze behavior in only four large AOI on the endoscopy monitor.

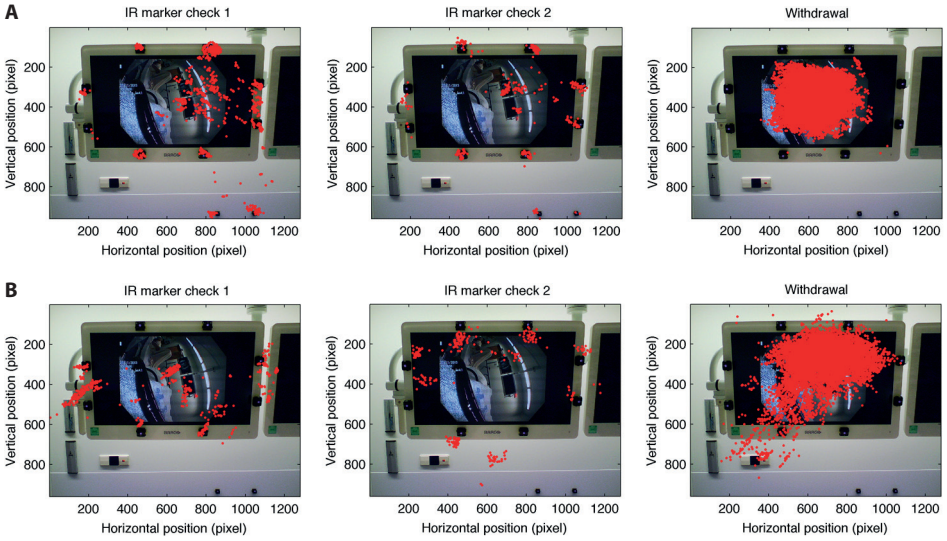


**Figure 3.** Measured eye position during first and second infrared marker check and withdrawal.
**A** Example where the first and second infrared marker check nicely overlapped with the infrared markers, indicating that the position of the eye tracking glasses had not moved during the colonoscopy.
**B** Example where the first and second infrared marker check did not overlap with the infrared markers, indicating that the position of the eye tracking glasses had moved during the colonoscopy.

## Gaze time and visits per area of interest

The relative total gaze times per AOI are shown in Table 1. On average, the relative total gaze times were 25.6% for the upper quadrant of the monitor, 24.4% for the lower

**Table 1.** Total withdrawal time, invalid eye gaze samples and relative total gaze time per area of the endoscopy monitor.

| Endoscopist | Sessions per endoscopist | Total withdrawal time (mm.ss) | Invalid eye gaze samples (%) | Relative total gaze time per area of interest (%) | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | Upper | Lower | Left | Right | Outside |
| 1 | 1 | 07.48 | 7.8 | 30.3 | 13.5 | 24.5 | 27.1 | 4.6 |
| 2 | 2 | 09.54 | 3.0 | 30.1 | 19.9 | 26.8 | 21.7 | 1.5 |
| 3 | 2 | 20.00 | 2.1 | 28.4 | 25.2 | 21.7 | 23.9 | 0.8 |
| 4 | 2 | 11.51 | 2.5 | 16.6 | 31.7 | 11.0 | 38.1 | 2.6 |
| 5 | 2 | 13.34 | 3.4 | 23.4 | 27.3 | 30.9 | 17.0 | 1.4 |
| 6 | 2 | 15.28 | 3.7 | 23.2 | 25.0 | 19.1 | 26.9 | 5.8 |
| 7 | 2 | 12.34 | 4.1 | 20.6 | 27.9 | 20.8 | 29.8 | 0.9 |
| 8 | 2 | 07.36 | 6.8 | 29.4 | 25.5 | 33.8 | 9.1 | 2.2 |
| 9 | 1 | 05.44 | 10.0 | 8.7 | 35.7 | 25.6 | 25.9 | 7.1 |
| 10 | 2 | 13.42 | 0.8 | 39.5 | 12.4 | 22.2 | 23.1 | 2.8 |
| **Total** | **18** | **118.11** | **3.9** | **25.6** | **24.4** | **23.5** | **24.0** | **2.5** |

**Table 2.** Transitions per second between and mean gaze time per area of the endoscopy monitor.

| Endo-scopist | Transitions per second (mean) | Mean gaze time (msec.) | Mean gaze time per area of interest (msec.) | | | | |
|---|---|---|---|---|---|---|---|
| | | | Upper | Lower | Left | Right | Outside |
| 1 | 1.29 | 774 | 738 | 735 | 849 | 910 | 619 |
| 2 | 1.45 | 688 | 722 | 654 | 722 | 658 | 428 |
| 3 | 1.24 | 804 | 883 | 809 | 735 | 785 | 520 |
| 4 | 1.27 | 787 | 761 | 779 | 630 | 861 | 751 |
| 5 | 1.09 | 917 | 824 | 986 | 953 | 867 | 596 |
| 6 | 1.48 | 676 | 723 | 617 | 630 | 731 | 619 |
| 7 | 1.32 | 759 | 665 | 791 | 766 | 839 | 259 |
| 8 | 1.35 | 746 | 762 | 758 | 708 | 556 | 554 |
| 9 | 1.01 | 981 | 728 | 1,052 | 1,089 | 968 | 705 |
| 10 | 1.04 | 966 | 1,047 | 848 | 935 | 909 | 721 |
| **Total** | **1.27** | **790** | **791** | **793** | **794** | **788** | **613** |



quadrant, 23.5% for the left quadrant and 24.0% for the right quadrant. However, considerable differences were observed with some endoscopists (for example 2, 3, 5 and 7) tending to spend the same amount of time in every AOI, while others (for example 4, 8, 9 and 10) spent significantly less time in certain AOI. Two-and-half per cent of the total gaze time was spent outside the monitor during withdrawal, ranging from 0.8% to 7.1%. Table 2 shows the mean number of transitions between AOI's and the mean gaze time per AOI, i.e. the mean time that an endoscopist spent in a certain area of the endoscopy monitor before moving to another. Mean number of transitions was 1.27 per second (range 1.01 – 1.45) and endoscopists spent a mean of 790 milliseconds per AOI (range 676 – 981). Overall, the mean gaze times were similar per AOI (ranging from 788 to 794 msec) but differed considerably between endoscopists with, for example, a mean gaze time for the upper area of the endoscopy monitor ranging from 665 to 1.047 msec.

To investigate how the relative total gaze time in a certain AOI's correlated with the mean gaze time and the number of visits to that particular AOI, we plotted these outcomes for each endoscopist (Figures 4a-c). Figure 4a shows that in all endoscopists the relative total gaze time per AOI depends on the mean gaze time per visit as well as the number of visits (Figure 4b). Figure 4c demonstrates that except for endoscopists 1 and 6, endoscopists spent more time per visit in the AOI where they mostly looked at. Finally, we plotted the number of transitions (arrows) and the total gaze time per AOI (heatmap) on a snapshot of the endoscopy monitor (Figure 5). Figure 5a shows an example of an endoscopist that spent the same amount of time in each AOI while the endoscopist in Figure 5b did not.

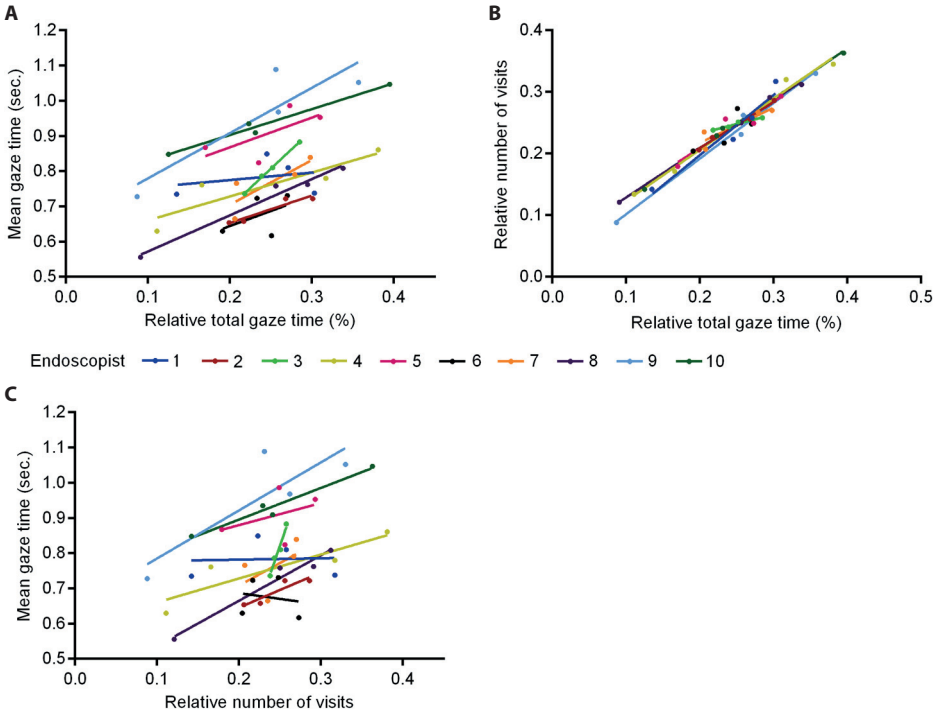


**Figure 4.** Correlation between relative total gaze time, mean gaze time and relative number of visits for every area of interest.
**A** The relative total gaze time correlated with the mean gaze time per visit in all endoscopists.
**B** The relative total gaze time correlated with the number of visits in all endoscopists.
**C** In all endoscopists except for endoscopists 1 and 6, the mean gaze time per visit was longest in areas to which they most frequently looked at.

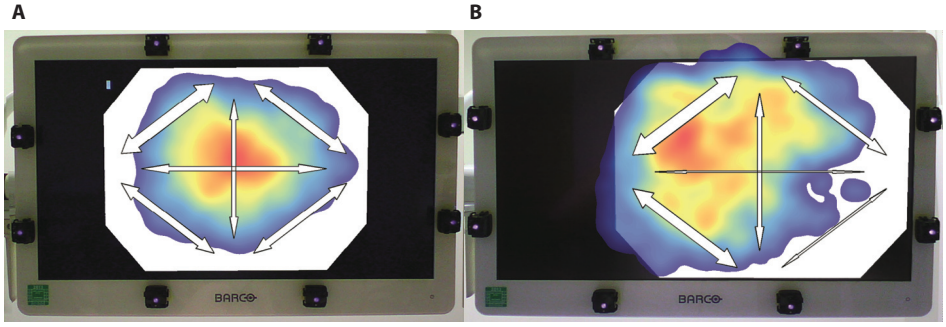


**Figure 5.** Example of transitions (arrows) and the total gaze time per AOI interest (heatmap) on a snapshot of the endoscopy monitor in an endoscopist that spent similar time in every AOI (**A**) and one that did not (**B**).

### Correlation between gaze across the endoscopy monitor and the colonic lumen

Table 3 shows the relative total gaze time per area of the colonic lumen as was found in random 30 seconds withdrawal videos of each gaze measurement. In 71.2% of the gaze samples, the location on the area of the endoscopy monitor, i.e. the AOI, overlapped exactly with the area of the colonic surface that was looked at (Cohen's kappa 0.66). The measured relative total gaze time per AOI correlated excellent with the relative total time per area of the colonic surface: upper ($r=0.91$, $p<0.001$), lower ($r=0.97$, $p<0.001$), left ($r=0.95$, $p<0.001$), right ($r=0.97$, $p<0.001$) (Figure 6).

**Table 3.** Relative total gaze time per colon segment and exact overlap with area on the endoscopy monitor.

| Endoscopist | Session | Relative total gaze time per colon segment (%) | | | | | Overlap between AOI and colon segments (%) |
|---|---|---|---|---|---|---|---|
| | | Upper | Lower | Left | Right | Outside | |
| 1 | 1 | 34.5 | 15.0 | 20.4 | 28.7 | 1.4 | 66.4 |
| 2 | 1 | 28.9 | 23.2 | 26.7 | 20.4 | 0.8 | 72.3 |
| 2 | 2 | 26.8 | 19.1 | 26.2 | 27.1 | 0.8 | 71.9 |
| 3 | 1 | 24.3 | 30.8 | 21.8 | 22.6 | 0.5 | 78.1 |
| 3 | 2 | 31.1 | 23.6 | 21.8 | 23.4 | 0.1 | 79.7 |
| 4 | 1 | 18.3 | 28.6 | 11.5 | 40.5 | 1.1 | 70.6 |
| 4 | 2 | 19.4 | 30.9 | 14.8 | 33.2 | 1.7 | 71.4 |
| 5 | 1 | 22.2 | 29.0 | 23.7 | 24.1 | 1.0 | 75.5 |
| 5 | 2 | 26.0 | 20.8 | 31.7 | 20.1 | 1.4 | 73.9 |
| 6 | 1 | 28.6 | 25.9 | 18.1 | 26.4 | 1.0 | 68.2 |
| 6 | 2 | 23.3 | 27.1 | 25.1 | 23.8 | 0.7 | 69.8 |
| 7 | 1 | 22.5 | 25.6 | 23.4 | 28.1 | 0.4 | 67.0 |
| 7 | 2 | 19.8 | 29.7 | 21.1 | 29.2 | 0.2 | 68.3 |
| 8 | 1 | 26.5 | 28.4 | 28.7 | 15.1 | 1.3 | 66.8 |
| 8 | 2 | 29.9 | 23.1 | 35.3 | 10.6 | 1.1 | 67.3 |
| 9 | 1 | 19.5 | 31.2 | 23.4 | 24.8 | 1.1 | 70.7 |
| 10 | 1 | 38.6 | 16.1 | 23.3 | 20.7 | 1.0 | 71.2 |
| 10 | 2 | 37.2 | 15.7 | 20.6 | 26.4 | 0.1 | 73.0 |
| **Total** | **18** | **26.5** | **24.7** | **23.2** | **24.7** | **0.9** | **71.2** |

### Years of experience and gaze parameters

As shown in Figure 7a, endoscopists with increasing years of colonoscopy experience tended to have an increased mean gaze time ($r = 0.52$, $p=0.06$). More experienced endoscopists also demonstrated a statistically significantly higher percentage of overlap between the measured gaze position in the different AOI's and the actual area of the colonic surface they were inspecting ($r=0.65$, $p=0.02$) as displayed in Figure 7b.

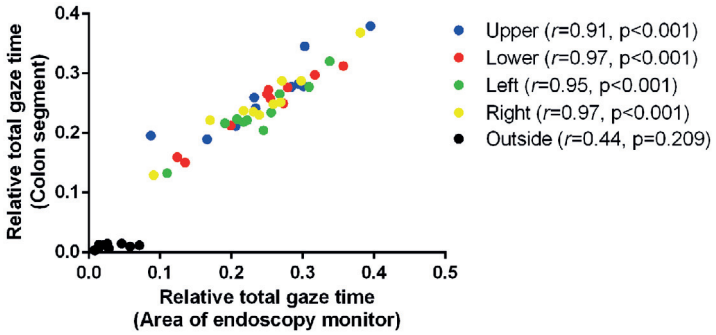


**Figure 6.** Correlation between the measured relative total gaze time per area of interest and the relative total time per area of the colonic surface.

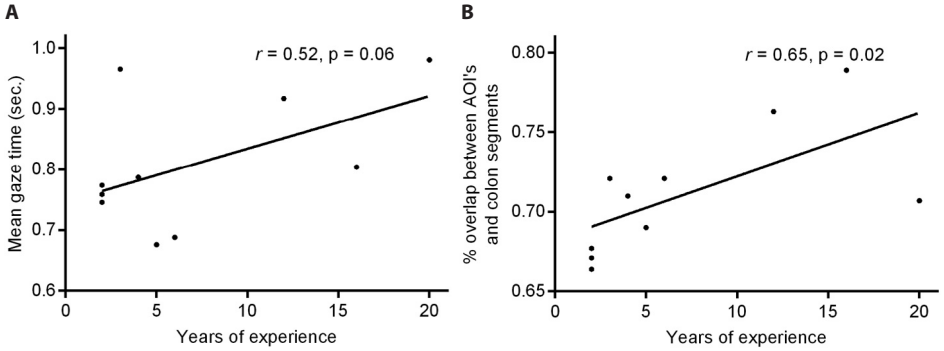


**Figure 7.** Correlation between years of experience and (A) mean gaze time and (B) the overlap between the measured relative total gaze time and the relative total time per area of the colonic surface.

## DISCUSSION

In this study we successfully measured gaze patterns in 18 of 20 self-performed colonoscopies by using a mobile eye tracking system. We demonstrated that the areas of the endoscopy monitor (AOI's) where endoscopists spent most time in total (i.e. total gaze time) differed considerably, with some endoscopists having more so-called blind areas than others. Furthermore, we showed that both the number of visits and the mean duration per visit (i.e. mean gaze time) contribute to the total time that was spent per AOI. The mean gaze time correlated with the years of colonoscopy experience and we found a strong correlation between the gaze time per area of the endoscopy monitor and the time per area of the colonic surface that was inspected. This indicates that the gaze across the endoscopy monitor, as measured with eye tracking technology, is a good measure for evaluating gaze across the colonic surface.

Eye tracking technology needs to fulfill certain requirements to be used for studying gaze patterns of endoscopists. We demonstrated that eye tracking technology during

real-time, self-performed colonoscopies is possible and provides almost complete data on the gaze of endoscopists. An advantage of the studied system is that the glasses are light and allow participants to move freely, which lowers the burden for the endoscopist as much as possible. The endoscopists that participated in this study reported no inconvenience of the glasses and could perform the colonoscopy normally, though some reported that it took some time to get used to the relatively thick frame (data not shown). The latter may intervene with viewing behavior, but the glasses itself were of sufficient size to be able to see the total endoscopy monitor without the endoscopists requiring to move their heads. Nonetheles glasses with a thinner frame are preferred for future studies. A second advantage of the current system is that it is easy to use during the measurements as it requires only a few minutes to install and to perform the calibration before the procedure. Third, the infrared markers that were positioned on the outskirt of the endoscopy monitor allow defining AOI's using real-world coordinates. This makes it relatively easy to measure gaze coordinates across the endoscopy monitor, although expertise is required to process the data. The used eye tracking system is only able to measure the gaze across a static AOI. In the case of colonoscopy we showed that gaze across the endoscopy monitor is a good measure for colon inspection since the relative total gaze time that was spent per AOI correlated well with the relative total gaze time per area of the colonic surface (Pearson correlation coefficients ranging from 0.91 to 0.97). However, the exact overlap for each individual gaze sample was on average 71.2% with a Cohen's kappa of 0.66. The exact overlap differed between endoscopists (ranging between 66.4% and 79.7%) and was positively associated with years of colonoscopy experience, which indicates that more experienced endoscopists are better able to keep the colonoscope centrally positioned in the colonic lumen during withdrawal compared to less experienced endoscopists.



A disadvantage of this eye tracking system is that it has a low sampling rate of 30 Hz. This is sufficient to provide data on gaze time and transitions between AOI's but is not enough to distinguish fixations and saccades. In order to determine viewing behaviour and investigate scan paths of endoscopists more precisely in future studies, eye tracking systems with higher temporal resolution are required. A second drawback of the current system is that an additional off-line calibration was required using self-written software to improve data quality.

How could endoscopy benefit from eye tracking technology? As we know from observational studies, significant differences exist between endoscopists with regard to adenoma detection rates, partly caused by differences in inspection of the colonic surface. An objective tool as eye tracking technology may help quantifying viewing behavior of endoscopists and can potentially be used to differentiate between gaze patterns associated with lower adenoma detection rates and those with higher adenoma detection rates. Measurement and training of colon inspection may subsequently improve the

diagnostic yield of colonoscopy. This has for example already been done in the field of radiology, in which eye tracking technology has successfully been used for training purposes and to improve diagnostic yields.[19-21]

The strengths of our study are that we investigated the feasibility of eye tracking technology in real-time, self-performed colonoscopies using a system that only minimally interferes with the procedure. As such, the results of our study probably better reflect how endoscopists inspect the colonic surface compared to a previous study in which participant's gaze patterns were measured while watching recorded colonoscopy videos.[16] On the other hand, a potential limitation is that factors such as patient restlessness, procedural difficulties and colonoscopy skills may have affected the measured gaze patterns. This may explain the found association between the level of experience, the mean gaze time per AOI and the degree of overlap between gaze across AOI's and the colonic surface. A second limitation is that we manually and in a frame-by-frame fashion determined to which area of the colonic surface the endoscopists was looking at in order to investigate the overlap with eye gaze across the endoscopy monitor. Unfortunately, techniques to measure this automatically are currently not available. Finally, as this was a pilot study, we only included a relatively small number of endoscopists, and did not collect data on clinically relevant outcomes such as adenoma detection rate.

In conclusion, the results of this study show that the use of eye tracking technology to measure gaze patterns of endoscopists during real-time, self-performed colonoscopy is feasible. Future studies should investigate whether potential differences in viewing behavior of endoscopists correlate with clinically relevant outcomes and whether eye tracking technology is useful for training purposes.

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# Part 2

## Factors associated with colorectal cancer development and survival

# Chapter 7

## Frequent use of antibiotics and colorectal cancer risk – results of a nested case-control study

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*Submitted.*

## ABSTRACT

### Background and study aim

Microbiotical dysbiosis induced by a Western diet seems to be associated with an increased risk of developing colorectal cancer (CRC). Few other factors with an effect on the colonic microbiota and their association with CRC have been evaluated. We investigated whether the use of antibiotics is associated with CRC risk.

### Methods

Data on the use of antibiotics and comedication were extracted from a health insurance database for subjects with a Diagnostic Related Group (DRG) for CRC between 2006-2011 and four age- and sex-matched controls. Antibiotic use was categorized according to the number of prescriptions during a 5-year follow-up period (1-6 years prior to CRC). Multivariable conditional binary logistic regression analysis was used to estimate odds ratios (OR) and 95% confidence intervals (95%CI) for different levels of use.

### Results

A total of 4,029 cases (47% male, mean age at diagnosis 71±11 years) and 15,988 controls were included. Antibiotics had been prescribed to 2,630 (65.3%) cases and 10,234 (64.0%) controls (p=0.13). An increasing use of antibiotics was associated with an increasing risk of CRC (multivariable OR for high (≥8 prescriptions) vs. no prescriptions: 1.26, 95%CI 1.11–1.44, p-trend<0.01). For each increase of 5 prescriptions, the OR for CRC was 1.05 (95%CI 1.01–1.09).

### Conclusion

We found an association between the use of antibiotics, especially when used frequently, and the risk of developing CRC. Further studies are needed to establish under which conditions the use of antibiotics increases the risk of developing CRC.

## INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer in men and second most common cancer in women worldwide.[1] Most cases of CRC develop according to the adenoma-carcinoma sequence, which is characterized by the accumulation of genetic and epigenetic mutations leading to benign premalignant lesions and eventually cancer.[2] Important risk factors associated with CRC include lifestyle factors, such as smoking, limited physical activity and obesity, and a Western diet which is rich in animal fat, red- and processed meat and poor in fibers.[3]

In the past few years an increasing interest has emerged on the role of the gut microbiota in the development of CRC. The human microbiota consists of approximately $10^{14}$ bacterial cells of 500-1000 different species and is important for the defense against pathogens, the metabolization of polysaccharides, the production of certain vitamins and plays a key role in maintaining a healthy immune system.[4] Furthermore, the colonic microbiota ferments undigested carbohydrates from fibers into short-chain fatty acids including butyrate, acetate and propionate[5,6] which are the preferred energy source of the colon mucosa and possess anti-inflammatory, anti-proliferative and anti-carcinogenic properties.[7-14] High intakes of meat and animal fat on the other hand, increase the bacterial production of genotoxic hydrogen sulfide and the secretion of bile acids which are metabolized into carcinogenic secondary bile acids by 7α-dehydroxylating bacteria.[15,16]



Only a few studies have investigated the association between the colonic microbiota and CRC development. These studies show important differences in the composition of the colon microbiota between low and high CRC risk populations based on their diet. For example, a reduced number of short-chain fatty acid producing bacteria such as the anti-inflammatory *Faecalibacterium prausnitzii* from the *Clostridium* cluster IV and *Eubacterium/Roseburia* species from cluster XIVa,[17] and an increase in secondary bile acid producing species are found in high CRC risk populations.[15,18] Furthermore, in CRC patients compared to healthy controls, short-chain fatty acid producing bacteria have been found to be depleted[19,20] while the proinflammatory *Fusobacterium* and *Porhyromonas* genera were increased.[19] Another study in which stools of CRC patients and healthy subjects were investigated, an increase in *Bacteroides-Prevotella* populations was demonstrated compared to healthy controls.[21]

These findings suggest a potentially important role for the gut microbiota in the development of CRC. It may well be possible that other factors, besides diet, known to induce a disbalance of the gut microbiota are associated with an increased risk of developing CRC. In this regard, the use of antibiotics may be of interest since its use may seriously affect the diversity of the colonic microbiota. We therefore hypothesize that the (frequent) use of antibiotics is associated with an increased CRC risk. In the current

study, we investigated whether the use of antibiotics and specific classes of antibiotics are associated with the risk of developing CRC in a population-based cohort. Secondly, we investigated potential effect modification by other factors that have an effect on the gut microbiota or have been found to be associated with CRC risk.

## METHODS

### Data collection

For this nested case-control study we used data of the Achmea Health Database in the Netherlands, which is a healthcare claims database covering approximately 1.2 million subjects (8% of the Dutch population). The database contains anonymized data on demographic characteristics, reimbursed Diagnostic Related Groups (DRGs) and medication. The population insured by the Achmea health insurance company represents the urbanized area of the Netherlands with regard to age, gender and socio-economic status.[22]

DRGs were introduced in the Netherlands in 2006 and are based on the International Classification of Disease, 9$^{th}$ revision (ICD-9). They are reimbursed per episode of care provided by secondary care physicians for in- and outpatient hospital care services. Data on DRGs were available between January 2006 and December 2011 and contained information on the colorectal cancer diagnosis and date of DRG registration, which usually is the first visit to the physician but can also be a follow-up visit.

Data on reimbursed medication was available between January 2001 and December 2011 and contained information on type of drug (ATC codes), date the drug was filled, number of Daily Defined Doses (DDD), the Prescribed Daily Dose (PDD) and the prescribing physician i.e. primary or secondary care. The DDD is the average maintenance dose per day for a drug used for its main indication in adults and is defined by the WHO Collaborating Centre for Drug Statistics Methodology.[23] The PDD is the fraction of DDD per day that is actually prescribed by the treating physician. In the Netherlands, antibiotics can only be obtained with a prescription of a physician and these prescriptions are registered in the Achmea Health Database for subjects insured with this insurance company. However, medication prescriptions during hospitalizations are not registered in the database.

This study was approved by the scientific and privacy committee of the Achmea health insurance company and was performed in accordance with the ethical guidelines of our institute.

### Study population

The complete database was searched for adult (≥18 years) subjects with a DRG for CRC between January 2006 and December 2011. An incidence CRC case was defined as a subject with at least two DRGs for CRC or one DRG for CRC surgery, in which the first DRG was not registered within the first 1.5 years of follow-up. This 1.5 years clean period was chosen to minimize the risk of including prevalent CRC cases and was based on the recommended follow-up of patients with CRC every six to twelve months until five years after initial treatment with curative intent, or more frequently in case of palliative treatment (according to the national guidelines at that time[24,25]). The date of CRC diagnosis was defined as the date of first DRG registration. Each case was matched with regard to sex and date of birth to four randomly selected controls without a DRG for CRC and with at least the same period of follow-up as their matched case. Both cases and controls were required to have at least six years of complete follow-up before CRC diagnosis. Cases and controls that at some point during follow-up had a DRG for inflammatory bowel disease were excluded.

### Antibiotic use

Antibiotics included were tetracyclines (ATC codes J01A), amphenicols (ATC codes J01B), penicillins (ATC codes J01C), cephalosporins (ATC codes J01D), sulfonamides and trimethoprim (ATC codes J01E), macrolides (ATC codes J01F), aminoglycosides (ATC codes J01G), quinolones (ATC codes J01M), imidazoles (ATC codes J01XD) and nitrofuran derivates (ATC codes J01XE) and others (ATC codes J01XA, J01XB, J01XC, J01XX). The number of days for which antibiotics were prescribed was calculated as prescribed days = DDD / PDD. For prescriptions with an unknown DDD (3.6%) or PDD (7.7%), values were imputed with SAS PROC MI procedure, under the missing at random assumption and based on ATC-code, primary or secondary care prescribing physician, sex and age. The use of antibiotics was measured as the number of prescriptions and the prescribed number of days during a 5-year period in the period 1-6 years prior to CRC diagnosis. Subjects were categorized as non-users and very low (1$^{st}$ to 50$^{th}$ percentile), low (51$^{st}$ to 75$^{th}$ percentile), intermediate (76$^{th}$ to 90$^{th}$ percentile) and high (above 90$^{th}$ percentile) users of antibiotics. For the analyses of anti-anaerobic agents and subtypes of antibiotics we categorized subjects as non-users and low (1$^{st}$ to 75$^{th}$ percentile), intermediate (76$^{th}$ to 90$^{th}$ percentile) and high (above 90$^{th}$ percentile) users.

### Covariates

Covariates included in this study were sex, age (continuous), insulin dependent diabetes (ATC codes A10A; no / yes), insulin independent diabetes (ATC codes A10B; no / yes) and the use of proton pump inhibitors (ATC codes A02BC), acetylsalicylic acids (ATC codes B01AC06 and B01AC08), non-steroidal anti-inflammatory drugs (ATC codes M01A), lipid-

lowering agents (ATC codes C10AA, C10BA and C10BX), estrogens (ATC codes G03AA, G03AB, G03FA and G03FB) and immunosuppressive drugs (ATC codes L04A). The cumulative number of prescribed days per drug were categorized as none and the 1st to 75th percentile, 76th to 90th percentile and above 90th percentile) within users.

### Statistical analyses

The use of antibiotics and comedication in cases and matched controls was assessed over a 5-year period between 1-6 years prior to CRC diagnosis. Medication use within one year prior to CRC diagnosis was not included in the analysis to minimize the risk of reversed causation. Differences in baseline characteristics were compared between cases and controls and expressed in means ± standard deviations (SD), medians (interquartile range; IQR) and frequencies whenever applicable. Student's t-test and Mann-Whitney U test were used for continuous variables and Pearson chi-square test for categorical variables.

Univariable and multivariable binary logistic regression analyses, conditioned on the matching factors sex and date of birth, were used to calculate the odd's ratio (OR) and 95% confidence intervals (95%-CI) for the use of antibiotics on a categorical and continuous scale and the risk of developing CRC. Linear trends over different categories were computed using median levels of antibiotic use within the categories in all subjects. Two models were tested: 1) a univariable conditioned model on the matching factors age and sex, and 2) a multivariable model conditioned on these matching factors and adjusted for factors statistically significantly associated with the outcome or the use of antibiotics.

Effect modification between the use of antibiotics and other factors that may affect the gut microbiota or that have previously been found to be associated with CRC risk, were tested by adding multiplicative interaction terms to the model and using likelihood ratio tests for interaction. For these analyses we used the interaction terms of overall antibiotic use (number of prescriptions, categorical) with insulin independent diabetes (no / yes), insulin dependent diabetes (no / yes), proton pump inhibitors (no / yes), acetylsalicylic acids (no / yes), non-steroidal anti-inflammatory drugs (no / yes), statins (no / yes), estrogens (no / yes) and immunosuppressive drugs (no / yes).

Sensitivity analyses were performed to study possible reversed causation by assessing the use of antibiotics between 2-7 years and 3-8 years prior to CRC diagnosis.

Statistical analyses were conducted with SAS 9.2 (SAS Institute Inc, Cary, USA). Two-sided p-values $<0.05$ were considered statistically significant.

## RESULTS

Between January 2006 and December 2011 8,141 subjects were identified with a DRG for CRC. After the exclusion of subjects with a DRG for inflammatory bowel disease (n=88), prevalent CRC cases (n=3,518) or subjects with less than six years of follow-up (n=506) before the first DRG, 4,029 incident CRC cases remained available for the analysis. These cases were matched to 15,988 controls without inflammatory bowel disease or CRC.

### Baseline characteristics

Baseline characteristics are shown in Table 1. Of all CRC cases, 47% were male and mean age at diagnosis was 71 ± 11 years. No statistically significantly differences were found between cases and controls with regard to insulin independent (p=0.32) and insulin dependent (p=0.45) diabetes, and use of proton pump inhibitors (p=0.14), acetylsalicylic acids (p=0.09), lipid-lowering agents (p=0.56), estrogens (p=0.48) and immunosuppressive drugs (p=0.52). However, subjects with CRC used less non-steroidal anti-inflammatory drugs (p<0.01) compared to controls. All these covariates were statistically significantly (p<0.001) associated with an increasing use of antibiotics.

The most frequently prescribed antibiotics included penicillins (31.6%), tetracyclines (20.7%), quinolones (13.9%), macrolides (9.6%), sulfonamides and trimethoprim (9.6%), and nitrofuran derivates (12.4%). Other antibiotics, including cephalosporins, aminoglycosides, amphenicols and imidazoles were rarely prescribed (combined 2.2%). During the five years follow-up period, antibiotics had been prescribed to 2,630 (65.3%) CRC cases and 10,234 (64.0%) controls (p=0.13). When excluding non-users, the median number of prescriptions of antibiotics was 2 (IQR 1-5) vs. 2 (1-5) times (p=0.07) for cases and controls respectively, corresponding with 17 (IQR 8-35) vs. 16 (8-34) days of use (p=0.10).

### Use of antibiotics and colorectal cancer risk

A high (≥8) number of prescriptions of antibiotics was associated with an increased risk of CRC (see Table 2). Univariable OR was 1.23 (95%CI 1.08–1.40, p-trend <0.01) when comparing a high (≥8) number vs. no prescriptions and was 1.04 (95%CI 1.01–1.07) for each increase of 5 prescriptions. Multivariable analyses adjusted for all measured potential confounders showed an OR of 1.26 (95%CI 1.11–1.44, p-trend <0.01) for a high (≥8) number vs. no prescriptions and an OR of 1.05 (95%CI 1.01–1.09) for each increase of 5 prescriptions.

The analyses for the number of prescribed days yielded a statistically significantly increased risk of CRC when antibiotics were used for ≥70 days vs. no use of antibiotics (univariable OR 1.24, 95%CI 1.08–1.44, p-trend <0.01; multivariable OR 1.28, 95%CI

**Table 1.** Baseline characteristics of colorectal cancer cases and matched controls.

| Characteristics | Cases (n=4,029) | Controls (n=15,988) | P-value[2] |
|---|---|---|---|
| **Age (years), mean ± SD** | 71.4 ± 11.4 | 71.4 ± 11.4 | 0.94 |
| **Male, n (%)** | 1,896 (47.1) | 7,527 (47.1) | 0.98 |
| **Insulin independent diabetes, n (%)** | 606 (15.0) | 2,305 (14.4) | 0.32 |
| **Insulin dependent diabetes, n (%)** | 215 (5.3) | 806 (5.0) | 0.45 |
| **Proton pump inhibitors[1], n (%)** | | | |
| None | 2,315 (57.5) | 9,187 (57.5) | 0.14 |
| Low | 1,312 (32.6) | 5,074 (31.7) | |
| Intermediate | 248 (6.2) | 986 (6.2) | |
| High | 154 (3.8) | 741 (4.6) | |
| **Acetylsalicylic acid[1], n (%)** | | | |
| None | 2,941 (73.0) | 11,502 (71.9) | 0.09 |
| Low | 825 (20.5) | 3,282 (20.5) | |
| Intermediate | 166 (4.1) | 708 (4.4) | |
| High | 97 (2.4) | 796 (3.1) | |
| **Non-steroidal anti-inflammatory drugs[1], n (%)** | | | |
| None | 1,677 (41.6) | 6,702 (41.9) | <0.01 |
| Low | 1,832 (45.5) | 6,895 (43.1) | |
| Intermediate | 327 (8.1) | 1,418 (8.9) | |
| High | 193 (4.8) | 973 (6.1) | |
| **Blood lipid lowering agents[1], n (%)** | | | |
| None | 2,703 (67.1) | 10,779 (67.4) | 0.56 |
| Low | 987 (24.5) | 3,872 (24.2) | |
| Intermediate | 191 (4.7) | 808 (5.1) | |
| High | 148 (3.7) | 529 (3.3) | |
| **Estrogens[1], n (%)** | | | |
| None | 3,917 (97.2) | 15,567 (97.4) | 0.48 |
| Low | 89 (2.2) | 311 (1.9) | |
| Intermediate | 12 (0.3) | 68 (0.4) | |
| High | 11 (0.3) | 42 (0.3) | |
| **Immunosuppressive drugs[1], n (%)** | | | |
| None | 3,966 (98.4) | 15,707 (98.2) | 0.52 |
| Low | 45 (1.1) | 213 (1.3) | |
| Intermediate | 9 (0.2) | 43 (0.3) | |
| High | 9 (0.2) | 25 (0.2) | |

1. Cut-off points are based on the 50$^{th}$, 75$^{th}$ and 90$^{th}$ percentile of prescriptions within users: proton pump inhibitors (1, 922, 1710), acetylsalicylic acid (1, 1740, 1825), non-steroidal anti-inflammatory drugs (1, 96, 392), blood lipid lowering agents (1, 1770, 1825), estrogens (1, 661, 953), immunosuppressive drugs (1, 1333, 1825).

2. Pearson chi-square test for categorical variables and students t-test for continuous variables.

SD = standard deviation.

**Table 2.** Univariable and multivariable odds ratio's for the overall use of antibiotics and colorectal cancer risk.

| | Cases n, % | Controls n, % | Univariable[3] OR (95%-CI) | Multivariable[4] OR (95%-CI) |
|---|---|---|---|---|
| **Prescriptions[1]** | | | | |
| None | 1,399 (34.7) | 5,754 (36.0) | ref. | ref. |
| Very low | 1,328 (33.0) | 5,245 (32.8) | 1.04 (0.96 – 1.13) | 1.05 (0.96 – 1.14) |
| Low | 549 (13.6) | 2,250 (14.1) | 1.01 (0.90 – 1.13) | 1.02 (0.91 – 1.14) |
| Intermediate | 358 (8.9) | 1,413 (8.8) | 1.05 (0.92 – 1.19) | 1.06 (0.93 – 1.22) |
| High | 395 (9.8) | 1,326 (8.3) | 1.23 (1.08 – 1.40) | 1.26 (1.11 – 1.44) |
| P-trend | | | <0.01 | <0.01 |
| Per 5 prescriptions | | | 1.04 (1.01 – 1.07) | 1.05 (1.01 – 1.09) |
| **Days[2]** | | | | |
| None | 1,399 (34.7) | 5,754 (36.0) | ref. | ref. |
| Very low | 1,243 (30.9) | 4,971 (31.1) | 1.03 (0.95 – 1.12) | 1.03 (0.95 – 1.13) |
| Low | 711 (17.6) | 2,722 (17.0) | 1.08 (0.97 – 1.19) | 1.09 (0.98 – 1.21) |
| Intermediate | 377 (9.4) | 1,550 (9.7) | 1.01 (0.89 – 1.14) | 1.02 (0.89 – 1.16) |
| High | 299 (7.4) | 991 (6.2) | 1.24 (1.08 – 1.44) | 1.28 (1.10 – 1.48) |
| P-trend | | | <0.01 | <0.01 |
| Per 25 days | | | 1.00 (0.99 – 1.01) | 1.00 (0.99 – 1.01) |

1. Cut-off points are based on the 50th, 75th and 90th percentile of prescriptions within users: very low (1-2), low (3-4), intermediate (5-7) and high (≥8).
2. Cut-off points are based on the 50th, 75th and 90th percentile of prescribed number of days within users: very low (1-15), low (16-34), intermediate (35-70) and high (≥70).
3. Univariable binary logistic regression analyses conditioned on age and sex.
4. Multivariable binary logistic regression analyses conditioned on age and sex and adjusted for insulin independent diabetes, insulin dependent diabetes and the use of proton pump inhibitors, acetylsalicylic acid, non-steroidal anti-inflammatory drugs, blood lipid lowering agents, estrogens and immunosuppressive drugs.
OR = odds ratio's, 95%-CI = 95% confidence interval.



1.10–1.48, p-trend <0.01). However, on a continuous scale (per 25 days increase) no association was found (multivariable OR 1.00, 95%-CI 0.99 – 1.01).

When specified for anti-aerobic and anti-anaerobic antibiotics (see Table 3) we found a positive association between the number of prescriptions and the risk of CRC for both anti-aerobic (multivariable high (≥8) vs. no prescriptions 1.25, 95%CI 1.08–1.45) and anti-anaerobic agents (multivariable high (≥5) vs. no prescriptions 1.45, 95%CI 1.07–1.97). When further categorized by classes of antibiotics we found an increased risk for penicillins (multivariable high (≥5) vs. no prescriptions 1.29, 95%CI 1.06–1.56) and quinolones (multivariable high (≥5) vs. no prescriptions 1.53, 95%CI 1.19–1.96), but not for tetracyclines, sulfonamides and trimethoprim, macrolides and nitrofuran derivates.

**Table 3.** Univariable and multivariable odds ratio's for the cumulative number of prescriptions for specific antibiotic groups and colorectal cancer risk.

| Number of prescriptions | Cases n, % | Controls n, % | Univariable[5] OR (95%-CI) | Multivariable[6] OR (95%-CI) |
|---|---|---|---|---|
| **Anti-aerobic agents[1,3], n (%)** | | | | |
| None | 1,399 (34.7) | 5,762 (36.0) | ref. | ref. |
| Very low | 1,329 (33.0) | 5.242 (32.8) | 1.05 (0.96 – 1.14) | 1.05 (0.96 – 1.14) |
| Low | 552 (13.7) | 2,255 (14.1) | 1.01 (0.91 – 1.13) | 1.02 (0.91 – 1.15) |
| Intermediate | 358 (8.9) | 1.413 (8.8) | 1.05 (0.92 – 1.19) | 1.06 (0.93 – 1.21) |
| High | 391 (9.7) | 1,316 (8.2) | 1.23 (1.08 – 1.40) | 1.25 (1.10 – 1.43) |
| **Only anti-aerobic agents[1,4], n (%)** | | | | |
| None | 1,535 (38.1) | 6,360 (39.8) | ref. | ref. |
| Very low | 1,367 (33.9) | 5,262 (32.9) | 1.08 (0.99 – 1.17) | 1.08 (0.99 – 1.18) |
| Low | 500 (12.4) | 2,088 (13.1) | 1.00 (0.89 – 1.11) | 1.01 (0.90 – 1.13) |
| Intermediate | 317 (7.9) | 1,227 (7.7) | 1.08 (0.94 – 1.23) | 1.09 (0.95 – 1.25) |
| High | 310 (7.7) | 1,051 (6.6) | 1.23 (1.07 – 1.41) | 1.25 (1.08 – 1.45) |
| **Anti-anaerobic agents[2], n (%)** | | | | |
| None | 3,090 (76.7) | 12,622 (79.0) | ref. | ref. |
| Low | 772 (19.2) | 2,842 (17.3) | 1.11 (1.02 – 1.22) | 1.12 (1.03 – 1.23) |
| Intermediate | 110 (2.7) | 360 (2.3) | 1.25 (1.01 – 1.55) | 1.27 (1.02 – 1.58) |
| High | 57 (1.4) | 164 (1.0) | 1.43 (1.05 – 1.93) | 1.45 (1.07 – 1.97) |
| **Penicillins[2], n (%)** | | | | |
| None | 2,356 (58.5) | 9,695 (60.6) | ref. | ref. |
| Low | 1,251 (31.0) | 4,821 (30.2) | 1.07 (0.99 – 1.15) | 1.08 (0.99 – 1.16) |
| Intermediate | 271 (6.7) | 979 (6.1) | 1.14 (0.99 – 1.32) | 1.16 (1.00 – 1.34) |
| High | 151 (3.7) | 493 (3.1) | 1.26 (1.05 – 1.53) | 1.29 (1.06 – 1.56) |
| **Tetracyclines[2], n (%)** | | | | |
| None | 2,871 (71.3) | 11,509 (72.0) | ref. | ref. |
| Low | 905 (22.5) | 3,549 (22.2) | 1.02 (0.94 – 1.11) | 1.02 (0.94 – 1.11) |
| Intermediate | 173 (4.3) | 612 (3.8) | 1.13 (0.95 – 1.35) | 1.15 (0.96 – 1.37) |
| High | 80 (2.0) | 318 (2.0) | 1.01 (0.79 – 1.29) | 1.02 (0.80 – 1.31) |
| **Sulfonamides and trimethoprim[2], n (%)** | | | | |
| None | 3,506 (87.0) | 14,085 (88.1) | ref. | ref. |
| Low | 410 (10.2) | 1,497 (9.4) | 1.11 (0.98 – 1.24) | 1.11 (0.99 – 1.25) |
| Intermediate | 70 (1.7) | 238 (1.5) | 1.19 (0.91 – 1.56) | 1.19 (0.91 – 1.56) |
| High | 43 (1.1) | 168 (1.1) | 1.03 (0.73 – 1.44) | 1.04 (0.74 – 1.46) |
| **Macrolides[2], n (%)** | | | | |
| None | 3,446 (85.5) | 13,696 (85.7) | ref. | ref. |
| Low | 501 (12.4) | 1,923 (12.0) | 1.04 (0.93 – 1.15) | 1.04 (0.93 – 1.16) |
| Intermediate | 50 (1.2) | 254 (1.6) | 0.78 (0.57 – 1.06) | 0.78 (0.57 – 1.06) |
| High | 32 (0.8) | 115 (0.7) | 1.11 (0.75 – 1.64) | 1.12 (0.75 – 1.66) |

**Table 3** (continued)

| Number of prescriptions | Cases n, % | Controls n, % | Univariable[5] OR (95%-CI) | Multivariable[6] OR (95%-CI) |
|---|---|---|---|---|
| **Quinolones[2], n (%)** | | | | |
| None | 3,324 (82.5) | 13,464 (84.2) | ref. | ref. |
| Low | 509 (12.6) | 1,897 (11.9) | 1.09 (0.98 – 1.22) | 1.10 (0.99 – 1.23) |
| Intermediate | 107 (2.7) | 385 (2.4) | 1.13 (0.91 – 1.40) | 1.14 (0.91 – 1.42) |
| High | 89 (2.2) | 242 (1.5) | 1.51 (1.18 – 1.93) | 1.53 (1.19 – 1.96) |
| **Nitrofuran derivates[2], n (%)** | | | | |
| None | 3,458 (85.8) | 13,835 (86.5) | ref. | ref. |
| Low | 415 (10.3) | 1,612 (10.1) | 1.04 (0.92 – 1.17) | 1.04 (0.92 – 1.17) |
| Intermediate | 93 (2.3) | 309 (1.9) | 1.21 (0.96 – 1.54) | 1.23 (0.97 – 1.56) |
| High | 63 (1.6) | 232 (1.5) | 1.10 (0.83 – 1.46) | 1.10 (0.83 – 1.46) |

1. Cut-off points are based on the 50$^{th}$, 75$^{th}$ and 90$^{th}$ percentile of prescriptions within users: very low (1-2), low (3-4), intermediate (5-7) and high (≥8).
2. Cut-off points are based on the 75$^{th}$ and 90$^{th}$ percentile of prescriptions within users: low (1-2), intermediate (3-4) and high (≥5).
3. Including anti-aerobic antibiotics with anti-anaerobic properties.
4. Excluding anti-aerobic antibiotics with anti-anaerobic properties.
5. Univariable binary logistic regression analyses conditioned on age and sex.
6. Multivariable binary logistic regression analyses conditioned on age and sex and adjusted for insulin independent diabetes, insulin dependent diabetes and the use of proton pump inhibitors, acetylsalicylic acid, non-steroidal anti-inflammatory drugs, blood lipid lowering agents, estrogens and immunosuppressive drugs.
OR = odds ratio's, 95%-CI = 95% confidence interval.



## Interaction with other factors

No statistically significantly interactions were observed between the use of antibiotics and insulin dependent diabetes (p=0.14), insulin independent diabetes (p=0.84), and the use of proton pump inhibitors (p=0.59), acetylsalicylic acids (p=0.62), non-steroidal anti-inflammatory drugs (p=0.46), lipid-lowering agents (p=0.96), estrogens (p=0.57) or immunosuppressive drugs (p=0.76).

## Sensitivity analysis

Sensitivity analyses to assess for reversed causation between the use of antibiotics and CRC showed that the OR increased when a less recent follow-up period was used. Multivariable OR's were 1.33 (95%CI 1.08–1.64) for ≥8 vs. 0 prescriptions and 1.17 (95%CI 0.95–1.43) for ≥70 vs. 0 days for antibiotics between seven to two years, and 1.37 (95%CI 1.10–1.70) for ≥8 vs. 0 prescriptions and 1.24 (95%CI 1.00–1.53) for ≥70 vs. 0 days for antibiotics between eight to three years prior to CRC diagnosis.

## DISCUSSION

The results of this nested case-control study indicate that the use of antibiotics is associated with an dose-dependent increased risk of developing CRC. The results were similar for models adjusted for sex and age, and models additionally adjusted for comorbidities and comedication. These positive associations were found for both anti-aerobic and anti-anaerobic drugs; however, when stratified for different classes of antibiotics we observed only statistically significantly associations for penicillins and quinolones.

Previous studies investigating the association between the use of antibiotics and cancer risk demonstrated similar results. A Finnish cohort study including over three million subjects found relative risks of 1.37 (95%-CI 1.34 - 1.40) for developing any cancer and 1.15 (95%-CI 1.04 - 1.26) for developing colon cancer when comparing subjects with ≥6 prescriptions to those with 0-1 prescriptions over a 3-year period prior to cancer diagnosis.[26] A recent nested case-control study by Wang *et al.* in almost twenty-eight thousand patients with type II diabetes also found a positive association between the use of anti-anaerobic antibiotics and both colon (OR 2.31, 95%-CI 2.12 – 2.52) and rectal cancer (OR 1.69, 95%-CI 1.50 – 1.90), but no association was found for anti-aerobic agents.[27] In contract, in our study we found a positive association between the use of anti-aerobic agents and developing CRC, although this was less pronounced when compared to anti-anaerobic agents. The gut microbiota is predominately composed of anaerobes and the findings reported by Wang *et al.* and those of our study suggest that particularly the use of anti-anaerobic agents may promote colorectal tumor growth, although caution is required when drawing conclusions about possible explanatory mechanisms.

Whether the observed associations between antibiotics and cancer risk reflect a causal relation is unclear. Antibiotics generally have no known genotoxic potential and evidence of possible carcinogenic effects of antibiotics is limited.[28] However, some antibiotics up-regulate cyclooxygenase-2 and increase the production of prostaglandins,[29] which are important in inflammatory responses and are known to promote the development of CRC.[30] Furthermore, it has been hypothesized that a depletion of anti-inflammatory and short-chain fatty acids producing species, such as *Faecalibacterium prausnitzii* and *Roseburia*, and the abundance of pro-inflammatory microorganisms such as *Fusobacterium*, *Porhyromonas*, *Enterococcaceae* and *Bacteroides-Prevotella*, and toxin producing species including *B. Fragilis* and some *E. Coli* strains, could change the gut microbiota in a more pro-carcinogenic environment.[31] This shift is thought to be dependent on subjects' age, diet and pathogen infections, but it can be hypothesized that the frequent use of antibiotics may alter short-chain fatty acids producing species by causing a dysbiosis of the colonic microbiota and thereby increasing the risk of developing CRC.[7-14] The observed association between the use of antibiotics and CRC risk in our study could also be caused by unmeasured confounding factors associated with

CRC risk and a higher use of antibiotics, such as socioeconomic status, smoking, body mass index and other lifestyle factors. Nonetheless, when we adjusted for potential confounding factors associated with lifestyle, including diabetes and the use of statins, acetylsalicylic acids and non-steroidal anti-inflammatory drugs, the results remained similar. An alternative explanation for the findings of the present study could be that subjects with a weakened immune system are more susceptible for developing cancer and more frequently develop infections requiring antibiotics. In that case, the observed associations may only be an indicator for an increased cancer risk in general rather than an effector. This may be why in previous studies positive associations have been found between the use of antibiotics and tumors in other organs, such as breast, prostate, lung and thyroid cancer and non-Hodgkin's lymphoma, which, as far as we currently understand, do not have an association with the gut microbiota,[26,32-36] We observed no statistically significantly interaction between the use of antibiotics and other factors that may affect the gut microbiota or that have previously been reported to be associated with CRC risk, which suggests that there is no synergetic effect of antibiotics with diabetes or other medications. We also did not find evidence for reversed causation since prolonging the lag time between the last time point of antibiotic use and CRC diagnosis from one to two or three years had no effect on the results. On the contrary, the risk estimates increased when a follow-up period further back in time was employed. This increases the likelihood of a causal effect since CRC has been estimated to develop over a period of eight to ten years.[37]



The strengths of this study include the large number of CRC cases and matched controls that were identified in a health claim database providing high quality data on the use of antibiotics and potential confounding medication and comorbidity. In the Netherlands, antibiotics can only be obtained with a prescription of a physician and therefore are registered in the health claim database. Both DRG and pharmacy registrations are complete and highly accurate because of the economic function of the database for the insurance company.[22] Furthermore, compared to most previous studies, we included a higher number of subjects from the general population.[26,27,32]

A limitation of our study is that the diagnosis of CRC could not be histologically confirmed. Second, as previously mentioned, there were no data available on potential confounding lifestyle factors, which is a limitation of the present study. Third, antibiotics prescribed during hospitalizations are not registered in the database. Therefore, we could not include the antibiotics that are more frequently prescribed during hospitalization, such as cephalosporins, aminoglycosides and imidazoles. There were also no data available on whether the dispensed antibiotics were actually used. Both may have diluted the true size of the association between antibiotics and CRC risk. Finally, we did not have data on the microbiota composition of the subjects included in our study. Combined data on the use of antibiotic agents and the composition of the gut microbiota could

be of additive value to further detangle the association between antibiotic use and CRC development. Nevertheless, the dose-dependent increase and the similar risk estimates for antibiotic use up to eight years before diagnosis suggest that a dysbiosis of the gut microbiota through the use of antibiotics may partially contribute to the development of CRC.

As of now, there is insufficient evidence to make a clinical recommendation regarding the use of antibiotics and CRC risk. The results of our study do however support the idea that a microbiotical disbalance in the colorectum may increase the risk of developing CRC. Two previous studies, of which one in a general population investigating a shorter exposure period and one only including subjects with type 2 diabetes, found a positive association between the use of antibiotics and CRC risk. These findings are now supported by our study in a general population. Additional epidemiological studies with long-term follow-up should focus on the mutual effects of antibiotic use and lifestyle factors to further elucidate the association between antibiotic use and CRC risk. Furthermore, observational studies including measurements of the (changes in) microbiota composition in relation to CRC risk may provide more insights in the role of the gut microbiota in the pathogenesis of CRC.

In conclusion, we observed a positive association between the use of antibiotics, especially when used frequently, and the risk of developing CRC. Whether this association resembles a causal relation must be investigated in future studies.

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# Chapter 8

## Coffee and tea consumption, genotype based *CYP1A2* and *NAT2* activity, and colorectal cancer risk - results from the EPIC cohort study

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*International Journal of Cancer. 2014 Jul 15;135(2):401-12.*

## ABSTRACT

Coffee and tea contain numerous antimutagenic and antioxidant components and high levels of caffeine that may protect against colorectal cancer. We investigated the association between coffee and tea consumption and colorectal cancer risk and studied potential effect modification by *CYP1A2* and *NAT2* genotypes, enzymes involved in the metabolization of caffeine. Data from 477,071 participants (70.2% female) of the European Investigation into Cancer and Nutrition (EPIC) cohort study were analyzed. At baseline (1992-2000) habitual (total, caffeinated and decaffeinated) coffee and tea consumption was assessed with dietary questionnaires. Cox proportional hazards models were used to estimate adjusted hazard ratio's (HR) and 95%-confidence intervals (95%-CI). Potential effect modification by genotype-based *CYP1A2* and *NAT2* activity was studied in a nested case-control set of 1,252 cases and 2,175 controls. After a median follow-up of 11.6 years, 4,234 participants developed colorectal cancer (mean age 64.7±8.3 years). Total coffee consumption (high vs. non/low) was not associated with colorectal cancer risk (HR 1.06, 95%-CI 0.95-1.18) or subsite cancers, and no significant associations were found for caffeinated (HR 1.10, 95%-CI 0.97-1.26) and decaffeinated coffee (HR 0.96, 95%-CI 0.84-1.11) and tea (HR 0.97, 95%-CI 0.86-1.09). High coffee and tea consuming subjects with slow *CYP1A2* or *NAT2* activity had a similar colorectal cancer risk compared to non/low coffee and tea consuming subjects with a fast *CYP1A2* or *NAT2* activity, which suggests that caffeine metabolism does not affect the link between coffee and tea consumption and colorectal cancer risk. This study shows that coffee and tea consumption is not likely to be associated with overall colorectal cancer.

## INTRODUCTION

Coffee and tea are among the most widespread and most consumed beverages in the world. Both beverages contain a mixture of components. Some of these have shown potential anticarcinogenic effects in animal models and human cell cultures and may play a protective role against colorectal cancer.[1-4] These components include phenolic compounds, chlorogenic acid and diterpenes (cafestol and kahweol) in coffee and catechins and polyphenols in tea.[5,6] In addition, cafestol and kahweol may lower colorectal cancer risk by reducing bile acid synthesis and secretion, while caffeine inhibits colon cancer cell growth and may lower carcinogen exposure of colonic epithelial cells by increasing colonic motility.[6-9]

Epidemiological studies are inconsistent regarding coffee and tea consumption and colorectal cancer risk. A recent meta-analysis reported a reduced colon cancer risk for high versus non/low coffee consumers (OR 0.79, 95%-CI 0.67-0.95) in case-control studies but not in cohort studies (OR 0.93, 95%-CI 0.86-1.01) or for rectal cancer.[10] However, studies were heterogeneous in design and population. Findings of a recent cohort study, only showed a protective effect of coffee against proximal colon cancer.[11] Similarly, in a pooled analysis of cohort studies, high tea consumption was found to be slightly positively associated with colon cancer risk,[12] while others have reported inverse or no associations.[11,13] These inconclusive findings from epidemiological studies could partly be explained by issues of study design, the number of colorectal cancer cases, differences in type of coffee (caffeinated/decaffeinated coffee and brewing methods) and tea (green and black) and residual confounding.

If caffeine, as one of the major coffee and tea components, lowers colorectal cancer risk, then the association between coffee and tea consumption and colorectal cancer risk might be modified by the metabolization rate of caffeine. However, no epidemiological studies have investigated this hypothesis as far as we know. Of the major coffee and tea components thought to impact colorectal cancer risk, caffeine is the only one that is almost completely hydroxylated in the liver by the cytochrome P450 isoform *CYP1A2* and acetylated by N-acetyltransferase (*NAT*) 2.[14,15] *CYP1A2* and *NAT2* activity varies widely between subjects and depends on genetic background (single nucleotide polymorphisms; SNPs) and environmental factors such as diet and certain medication.[16,17]

Due to a limited number of colorectal cancer cases in most previous studies, separate analyses for proximal colon, distal colon and rectal cancer are scarce. Since considerable differences may exist for subsite colorectal cancers with regard to particular risk factors and sex,[18] subsite analyses on the association between coffee and tea consumption and colorectal cancer risk are warranted. Furthermore, the *CYP1A2* and *NAT2* depended metabolization of caffeine - present in both coffee and tea - with it's possible link to colorectal cancer risk, makes it of high interest to study genetic heterogeneity in *CYP1A2*

and *NAT2*. In the present large size prospective cohort study we aim to clarify the overall effect of coffee, caffeinated coffee, decaffeinated coffee and tea consumption on the risk of developing colorectal cancer and subsite cancers. We further study whether *CYP1A2* and *NAT2* activity modify the association between (caffeinated) coffee and tea consumption and colorectal cancer risk within a nested case-control dataset.

## METHODS

### Study population

The European Investigation into Cancer and Nutrition (EPIC) study is an ongoing multicenter population-based cohort study to investigate the relation between diet, nutritional and metabolic characteristics, lifestyle factors, and subsequent cancer incidence and cause specific mortality. The cohort consists of 521,448 participants (70% women and mostly aged between 25 and 70 years), enrolled between 1992 and 2000, and followed within 23 centers in 10 different countries, i.e. Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden and United Kingdom. Detailed information about the selection of the study-population, data collection and follow-up procedures were reported previously.[19,20] All participants of the EPIC cohort gave written informed consent. The study was approved by the International Agency for Research on Cancer ethical review committee and by the local committees at the participating centers.

### Data collection

*Exposure assessment*

Usual dietary intake was assessed with country-specific validated dietary questionnaires.[21] Coffee and tea consumption in milliliters (ml) per day was calculated for each center separately and was based on the recorded number of cups per day/week/month; the exact questions varied slightly by center and questionnaire. Complete information on both caffeinated and decaffeinated coffee consumption was only available for centers from France, Germany, Italy (Florence, Varese and Turin only), the Netherlands and the United Kingdom. Information on tea consumption was not available in Norway and to low in Greece (median 0.46 ml/day).

Non-dietary data on demographic characteristics, lifestyle habits, risk factors and presence of chronic diseases were collected through questionnaires at study enrolment. Anthropometric measurements were taken at recruitment by trained health professionals in most centers, except for part of the Oxford cohort, the Norwegian cohort, and approximately two-thirds of the French cohort, among whom weight and height were self-reported.

*Colorectal cancer ascertainment*

The outcomes of interests were first incidence of primary (adeno)carcinoma located in the colorectum. In most of the participating countries, identification of colorectal cancer cases is based on the regional cancer registries as well as through self-reporting in the postal follow-up questionnaires (Denmark, Italy, the Netherlands, Norway, Spain, Sweden and the United Kingdom). In addition, information on vital status and movement of participants is obtained through linkage with the municipal administration registries. In France, Germany and Greece participants are actively followed-up to obtain information on cancer cases and vital status.

The second edition of the International Classification of Diseases-Oncology (ICD-O) was used to code colorectal cancer localization.[22] Right/proximal colon tumors included caecum, appendix, ascending colon, hepatic flexure, transverse colon, and splenic flexure (C18.0 - 18.5). Left/distal colon tumors included the descending (C18.6) and sigmoid colon (C18.7). Overlapping (C18.8) and unspecified lesions (C18.9) of the colon were grouped among all colon cancers (C18.0-C18.9). Cancer of the rectum included tumors occurring at the rectosigmoid junction (C19) and rectum (C20).

*Nested case-control study*

A subset of colorectal cancer cases were randomly selected from colorectal cancer cases diagnosed before 2005 in all EPIC centers except for Denmark and were matched with controls (1:2) by sex, age at blood collection (± 6-24 months), study center and menopausal status (premenopausal, postmenopausal, perimenopausal, unknown). Controls were selected from all cohort members alive and free of cancer (except non melanoma skin cancer) at the time of diagnosis of the matching cases. After excluding subjects with low DNA concentration or low quality of DNA extracted from the buffy coat samples (n=484), and removing incomplete case sets (n=243), a total of 1,252 colorectal cancer cases (829 colon, 423 rectum) and 2,175 matched controls remained for final analyses. The distribution of cases (colon/rectum) per country was: France 27/7, Germany 129/88, Greece 24/22, Italy 166/60, the Netherlands 119/61, Norway 15/4, Spain 99/54, Sweden 72/45, United Kingdom 178/82. There were no samples available from Denmark.

*Collection and storage of blood samples*

In each of the participating centers, blood samples of at least 30 ml were obtained and stored at 5°C to 10°C, protected from light, and transported to local laboratories for processing and stored as previously described.[19,20] The blood samples were stored as plasma, serum, buffy coat and erythrocytes in 0.5 ml straws under liquid nitrogen at -196°C (except for Sweden where samples were stored in -80°C freezers).

*Genotyping and classification of CYP1A2 and NAT2 activity*

DNA was extracted from buffy coat samples with the Autopure LS (Qiagen). SNPs were genotyped using the Illumina Metabochip in the *CNRS UMR8199* laboratory as previously described.[23] Genotyped SNPs included *CYP1A2 -164A>C* (rs762551) and for *NAT2 191G>A* (rs1801279), *590G>A* (rs1799930), *857G>A* (rs1799931) and *481C>T* (rs1799929). Within controls, the SNP distributions did not deviate from Hardy-Weinberg equilibrium.

Subjects carrying a *CYP1A2 C/C* or *A/C* genotype were characterized as slow metabolizers, while subjects with an *A/A* genotype were characterized as fast metabolizers.[16] *NAT2* haplotype pairs were predicted using Plink software (v1.07),[24,25] and were used to classify subjects by most probable acetylation status.[26] A slow *NAT2* acetylation status was defined as the presence of two slow *NAT2* alleles, which are characterized by the presence of one or more of the SNPs *191G>A*, *590G>A*, *857G>A* or *341T>C*. For this study *481C>T* was used as a proxy for *341T>C* ($R^2$ 0.89). Subjects carrying one or two fast (wild type) alleles were classified as fast acetylators.

## Data analyses

*Whole cohort analyses*

Analyses of this study were conducted in 477,071 participants (70.2% female) of whom 4,234 developed first primary colorectal (adeno)carcinoma. Before analyses we excluded participants with any type of prevalent cancer at enrolment and/or incomplete follow-up (n=28,150), incomplete (non-)dietary data (n=6,253), with the highest and lowest 1% of the distribution for the ratio between energy intake to estimated energy requirement (n=9,601), carcinoma in situ (n=133), unknown histology of the tumor (n=105), unknown first incidence tumor (n=14) or a colorectal tumor originating from other organs (n=3).

Follow-up time in person years was calculated from study enrolment until censoring at the date of first diagnosis of any type of cancer, death, loss to follow-up or the date at which follow-up ended, whatever came first. End of follow-up was defined as the last date at which follow-up data were judged to be complete or the last date of contact in the centers that used active follow-up.

Cohort-wide quintiles (coffee, caffeinated coffee and tea) or tertiles (decaffeinated coffee) for levels of consumption were computed after excluding non-consumers. Multivariable Cox proportional hazard regression models were used to estimate adjusted hazard ratios (HR) and corresponding 95% confidence intervals (95%-CI) for different levels of consumption, in which non- and low-consumers were combined. Linear trends over different categories were computed using median consumption levels within the categories in all subjects. Additional Cox proportional hazard regression models were used with coffee and tea intake as a continuous variable to compute HR per 100 ml/day increase of consumption. All models were stratified by age (1-year intervals), sex,

and center to adjust for differences in follow-up procedures and questionnaire design between the participating centers. Age at enrolment and age at end of follow-up were used as the underlying time variables. All models were adjusted for body mass index (BMI; continuous), self-reported diabetes (DM; yes, no), menopausal status (pre-menopausal, perimenopausal, postmenopausal), hormone replacement therapy (HRT; yes, no), physical activity according to the Cambridge Physical Activity Index (CPAI; inactive, moderately inactive, moderately active, active), educational level as a proxy of socioeconomic status (none, primary school, technical/professional school, secondary school, university), smoking status/duration/intensity (never, former: quitted ≥ 10 years, former: quitted < 10 years, former: time since quitting unknown, current: 1-10 cig. per day, current: 11-20 cig. per day, current: 21+ cig. per day, current: number of cig. per day unknown, smoking status unknown), and intake of energy from fat, energy from non-fat, alcohol at recruitment, fibers, dairy products, red meat and processed meat (all continuous). Missing categories were included for categorical variables with missing data. Additional models in which coffee and tea were mutually adjusted to examine substitution behavior did not change the results and were therefore omitted. Furthermore, the use of contraceptive medication and the consumption of fruit, vegetables and fish were considered as potential confounders but were not included in the final models because they did not alter the results.

Effect modification by factors that may interact with the potential antioxidant effects of coffee and tea, and possible heterogeneity of effects among countries, were tested by adding multiplicative interaction terms to the model and using likelihood ratio tests for interaction. For these analyses we used the interaction terms of consumption categories with country, sex, diabetes, smoking status (never, former, current) and tertiles of BMI, red meat and processed meat intake.

Sensitivity analyses to examine potential pre-diagnostic disease related changes in consumption habits were performed by excluding colorectal cancer cases that were diagnosed within the first two years of follow-up. Finally, we also conducted analyses using country-specific levels of consumption instead of cohort-wide levels of consumption.

*Nested case-control analyses*

Joint effects of coffee and tea consumption, *CYP1A2* metabolization status and *NAT2* acetylator status were tested using multivariable conditional logistic regression models and by adding multiplicative interaction to the model and using likelihood ratio tests for interaction. Subjects with non/low coffee and tea consumption and a fast *CYP1A2* and *NAT2* metabolization status were used as the reference categories. All models were stratified by matching factors and adjusted for the same (potential) risk factors as used in the whole cohort analyses except for matching factors. Due to low number of cases

in site-specific analyses, moderately low and moderate consumers were combined as moderate consumers, and moderately high and high consumers were combined as high consumers.

All statistical analyses were conducted with SAS 9.2 (SAS Institute Inc, Cary, USA). Two-sided p-values < 0.05 were considered statistically significant.

## RESULTS

### Baseline characteristics

After a median follow-up of 11.6 years (inter quartile range 10.1-12.6), 4,234 participants (70% female) had developed a first primary colorectal tumor at a mean age of 64.7 ± 8.3 years. Colon cancer was diagnosed in 2,691 (64%) participants (1,242 proximal and 1,202 distal colon, 247 unspecified) and rectal cancer in 1,543 (36%) participants.

In the total cohort, 93% of the participants consumed coffee with a median consumption of 310 ml/day (interquartile range; IQR 131-556) among consumers. Median consumption was 270 ml/day (IQR 90-475) for caffeinated coffee and 38 ml/day (IQR 2-150) for decaffeinated coffee. Within coffee consumers, 55% exclusively drank caffeinated coffee whereas 4% only consumed decaffeinated coffee. High coffee consumption was positively associated with male sex, physical activity, current smoking status, number of cigarettes per day, meat consumption and intake of dairy products (Table 1). Tea was consumed by 67% of the study population and median tea consumption was 190 ml/day (IQR 28-475) among consumers. High tea consumption was positively associated

**Table 1.** Baseline characteristics and risk factor distribution according to level of coffee and tea consumption in 477,071 participants.

| | Total | Coffee[1] | | Tea[2] | |
|---|---|---|---|---|---|
| | | Non / low consumers[3] | High consumers[4] | Non / low consumers[3] | High consumers[4] |
| **Follow-up, person years** | 5,261,297 | 1,335,268 | 1,027,885 | 2,311,778 | 619,225 |
| **Male, %** | 29.8 | 27.3 | 38.6 | 35.0 | 27.9 |
| **Age at recruitment, mean (years)** | 51.2 | 50.6 | 51.8 | 51.8 | 52.5 |
| **Body mass index, mean (kg/m2)** | 25.4 | 25.5 | 25.5 | 26.2 | 24.0 |
| **Diabetes mellitus, %** | 2.7 | 3.3 | 2.3 | 3.6 | 2.0 |
| **Menopausal status, %** | | | | | |
| Premenopausal | 34.8 | 38.9 | 28.4 | 34.5 | 35.1 |
| Perimenopausal | 18.9 | 13.6 | 21.5 | 17.3 | 15.9 |
| Postmenopausal | 46.3 | 44.8 | 50.1 | 48.2 | 49.0 |

**Table 1** (continued)

| | Total | Coffee[1] | | Tea[2] | |
|---|---|---|---|---|---|
| | | Non / low consumers[3] | High consumers[4] | Non / low consumers[3] | High consumers[4] |
| **Ever used hormone therapy, %** | 26.0 | 21.0 | 30.6 | 22.2 | 28.4 |
| **Physical activity, %** [5] | | | | | |
| Inactive | 22.6 | 28.8 | 15.5 | 27.9 | 20.8 |
| Moderatevely intactive | 34.4 | 34.0 | 32.2 | 34.3 | 33.1 |
| Moderatevely active | 24.4 | 22.1 | 25.3 | 22.5 | 25.3 |
| Active | 18.6 | 15.1 | 27.1 | 15.3 | 20.8 |
| **Level of education, %** | | | | | |
| None | 4.6 | 9.8 | 0.4 | 9.4 | 0.1 |
| Primary school completed | 26.5 | 27.7 | 26.4 | 34.4 | 16.7 |
| Technical/professional school | 23.1 | 15.7 | 33.1 | 17.6 | 27.6 |
| Secondary school | 21.2 | 22.6 | 16.7 | 18.4 | 20.5 |
| College or university degree | 24.7 | 24.2 | 23.4 | 20.2 | 35.1 |
| **Smoking status, %** | | | | | |
| Never | 48.9 | 60.1 | 32.4 | 48.7 | 51.8 |
| Former smoker, time since quitting ≥ 10 years | 16.5 | 14.4 | 17.2 | 14.0 | 21.1 |
| Former smoker, time since quitting < 10 years | 9.1 | 8.2 | 10.4 | 9.1 | 8.3 |
| Former smoker, time since quitting unknown | 1.0 | 0.8 | 1.5 | 0.7 | 1.6 |
| Current smoker, 1-10 cig. per day | 9.0 | 6.3 | 11.8 | 8.7 | 6.1 |
| Current smoker, 11-20 cig. per day | 8.3 | 4.7 | 16.7 | 10.1 | 5.1 |
| Current smoker, 21+ cig. per day | 3.2 | 2.1 | 5.2 | 5.0 | 1.3 |
| Current smoker, number cig. unknown | 2.0 | 1.4 | 3.5 | 2.1 | 2.3 |
| Smoking status unknown | 2.0 | 2.0 | 1.3 | 1.6 | 2.4 |
| **Total energy from fat, median (kcal/day)** | 695 | 686 | 720 | 734 | 685 |
| **Total energy from non-fat, median (kcal/day)** | 1,289 | 1,278 | 1,406 | 1,355 | 1.331 |
| **Alcohol intake, median (g/day)** | 5 | 3 | 8 | 6 | 6 |
| **Fiber intake, median (g/day)** | 22 | 22 | 22 | 21 | 24 |
| **Red meat intake, median (g/day)** | 35 | 32 | 50 | 40 | 32 |
| **Processed meat intake, median (g/day)** | 24 | 18 | 28 | 24 | 18 |
| **Dairy products intake, median (g/day)** | 277 | 250 | 318 | 252 | 364 |

1. Cut-off points (ml) for coffee quintiles were 100, 230, 450 and 625.
2. Cut-off points (ml) for tea quintiles were 16, 107, 300 and 514.
3. Low consumption is defined as the lowest quintile within consumers of coffee and tea.
4. High consumption is defined as the highest quintile within consumers of coffee and tea.
5. According to the Cambridge physical activity index.

with female sex, physical activity, level of education and intake of dairy products, and was inversely associated with BMI, current smoking status and meat consumption.

### Coffee and tea consumption and colorectal cancer risk

Hazard ratio's for coffee (total, caffeinated and decaffeinated) consumption and colorectal cancer risk are shown in Table 2. Coffee consumption was not associated with overall colorectal cancer risk (HR 1.06, 95%-CI 0.95-1.18 for high vs. non/low consumption; p-trend 0.58), but tended to be associated with an increased rectal cancer risk for high consumers (HR 1.20, 95%-CI 1.00-1.44; p-trend 0.15). However, the effect size per 100 ml/day in the continuous model was not statistically significant (HR 1.02, 95%-CI 1.00-1.03). Separate analyses for caffeinated and decaffeinated coffee showed no statistically significant associations with the risk of colorectal cancer or subsite cancer, although the risk estimates for caffeinated coffee consumption and rectal cancer risk (HR for high vs. non/low consumers 1.18, 95%-CI 0.95-1.47, p-trend 0.15) were similar to that of total coffee consumption and rectal cancer risk.

The association between coffee consumption and colorectal cancer was not significantly modified by diabetes (p = 0.38), smoking status (p = 0.22), BMI (p = 0.35) and intake of red meat (p = 0.30) and processed meat (p = 0.22). Effect modification by sex was observed for coffee consumption and risk of colon cancer (p = 0.03) but not for overall colorectal cancer (p = 0.16); stratified analyses showed an inverse association for distal

**Table 2.** Adjusted hazard ratio's[1] for colorectal cancer and subsite cancers according to level of total coffee, caffeinated coffee and decaffeinated coffee consumption.

| | Coffee[2] | | Caffeinated coffee[3,5] | | Decaffeinated coffee[4,5] | |
|---|---|---|---|---|---|---|
| | **Cases** | **HR (95%-CI)** | **Cases** | **HR (95%-CI)** | **Cases** | **HR (95%-CI)** |
| **Colorectal cancer** | | | | | | |
| Non/low consumers | 914 | ref. | 666 | ref. | 1,446 | ref. |
| Moderately low | 761 | 1.04 (0.94-1.15) | 373 | 1.03 (0.90-1.17) | 359 | 1.00 (0.86-1.16) |
| Moderate | 694 | 1.06 (0.95-1.19) | 542 | 1.07 (0.95-1.21) | 326 | 0.96 (0.84-1.11) |
| Moderately high | 863 | 0.99 (0.89-1.10) | 478 | 1.01 (0.89-1.14) | - | - |
| High | 1,002 | 1.06 (0.95-1.18) | 517 | 1.10 (0.97-1.26) | - | - |
| P-trend | | 0.58 | | 0.29 | | 0.74 |
| Per 100 ml/day | | 1.01 (0.99-1.02) | | 1.01 (1.00-1.03) | | 0.98 (0.95-1.01) |
| **Colon cancer** | | | | | | |
| Non/low consumers | 626 | ref. | 457 | ref. | 955 | ref. |
| Moderately low | 511 | 1.03 (0.91-1.16) | 261 | 1.05 (0.90-1.22) | 233 | 1.04 (0.86-1.25) |
| Moderate | 441 | 1.01 (0.88-1.17) | 351 | 1.04 (0.90-1.21) | 210 | 1.01 (0.85-1.19) |
| Moderately high | 533 | 0.93 (0.82-1.07) | 293 | 0.94 (0.80-1.10) | - | - |
| High | 580 | 0.99 (0.86-1.13) | 310 | 1.06 (0.90-1.26) | - | - |

**Table 2** (continued)

| | Coffee[2] | | Caffeinated coffee[3,5] | | Decaffeinated coffee[4,5] | |
|---|---|---|---|---|---|---|
| | **Cases** | **HR (95%-CI)** | **Cases** | **HR (95%-CI)** | **Cases** | **HR (95%-CI)** |
| P-trend | | 0.65 | | 0.82 | | 0.97 |
| Per 100 ml/day | | 1.00 (0.99-1.01) | | 1.01 (0.99-1.02) | | 0.99 (0.95-1.02) |
| **Proximal colon cancer** | | | | | | |
| Non/low consumers | 264 | ref. | 206 | ref. | 436 | ref. |
| Moderately low | 221 | 1.00 (0.83-1.20) | 106 | 0.95 (0.75-1.21) | 118 | 1.03 (0.78-1.34) |
| Moderate | 216 | 1.05 (0.85-1.29) | 188 | 1.14 (0.92-1.41) | 100 | 0.93 (0.72-1.19) |
| Moderately high | 254 | 0.94 (0.77-1.14) | 145 | 0.93 (0.74-1.17) | - | - |
| High | 287 | 1.06 (0.87-1.30) | 163 | 1.12 (0.88-1.42) | - | - |
| P-trend | | 0.50 | | 0.78 | | 0.52 |
| Per 100 ml/day | | 1.01 (0.99-1.03) | | 1.01 (0.99-1.04) | | 0.98 (0.92-1.03) |
| **Distal colon cancer** | | | | | | |
| Non/low consumers | 294 | ref. | 188 | ref. | 396 | ref. |
| Moderately low | 227 | 1.02 (0.85-1.22) | 129 | 1.25 (0.99-1.58) | 98 | 1.04 (0.79-1.39) |
| Moderate | 187 | 0.99 (0.80-1.22) | 134 | 1.00 (0.79-1.27) | 97 | 1.16 (0.89-1.50) |
| Moderately high | 234 | 0.92 (0.75-1.12) | 122 | 1.00 (0.78-1.28) | - | - |
| High | 260 | 0.94 (0.76-1.15) | 127 | 1.08 (0.83-1.39) | - | - |
| P-trend | | 0.26 | | 0.77 | | 0.29 |
| Per 100 ml/day | | 0.99 (0.97-1.01) | | 1.00 (0.97-1.03) | | 1.01 (0.96-1.06) |
| **Rectal cancer** | | | | | | |
| Non/low consumers | 288 | ref. | 209 | ref. | 491 | ref. |
| Moderately low | 250 | 1.07 (0.90-1.27) | 112 | 0.99 (0.78-1.25) | 126 | 0.93 (0.72-1.21) |
| Moderate | 253 | 1.17 (0.96-1.41) | 191 | 1.12 (0.91-1.38) | 116 | 0.89 (0.70-1.12) |
| Moderately high | 330 | 1.09 (0.91-1.31) | 185 | 1.13 (0.92-1.40) | - | - |
| High | 422 | 1.20 (1.00-1.44) | 207 | 1.18 (0.95-1.47) | - | - |
| P-trend | | 0.15 | | 0.15 | | 0.18 |
| Per 100 ml/day | | 1.02 (1.00-1.03) | | 1.02 (1.00-1.04) | | 0.97 (0.93-1.03) |

1. All models were stratified by age (1-year intervals), sex and center, and adjusted for body mass index (continuous), diabetes mellitus (yes, no), menopausal status (premenopausal, perimenopausal, postmenopausal), hormone replacement therapy (yes, no), physical activity (inactive, moderately inactive, moderately active, active), educational level (none, primary school, technical/professional school, secondary school, university), smoking status (never, former: quitted ≥ 10 years, former: quitted < 10 years, former: time since quitting unknown, current: 1-10 cig. per day, current: 11-20 cig. per day, current: 21+ cig. per day, current: number of cig. per day unknown, smoking status unknown), and baseline intake of energy from fat, energy from non-fat, alcohol, fibers, dairy products, red meat and processed meat (all continuous).
2. Cut-off points (ml) for coffee quintiles were 100, 230, 450 and 625.
3. Cut-off points (ml) for caffeinated coffee quintiles were 70, 190, 387 and 550.
4. Cut-off points (ml) for decaffeinated coffee tertiles were 6 and 82.
5. Complete information on both caffeinated and decaffeinated coffee consumption is only available in centers from France, Germany, Italy (Florence, Varese and Turin only), the Netherlands, Sweden (Malmö only) and the United Kingdom.

colon cancer in men (HR 0.73, 95%-CI 0.53-1.00 for high vs. non/low consumption), with a p-trend of 0.03 and a minor though statistically significant continuous risk estimate (HR 0.97, 95%CI 0.95-0.99, p = 0.04) (Table 3). In contrast, coffee consuming women had an increased rectal cancer risk (HR 1.31 for high vs. non/low, 95%-CI 1.02-1.68), but similar risk estimates were found for moderate and moderately high coffee consuming women and no statistically significant dose dependent association (p-trend 0.24) or continuous association per 100 ml/day was found, nor statistically significant effect modification by sex (p = 0.38). No significant associations were observed for caffeinated coffee consumption and colon cancer risk in men, and rectal cancer risk in women (data not shown).

For tea consumption we found no associations with colorectal cancer (HR 0.97, 95%-CI 0.86-1.09 for high vs. non/low consumption) or subsite cancers (Table 4). The risk

**Table 3.** Sex-specific adjusted hazard ratio's[1,2] for colorectal cancer and subsite cancers according to level of total coffee consumption[3].

| | Men | | Women | | P-value for interaction |
|---|---|---|---|---|---|
| | Cases | HR (95%-CI) | Cases | HR (95%-CI) | |
| **Colorectal cancer** | | | | | |
| No/low consumption | 409 | ref. | 505 | ref. | |
| Moderately low | 330 | 0.98 (0.84-1.14) | 431 | 1.09 (0.95-1.24) | |
| Moderate | 234 | 0.96 (0.80-1.16) | 460 | 1.15 (0.99-1.33) | |
| Moderately high | 355 | 0.87 (0.74-1.02) | 508 | 1.09 (0.95-1.25) | 0.16 |
| High | 477 | 0.91 (0.77-1.07) | 525 | 1.19 (1.03-1.38) | |
| P-trend | | 0.36 | | 0.12 | |
| Per 100 ml/day[4] | | 0.99 (0.98-1.01) | | 1.02 (1.00-1.03) | |
| **Colon cancer** | | | | | |
| No/low consumption | 271 | ref. | 355 | ref. | |
| Moderately low | 212 | 0.97 (0.80-1.17) | 299 | 1.07 (0.91-1.25) | |
| Moderate | 131 | 0.88 (0.69-1.12) | 310 | 1.12 (0.94-1.33) | |
| Moderately high | 189 | 0.73 (0.59-0.91) | 344 | 1.10 (0.93-1.31) | 0.03 |
| High | 256 | 0.81 (0.65-1.00) | 324 | 1.14 (0.95-1.36) | |
| P-trend | | 0.05 | | 0.29 | |
| Per 100 ml/day[4] | | 0.98 (0.96-1.00) | | 1.01 (0.99-1.03) | |
| **Proximal colon cancer** | | | | | |
| No/low consumption | 110 | ref. | 154 | ref. | |
| Moderately low | 91 | 0.96 (0.72-1.28) | 130 | 1.03 (0.81-1.31) | |
| Moderate | 53 | 0.77 (0.53-1.12) | 163 | 1.23 (0.96-1.59) | |
| Moderately high | 83 | 0.69 (0.50-0.95) | 171 | 1.13 (0.88-1.46) | 0.05 |
| High | 123 | 0.89 (0.65-1.23) | 164 | 1.19 (0.91-1.55) | |
| P-trend | | 0.59 | | 0.20 | |
| Per 100 ml/day[4] | | 1.00 (0.97-1.03) | | 1.01 (0.99-1.04) | |

**Table 3** (continued)

| | Men | | Women | | P-value for interaction |
|---|---|---|---|---|---|
| | Cases | HR (95%-CI) | Cases | HR (95%-CI) | |
| **Distal colon cancer** | | | | | |
| No/low consumption | 134 | ref. | 160 | ref. | |
| Moderately low | 97 | 0.95 (0.72-1.24) | 130 | 1.08 (0.85-1.37) | |
| Moderate | 67 | 0.99 (0.70-1.39) | 120 | 1.02 (0.78-1.34) | |
| Moderately high | 91 | 0.77 (0.56-1.04) | 143 | 1.05 (0.80-1.36) | 0.19 |
| High | 116 | 0.73 (0.53-1.00) | 144 | 1.14 (0.86-1.50) | |
| P-trend | | 0.03 | | 0.65 | |
| Per 100 ml/day[4] | | 0.97 (0.95-0.99) | | 1.01 (0.99-1.04) | |
| **Rectal cancer** | | | | | |
| No/low consumption | 138 | ref. | 150 | ref. | |
| Moderately low | 118 | 1.00 (0.78-1.29) | 132 | 1.13 (0.89-1.44) | |
| Moderate | 103 | 1.12 (0.84-1.51) | 150 | 1.21 (0.94-1.56) | |
| Moderately high | 166 | 1.11 (0.86-1.45) | 164 | 1.07 (0.83-1.37) | 0.38 |
| High | 221 | 1.08 (0.83-1.42) | 201 | 1.31 (1.02-1.68) | |
| P-trend | | 0.42 | | 0.24 | |
| Per 100 ml/day[4] | | 1.01 (0.99-1.03) | | 1.02 (0.99-1.05) | |

1. Models were stratified by age (1-year intervals) and center, and adjusted for body mass index (continuous), diabetes mellitus (yes, no), physical activity (inactive, moderately inactive, moderately active, active), educational level (none, primary school, technical/professional school, secondary school, university), smoking status (never, former: quitted ≥ 10 years, former: quitted < 10 years, former: time since quitting unknown, current: 1-10 cig. per day, current: 11-20 cig. per day, current: 21+ cig. per day, current: number of cig. per day unknown, smoking status unknown), and baseline intake of energy from fat, energy from non-fat, alcohol, fibers, dairy products, red meat and processed meat (all continuous).
2. Same model as for men and additionally adjusted for menopausal status (premenopausal, perimenopausal, postmenopausal) and hormone replacement therapy (yes, no).
3. Cut-off points (ml) for coffee quintiles were 16, 107, 300 and 514.



estimates for tea consumption and colorectal cancer risk were not modified by sex (p = 0.33), diabetes (p = 0.49), BMI (p = 0.28) and intake of red meat (p = 0.27) and processed meat (p = 0.76). Significant effect modification was observed for smoking status (p < 0.01), but no statically significant associations between tea consumption and colorectal cancer risk were observed when the analyses were done separately for never, former and current smokers (data not shown).

There was no statistically significant heterogeneity among countries regarding coffee and tea consumption and colorectal cancer risk. Analyses using country-specific levels of consumption yielded similar results. Finally, sensitivity analyses excluding colorectal cancer cases diagnosed within the first two years of follow-up did not materially change our findings: coffee and colorectal cancer risk HR 1.09 (95%-CI 0.98-1.21), tea and colorectal cancer risk HR 1.00 (95%-CI 0.90-1.12) for high vs. non/low consumers.

**Table 4.** Adjusted hazard ratio's[1] for colorectal cancer and subsite cancers according to level of tea consumption[2].

| | Non/low consumers | Moderately low | Moderate | Moderately high | High | P-trend | Per 100 ml/day[4] |
|---|---|---|---|---|---|---|---|
| **Colorectal cancer** | | | | | | | |
| *Cases* | *1,867* | *589* | *486* | *554* | *534* | | |
| HR (95%-CI) | ref. | 0.98 (0.88-1.08) | 1.04 (0.93-1.16) | 1.03 (0.92-1.16) | 0.97 (0.86-1.09) | 0.56 | 1.00 (0.99-1.01) |
| **Colon cancer** | | | | | | | |
| *Cases* | *1,206* | *369* | *301* | *354* | *330* | | |
| HR (95%-CI) | ref. | 0.95 (0.83-1.08) | 0.97 (0.84-1.12) | 0.99 (0.85-1.14) | 0.88 (0.75-1.03) | 0.18 | 0.99 (0.98-1.01) |
| **Proximal colon cancer** | | | | | | | |
| *Cases* | *550* | *156* | *135* | *178* | *159* | | |
| HR (95%-CI) | ref. | 0.87 (0.71-1.06) | 0.91 (0.74-1.13) | 1.02 (0.83-1.26) | 0.85 (0.68-1.07) | 0.86 | 1.00 (0.97-1.02) |
| **Distal colon cancer** | | | | | | | |
| *Cases* | *531* | *185* | *143* | *138* | *146* | | |
| HR (95%-CI) | ref. | 1.09 (0.91-1.32) | 1.08 (0.88-1.34) | 0.94 (0.75-1.17) | 0.98 (0.78-1.24) | 0.18 | 0.99 (0.97-1.02) |
| **Rectal cancer** | | | | | | | |
| *Cases* | *661* | *220* | *185* | *200* | *204* | | |
| HR (95%-CI) | ref. | 1.04 (0.87-1.23) | 1.17 (0.97-1.40) | 1.11 (0.91-1.34) | 1.13 (0.93-1.38) | 0.42 | 1.01 (0.99-1.03) |

1. All models were stratified by age (1-year intervals), sex and center, and adjusted for body mass index (continuous), diabetes mellitus (yes, no), menopausal status (premenopausal, perimenopausal, postmenopausal), hormone replacement therapy (yes, no), physical activity (inactive, moderately inactive, moderately active, active), educational level (none, primary school, technical/professional school, secondary school, university), smoking status (never, former: quitted ≥ 10 years, former: quitted < 10 years, former: time since quitting unknown, current: 1-10 cig. per day, current: 11-20 cig. per day, current: 21+ cig. per day, current: number of cig. per day unknown, smoking status unknown), and baseline intake of energy from fat, energy from non-fat, alcohol, fibers, dairy products, red meat and processed meat (all continuous).
2. Country-specific cut-off points (ml) for tea quintiles were as follows: Denmark 16, 86, 499, 500; France 37, 143, 300, 505; Germany 12, 25, 107, 300; Italy 10, 21, 43, 150; the Netherlands 68, 206, 305, 475; Spain 43, 86, 150, 200; Sweden 16, 36, 179, 250; United Kingdom 150, 474, 475, 855. Information on tea consumption was not available in Norway and to low in Greece (median 0.46 ml/day).

### Effect modification by genotype based CYP1A2 and NAT2 activity

Compared to controls, colorectal cancer cases had higher BMI, were less physically active, were higher educated but had lower intake of dairy products (Supplemental Table 2). A slow *CYP1A2* metabolization status was present in 50.8% of cases and 49.6% of controls (p = 0.50), whereas a slow *NAT2* acetylation status was present in 58.5% of cases and 56.1% of controls (p = 0.16). Adjusted for colorectal cancer risk factors, slow *CYP1A2* (OR 1.03, 95%-CI 0.90-1.19) as well as slow *NAT2* status (OR 1.12, 95%-CI 0.97-1.29) were not statistically significantly associated with risk of colorectal cancer (Table 5).

We observed no significant joint effect for coffee consumption and *CYP1A2* with overall colorectal cancer and subsite cancer risk (Table 5). High coffee consuming subjects with slow *CYP1A2* activity had a similar colorectal cancer risk compared to low coffee consuming subjects with a fast *CYP1A2* activity (OR 1.15, 95%-CI 0.85-1.55). In addition, for coffee consumption and *NAT2* activity no joint effects were found. High coffee consuming subjects with slow *NAT2* activity had a similar colorectal cancer risk compared to low coffee consuming subjects with a fast *NAT2* activity (OR 1.10, 95%-CI 0.81-1.49). For both caffeinated coffee and tea consumption, and *CYP1A2* and *NAT2* activity we found no significant joint effects on overall colorectal cancer or subsite cancer risk (Supplemental Tables 3 and 4).

## DISCUSSION



In this large prospective cohort study, we found no association between total coffee, caffeinated coffee and decaffeinated coffee consumption and overall colorectal cancer and subsite cancer risk. However, sex-specific differences for coffee consumption and colon cancer risk cannot be ruled out. Genotyped based *CYP1A2* metabolization status and *NAT2* acetylation status did not modify the association between (total and caffeinated) coffee consumption and colorectal cancer risk convincingly. For tea consumption we found no association with overall colorectal cancer and subsite cancer risk and no joint effects with *CYP1A2* and *NAT2* activity were observed. No significant effect modification by known colorectal cancer risk factors was observed.

In general, prospective cohort studies have found no significant associations with either proximal colon, distal colon or rectal cancer.[27-32] A recent meta-analysis of cohort studies only found a non-significant reduced colon cancer risk for high coffee consumers.[10] In contrast, a recent prospective cohort study (NIH-AARP Diet and Health study) showed a protective effect of coffee against proximal colon cancer.[11] Besides a minor decreased distal colon cancer risk among coffee consuming men, we found no significant protective effect of coffee in the present study. It is hypothesized that the possibly protective effect of coffee against colorectal cancer found in some studies may

**Table 5.** Adjusted odds ratio's[1] for *CYP1A2* and *NAT2* activity and joint effects of *CYP1A2* and *NAT2* activity with coffee consumption.

| | Total cohort | | Non / low consumers | | Moderate consumers | | High consumers | | P-value for interaction |
|---|---|---|---|---|---|---|---|---|---|
| | Cases/ controls | OR (95%-CI) | Cases/ controls | OR (95%-CI) | Cases/ controls | OR (95%-CI) | Cases/ controls | OR (95%-CI) | |
| **COLORECTAL CANCER** | | | | | | | | | |
| ***CYP1A2 -164A>C (rs762551)*** | | | | | | | | | |
| Fast (AA) | 616/1,096 | ref. | 156/293 | ref. | 264/416 | 1.21 (0.92-1.58) | 196/387 | 0.95 (0.70-1.28) | 0.22 |
| Slow (CC / AC) | 636/1,079 | 1.03 (0.90-1.19) | 193/307 | 1.21 (0.92-1.60) | 249/443 | 1.00 (0.77-1.30) | 194/329 | 1.15 (0.85-1.55) | |
| ***NAT2* acetylation status** | | | | | | | | | |
| Fast | 519/955 | ref. | 143/284 | ref. | 208/357 | 1.07 (0.81-1.42) | 168/314 | 1.06 (0.77-1.45) | 0.63 |
| Slow | 733/1,220 | 1.12 (0.97-1.29) | 206/316 | 1.25 (0.95-1.65) | 305/502 | 1.17 (0.90-1.53) | 222/402 | 1.10 (0.81-1.49) | |
| **COLON CANCER** | | | | | | | | | |
| ***CYP1A2 -164A>C (rs762551)*** | | | | | | | | | |
| Fast (AA) | 422/7456 | ref. | 105/206 | ref. | 187/275 | 1.31 (0.94-1.83) | 130/264 | 0.90 (0.62-1.31) | 0.10 |
| Slow (CC / AC) | 407/714 | 0.96 (0.81-1.15) | 133/201 | 1.26 (0.90-1.77) | 156/291 | 0.94 (0.68-1.31) | 118/222 | 0.99 (0.68-1.45) | |
| ***NAT2* acetylation status** | | | | | | | | | |
| Fast | 355/634 | ref. | 103/195 | ref. | 147/226 | 1.11 (0.79-1.56) | 105/213 | 0.84 (0.57-1.24) | 0.67 |
| Slow | 474/825 | 1.04 (0.87-1.25) | 135/212 | 1.14 (0.81-1.60) | 196/340 | 1.02 (0.73-1.41) | 143/273 | 0.94 (0.64-1.36) | |
| **RECTAL CANCER** | | | | | | | | | |
| ***CYP1A2 -164A>C (rs762551)*** | | | | | | | | | |
| Fast (AA) | 194/351 | ref. | 51/87 | ref. | 77/141 | 0.98 (0.61-1.58) | 66/123 | 1.09 (0.63-1.87) | 0.44 |
| Slow (CC / AC) | 229/365 | 1.22 (0.95-1.58) | 60/106 | 1.10 (0.67-1.82) | 93/152 | 1.13 (0.72-1.77) | 76/107 | 1.55 (0.92-2.61) | |
| ***NAT2* acetylation status** | | | | | | | | | |
| Fast | 164/321 | ref. | 40/89 | ref. | 61/131 | 1.04 (0.62-1.76) | 63/101 | 1.84 (1.04-3.25) | 0.11 |
| Slow | 259/395 | 1.25 (0.97-1.61) | 71/104 | 1.58 (0.95-2.63) | 109/162 | 1.56 (0.97-2.50) | 79/129 | 1.54 (0.90-2.66) | |

All models were stratified by the matching factors sex, age at blood collection (± 6-24 months), study center and menopausal status (premenopausal, postmenopausal, perimenopausal, unknown) and adjusted for body mass index (continuous), diabetes mellitus (yes, no), hormone replacement therapy (yes, no), physical activity (inactive, moderately inactive, moderately active, active), educational level (none, primary school, technical/professional school, secondary school, university), smoking status (never, former: quitted ≥ 10 years, former: quitted < 10 years, former: time since quitting unknown, current: 1-10 cig. per day, current: 11-20 cig. per day, current: 21+ cig. per day, current: number of cig. per day unknown, smoking status unknown), and intake of energy from fat, energy from non-fat, alcohol, fibers, dairy products, red meat and processed meat (all continuous).

be related to antioxidant and antimutagenic effects of phenolic compounds (mainly chlorogenic acid),[6,33] inhibition of colon cancer cell growth by caffeine,[8,9] and cafestol and kahweol mediated reduction of bile acid synthesis[2,34,35] and inhibition of *CYP1A2* and *NAT2* activity.[36-39] In addition, caffeine may specifically protect against distal colon cancer by increasing the motility of the distal colon and, as a consequence, lowering carcinogen exposure of colonic epithelial cells.[7] Although in the present study specific data on caffeinated and decaffeinated coffee was only available in approximately half of the participating centers, separate analyses for caffeinated coffee did not demonstrate a significant protective effect of caffeinated coffee against colorectal cancer.

Caffeine is metabolized by *CYP1A2* and *NAT2* and the activity of these enzymes partially depend on certain SNPs that may alter the metabolization rate of caffeine.[14-17] We therefore hypothesized that a possible association between (caffeinated) coffee and tea intake and colorectal cancer might depend on *CYP1A2* and *NAT2* activity. This is however not supported by the results of present study in which we observed no convincing joint effects of (caffeinated) coffee and tea consumption with *CYP1A2* and *NAT2* activity on colorectal cancer risk. However, multiple factors may have contributed to the present null-findings including confounding by environmental factors (diet, smoking habits, medication) that influence *CYP1A2* and *NAT2* phenotype,[17] and misclassification of *NAT2* acetylation status. Based on a study that determined the accuracy of different *NAT2* SNP genotyping panels to infer acetylator phenotypes, we estimate misclassification to be approximately 5-8% in the present study.[40] Furthermore, high coffee consumption has been reported to induce *CYP1A2* activity, especially in subjects with two rapid alleles (*CYP1A2*1A*) and this may have influenced our results.[41,42]



It is hypothesized that tea consumption may lower colorectal cancer risk through its antioxidant components protecting colonic epithelial cells against oxidative radicals.[43,44] Despite the consistently observed protective effect of tea components in animal studies, a protective effect has, in general, not been demonstrated in epidemiological studies,[11,13] and is further confirmed by the present study. However, disparities can be observed between findings from Western and Asian studies, which might be caused by differences in type of tea (black or green) consumed. Epidemiological studies that found a protective effect of tea mainly come from Asia, where green tea is mostly consumed, while Western studies, where black tea is mostly consumed, do not find inverse associations with colorectal cancer risk.[12,13] It might be possible that green tea contains more putative anticarcinogenic compounds than black tea, though other environmental sources of bias should be considered, as well as differences in study design and number of cases included. To elucidate these conflicting results, future epidemiological studies should focus on differences in green and black tea consumption in various populations, mode of preparation, and uptake of antioxidant components present in tea, in relation to colorectal cancer risk. However, our results strongly sug-

gest that black tea may not be a clear inhibitor of risk of colorectal cancer in European populations.

Strengths of this study include the prospective population-based design, including multiple populations, comprehensive pre-diagnostic assessment of dietary and lifestyle risk factors, considerable follow-up and a large number of participants and cases. In addition, we were able to perform analyses by anatomical subsite, study differences between caffeinated and decaffeinated coffee and to investigate possible effect modification by *CYP1A2* and *NAT2* with regard to coffee and tea consumption and colorectal cancer risk. Limitations include the self-reported consumption, a single assessment and the absence of data on brewing methods, cup size and levels of caffeine, cafestol, kahweol, and antioxidants. Furthermore, large variations in volume and concentration of coffee and tea consumed may exist between countries. Using cohort-wide quintiles (total coffee, caffeinated coffee and tea) and tertiles (decaffeinated coffee) exploits the full range of exposures, but may have influenced the risk estimates due to some centers being overrepresented at one side of the distribution and other centers to the opposite side of the distribution. However, sensitivity analyses with country-specific quintiles and tertiles showed similar effects compared to the primary analyses with cohort-wide categories. A limitation that applies to the analyses on *CYP1A2* and *NAT2* is the possible misclassification of metabolization and acetylation status based on the genotyped SNPs, although this is probably minimal. Furthermore, not all cases were matched to two controls in the analyses due to low quality or concentration of DNA. We also did not have data on medication use that may influence *CYP1A2* and *NAT2* activity.

In conclusion, this large prospective cohort study showed no association between coffee and tea consumption and overall colorectal cancer risk, though sex-specific differences cannot be ruled out for coffee consumption and colon cancer risk. Genotype based *CYP1A2* and *NAT2* activity did not modify the risk estimates for tea and coffee consumption and colorectal cancer risk, implying that caffeine intake is not likely to be associated with colorectal cancer risk. Future studies are needed to explore differences in types of coffee and tea consumed, preparation methods, and uptake of diterpenes and antioxidant components in relation to colorectal cancer risk.

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## SUPPLEMENTAL TABLES

**Supplemental Table 1.** Baseline characteristics and risk factor distribution according to level of caffeinated and decaffeinated coffee consumption.

| | Caffeinated coffee[1] | | Decaffeinated coffee[4] | |
|---|---|---|---|---|
| | Non / low consumers[2] | High consumers[3] | Non / low consumers[5] | High consumers[6] |
| **Follow-up, person years** | 938,870 | 577,247 | 1,706,796 | 485,531 |
| **Male, %** | 20.0 | 32.7 | 24.4 | 26.0 |
| **Age at recruitment, mean (years)** | 51.3 | 50.3 | 52.0 | 49.6 |
| **Body mass index, mean (kg/m2)** | 24.3 | 24.8 | 24.7 | 24.9 |
| **Diabetes mellitus, %** | 2.6 | 2.6 | 2.5 | 2.3 |
| **Menopausal status, %** | | | | |
| Premenopausal | 34.4 | 35.7 | 32.7 | 41.5 |
| Perimenopausal | 19.5 | 21.6 | 20.8 | 14.8 |
| Postmenopausal | 46.1 | 42.7 | 46.5 | 43.7 |
| **Ever used hormone therapy, %** | 27.6 | 27.3 | 29.3 | 23.8 |
| **Physical activity,%** [7] | | | | |
| Inactive | 20.2 | 18.8 | 20.5 | 17.4 |
| Moderatevely intactive | 36.9 | 35.6 | 37.7 | 34.1 |
| Moderatevely active | 26.4 | 25.8 | 26.5 | 25.3 |
| Active | 16.5 | 19.8 | 15.4 | 23.2 |
| **Level of education, %** | | | | |
| None | 0.5 | 0.3 | 0.5 | 0.2 |
| Primary school completed | 20.6 | 22.9 | 24.2 | 15.5 |
| Technical/professional school | 18.2 | 26.7 | 18.0 | 30.8 |
| Secondary school | 29.9 | 21.4 | 28.5 | 21.3 |
| College or university degree | 30.8 | 28.7 | 28.8 | 32.2 |
| **Smoking status, %** | | | | |
| Never | 61.0 | 38.4 | 53.7 | 38.5 |
| Former smoker, time since quitting ≥ 10 years | 17.2 | 17.6 | 17.8 | 23.5 |
| Former smoker, time since quitting < 10 years | 7.1 | 10.4 | 7.9 | 10.4 |
| Former smoker, time since quitting unknown | 1.0 | 0.8 | 1.1 | 0.3 |
| Current smoker, 1-10 cig. per day | 5.2 | 9.1 | 6.5 | 10.1 |
| Current smoker, 11-20 cig. per day | 3.6 | 13.2 | 5.7 | 12.0 |
| Current smoker, 21+ cig. per day | 1.2 | 6.2 | 2.7 | 2.3 |
| Current smoker, number cig. Unknown | 1.1 | 2.5 | 1.5 | 2.8 |
| Smoking status unknown | 2.6 | 1.8 | 3.1 | 0.1 |
| **Total energy from fat, median (kcal/day)** | 683 | 756 | 722 | 658 |
| **Total energy from non-fat, median (kcal/day)** | 1,280 | 1,368 | 1,326 | 1,293 |
| **Alcohol intake, median (g/day)** | 4 | 8 | 7 | 5 |

**Supplemental Table 1** (continued)

| | Caffeinated coffee[1] | | Decaffeinated coffee[4] | |
|---|---|---|---|---|
| | Non / low consumers[2] | High consumers[3] | Non / low consumers[5] | High consumers[6] |
| **Fiber intake, median (g/day)** | 22 | 22 | 21 | 23 |
| **Red meat intake, median (g/day)** | 32 | 39 | 38 | 27 |
| **Processed meat intake, median (g/day)** | 22 | 31 | 28 | 17 |
| **Dairy products intake, median (g/day)** | 289 | 289 | 259 | 354 |

1. Country-specific cut-off points (ml) for caffeinated coffee quintiles were as follows: France 103, 200, 300, 450; Germany 150, 290, 450, 580; Italy (Florence, Varese and Turin only) 33, 60, 90, 130; the Netherlands 188, 338, 450, 675; Sweden (Malmö only) 225, 400, 525, 750; United Kingdom 13, 190, 475, 476.
2. Low consumption is defined as the lowest country-specific quintile within consumers of caffeinated coffee.
3. High consumption is defined as the highest country-specific quintile within consumers of caffeinated coffee.
4. Country-specific cut-off points (ml) for decaffeinated coffee tertiles were as follows: France 70, 200; Germany 19, 150; Italy (Florence, Varese and Turin only) 7, 20; the Netherlands 50, 100; United Kingdom.
5. Low consumption is defined as the lowest country-specific tertile within consumers of decaffeinated coffee.
6. High consumption is defined as the highest country-specific tertile within consumers of decaffeinated coffee.
7. According to the Cambridge physical activity index.

**Supplemental Table 2.** Baseline characteristics and risk factor distribution within 1,252 CRC cases and 2,175 matched controls.

| | Cases | Controls | P-value |
|---|---|---|---|
| **Male, %** | 46.7 | 46.1 | 0.71 |
| **Age at recruitment, mean (years)** | 58.1 | 57.9 | 0.45 |
| **Body mass index, mean (kg/m2)** | 26.8 | 26.4 | <0.01 |
| **Diabetes mellitus, %** | 5.1 | 4.3 | 0.27 |
| **Menopausal status, %** | | | |
| Premenopausal | 12.9 | 13.5 | |
| Perimenopausal | 75.3 | 73.6 | 0.72 |
| Postmenopausal | 11.8 | 12.9 | |
| **Ever used hormone therapy, %** | 25.2 | 26.1 | 0.70 |
| **Physical activity,%** [1] | | | |
| Inactive | 30.8 | 26.9 | |
| Moderatevely intactive | 33.2 | 34.1 | <0.01 |
| Moderatevely active | 21.0 | 19.8 | |
| Active | 15.0 | 19.2 | |

**Supplemental Table 2** (continued)

| | Cases | Controls | P-value |
|---|---|---|---|
| **Level of education, %** | | | |
| None | 6.7 | 6.6 | |
| Primary school completed | 35.7 | 36.7 | |
| Technical/professional school | 22.1 | 25.3 | 0.01 |
| Secondary school | 17.7 | 13.5 | |
| College or university degree | 17.8 | 17.9 | |
| **Smoking status, %** | | | |
| Never | 43.9 | 47.5 | |
| Former smoker, time since quitting ≥ 10 years | 23.7 | 22.0 | |
| Former smoker, time since quitting < 10 years | 10.1 | 8.3 | |
| Former smoker, time since quitting unknown | 0.7 | 0.8 | |
| Current smoker, 1-10 cig. per day | 6.7 | 7.5 | 0.19 |
| Current smoker, 11-20 cig. per day | 6.5 | 6.9 | |
| Current smoker, 21+ cig. per day | 3.2 | 3.2 | |
| Current smoker, number cig. Unknown | 3.5 | 2.5 | |
| Smoking status unknown | 1.7 | 1.3 | |
| **Alcohol intake, median (g/day)** | 6 | 5 | 0.47 |
| **Total energy from fat, median (kcal/day)** | 679 | 671 | 0.80 |
| **Total energy from non-fat, median (kcal/day)** | 1,320 | 1,279 | 0.28 |
| **Fiber intake, median (g/day)** | 21 | 22 | 0.01 |
| **Red meat intake, median (g/day)** | 36 | 34 | 0.09 |
| **Processed meat intake, median (g/day)** | 26 | 25 | 0.12 |
| **Dairy products intake, median (g/day)** | 277 | 295 | 0.02 |

1. According to the Cambridge physical activity index.

**Supplemental Table 3.** Adjusted odds ratio's[1] for joint effects of *CYP1A2* and *NAT2* activity with caffeinated coffee consumption and colorectal cancer risk.

| | Non / low consumers | | Moderate consumers | | High consumers | | P-value for interaction |
|---|---|---|---|---|---|---|---|
| | Cases/controls | HR (95%-CI) | Cases/controls | HR (95%-CI) | Cases/controls | HR (95%-CI) | |
| **COLORECTAL CANCER** | | | | | | | |
| ***CYP1A2 -164A>C (rs762551)*** | | | | | | | |
| Fast (AA) | 95/166 | ref. | 187/328 | 1.34 (0.97 - 1.86) | 171/298 | 0.94 (0.68 - 1.28) | 0.13 |
| Slow (CC / AC) | 110/168 | 1.13 (0.81 - 1.57) | 187/360 | 1.02 (0.74 - 1.40) | 147/259 | 1.04 (0.76 - 1.42) | |
| ***NAT2* acetylation status** | | | | | | | |
| Fast | 87/149 | ref. | 145/319 | 1.08 (0.76 - 1.51) | 150/233 | 1.10 (0.79 - 1.53) | 0.24 |
| Slow | 118/185 | 1.24 (0.89 - 1.73) | 229/369 | 1.35 (0.99 - 1.85) | 168/324 | 1.01 (0.75 - 1.38) | |
| **COLON CANCER** | | | | | | | |
| ***CYP1A2 -164A>C (rs762551)*** | | | | | | | |
| Fast (AA) | 60/108 | ref. | 135/230 | 1.24 (0.83 - 1.85) | 116/206 | 0.78 (0.53 - 1.15) | 0.21 |
| Slow (CC / AC) | 79/107 | 1.00 (0.67 - 1.51) | 120/259 | 0.88 (0.59 - 1.31) | 94/167 | 0.85 (0.58 - 1.25) | |
| ***NAT2* acetylation status** | | | | | | | |
| Fast | 65/100 | ref. | 99/213 | 1.02 (0.67 - 1.55) | 98/152 | 0.88 (0.59 - 1.32) | 0.55 |
| Slow | 74/115 | 1.06 (0.70 - 1.60) | 156/276 | 1.13 (0.77 - 1.66) | 112/221 | 0.82 (0.56 - 1.20) | |
| **RECTAL CANCER** | | | | | | | |
| ***CYP1A2 -164A>C (rs762551)*** | | | | | | | |
| Fast (AA) | 35/58 | ref. | 52/98 | 1.55 (0.86 - 2.80) | 55/92 | 1.42 (0.80 - 2.52) | 0.52 |
| Slow (CC / AC) | 31/61 | 1.51 (0.82 - 2.78) | 67/101 | 1.41 (0.80 - 2.47) | 53/92 | 1.58 (0.91 - 2.74) | |
| ***NAT2* acetylation status** | | | | | | | |
| Fast | 22/49 | ref. | 46/106 | 1.16 (0.63 - 2.16) | 52/81 | 1.88 (1.03 - 3.42) | 0.08 |
| Slow | 44/70 | 1.67 (0.92 - 3.02) | 73/93 | 1.98 (1.12 - 3.50) | 56/103 | 1.48 (0.85 - 2.60) | |

1. All models were stratified by the matching factors sex, age at blood collection (± 6-24 months), study center and menopausal status (premenopausal, postmenopausal, perimenopausal, unknown) and adjusted for body mass index (continuous), diabetes mellitus (yes, no), hormone replacement therapy (yes, no), physical activity

(inactive, moderately inactive, moderately active, active), educational level (none, primary school, technical/professional school, secondary school, university), smoking status (never, former: quitted ≥ 10 years, former: quitted < 10 years, former: time since quitting unknown, current: 1-10 cig. per day, current: 11-20 cig. per day, current: 21+ cig. per day, current: number of cig. per day unknown, smoking status unknown), and intake of energy from fat, energy from non-fat, alcohol, fibers, dairy products, red meat and processed meat (all continuous).

**Supplemental Table 4.** Adjusted odds ratio's[1] for joint effects of *CYP1A2* and *NAT2* activity with tea consumption and colorectal cancer risk.

| | Non / low consumers | | Moderate consumers | | High consumers | | P-value for interaction |
|---|---|---|---|---|---|---|---|
| | Cases/ controls | HR (95%-CI) | Cases/ controls | HR (95%-CI) | Cases/ controls | HR (95%-CI) | |
| **COLORECTAL CANCER** | | | | | | | |
| ***CYP1A2 -164A>C (rs762551)*** | | | | | | | |
| Fast (AA) | 244/432 | ref. | 142/242 | 0.92 (0.69 - 1.22) | 202/355 | 0.98 (0.75 - 1.28) | 0.88 |
| Slow (CC / AC) | 254/434 | 0.96 (0.77 - 1.21) | 157/271 | 0.97 (0.74 - 1.28) | 188/326 | 1.01 (0.77 - 1.31) | |
| ***NAT2* acetylation status** | | | | | | | |
| Fast | 205/369 | ref. | 135/219 | 1.04 (0.77 - 1.41) | 154/307 | 0.94 (0.70 - 1.25) | 0.41 |
| Slow | 293/497 | 1.07 (0.85 - 1.36) | 164/294 | 0.98 (0.74 - 1.31) | 236/374 | 1.16 (0.89 - 1.51) | |
| **COLON CANCER** | | | | | | | |
| ***CYP1A2 -164A>C (rs762551)*** | | | | | | | |
| Fast (AA) | 173/292 | ref. | 97/173 | 0.85 (0.60 - 1.19) | 134/234 | 0.95 (0.69 - 1.31) | 0.45 |
| Slow (CC / AC) | 162/293 | 0.81 (0.61 - 1.08) | 104/183 | 0.90 (0.95 - 1.27) | 120/210 | 0.94 (0.68 - 1.32) | |
| ***NAT2* acetylation status** | | | | | | | |
| Fast | 134/248 | ref. | 95/149 | 1.15 (0.80 - 1.66) | 108/193 | 1.14 (0.80 - 1.62) | 0.42 |
| Slow | 201/337 | 1.16 (0.87 - 1.56) | 106/207 | 0.98 (0.69 - 1.40) | 146/251 | 1.15 (0.82 - 1.61) | |
| **RECTAL CANCER** | | | | | | | |
| ***CYP1A2 -164A>C (rs762551)*** | | | | | | | |
| Fast (AA) | 71/140 | ref. | 45/69 | 1.22 (0.72 - 2.09) | 68/121 | 1.12 (0.70 - 1.81) | 0.50 |
| Slow (CC / AC) | 92/141 | 1.46 (0.96 - 2.21) | 53/88 | 1.23 (0.75 - 2.01) | 68/116 | 1.25 (0.79 - 1.99) | |

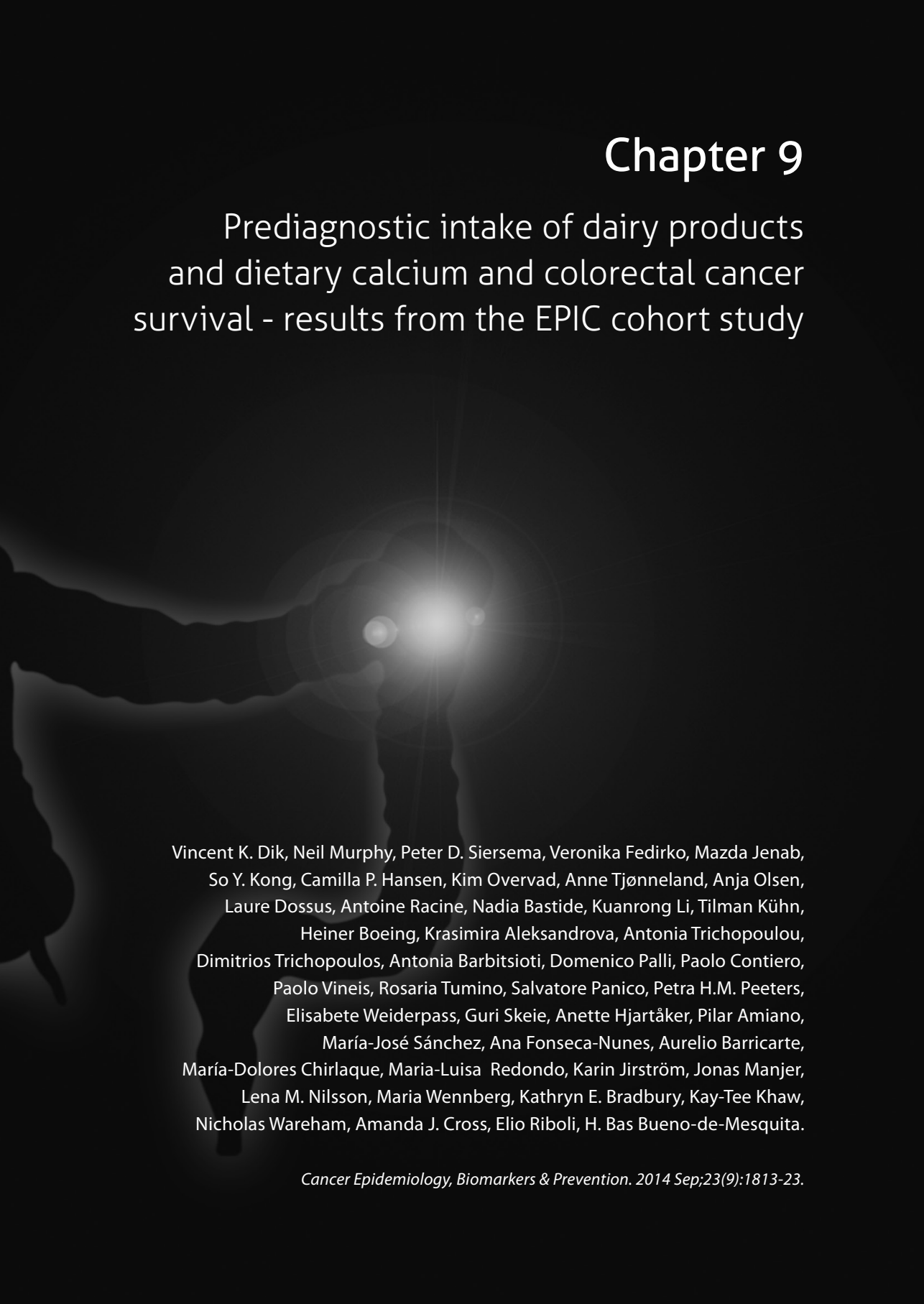
**Supplemental Table 4** (continued)

| | Non / low consumers | | Moderate consumers | | High consumers | | P-value for interaction |
|---|---|---|---|---|---|---|---|
| | Cases/ controls | HR (95%-CI) | Cases/ controls | HR (95%-CI) | Cases/ controls | HR (95%-CI) | |
| ***NAT2* acetylation status** | | | | | | | |
| Fast | 71/121 | ref. | 40/70 | 0.93 (0.53 - 1.61) | 46/114 | 0.61 (0.36 - 1.03) | 0.05 |
| Slow | 92/160 | 0.89 (0.59 - 1.34) | 58/87 | 0.97 (0.58 - 1.63) | 90/123 | 1.18 (0.75 - 1.86) | |

1. All models were stratified by the matching factors sex, age at blood collection (± 6-24 months), study center and menopausal status (premenopausal, postmenopausal, perimenopausal, unknown) and adjusted for body mass index (continuous), diabetes mellitus (yes, no), hormone replacement therapy (yes, no), physical activity (inactive, moderately inactive, moderately active, active), educational level (none, primary school, technical/professional school, secondary school, university), smoking status (never, former: quitted ≥ 10 years, former: quitted < 10 years, former: time since quitting unknown, current: 1-10 cig. per day, current: 11-20 cig. per day, current: 21+ cig. per day, current: number of cig. per day unknown, smoking status unknown), and intake of energy from fat, energy from non-fat, alcohol, fibers, dairy products, red meat and processed meat (all continuous).

# Chapter 9

## Prediagnostic intake of dairy products and dietary calcium and colorectal cancer survival - results from the EPIC cohort study



Vincent K. Dik, Neil Murphy, Peter D. Siersema, Veronika Fedirko, Mazda Jenab, So Y. Kong, Camilla P. Hansen, Kim Overvad, Anne Tjønneland, Anja Olsen, Laure Dossus, Antoine Racine, Nadia Bastide, Kuanrong Li, Tilman Kühn, Heiner Boeing, Krasimira Aleksandrova, Antonia Trichopoulou, Dimitrios Trichopoulos, Antonia Barbitsioti, Domenico Palli, Paolo Contiero, Paolo Vineis, Rosaria Tumino, Salvatore Panico, Petra H.M. Peeters, Elisabete Weiderpass, Guri Skeie, Anette Hjartåker, Pilar Amiano, María-José Sánchez, Ana Fonseca-Nunes, Aurelio Barricarte, María-Dolores Chirlaque, Maria-Luisa Redondo, Karin Jirström, Jonas Manjer, Lena M. Nilsson, Maria Wennberg, Kathryn E. Bradbury, Kay-Tee Khaw, Nicholas Wareham, Amanda J. Cross, Elio Riboli, H. Bas Bueno-de-Mesquita.

*Cancer Epidemiology, Biomarkers & Prevention. 2014 Sep;23(9):1813-23.*

## ABSTRACT

### Background

We investigated whether prediagnostic reported intake of dairy products and dietary calcium are associated with colorectal cancer survival.

### Methods

Data from 3,859 subjects with colorectal cancer (42.1% male, mean age at diagnosis 64.2 ± 8.1 years) in the European Investigation into Cancer and Nutrition (EPIC) cohort were analyzed. Intake of dairy products and dietary calcium was assessed at baseline (1992-2000) using validated, country-specific dietary questionnaires. Multivariable Cox regression models were used to calculate hazard ratios (HR) and corresponding 95% confidence intervals (95%-CI) for colorectal cancer-specific death (n=1,028) and all-cause death (n=1,525) for different quartiles of intake.

### Results

The consumption of total dairy products was not statistically significantly associated with risk of colorectal cancer-specific death (adjusted HR Q4 vs. Q1: 1.17 95%-CI 0.97-1.43) nor of all-cause death (Q4 vs. Q1: 1.16 95%-CI 0.98-1.36). Multivariable adjusted HRs for colorectal cancer-specific death (Q4 vs. Q1) were 1.21 (95%-CI 0.99-1.48) for milk, 1.09 (95%-CI 0.88-1.34) for yoghurt and 0.93 (95%-CI 0.76-1.14) for cheese. The intake of dietary calcium was not associated with the risk of colorectal cancer-specific (adjusted HR Q4 vs. Q1: 1.01 95%-CI 0.81-1.26) nor of all-cause death (Q4 vs. Q1: 1.01 95%-CI 0.84-1.21).

### Conclusion

The prediagnostic reported intake of dairy products and dietary calcium are not associated with disease-specific or all-cause risk of death in patients diagnosed with colorectal cancer.

## INTRODUCTION

Worldwide, colorectal cancer is the third most commonly diagnosed cancer in men and second in women and accounts for an estimated total deaths of 608,000 per year.[1] A great number of studies have shown that colorectal cancer development depends, to a large extent, on diet and lifestyle factors.[2] However, the impact of diet on colorectal cancer survival is largely unknown. Studies are scarce, often small and retrospective, and have not resulted in definitive conclusions, as was also concluded in three recent systematic reviews including the second World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) expert report.[2-4]

With respect to colorectal cancer survival, dairy products are of potential interest as the consumption of dairy products has been reported to be associated with a decreased risk for developing colorectal cancer and especially colon cancer.[5,6] The reported inverse associations between the consumption of dairy products and colorectal cancer have mainly been attributed to calcium.[6-12] Studies have shown that calcium can induce apoptosis,[9] prevent colonic *K-ras* mutations,[13] inhibit heme-induced promotion of colon carcinogenesis,[14] and has an anti-proliferative effect on colonic epithelium cells directly[15] and indirectly by binding toxic bile and fatty acids, rendering them inert.[16,17] In addition, results from intervention trials suggest that calcium supplementation reduces colorectal adenoma recurrence risk,[18] and may modulate potential biomarkers of risk for colorectal neoplasms such as oxidative DNA damage.[19,20] In contrast, however, milk consumption is also associated with increased levels of insulin-like growth factor-I (IGF-I)[21] and a high ratio of IGF-I and IGF-binding protein-3 has been reported to be associated with an increased colon cancer risk.[22,23] In addition, IGF-I has been found to stimulate proliferation of colon cancer cell lines[24,25] and to induce VEGF,[26] an angiogenic factor that stimulates tumor growth.

Except for a small French study,[27] no studies have reported on the prediagnostic intakes of dairy products and calcium and survival after colorectal cancer diagnosis. We therefore investigated whether prediagnostic intake of dairy products (total, milk, yoghurt, and cheese) and dietary calcium (total, dairy, and nondairy) is associated with colorectal cancer-specific and all-cause death in a large cohort of patients with colorectal cancer that were included in the European Investigation into Cancer and Nutrition (EPIC) cohort.

## METHODS

### Study population

The EPIC study is a multicenter population-based cohort study to investigate the relation between diet, nutritional and metabolic characteristics, lifestyle factors, and subsequent cancer incidence and cause specific mortality. Between 1992 and 2000, 521,448 participants (70% women and mostly ages between 25 and 70 years at inclusion) were included in 23 centers from 10 European countries, i.e., Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden, and United Kingdom. Detailed information about the rationale of the study, the selection of the study population, data collection, and follow-up procedures was reported previously.[28,29] The study was approved by the International Agency for Research on Cancer ethical review committee and by the local committees at the participating centers.

### Data collection

Diet over the previous 12 months was assessed at inclusion by validated country-specific questionnaires.[30] Consumption of dairy products and individual categories of dairy products, including milk, yoghurt and cheese, was calculated in grams per day (g/day). Yoghurt included natural and flavored products, and fermented milk in Denmark, Norway, and Sweden. Cheese included fresh, fermented, and matured cheese products. Other categories of dairy products, such as ice cream, cream deserts, milk-based puddings, and milk beverages, were not analyzed individually due to incomplete measurements across centers and relatively low consumption. Dietary intake of calcium (total, dairy, and nondairy in milligrams per day) was calculated using the standardized EPIC Nutrient Data Base.[31] There were no data available on the use of calcium supplements and thus were not included with calcium intake. Non-dietary data on demographic characteristics, lifestyle habits, risk factors, and presence of chronic diseases were collected through questionnaires at study enrollment. Anthropometric measurements were taken at recruitment by trained health professionals in most centers, except for part of the Oxford cohort, the Norwegian cohort, and approximately two thirds of the French cohort, among whom weight and height were self-reported.

### Colorectal cancer ascertainment and selection

Identification of cancer cases was done through linkage with regional cancer registries (Denmark, Italy, the Netherlands, Norway, Spain, Sweden, and the United Kingdom; complete up to December 2006) or via a combination of methods, including linkage with health insurance and pathology registries and active follow-up (France, Germany, Greece, and Naples; complete up to June 2010). Tumors included those in the colon (C18.0-C18.7), rectum (C19 and C20), and overlapping/unspecified localization (C18.8

and C18.9) according to the second edition of the International Classification of Diseases for Oncology (ICD-O).[32]

Information on tumor stage differed between centers. A harmonization procedure was performed to assign a broad category for tumor stage (I-IV and unknown) using available information on the tumor-node-metastasis (TNM) classification (n = 1,787), Dukes classification (n = 442), and/or classification provided by the centers (i.e., localized, metastatic regional, metastatic distant, metastatic; n = 994) as previously described.[33] Differentiation grade of the tumor was categorized as well, moderately, poorly, or unknown differentiation. There was no information available on tumor stage for cases from Malmø and Oxford (n = 636) and on differentiation grade for cases from Aarhus, Cambridge, Copenhagen, Malmø, Oxford, and Umea (n = 1,815).

After excluding cases diagnosed with colorectal cancer after the dates of complete follow-up (see "Vital status follow-up"; n = 426), with in situ or a metastatic tumor (n = 172), non-adenocarcinoma or unknown morphology (n = 144), missing date of death or diagnosis (n = 21), unknown cause of death (n = 8) or cases in which cancer diagnosis was obtained from a death certificate or autopsy report (n = 6), cases who withdrew consent (n = 3) or emigrated to another region (n = 3) or country (n = 6), and cases with no information on intake of dairy products (n = 65), a total number of 3,859 cases who developed a first primary adenocarcinoma (2,423 colon and 1,436 rectum) remained for the analyses of this study.

**Vital status follow-up**

Information on vital status and movement of participants (98.5% complete) was obtained through record linkage with the municipal and national mortality registries in all countries except France, Germany, and Greece, where data were collected through a combination of methods, including health insurance records, cancer and pathology registries, and active follow-up of study subjects and their next-of-kin. The date of colorectal cancer diagnosis was used as the start of follow-up for this study. The date of censoring was defined as the last date at which follow-up data were judged to be complete, the last date of contact, or date of death. Censoring dates for complete follow-up were between June 2005 and June 2009 in Denmark, Italy, the Netherlands, Norway, Spain, Sweden, and the United Kingdom, and between December 2007 and December 2009 in France, Germany, and Greece.

Cause-specific mortality was coded according to the 10th revision of the International Classification of Diseases, Injuries and Causes of Death (ICD-10). Up to six qualifiers of the cause of death were reviewed, and colorectal cancer-specific death was assigned based on the underlying cause of death.

## Statistical analyses

The primary endpoint of this study was colorectal cancer-specific death and the secondary endpoint was death from any cause. Quartiles for prediagnostic intake of dairy products (total, milk, yoghurt, and cheese) and dietary calcium (total, dairy, and nondairy) were computed. EPIC-wide cutoff points were as follows: total dairy, 150, 276, and 452 g/day; milk, 24, 148, and 293 g/day; yoghurt, 2, 25, and 89 g/day; cheese, 15, 26, and 49 g/day; total dietary calcium, 699, 921, and 1,201 mg/day; dairy calcium, 327, 525, and 775 mg/day; nondairy calcium 299, 372, and 471 mg/day. Age-adjusted and multivariable Cox regression models were used to calculate HR and corresponding 95% confidence intervals (95%-CI) for colorectal cancer-specific and all-cause death for different levels of consumption and by using the first quartile as a reference. All models were stratified by center and adjusted for age at colorectal cancer diagnosis (continuous per one year increase). Age at colorectal cancer diagnosis and age at death or censoring were used as the underlying time variables. Two multivariable-adjusted models were tested: one adjusted for age at colorectal cancer diagnosis, sex, prediagnostic body mass index (BMI; continuous), smoking status (never, former, current, unknown), and energy intake (continuous), and one model additionally adjusted for tumor subsite (colon or rectum), disease stage (I, II, III, IV, unknown, unavailable for center), and differentiation grade (well, moderately, poorly, unknown, unavailable for center). Other potential confounding factors that were considered but not included in the models due to a less than 10% change of the risk estimates of outcomes of interest were year of diagnosis, physical activity, level of education, menopausal status, ever hormone replacement therapy, number of cigarettes per day, and intake of alcohol, fibers, and red- and processed meat. Country-specific quartiles for the consumption of dairy products (total, milk, yoghurt, and cheese) were used in sensitivity analyses.

Cox regression models were used to compute the risk estimates on a continuous scale for the intake of total dairy products (per 100 g/day), milk (per 100 g/day), yoghurt (per 50 g/day), cheese (per 25 g/day) and intake of dietary calcium (total, dairy, and nondairy per 200 mg/day).

Potential effect modification was tested by adding multiplicative interaction terms to the models and using likelihood ratio tests for interaction. For these analyses, we used the interaction terms of quartiles of consumption for total dairy and dietary calcium with categorical variables for tumor stage (I, II, III, IV), tumor subsite (colon and rectum), time between study inclusion and colorectal cancer diagnosis (<3, 3-6, 6-9, >9 years), sex, age at colorectal cancer diagnosis (<60, 60-69, >70), smoking status (never, former, current), and BMI (<25, 25-30, >30 kg/m2). Stratified analyses were conducted to explore potential differences according to disease stage (I, II, III, IV) and tumor subsite (colon and rectum).

The effect of unavailable information on disease stage for Malmø and Oxford and unknown disease stage for other centers was investigated using multiple approaches: (i) using a separate "missing" category for unavailable disease stage for Malmø and Oxford and one for unknown disease stage for other centers (primary analysis), (ii) combining unavailable disease stage for Malmø and Oxford and unknown disease stage for other centers in one "missing" category, (iii) analysis excluding colorectal cancer cases from Malmø and Oxford, and (iv) imputation of missing values for disease stage in Malmø and Oxford with SAS PROC MI procedure, under the missing at random assumption, based on sex, age at colorectal cancer diagnosis, year of diagnosis, vital status, tumor subsite, and period between colorectal cancer diagnosis and death or censoring.

All statistical analyses were conducted with SAS 9.2 (SAS Institute Inc. , Cary, USA). Two-sided P values of <0.05 were considered statistically significant.

## RESULTS

### Patient characteristics

Of the 3,859 colorectal cancer cases that were included in this study, a total of 1,525 subjects died (1,028 colorectal cancer-specific deaths). Mean age at colorectal cancer diagnosis was 64.2 ± 8.1 years and 42.1% of the subjects were male. Mean time from colorectal cancer diagnosis to end of follow-up was 4.1 ± 3.3 years and to death was 2.2 ± 2.2 years. The median prediagnostic consumption of dairy products was 276 g/day and ranged between 166 g/day in Germany and 374 g/day in the Netherlands (Table 1).

**Table 1.** Number of cases and median intake of dairy products and dietary calcium per EPIC center in 3,859 colorectal cancer cases.

| Country | Cases | Median intake per day | | | | |
|---|---|---|---|---|---|---|
| | | Total dairy (g/day) | Milk (g/day) | Yoghurt (g/day) | Cheese (g/day) | Dietary calcium (mg/day) |
| Denmark | 719 | 286 | 168 | 21 | 24 | 974 |
| France | 310 | 243 | 84 | 70 | 52 | 978 |
| Germany | 401 | 166 | 25 | 28 | 29 | 789 |
| Greece | 80 | 208 | 83 | 40 | 62 | 947 |
| Italy | 387 | 197 | 106 | 4 | 54 | 933 |
| Netherlands | 374 | 374 | 202 | 46 | 30 | 1,018 |
| Norway | 173 | 198 | 111 | 25 | 24 | 599 |
| Spain | 319 | 230 | 188 | 0 | 14 | 803 |
| Sweden | 542 | 353 | 195 | 67 | 24 | 918 |
| United Kingdom | 554 | 370 | 293 | 18 | 15 | 1,026 |
| **Total** | **3,859** | **276** | **148** | **25** | **26** | **921** |

Median consumption of milk was 148 g/day, of yoghurt was 25 g/day, and of cheese was 26 g/day. The median intake of dietary calcium was 921 mg/day and ranged between 599 mg/day in Norway and 1,026 mg/day in the United Kingdom. The percentages of non-consumers for dairy products, milk, yoghurt, and cheese were 0.1%, 9.2%, 23.2%, and 3.5%, respectively. High consumption of dairy products was positively associated with age at colorectal cancer diagnosis and female sex and inversely associated with current smoking status and more advanced disease stage. Further patient characteristics are shown in Table 2.

**Table 2.** Characteristics of 3,859 colorectal cancer cases according to intake of dairy products.

| | Q1 | Q2 | Q3 | Q4 | P-value |
|---|---|---|---|---|---|
| **Intake of dairy products** | **< 150 g/day** | **150 - 276 g/day** | **276 - 452 g/day** | **> 452 g/day** | |
| **Number of cases** | 964 | 967 | 963 | 965 | - |
| **Follow-up, mean ± SD (years)** | | | | | |
| Baseline to diagnosis | 6.4 ± 3.4 | 6.5 ± 3.5 | 6.3 ± 3.3 | 6.5 ± 3.4 | 0.38 |
| Diagnosis to end of follow-up | 4.0 ± 3.2 | 4.2 ± 3.4 | 4.2 ± 3.3 | 3.8 ± 3.2 | 0.01 |
| Diagnosis to death | 2.3 ± 2.2 | 2.2 ± 2.2 | 2.4 ± 2.2 | 2.1 ± 2.1 | 0.35 |
| **Male, %** | 49.4 | 37.8 | 40.0 | 41.4 | <0.0001 |
| **Age at diagnosis, mean (years)** | 63.1 | 63.1 | 64.8 | 65.7 | <0.0001 |
| **Body mass index, mean (kg/m$^2$)** | 26.5 | 26.3 | 26.6 | 26.2 | 0.11 |
| **Energy intake, median (kcal/day)** | 1,924 | 1,934 | 2,047 | 2,202 | <0.0001 |
| **Milk intake, median (g/day)** | 9 | 113 | 218 | 440 | <0.0001 |
| **Yoghurt intake, median (g/day)** | 3 | 25 | 48 | 63 | <0.0001 |
| **Cheese intake, median (g/day)** | 24 | 27 | 27 | 26 | <0.0001 |
| **Calcium intake, median (mg/day)** | 615 | 791 | 998 | 1,334 | <0.0001 |
| **Smoking status, %** | | | | | |
| Never | 25.8 | 43.3 | 43.3 | 42.8 | <0.01 |
| Former | 33.8 | 31.4 | 33.7 | 34.9 | |
| Current | 27.9 | 23.5 | 22.0 | 20.8 | |
| Unknown | 2.0 | 1.8 | 1.0 | 1.5 | |
| **Tumor localization, %** | | | | | |
| Colon | 61.9 | 63.1 | 65.1 | 61.0 | 0.28 |
| Rectum | 38.1 | 36.9 | 34.9 | 39.0 | |
| **Disease stage**[1] | | | | | |
| I | 21.1 | 21.2 | 22.3 | 22.7 | <0.0001 |
| II | 21.1 | 21.5 | 21.0 | 21.4 | |
| III | 33.3 | 32.8 | 33.7 | 34.7 | |
| IV | 14.6 | 12.8 | 11.8 | 9.8 | |
| Unknown | 9.9 | 11.7 | 11.2 | 11.4 | |

**Table 2** (continued)

| Intake of dairy products | Q1 < 150 g/day | Q2 150 - 276 g/day | Q3 276 - 452 g/day | Q4 > 452 g/day | P-value |
|---|---|---|---|---|---|
| **Differentiation grade[2]** | | | | | |
| Well differentiated | 12.6 | 15.5 | 13.7 | 13.0 | <0.0001 |
| Moderately differentiated | 54.3 | 53.0 | 55.7 | 60.8 | |
| Poorly differentiated | 15.6 | 14.6 | 14.3 | 14.5 | |
| Unknown | 17.5 | 16.9 | 16.3 | 11.7 | |

1. No information available about disease stage for subjects from Malmø and Oxford.
2. No information available about tumor differentiation grade for subjects from Aarhus, Cambridge, Copenhagen, Malmø, Oxford and Umea.

## Dairy products and survival

Main results for the prediagnostic consumption of total dairy, milk, yoghurt, and cheese are presented in Table 3. The consumption of total dairy products was neither statistically significantly associated with colorectal cancer-specific (multivariable-adjusted HR for Q4 vs. Q1, 1.17; 95%-CI, 0.96-1.43; P-trend, 0.06) nor all-cause death (multivariable-adjusted HR for Q4 vs. Q1, 1.16; 95%-CI, 0.98-1.36; P-trend, 0.05) in patients with colorectal cancer. Also on a continuous scale per 100 g/day increase, we found no statistically significant associations for the consumption of dairy products and risk of death. For the individual products of milk, yoghurt, and cheese, no statistically significant associations were observed with colorectal cancer-specific and all-cause death, with the exception of an increased risk in the upper quartile of milk consumption and all-cause death (multivariable-adjusted HR for Q4 vs. Q1, 1.21; 95%-CI, 1.03-1.43; P-trend, 0.09). Multivariable-adjusted HRs for colorectal cancer-specific death in the highest quartiles compared with the lowest quartiles of consumption were 1.21 (95%-CI, 0.99-1.48; P-trend, 0.05) for milk, 1.09 (95%-CI, 0.88-1.34; P-trend, 0.59) for yoghurt, and 0.93 (95%-CI, 0.76-1.14; P-trend, 0.48) for cheese. Of note, compared with the null results of the age-adjusted models and multivariable models not adjusted for disease characteristics, increasing intakes of total dairy and of milk were associated with increasing risk of death in the multivariable models adjusted for disease characteristics. This was largely due to the adjustment for disease stage.

## Dietary calcium intake and survival

Main results for the prediagnostic intake of total dietary calcium and calcium intake from dairy and non-dairy products are presented in Table 4. The intake of dietary calcium was neither associated with colorectal cancer-specific (multivariable-adjusted HR for Q4 vs. Q1, 1.01; 95%-CI, 0.81-1.26; P-trend, 0.95) nor with all-cause death (multivariable-adjusted HR for Q4 vs. Q1, 1.01; 95%-CI, 0.84-1.21; P-trend, 0.84). We did not find any

**Table 3.** Age adjusted and multivariable adjusted hazard ratios for colorectal cancer-specific and all-cause death according to the intake of dairy products.

| Dairy products | Daily intake (g/day) | Cases | CRC-specific death | | | |
|---|---|---|---|---|---|---|
| | | | CRC-specific deaths | Age adjusted HR (95%-CI) | Multivariable[1] HR (95%-CI) | Multivariable[1,2] HR (95%-CI) |
| **Total** | | | | | | |
| Quartile 1 | < 150 | 964 | 245 | ref. | ref. | ref. |
| Quartile 2 | 150 - 276 | 967 | 239 | 0.94 (0.78 - 1.13) | 0.94 (0.78 - 1.13) | 0.96 (0.80 - 1.16) |
| Quartile 3 | 276 - 452 | 963 | 255 | 0.89 (0.74 - 1.08) | 0.90 (0.75 - 1.09) | 0.97 (0.80 - 1.18) |
| Quartile 4 | > 452 | 965 | 289 | 1.02 (0.85 - 1.23) | 1.05 (0.86 - 1.27) | 1.17 (0.96 - 1.43) |
| P-trend | | | | 0.68 | 0.49 | 0.06 |
| Per 100 g/day | | | | 1.00 (0.97 - 1.03) | 1.00 (0.98 - 1.03) | 1.02 (0.99 - 1.05) |
| **Milk** | | | | | | |
| Quartile 1 | < 24 | 965 | 220 | ref. | ref. | ref. |
| Quartile 2 | 24 - 148 | 970 | 256 | 1.01 (0.84 - 1.22) | 1.01 (0.84 - 1.22) | 1.03 (0.85 - 1.25) |
| Quartile 3 | 148 - 293 | 993 | 264 | 0.91 (0.75 - 1.11) | 0.91 (0.75 - 1.11) | 0.99 (0.81 - 1.20) |
| Quartile 4 | > 293 | 931 | 288 | 1.07 (0.88 - 1.29) | 1.08 (0.89 - 1.32) | 1.21 (0.99 - 1.48) |
| P-trend | | | | 0.48 | 0.40 | 0.05 |
| Per 100 g/day | | | | 1.01 (0.98 - 1.04) | 1.01 (0.98 - 1.04) | 1.02 (0.99 - 1.05) |
| **Yoghurt** | | | | | | |
| Quartile 1 | < 2 | 936 | 245 | ref. | ref. | ref. |
| Quartile 2 | 2 - 25 | 993 | 262 | 0.96 (0.78 - 1.18) | 0.95 (0.78.- 1.17) | 1.06 (0.86 - 1.31) |
| Quartile 3 | 25 - 89 | 965 | 273 | 1.06 (0.88 - 1.28) | 1.06 (0.87 - 1.29) | 1.15 (0.94 - 1.40) |
| Quartile 4 | > 89 | 965 | 248 | 0.98 (0.80 - 1.19) | 1.00 (0.81 - 1.22) | 1.09 (0.88 - 1.34) |
| P-trend | | | | 0.96 | 0.83 | 0.59 |
| Per 50 g/day | | | | 0.99 (0.95 - 1.03) | 0.99 (0.96 - 1.03) | 1.01 (0.97 - 1.04) |
| **Cheese** | | | | | | |
| Quartile 1 | < 15 | 943 | 270 | ref. | ref. | ref. |
| Quartile 2 | 15 - 26 | 985 | 277 | 0.93 (0.78 - 1.10) | 0.93 (0.78 - 1.11) | 0.97 (0.81 - 1.16) |
| Quartile 3 | 26 - 49 | 966 | 236 | 0.91 (0.75 - 1.10) | 0.92 (0.76 - 1.12) | 0.93 (0.77 - 1.14) |
| Quartile 4 | > 49 | 965 | 245 | 0.89 (0.73 - 1.08) | 0.91 (0.74 - 1.12) | 0.93 (0.76 - 1.14) |
| P-trend | | | | 0.30 | 0.44 | 0.48 |
| Per 25 g/day | | | | 0.97 (0.92 - 1.01) | 0.97 (0.91 - 1.04) | 0.98 (0.92 - 1.05) |

1. Stratified by center and adjusted for age at CRC diagnosis (continuously per one year increase), sex, prediagnostic body mass index (BMI; continuous), smoking status (never, former, current, unknown) and energy intake (continuous).
2. Additionally adjusted for tumor localization (colon, rectum), disease stage (I, II, III, IV, unknown, unavailable for center) and differentiation grade (well, moderately, poorly, unknown, unavailable for center).
CRC = colorectal cancer, HR = hazard ratio, 95%-CI = 95% confidence interval.

**Table 3** (continued)

| All-cause death | | | |
|---|---|---|---|
| **Total deaths** | **Age adjusted HR (95%-CI)** | **Multivariable[1] HR (95%-CI)** | **Multivariable[1,2] HR (95%-CI)** |
| 369 | ref. | ref. | ref. |
| 359 | 0.93 (0.80 - 1.09) | 0.95 (0.81 - 1.10) | 0.98 (0.84 - 1.14) |
| 387 | 0.90 (0.78 - 1.05) | 0.93 (0.79 - 1.08) | 0.99 (0.84 - 1.16) |
| 410 | 0.99 (0.85 - 1.15) | 1.02 (0.87 - 1.20) | 1.16 (0.98 - 1.36) |
| | 0.95 | 0.62 | 0.05 |
| | 1.00 (0.98 - 1.02) | 1.00 (0.98 - 1.02) | 1.02 (0.99 -1.04) |
| 351 | ref. | ref. | ref. |
| 373 | 1.02 (0.88 - 1.19) | 1.03 (0.88 - 1.20) | 1.05 (0.90 - 1.23) |
| 394 | 0.97 (0.83 - 1.13) | 0.97 (0.83 - 1.14) | 1.04 (0.89 - 1.22) |
| 407 | 1.07 (0.91 - 1.25) | 1.09 (0.93 - 1.28) | 1.21 (1.03 - 1.43) |
| | 0.45 | 0.32 | 0.09 |
| | 1.01 (0.98 - 1.03) | 1.01 (0.98 - 1.03) | 1.02 (0.99 - 1.05) |
| 380 | ref. | ref. | ref. |
| 374 | 0.91 (0.77 - 1.07) | 0.91 (0.77 - 1.08) | 1.01 (0.85 - 1.20) |
| 400 | 1.03 (0.89 - 1.21) | 1.06 (0.91 - 1.24) | 1.13 (0.96 - 1.33) |
| 371 | 0.94 (0.80 - 1.10) | 0.98 (0.83 - 1.15) | 1.08 (0.92 - 1.28) |
| | 0.82 | 0.74 | 0.34 |
| | 0.98 (0.95 - 1.01) | 0.99 (0.96 - 1.02) | 1.01 (0.98 - 1.04) |
| 416 | ref. | ref. | ref. |
| 401 | 0.84 (0.73 - 0.97) | 0.85 (0.74 - 0.98) | 0.90 (0.78 - 1.04) |
| 358 | 0.87 (0.75 - 1.01) | 0.88 (0.75 - 1.03) | 0.92 (0.79 - 1.08) |
| 350 | 0.83 (0.71 - 0.98) | 0.85 (0.72 - 1.00) | 0.87 (0.74 - 1.04) |
| | 0.07 | 0.12 | 0.19 |
| | 0.97 (0.92 - 1.01) | 0.97 (0.92 - 1.02) | 0.98 (0.93 - 1.03) |

**Table 4.** Age adjusted and multivariable adjusted hazard ratios for colorectal cancer-specific and all-cause death according to the intake of dietary calcium.

| Dietary calcium | Daily intake (mg/day) | Cases | CRC-specific death | | | |
|---|---|---|---|---|---|---|
| | | | CRC-specific deaths | Age adjusted HR (95%-CI) | Multivariable[1] HR (95%-CI) | Multivariable[1,2] HR (95%-CI) |
| **Total** | | | | | | |
| Quartile 1 | < 699 | 963 | 249 | ref. | ref. | ref. |
| Quartile 2 | 699 - 920 | 966 | 255 | 1.03 (0.86 - 1.23) | 1.04 (0.86 - 1.25) | 1.06 (0.88 - 1.29) |
| Quartile 3 | 921 - 1,200 | 966 | 264 | 1.03 (0.85 - 1.23) | 1.05 (0.86 - 1.27) | 1.08 (0.89 - 1.32) |
| Quartile 4 | >1,200 | 964 | 260 | 0.94 (0.78 - 1.13) | 0.97 (0.78 - 1.20) | 1.01 (0.81 - 1.26) |
| P-trend | | | | 0.41 | 0.69 | 0.95 |
| Per 200 mg/day | | | | 0.99 (0.96 - 1.02) | 0.99 (0.95 - 1.03) | 1.01 (0.97 - 1.05) |
| **From dairy** | | | | | | |
| Quartile 1 | < 327 | 966 | 249 | ref. | ref. | ref. |
| Quartile 2 | 327 - 524 | 963 | 246 | 0.93 (0.78 - 1.12) | 0.94 (0.78 - 1.13) | 0.94 (0.78 - 1.13) |
| Quartile 3 | 525 - 774 | 964 | 275 | 1.06 (0.89 - 1.27) | 1.09 (0.90 - 1.31) | 1.16 (0.96 - 1.40) |
| Quartile 4 | > 774 | 962 | 256 | 0.91 (0.76 - 1.10) | 0.94 (0.77 - 1.15) | 1.02 (0.83 - 1.25) |
| P-trend | | | | 0.53 | 0.79 | 0.54 |
| Per 200 mg/day | | | | 0.99 (0.95 - 1.02) | 0.99 (0.95 - 1.03) | 1.01 (0.98 - 1.06) |
| **From non-dairy** | | | | | | |
| Quartile 1 | < 299 | 959 | 277 | ref. | ref. | ref. |
| Quartile 2 | 299 - 371 | 964 | 260 | 0.98 (0.81 - 1.18) | 1.01 (0.83 - 1.22) | 0.93 (0.77 - 1.13) |
| Quartile 3 | 372 - 470 | 971 | 227 | 0.84 (0.69 - 1.02) | 0.87 (0.70 - 1.08) | 0.84 (0.67 - 1.05) |
| Quartile 4 | > 470 | 961 | 262 | 0.97 (0.79 - 1.19) | 1.03 (0.79 - 1.34) | 0.96 (0.74 - 1.26) |
| P-trend | | | | 0.66 | 0.92 | 0.83 |
| Per 200 mg/day | | | | 0.98 (0.89 - 1.09) | 1.03 (0.89 - 1.19) | 0.98 (0.84 - 1.14) |

1. Stratified by center and adjusted for age at CRC diagnosis (continuously per one year increase), sex, prediagnostic body mass index (BMI; continuous), smoking status (never, former, current, unknown) and energy intake (continuous).
2. Additionally adjusted for tumor localization (colon, rectum), disease stage (I, II, III, IV, unknown, unavailable for center) and differentiation grade (well, moderately, poorly, unknown, unavailable for center).
CRC = colorectal cancer, HR = hazard ratio, 95%-CI = 95% confidence interval.

association with colorectal cancer-specific and all-cause death either when the analyses were performed on a continuous scale per 200 mg/day increase of calcium, or when calcium intake was stratified by dairy and nondairy sources.

**Table 4** (continued)

| All-cause death | | | |
|---|---|---|---|
| **Total deaths** | **Age adjusted HR (95%-CI)** | **Multivariable[1] HR (95%-CI)** | **Multivariable[1,2] HR (95%-CI)** |
| 378 | ref. | ref. | ref. |
| 368 | 0.98 (0.85 - 1.14) | 1.00 (0.86 - 1.16) | 1.01 (0.86 - 1.18) |
| 400 | 1.03 (0.89 - 1.19) | 1.05 (0.90 - 1.23) | 1.10 (0.93 - 1.29) |
| 379 | 0.94 (0.80 - 1.09) | 0.96 (0.80 - 1.15) | 1.01 (0.84 - 1.21) |
| | 0.48 | 0.72 | 0.84 |
| | 0.99 (0.97 - 1.02) | 1.00 (0.97 - 1.03) | 1.02 (0.98 - 1.05) |
| 387 | ref. | ref. | ref. |
| 361 | 0.87 (0.75 - 1.01) | 0.88 (0.76 - 1.02) | 0.89 (0.76 - 1.03) |
| 399 | 1.00 (0.86 - 1.15) | 1.03 (0.88 - 1.19) | 1.10 (0.94 - 1.28) |
| 376 | 0.91 (0.78 - 1.05) | 0.94 (0.80 - 1.10) | 1.02 (0.87 - 1.21) |
| | 0.49 | 0.82 | 0.35 |
| | 0.99 (0.96 - 1.02) | 0.99 (0.96 - 1.03) | 1.02 (0.98 - 1.05) |
| 394 | ref. | ref. | ref. |
| 384 | 1.03 (0.89 - 1.20) | 1.07 (0.91 - 1.25) | 0.97 (0.83 - 1.14) |
| 354 | 0.89 (0.76 - 1.04) | 0.92 (0.77 - 1.10) | 0.88 (0.74 - 1.05) |
| 391 | 1.04 (0.88 - 1.23) | 1.10 (0.88 - 1.36) | 1.01 (0.82 - 1.26) |
| | 0.84 | 0.54 | 0.90 |
| | 1.01 (0.93 - 1.10) | 1.06 (0.94 - 1.19) | 1.01 (0.89 - 1.14) |



## Effect modification by factors associated with colorectal cancer survival and stratified analyses for disease stage and tumor subsite

None of the examined factors known to be associated with colorectal cancer survival showed statistically significant interaction with the intake of dairy products and colorectal cancer-specific survival: time between study inclusion and colorectal cancer diagnosis, P = 0.99; age at colorectal cancer diagnosis, P =0.97; sex, P= 0.66; BMI, P = 0.99; smoking, P = 0.56; disease stage, P = 0.31; and tumor subsite, P = 0.90. In addition, these factors also did not statistically significantly modify the association between dietary calcium intake and colorectal cancer-specific survival: time between study inclusion and colorectal cancer diagnosis, P = 0.13; age at colorectal cancer diagnosis, P = 0.09; sex, P = 0.91; BMI, P = 0.64; smoking, P = 0.32; disease stage, P = 0.52; and tumor subsite, P = 0.64. Similar results were found for all-cause death. Except for an increased overall risk

of death after rectal cancer in the upper quartile of dairy intake (multivariable-adjusted HR for Q4 vs. Q1, 1.36; 95%-CI, 1.03-1.78; P-trend, 0.02), non-significant risk estimates for colorectal cancer-specific and overall risk of death were found when the analyses for dairy products and dietary calcium intake were stratified by disease stage and tumor subsite (Supplementary Tables S1 and S2).

### Sensitivity analyses

Sensitivity analyses with country-specific cutoff points attenuated the risk estimates for the consumption of dairy products and resulted in non-significant associations for colorectal cancer-specific (multivariable-adjusted HR for Q4 vs. Q1, 1.07; 95%-CI, 0.92-1.25) and overall risk of death (multivariable-adjusted HR for Q4 vs. Q1, 1.09; 95%-CI, 0.90-1.32). Similar results were found for country-specific quartiles of milk consumption and colorectal cancer-specific (multivariable-adjusted HR for Q4 vs. Q1, 1.06; 95%-CI, 0.89-1.25) and overall risk of death (multivariable-adjusted HR for Q4 vs. Q1, 1.07; 95%-CI, 0.90-1.27). To estimate the effect of unavailable information about disease stage, we used multiple approaches. Similar results were found when using a separate "missing" category for unavailable disease stage for Malmø and Oxford and one for unknown disease stage for other centers (primary analysis), as compared with analyses combining unavailable disease stage for Malmø and Oxford and unknown disease stage for other centers in one "missing" category, excluding centers with no information on disease stage (complete case analysis), or when multiple imputation for disease stage was used (data not shown).

## DISCUSSION

The results of the present study demonstrate that the prediagnostic consumption of dairy products (total, milk, yoghurt, and cheese) and dietary intake of calcium (total, dairy, and nondairy) are neither associated with disease-specific nor with all-cause death in patients with colorectal cancer. In addition, no statistically significant effect modification by factors known to be associated with colorectal cancer survival was found, and stratified analyses by disease stage and tumor subsite showed no statistically significant associations for the intake of dairy products and dietary calcium and the risk of disease-specific and all-cause death.

In contrast to the large number of studies that investigated the relation between diet and colorectal cancer risk, only very few studies have investigated the role of diet in relation to colorectal cancer survival.[3] In a relatively small French case-control study, including 148 patients with colorectal cancer who underwent a resection of the tumor, high energy intake was associated with an improved 5-year survival, but no significant

associations for specific foods, including dairy products (RR for third vs. first tertile, 0.63; 95%-CI, 0.30-1.33), were found.[27] A prospective U.S. study with 1,009 patients with stage III colon cancer showed a reduced survival for patients with a Western dietary pattern compared with those with a prudent dietary pattern.[34] Individual foods were not investigated, but a Western diet was characterized by high intakes of meat, fat, grains, and desserts, whereas a prudent diet was characterized by high intakes of fruit, vegetables, poultry, and fish. The same group also found that an increasing dietary glycemic load and total carbohydrate intake were associated with a higher risk of cancer recurrence or death.[35] Furthermore, an increasing intake of red and processed meat, a risk factor for colorectal cancer development, has been shown to be associated with a poorer prognosis among patients with non-metastatic colorectal cancer.[36]

A large number of studies, including a recent analysis within the EPIC cohort,[5,6] demonstrate that the consumption of dairy products and dietary calcium is associated with a reduced colorectal cancer and especially reduced colon cancer risk. However, as far as we are aware, few studies have reported on the intake of dairy and dietary calcium in relation to colorectal cancer survival. Calcium is, at least partially, thought to lower colorectal cancer risk by preventing colonic *K-ras* mutations and by its direct anti-proliferative effect on colonic epithelium cells.[13, 15] We hypothesized that these anti-carcinogenic properties of calcium against cancer development may also affect the chance of survival after colorectal cancer diagnosis. The results of the present study show however no association between increasing prediagnostic intake of dairy and calcium and improved colorectal cancer survival. In contrast, a small non-significant increased risk of colorectal cancer-specific death and a borderline significant increased risk of all-cause death were observed for the upper quartile of milk consumption in the multivariable-adjusted models, which however attenuated when using country-specific cutoff points. This counterintuitive increased risk of death was largely due to the adjustment for disease stage and may be explained as a chance finding or by the fact that subjects in the upper quartile of dairy intake less frequently had stage IV disease. However, based on this observation, it can be argued that subjects with a high intake of dairy products that do have stage IV colorectal cancer might have biologically and prognostically different tumors.

Thus, our observations indicate that the intake of dairy products and dietary calcium is not associated with improved survival in patients with colorectal cancer. Although these findings may be surprising when considering the strong inverse associations that have been found for especially colon cancer development, it may well be that once cancer has developed, the assumed anti-proliferative and anti-carcinogenic properties of calcium only have a minor or no effect on tumor progression and survival. On the other hand, the consumption of milk has been found to be associated with increased levels of IGFI,[21] and increasing IGF-I levels have been hypothesized to promote tumor progression and

to alter colorectal cancer survival[37-39] through increased cell proliferation and promotion of angiogenesis.[25,26,40] Finally, colorectal cancer survival largely depends on important clinical factors such as disease stage, comorbidities, general physical condition, treatment, and lifestyle factors like smoking habits and BMI. If calcium intake, by any means, does influence tumor growth and progression, then the effect might be diminished by more important clinical factors.

The strengths of this study include the prospective design, the large number of colorectal cancer cases, and the detailed information on potential dietary and lifestyle confounders. However, several limitations of this study may have influenced our results and need to be considered before making final conclusions. First, the assessment of usual diet took place before the diagnosis of colorectal cancer and may not reflect the true dietary intake of dairy products and dietary calcium at time of diagnosis and thereafter. However, Norwegian research among colorectal cancer survivors has shown that the consumption of milk does not significantly change after colorectal cancer diagnosis.[41] Another limitation of this study is the lack of data on calcium supplements use in the EPIC cohort. This was however assessed in EPIC-Heidelberg, which showed that calcium supplements were used by less than 10% of subjects.[42] Furthermore, results of a randomized controlled trial, investigating the risk of cancer death in over 5,000 subjects with previous fractures who were randomized to use calcium supplements, showed no association between calcium supplements use and cancer mortality.[43] Nevertheless, the prediagnostic assessment and the lacking data on calcium supplements may have led, in combination with the self-reported design of the questionnaires, to attenuated risk estimates. Another limitation of the present study is the registration of disease stage. Different classification systems across centers were used (i.e., TNM, Dukes, and EPIC classification) which needed to be combined in one overall disease stage. In addition, there was no data available about disease stage and tumor differentiation grade in several centers, but comprehensive sensitivity analyses to estimate the effect of unavailable information showed similar results compared with the primary analysis. Finally, there was no data available on colorectal cancer treatment. Although we do not expect significant differences in treatment and outcomes between centers included in this study, we did perform the analyses stratified by center.

To conclude, in this large cohort of patients with colorectal cancer, we found no evidence for an association between prediagnostically reported intake of dairy products and dietary calcium and risk of colorectal cancer-specific and overall death. We observed no heterogeneity by tumor subsite or disease stage. More observational studies in patients with colorectal cancer are needed to provide better insights into the role of prediagnostic and postdiagnostic diet and lifestyle in relation to disease progression and survival.

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**Supplemental Table 1.** Age adjusted and multivariable adjusted hazard ratios for CRC-specific and all-cause death according to the intake of dairy products and stratifed by disease stage.

| Total dairy products | Daily intake (g/day) | Cases | CRC-specific death | | | All-cause death | | |
|---|---|---|---|---|---|---|---|---|
| | | | CRC-specific deaths | Age adjusted HR (95%-CI) | Multivariable[1] HR (95%-CI) | Total deaths | Age adjusted HR (95%-CI) | Multivariable[1] HR (95%-CI) |
| **Stage I+II[2]** | | | | | | | | |
| Quartile 1 | < 150 | 362 | 31 | ref. | ref. | 57 | ref. | ref. |
| Quartile 2 | 150 - 276 | 362 | 38 | 1.20 (0.73 - 1.99) | 1.16 (0.69 - 1.93) | 68 | 1.21 (0.83 - 1.75) | 1.17 (0.80 - 1.71) |
| Quartile 3 | 276 - 452 | 338 | 43 | 1.24 (0.75 - 2.03) | 1.23 (0.74 - 2.04) | 71 | 1.14 (0.78 - 1.65) | 1.20 (0.81 - 1.77) |
| Quartile 4 | > 452 | 324 | 31 | 0.95 (0.55 - 1.64) | 0.92 (0.52 - 1.64) | 61 | 1.07 (0.72 - 1.60) | 1.14 (0.74 - 1.74) |
| P-trend | | | | 0.71 | 0.67 | | 0.92 | 0.65 |
| Per 100 g/day | | | | 0.99 (0.92 - 1.06) | 0.99 (0.91 - 1.07) | | 1.01 (0.96 - 1.06) | 1.02 (0.97 - 1.08) |
| **Stage III+IV[2]** | | | | | | | | |
| Quartile 1 | < 150 | 412 | 161 | ref. | ref. | 233 | ref. | ref. |
| Quartile 2 | 150 - 276 | 387 | 139 | 0.96 (0.75 - 1.23) | 0.96 (0.75 - 1.23) | 205 | 0.92 (0.75 - 1.13) | 0.94 (0.76 - 1.15) |
| Quartile 3 | 276 - 452 | 355 | 138 | 0.93 (0.72 - 1.20) | 0.94 (0.72 - 1.22) | 203 | 0.89 (0.72 - 1.10) | 0.91 (0.73 - 1.13) |
| Quartile 4 | > 452 | 327 | 159 | 1.11 (0.87 - 1.43) | 1.15 (0.88 - 1.49) | 208 | 1.01 (0.82 - 1.25) | 1.04 (0.84 - 1.30) |
| P-trend | | | | 0.34 | 0.24 | | 0.82 | 0.62 |
| Per 100 g/day | | | | 1.00 (0.96 - 1.03) | 1.00 (0.97 - 1.04) | | 0.99 (0.96 - 1.02) | 1.00 (0.97 - 1.03) |
| **Colon cancer[3]** | | | | | | | | |
| Quartile 1 | < 150 | 597 | 142 | ref. | ref. | 221 | ref. | ref. |
| Quartile 2 | 150 - 276 | 610 | 151 | 1.01 (0.79 - 1.28) | 1.01 (0.78 - 1.29) | 229 | 0.97 (0.80 - 1.18) | 0.98 (0.80 - 1.20) |
| Quartile 3 | 276 - 452 | 627 | 170 | 0.95 (0.75 - 1.21) | 0.99 (0.77 - 1.28) | 263 | 0.96 (0.79 - 1.16) | 1.03 (0.84 - 1.26) |
| Quartile 4 | > 452 | 589 | 182 | 1.03 (0.81 - 1.32) | 1.18 (0.91 - 1.53) | 256 | 0.99 (0.81 - 1.21) | 1.13 (0.92 - 1.40) |
| P-trend | | | | 0.79 | 0.16 | | 0.95 | 0.17 |
| Per 100 g/day | | | | 0.99 (0.96 - 1.03) | 0.92 (0.98 - 1.05) | | 0.99 (0.96 - 1.02) | 1.01 (0.98 - 1.04) |

**Supplemental Table 1** (continued)

| Total dairy products | Daily intake (g/day) | Cases | CRC-specific death | | | All-cause death | | |
|---|---|---|---|---|---|---|---|---|
| | | | CRC-specific deaths | Age adjusted | Multivariable[1] | Total deaths | Age adjusted | Multivariable[1] |
| | | | | HR (95%-CI) | HR (95%-CI) | | HR (95%-CI) | HR (95%-CI) |
| **Rectal cancer[3]** | | | | | | | | |
| Quartile 1 | < 150 | 367 | 103 | ref. | ref. | 148 | ref. | ref. |
| Quartile 2 | 150 - 276 | 357 | 88 | 0.86 (0.63 - 1.18) | 0.96 (0.69 - 1.34) | 130 | 0.88 (0.68 - 1.14) | 1.02 (0.78 - 1.33) |
| Quartile 3 | 276 - 452 | 336 | 85 | 0.83 (0.61 - 1.14) | 0.97 (0.70 - 1.36) | 124 | 0.84 (0.65 - 1.09) | 0.99 (0.75 - 1.30) |
| Quartile 4 | > 452 | 376 | 107 | 1.05 (0.77 - 1.41) | 1.27 (0.92 - 1.75) | 154 | 1.06 (0.82 - 1.36) | 1.36 (1.03 - 1.78) |
| P-trend | | | | 0.60 | 0.12 | | 0.49 | 0.02 |
| Per 100 g/day | | | | 1.01 (0.97 - 1.05) | 1.03 (0.99 - 1.08) | | 1.01 (0.98 - 1.05) | 1.04 (1.00 - 1.08) |

1. Stratified by center and adjusted for age at CRC diagnosis (continuously per one year increase), sex, prediagnostic body mass index (BMI; continuous), smoking status (never, former, current, unknown), energy intake (continuous) and differentiation grade (well, moderately, poorly, unknown, unavailable for center).
2. Additionally adjusted for tumor localization (colon, rectum).
3. Additionally adjusted for disease stage (I, II, III, IV, unknown, unavailable for center).

**Supplemental Table 2.** Age adjusted and multivariable adjusted hazard ratios for CRC-specific and all-cause death according to the intake of dietary calcium and stratified by disease stage.

| Total dairy products | Daily intake (mg/day) | Cases | CRC-specific death | | | All-cause death | | |
|---|---|---|---|---|---|---|---|---|
| | | | CRC-specific deaths | Age adjusted HR (95%-CI) | Multivariable[1] HR (95%-CI) | Total deaths | Age adjusted HR (95%-CI) | Multivariable[1] HR (95%-CI) |
| **Stage I+II[2]** | | | | | | | | |
| Quartile 1 | < 699 | 361 | 36 | ref. | ref. | 67 | ref. | ref. |
| Quartile 2 | 699 - 920 | 350 | 37 | 0.98 (0.60 - 1.61) | 1.00 (0.60 - 1.69) | 59 | 0.81 (0.56 - 1.17) | 0.85 (0.58 - 1.27) |
| Quartile 3 | 921 - 1,200 | 338 | 39 | 1.10 (0.68 - 1.80) | 1.08 (0.63 - 1.84) | 77 | 1.21 (0.85 - 1.72) | 1.27 (0.86 - 1.87) |
| Quartile 4 | >1,200 | 337 | 31 | 0.82 (0.49 - 1.38) | 0.80 (0.43 - 1.48) | 54 | 0.76 (0.52 - 1.13) | 0.81 (0.51 - 1.29) |
| P-trend | | | | 0.49 | 0.47 | | 0.38 | 0.63 |
| Per 200 mg/day | | | | 0.98 (0.94 - 1.03) | 0.98 (0.92 - 1.03) | | 0.99 (0.96 - 1.02) | 1.00 (0.96 - 1.04) |
| **Stage III+IV[2]** | | | | | | | | |
| Quartile 1 | < 699 | 400 | 156 | ref. | ref. | 228 | ref. | ref. |
| Quartile 2 | 699 - 920 | 382 | 148 | 1.00 (0.78 - 1.28) | 1.05 (0.81 - 1.35) | 210 | 0.93 (0.76 - 1.14) | 0.98 (0.79 - 1.21) |
| Quartile 3 | 921 - 1,200 | 351 | 147 | 0.99 (0.77 - 1.27) | 1.04 (0.79 - 1.36) | 207 | 0.95 (0.77 - 1.18) | 1.00 (0.80 - 1.25) |
| Quartile 4 | >1,200 | 348 | 146 | 0.89 (0.69 - 1.15) | 0.92 (0.68 - 1.25) | 204 | 0.88 (0.71 - 1.10) | 0.91 (0.70 - 1.18) |
| P-trend | | | | 0.33 | 0.52 | | 0.30 | 0.49 |
| Per 200 mg/day | | | | 0.99 (0.97 - 1.01) | 0.99 (0.96 - 1.02) | | 0.99 (0.97 - 1.01) | 0.99 (0.97 - 1.02) |
| **Colon cancer[3]** | | | | | | | | |
| Quartile 1 | < 150 | 593 | 146 | ref. | ref. | 229 | ref. | ref. |
| Quartile 2 | 150 - 276 | 625 | 171 | 1.12 (0.88 - 1.42) | 1.17 (0.91 - 1.50) | 247 | 1.06 (0.88 - 1.28) | 1.09 (0.89 - 1.33) |
| Quartile 3 | 276 - 452 | 604 | 165 | 1.04 (0.82 - 1.33) | 1.11 (0.85 - 1.45) | 256 | 1.05 (0.87 - 1.28) | 1.12 (0.91 - 1.38) |
| Quartile 4 | > 452 | 601 | 163 | 0.95 (0.74 - 1.21) | 1.10 (0.82 - 1.49) | 237 | 0.95 (0.77 - 1.15) | 1.03 (0.81 - 1.31) |
| P-trend | | | | 0.43 | 0.15 | | 0.46 | 0.91 |
| Per 100 g/day | | | | 0.99 (0.97 - 1.01) | 1.01 (0.98 - 1.04) | | 1.01 (0.98 - 1.01) | 1.01 (0.99 - 1.03) |

**Supplemental Table 2.** (continued)

| Total dairy products | Daily intake (mg/day) | Cases | CRC-specific death | | | All-cause death | | |
|---|---|---|---|---|---|---|---|---|
| | | | CRC-specific deaths | Age adjusted | Multivariable[1] | Total deaths | Age adjusted | Multivariable[1] |
| | | | | HR (95%-CI) | HR (95%-CI) | | HR (95%-CI) | HR (95%-CI) |
| **Rectal cancer[3]** | | | | | | | | |
| Quartile 1 | < 150 | 370 | 103 | ref. | ref. | 149 | ref. | ref. |
| Quartile 2 | 150 - 276 | 341 | 84 | 0.95 (0.70 - 1.30) | 0.94 (0.67 - 1.31) | 121 | 0.93 (0.72 - 1.21) | 0.96 (0.73 – 1.26) |
| Quartile 3 | 276 - 452 | 362 | 99 | 1.05 (0.77 - 1.42) | 1.09 (0.78 - 1.53) | 144 | 1.05 (0.82 - 1.35) | 1.16 (0.88 – 1.53) |
| Quartile 4 | > 452 | 363 | 97 | 0.99 (0.73 - 1.34) | 1.00 (0.69 - 1.45) | 142 | 1.01 (0.79 - 1.31) | 1.19 (0.87 – 1.61) |
| P-trend | | | | 0.97 | 0.87 | | 0.75 | 0.17 |
| Per 100 g/day | | | | 1.00 (0.98 - 1.03) | 1.01 (0.98 - 1.05) | | 1.00 (0.98 - 1.02) | 1.03 (0.99 – 1.05) |

1. Stratified by center and adjusted for age at CRC diagnosis (continuously per one year increase), sex, prediagnostic body mass index (BMI; continuous), smoking status (never, former, current, unknown), energy intake (continuous), tumor localization (colon, rectum) and differentiation grade (well, moderately, poorly, unknown, unavailable for center).

2. Additionally adjusted for tumor localization (colon, rectum).

3. Additionally adjusted for disease stage (I, II, III, IV, unknown, unavailable for center).

# Chapter 10

## Association between socioeconomic status, surgical treatment and mortality in patients with colorectal cancer

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*British Journal of Surgery. 2014 Aug;101(9):1173-82.*

## ABSTRACT

### Background

High socioeconomic status is associated with better survival in colorectal cancer. This study investigated whether socioeconomic status is associated with differences in surgical treatment and mortality in patients with colorectal cancer.

### Methods

Patients diagnosed with stage I-III colorectal cancer between 2005 and 2010 in the Eindhoven Cancer Registry area in the Netherlands were included. Socioeconomic status was determined at a neighborhood level by combining the mean household income and the mean value of the housing.

### Results

Some 4,422 patients with colonic cancer and 2,314 with rectal cancer were included. Patients with colonic cancer and high socioeconomic status were operated on with laparotomy (70.7% vs. 77.6%, P =0.017), had laparoscopy converted to laparotomy (15.7% vs. 29.5%, P =0.008) and developed anastomotic leakage or abscess (9.6% vs. 12.6%, P =0.049) less frequently than patients with low socioeconomic status. These differences remained significant after adjustment for patient and tumor characteristics. In rectal cancer, patients with high socioeconomic status were more likely to undergo resection (96.3% vs. 93.7%, P =0.083), but this was not significant in multivariable analysis (odds ratio (OR) 1.44, 95% confidence interval (95%-CI) 0.84-2.46). The difference in 30-day postoperative mortality in patients with colonic cancer and high and low socioeconomic status (3.6% vs. 6.8%, P <0.001) was not significant after adjusting for age, co-morbidities, emergency surgery, and anastomotic leakage or abscess formation (OR 0.90, 95%-CI 0.51-1.57).

### Conclusion

Patients with colorectal cancer and high socioeconomic status have more favorable surgical treatment characteristics than patients with low socioeconomic status. The lower 30-day postoperative mortality found in patients with colonic cancer and high socioeconomic status is largely explained by patient and surgical factors.

## INTRODUCTION

Colorectal cancer is one of the commonest cancers in the Western world. Depending on the exact tumor and nodal stage, 5-year survival rates for patients with non-metastatic (stage I–III) colorectal cancer range between 50% and 95%.[1] Previous studies[2,3] have shown that low socioeconomic status is associated with an increased mortality risk in patients with colorectal cancer, particularly in the first month of follow-up.[4] The reasons for this difference are not precisely known, but lifestyle, access and use of medical care, tumor stage at diagnosis and presence of co-morbidities have all been suggested to influence mortality.[5–9] Differences in the administration and adequate dosing of adjuvant and neoadjuvant treatment in relation to socioeconomic status have been reported, and may affect prognosis in different subgroups of patients.[10–13]

Patients with non-metastatic colorectal cancer are advised to undergo treatment with curative intent. Besides older age and the presence of co-morbidities, factors associated with a poor prognosis after surgical treatment include a low number of examined lymph nodes, residual tumor after surgery, narrow circumferential resection margin (CRM), anastomotic leakage, abscess formation and emergency surgery.[14–16] Several studies[17–19] have indicated socioeconomic status to be associated with postsurgical mortality. Only a few studies[18,20,21] have focused on socioeconomic status-specific disparities regarding surgical treatment characteristics and complications, and short-term outcome after surgery in patients with colorectal cancer. The aims of the present study were to investigate whether socioeconomic status is associated with differences in surgical treatment and short-term outcomes after surgery, what tumor- and patient-related factors contribute to these associations, and whether surgical treatment characteristics are associated with short-term survival differences in patients with stage I-III colorectal cancer.

## METHODS



Data were extracted from the Eindhoven Cancer Registry, which covers an area in the southern part of the Netherlands and represents approximately 2.3 million people (about 15% of the Dutch population). For this study, all patients diagnosed with stage I–III colonic (C18.0-C18.7) or rectal (C19-C20) cancer, according to the International Classification of Diseases for Oncology, third edition (ICD-O-3),[22] between January 2005 and December 2010 were included.

### Data collection

Data in the registry were routinely extracted from medical records by trained registrars in ten community hospitals, six departments of pathology and two radiotherapy insti-

tutes. Patient characteristics used in this study included sex, date of birth, postcode and presence of co-morbidities (0, 1, or 2 or more) according to a slightly adapted version of the Charlson classification.[23] Postcodes were used to determine socioeconomic status at a neighborhood level by combining the mean household income and the mean value of the housing. These data were provided at an aggregated level by Statistics Netherlands.[24] Postcodes were assigned to one of three predefined socioeconomic status levels: low (first to third decile), intermediate (fourth to seventh decile) and high (eighth to tenth decile). Subjects who lived in an area where a care-providing institution such as a nursing home or jail was present were assigned to a fourth, separate, socioeconomic status category because of difficulties in assigning socioeconomic status. A Dutch postcode contains on average 17 households.

Tumor characteristics used for the study included date of diagnosis, tumor localization (proximal colon, distal colon, rectum), histology (non-mucinous, mucinous, other/unspecified) and differentiation grade (well/moderate, poor/undifferentiated, unknown) according to ICD-O-322, and postoperative disease stage according to the tumor node metastasis (TNM) classification (6$^{th}$ edition[25] for 2005-2009 and 7th edition[26] for 2010). Data on treatment included hospital of surgical treatment, neoadjuvant (chemo)radiotherapy, endoscopic resection (local, polypectomy or transanal endoscopic microsurgery (TEM)), and surgical resection of the primary tumor, number of examined lymph nodes (fewer than 10, or 10 or more), residual tumor (none, microscopic, macroscopic), and, available from 2008 only, CRM (in rectal cancer; more than 1mm or 1mm or less), surgical technique (open, laparoscopic, converted from laparoscopic surgery), emergency surgery (no, yes; only for colonic cancer), and anastomotic leakage or abscess formation (no leak or abscess, leak or abscess, no anastomosis). Data on vital status were obtained from hospital medical charts and municipal databases, and were complete to 1 January 2012 for all patients.

### Statistical analysis

Separate analyses were performed for colonic and rectal cancer. The distribution of patient, tumor and treatment characteristics, and 30-day postoperative mortality are presented according to socioeconomic status categories and tested using Pearson $\chi 2$ tests. Socioeconomic status-specific differences in mean age at diagnosis were tested with Student's t tests.

Univariable and multivariable binomial logistic regression analyses were used to investigate whether socioeconomic status was associated with surgical treatment characteristics. Multivariable analyses included models adjusted for patient characteristics only, tumor characteristics only, and models combining patient and tumor characteristics. Patient and tumor characteristics were included in multivariable models only when associated ($P < 0.100$) in univariable analysis with the surgical outcome of interest. To

examine potential geographical differences in surgical treatment, sensitivity analyses were performed including adjustment for the hospital where the surgical treatment was performed.

To study the association between socioeconomic status and 30-day postoperative mortality in relation to patient, tumor and surgical treatment characteristics, univariable and multivariable binomial logistic regression analyses were performed. Multivariable models were adjusted for variables that were associated (P <0.100) in univariable analysis with 30-day postoperative mortality, including age, co-morbidities, disease stage, anastomotic leakage or abscess formation, and, for colonic cancer, emergency surgery. Sensitivity analyses were performed including adjustment for the hospital where the surgical treatment was performed to correct for possible differences in mortality risk between hospitals.

Imputation of missing values for the number of co-morbidities and tumor differentiation grade was performed with SAS® PROC MI procedure under the missing-at-random assumption. Imputed values for the number of co-morbidities and tumor differentiation grade were based on socioeconomic status, sex, age at diagnosis of colorectal cancer, disease stage, tumor histology, tumor localization and type of resection. Ten data sets with imputed data were created and the results of standard regression analyses for each data set were combined to generate a valid statistical inference for missing values using the SAS® PROC MIANALYZE procedure. All statistical analyses were performed using SAS® 9.2 (SAS Institute, Cary, North Carolina, USA). Two-sided P <0.050 was considered statistically significant. odds ratios (OR) are presented with 95% confidence intervals (95%-CI).

## RESULTS



After excluding 98 patients with overlapping (C18.8) and unspecified (C18.9) tumors, 323 patients living in an area including a care-providing institution, and 255 patients with unknown socioeconomic status, a total of 4,422 patients with stage I-III colonic cancer (2,300 men; 52.0%) and 2,314 patients with stage I-III rectal cancer (1,406 men; 60.8%) remained for the analysis.

In colonic and rectal cancer, patients with a high socioeconomic status were younger (mean age at diagnosis: 69.0 vs. 73.1 years for colonic cancer and 66.1 vs. 69.9 years for rectal cancer; both P <0.001), were more often male and had fewer co-morbidities compared with patients with low socioeconomic status. Other patient, tumor and treatment characteristics are summarized in Tables 1 and 2.

**Table 1.** Baseline characteristics of 4,422 patients with colonic cancer.

| Patient, tumor and treatment characteristics (%) | No. missing | Total (n=4,422) | Socioeconomic status | | | P-value |
|---|---|---|---|---|---|---|
| | | | Low (n=1,245) | Intermediate (n=1,795) | High (n=1,382) | |
| **Age** | 0 | | | | | <0.001 |
| <60 years | | 727 (16.4) | 138 (11.1) | 327 (18.2) | 262 (19.0) | |
| 60 - 70 years | | 1,154 (26.1) | 247 (19.8) | 495 (27.6) | 412 (29.8) | |
| 70 - 80 years | | 1,644 (37.2) | 498 (40.0) | 659 (36.7) | 487 (35.2) | |
| >80 years | | 897 (20.3) | 362 (29.1) | 314 (17.5) | 221 (16.0) | |
| **Male gender** | 0 | 2,300 (52.0) | 594 (47.7) | 939 (52.3) | 767 (55.5) | <0.001 |
| **Nº of co-comorbidities** | 331 | | | | | <0.001 |
| 0 | | 1,141 (27.9) | 237 (20.3) | 471 (28.7) | 433 (33.8) | |
| 1 | | 1,332 (32.6) | 376 (32.2) | 533 (32.5) | 423 (33.1) | |
| 2+ | | 1,618 (39.5) | 556 (47.5) | 638 (38.8) | 424 (33.1) | |
| **Proximal localization** | 0 | 2,439 (55.2) | 728 (58.5) | 973 (54.2) | 738 (53.4) | 0.019 |
| **Disease stage**[1] | 0 | | | | | 0.452 |
| Stage I | | 1,003 (22.7) | 269 (21.6) | 403 (22.5) | 331 (23.9) | |
| Stage II | | 1,915 (43.3) | 558 (44.8) | 784 (43.7) | 573 (41.5) | |
| Stage III | | 1,504 (34.0) | 418 (33.6) | 608 (33.8) | 478 (34.6) | |
| **Histology of primary tumor** | 0 | | | | | 0.024 |
| Adenocarcinoma, non-mucinous | | 3,762 (85.1) | 1,041 (83.6) | 1,520 (84.7) | 1,201 (86.9) | |
| Adenocarcinoma, mucinous | | 599 (13.5) | 178 (14.3) | 251 (14.0) | 170 (12.3) | |
| Other/ unspecified | | 61 (1.4) | 26 (2.1) | 170 (1.3) | 11 (0.8) | |
| **Differentiation of primary tumor** | 463 | | | | | 0.156 |
| Well / moderately | | 3,224 (81.4) | 896 (79.8) | 1,319 (82.7) | 1,009 (81.3) | |
| Poorly / undifferentiated | | 735 (18.6) | 227 (20.2) | 276 (17.3) | 232 (18.7) | |
| **Resection of the primary tumor** | 0 | 4,348 (98.3) | 1,223 (98.2) | 1,759 (98.0) | 1,366 (98.8) | 0.174 |
| **Type of resection** | 0 | | | | | 0.874 |
| Endoscopic resection only | | 155 (3.6) | 45 (3.7) | 65 (3.7) | 45 (3.3) | |
| Endoscopic followed by surgical resection | | 84 (1.9) | 21 (1.7) | 33 (1.9) | 30 (2.2) | |
| Surgical resection only | | 4,109 (94.5) | 1,157 (94.6) | 1,661 (94.4) | 1,291 (94.5) | |
| **Laparoscopy**[2,3] | 16 | 473 (25.8) | 139 (22.4) | 230 (25.3) | 204 (29.3) | 0.017 |
| **Laparoscopy converted to laparotomy**[2,4] | 0 | 120 (20.9) | 41 (29.5) | 47 (20.4) | 32 (15.7) | 0.008 |
| **Emergency surgery**[2,3] | 17 | 202 (9.1) | 51 (8.2) | 97 (10.7) | 54 (7.7) | 0.086 |
| **Anastomotic leakage / abscess**[2,3] | 20 | | | | | 0.049 |
| No leakage, no abscess | | 1,902 (88.0) | 520 (87.4) | 767 (89.5) | 615 (90.4) | |
| Leakage and/or abscess | | 260 (12.0) | 75 (12.6) | 120 (13.5) | 65 (9.6) | |

**Table 1** (continued)

| Patient, tumor and treatment characteristics (%) | No. missing | Total (n=4,422) | Socioeconomic status | | | P-value |
|---|---|---|---|---|---|---|
| | | | Low (n=1,245) | Intermediate (n=1,795) | High (n=1,382) | |
| **Residual tumor[2]** | 151 | | | | | 0.998 |
| No | | 3,927 (97.1) | 1,103 (97.0) | 1,589 (97.2) | 1,235 (97.2) | |
| Microscopic | | 75 (1.9) | 22 (1.9) | 30 (1.8) | 23 (1.8) | |
| Macroscopic | | 40 (1.0) | 12 (1.1) | 16 (1.0) | 12 (1.0) | |
| **Number of examined lymph nodes[2]** | 89 | | | | | 0.667 |
| 0 - 6 | | 912 (22.2) | 246 (21.3) | 361 (21.8) | 305 (23.6) | |
| 7 -11 | | 1,378 (33.6) | 390 (33.8) | 554 (33.4) | 434 (33.5) | |
| 12 or more | | 1,814 (44.2) | 517 (44.9) | 742 (44.8) | 555 (42.9) | |

1. Postoperative disease stage based on TNM classification.
2. Only patients included who underwent surgical resection of the primary tumor.
3. Only available from 2008.
4. Only patients included who underwent laparoscopic resection of the primary tumor.

**Table 2.** Baseline characteristics of 2,314 patients with rectal cancer.

| Patient, tumor and treatment characteristics (%) | No. missing | Total (n=2,314) | Socioeconomic status | | | P-value |
|---|---|---|---|---|---|---|
| | | | Low (n=522) | Intermediate (n=1,005) | High (n=787) | |
| **Age** | 0 | | | | | <0.001 |
| <60 years | | 557 (24.1) | 90 (17.2) | 259 (25.8) | 208 (26.4) | |
| 60 - 70 years | | 736 (31.8) | 135 (25.9) | 321 (31.9) | 280 (35.6) | |
| 70 - 80 years | | 719 (31.1) | 196 (37.6) | 305 (30.4) | 218 (27.7) | |
| >80 years | | 302 (13.0) | 101 (19.3) | 120 (11.9) | 81 (10.3) | |
| **Male gender** | 0 | 1,406 (60.8) | 274 (52.5) | 635 (63.2) | 497 (63.2) | <0.001 |
| **№ of co-comorbidities** | 172 | | | | | <0.001 |
| 0 | | 808 (37.7) | 143 (28.7) | 366 (40.0) | 299 (41.0) | |
| 1 | | 706 (33.0) | 171 (34.3) | 293 (32.1) | 242 (33.1) | |
| 2+ | | 628 (29.3) | 184 (37.0) | 255 (27.9) | 189 (25.9) | |
| **Disease stage[1]** | 0 | | | | | 0.363 |
| Stage I | | 833 (36.0) | 186 (35.6) | 342 (34.0) | 305 (38.8) | |
| Stage II | | 696 (30.1) | 159 (30.5) | 311 (31.0) | 226 (28.7) | |
| Stage III | | 785 (33.9) | 177 (33.9) | 352 (35.0) | 256 (32.5) | |
| **Histology of primary tumor** | 0 | | | | | 0.052 |
| Adenocarcinoma, non-mucinous | | 2,107 (91.0) | 469 (89.8) | 915 (91.0) | 723 (91.9) | |
| Adenocarcinoma, mucinous | | 184 (8.0) | 50 (9.6) | 83 (8.3) | 51 (6.5) | |
| Other / unspecified | | 23 (1.0) | 3 (0.6) | 7 (0.7) | 13 (1.6) | |

**Table 2** (continued)

| Patient, tumor and treatment characteristics (%) | No. missing | Total (n=2,314) | Socioeconomic status | | | P-value |
|---|---|---|---|---|---|---|
| | | | Low (n=522) | Intermediate (n=1,005) | High (n=787) | |
| **Differentiation of primary tumor** | 382 | | | | | 0.781 |
| Well / moderately | | 1,269 (65.7) | 285 (64.6) | 563 (67.1) | 421 (64.6) | |
| Poorly / undifferentiated | | 184 (9.5) | 44 (10.0) | 73 (8.7) | 67 (10.3) | |
| Neo-adjuvant treatment | | 479 (24.8) | 112 (25.4) | 203 (24.2) | 164 (25.1) | |
| **Neo-adjuvant (chemo) radiotherapy[2]** | 0 | 1,191 (58.5) | 270 (59.6) | 509 (57.8) | 412 (58.7) | 0.821 |
| **Resection of the primary tumor** | 0 | 2,199 (95.0) | 489 (93.7) | 952 (94.7) | 758 (96.3) | 0.083 |
| **Type of resection[2]** | 0 | | | | | 0.999 |
| Endoscopic/TEM resection only | | 164 (7.4) | 36 (7.4) | 72 (7.6) | 56 (7.4) | |
| Endoscopic/TEM followed by surgical resection | | 48 (2.2) | 11 (2.2) | 20 (2.1) | 17 (2.2) | |
| Surgical resection only | | 1,987 (90.4) | 442 (90.4) | 860 (90.3) | 685 (90.4) | |
| **Laparoscopy[2,3]** | 3 | 243 (26.7) | 45 (19.8) | 108 (26.6) | 90 (25.6) | 0.150 |
| **Laparoscopy converted to laparotomy[2,4]** | 0 | 50 (20.6) | 10 (22.2) | 24 (22.2) | 16 (17.8) | 0.710 |
| **Anastomotic leakage / abscess[2,3]** | 7 | | | | | 0.792 |
| No leakage, no abscess | | 715 (83.4) | 173 (84.8) | 297 (83.4) | 245 (82.5) | |
| Leakage and/or abscess | | 142 (16.6) | 31 (15.2) | 59 (16.6) | 52 (17.5) | |
| **Residual tumor[2]** | 65 | | | | | 0.640 |
| No | | 1,900 (96.4) | 425 (95.9) | 816 (96.3) | 659 (96.9) | |
| Microscopic | | 51 (2.6) | 12 (2.7) | 25 (3.0) | 14 (2.1) | |
| Macroscopic | | 19 (1.0) | 6 (1.4) | 6 (0.7) | 7 (1.0) | |
| **Circumferential resection margin[2,3]** | 164 | | | | | 0.565 |
| > 1 mm | | 663 (88.3) | 142 (88.2) | 274 (87.0) | 247 (89.8) | |
| ≤1 mm | | 88 (11.7) | 19 (11.8) | 41 (13.0) | 28 (10.2) | |
| **Number of examined lymph nodes[2]** | 49 | | | | | 0.225 |
| 0 – 6 | | 758 (38.2) | 184 (41.4) | 318 (37.1) | 256 (37.3) | |
| 7 -11 | | 657 (33.1) | 133 (30.0) | 303 (35.4) | 221 (32.2) | |
| 12 or more | | 209 (28.8) | 127 (28.6) | 235 (27.5) | 209 (30.5) | |

1. Postoperative disease stage based on TNM classification.
2. Only patients included who underwent surgical resection of the primary tumor.
3. Only available from 2008.
4. Only patients included who underwent laparoscopic resection of the primary tumor.

TEM = Transanal Endoscopic Microsurgery.

### Surgical treatment characteristics

Endoscopic or surgical resection of the primary tumor was performed in 4,348 patients (98.3%) with colonic cancer and in 2,199 (95.0%) with rectal cancer.

In patients with colonic cancer who had surgical resection, patients with high socioeconomic status more frequently underwent laparoscopy (204 (29.3%) of 697 vs. 139 (22.4%) of 620; P =0.017), less often had a laparoscopy converted to laparotomy (32 (15.7%) of 204 vs. 41 (29.5%) of 139; P =0.008) and less frequently developed anastomotic leakage or abscess formation (65 (9.6%) of 680 vs. 75 (12.6%) of 595; P =0.049) compared with patients with low socioeconomic status (Table 1). Similar results were found when adjusted for patient factors (age, sex and co-morbidities) and tumor characteristics for patients with high socioeconomic status versus those with low socioeconomic status: laparoscopy (OR 1.39, 95%-CI 1.08-1.79); laparoscopic surgery converted to laparotomy (OR 0.53, 95%-CI 0.31-0.92); and anastomotic leak or abscess (OR 0.70, 95%-CI 0.49-1.00) (Table 3).

In rectal cancer, patients with high socioeconomic status more frequently had resection of the primary tumor (758 (96.3%) of 787 vs. 489 (93.7%) of 522; P =0.083) compared with patients with low socioeconomic status (Table 2). This difference remained after ad-

**Table 3.** Unadjusted and adjusted odds ratios for surgical treatment characteristics and complications in patients with colonic cancer.

| Socioeconomic status | Unadjusted OR (95%-CI) | Adjusted for patient variables OR (95%-CI) | Adjusted for tumor variables OR (95%-CI) | Adjusted for patient and tumor variables OR (95%-CI) |
|---|---|---|---|---|
| | | **Laparoscopy**[1,2,3] | | |
| Low | ref. | ref. | ref. | ref. |
| Intermediate | 1.19 (0.93-1.51) | 1.15 (0.90-1.46) | 1.18 (0.92-1.50) | 1.15 (0.90-1.46) |
| High | 1.44 (1.12-1.85) | 1.37 (1.07-1.77) | 1.44 (1.12-1.85) | 1.39 (1.08-1.79) |
| | | **Laparoscopy converted to laparotomy**[1,2,4,5] | | |
| Low | ref. | ref. | ref. | ref. |
| Intermediate | 0.61 (0.38-0.99) | 0.75 (0.45-1.24) | 0.61 (0.38-0.99) | 0.76 (0.46-1.26) |
| High | 0.45 (0.26-0.75) | 0.53 (0.31-0.92) | 0.44 (0.26-0.74) | 0.53 (0.31-0.92) |
| | | **Anastomotic leakage and/or abscess**[1,2,4,5] | | |
| Low | ref. | ref. | ref. | ref. |
| Intermediate | 1.09 (0.80-1.48) | 1.04 (0.76-1.43) | 1.09 (0.80-1.49) | 1.05 (0.76-1.44) |
| High | 0.73 (0.52-1.04) | 0.70 (0.49-1.00) | 0.73 (0.51-1.04) | 0.70 (0.49-1.00) |

1. Only patients included who underwent surgical resection of primary tumour.
2. Patient variables adjusted models include age, gender and number of comorbidities.
3. Tumour variables adjusted models include disease stage, localization and differentiation grade.
4. Tumour variables adjusted models include disease stage.
5. Only available from 2008.

OR = odds ratio, 95%-CI = 95% confidence interval.

**Table 4.** Unadjusted and adjusted odds ratios for surgical treatment characteristics and complications in patients with rectal cancer.

| Socioeconomic status | Unadjusted OR (95%-CI) | Adjusted for patient variables OR (95%-CI) | Adjusted for tumor variables OR (95%-CI) | Adjusted for patient and tumor variables OR (95%-CI) |
|---|---|---|---|---|
| | | **Resection of the primary tumour**[1,2] | | |
| Low | ref. | ref. | ref. | ref. |
| Intermediate | 1.21 (0.77-1.90) | 1.00 (0.63-1.58) | 1.28 (0.81-2.01) | 1.04 (0.65-1.66) |
| High | 1.76 (1.06-2.94) | 1.41 (0.84-2.38) | 1.82 (1.08-3.07) | 1.44 (0.84-2.46) |
| | | **Endoscopic/TEM resection followed by surgery**[1,3,4] | | |
| Low | ref. | ref. | ref. | ref. |
| Intermediate | 0.91 (0.39-2.10) | 0.65 (0.26-1.58) | 0.46 (0.18-1.18) | 0.32 (0.12-0.88) |
| High | 0.99 (0.42-2.36) | 0.66 (0.26-1.67) | 0.84 (0.34-2.08) | 0.62 (0.24-1.59) |
| | | **Laparoscopy**[1,3,5] | | |
| Low | ref. | ref. | ref. | ref. |
| Intermediate | 1.47 (1.00-2.27) | 1.44 (0.97-2.14) | 1.48 (1.00-2.19) | 1.45 (0.97-2.16) |
| High | 1.36 (0.91-2.17) | 1.33 (0.88-2.00) | 1.36 (0.91-2.04) | 1.33 (0.88-2.01) |

1. Only patients included who underwent surgical resection of primary tumour.
2. Patient variables adjusted models include age, gender and number of comorbidities.
3. Tumour variables adjusted models include disease stage, localization and differentiation grade.
4. Tumour variables adjusted models include disease stage.
5. Only available from 2008.

OR = odds ratio, 95%-CI = 95% confidence interval, TEM = Transanal Endoscopic Microsurgery.

justing for tumor characteristics (OR 1.82, 95%-CI 1.08-3.07), but not when adjusted for patient characteristics (OR 1.41, 95%-CI 0.84-2.38), or tumor and patient characteristics combined (OR 1.44, 95%-CI 0.84-2.46) (Table 4). Laparoscopic surgery was performed more frequently in patients with intermediate socioeconomic status (108 (26.6%) of 406 patients) and high socioeconomic status (90 (25.6%) of 352) compared with those with low socioeconomic status (45 (19.8%) of 227) (Table 2), although the difference was not significant after adjustment for tumor and patient characteristics: OR 1.45 (95%-CI 0.97-2.16) and OR 1.33 (95%-CI 0.88-2.01) respectively (Table 4).

Sensitivity analysis with additional adjustment for the hospital where the surgery was performed did not affect the results substantially; the risk estimates for socioeconomic status changed by less than 10%.

## Thirty-day postoperative mortality

The 30-day postoperative mortality rate was 4.6% in patients with colonic cancer, and was lower in patients with high (47 (3.6%) of 1,321) and intermediate (64 (3.8%) of 1694) socioeconomic status than in patients with low socioeconomic status (80 (6.8%) of 1,178) (P <0.001 for all). The difference in 30-day mortality between patients with low

**Table 5.** Unadjusted and adjusted odds ratios for 30-day postsurgical mortality in patients with colonic cancer.

| Socioeconomic status | Unadjusted OR (95%-CI) | Adjusted for patient variables[1] OR (95%-CI) | Adjusted for tumor variables[2] OR (95%-CI) | Adjusted for surgical variables[3,4] OR (95%-CI) | Adjusted for patient, tumor and surgical variables OR (95%-CI) |
|---|---|---|---|---|---|
| Low | ref. | ref. | ref. | ref. | ref. |
| Intermediate | 0.54 (0.39-0.76) | 0.70 (0.50-0.99) | 0.54 (0.39-0.76) | 0.55 (0.33-0.91) | 0.72 (0.43-1.21) |
| High | 0.51 (0.35-0.73) | 0.71 (0.49-1.04) | 0.51 (0.35-0.74) | 0.63 (0.37-1.09) | 0.90 (0.51-1.57) |

1. Adjusted for age and number of comorbidities.
2. Adjusted for disease stage.
3. Adjusted for emergency surgery and anastomotic leakage and/or abscess formation.
4. Only available from 2008.
OR = odds ratio, 95%-CI = 95% confidence interval.

and high socioeconomic status remained significant when adjusted for disease stage, but not when adjusted for age and co-morbidities (OR 0.71, 95%-CI 0.49-1.04) or for emergency surgery and anastomotic leak or abscess formation (OR 0.63, 95%-CI 0.37-1.09). When adjusted for patient, tumor and surgical treatment characteristics, the risk of 30-day postoperative mortality was similar in patients high vs. low socioeconomic status (OR 0.90, 95%-CI 0.51-1.57) (Table 5).

The 30-day postoperative mortality rate in rectal cancer was 2.7% in the total group, and was 16 (3.5%) of 452, 21 (2.4%) of 880, and 17 (2.4%) of 702 for patients with low, intermediate and high socioeconomic status respectively, although these differences were not significant. When adjusted for patient, tumor and surgical treatment characteristics, no effect of socioeconomic status could be demonstrated (Table 6).

**Table 6.** Unadjusted and adjusted odds ratios for 30-day postsurgical mortality in patients with rectal cancer.

| Socioeconomic status | Unadjusted OR (95%-CI) | Adjusted for patient variables[1] OR (95%-CI) | Adjusted for tumor variables[2] OR (95%-CI) | Adjusted for surgical variables[3,4] OR (95%-CI) | Adjusted for patient, tumor and surgical variables OR (95%-CI) |
|---|---|---|---|---|---|
| Low | ref. | ref. | ref. | ref. | ref. |
| Intermediate | 0.67 (0.34-1.29) | 0.95 (0.48-1.88) | 0.67 (0.34-1.28) | 0.55 (0.23-1.36) | 0.86 (0.33-2.18) |
| High | 0.68 (0.34-1.35) | 1.00 (0.49-2.04) | 0.68 (0.34-1.36) | 0.39 (0.14-1.10) | 0.60 (0.21-1.76) |

1. Adjusted for age and number of comorbidities.
2. Adjusted for disease stage.
3. Adjusted for anastomotic leakage and/or abscess formation.
4. Only available from 2008.
OR = odds ratio, 95%-CI = 95% confidence interval.

None of the risk estimates for socioeconomic status and 30-day postoperative mortality changed more than 10% when adjusted additionally for treatment hospital, for either colonic or rectal cancer.

## DISCUSSION

The results of this study show differences with regard to surgical treatment and short-term mortality associated with socioeconomic status in patients with stage I-III colorectal cancer. In colonic cancer, patients with high socioeconomic status had lower odds for open or converted laparoscopic surgery and for anastomotic leakage or abscess formation in comparison with patients with low socioeconomic status. These differences were independent of age, sex, number of co-morbidities and tumor characteristics, indicating that socioeconomic status-specific differences in surgical treatment characteristics cannot be explained by differences in co-morbidity or more advanced disease at presentation. In addition, patients with colonic cancer and high socioeconomic status had a lower 30-day mortality rate than patients with low socioeconomic status. Differences in 30-day postsurgical mortality were affected mainly by age, co-morbidities and differences in surgical treatment, as adjusting for these factors resulted in a similar mortality risk for all categories of socioeconomic status. Patients with rectal cancer and high socioeconomic status had high odds for resection of the primary tumor compared with patients with low socioeconomic status.

Socioeconomic status has been reported to be associated with colorectal cancer survival.[2] The main factors associated with better survival in patients with high socioeconomic status have been suggested to be the relatively lower number of co-morbidities, a more favorable lifestyle, earlier disease stage at diagnosis, and more favorable treatment.[2,6,12,13,17,27] Socioeconomic status-specific differences in surgical treatment characteristics, including procedural technique, emergency surgery, quality outcomes and complications, have also been reported as factors explaining the favorable results in patients with high socioeconomic status, although studies on this topic are relatively scarce and not all surgical factors were examined together or in relation to surgical treatment outcomes in most previous studies.[17–19] The differences in surgical treatment observed in the present study are in agreement with findings from previous studies, with patients with colorectal cancer and high socioeconomic status being at lower risk of surgical complications[5] and having a higher probability of undergoing minimally invasive surgery.[21] However, findings of a previous study[20] in which patients with high socioeconomic status were more likely to have 12 or more lymph nodes examined could not be confirmed. Two of these previous studies[20,21] were performed in the USA and cannot be compared directly with the present findings. In studies from the USA, high

numbers of poor or uninsured patients are often included among those with low socioeconomic status with little access to high-quality medical care. In the Netherlands, the population has an obligatory health insurance that covers costs for oncological care. The Dutch healthcare system does not offer the possibility of additional private healthcare insurance. Based on this, it is likely, although not proven, that all patients in the present study had equal access to healthcare with no disparities in oncological treatment or access to the most experienced oncological surgeons owing to differences in healthcare coverage.[28]

In contrast to what has been hypothesized previously, the observed differences in surgical approach and complications appeared independent of age, sex, co-morbidities and disease stage at diagnosis. Differences between hospitals performing the surgical treatment could also not explain the socioeconomic gradient observed in the sensitivity analyses of the present study. Other tumor- and patient-related factors may play a role in the surgical treatment of patients and the risk of surgical complications, such as a previous history of intra-abdominal and pelvic surgery, body mass index, cardiac and pulmonary function, and smoking habit.[29–33] These factors are associated with socioeconomic status but were not available in the present study. It could be speculated that the healthcare behavior of patients may also be different between groups of different socioeconomic status. In this study, patients with colonic cancer and high socioeconomic status had lower odds of dying within 30 days following surgical resection of the primary tumor. After adjustment for tumor characteristics, the odds for 30-day postoperative mortality remained lower in patients with high vs. low socioeconomic status. However, when adjusted for age and co-morbidities the odds for 30-day mortality attenuated considerably and were no longer significant when further adjusted for emergency surgery and anastomotic leakage or abscess formation. This indicates that age and co-morbidities, and also factors associated with surgical treatment, largely influence socioeconomic differences with regard to short-term mortality after surgery. Two other studies[17,19] have shown similar results, with low income, low level of education and rental housing status being associated with higher 30-day postoperative mortality rates after elective surgery. These findings were explained largely by differences in health performance status, co-morbidities and, according to one of the studies,[17] lifestyle-related factors. In contrast, Morris and colleagues[18] reported that low income remained associated with increased 30-day mortality after adjusting for tumor characteristics, co-morbidities and urgency of the surgical resection in patients with colorectal cancer.

A strength of this population-based study is that it included an unselected group of patients from a cancer registry area, 95% completeness of registration, and comprehensive data on disease stage, co-morbidities, and surgical treatment, complications and mortality.[34] There were no data on causes of death, which made it impossible to determine colorectal cancer-specific mortality. The present study focused only on 30-

day postoperative mortality, and because deaths occurring in this period are most likely related to complications of the malignancy or surgery, the difference between overall and colorectal cancer-specific mortality is most likely low. Another limitation of the study may be the use of an indicator of socioeconomic status based on the postcode of the residential area. Routinely collected income tax data have, however, been reported to provide reliable estimates of household income in the Netherlands and it has been shown that socioeconomic differences based on neighborhood data accurately reflect socioeconomic differences at an individual level.[35] Subjects living in a postcode area with a nursing home or other care-providing institution were excluded from the analyses because assigning socioeconomic status is difficult in this group. This may have caused a bias as elderly people who cannot afford to maintain their household, for example by hiring individual care providers at home, are more likely to move to a care-providing institution.[24]

It should be noted that the quality of surgical treatment has improved rapidly in the past few years and does not reflect completely the status of oncological treatment during the study period (2005-2010). For example, 30-day postsurgical mortality rates in colonic and rectal cancer were 4.6% and 2.7% in the present investigation, but according to data from the Dutch Surgical Colorectal Audit[36] (nationwide coverage), 30-day postsurgical mortality rates dropped between 2009 and 2012 from 4.5% to 3.2% in colonic cancer and from 2.4% to 1.5% in rectal cancer. Laparoscopic surgery was performed in only about 20% of the patients in the present study with data to 2010, compared with 50% in 2012.[36] Similarly, a large decrease in anastomotic leakage and abscess formation, and an increase in number of examined lymph nodes have been observed in recent years. It would be interesting to determine whether the overall improvements in surgical outcomes of the past few years are of similar magnitude in different socioeconomic status subgroups.

This study has demonstrated considerable socioeconomic status-specific differences in surgical treatment and postsurgical complications in patients with colonic cancer. These differences appeared independent of age, sex, co-morbidities and disease stage at diagnosis, and may be explained by patient-related factors that were not measured in this study. Patient and surgical treatment characteristics assessed in this study did explain the lower risk of 30-day postoperative mortality among patients with stage I-III colonic cancer and high socioeconomic status.

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# Part 3

## Discussion and summary

# Chapter 11

## General discussion and final conclusions

## PART 1. STRATEGIES TO IMPROVE THE DETECTION OF COLORECTAL ADENOMAS

Colorectal cancer is a major cause of cancer related morbidity and mortality in the Western world with an estimated 725 thousands new cases per year in developed countries.[1] The development of colorectal cancer from precursor lesions, i.e. adenomas, takes on average 10 years.[2-4] This relatively slow transition allows for screening, detecting and removing adenomas before becoming malignant. In recent years, Western countries including the Netherlands have implemented screening programs in order to reduce colorectal cancer incidence and mortality rates.[5-8] Screening modalities that are mostly used include fecal occult blood testing (FOBT), sigmoidoscopy and colonoscopy. In the US, colonoscopy is the most widely used screening method while in Europe a two-step approach is chosen starting with FOBT or sigmoidoscopy followed by colonoscopy in case of positive findings. To ensure that screening and surveillance programs lead to what they should do, i.e. lowering the colorectal cancer burden, the diagnostic procedures should be of the highest quality possible. Colonoscopy is the most sensitive method for detecting colorectal adenomas and lowers colorectal cancer incidence and mortality considerably,[9-13] but it is not perfect as polypectomy reduces cancer incidence and mortality only by approximately 50%,[14-17] 3%-8% of patients with colorectal cancer had a colonoscopy within 3-5 years prior to their diagnosis,[17-21] and relatively high adenoma miss rates of approximately 25% have been reported.[22] These findings emphasize the need for improving quality of colonoscopy by increasing the detection of adenomas and early cancers.

Increasing adenoma detection rates and thereby improving quality of colonoscopy in general will require the improvement of various aspects of the procedure, including optimization of bowel cleansing, improving visualization behind folds and flexures, better recognition of flat and subtle lesions, and improving colon inspection technique of endoscopists. The aim of the first part of this thesis was to study a variety of new modalities that cover all these aspects and may help to improve quality of colonoscopy.

### Improving bowel cleansing

Recent studies still report inadequate bowel preparation in 10%-30% of colonoscopies,[23-28] which is associated with incomplete colonoscopy, lower adenoma detection rates, increased procedure times and need to repeat the procedure.[26,27,29-31] It is not surprising that many endoscopy units do not manage to achieve adequate bowel preparation in all of the patients. Bowel cleansing is a complex undertaking that requires patients to modify their diet and to ingest large volumes of laxatives which is burdensome for subjects scheduled to undergo colonoscopy. The quality of bowel cleansing depends on adherence to the bowel preparation regimen,[32-35] the timing of

bowel preparation,[36,37] and biological factors influencing bowel motility.[24,25,29,32,33,35,38,39] Patient education is the first step and is essential to achieve high compliance to dietary and pharmacy instructions.[40] Split-dose bowel preparation has improved cleansing rates considerably and is currently advised as optimal bowel preparation.[41,42] In current standard practice all subjects are exposed to large volumes of laxatives to achieve optimal bowel cleansing. This is sufficient for most patients, although there is a demand for more tailored intensity regiments. The challenge is to create a more individualized approach in which subjects are categorized in those who will have adequate bowel preparation with standard regimens and those who require less, but even more important, more intensified regimens. Such an approach may help to prevent unnecessary repeat endoscopies, lead to cost-savings and increase adenoma detection.

In **chapter 2** of this thesis we studied data from a cohort of almost two thousand consecutive colonoscopies in four medium to large size centers (three non-academic and one academic center) to identify independent risk factors for inadequate bowel preparation. Independent risk factors known to negatively affect bowel preparation by inhibiting bowel motility were used to develop and validate a prediction score for identifying subjects at increased risk for inadequate bowel preparation. The discriminatory ability of the prediction score was good. Factors that we included were the American Society of Anesthesiologists (ASA) physical status classification score of ≥3, use of tricyclic antidepressants or opioids, diabetes, chronic constipation, history of abdominal and/or pelvic surgery, history of inadequate bowel preparation and current hospitalization.

The prediction score that we developed is the first that has an acceptable level of discriminative power. One other prediction score developed by Hassan *et al.*[25] had an AUC of 0.63. A strength of our risk score is that it was developed using data of a well-defined and representative population undergoing split-dose bowel preparation, which is currently recommended as standard bowel cleansing by both the European Society of Gastrointestinal Endoscopy and the U.S. Multi-Society Task Force on Colorectal Cancer.[41,42] In contrast, in the population studied by Hassan *et al.* only 12.3% of the subjects had used split-dose bowel preparation, inadequate bowel preparation was reported in 32.9% (compared to 12.5% in our study) and the model mainly included risk factors associated with non-adherence. We believe that with the inclusion of factors related to bowel motility, we developed a prediction score that is specifically suitable to identify subjects that potentially benefit from intensified bowel preparation with larger volumes of bowel preparation, a prolonged period of fiber free diet or the addition of bisacodyl or sennosides to standard preparation.[43-45] This hypothesis is yet to be investigated in future studies that should focus on validating our prediction score in other populations and investigate whether the implementation in clinical practice leads to higher cleansing rates, fewer incomplete and repeat colonoscopies and ultimately higher adenoma detection rates.

### Improving visualization of the colonic surface

Based on the findings of back-to-back colonoscopy studies it is estimated that approximately 20% to 25% of polyps and adenomas are missed during standard colonoscopy.[22] A considerable proportion of polyps and adenomas are missed due to poor visualization behind folds and the inner curves of flexures, or by flat morphology or subtle appearance of lesions. This has led to the development of new technological features aiming to improve the visualization of such lesions. In **chapter 3** we presented an overview of technological developments and discussed their diagnostic yield. High definition colonoscopes and virtual chromoendoscopy technologies have been developed to enable endoscopists to better recognize flat and small lesions. High definition colonoscopes indeed provide a clearer view and some[46-49] but not all studies[50,51] have demonstrated a better detection of especially small, right-sided adenomas although the absolute increase in adenoma detection rate was only 3.5%.[52] Studies with virtual chromoendoscopy techniques, i.e. NBI, FICE and AFI, have demonstrated higher adenoma detection rates and lower adenoma miss rates compared to standard white light colonoscopy,[48,53-57] but not to high definition colonoscopy.[58] This resulted in the conclusion that the additional yield of these techniques is probably attributable to the high definition component. The effect of virtual chromoendoscopy during complete withdrawal seems limited with only a minor benefit on the detection of small and flat lesions. The quality of the images produced with virtual chromoendoscopy technologies requires further improvement before the general application of such technologies can be fully recommended.

Cap-assisted colonoscopy[59] and water-infusion (water-immersion and water-exchange) colonoscopy[60-65] were originally designed to facilitate cecal intubation and increase patient comfort. Studies have in general only shown a marginal or no benefit at all on polyp and adenoma detection. Unfortunately, the applicability of water-infusion methods has only been studied in highly experienced hands and is more time consuming compared to standard colonoscopy. Studies evaluating colonoscopy with the Third-Eye Retroscope showed considerable lower miss rates compared to standard colonoscopy.[66-68] The usability is however inconvenient in case of polypectomy, as the device first needs to be removed, impacts suction capabilities and adds to total colonoscopy time.

Novel colonoscopy techniques should provide an optimal view of the entire colonic mucosa while maintaining sufficient washing, suction and therapeutic capabilities. In **chapter 4** and **chapter 5** we investigated two novel technologies that may answer those needs, i.e. Full Spectrum Endoscopy (Fuse) colonoscopy and EndoRings colonoscopy. Both studies were multicenter, randomized back-to-back, tandem studies that were performed with the primary aim to compare adenoma miss rates between these techniques and standard colonoscopy. The adenoma miss rate with Fuse colonoscopy (7%) was statistically significantly lower compared to standard colonoscopy (41%). Although the

adenoma detection rate of Fuse colonoscopy (34%) and of standard colonoscopy (28%) were not statistically significantly different, Fuse colonoscopy resulted in significantly fewer false negative colonoscopies for adenomas (0%) compared to standard colonoscopy (6%). Similar results were obtained when EndoRings was compared to standard colonoscopy. The adenoma miss rate of EndoRings colonoscopy (10%) was also statistically significantly and substantially lower as compared to standard colonoscopy (48%). In addition, the adenoma detection rate was statistically significantly higher with EndoRings colonoscopy (51% vs. 29%) while the frequency of false negative colonoscopies was lower (0% vs. 17%).

The findings of these studies indicate that the diagnostic yield of both Fuse colonoscopy and EndoRings colonoscopy is in the upper range of other devices or techniques designed to improve visualization of the colonic surface such as cap-assisted colonoscopy,[69,70] virtual chromoendoscopy,[58] Third Eye Retroscope colonoscopy[67] and the recently introduced Endocuff colonoscopy.[71] A remarkable finding of both studies is the high adenoma miss rate that was found with standard colonoscopy. A plausible explanation is that these percentages have previously been underestimated because back-to-back procedures were both performed with standard colonoscopes. This means that adenomas that are located behind folds may have been missed twice with standard 140-170 degrees colonoscopes but would have been picked up with techniques that improve visualization behind these folds. Nonetheless, due to the nature of back-to-back colonoscopy studies, in which endoscopists usually perform both colonoscopies and are therefore not blinded, bias may have been introduced when not the same effort is used during both procedures to inspect the colonic mucosa.

Both Fuse and EndoRings colonoscopy seem promising improvements to the toolbox of endoscopists, even though the effects on post-colonoscopy colorectal cancer incidence and mortality rates are not yet studied. In our studies, only three advanced adenomas (larger than 10mm, villous histology or high grade dysplasia) were missed with standard colonoscopy and detected with Fuse colonoscopy in the Fuse study, while no advanced adenomas were missed with standard colonoscopy in the EndoRings study. Most missed adenomas were small tubular adenomas that may have been picked up during future surveillance colonoscopies. On the other hand, standard colonoscopy resulted in a considerable number of false negative colonoscopies, while Fuse colonoscopy and EndoRings colonoscopy did not. This implies that such patients would not undergo regular surveillance colonoscopies, with the possibility that (at least some) of these missed adenomas consequently may progress. In addition, our studies showed that in subjects that underwent Fuse colonoscopy or EndoRings colonoscopy first, the recommended surveillance interval was significantly less often shortened after a second colonoscopy as compared to subjects that underwent a standard colonoscopy first. Future studies, preferably with a randomized comparison design, are required to confirm

our findings, to determine whether more advanced lesions are found, to investigate the cost-effectiveness and to study whether these new developments indeed result in lower colorectal cancer incidence and mortality rates.

### Automated adenoma detection and real-time feedback technologies

Technological advancements designed to increase adenoma detection that are currently available, focus on improving the quality of images (e.g. high definition colonoscopes and virtual chromoendoscopy) or enlarging the field of view (e.g. Third Eye Retroscope, Fuse, EndoRings and Endocuff). These novel devices seem to substantially increase adenoma detection rates but still do not result in zero lesions being missed. The detection of neoplastic lesions keeps depended on the inspection by the endoscopist. Endoscopists are unable to fully examine every aspect of the colonic mucosa regardless of using a technique or technology that optimizes the total view of the colonic surface. This problem may be handled in several ways: 1) developing computerized systems that automatically detect neoplastic lesions, 2) developing computerized systems that give real-time feedback to the endoscopist about areas that are not adequately visualized and 3) measuring, evaluating and training colon inspection of individual endoscopists.

Some systems have recently been developed that are able to automatically detect polyps using wireless videocapsules[72,73] and colonoscopes[74] with promising results. For example, the PillCam COLON 2 uses algorithms to detect protrusions from the surrounding mucosal surface and one study showed that polyps can be detected with this technique.[72] A recent publication by Hong *et al.* reports on an automated 3D reconstruction technique that can be used to determine how much of the colonic surface is visualized during colonoscopy.[75] Such a technique may give real-time feedback to the endoscopist and allows revisiting colon segments that have not been adequately visualized. It may also be helpful for training purposes to teach endoscopist trainees how to maneuver the tip of the colonoscope during withdrawal. Besides improving the visualization of the colonic surface, ameliorating the quality of colon inspection by the endoscopist should be an important objective.

### Measuring the viewing behavior of endoscopists

Previous studies have shown considerable differences in adenoma detection rates between endoscopists resulting in higher post-colonoscopy colorectal cancer incidence and mortality rates in endoscopists with lower adenoma detection rates.[10,76] Adenoma detection rates correlate with withdrawal times.[77-81] A minimal withdrawal time of six minutes is currently regarded as a standard quality indicator.[82] However, careful examination of the colonic surface may be a better quality indicator than withdrawal time itself.[81,83] If we are able to measure viewing behavior of individual endoscopists it can be used to assist in monitoring, and in training and optimizing colonic inspec-

tion. In **chapter 6** we investigated the feasibility of eye tracking technology to measure viewing behavior during real-time, self-performed colonoscopies. In a pilot study, ten endoscopists each performed two colonoscopies with a mobile eye-tracking system. We demonstrated that gaze patterns could successfully be measured in almost all procedures with only limited missing data. Our results demonstrate that the areas of the endoscopy monitor where endoscopists spent most time differed considerably, with some endoscopists having more blind spots than others. A strong correlation was found between the measured time per area of the endoscopy monitor and the time per area of the colonic surface that was inspected, indicating that eye tracking technology may be a good way to evaluate the inspection of the colonic surface. This would allow measuring differences in viewing behavior between endoscopists and investigating why some endoscopists achieve higher adenoma detection rates than others. If viewing behavior can be correlated with adenoma detection rates, then eye tracking technology could be used for interventions or training programs to improve the quality of colonoscopy.

### Final conclusions

- Standard colonoscopy results in a significant adenoma miss rate and is currently unable to fully protect against future colorectal cancer.
- To improve colonoscopy quality in general, adenoma detection rates must be increased by optimizing bowel cleansing, improving complete visualization of the colonic surface and measuring colon inspection of endoscopists.
- Prediction scores to distinguish subjects that require intensified bowel preparation may lead to more personalized bowel cleansing regimens and aid in preventing unnecessary repeat colonoscopies and increase adenoma detection rates.
- Image enhancement techniques such as high definition and virtual chromoendoscopy do not substantially improve adenoma detection.
- Novel technologies including Fuse colonoscopy and EndoRings colonoscopy seem to considerably lower adenoma miss rates compared to standard colonoscopy.
- Eye tracking technology can be used to measure colon inspection during self-performed colonoscopies and may be able to distinguish gaze patterns associated with high adenoma detection rates from those with lower adenoma detection rates.

## PART 2. FACTORS ASSOCIATED WITH COLORECTAL CANCER DEVELOPMENT AND SURVIVAL

From a large number of epidemiological studies we have learned that smoking, obesity, physical activity and dietary factors are associated with the risk of developing colorectal cancer.[84,85] Several studies have suggested that gut microbiota also plays a role in the

development of colorectal cancer.[86-89] It is likely that these factors largely explain the higher incidence of colorectal cancer that is observed in Western compared to non-Western countries.[1] Although a large number of lifestyle and dietary risk factors have been identified, the total picture still needs to be unraveled. The underlying mechanisms that explain the observed associations are often poorly understood and the potentially important role of the gut microbiota is largely unknown. Only a limited number of studies have investigated the impact of lifestyle and diet on colorectal cancer survival, or the usefulness of secondary and tertiary prevention measures.[85] Hence, epidemiological studies that investigate the association between lifestyle, diet and colorectal cancer survival are warranted in order to study, promote and incorporate secondary prevention measures and improve colorectal cancer survival in general. The aim of the second part of this thesis was to provide more insight in factors associated with colorectal cancer development and survival.

### Use of antibiotics and colorectal cancer risk

A recent increasing interest has emerged into the role of the microbiota in colorectal cancer development. Important differences in the composition of the colon microbiota have been found between subjects with a low and high risk of developing colorectal cancer based on their diet. It has been hypothesized that a depletion of anti-inflammatory and short-chain fatty acids producing species and the abundance of pro-inflammatory microorganisms and toxin producing species could change the gut microbiota in a more pro-carcinogenic environment.[90] This shift is thought to be dependent on subjects' age, diet and pathogen infections.[88,91-97]

In **chapter 7** we describe the results of a nested case-control study in subjects included in a large health insurance database and observed that the frequent use of antibiotics is associated with an increased risk of developing colorectal cancer. This association was dose-dependent and the results were similar for regression analysis models adjusted for sex and age, and after additional adjustment for comorbidities and comedication associated with colorectal cancer risk and/or use of antibiotics. A Finnish cohort study including over three million subjects also found increased relative risks in the same range as in our study for developing colon cancer when comparing subjects with ≥6 prescriptions to those with 0-1 prescriptions over a 3-year period prior to cancer diagnosis.[98] A recent cohort study by Wang *et al.* in almost twenty-eight thousand patients with type II diabetes found a positive association between the use of anti-anaerobic antibiotics and both colon and rectal cancer, but no association was found for anti-aerobic agents.[99] We also found a positive association for anti-aerobic agents, although it was less pronounced when compared to anti-anaerobic agents. Since the gut microbiota is predominately composed of anaerobes, our findings suggest that particularly the use of anti-anaerobic agents may promote colorectal tumor growth. We hypothesize that

the (frequent) use of antibiotics increases the risk of developing colorectal cancer by causing a dysbiosis of the colonic microbiota, which could alter the bacterial production of short-chain fatty acids with known anti-inflammatory, anti-proliferative and anti-carcinogenic properties.[88,91-97] We recognize however that more epidemiological studies with longer follow-up on the use of antibiotics and data on dietary and lifestyle factors that may mutually affect this potential association are required.

### Coffee and tea consumption and colorectal cancer risk

Consumption of coffee may protect against colorectal cancer through antioxidant and antimutagenic effects of phenolic compounds,[100,101] inhibition of colon cancer cell growth by caffeine,[102,103] cafestol and kahweol-mediated reduction of bile acid synthesis,[104-106] and by lowering colonic epithelial cells to carcinogen exposure as a result of caffeine induced increase of the colon motility.[107] Tea consumption has been postulated to lower colorectal cancer risk through its antioxidant components protecting colonic epithelial cells against oxidative radicals.[108,109] In **chapter 8** we found no significant associations between the consumption of coffee or tea and the risk of developing colorectal cancer. Furthermore, no convincing joint effects of (caffeinated) coffee and tea consumption with *CYP1A2* and *NAT2* activity on colorectal cancer risk were observed. This was studied because these enzymes metabolize caffeine and as important components of coffee and tea, the risk of developing colorectal cancer might depend on *CYP1A2* and *NAT2* activity.

Our results support the findings of most previous prospective cohort studies,[110-115] although a recent prospective cohort study (NIH-AARP Diet and Health study) did show an inverse association between coffee and risk of proximal colon cancer.[116] In addition, an inverse association with drinking tea has generally not been demonstrated in epidemiological studies,[116,117] which is confirmed by our study. Disparities have however been observed between Western and Asian populations,[117] which may be caused by differences in type of tea (black or green) consumed. Epidemiological studies that found a protective effect of tea mainly come from Asia, where mostly green tea is consumed, while in Western studies, where black tea is mostly consumed, an inverse association with colorectal cancer risk has not been observed.[117,118] Green tea possibly contains more putative anticarcinogenic compounds than black tea, although other environmental sources of bias should be considered, as well as differences in study design and number of cases included. To elucidate these conflicting results, future epidemiological studies should focus on differences in green and black tea consumption in various populations, mode of preparation, and uptake of antioxidant components present in tea, in relation to colorectal cancer risk.

### Intake of dairy products and dietary calcium and colorectal cancer survival

Studies reporting on diet and lifestyle and colorectal cancer survival are scarce.[85] In **chapter 9** we investigated whether the pre-diagnostic intake of dairy product and dietary calcium are associated with survival after colorectal cancer diagnosis, which is of interest because a large number of studies, including a recent analysis within the EPIC cohort, demonstrated an inverse association between the intake of dairy and calcium and colorectal cancer risk.[119,120] These observations have mainly been attributed to dietary calcium which is thought to lower colorectal cancer risk in part by preventing colonic *K-ras* mutations and by its direct anti-proliferative effect on colonic epithelium cells.[121,122] We hypothesized that the anti-carcinogenic properties of calcium may also affect the chance of survival after colorectal cancer diagnosis. However, the results of our study show that prediagnostic consumption of dairy products (total, milk, yoghurt, and cheese) and dietary intake of calcium (total, dairy, and nondairy) were neither associated with disease-specific nor with all-cause mortality in patients with colorectal cancer. Based on our findings we argue that once colorectal cancer has developed, the assumed anti-proliferative and anti-carcinogenic properties of calcium only have a minor or no effect on tumor progression and survival. Colorectal cancer survival largely depends on disease stage, comorbidities, general physical condition and treatment. If calcium intake, by any means, influences tumor growth and progression, then the effect might be diminished by these more important clinical factors. Nonetheless, we believe that more epidemiological studies should be performed to study the impact of lifestyle and diet on colorectal cancer survival. This is indicated in order to study, promote and incorporate tertiary prevention measures and improve colorectal cancer survival in general.

### Socioeconomic status, surgical treatment and postsurgical mortality in colorectal cancer

In **chapter 10** we show socioeconomic differences in surgical treatment and short-term mortality in patients with stage I-III colorectal cancer. For colonic cancer, patients with high socioeconomic status had lower odds for open or converted laparoscopic surgery and for anastomotic leakage or abscess formation in comparison with patients with low socioeconomic status. These associations were independent of age, sex, number of co-morbidities and tumor characteristics. This indicates that socioeconomic status-specific differences in surgical treatment characteristics cannot be explained by differences in co-morbidity or more advanced disease at presentation as previously has been hypothesized.[123-125] Other tumor- and patient-related factors may play a role in the surgical treatment of patients and the risk of surgical complications, such as a previous history of intra-abdominal and pelvic surgery, body mass index, cardiac and pulmonary function, and smoking habits,[126-130] but these data were unfortunately not available in this study. Healthcare seeking behavior of patients may also be different between groups

of different socioeconomic status. Nonetheless, our findings are in agreement with findings from previous studies showing that patients with colorectal cancer and a high socioeconomic status were at a lower risk of surgical complications[131] and have a higher probability of undergoing minimally invasive surgery.[132]

In this study, patients with colonic cancer and high socioeconomic status also had a lower odds of dying within 30 days after surgical resection of the primary tumor. This remained present after adjustment for tumor characteristics, but was attenuated when adjusted for age and co-morbidities and was no longer statistically significant when further adjusted for emergency surgery and anastomotic leakage or abscess formation. This indicates that age and co-morbidities, and factors associated with surgical treatment, largely explain socioeconomic-specific differences with regard to short-term mortality after surgery. Similar results were found by other authors,[124,133] with low income, low level of education and rental housing status being associated with higher 30-day postoperative mortality rates after elective surgery. This was largely explained by differences in health performance status, co-morbidities and, according to one of the studies,[124] lifestyle-related factors.

The quality of surgical treatment has recently improved rapidly with lower 30-day postsurgical mortality rates, increasing laparoscopic resections, increasing number of examined lymph nodes and a large decrease in anastomotic leakage and abscess formation.[134] It would therefore be of clinical interest to determine whether the overall improvements in surgical outcomes of the past few years are of similar magnitude in different socioeconomic status subgroups.

## Final conclusions

- Before promoting and incorporating secondary and tertiary prevention measures to increase colorectal cancer survival rates, prospective studies in colorectal cancer patients are required investigating the effect of diet and lifestyle.
- The (frequent) use of antibiotics is associated with an increased colorectal cancer risk and supports the hypothesis that the gut microbiota are involved in the development of colorectal cancer.
- Coffee and tea consumption are not associated with colorectal cancer risk.
- The pre-diagnostic consumption of dairy products is not associated with colorectal cancer survival.
- Patients with colorectal cancer and high socioeconomic status have more favorable surgical treatment characteristics and a lower 30-day postoperative mortality risk than patients with low socioeconomic status.

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# Chapter 12

## Summary

Colorectal cancer is a major cause of cancer related morbidity and mortality in the Western world with an estimated 725 thousands new cases per year in developed countries. The development of colorectal cancer from precursor lesions, i.e. adenomas, takes approximately 10 years. This relatively slow transition allows for screening, detecting and removing adenomas before they become malignant. Colonoscopy is the most sensitive method for detecting colorectal adenomas and lowers colorectal cancer incidence and mortality considerably. However, colonoscopy is not perfect as polypectomy reduces colorectal cancer incidence and mortality only about 50%. Furthermore, 3%-8% of patients with colorectal cancer had a colonoscopy within 3-5 years prior to their diagnosis and significant adenoma miss rates of 20% to 25% have been reported. These findings emphasize the need for improving quality of colonoscopy by increasing the detection of adenomas and early cancers.

## PART 1. STRATEGIES TO IMPROVE THE DETECTION OF COLORECTAL ADENOMAS

The aim of the first part of this thesis is to study a variety of new modalities that specifically may help to increase adenoma detection and thereby improve quality of colonoscopy in general.

Recent studies still report inadequate bowel preparation in 10% to 30% of colonoscopies. In **chapter 2** we used data from a cohort of almost two thousand consecutive colonoscopies to identify independent risk factors related for inadequate bowel preparation, and developed a prediction score for identifying subjects at risk for inadequate bowel preparation. The discriminative ability of the prediction score was well and may specifically be suitable to identify subjects that could benefit from intensified bowel preparation.

In **chapter 3** we present an overview of technological developments and discuss their diagnostic yield. High definition colonoscopes may lead to a better detection of especially small, right-sided adenomas, even though the absolute increase in adenoma detection rate is only 3.5%. Virtual chromoendoscopy techniques, including NBI, FICE and AFI also result in slightly higher adenoma detection rates and lower adenoma miss rates when comparing such techniques to standard white light colonoscopy, but not when comparing them to high definition colonoscopy. Cap-assisted colonoscopy and water-exchange colonoscopy marginally increase polyp and adenoma detection. The Third-Eye Retroscope lowers adenoma miss rates considerably compared to standard colonoscopy, but this device has an impact on suction capabilities through the working

channel and is inconvenient in case of polypectomy as it adds to total colonoscopy time. We conclude that new colonoscopy techniques are required that provide an optimal view of the total colonic mucosa while maintaining optimal washing, suction and therapeutic capabilities.

In **chapter 4** and **chapter 5** two novel technologies are studied that are designed to improve visualization at the proximal sides of folds and inner curves of flexures: Full Spectrum Endoscopy (Fuse) colonoscopy and EndoRings colonoscopy. Both Fuse colonoscopy (7% vs. 41%) and EndoRings colonoscopy (10% vs. 48%) had significantly lower adenoma miss rates when compared to standard colonoscopy. Both devices also resulted in zero false negative colonoscopies for adenomas while this was 6% and 17% with standard colonoscopy, respectively. These findings indicate that the diagnostic yield of these devices is higher than standard colonoscopy. Further studies evaluating their use in daily clinical practice are required.

The detection of adenomas differs considerably between endoscopists and critically depends on the quality of colonic inspection. **Chapter 6** describes the results of a pilot study in which we investigate the feasibility of eye tracking technology to measure viewing behavior of endoscopists during real-time and self-performed colonoscopies. Gaze patterns were successfully measured in 90% of the procedures. Our results show that the areas of the endoscopy monitor where endoscopists look the most time in total are also the areas where they most frequently look and look for the longest time before moving to another area. The total time that was spent per area of the endoscopy monitor correlated well with the time spent on the same area of the colonic surface, indicating that gaze patterns across the endoscopy monitor could serve as a good measure for colon inspection. This correlation was found to be stronger in endoscopists with more years of colonoscopy experience. We conclude that the use of eye tracking technology to measure gaze patterns of endoscopists during real-time, self-performed colonoscopies is feasible and that this technique can be applied to measure and compare viewing behavior of individual endoscopists.

## PART 2. FACTORS ASSOCIATED WITH COLORECTAL CANCER DEVELOPMENT AND SURVIVAL

The aim of the second part of this thesis is to provide more insight in factors that might be associated with colorectal cancer development and survival, i.e. use of antibiotics, coffee & tea consumption, intake of dairy products and socioeconomic status.

In **chapter 7** we describe the results of a nested case-control study in which we demonstrated that the use of antibiotics is associated with an increased risk of developing colorectal cancer. This association was dose-dependent and the results were similar in models adjusted for sex and age and models that were additionally adjusted for comorbidities and comedication. Multivariable analyses adjusted for all measured potential confounders showed an odds ratio of 1.26 (95% confidence interval 1.11-1.44; p-trend<0.01) for ≥8 vs. 0 prescriptions and 1.05 (95% confidence interval: 1.01-1.09) for every increase of 5 prescriptions. Our findings are in line with two previous studies and suggest that the use of antibiotics may promote colorectal tumor growth. We hypothesize that the (frequent) use of antibiotics may increase the risk of developing colorectal cancer by causing a dysbiosis of the colonic microbiota. This could change the bacterial production of short-chain fatty acids, which are known to have anti-inflammatory, anti-proliferative and anti-carcinogenic properties.

Consumption of coffee and tea may protect against colorectal cancer through its antioxidant components and inhibition of colon cancer cell growth, amongst others. In **chapter 8** we describe the results of large prospective cohort study in which no significant associations were found between the consumption of coffee and tea and the risk of developing colorectal cancer. As caffeine is metabolized by *CYP1A2* and *NAT2* enzymes, the association caffeine and the risk of developing colorectal cancer might depend on the activity of these enzymes. We did not find convincing joint effects of (caffeinated) coffee and tea consumption, and *CYP1A2* and *NAT2* activity on colorectal cancer risk.

The consumption of dairy products is inversely associated with colorectal cancer development. This association is probably attributable to the negative effect of calcium on cell proliferation. In **chapter 9** we showed that the prediagnostic measured consumption of dairy products (total, milk, yoghurt, and cheese) and dietary intake of calcium (total, dairy and nondairy) are neither associated with disease-specific nor with all-cause death in patients with colorectal cancer. We hypothesize that once cancer has developed, the assumed anti-proliferative and anti-carcinogenic properties of calcium only have a minor or no effect on tumor progression and survival.

Socioeconomic status has repeatedly been associated with colorectal cancer survival. **Chapter 10** describes the findings of a cohort study in which we observed that colon cancer patients with high socioeconomic status have lower odds for undergoing open or converted laparoscopic surgery and for anastomotic leakage or abscess formation in comparison with patients with low socioeconomic status. These associations were independent of age, sex, number of comorbidities and tumor characteristics including stage, differentiation grade and localization. Patients with colonic cancer and high so-

cioeconomic status also have a lower 30 days mortality risk following surgical resection of the primary tumor. This is independent of tumor characteristics, but not of age, co-morbidities and surgical characteristics including emergency surgery and anastomotic leakage or abscess formation. Patients with rectal cancer and high socioeconomic status more frequently have a resection of the primary tumor. This appeared partially depended on differences in age, sex and co-morbidities, but not tumor characteristics. In conclusion, socioeconomic status is associated with surgical outcomes in patients with colorectal cancer, which is only partially explained by patient and tumor characteristics.

# Chapter 13

## Summary in Dutch

## Samenvatting in het Nederlands

Colorectaal carcinoom is een belangrijke oorzaak van kanker gerelateerde morbiditeit en mortaliteit met een incidentie van ongeveer 725 duizend nieuwe gevallen per jaar in de Westerse wereld. Het ontstaan van colorectaal carcinoom uit adenomen duurt ongeveer 10 jaar. Deze relatief langzame groei maakt het mogelijk om te screenen en gedetecteerde adenomen te verwijderen voordat deze maligne ontaarden. Colonoscopie is de meest gevoelige methode voor het opsporen van adenomen in het colorectum en verlaagt de incidentie van en de sterfte aan colorectaal carcinoom aanzienlijk. Colonoscopie is echter geen perfect onderzoek aangezien poliepectomie de incidentie van colorectaal carcinoom en de sterfte als gevolg daarvan slechts met de helft verminderd. Daarnaast blijkt dat 3% tot 8% van de patiënten met een colorectaal carcinoom een colonoscopie heeft gehad in de 3 tot 5 jaar vóór de diagnose. Tenslotte is bekend dat ongeveer 25% van de adenomen gemist worden tijdens colonoscopie. Deze bevindingen benadrukken het belang van het verbeteren van de kwaliteit van colonoscopie door de detectiegraad van adenomen en vroege stadia van kanker te verhogen.

## DEEL 1 STRATEGIEËN OM DE DETECTIE VAN COLORECTALE ADENOMEN TE VERBETEREN

Het doel van het eerste deel van dit proefschrift is om nieuwe modaliteiten te onderzoeken die specifiek kunnen helpen om de detectie van adenomen te verhogen en derhalve de kwaliteit van colonoscopie te verbeteren.

Recente studies laten zien dat er nog in 10% tot 30% van de colonoscopieën sprake is van onvoldoende darmreiniging. In **hoofdstuk 2** hebben we gebruik gemaakt van data van een cohort van bijna tweeduizend opeenvolgende colonoscopieën om onafhankelijke risicofactoren voor onvoldoende darmreiniging te identificeren. Vervolgens werd een predictiescore ontwikkeld om patiënten met een verhoogd risico op onvoldoende darmreiniging te kunnen identificeren. Het onderscheidend vermogen van deze predictie score was redelijk goed en zou derhalve gebruikt kunnen worden om personen te identificeren die mogelijk profiteren van een intensievere darmvoorbereiding.

In **hoofdstuk 3** presenteren we een overzicht van de technologische ontwikkelingen op het gebied van colonoscopie en bespreken hun diagnostische opbrengst. Het gebruik van 'high definition' colonoscopen leidt tot een betere opsporing van met name kleine, rechtszijdige adenomen, hoewel de absolute toename van de adenoom detectie slechts 3,5% bedraagt. Virtuele chromoendoscopische technieken, waaronder NBI, FICE en AFI resulteren ook in een iets hogere kans om adenomen te detecteren en een lagere kans om adenomen te missen in vergelijking met standaard colonoscopie met wit licht,

echter niet wanneer 'high definition' colonoscopie wordt gebruikt. Zowel colonoscopie met een cap als 'water-infusion' colonoscopie leiden slechts tot een geringe toename van de adenoom detectie. De 'Third-Eye Retroscope' verlaagt de kans op het missen van adenomen aanzienlijk in vergelijking met standaard colonoscopie. Echter, dit hulpmiddel beïnvloedt de afzuigmogelijkheden door het werkkanaal, wat lastig is in het geval wanneer poliepectomie wordt verricht. Hierdoor neem ook de totale colonoscopie tijd toe. We concluderen dat er behoefte is aan nieuwe colonoscopische technieken die een optimaal zicht geven van de gehele mucosa waarbij de mogelijkheden tot spoelen, afzuigen en therapeutische interventies optimaal gebruikt kunnen worden.

In **hoofdstuk 4** en **hoofdstuk 5** worden twee nieuwe technologieën onderzocht die zijn ontworpen om de visualisatie aan de proximale zijde van darmplooien te verbeteren: Full Spectrum Endoscopie (Fuse) en EndoRings colonoscopie. Zowel met Fuse colonoscopie (7% versus 41%) als met EndoRings colonoscopie (10% versus 48%) was de kans op het missen van adenomen aanzienlijk verlaagd in vergelijking met standaard colonoscopie. Bij beide technieken bleek de kans op een vals-negatieve colonoscopie nihil terwijl dit met standaard colonoscopie respectievelijk 6% en 17% was. Deze bevindingen laten zien dat de diagnostische opbrengst van deze technieken hoger is dan met standaard colonoscopie. Verder onderzoek is echter nodig om de toegevoegde waarde in de dagelijkse klinische praktijk vast te stellen.

De detectie van adenomen verschilt aanzienlijk tussen endoscopisten en is erg afhankelijk van de kwaliteit van inspectie van het colon. **Hoofdstuk 6** beschrijft de resultaten van een pilot studie waarin we onderzoek doen naar de haalbaarheid van 'eye tracking' technologie om het kijkgedrag van endoscopisten te meten tijdens zelfuitgevoerde coloscopieën. In 90% van de procedures konden de kijkpatronen succesvol worden gemeten. De resultaten laten zien dat de gebieden op de endoscopie monitor waar endoscopisten het grootste deel van de tijd kijken ook de gebieden zijn waar ze het meest frequent en het langst kijken voordat hun blik naar een ander gebied verplaatst wordt. De totale tijd die per gebied op de endoscopie monitor werd bekeken correleerde goed met de tijd die werd besteed om de corresponderende gebieden van het darmoppervlakte te bekijken. Dit betekent dat het kijkpatroon over de endoscopie monitor mogelijk een goede maat is voor inspectie van het colon. Deze correlatie was sterker bij endoscopisten met meer colonoscopie ervaring. We concluderen dat het gebruik van 'eye tracking' technologie om kijkpatronen van endoscopisten te meten tijdens colonoscopieën haalbaar is en dat deze techniek toegepast kan worden om het kijkgedrag van individuele endoscopisten te meten en te vergelijken.

## DEEL 2 FACTOREN DIE GEASSOCIEERD ZIJN MET DE ONTWIKKELING VAN EN STERFTE ALS GEVOLG VAN COLORECTAAL CARCINOOM

Het doel van het tweede deel van dit proefschrift is om meer inzicht te verschaffen in factoren die mogelijk samenhangen met de ontwikkeling van en sterfte als gevolg van colorectaal carcinoom, namelijk het gebruik van antibiotica, de consumptie van koffie en thee, inname van zuivelproducten en sociaaleconomische status.

In **hoofdstuk 7** beschrijven we de resultaten van een 'geneste' case-control studie waarin we aantonen dat het gebruik van antibiotica geassocieerd is met een verhoogd risico op het ontstaan van colorectaal carcinoom. Deze associatie was dosis-afhankelijk en de resultaten waren vergelijkbaar in statistische modellen waarin gecorrigeerd werd voor geslacht en leeftijd en modellen waarin tevens werd gecorrigeerd voor comorbiditeit en comedicatie. Multivariabele analyses gecorrigeerd voor alle gemeten potentiële confounders toonde een verhoogde kans (odds ratio) van 1,26 (95% betrouwbaarheids interval: 1,11-1,44; p-trend<0,01) voor ≥8 versus 0 recepten en 1,05 (95% betrouwbaarheids interval: 1,01-1,09) voor elke toename van 5 recepten. Onze resultaten bevestigen de bevindingen van twee eerdere studies en suggereren dat het gebruik van antibiotica de groei van colorectaal carcinoom zou kunnen bevorderen. Onze hypothese is dat het (frequente) gebruik van antibiotica het risico op colorectaal carcinoom verhoogd doordat zij een dysbiosis van de microbiële flora in het colon veroorzaken. Hierdoor wordt de bacteriële productie van korte keten vetzuren verminderd die anti-inflammatoire, anti-proliferatieve en anti-carcinogene eigenschappen bezitten.

De consumptie van koffie en thee beschermt mogelijk tegen colorectaal carcinoom via bestanddelen met een anti-oxidante  werking en/of via inhibitie van de groei van kankercellen. In **hoofdstuk 8** beschrijven we de resultaten van een grote prospectieve cohort studie waarin we geen significante associaties vonden tussen de consumptie van koffie en thee en het risico op het ontstaan van colorectaal carcinoom. Omdat cafeïne wordt gemetaboliseerd door *CYP1A2* en *NAT2* enzymen, zou de associatie tussen cafeine en het risico op colorectaal carcinoom kunnen afhangen van de activiteit van deze enzymen. Wij vonden echter geen overtuigend bewijs voor een gezamenlijk effect van de consumptie van (cafeïne bevattende) koffie en thee, *CYP1A2* en *NAT2* activiteit op het risico voor het krijgen van colorectaal carcinoom.

De consumptie van zuivelproducten heeft een inverse associatie met het krijgen van colorectaal carcinoom. Deze associatie wordt met name toegeschreven aan het negatieve effect van calcium op de celproliferatie. In **hoofdstuk 9** vonden we dat de consumptie van zuivelproducten (totaal, melk, yoghurt en kaas) en de inname van calcium (totaal,

uit zuivel en uit niet zuivel producten) voorafgaand aan de diagnose niet geassocieerd is met ziekte-specifieke, noch met totale sterfte van patiënten met een colorectaal carcinoom. Onze hypothese is dat wanneer een colorectaal carcinoom zich heeft ontwikkeld, de veronderstelde anti-proliferatieve en anti-carcinogene eigenschappen van calcium slechts een gering of geen effect hebben op progressie van de tumor en overleving.

Sociaaleconomische status is herhaaldelijk in verband gebracht met sterfte aan colorectaal carcinoom. **Hoofdstuk 10** beschrijft de resultaten van een cohort studie waarin we vonden dat patiënten met een coloncarcinoom en een hoge sociaaleconomische status een lagere kans hebben om een open of een geconverteerde laparoscopische operatie te ondergaan, en een lagere kans hebben op naadlekkage of abcesvorming in vergelijking met patiënten met een lage sociaaleconomische status. Deze associaties bleken onafhankelijk van leeftijd, geslacht, comorbiditeit en tumoreigenschappen zoals stadium, differentiatiegraad en lokalisatie. Patiënten met een coloncarcinoom en een hoge sociaaleconomische status hadden daarnaast minder kans op sterfte binnen 30 dagen na chirurgische resectie van de primaire tumor. Dit bleek onafhankelijk van tumoreigenschappen, maar niet die van de leeftijd, comorbiditeit en chirurgische kenmerken zoals spoedoperatie en naadlekkage of abcesvorming. Patiënten met rectumcarcinoom en een hoge sociaaleconomische status ondergingen vaker een resectie van de primaire tumor, wat gedeeltelijk verklaard werd door verschillen in leeftijd, geslacht en comorbiditeit, maar niet tumoreigenschappen. Concluderend is sociaaleconomische status geassocieerd met chirurgische uitkomsten in patiënten met een colorectaal carcinoom en is dit slechts gedeeltelijk te verklaren door patiënt- en tumorkarakteristieken.

## ACKNOWLEDGEMENTS – DANKWOORD

Nu mijn proefschrift klaar is, het einde van de tunnel daar is, het caecum is bereikt, besef ik mij wat een geluk ik heb. Het moet je meezitten, maar dat kan niet zonder een aantal belangrijke mensen. Deze mensen ben ik ontzettend veel dank verschuldigd en verdienen het om hier genoemd te worden.

Beste **prof. dr. P.D. Siersema**, beste Peter, hartelijk dank voor het vertrouwen dat u mij begin 2011 gegeven heeft toen ik vanuit de regio Amsterdam bij u kwam voor een open sollicitatie naar een plek als arts-onderzoeker. De afgelopen jaren heb ik gewerkt aan zeer uiteenlopende projecten, sommige (PICNIC) nog tijdrovender dan andere (EPIC en back-to-back studies), waarbij de richting van mijn proefschrift me niet altijd duidelijk was. Dankzij u heb ik in korte tijd ontzettend veel geleerd, ben ik nog enthousiaster over het vak en is mijn proefschrift een mooi boekwerk geworden. Hartelijk dank ook voor de steun en de opbeurende woorden "het komt goed" en "je moet het niet zo somber inzien" op de momenten dat ik het even niet zag zitten. Ik heb met veel plezier op uw afdeling gewerkt!

**Dr. M.G.H. van Oijen**, beste Martijn, vanaf het begin wist ik dat ik van jou veel kon leren. Van grote subsidie aanvragen schrijven (soms misschien té groot) tot fancy posters maken en skypen. De vragen "waarom is deze studie klinisch relevant?", "wat is de so what factor?" en "hoe kunnen we het opleuken?" hebben me altijd aan het denken gezet en hebben menig artikel ook werkelijk leuker gemaakt. In de tijd die we samen (meer buiten dan) in Utrecht hebben gehad heb ik veel van je mogen leren en ben ik wetenschappelijk volwassen geworden.

**Dr. H.B. Bueno-de-Mesquita**, beste Bas, jij hebt me de epidemiologische kneepjes van het vak geleerd. Tijdens mijn eerste overleg met jou wist ik niets van SAS, EPIC (dat is toch een elektronisch patiënten dossier?), Cox regressie analyses, residual confounding, reversed causation, sensitiviteitsanalyses en ga zo maar door. Van het PF-1 formulier dat ik geschreven heb in mijn eerste week als onderzoeker snapte ik driekwart niet. Dat is nu wel anders. De vele gesprekken over onderzoek naar voeding en kanker hebben mij veel kennis opgeleverd. Ik kijk met veel plezier terug op jouw hartelijkheid en op onze samenwerking.

**Dr. M. Koopman**, beste Miriam, hoewel jij niet officieel een van mijn co-promotoren bent voelt dat wel een beetje zo. Ik heb in de afgelopen jaren met jou mogen werken aan een prachtig initiatief gericht op behandeling en overleving van colorectaal carcinoom, het PICNIC project. We hebben samen veel tijd doorgebracht en menig overleg gevoerd

met verscheidene partijen binnen en buiten het ziekenhuis. Daarbij heb ik veel van je geleerd over de politieke kant van onderzoek. Jouw enorme enthousiasme en doorzettingsvermogen werken zeer aanstekelijk en daarmee weet je vele hordes succesvol te nemen. Ik hoop in de toekomst nog vaker met je te mogen samenwerken.

**Dr. L.M.G. Moons**, beste Leon, hartelijk dank voor het uitvoeren van back-to-back coloscopieën met Fuse en EndoRings, de hulp bij het verzamelen van gegevens voor het ontwikkelen van een bowel prep predictiescore en je nuttige input in meerdere artikelen waar jij co-auteur van bent. Ik hoop dat ik nog veel van jou mag leren op endoscopisch gebied.

**Dr. I.T. Hooge**, beste Ignace, jouw bijdrage aan de eye gaze studie is van onschatbare waarde geweest. Zonder jouw kennis en advies hadden we dit project niet kunnen uitvoeren. De samenwerking met een wetenschapper buiten het medische circuit zoals jij, in combinatie met jouw unieke persoonlijkheid, gaven een verfrissende en positieve wending aan mijn werk.

**Meytal**, what's up?! For three years we kept a hotline between the two of us. During those years we worked on two randomized trials that resulted in high quality papers. Thank you for the successful cooperation. For the future I hope that you will show up with more great ideas to increase adenoma detection and that we may work together again.

**Alle co-auteurs** van de artikelen binnen en buiten dit proefschrift. Ik wil jullie bedanken voor de input van gegevens, jullie nuttige commentaar op manuscripten en de fijne samenwerking.

**Stafleden en arts-assistenten** van MDL afdeling, dank voor jullie medewerking aan de eye gaze studie, jullie suggesties en vragen tijdens de research besprekingen en jullie gezelligheid na werktijd. Ik zie uit naar de tijd dat ik als collega in de kliniek met jullie mag samenwerken.

Bijzonder veel dank gaat uit naar al mijn collega **(arts-)onderzoekers**. Mede dankzij jullie heb ik een ontzettend leuke periode mogen beleven binnen en buiten werktijd. De wintersportvakanties, vele borrels, lunch- en koffiepauzes zorgden voor veel gezelligheid en een fantastische (werk)sfeer! Ik bewaar veel mooie herinneringen aan de tijd dat ik met jullie heb doorgebracht. **Christine**, altijd enthousiast over Barrrret cellen en altijd in voor borrrrel. Je hebt weleens gezegd dat het eindelijk lekker rustig zou worden nu de meeste mannen zijn gevlogen, maar stiekem vind je dat heel jammer. Ik hoop dat we

nog vele borrrreltjes mogen doen in de toekomst. **Daisy**, ik kijk met veel plezier terug op onze trainingsrondjes, dagelijks geklets over het te volgen trainingsprogramma, de meerdere halve marathons en uiteindelijk de hele marathon van Berlijn. Je bent een geliefde collega en ik heb veel zin om de komende jaren met jou samen te werken als collega AIOS. Bedankt dat je mijn paranimf wilt zijn! **Erik**, jouw kritische blik en heldere kijk op zaken zijn werkelijk ongeëvenaard. Je dacht graag mee zowel op wetenschappelijk als sportief vlak, bedankt hiervoor. **Femke**, bedankt voor de nodige (politieke) afleiding toen je naast mij zat op D2 oost, je kritische blik als onderzoeker en de gezamenlijke zorg over onze plant. **Jan-Steven**, jij bent het ultieme voorbeeld van iemand die weet te strijden voor zijn doel, en met succes! De manier waarop jij met tegenslagen omgaat zijn bewonderenswaardig en een voorbeeld voor iedereen. **Jorrit**, de rust zelve en een heerlijke droge humor. Je paste daarmee precies in het profiel van de andere mannelijke onderzoekers. De skibril waarmee je als Cyclops steady van pistes gleed was ook legendarisch. **Lotte**, ook jouw gezelligheid tijdens de hardlooprondjes richting de halve marathon van Utrecht en je aanmoediging tijdens de marathon van Berlijn waren onmisbaar. Ik vind het leuk dat we elkaar nu op een andere plek opnieuw tegen zijn gekomen. **Max**, bedankt voor je vele hulp bij de analyses met SAS. Dankzij jou is mij een hoop syntax frustratie gespaard gebleven en kan ik het nu zelf. Ook bedankt voor de keren dat ik bij je mocht neerstrijken op je aerobed en voor de muzikale momenten met zanger Rinus… yes, yes, yes. **Meike** en **Romy**, jullie zijn onafscheidelijke matties die ik moeilijk los van elkaar kan zien. Dank voor jullie vrolijke en gezellige inbreng tijdens en na het werk. **Mike**, een collega die altijd in is voor een goede grap. Maar als jij stil wordt dan moet je oppassen want dan broeit er wat. Ik heb dan ook regelmatig gelachen op momenten dat je uit de hoek kwam met een gewaagde opmerking. **Mirjam**, in mijn laatste maand als onderzoeker zorgde jij ervoor dat ik niet altijd de vroegste was. Het is daarom jammer dat je niet al twee jaar geleden bent begonnen want dan had ik niet het eerste uur zo alleen gezeten. **Mirthe**, jouw spontaniteit, vrolijkheid en impulsiviteit zijn ongekend en je weet altijd een goed feestje te bouwen. Ook met jou heb ik genoten van de trainingsrondjes in de vroege ochtend, ook al was het soms even wachten tot je kwam. Op een gegeven moment moest je even geprikkeld worden maar uiteindelijk stond je er en hebben we Berlijn met z'n drieën gehaald. Ik hoop dat we elkaar nog vaak tegen zullen komen. **Nicolette**, bedankt voor jouw presentaties over predictie modellen. Ik heb daar veel nuttige dingen van opgestoken en kunnen gebruiken voor mijn eigen onderzoek. Natuurlijk ook bedankt voor de leuke tijd op D2 oost. **Suzanne**, toen je net begon had je het af en toe zwaar te verduren met bijna alleen maar mannen om je heen. Je hebt je mannetje gestaan en gelukkig ook veel mee kunnen lachen. **Tim**, de koorbal van het stel, wat heb ik gelachen om jouw droge humor. Ook op de momenten van gedeelde smart of wanneer alleen jou of mij iets tegen zat. Bedankt ook voor jouw bijdrage aan de EndoRings studie, ik weet dat je het met plezier gedaan hebt. Super dat

je samen met je vriendin mijn paranimf wilt zijn! **Wouter**, je hebt weleens gezegd dat je in het begin je plekje moest vinden, maar met jouw grote mond en grove humor was dit snel voor elkaar. Jouw lijfspreuk "shit rolls downhill" staat in mijn geheugen gegrift.

**Melek**, **Harinakshi** en **Eelco** dank voor jullie onmiskenbare bijdrage aan enkele studies. Het is fijn voor een promovendus om hulp te krijgen van gemotiveerde studenten. Ik wens jullie veel succes in de toekomst.

**Linda**, **Marja**, **Cora** en **Paul**, dank voor jullie hulp bij het inplannen van coloscopie tijd voor studiepatiënten. Zonder jullie medewerking zou dit absoluut onmogelijk zijn geweest.

**Familie en vrienden**, bedankt voor jullie liefde, gezelligheid in mijn vrije tijd en voor jullie interesse in mijn werk. Jullie wisten dat ik onderzoek deed naar iets met darmkanker. Ik hoop dat de Nederlandse samenvatting jullie nog wat meer duidelijkheid schept.

Lieve **vader**, **moeder** en **zusje**, jullie liefde, steun en stimulans zijn de redenen dat ik hier nu sta. Ik ben jullie zeer veel dank verschuldigd en ik hou van jullie.

Allerliefste **Maaike**, jij geeft mijn leven kleur. Jouw grenzeloze geduld, steun, vrolijkheid en liefde zijn van onschatbare waarde. Ik hoop dat we samen oud worden en met elkaar mogen genieten van het leven. Ik hou van je!

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## CURRICULUM VITAE

Vincent Kristian Dik werd geboren op 2 januari 1986 te Heerhugowaard. Hij volgde aldaar het VWO op het Han Fortmann college en behaalde zijn diploma in 2004. Daarna studeerde hij geneeskunde op de Vrije Universiteit in Amsterdam. Zijn wetenschappelijke stage deed hij op de afdeling reumatologie onder begeleiding van dr. M.J. Peters en dr. M.T. Nurmohamed, welke resulteerde in zijn eerste wetenschappelijke publicatie. Tijdens zijn studie deed hij in samenwerking met dr. A.A. van Bodegraven en prof. dr. C.J. Mulder onderzoek op de afdeling maag-, darm en leverziekten van het VU medisch centrum in Amsterdam en liep hij een co-schap hepatologie in het Queen's Elizabeth Hospital in Birmingham (Verenigd Koninkrijk) en een co-schap spoedeisende hulp in het Kalafong Hospital in Pretoria (Zuid-Afrika). Na zijn studie is hij begonnen aan een promotietraject op de afdeling maag-, darm- en leverziekten van het Universitair Medisch Centrum Utrecht onder begeleiding van prof. dr. P.D. Siersema, dr. M.G.H. van Oijen en dr. H.B. Bueno-de-Mesquita. In april 2014 is hij gestart met de opleiding tot maag-, darm- en leverarts (opleiders dr. B. Oldenburg en dr. R. Timmer). Momenteel doorloopt hij de vooropleiding interne geneeskunde in het Meander Medisch Centrum in Amersfoort (opleider dr. R. Fijnheer).