Risk and survival for colorectal cancer in northern Sweden

Sociodemographic factors and surveillance programs

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To my family
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Abstract

Background
Colorectal cancer (CRC) – i.e., cancer in the colon or rectum – is one of the most common cancers both globally and in Sweden. The risk for CRC is mainly related to age, heredity, and life-style risk factors. Previous studies have also demonstrated that individuals with lower socioeconomic status (SES), living alone, or far from care facilities may have a higher risk for CRC or a worse outcome. In contrast to life-style or sociodemographic-associated risks, an inherited risk for CRC is difficult to modify. However, colonoscopic surveillance programs can be help prevent CRC in families with a known hereditary risk.

The Northern Health Care Region (northern Sweden) is the most sparsely populated region in Sweden, and travel distances to care can be long. The population in Northern Sweden is on average older and has lower SES compared with the rest of the country. The impact of these sociodemographic differences on CRC in northern Sweden is not well known.

Aim
This thesis analyses CRC in a northern Sweden setting with regards to incidence, survival, and associated sociodemographic risk factors, including prevention for individuals with increased hereditary risk.

Methods
Papers I and II, cohort studies from the Risk North database, link individual data from health care registers to other sociodemographic registers. In Paper I, the incidence, mortality, and survival for all CRC cases in northern Sweden were compared with the rest of Sweden for the period 2007-2013. Uni- and multivariable Cox regression analysis were used to assess the impact of sociodemographic factors and tumour stage on survival by calculating hazard ratios (HR). In Paper II, we analysed any association between travel time to care and CRC survival in northern Sweden during 2007-2013 using the same type of Cox regression analysis.

Papers III and IV are based on a cohort of individuals with a family history of CRC, prospectively recorded from 1995 to 2012 in the colonoscopic surveillance register at the Cancer Prevention Clinic at Umeå University Hospital. In Paper III, we evaluated the cancer preventive effect of the performed colonoscopic surveillance. Observed cases of CRC were compared to a cohort estimate of cases without surveillance. Compliance with surveillance and colonoscopic quality was also analysed. In Paper IV, we examined the cost-effectiveness of the colonoscopic surveillance program in Paper III. A cost-utility analysis with a societal perspective was used and the stability of the results was tested in a sensitivity analysis.
Results

The age-adjusted incidence in colon cancer was 12.7% lower in northern compared to southern Sweden or 35.9/100 000 vs. 41.1/100 000 person years (p < 0.01). For rectal cancer, the incidence was 10.5% lower in the north (17.6 vs. 19.7 p < 0.01). In subgroup analysis, the largest difference in incidence between northern and southern Sweden was found among individuals > 79 years age (colon - 190 vs. 237 = 19.6%, rectal 72.4 vs. 88.0 = 17.7%). For all of Sweden, the incidence in colorectal cancer was higher in males, individuals with lower SES, or individuals living alone.

In univariable analyses of survival (all-cause and cause-specific) for colon and rectal cancer patients in all of Sweden, patients with high SES or co-habiting had a significantly better outcome compared to patients with low SES or living alone. HR for death ranged from 0.60 to 0.85 in the better-favoured risk group. No differences in colon or rectal cancer survival between northern and southern Sweden were demonstrated in the univariable analysis.

However, in multivariable survival analysis, all-cause survival for colon cancer patients was better in southern Sweden (HR 0.92; 95% CI 0.86 – 0.97). For cause-specific survival for colon cancer or in any analysis for rectal cancer, no differences between northern and southern Sweden were demonstrated. In analysis of travel time, no association between travel time and survival was found.

In the evaluation of the colonoscopic surveillance programme, one case of CRC was observed, compared to 9.5-10.5 expected cases. Standardised Incidence Ratio (SIR) between observed and expected cases of CRC was 0.10 (CI 95% 0.0012–0.53) to 0.11 (CI 95% 0.0014–0.59. The compliance to the surveillance program was 90%. The adenoma detection rate was 14%, and 10% of the examinations were incomplete. In the cost-utility analysis, the net cost for surveillance was 233 038 €, while saving 64.8 Quality Adjusted Life Years (QALYs) compared to non-surveillance. The resulting Incremental Cost-Effectiveness Ratio (ICER) was 3596 €/QALY, ranging from -4620 €/QALY in the best-case scenario to 33 779 €/QALY in the worst-case scenario.

Conclusion

The incidence of CRC was lower in northern Sweden and most evident in the elderly, raising questions on differences in life-style between northern and southern Sweden in the past. There were considerable sociodemographic disparities in CRC survival in Sweden, including a lower all-cause survival for colon cancer patients in the north. In this study, travel time to care in northern Sweden did not affect survival and the lower all-cause survival in northern Sweden cannot be fully explained. The colonoscopic surveillance of families in northern Sweden with inherited risk for CRC had a good cancer preventive effect, including a high cost-effectiveness. The reasons for the good effect may be high compliance, since the quality of the colonoscopies was moderate.
Original Papers

This thesis is based on the following Papers:


II. Sjöström O, Dahlin A, Silander G, Syk I, Melin B, Hellquist BN. Travel time to care and colorectal cancer survival – a cohort study from the Risk North database. In manuscript.


**Abbreviations**

**APC** - Adenomatous polyposis coli

**CDR** - Cause of death register

**CRC** – Colorectal cancer

**CT**- Computed tomography

**FAP** - Familial adenomatous polyposis

**FCRC** – Familial Colorectal Cancer

**FDR** - First-degree relative

**FIT** - Faecal immunochemical test

**GD** - Geography database

**HCRC** – Hereditary Colorectal Cancer

**HR** – Hazard Ratio

**HRA** – High-risk adenoma

**IBD** - Inflammatory Bowel Disease

**ICER** - Incremental Cost-Effectiveness Ratio

**LISA** - Longitudinal integration database for health insurance and labour market studies

**MRI** - Magnetic resonance imaging

**MSI** – Micro satellite instability

**MMR** – Mismatch Repair

**NREV** - Swedish National Register for Oesophageal and Gastric Cancer

**QALY** - Quality-adjusted life years
RCC – Regional Cancer Centre

SCB – Statistics Sweden

SCRCR - Swedish Colorectal Cancer Registry

SES – Socioeconomic status

SIR - Standard Incidence Ratios

TPR - Total Population Register

WLR - Weighted Log Rank Test
Enkel sammanfattning på svenska

Bakgrund


Syfte

Att undersöka kolorektalcancer i norra Sverige – om hur utbildningsnivå, att leva ensam eller långt från sjukhus påverkar antalet nyinsjuknade (risken) eller överlevnaden i sjukdomen. Dessutom att utvärdera om ett program med regelbundna koloskopiundersökningar kan förhindra ärlig kolorektalcancer.

Metod


Resultat

Antalet nyinsjuknade per år, d.v.s. risk att få kolorektalcancer, var över 10 % lägre i norra jämfört med södra Sverige, trots att utbildningsnivån var högre i södra Sverige. Största skillnaden i risk mellan norra och södra Sverige fanns bland människor över 79 år.

I hela Sverige var överlevnaden sämre för ensamboende patienter eller de med låg utbildningsnivå. I en överlevnadsanalys som jämför norra och södra Sverige, fanns inga skillnader i risken att dö i tjock- eller ändtarmscancer för patienter som diagnosticerats med en sådan cancer (sjukdomsspecifik överlevnad). Däremot hade patienter med tjocktarmscancer i norra Sverige en sämre överlevnad om man inkluderar alla dödsorsaker(total överlevnad). För ändtarmscancer fanns inga skillnader i total överlevnad. Avståndet till sjukhus påverkade inte överlevnaden.

Utvärderingen av koloskopiprogrammet för individer med misstänkt ärfilt kolorektalcancer visade att endast 1 person av 261 undersökta fick cancer jämfört med ett förväntat antal av ca 10 personer under studietiden. I kostnadseffektivitetsanalysen av programmet var kostnaden för att rädda ett s.k. kvalitetsjusterat levnadsår ca 36 000 kr.

Slutsats

Background

Epidemiology

**Incidence**
Colorectal cancer (CRC) – cancer in the colon or rectum – is a common form of cancer. In an estimate of worldwide cancer incidence and mortality from 2012, CRC accounted for 1.4 million new cases and 700 000 deaths.\(^1\)

In Sweden, almost 4700 new cases of colon cancer and 2150 new cases of rectal cancer were diagnosed in 2016.\(^2\) During the same year, colon and rectal cancer accounted for about 2700 and 800 deaths, respectively. In total, CRC was the fourth most common cancer in Sweden, with a lifetime risk of about 5%. CRC was also the second most common cancer cause of death in Sweden.\(^3\) The incidence of CRC increases strongly with age (Figure 1): the Swedish median age at diagnosis was 74 for colon cancer and 71 for rectal cancer.

![Figure 1. Incidence/100 000 individuals (crude rate) for colorectal cancer by age in Sweden in 2016. Data from the National Board of Health and Welfare.\(^4\)](image)

Historically, the incidence in CRC has been highest in the developed countries of the west. In the last few decades, there has been a global trend of increasing incidence closely linked to economic development.\(^5\) This increase is due not only to demographic ageing, but also to the acquisition of western life-style risk factors for CRC.\(^6\)
However, in some high-income countries, such as the USA or Germany, the incidence of CRC is decreasing. This decline has been attributed to prevention through effective CRC screening. In Sweden, which is yet to start nationwide CRC screening, the CRC incidence is still increasing (Figure 2).

Figure 2. Time trends for age standardised CRC incidence and mortality in Sweden. Data from the National Board of Health and Welfare.
Risk factors for colorectal cancer

The higher incidence of CRC in the elderly, males, and high-income countries could be expressed as being older, being male, and living a western life-style are risk factors for developing CRC. Table 1 provides a summary of some of the most important known risk factors for CRC. The strongest increases in risk are found for risk factors difficult to influence, such as age, family history for CRC, and inflammatory bowel disease (IBD). A more moderate increase in risk is demonstrated for factors associated to life-style such as diabetes, obesity, alcohol consumption, smoking, and intake of red and processed meat. There are also preventive factors that reduce the risk for developing CRC associated to life-style factors such as physical activity and high intake of dairy and fibre products. On an individual level, risk or preventive factors often occur simultaneously and interact. At the population level, there is no single risk factor – apart from age – that is attributed to most cases of CRC. Life-style risk factors for CRC are common and despite a moderate increase in relative risk, together they account for a large proportion of CRC cases.
Table 1. Risk and preventive factors for developing CRC.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Relative Risk for CRC</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>5 to 7 times risk increase</td>
<td>Age group 50-54 vs. 70-74, Sweden 2014-2016</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.33</td>
<td>Males vs. Females USA 2000-2014</td>
</tr>
<tr>
<td>Family history of CRC</td>
<td>2.24 (95% CI 2.06 to 2.43)</td>
<td>1 affected first-degree relative (FDR)</td>
</tr>
<tr>
<td></td>
<td>3.97 (95% CI 2.60 to 6.06)</td>
<td>≥ 2 affected FDRs</td>
</tr>
<tr>
<td>Inflammatory bowel disease (IBD)</td>
<td>2.93 (95% CI 1.79-4.81)</td>
<td>Ulcerative colitis and Mb Crohn vs. non IBD</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.28 (95% CI 1.19-1.39)</td>
<td>Diabetes vs. non Diabetes</td>
</tr>
<tr>
<td>Body Height</td>
<td>1.05 (95% CI 1.02 – 1.07)</td>
<td>Per 5 cm</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.18 (95% CI 1.11-1.25)</td>
<td>Smokers vs. never smokers</td>
</tr>
<tr>
<td>Alcohol</td>
<td>1.07 (95% CI 1.05 – 1.08)</td>
<td>Per 10 g/day</td>
</tr>
<tr>
<td>Obesity</td>
<td>1.08 (95% CI 1.04 – 1.11)</td>
<td>Males</td>
</tr>
<tr>
<td></td>
<td>1.05 (95% CI 1.02 – 1.02)</td>
<td>Females&lt;br&gt;Per 5/kg m² above BMI</td>
</tr>
<tr>
<td>Red meat</td>
<td>1.12 (95% CI 1.00 – 1.25)</td>
<td>Per 100 g/day</td>
</tr>
<tr>
<td>Processed meat</td>
<td>1.16 (95% CI 1.08 – 1.26)</td>
<td>Per 50g/day</td>
</tr>
<tr>
<td>Whole grain</td>
<td>0.83 (95% CI 0.78 – 0.89)</td>
<td>Per 90 g/day</td>
</tr>
<tr>
<td>Dietary fibers</td>
<td>0.93 (95% CI 0.87 – 1.00)</td>
<td>Per 10 g/day</td>
</tr>
<tr>
<td>Diary products</td>
<td>0.84 (0.80-0.89)</td>
<td>Males</td>
</tr>
<tr>
<td></td>
<td>0.86 (0.78-0.96)</td>
<td>Females&lt;br&gt;Per 400 g/day</td>
</tr>
</tbody>
</table>
**Mortality and survival**

In many high-income countries with still increasing CRC incidence, such as Sweden, the mortality in CRC has nevertheless decreased (Figure 2). Hence, the survival rates for patients with CRC has improved, probably due to better treatment and efforts for early detection.  

Survival for patients with CRC can be measured with regards to all causes of death (i.e., as all-cause or overall survival) or as cause-specific survival (i.e., the possibility of surviving just CRC). However, since CRC is a disease mainly affecting elderly patients, overall survival can be greatly influenced by comorbidities, as they are competing risks for death.  

Relative survival can be considered as a hybrid between all-cause and cause-specific survival. To calculate relative survival in CRC, the overall survival for a studied group is divided by the survival for a similar group without CRC. The relative survival is then an indirect measure of cause-specific survival in CRC. In Sweden in 2016, the five-year relative survival rates for colon cancer were 64.2% in males and 67.6% in females. For rectal cancer, the five-year relative survival rate was approximately 66% for both sexes.  

The most important disease-specific prognostic factor for CRC survival is tumour stage at diagnosis. In patients with only localised CRC at diagnosis (stage I-II), the five-year relative survival rate is approximately 90% in Sweden. For patients with already distant metastasis (stage IV) at diagnosis, the survival rate is only 10 to 20%.  

A number of factors that influence the risk for CRC are also prognostic factors in CRC. Both smoking and excessive alcohol consumption have been associated with lower survival. Physical activity, on the other hand, may have a favourable effect on outcome.  

**Disparities in colorectal cancer**

Differences in health between groups, which “systematically and negatively impact less advantaged groups”, are often referred to as disparities. These disparities can be based on ethnicity, gender, and socioeconomic status (SES). A person’s SES is often measured by income, education, and occupation, alone or in combination.  

In the U.S., low SES has been associated with higher risk for CRC. The opposite relationship has been found in Europe, where low SES has been associated with lower risk for CRC.
In Europe, low SES has historically been associated with low BMI and traditional diets with low risk for CRC, but these patterns are changing.\textsuperscript{24, 25}

For CRC survival, there is a consistent global pattern of poorer outcome in patients with lower SES.\textsuperscript{25} The possible association between CRC incidence or survival and SES could be mediated through several mechanisms: differences in life-style factors or co-morbidities, differences in access to care (including screening), and differences in treatment.

Other factors have also been associated with CRC disparities. Social support in terms of living together or being married has been associated with lower risk for CRC or CRC death, although the results are not totally consistent.\textsuperscript{26-29} Long travel time to care has also been associated with worse outcome in CRC.\textsuperscript{30-32} Whether this is a consequence of lower access to care and/or lower SES in remote areas is not fully understood.

**Cancer disparities in Sweden**

Sweden has a universal health care system that aims to provide equal health to all its citizens irrespective of SES or residence. Despite these goals, reports from the National Board of Health and Welfare and The Swedish Cancer Society have demonstrated considerable disparities in cancer health in Sweden.\textsuperscript{3, 33, 34} In CRC, worse outcome in patients with low SES have been shown in several studies.\textsuperscript{35-37} Reports also indicate geographical differences, both regarding incidence and survival.\textsuperscript{34}

The Northern Health Region in Sweden, consisting of the four northern-most county councils in the country, have been shown to have a generally lower incidence of cancer compared with the rest of the country.\textsuperscript{34} However, reports also indicate a lower survival for many types of cancers in the same region.\textsuperscript{34-38} The reasons for these differences (e.g., for CRC between the Northern Health Care Region (northern Sweden) and the rest of Sweden) are neither fully known nor have they been investigated. Northern Sweden differs in many other aspects from the rest of Sweden: the population is older, has lower SES, and travel distances to health care can be long.\textsuperscript{39}

Thus, the cause of possible CRC disparities between the northern and southern Sweden might be complex, probably reflecting multiple interacting differences in factors related to health care, life-style, demography, and socioeconomy.
Colorectal development

The causes for CRC are heterogeneous and multifactorial even at the genetic level. On average, each CRC has about 80 mutations, although a more limited number of genes are thought to be the necessary “drivers” in oncogenesis.\textsuperscript{40, 41} There are several theories that are used to classify CRC development into distinct separate pathways to cancer.\textsuperscript{42-45}

Historically, CRC oncogenesis has been classified according to the adenoma-carcinoma sequence or pathway, which holds for a majority of CRC cases.\textsuperscript{42, 46} This sequence consists of a stepwise progression from normal bowel epithelium through the development of an increasingly advanced adenoma and finally a carcinoma. The entire sequence is considered to be slow – up to ten years from a normal epithelium to cancer.\textsuperscript{5}

Each step in the morphological progression to cancer is caused by a set of genetic alterations.\textsuperscript{42} Early in this sequence, the tumour suppressor gene adenomatous polyposis (APC) mutates and these mutations are found in a majority of all CRCs. Other important sequel genetic events in this pathway are activations of the KRAS oncogene and inactivation of the TP53 tumour suppressor gene. These mutations often changes the amount of chromosomal material or structure of chromosomes in the cancer cell – i.e., chromosomal instability. Therefore, this pathway is referred to as either the chromosomal instability pathway or the microsatellite stable pathway. The latter term is to distinguish it from the other major pathway to CRC – the microsatellite instability pathway.\textsuperscript{43, 44} On a molecular level, cancers in this pathway are characterised by a more diffuse genomic instability – microsatellite instability (MSI) – caused by mutations in mismatch repair (MMR) suppressor genes. Activating mutations in the BRAF oncogene are also a common feature in this pathway.

An alternative, to some extent overlapping, classification is according to methylation status of the CpG islands promoter regions in the cancer cell’s genome.\textsuperscript{44, 47, 48} In these regions, hypermethylation results in CRCs characterised by gene silencing, predominately of tumour suppressor genes. According to this classification, some CRCs originate from flat so-called sessile serrated adenomas instead of ordinary adenomatous polyps. The progress from a sessile serrated adenoma to carcinoma is also considered to be faster.\textsuperscript{47, 49}

Knowledge about CRC oncogenesis is important for several reasons: the adenoma-carcinoma pathway is the fundament for CRC prevention by detection and polypectomy of precursor adenomas; understanding molecular pathogenesis helps us understand the genetic background of inherited forms of
CRC and targets for therapy; and genetic markers can provide information on both prognosis and therapy response.

Another a question regarding colorectal oncogenesis, is whether CRC is one disease in the bowel epithelium or two separate diseases – colon and rectal cancer. The differences in anatomy between the colon and the rectum have great clinical implications in terms of management. There is also growing evidence that colon and rectal cancers to some extent are different even on a molecular level. However, for this thesis, colon and rectal cancer can be considered so highly related that they can be discussed as one disease – CRC.

**Diagnosis of colorectal cancer**

Sporadic CRC is a disease that develops slowly over several years. Diffuse symptoms such as anaemia, changed bowels habits, rectal bleeding, or weight loss gradually worsen. Finally, the symptoms are more distinct, and the patient is referred for bowel examination by colonoscopy or x-ray. However, about 20% of all colon cancer cases present as an emergency due to bowel obstruction, bleeding, or perforation, often coinciding with an advanced tumour stage at presentation. The emergency presentation in itself is also a risk factor for worse outcome. Consequently, early diagnosis is important to avoid both emergency operations and late tumour stage at diagnosis.

One way to achieve early diagnosis or even prevention is through CRC screening in the general population. Screening is something employed in an average risk population, whereas surveillance follow-ups, as described later in this thesis, are used for individuals at increased risk for disease.

In international clinical practice, CRC screening is mainly performed using one of three methods: faecal occult blood tests, sigmoidoscopy, or complete colonoscopy. Numerous studies have shown that these methods are effective in preventive CRC. However, it has yet to be determined which of these methods has the best mortality reduction and cost-effectiveness. In Sweden, the Stockholm-Gotland Health Care Region implemented CRC screening in 2008. This screening uses biennial faecal occult blood tests for individuals aged 60-69 followed by colonoscopy for individuals with positive faecal test.
In 2014, the National Board of Health and Welfare in Sweden recommended nationwide CRC screening using biennial faecal blood tests for individuals aged 60–74 years, but this recommendation has not been implemented. Instead, an almost nation-wide large randomised clinical trial called SCREESCO (NCT02078804) has been running that compares faecal occult blood tests and colonoscopy results. The primary results in terms of reduction in mortality from CRC in the Swedish population are expected in 15 years.

Endoscopy has a major advantage over faecal blood test thanks to a higher sensitivity for pre-cursor adenomas – i.e., a higher possibility of prevention and not just early diagnosis. Colonoscopy does have some drawbacks: the patient has to endure laxation and discomfort during the procedure, the examination takes time and resources, and there is a risk, albeit small, for complications. These disadvantages may result in low patient compliance to screening/surveillance or a low cost-effectiveness per CRC prevented. To balance the disadvantages, it is important to maximise the potential gain from each colonoscopy by ensuring high quality examinations.

If an adenoma is detected by colonoscopy, the standard procedure is to remove the adenoma by endoscopic polypectomy and send the adenoma for histopathological analysis. Traditional adenomas have been classified according to size, morphology (tubular, tubulo-villous, and villous), and dysplasia. Advanced or high-risk adenomas for developing CRC have often been defined as > 10 mm in diameter or with high-grade dysplasia or with a villous component > 20%. Serrated lesions have their own classification system.

Another way of achieving early diagnosis is to increase the awareness of CRC’s diffuse symptomatology both among the population and the health care sector, including the facilitation of swift referrals for colonoscopy. The need for early CRC diagnosis is one of the reasons for establishing standardised cancer patient pathways such as the NICE pathways in the U.K., Pakkeføllopp in Denmark, and Standardiserade Vårdförlöpp in Sweden.

In the elective setting, diagnosis of CRC is verified through histopathological analysis from endoscopic biopsies. The next step in the diagnostic work-up process is to stage the cancer according to the TNM classification system by diagnostic imaging (Tables 2 & 3). About 20% of all patients in Sweden have distant metastases (M-stage) at diagnosis (Table 4). The most common metastasis location is the liver, followed by the lungs. The stage of the primary tumour is assessed regarding local invasion (T stage) and lymph node involvement (N-stage). The current guidelines for CRC in Sweden recommends Computed Tomography (CT) for staging with the addition of Magnetic Resonance Imaging (MRI) in rectal cancer.
Once the diagnostic work-up is complete, decisions on recommended treatment can be made.73 Today, according to the Swedish national guidelines, treatment decisions are usually made by multidisciplinary teams that include surgeons, oncologists, radiologists, pathologists, and specialist nurses. Most patients with colon cancer (stage I-III), are recommended curative surgery without neoadjuvant therapy. Patients with rectal cancer are often recommended neoadjuvant therapy depending on, for example, the height from the anal verge and T and N stage. For rectal cancer, neo-adjuvant therapy includes radiation, sometimes in combination with chemotherapy, then followed by curative surgery. Neo-adjuvant chemotherapy can also be an option for locally-advanced non-direct resectable colon cancers. CRC patients with distant metastases (stage IV) are assessed whether curative surgery of the metastases is possible, directly or after neoadjuvant therapy. The overall assessment that a CRC is curable is mostly based on the extent of the distant metastases. However, many elderly patients may have a theoretically curable CRC, but are too fragile and have too many co-morbidities for curative treatment.

Table 2. Simplified UICC TNM classification of CRC according local invasion depth (T-stage), regional lymph node involvement (N-stage), and distant metastases (M-stage).75

<table>
<thead>
<tr>
<th>T stage</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tx</td>
<td>No information available.</td>
</tr>
<tr>
<td>Tis</td>
<td>Tumour restricted to mucosa(in situ).</td>
</tr>
<tr>
<td>T1</td>
<td>Infiltration into submucosa</td>
</tr>
<tr>
<td>T2</td>
<td>Infiltration into, but not beyond, lamina muscularis propia.</td>
</tr>
<tr>
<td>T3</td>
<td>Infiltration beyond lamina muscularis propia, but not into the serosa or neighbouring organs.</td>
</tr>
<tr>
<td>T4</td>
<td>Infiltration of the serosa or neighbouring organs.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>N stage</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nx</td>
<td>No information available.</td>
</tr>
<tr>
<td>No</td>
<td>No lymph node involvement.</td>
</tr>
<tr>
<td>N1</td>
<td>Cancer cells in 1-3 regional lymph nodes.</td>
</tr>
<tr>
<td>N2</td>
<td>Cancer cells in &gt; 3 regional lymph nodes.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>M-stage</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mx</td>
<td>No information available.</td>
</tr>
<tr>
<td>M0</td>
<td>No detectable distant metastases.</td>
</tr>
<tr>
<td>M1</td>
<td>Metastasis to distant organ or distant lymph node.</td>
</tr>
</tbody>
</table>
**Table 3.** Simplified overall stage classification for CRC according to UICC by combination of stages for local invasion (T), regional lymph node involvement (N), and distant metastases (M).\textsuperscript{75}

<table>
<thead>
<tr>
<th>Overall stage</th>
<th>T-stage</th>
<th>N-stage</th>
<th>M-stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>Tis</td>
<td>No</td>
<td>Mo</td>
</tr>
<tr>
<td>Stage I</td>
<td>T1/T2</td>
<td>No</td>
<td>Mo</td>
</tr>
<tr>
<td>Stage II</td>
<td>T3/T4</td>
<td>No</td>
<td>Mo</td>
</tr>
<tr>
<td>Stage III</td>
<td>Any</td>
<td>N1/N2</td>
<td>Mo</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Any</td>
<td>Any</td>
<td>M1</td>
</tr>
</tbody>
</table>

**Table 4.** Overall tumour stage at diagnosis in Sweden for patients with colon cancer between 2007 and 2011\textsuperscript{52} and rectal cancer between 1995 and 2005\textsuperscript{55}. Proportion of patients in each stage is given. Stage 0 is not included.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Colon cancer</th>
<th>Rectal cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>11.9 %</td>
<td>20.3 %</td>
</tr>
<tr>
<td>II</td>
<td>29.9 %</td>
<td>25.3 %</td>
</tr>
<tr>
<td>III</td>
<td>25.7 %</td>
<td>25.5 %</td>
</tr>
<tr>
<td>IV</td>
<td>19.9 %</td>
<td>16.6 %</td>
</tr>
<tr>
<td>Missing</td>
<td>12.7 %</td>
<td>12.3 %</td>
</tr>
</tbody>
</table>
Treatment of colorectal cancer

**Surgery**
The fundament for curing patients with CRC is to achieve surgery with clear resected margins – i.e., the removal of all cancer tissue with the margins.\(^74\)

In rectal cancer, the standard evidence-based surgical procedure is total mesorectal excision.\(^73, 76\) That is, the rectum and the surrounding fatty lymphovascular tissue (the mesorectum) are resected. In low rectal tumours, an anastomosis to reconstruct the bowel continuity is sometimes unfeasible and the patient receives a permanent stoma.

Colon cancer surgery includes segmental resection of the colon segment with the tumour, including the mesocolon, with the lymph vessel, which is followed, in the majority of cases, by the construction of a bowel anastomosis.\(^52, 77\) There is insufficient data on how extensive the mesocolon excision should be, but some surgeons propose complete excision of the meso also in colon cancer.\(^74\) Surgery of resectable metastases can be performed before, at the same time (liver), or after the operation of the primary tumour in the bowel.

In Sweden, elective CRC surgery is associated with a postoperative mortality of a couple percent.\(^17, 18\) Following emergency surgery, mortality is much higher. The overall post-operative morbidity is high, up to 20-25%, reflecting not only procedure-related risks, but also the fragility in terms of age and co-morbidity for many CRC patients.\(^78\)

**Chemotherapy**
In the current Swedish guidelines for CRC, adjuvant chemotherapy to reduce the risk for relapse is recommended for colon cancer patients in tumour stage III and high-risk patients in stage II.\(^73\) Traditionally, the risk for recurrence within three to five years from diagnosis has been estimated to be approximately 50% in stage III.\(^79\) Standard adjuvant treatment with fluorouracil in combination with oxaliplatin reduces the risk of occurrence by half.\(^80\) For rectal cancer, there is less evidence for the effectiveness of adjuvant therapy, but practices resemble guidelines for colon cancer.

The growing knowledge of the molecular pathogenesis of CRC has increased the possibilities to customize chemotherapy for gene expression in the individual tumour.\(^48\) Tumours showing a high grade MSI are thought to have a better overall prognosis, but probably have a lesser response to fluorouracil chemotherapy.\(^81, 82\) Mutation in the *KRAS* or *BRAF* genes can be used to predict response to more modern chemotherapy such as antibody therapy.\(^5, 83\)
Palliative chemotherapy for incurable patients can slow down progression of CRC and delay death for months or even years. The decision to use palliative options is a delicate balance of risks and benefits for the individual patient as this decision should consider the prognosis as well as the patient’s attitude, quality of life, and ability to cope with side effects.

**Equalising colorectal cancer treatment in Sweden**

Over the last few decades, the medical community and governmental bodies in Sweden have taken several measures to improve and equalise CRC care. The Swedish Rectal Cancer Registry was started in 1995, followed by the Colon Cancer Registry in 2007, which later merged to form the Swedish Colorectal Cancer Registry (SCRCR). The registry aims to improve the quality of CRC care in Sweden. Hospitals use the data in the registry to assess and compare their results with other hospitals, information that they can use to make improvements in their care protocols. Recently, a general trend towards better and more equal outcomes has been noticed. CRC surgery, particularly rectal surgery, has also been centralised to fewer hospitals. National guidelines for CRC care are produced and revised regularly; the most recent revision was in 2016. Regional Cancer Centres have also been established to ensure well-functioning cancer care in the whole country. Despite these efforts, reports indicate worse outcomes in parts of the Northern Health Care Region compared to the rest of Sweden. As previously stated, these regional cancer disparities have rarely been described and analysed.
Family history and colorectal cancer

From 10 to 30% of all patients with CRC report close relatives with the same disease (Figure 3). However, the family history for many CRC patients is just a coincidence as sporadic (not inherited) CRC is a common disease. The risk for an inherited form of CRC increases with the number of relatives with the same disease, closeness of kinship, and young age at diagnosis in the family.

Figure 3. Aetiology and heredity in CRC

A strong dominant pattern of inheritance, as shown in the pedigree in Figure 4, indicates a hereditary colorectal cancer (HCRC) with a probable monogenic cause. This dominant pattern is found in less than 5% of all patients with CRC. For the majority of patients, any familial clustering is less extensive. Suspected inherited CRC in families with a lesser history of CRC are often referred to as familial colorectal cancer (FCRC). There are no globally accepted definitions for HCRC or FCRC. In this thesis, we define HCRC and FCRC according to definitions in Table 5. These definitions indicate that the family history for FCRC corresponds to at least a doubled life-time risk for CRC (10% rather than 5%). The estimations of familial risk for CRC are based on a metanalysis from Butterworth et al.
Table 5. Definitions for familial and hereditary colorectal cancer used in this study

<table>
<thead>
<tr>
<th>Familial colorectal cancer (FCRC)</th>
<th>≥ 2 First or second-degree relatives with CRC with diagnosis received before the age of 70. No mutations have been found or genetic testing has not been performed.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hereditary colorectal cancer (HCRC)</td>
<td>Families who fulfil the Amsterdam criteria I or II (Table 6) and families with a mutation for a known genetic syndrome regardless of family history.</td>
</tr>
</tbody>
</table>

Hereditary colorectal cancer (HCRC)

The most well-known or common forms of HCRC are familial adenomatosis polyposis (FAP) and Lynch syndrome (also referred to as Hereditary nonpolyposis colorectal cancer, HNPCC). More uncommon or less-known forms of HCRC are Juvenile polyposis syndrome, Peutz-Jeghers syndrome and MYH-associated polyposis.

Familial adenomatosis polyposis (FAP) accounts for less than 1% of all CRC. FAP is caused by germline mutations in the APC gene. The mutations give rise to massive colonic polyposis as early as in adolescence, often resulting in early colectomy to prevent an almost 100% risk for CRC. FAP also exists in a milder form – attenuated FAP – with a slightly lower risk for CRC.

Lynch syndrome, the most common form of HCRC, accounts for 1 to 7% of all CRCs. The syndrome is caused by germline mutation in one of the mismatch-repair genes (MMR), which results in microsatellite instability (MSI) in the genome. The following MMR genes have so far been identified as mutated in Lynch syndrome: MLH1, MSH2, MSH6, or PMS2. At birth, the patients have a germline mutation in one allele in a MMR gene. Oncogenesis can start if the other normal allele becomes somatically inactivated during the patient’s life.

For individuals with Lynch syndrome, the lifetime risk for CRC can be over 80%, including an elevated risk for cancers in the endometrium, stomach, ovary, ureter/renal-pelvis, brain, small bowel, hepatobiliary tract, and the skin. In Lynch syndrome, most CRCs are localized in proximal colon, unlike sporadic CRCs, which are mostly localised distal of the splenic flexure. The mean age at diagnosis in Lynch syndrome is about 45 years, and the adenoma-carcinoma sequence is accelerated to two to three years from a colon adenoma to cancer.
The Amsterdam criteria have been formulated to recognise and diagnose families with Lynch syndrome (Table 3). When Amsterdam criteria are used as diagnostic criteria for Lynch syndrome, the syndrome accounts for 1-6% of all CRCs, with a mean age at diagnosis of 45 years. If molecular screening for mutations in MMR is performed in un-selected patients with CRC, 2 – 7 % have Lynch syndrome.

There are families who fulfil Amsterdam criteria I but have no mutated MMR genes. These families are sometimes called Familial colorectal cancer type X although it is a HCRC and not a FCRC according to the definitions used in this thesis. The X stands for unknown cause, and the group includes both families with yet undiagnosed monogenetic disorders and those with multifactorial background in terms of gene-environmental interaction.

**Table 6. Amsterdam I and II criteria for Lynch syndrome**

<table>
<thead>
<tr>
<th>Amsterdam I</th>
<th>At least three relatives must have histologically verified colorectal cancer:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• One must be a first-degree relative of the other two.</td>
</tr>
<tr>
<td></td>
<td>• At least two successive generations must be affected.</td>
</tr>
<tr>
<td></td>
<td>• At least one of the relatives with colorectal cancer must have received the diagnosis before the age of 50 years.</td>
</tr>
<tr>
<td></td>
<td>• Familial adenomatous polyposis must have been excluded.</td>
</tr>
<tr>
<td>Amsterdam II</td>
<td>At least three relatives must have a cancer associated with hereditary non-polyposis colorectal cancer (colorectal, endometrial, stomach, ovary, ureter or renal-pelvis, brain, small-bowel, hepatobiliary tract, or skin [sebaceous tumours]):</td>
</tr>
<tr>
<td></td>
<td>• One must be a first-degree relative of the other two.</td>
</tr>
<tr>
<td></td>
<td>• At least two successive generations must be affected.</td>
</tr>
<tr>
<td></td>
<td>• At least one of the relatives with colorectal cancer must have received the diagnosis before the age of 50.</td>
</tr>
<tr>
<td></td>
<td>• Familial adenomatous polyposis must have been excluded.</td>
</tr>
<tr>
<td></td>
<td>• Tumours should be verified whenever possible.</td>
</tr>
</tbody>
</table>
Figure 4. Fictive pedigree example from a family with Lynch syndrome. Proband (arrow) is the individual initiating the investigations. The proband’s sister was diagnosed with rectal cancer at age 56, their mother with colon cancer at age 55, their aunt with colon cancer at age 72, and their deceased grandfather with rectal cancer at age 45. Consequently, the pedigree fulfills Amsterdam criteria I. Subsequent analyses of tumour material show that the proband’s sister and mother are MSI positive (high). The aunt’s colon cancer was sporadic and no tumour material was available from the grandfather. DNA sequencing reveals that the proband and the proband’s mother, sister, and daughter are carriers of MSH1, a known mutation causing Lynch Syndrome.
**Familial colorectal cancer (FCRC)**

As previously mentioned, FCRC has no universal or exact definition. The concept comprises families with greater aggregation of CRC than normal, but less compared to true HCRC syndromes such as Lynch syndrome. The less dominant pattern of inheritance in FCRC can indicate a multifactorial genetic causality or a greater significance of gene-environmental interaction and gene penetrance. No specific genetic causes have so far been identified in FCRC.\

**Genetic counselling**

The purpose for genetic counselling with families with clustering of CRC is to estimate the risk for cancer and thus the need for prevention through regular colonoscopies (i.e., colonoscopic surveillance). The basis for the risk assessment is family history. If the family history strongly suggests HCRC, genetic testing for known genetic syndromes is performed. The genetic testing can be performed both on tumour material from CRC cases in the family and DNA sequencing of family members at risk for CRC.

**Prevention of inherited colorectal cancer**

The primary aim of a colonoscopic surveillance program for inherited CRC is to detect and remove advanced adenomas before they progress to cancer. For families with HCRC, with or without a verified genetic syndrome (Lynch syndrome), several studies have shown that colonoscopic surveillance of the family members reduces the risk for CRC and mortality. Most modern surveillance programs for families with Lynch syndrome recommend colonoscopy from 20 to 25 years, with an interval of one to two years. Prevention of FAP and other HCRC syndromes is outside the scope of this thesis.

For FCRC, the scientific evidence for surveillance is less. Guidelines and expert opinions often recommend surveillance when family history indicates at least a double lifetime risk (10% rather than 5%) for CRC. A doubled lifetime risk corresponds to the necessary family history to fulfil the definition for FCRC used in this thesis.

The recommendations on how to perform surveillance for FCRC vary. Most guidelines try to subdivide FCRC according to risk. Families with higher risks are often recommended to start colonoscopies with some margin about the age of disease onset in the family and then every three to six years. For members in low risk families, a single colonoscopy is sometimes considered to be sufficient.
However, intensive surveillance programs aiming to achieve high sensitivity for detecting adenomas may come at the price of many colonoscopy without findings and thus a high cost per CRC prevented. In FCRC, there are no genetic tests to identify the carriers for inherited cancer risk within family; consequently, all family members are recommended surveillance regardless of their true individual risk for CRC. This holds also for families with HCRC of unknown genetic cause. However, no studies have investigated the cost-effectiveness of existing surveillance programs.

In the Northern Health Care Region in Sweden, genetic counselling and risk assessment is centralised to the Cancer Prevention Clinic at Umeå University Hospital. The colonoscopic surveillance is decentralised to the hospitals throughout the region. The Cancer Prevention Clinic coordinates the surveillance, including reminding letters if examinations are not performed. All individuals who are recommended surveillance due to HCRC or FCRC have been prospectively recorded since 1995 in a register at the Cancer Prevention Clinic. The recommended surveillance for the individuals in the register has never been evaluated for cancer prevention effectiveness or for cost effectiveness.

In health economics, cost-effectiveness analyses are methods to relate the costs to the effects (outcomes) for a health care intervention, such as a new drug or a surveillance program for inherited CRC. Cost-effectiveness analysis can be used to compare different health care interventions in order to allocate resources for maximal health gained in a population. In Sweden, cost-effectiveness analyses are often performed as cost-utility analyses. A cost-utility analysis can be considered as a special form of cost-effectiveness analysis, although the terms are sometimes used interchangeable. In a cost-utility analysis, the effect of a health care intervention – i.e., colonoscopic surveillance compared to no surveillance – is measured in utilities, often in saved quality adjusted life years (QALYs). The result in a cost-utility analysis can be expressed as the incremental cost-effectiveness ratio (ICER) in cost/QALY saved. The ICERs can be used as a measure of cost-effectiveness of different health care interventions. Many countries or health care systems have more or less established thresholds, expressed as ICERs, that determine whether new treatments or health technologies should be adopted. However, the National Board of Health and Welfare in Sweden uses the following threshold in their national guidelines: less than 100 000 SEK per QALY saved is considered a low cost intervention, 100 000 – 500 000 SEK is considered a moderate cost but generally acceptable, 500 000 – 1000 000 SEK is a high cost, and over 1 000 000 SEK per QALY is a very high cost.
Aims

This thesis investigates CRC in a northern Sweden with regards to incidence, survival, and associated sociodemographic risk factors, including prevention for individuals with increased hereditary risk.

The specific aims of the included papers are described below:

I. To analyse sociodemographic disparities in CRC, especially between the Northern Health Care Region and the rest of Sweden to identify risk groups or regions with different incidence or survival.

II. To analyse a possible association between the patient’s travel time to the nearest hospital and CRC survival in the Northern Health Care Region.

III. To evaluate a surveillance programme in the Northern Health Care Region for individuals with increased hereditary risk for CRC regarding cancer prevention effect, compliance to surveillance, and colonoscopic quality.

IV. To investigate whether the surveillance programme in the Northern Health Care Region for individuals with increased hereditary risk for CRC is a cost-effective method to prevent CRC.
## Materials and Methods

This thesis is based on four Papers with material from two data sources. An overview of the material and methods is given in Table 7.

*Table 7. Summary of main research questions and study designs for all included Papers.*

<table>
<thead>
<tr>
<th>Paper</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Main research question</td>
<td>Are there disparities in CRC between the Northern Health Care Region and the rest of Sweden?</td>
<td>Is survival for CRC patients associated with travel time to their nearest hospital?</td>
<td>Does colonoscopic surveillance of individuals with FCRC or HCRC prevent CRC?</td>
<td>Is colonoscopic surveillance of individuals with FCRC or HCRC cost-effective?</td>
</tr>
<tr>
<td>Type of study</td>
<td>Register based cohort study</td>
<td>Register based cohort study</td>
<td>Prospective register based study</td>
<td>Cost-utility analysis</td>
</tr>
<tr>
<td>Data source</td>
<td>Risk North database</td>
<td>Risk North database</td>
<td>Colonoscopic surveillance register</td>
<td>Colonoscopic surveillance register</td>
</tr>
<tr>
<td>N</td>
<td>41325</td>
<td>3718</td>
<td>261</td>
<td>259</td>
</tr>
<tr>
<td>Inclusion criteria</td>
<td>Diagnosis of CRC.</td>
<td>Diagnosis of CRC and residing in the Northern Health Care Region</td>
<td>FCRC or HCRC</td>
<td>FCRC or HCRC</td>
</tr>
<tr>
<td>Main Outcome Measures</td>
<td>Differences in incidence and survival.</td>
<td>Difference in CRC specific survival between patients with different travel time to their nearest hospital.</td>
<td>Observed findings of CRC with surveillance compared to expected cases without surveillance.</td>
<td>Incremental cost-effectiveness ratio (ICER) between surveillance and non-surveillance.</td>
</tr>
</tbody>
</table>
**Material Papers I and II**

Papers I and II are based on data from the Risk North database. A brief general account of the entire Risk North project and database will be given followed by a description of the specific data from the Risk North used in each paper.

**The Risk North database**

The Risk North database was created at the Regional Cancer Centre (RCC Norr) in Umeå to study regional cancer disparities in the Northern Health Care Region.

The core of the Risk North is individual data on all patients (both in northern and southern Sweden) registered in three national cancer quality registers supported by RCC Norr: the Swedish Colorectal Cancer Registry (SCRCR) between 2007 and 2013, the Swedish National Register for Oesophageal and Gastric Cancer (NREV) between 2006 and 2012, and the National Quality Registry for Brain Tumours between 2009 and 2013.

Individual data from the quality registers are linked to information from other demographic and health care registers such as place of residence, socioeconomic status, or co-morbidity (Figure 5). The link is possible thanks to the unique personal identity number of every person residing in Sweden.
Figure 5. The Risk North database – linkage and included registers.
**Data from the Risk North database used in Papers I and II**

Paper I studied differences in incidence, mortality, and survival in CRC between the Northern Health Care Region and the rest of Sweden. The study population in Paper I was all patients in Sweden with a new colorectal cancer diagnosis registered in the SCRCR and thus in the Risk North database during between 2007 and 2013. Paper II studied a possible association between travel time to care and survival for patients with colorectal cancer in the Northern Health Care Region. The study cohort in Paper II was all patients in the Northern Health Care Region registered with a new colorectal cancer in the SCRCR and consequently in the Risk North database from 2007 to 2013.

In addition to the information from the SCRCR in Risk North, we used linked information in Risk North originating from four other registers: The cause of death register (CDR), the Longitudinal integration database for health insurance and labour market studies (LISA, Swedish acronym), the Geography database (GD), and the Total population register (TPR). All originating register sources to the variables used from Risk North are described below.

**The Swedish Colorectal Cancer Registry (SCRCR)**

The SCRCR is a development and a merge of the national quality registry for rectal cancer started in 1995 and the registry for colon cancer started in 2007. The registry contains individual data on diagnostic work-ups and findings, treatment, and outcomes, resulting in over 100 variables.

In Paper I, we used the SCRCR to collect the following data: age, gender, date of CRC diagnosis, and whether the patient had metastases at the time of diagnosis (M0 or M1). In addition, we used data from the SCRCR to calculate incidence and mortality rates. In Paper II, we used additional data on tumour stage, operating hospital, and elective or emergency surgery. Tumour stage in the SCRCR is according to the Union for International Cancer Control (UICC) TNM classification 7th edition (before 2009, the 6th edition was used).

The SCRCR records include both the clinical tumour staging of preoperative investigations (cTNM) and the histopathological staging (pTNM) of surgical specimens. Tumour stage was computed according to the following algorithm: Data on T and N were primarily based on histopathology; if histopathology was missing – i.e., the patient is not operated – the clinical stage is used. Data on M was primarily based on the clinical stage. Emergency surgery, according to definitions in the SCRCR, is an operation caused by an acute medical condition during an unplanned hospital admission.
The cause of death registry (CDR)

The CDR at the National Board of Health and Welfare, as the name suggests, registers the cause of death for every death in Sweden and includes underlying diseases and date of death. Data from the CDR were used in Papers I and II to calculate mortality and survival. We defined cause-specific death in CRC if colon or rectal cancer were stated as the main or one of two first contributing causes of death.

The Longitudinal integration database for health insurance and labour market studies (LISA)

The governmental agency Statistics Sweden (SCB) administers the LISA database. LISA's primary aim is to provide data for researchers who investigate the labour market and health insurance, but it has also been used for medical epidemiological research. LISA contains data on income, employment, residence, and education on all persons 16 years and older residing in Sweden. The database is updated on a yearly basis.

In both Papers I and II, the study subjects’ educational level and cohabiting status were determined using information from LISA. Education was divided into three levels: low (up to nine years of compulsory school); middle (two to three years of secondary education; and high (university). We did not include children (<18 years) in calculations for educational level.

Cohabiting status – living alone vs. not living alone – was defined whether another person was living at the same address as the study subject the year before colorectal cancer diagnosis. The time – the year before diagnosis rather than the year of diagnosis – was chosen to avoid changes in co-habiting status caused by the diagnosis.

The Geography database (GD)

The GD, at SCB contains geographical coordinates of residence for all persons residing in Sweden. The coordinates delivered to the Risk North database have a precision of 250 x 250 m in urban areas and 1000 x 1000 m elsewhere. Similar to co-habiting status, residence the year before diagnosis was used. In Paper I, data from the GD was used to determine whether the patient was living in the Northern Health Care Region. For Paper II, the coordinates were used to calculate travel time to hospital.
The total population register (TPR)

The TPR is also at SCB and includes, among other data, personal identity number, gender, and age of all individuals living in Sweden. Information in the TPR was used to calculate incidence and mortality rates and co-habiting status (together with information from the SCRCR and LISA, respectively – see above).

Methods Paper I

Paper I is mainly a descriptive study on CRC disparities that compares incidence, mortality, and survival rates in Northern Health Care Region with the rest of Sweden. Based on the Swedish population in 2000, we calculated age-adjusted incidence and mortality rates in total and for sub-groups based on age, gender, co-habiting status, and level of education. A patient with synchronous tumours of the same type was counted as one new case for each tumour. We used Chi-square tests to compare categorical data (α=0.05). Calculations of baseline demographic differences between the north and south were based on public data from SCB.

The survival analysis started with a univariable Cox proportional hazard regression analysis to explore each co-variable (region, age, gender, co-habiting status, education level, and M-stage) association to all-cause and cause-specific survival. Additional weighted log rank tests were performed for variables where the proportional hazard assumption for Cox regression analysis was violated. The univariable analysis was not included in the already published version of Paper I.

Survival was further explored with a multivariable Cox regression analysis to estimate hazard ratios between northern and southern Sweden, stratified over gender and age in 10-year groups and adjusted for co-habiting status, educational level, and M-stage. In the already published version of Paper I, the multivariable Cox regression analysis was stratified for M-stage and not adjusted for M-stage. All patients in the survival analysis were followed until death or 31 December 2014 (end of follow-up). We used R version 3.2.3 for all calculations and statistical analysis.
Methods Paper II

Paper II investigated whether travel time to care for patients with CRC was associated with survival. We also analysed some proposed mediating or confounding factors to this association, such as age, level of education (socioeconomic status), co-habiting status, tumour stage, proportion of surgical resection, and emergency operations. A patient with synchronous tumours of the same type was counted as one total new case. Any association between these factors and the patient’s travel time was analysed using Student’s t-test for continuous parametric variables and Spearman’s test for non-parametric ranked variables ($\alpha=0.05$).

Analysis of travel time

Travel time by car was measured from the patient’s registered address to the nearest hospital and, if the patient was operated, to the operating hospital. The nearest hospital was defined as the nearest hospital in the patient’s county council with facilities to diagnose a CRC (i.e., facilities with an endoscopy and/or radiology department).

We used geographical coordinates in the Risk North originally from the GD for the patient’s place of residence. For the hospital coordinates, we used free data from the search engine Eniro.se.

The actual calculation on travel time was performed with ArcGIS® Pro (2.1.2) and ArcGIS online (Esri, Redlands, CA, USA). We created 10-minute interval drive time areas by car from the hospitals, and every patient’s individual driving time was defined with a precision of 10-minute intervals. The lowest value of the 10-minute intervals was used for analyses using travel time as a continuous variable. No adjustment for traffic was made.

Analysis of survival

The proposed association between travel time and survival was analysed by estimating hazard ratios for patients with different travel times – first in a univariate model using univariate Cox regression analysis and Kaplan Meier estimates and then using a multiple Cox regression analysis to take into account possible cofounders and mediators.
The multiple Cox regression analysis was stratified by age (10-year groups) and gender and adjusted for educational level, co-habiting status, tumour stage, and emergency operation. Using our main multiple regression model, we compared differences in colon cancer and rectal cancer specific survival for operated patients. Colon or rectal cancer specific survival was defined as the time from the CRC diagnosis to date of death caused by colorectal cancer. Patients were censored at time of death due to other causes or at end of follow-up (31 December 2014).

For sensitivity analysis, we performed the multiple regression model for survival in five other settings: 1) overall survival — instead of cause-specific survival; 2) colorectal cancer survival — instead of colon and rectal cancer specific separately; 3) survival analysis without adjusting for tumour stage and emergency operations; 4) survival analysis while excluding patients with tumour stage IV; and 5) analysing survival and association with travel time to the operating instead of the nearest hospital.

**Material Papers III and IV**

Paper III and IV are based on the same cohort of individuals in the Northern Health Care Region recorded in the Colonoscopic Surveillance Register at the Cancer Prevention Clinic at Umeå University Hospital between 1 January 1995 and 1 September 2012. In both Papers III and IV, colon and rectal cancer are handled as one phenomenon — CRC.

Since 1995, the colonoscopic surveillance register prospectively records all individuals with FCRC or HCRC who the Cancer Prevention Clinic recommended colonoscopic surveillance. The register contains both basic information such as age, gender, and address as well as data on estimated cancer risk (i.e., recommended surveillance) and results of any genetic testing. In addition, the register records the results of the recommended colonoscopies and reasons for incomplete examinations.

We classified all individuals in this register into six groups according to their risk for CRC (Table 8). Individuals in risk group 1 and 4 together with subjects with prior CRC were not included in the study. We considered risk group 1 as having a too low CRC risk, and the surveillance of known APC carriers (risk group 4) was outside the study objective.
**Table 8.** Classification of CRC risk and recommended surveillance by the Cancer Prevention Clinic in Umeå.

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Family History (FDR = First-degree relative)</th>
<th>Recommended surveillance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Familial colorectal cancer (FRCR)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1*</td>
<td>At least two relatives** with CRC diagnosed over age 70</td>
<td>Individually</td>
</tr>
<tr>
<td>2</td>
<td>2 FDR with CRC diagnosed under age 70</td>
<td>Start of surveillance 5–10 years before the age of first diagnosed CRC case in the family, thereafter every 5 years.</td>
</tr>
<tr>
<td>3a</td>
<td>3 FDR with CRC diagnosed under age 70</td>
<td>—/—</td>
</tr>
<tr>
<td>3b</td>
<td>Fulfilling all Amsterdam criteria except one</td>
<td>—/—</td>
</tr>
<tr>
<td><strong>Hereditary colorectal cancer (HCRC)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3c</td>
<td>Fulfilling Amsterdam Criteria or MSI positive or MMR mutation regardless of family history</td>
<td>Start of surveillance at age 25, thereafter every second year.</td>
</tr>
<tr>
<td>4*</td>
<td>Known APC carrier***</td>
<td>Start of surveillance at age 12, thereafter every second year.</td>
</tr>
</tbody>
</table>

* Excluded from analysis
** First- or second-degree relatives
*** Familial adenomatous polyposis (FAP) or Attenuated familial adenomatous polyposis (AFAP)
Methods Paper III

The main research question in Paper III was whether colonoscopic surveillance of individuals with FCRC and HCRC is associated with the prevention of CRC. The corresponding main outcome measure was observed findings of CRC with surveillance in the study cohort from 1 January 1995 to 1 September 2012, compared to expected cases without surveillance. To validate findings of CRC, all study subjects were cross-checked with the Regional Cancer Registry.

To estimate the expected cases of CRC without surveillance, we performed a cohort analysis based on age-specific CRC incidence rates for the general population in Sweden and age-specific relative risks according to CRC heredity proposed by Dowe-Edwin et al. The set of relative risks from Dowe-Edwin et al. is given in three categories—lowest, best, and highest estimate of CRC risk.

We used two different methods – A and B – to calculate the expected cases of CRC; however, both methods are based on the same above-mentioned data from Dowe-Edwin et al. In method A, we used Excel® for Mac to multiply person-years at risk by appropriate age-specific population incidence rates and relative risk according to family history of CRC. For method B, we used an already developed program for cancer incidence calculations – Person Years (PYRS).

To compare observed vs. expected cases of CRC, we used Byar’s formula to calculate two tailed standard incidence ratios (SIR) with 95% confidence intervals.

Secondary outcome measures were colonoscopic findings of high-risk adenomas (HRA), the study subject’s compliance to recommended surveillance, and the quality of the colonoscopies. We defined HRA as an adenoma ≥ 10 mm in diameter or with villous histology or with high-grade dysplasia.

We used Independent t-test or Chi square test to compare baseline characteristics in different risk groups and binary logistic regression to analyse findings at surveillance colonoscopies. When appropriate, the regression analysis was adjusted for gender, age, and risk. We used IBM®Statistics SPSS® version 20 and 22 for Mac for the statistical analysis.
**Methods Paper IV**

Paper IV evaluates the cost-effectiveness of the surveillance for FCRC and HCRC in Paper III using a cost-utility analysis with a contra factual design. Real costs and effects of the surveillance during the study period are compared to expected costs (i.e., contra factual costs) and effects without surveillance. This approach produced two comparable alternatives: surveillance vs. non-surveillance (Figure 6).

![Diagram of cost-utility analysis](image)

**Figure 6. Model for the contra factual design of the cost-utility analysis comparing colonoscopic surveillance vs. non-surveillance to calculate the Incremental cost effectiveness ratio (ICER).**

The calculations of the costs for each alternative were performed with a societal perspective – i.e., costs both for the health care sector and all other sectors in the society were considered and included. The estimations on the effects of surveillance were based on differences in CRC cases between surveillance and non-surveillance translated into differences in age- and sexspecific remaining quality-adjusted life years (QALYs). Finally, the Incremental cost-effectiveness ratio (ICER) between the two comparable alternatives surveillance versus non-surveillance could be calculated as the ratios between the increase in cost and increase in effectiveness (cost per QALY gained).
Calculation of costs

We created a model to calculate costs, guided by national guidelines for CRC care and cost tariffs from the collaborations of Swedish county councils. The tariffs were chosen as they supposedly reflect real costs for the county councils. However, for some inputs on costs, we used estimations from health care staff and departments. All calculations on costs were performed in Euros at the exchange rate from December 2015 (1€ ≈ 9.2 SEK). For details of the model input and costs assumptions, see Table 9.

The costs for genetic counselling, testing, and the surveillance register were actual costs from the budget of the Cancer Prevention Clinic in Umeå during the study period. This includes costs for all referred patients to the clinic with possible inherited CRC, not just those with recommended surveillance. The inclusion of costs for all referred patients enabled us to study the cost-effectiveness of maintaining a surveillance programme with a population health perspective.

Calculations of QALYs

We calculated the cohorts’ remaining QALYs from the year the study subjects entered the study (i.e., their first planned colonoscopy) to their expected year of death and the health-related quality of life (HRQoL) during the remaining years. The estimations on remaining lifetime (year of death) and HRQoL were based on Swedish age- and gender-specific data. The amounts for the loss of QALYs due to CRC were taken from stage-specific data by Hess et al. and Ness et al. (Table 10).
### Table 9. Model inputs for calculation on costs

<table>
<thead>
<tr>
<th>Health care costs per unit or patient (€), price level 2015</th>
<th>Price (€)</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Colonoscopy</strong></td>
<td>616</td>
<td>Tariff scale Northern Health Care Region 2015[^17]</td>
</tr>
<tr>
<td><strong>Addition for colonoscopy with polypectomy</strong></td>
<td>594</td>
<td>Tariff scale Southern Health Care Region 2015[^18]</td>
</tr>
<tr>
<td><strong>Diagnostic work up CRC[^A]</strong></td>
<td>1224</td>
<td>Tariff scale Southern Health Care Region 2015[^18]</td>
</tr>
<tr>
<td><strong>Curative Surgery[^B]</strong></td>
<td>19 565</td>
<td>Tariff scale Northern Health Care Region 2015[^17]</td>
</tr>
<tr>
<td><strong>Adjuvant chemotherapy[^C]</strong></td>
<td>11 866</td>
<td>National Board of Health and Welfare Sweden 2014[^109]</td>
</tr>
<tr>
<td><strong>Palliative care[^D]</strong></td>
<td>88 744</td>
<td>National Board of Health and Welfare Sweden 2014[^109]</td>
</tr>
<tr>
<td><strong>Follow up CRC[^E]</strong></td>
<td>2272</td>
<td>National Board of Health and Welfare Sweden 2014[^109] and Tariff scale Southern Health Care Region 2015[^18]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Societal costs for loss of production in absence from work per unit or patient and mean income 2015 in Sweden</th>
<th>Loss of production</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Genetic counselling</strong></td>
<td>2-h absence from work</td>
</tr>
<tr>
<td><strong>Colonoscopy</strong></td>
<td>4-h absence from work</td>
</tr>
<tr>
<td><strong>CRC-Diagnostic work up, operation and convalescence</strong></td>
<td>2-month absence from work</td>
</tr>
<tr>
<td><strong>Adjuvant chemotherapy[^C]</strong></td>
<td>6-month absence from work</td>
</tr>
<tr>
<td><strong>Terminal care</strong></td>
<td>12-month absence from work</td>
</tr>
<tr>
<td><strong>Follow-up[^E]</strong></td>
<td>20-h absence from work</td>
</tr>
</tbody>
</table>

**Mean income/h[^G]**                                        | 26 €       | SCB[^39] |

[^A]: Diagnostic work up includes imaging and preoperative visits.
[^B]: Based on an expected case mix colon/rectal cancer and men/women.
[^C]: Standard combination therapy oxaliplatin/5-Fu 12 cycles, only for stage III patients.
[^D]: Includes possible palliative surgery and/or chemotherapy.
[^E]: Annual CT scan and return visits for three years, and colonoscopy three years after operation and then every fifth year up to 75 years, according to national guidelines.
[^F]: Costs were converted to the 2015 price level.
[^G]: Mean income for individuals age 20-64 years, including social fees and taxes.
We did not include possible losses of QALYs from the surveillance colonoscopies. Previous studies have shown the impact on quality of life from a colonoscopy is short and thus very small in a lifetime perspective.\textsuperscript{119,120}

**Sensitivity analysis**

We performed a sensitivity analysis by varying model inputs in our base case model, constructing worst-case and best-case scenarios for the cost-effectiveness of surveillance. In a worst-case scenario, the incidence of CRC is low without surveillance, combined with high costs for surveillance and low costs for CRC care. For this scenario, we used the following values: lowest estimate from Paper III of expected cases of CRC without surveillance; 25% increase of costs for the surveillance program; 100% increase in absence from work for the colonoscopies; 25% decrease of health care CRC costs; and 25% decrease in absence from work for CRC care. The best-case scenario is a high incidence of CRC without surveillance, low costs for surveillance, and high cost for CRC care. In this scenario, we used the highest estimate of expected CRC and decreased health care costs for surveillance by 25%, while leaving absence from work due colonoscopies unchanged. Costs and absence of work for CRC care were increased by 25%. In both the worst-case and the best-case scenarios, the study subjects’ mean income were varied by ± 25% where appropriate to achieve the largest impact.
Ethics


Like most Swedish research based on quality registers, the studies in Papers I and II were performed without informed consent from the study subjects. The benefits of large-scale epidemiological research are considered to outweigh the disadvantages, as informed consent from 10,000 patients is practically unfeasible. Patients – i.e., potential study subjects – are not asked by their caregiver if they want to be registered in a quality register, but they must actively request not to be registered. However, the caregiver must provide general information about the quality register and give the patient an opportunity to decline registration. As no interventions were done in Papers I and II, the greatest potential risk for harming the study subjects is a breach of confidentiality. In the Risk North database, anonymity is protected. The data from the quality register was first sent to SCB, who constructed an individual code key and serial number for each study subject. The holders of all registers contributing to RiskNorr used the code key and serial number to link individual data. Finally, the complete and now anonymised dataset was delivered and is kept within the Risk North database at the Department of Radiations Sciences at Umeå University in a securely locked part of the department at the Regional Cancer Centre North.

In Papers III and IV, the study subjects gave informed consent to be registered in the colonoscopic surveillance registry at the Cancer Prevention Clinic in Umeå. To protect anonymity, special family and subject numbers are used for each individual. A list matching each individual’s subject number to his or her personal identification number is kept at the clinic. The register data are kept in a securely locked part of the Regional Cancer Centre North in Umeå.
Results

Results Paper I

Differences in baseline demographics between the populations in the Northern Health Care Region vs. the rest of Sweden.

During our study period, the population in the Northern Health Care Region represented 9% of Sweden’s total population (mean population 877,670/9,411,305). In northern Sweden, 28% of the population was over 59 years old compared to 24% in the southern Sweden (Figure 7). Mean age in northern Sweden was 42.7; mean age in southern Sweden was 41 years. The proportion of high level education was higher in southern Sweden (32%) than in northern Sweden (27%), whereas a larger share of the population in northern Sweden had a medium level of education (north – 48%; south – 43%). About the same share of the population were living alone in both northern and southern Sweden (north – 19%; south – 18%).

Figure 7. Distribution of age, co-habiting status, and level of education in northern and southern Sweden
Overall sociodemographic differences in colorectal cancer incidence in Sweden

During the study period, 27,820 cases of colon cancer were reported – 2,561 in northern and 25,259 in southern Sweden. For rectal cancer, 13,505 cases were reported – 1,264 in northern and 12,241 in southern Sweden. Mean age at diagnosis for colon cancer was 73 years in northern and 72 years in southern Sweden. For rectal cancer, the mean age at diagnosis was 70 years in southern and 69 years in northern Sweden.

Throughout Sweden, the incidence in colon and rectal cancer was higher in males than females and higher in individuals living alone than co-habiting (Table 11). The incidence also differed by education level – subjects with low education had higher incidence.

Table 11. Age-adjusted incidence per 100,000 person-years for colon and rectal cancer in Sweden (2007-2013) by gender, co-habiting status, and level of education.

<table>
<thead>
<tr>
<th>Incidence</th>
<th>Colon Cancer</th>
<th>Rectal Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td><strong>40.6</strong></td>
<td><strong>19.5</strong></td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>37.7</td>
<td>14.8</td>
</tr>
<tr>
<td>Male</td>
<td>44.5</td>
<td>25.1</td>
</tr>
<tr>
<td><strong>p-value</strong></td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Cohabiting status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Living alone</td>
<td>55.0</td>
<td>26.3</td>
</tr>
<tr>
<td>Not living alone</td>
<td>35.5</td>
<td>19.3</td>
</tr>
<tr>
<td><strong>p-value</strong></td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Education level</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>42.7</td>
<td>21.5</td>
</tr>
<tr>
<td>Medium</td>
<td>40.7</td>
<td>19.6</td>
</tr>
<tr>
<td>High</td>
<td>40.9</td>
<td>16.7</td>
</tr>
<tr>
<td><strong>p-value</strong></td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>
Differences in colorectal cancer incidence and mortality between northern and southern Sweden

The overall age-adjusted incidence/100 000 person-years in colon cancer was 12.7 % lower in northern Sweden than in the southern Sweden (35.9/100 000 vs. 41.1/100 000 p< 0.01). For rectal cancer, the incidence was 10.5% lower in northern Sweden (17.6/100 000 vs. 19.7/100 000 p<0.01).

In subgroup analysis for colon cancer, the difference in incidence between northern and southern Sweden was significant in all subgroups except for the youngest (i.e., aged 0-59). The largest difference was found among the oldest individuals (aged > 79 – 190/100 000 vs. 237/100 000; 19.6%) (Table 12).

In sub-group analysis for rectal cancer, the largest difference in incidence between northern and southern Sweden was also found in persons > 79 years old (72.4/100 000 vs. 88.0/100 000; 17.7%). In total, the incidence was significantly lower in northern Sweden in 8 out of 13 sub-groups for rectal cancer (Table 12).

The proportion of metastatic disease at diagnosis for colon cancer was 551/2561 (=21.5%) northern Sweden and 5655/25259 (=22.3%) in southern Sweden. In rectal cancer, 260/1264 (20.6%) of the patients in the north had metastases at diagnosis, compared to 2675/12241 (21.9%) in the south (Table 11).

The overall age-adjusted mortality in colon cancer was 10.0% lower in northern than southern Sweden (11.0/100 000 vs. 12.2/100 000; p=0.01). For rectal cancer, the mortality was 9.5% lower in northern Sweden (5.33/100 000 vs. 5.89/100 000).
**Table 12.** Comparison of the age-adjusted incidence per 100,000 person-years in colon and rectal cancer (2007-2013) in northern and southern Sweden.

<table>
<thead>
<tr>
<th>Incidence</th>
<th>Colon cancer</th>
<th>Rectal Cancer</th>
<th>P</th>
<th>Northern (n)</th>
<th>Southern (n)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age all</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-59</td>
<td>7.08 (314)</td>
<td>7.51 (3380)</td>
<td>0.33</td>
<td>5.16 (229)</td>
<td>4.89 (2203)</td>
<td>0.46</td>
</tr>
<tr>
<td>60-69</td>
<td>76.67 (626)</td>
<td>82.05 (5911)</td>
<td>0.11</td>
<td>45.68 (373)</td>
<td>48.83 (3518)</td>
<td>0.23</td>
</tr>
<tr>
<td>70-79</td>
<td>176.29 (950)</td>
<td>195.85 (8584)</td>
<td>&lt;0.01</td>
<td>75.53 (407)</td>
<td>86.20 (3778)</td>
<td>0.01</td>
</tr>
<tr>
<td>80+</td>
<td>190.46 (671)</td>
<td>236.88 (7384)</td>
<td>&lt;0.01</td>
<td>72.38 (253)</td>
<td>87.97 (2742)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>33.85 (1292)</td>
<td>38.03 (12784)</td>
<td>&lt;0.01</td>
<td>13.39 (502)</td>
<td>14.99 (5011)</td>
<td>0.02</td>
</tr>
<tr>
<td>Male</td>
<td>38.38 (1263)</td>
<td>45.09 (12443)</td>
<td>&lt;0.01</td>
<td>22.50 (757)</td>
<td>25.37 (7216)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Cohabiting status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Living alone</td>
<td>50.90 (1124)</td>
<td>55.28 (10975)</td>
<td>&lt;0.01</td>
<td>24.85 (498)</td>
<td>26.48 (4921)</td>
<td>0.18</td>
</tr>
<tr>
<td>Not living alone</td>
<td>30.99 (1437)</td>
<td>35.95 (14286)</td>
<td>&lt;0.01</td>
<td>15.92 (766)</td>
<td>17.49 (7320)</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Education</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>39.00 (1108)</td>
<td>43.02 (10435)</td>
<td>&lt;0.01</td>
<td>18.69 (486)</td>
<td>21.87 (5004)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Medium</td>
<td>34.21 (994)</td>
<td>41.46 (9278)</td>
<td>&lt;0.01</td>
<td>18.17 (555)</td>
<td>19.79 (457)</td>
<td>0.06</td>
</tr>
<tr>
<td>High</td>
<td>35.28 (447)</td>
<td>41.35 (5192)</td>
<td>&lt;0.01</td>
<td>15.21 (217)</td>
<td>16.82 (2427)</td>
<td>0.17</td>
</tr>
<tr>
<td><strong>Metastatic disease</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>7.66 (551)</td>
<td>9.14 (5655)</td>
<td>&lt;0.01</td>
<td>3.63 (260)</td>
<td>4.30 (2675)</td>
<td>0.01</td>
</tr>
<tr>
<td>No</td>
<td>24.57 (1751)</td>
<td>28.32 (17375)</td>
<td>&lt;0.01</td>
<td>13.11 (941)</td>
<td>14.43 (8966)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Comparison with p-values – overall and for different subgroups. (n=number of patients). Sums (n) for subgroups may not match the total due to missing data.

* Low: up to nine years of compulsory school; Medium: secondary education 2-3 years; High: university or college education.

** At the time of CRC diagnosis.
Sociodemographic differences in survival for colorectal cancer patients in Sweden

Univariable survival analysis

In univariable analysis of all-cause and cause-specific survival for colon cancer and rectal cancer patients separately for all of Sweden, increasing age, low education (SES), and living alone were associated with lower survival in all analyses (Tables 13 & 14). Male gender was associated to lower all-cause survival, but not to cause-specific survival. The univariable analysis revealed no differences in either all-cause or cause-specific survival for colon or rectal cancer between northern and southern Sweden (Table 13 & 14).

Table 13. Univariable analysis of all-cause survival for colon and rectal cancer patients in Sweden (2007-2013). HR estimated in a Cox regression model. Additional weighted log rank tests (WLR) were performed for analyses where the proportional assumption for Cox regression was violated.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Subgroup</th>
<th>Colon Cancer</th>
<th>Rectal Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Region</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Northern Sweden (ref)</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Southern Sweden</td>
<td>0.96 [0.91-1.02]</td>
<td>1.05 [0.95 - 1.15]</td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.02 [1.01 - 1.02]</td>
<td>1.04 [1.04 - 1.04]</td>
<td></td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (ref)</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>0.94 [0.91-0.98][a]</td>
<td>0.94 [0.89 - 0.99]</td>
<td></td>
</tr>
<tr>
<td><strong>Education level</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medium</td>
<td>0.79 [0.76 - 0.82][b]</td>
<td>0.73 [0.69 - 0.78]</td>
<td></td>
</tr>
<tr>
<td>Higher</td>
<td>0.68 [0.65 - 0.71][b]</td>
<td>0.60 [0.56 - 0.65]</td>
<td></td>
</tr>
<tr>
<td><strong>Cohabitation status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Living alone (ref)</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Not living alone</td>
<td>0.73 [0.70 - 0.75][c]</td>
<td>0.69 [0.65 - 0.72][d]</td>
<td></td>
</tr>
<tr>
<td><strong>M-stage at diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M0(ref)</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>M1</td>
<td>5.46 [5.25 - 5.67]</td>
<td>5.65 [5.34 - 5.98]</td>
<td></td>
</tr>
<tr>
<td>Mx[e]</td>
<td>1.41 [1.30 - 1.52]</td>
<td>1.85 [1.62 - 2.11]</td>
<td></td>
</tr>
</tbody>
</table>

[a] WLR p<0.01
[b] WLR p<0.01; low education vs. medium and high
[c] WLR p <0.01
[d] WLR p < 0.01
[e] Mx Includes both not staged patients and patients with missing data on stage.
Table 14. Univariable analysis of cause-specific survival for colon and rectal cancer patients in Sweden (2007-2013). HR estimated in a Cox regression model. Additional weighted log rank tests (WLR) were performed for analyses where the proportional assumption for Cox regression was violated.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Subgroup</th>
<th>HR [CI 95%]</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Region</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Northern Sweden (ref)</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Southern Sweden</td>
<td>0.96 [0.90 - 1.04]</td>
<td>0.99 [0.89 - 1.10]</td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.01 [1.01 - 1.01]</td>
<td>b</td>
<td>1.03 [1.02 - 1.03]</td>
<td>c</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male (ref)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>1.00 [0.95 - 1.04]</td>
<td>d</td>
<td>1.02 [0.96 - 1.09]</td>
</tr>
<tr>
<td><strong>Education level</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lower (ref)</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Medium</td>
<td>0.85 [0.81 - 0.89]</td>
<td>e</td>
<td>0.78 [0.73 - 0.84]</td>
</tr>
<tr>
<td></td>
<td>Higher</td>
<td>0.79 [0.74 - 0.84]</td>
<td>f</td>
<td>0.66 [0.61 - 0.73]</td>
</tr>
<tr>
<td><strong>Cohabitation status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Living alone (ref)</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Not living alone</td>
<td>0.79 [0.76 - 0.83]</td>
<td>g</td>
<td>0.73 [0.69 - 0.78]</td>
</tr>
<tr>
<td><strong>M-stage at diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mo (ref)</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mx</td>
<td>1.65 [1.50 - 1.82]</td>
<td>h</td>
<td>1.64 [1.37 - 1.97]</td>
</tr>
</tbody>
</table>

a WLR p=0.32  
b WLR p<0.01  
c WLR p<0.01  
d WLR p=0.10  
e WLR p<0.01; low education vs. medium and high  
f WLR p<0.01; low education vs. medium and high  
g WLR p<0.01  
h WLR p<0.01  
i Mx Includes both not staged patients and patients with missing data on stage.
Multivariable analysis of differences in colorectal cancer survival between Northern and Southern Sweden.

The multivariable survival analyses were stratified for sex and age in ten-year groups and adjusted for education level, cohabiting status, and m-stage. In the analysis of all-cause survival, the outcome was better for colon cancer patients in southern than in northern Sweden (HR 0.92 [CI 95% 0.86 – 0.98]) (Table 15). No differences in all cause survival between the southern and the northern Sweden were demonstrated for rectal cancer (HR 0.99 [CI 95 % 0.90 - 1.09]).

When analysing cause-specific survival, no differences between southern and northern Sweden were demonstrated: colon cancer – HR 0.93 [CI 95% 0.86 - 1.00]; rectal cancer – HR 0.95 [CI 95% 0.85-1.06] (Table 16)

As a sensitivity analysis, we added the variables to the multivariable survival model one at a time and performed repeated survival analysis after each included variable. In the sensitivity analysis for all-cause survival for colon cancer, no differences between northern and southern Sweden were demonstrated before m-stage was added to the model.

Table 15. Analysis of all-cause survival for colon and rectal cancer patients in Sweden (2007-2013). HR estimated in a multivariable Cox regression model stratified over sex and age at diagnosis (10-year groups) and adjusted for education level, cohabitation status, and m-stage.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Subgroup</th>
<th>Colon Cancer</th>
<th>Rectal Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Region</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Northern Sweden (ref)</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Southern Sweden</td>
<td>0.92[0.86 – 0.98]</td>
<td>0.99[0.90 - 1.09]</td>
<td></td>
</tr>
<tr>
<td><strong>Education level</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower (ref)</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Medium</td>
<td>0.91[0.87 – 0.94]</td>
<td>0.89[0.84 - 0.94]</td>
<td></td>
</tr>
<tr>
<td>Higher</td>
<td>0.81[0.76 – 0.85]</td>
<td>0.80[0.74 - 0.87]</td>
<td></td>
</tr>
<tr>
<td><strong>Cohabitation status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Living alone (ref)</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Not living alone</td>
<td>0.80[0.77 - 0.83]</td>
<td>0.80[0.76 - 0.85]</td>
<td></td>
</tr>
<tr>
<td><strong>M-stage at diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M0(ref)</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>M1</td>
<td>6.6 [6.3 -6.8]</td>
<td>6.38[6.03 - 6.76]</td>
<td></td>
</tr>
<tr>
<td>Mx*</td>
<td>1.4[1.3- 1.5]</td>
<td>1.5[1.31 - 1.72]</td>
<td></td>
</tr>
</tbody>
</table>

* Mx Includes both not staged patients and patients with missing data on stage.
Table 16. Analysis of cause-specific survival for colon and rectal cancer patients in Sweden (2007-2013). HR estimated in a multivariable Cox regression model stratified over sex and age at diagnosis (10-year groups) and adjusted for education level, cohabitation status, and m-stage.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Subgroup</th>
<th>HR [CI 95%] Colon Cancer</th>
<th>HR [CI 95%] Rectal Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Region</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Northern Sweden (ref)</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Southern Sweden</td>
<td>0.93 [0.86 - 1.00]</td>
<td>0.95 [0.85 - 1.06]</td>
<td></td>
</tr>
<tr>
<td><strong>Education level</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower (ref)</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Medium</td>
<td>0.91 [0.86 - 0.95]</td>
<td>0.89 [0.83 - 0.96]</td>
<td></td>
</tr>
<tr>
<td>Higher</td>
<td>0.86 [0.81 - 0.92]</td>
<td>0.82 [0.75 - 0.90]</td>
<td></td>
</tr>
<tr>
<td><strong>Cohabitation status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Living alone (ref)</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Not living alone</td>
<td>0.82 [0.78 - 0.86]</td>
<td>0.84 [0.78 - 0.89]</td>
<td></td>
</tr>
<tr>
<td><strong>M-stage at diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M0 (ref)</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>M1</td>
<td>9.73 [9.27 - 10.2]</td>
<td>8.94 [8.36 - 9.56]</td>
<td></td>
</tr>
<tr>
<td>Mx*</td>
<td>1.61 [1.46 - 1.77]</td>
<td>1.36 [1.13 - 1.63]</td>
<td></td>
</tr>
</tbody>
</table>

* Mx Includes both not staged patients and patients with missing data on stage.

Missing data

Data were missing for gender (1.3%), education level (1.3%), and m-stage (7.7%). There were no missing data for co-habiting status. Missing data on m-stage includes both un-staged patients and staged patients with missing data. Missing data on m-stage was 7.6% in southern Sweden and 8.4% in the northern Sweden. The proportion of missing data on m-stage increased by age, in patients > 90 years old; 1142/841 (16.9%) of these patients had no data on m-stage. Date of death was missing for 88 patients.
Results Paper II

Baseline patient characteristics
During the study period (2007-2013), a total of 3721 patients with CRC were diagnosed in the Northern Health Care Region and registered in the Risk North database. The final study population was 3718 patients, as three patients were excluded due to missing geographical coordinates. The study population consisted of 47% females (1737/3718) and 33.8% (1253) of all patients had rectal cancers, and 66.2% (2463) had colon cancers. Distribution of tumour stage at diagnosis was 15.1% (563) stage I, 27.0% (1005) stage II, 28.6% (1063) stage III, and 21.2% (787) stage IV. Regarding surgery, 14.5% (470) of the patients were not operated or had missing data on operation. Operated patients include all types of surgery, regardless of curative or palliative indication. The level of education in study population was as follows: 41.6% (1545) low level, 40.6% (1509) medium level, and 17.4% (646) high level. A relatively large number of patients (42.4%; 1577) were living alone. The patient’s mean travel time by car to the nearest hospital was 23.85 minutes. About one-third of the patients had less than a ten-minute travel time and about 15% had more than 60 minutes of travel time. Missing data were less then <1% for all variables, except for tumour stage, where 300 patients (8.1%) had missing data.

Analysis of patient characteristics and travel time
Longer travel time was associated with older age (p=0.04), lower educational level (socioeconomic status) (p < 0.01), and living alone (p<0.01) (Figure 8). There were no differences in mean travel time to the nearest hospital between patients with different stage at stage at diagnosis (all colorectal patients, p=0.43). However, for patients with colon cancer, a rising trend in travel time from stage I to III was noticed (Table 17). In a following separate analysis for colon cancer excluding stage IV patients, a significant association between travel time and stage was demonstrated (p=0.03).

We found no difference in mean travel time between emergency operated and non-emergency operated patients: all colorectal patients (p=0.63); colon patients (p=0.90); and rectum patients (p=0.96) (Table 17). In addition we found no differences in the proportion of non-operated patients with respect to given travel time to the nearest hospital.

1 The slight difference in total numbers of patients in Northern Sweden with CRC in Paper II compared to Paper I is due to different definitions for patients with synchronous tumours.
Table 17. The study subject’s mean travel time in minutes to the nearest hospital by tumour stage and emergency or elective surgery.

<table>
<thead>
<tr>
<th>Tumour site</th>
<th>Tumour stage</th>
<th>Emergency surgery</th>
<th>p</th>
<th>Yes</th>
<th>No</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon</td>
<td>I</td>
<td>II</td>
<td>III</td>
<td>IV</td>
<td>p</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>20.7</td>
<td>22.6</td>
<td>24.7</td>
<td>22.9</td>
<td>0.06</td>
<td>23.3</td>
</tr>
<tr>
<td>Rectum</td>
<td>27.3</td>
<td>25.6</td>
<td>24.8</td>
<td>22.5</td>
<td>0.30</td>
<td>25.0</td>
</tr>
</tbody>
</table>

Figure 8. Proportion of colorectal patients living alone and level of education by travel time to the nearest hospital.

Analysis of travel time and survival

In our univariable analysis including all patients, we found no significant differences in cause-specific survival given the patients travel time to the nearest hospital (colon HR 1.001; 95% CI 0.9985 - 1.003; rectal cancer HR 0.9983; 95% CI 0.9952 -1.002).

In addition, the following multiple Cox regression analysis of operated patients did not reveal a statistically significant difference in cause-specific survival in relation to travel time (colon cancer HR 0.999; 95% CI 0.997 – 1.002; rectal cancer HR 0.997 95% CI 0.992 – 1.002).
Figure 9. Forest plot showing hazard ratios with 95% CI for cause-specific survival for operated colon cancer patients estimated in a multiple cox regression analysis; stratified by sex and age at diagnosis (10-year groups) and adjusted for educational level, cohabiting status, elective/emergency surgery, and tumour stage.

To test the stability of the results of the multivariable analysis, we performed a sensitivity analysis in the following five settings: colorectal cancer survival as one entity; over-all survival; cause-specific survival without adjusting for stage and emergency operations; travel time to the operating hospital instead of the nearest hospital; and exclusion of all patients with tumour stage IV. For all five settings, the sensitivity analysis revealed no association between travel time and survival.
Results Paper III

Baseline patient characteristics
The study included 261 subjects who were recommended surveillance: 238 were examined at least once and 146 were examined at least twice (Figure 10). The total follow-up time regarding risk for CRC was 1256 person-years (time from planned date of first colonoscopy until cross-check with the regional cancer registry at the end of study). The follow-up time for developing adenomas between sequent colonoscopies was 760 person-years, based on those who were examined at least twice.

Mean age at the first planned colonoscopy was 52.8 years and the majority of the study subjects were females (159/261; ≈61%). For other baseline characteristics, see Table 18.

Study subjects with HCRC started their surveillance at an earlier age compared to subjects with FCRC (p < 0.0001). Risk group 3c (HCRC) was also the largest sub-group: 141 individuals with a total follow-up time of 796 person-years. The 3c risk group consisted of 73 individuals with MMR mutations, 28 individuals fulfilling the Amsterdam criteria for HCRC without being mutation carriers, and 40 individuals fulfilling the Amsterdam criteria but who had not been tested for MMR mutations.

Table 18. Baseline characteristics of the study subjects in Paper III

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Families n (%)</th>
<th>Individuals n (%)</th>
<th>Mean age at first planned colonoscopy (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Familial colorectal cancer</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 (2 FDR)</td>
<td>21(19)</td>
<td>27(10)</td>
<td>52.3 (32-72)</td>
</tr>
<tr>
<td>3a (3 FDR)</td>
<td>29(27)</td>
<td>62(24)</td>
<td>54.6 (34-75)</td>
</tr>
<tr>
<td>3b (Amsterdam-)</td>
<td>11(10)</td>
<td>29(11)</td>
<td>60.1(39-79)</td>
</tr>
<tr>
<td><strong>Hereditary colorectal cancer</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3c</td>
<td>47(44)</td>
<td>141(54)</td>
<td>50.7</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>108(100)</strong></td>
<td><strong>259(100)</strong></td>
<td><strong>52.8</strong></td>
</tr>
</tbody>
</table>

*a Missing data in some variable for two study subjects
All individuals recorded in the colonoscopic surveillance register 1995 – 1 Sept 2012 (n=278)

Excluded
Risk group 1 (n=10)
Risk group 4 (n=7)

Included study subjects (n=261)

Study subjects examined at least once (n=238)

Study subjects only examined once (n=92)

Study subjects examined at least twice (n=146)

Analysis for risk of developing CRC during the study period by cross-check with local Cancer Registry (n=261)

Analysis of findings at the first colonoscopy (n=237)

Missing data (n=1)

Analysis of findings at sequent colonoscopies i.e. risk of developing adenomas/CRC between examinations (No. examinations = 356)

Missing data on 3 examinations

Included study subjects

Never examined (n=23)

Figure 10. Study flow chart Paper III
Findings at the surveillance colonoscopies

At the individuals first surveillance colonoscopy – i.e., when entering the study – 191 out of 237 (=81%) analysed examinations were normal. No CRC was diagnosed, but 14 colonoscopies revealed a HRA. Males, compared to females, had an increased risk for HRA on their first examination (7.6% (11/145) vs. 3.3% (3/92), p = 0.008). The risk for HRA also increased with age (p<0.0001) but was not associated with the subject’s risk group (p=0.79) (Table 19).

For the study period’s sequent follow-up surveillance colonoscopies, 281 out of 356 analysed examinations were normal (78.9%) and 12 HRAs and one CRC were found at surveillance. No CRC was diagnosed in intervals between scheduled examinations. At the follow-up examinations, the risk for HRA was associated with age (p<0.0001), but not with gender (p=0.89) or risk group (p=0.94) (Table 19). The findings at the first and follow-up examinations were compared: any kind of adenomas or CRC at the initial examination was associated with adenomas at follow-up (p=0.007)

Table 19. Most advanced colonoscopic findings for each risk group at first and follow-up examinations.

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Familial colorectal cancer (FCRC)</th>
<th>Hereditary colorectal cancer (HCRC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Examination</td>
<td>First (n)</td>
<td>Follow-up (n)</td>
</tr>
<tr>
<td>Findings n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>19(79)</td>
<td>12(92)</td>
</tr>
<tr>
<td>Metaplastic polyp</td>
<td>2(8)</td>
<td>1(8)</td>
</tr>
<tr>
<td>Simple adenoma</td>
<td>1(4)</td>
<td>0</td>
</tr>
<tr>
<td>Multiple adenoma</td>
<td>1(4)</td>
<td>0</td>
</tr>
<tr>
<td>High-risk adenoma (HRA)</td>
<td>1(4)</td>
<td>0</td>
</tr>
<tr>
<td>CRC</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>24(100)</td>
<td>13(100)</td>
</tr>
</tbody>
</table>

a Missing data in total for four performed examinations.
**Expected vs. observed cases of colorectal cancer**

The best estimates for the expected cases of CRC in the cohort without surveillance during the study period ranged from 9.5 (Method A) to 10.5 (Method B). The lowest estimates for expected cases of CRC were between 4.3 and 4.9 and the highest estimate was between 14.2 and 16 for Method A and Method B, respectively.

Based on the best estimates, the standardized incidence ratio (SIR) between observed and expected cases of CRC was 0.10 (CI 95% 0.0012–0.53) or 0.11 (CI 95% 0.0014–0.59), respectively.

**Compliance to the surveillance programme**

Originally, 662 examinations were planned, but only 597 were performed, resulting in 90% compliance with the surveillance program. We found no significant differences in mean age (p=0.23), gender (p=0.18), and risk group (p=0.056) between non-compliant and compliant individuals.

**Quality of the colonoscopies**

About 10% (60/597) of the performed examinations were not complete. The most common reason for incomplete examination was failure to reach the caecum (50/60), followed by inadequate bowel cleaning (10/60). However, 28 out of the 60 incomplete examinations were later completed with a new colonoscopy or diagnostic imaging. The mean adenoma detection rate for all performed colonoscopies with reported findings was 14%, as adenomas were detected at 86 colonoscopies.
Results Paper IV

In the cost-utility analysis in Paper IV, we included only individuals from Paper III with no missing data in baseline characteristics (Table 18). Hence, the study population in Paper IV was 259 instead of 261 individuals.

Differences in costs – surveillance vs. non-surveillance

The total costs for the surveillance programme during the studied years was 975 233 €, including 866 325 € in health care costs and 108 898 € in loss of production. Of the health care costs, 831 397 € were related to genetic counselling and colonoscopies, and 34 928 € were related to the observed case of CRC in surveillance. Based on the best estimate of 9.5 expected cases of CRC without surveillance, non-surveillance costs were 742 186 €, including 488 278 € in health care costs and 253 908 € loss of production. The difference in total costs (975 233 € − 742 185 €) gives the net cost for surveillance – i.e., 233 038 €.

Differences in Quality Adjusted Life Years (QALYs)

The remaining QALYs in the study population measured from the year of their first planned colonoscopy were 3893. In surveillance, 3.8 QALYs were lost due to the observed case of CRC. In the contra-factual alternative (i.e., non-surveillance), 68.6 QALYs were lost due to 9.5 expected cases of CRC. Consequently, surveillance saved 64.8 QALYs (1.7%) compared to non-surveillance.

Calculations of main outcome measure and sensitivity analysis

Based on the differences in costs and QALYs, the ICER for surveillance vs. non-surveillance was calculated. In the base case, the ICER comparing surveillance and non-surveillance was 3596 €/QALY = 36000 SEK/QALY. (Less than 100 000 SEK per QALY saved is considered a low cost intervention in Sweden.) In the sensitivity analysis, the ICER was ~4620 €/QALY in the best-case scenario and 33 779 €/QALY in the worst-case scenario.
Discussion

Main findings in relation to aims
The overall scope of this thesis was to analyse CRC in northern Sweden with regards to incidence, survival, and associated sociodemographic risk factors, including prevention for individuals with increased hereditary risk.

Sociodemographic disparities in colorectal cancer within Sweden
In Paper I, we demonstrated a higher incidence of CRC in individuals living alone and those with lower education level in all of Sweden. These risk groups were more common in the Northern Health Care Region than in the rest of the country, but the incidence in CRC was still lower in northern Sweden. The largest regional difference in incidence was found among the elderly.

In the survival analysis of CRC in Paper I, the outcome was worse in patients living alone and in patients with a low education level. All-cause survival for colon cancer patients was lower in northern Sweden than in southern Sweden. No regional differences were found in cause-specific survival for colon cancer or in any survival analysis for patients with rectal cancer.

Association between travel time to care and colorectal cancer survival
In Paper II, we found no association between travel time to the nearest hospital and CRC survival in northern Sweden – i.e., travel time was not a prognostic factor for worse outcome.

Prevention of hereditary risk for colorectal cancer
In Paper III, we found a decreased risk for developing CRC for individuals in a colonoscopic surveillance programme compared to an expected outcome without surveillance. Paper IV showed that the surveillance programme, compared to current thresholds, is a cost-effective method for preventing CRC.
Methodological considerations

Study size

Although Papers I, II, and III all share a cohort study design, they are very diverse regarding size of the study population: 41325 studied individuals in Paper I, over the 3718 individuals in Paper II, and 261 individuals in Paper III.

The possibility to study unusual phenomena with sufficient statistical strength is one of the great advantages of large register-based cohort studies. However, when doing multiple analyses with a large number of co-variables, the risks for type I errors (false positive findings) can be a problem.

In Paper I, when comparing the incidence and mortality of colon and rectal cancer in northern and southern Sweden, over 50 analyses for different subgroups with stated p-values were performed. About half of the p-values were smaller than the standard significance level of 0.05. Consequently, some of these statistically significant differences between northern and southern Sweden might be coincidences due to a large number of analyses. To decide if a hypothesis is plausible, the magnitude (effect size) or the importance of an effect must be considered, not just the p-value. The overall demonstrated difference in incidence for CRC between northern and southern Sweden was quite large - (over 10%) and the finding was repeated in most sub-group analyses. The effect size and the overall pattern in the sub-group analyses strengthen the conclusion that there is a real difference in CRC incidence between northern and southern Sweden.

In Paper II, most patients lived rather close to the nearest hospital and only 15% had > 1 h travel time. This represents a potential lack of statistical power and our finding of no association between travel time and survival may be false negative (i.e., a type II error). However, we performed a sensitive analysis, analysing the association between travel time and survival in five alternative settings. In all settings, the results remained robust, with point estimates for the HR close to 1 and narrow confidence intervals.

In Paper III, the study population is even smaller, increasing the risk for type II errors. The study population also heterogeneous in terms of risk for CRC. This makes subgroup analysis necessary although difficult to perform with sufficient statistical strength. Especially in FCRC, differences in colonoscopic findings within the FCRC group can be hard to demonstrate, and conclusions aiming to optimize future surveillance programs are difficult to draw.
However, the entire study population is probably large enough to evaluate the surveillance program’s effect as a whole. Another factor linked to study size and risk for cancer is follow-up time. The total follow-up time in Paper III was 1256 person-years at risk, but the median follow-up time was only about five years. This might be a too short period for even an inherited CRC to develop.

**Data quality**

**Data from the SCRCR**

All important CRC data in Paper I and II originate from the SCRCR. The completeness of the SCRCR is ensured by cross matching with the National Cancer Registry. The latest evaluation of the SCRCR (2018) by Moberg et al. covers the years 2008-2015. During this period, the SCRCR had almost 100% completeness. However, the annual reports from the SCRCR during our study period (2007-2013) reveals a few years at the beginning of the study period with 1-3% percent lower coverage in the Northern Health Care Region compared with the rest of Sweden. The difference in coverage constitutes a potential differential bias in the comparisons of northern and southern Sweden.

Moberg et al. showed an average agreement of 90% when comparing hospital records with variables in the SCRCR. One of the lowest agreements including many cases of missing data was found in preoperative staging of the primary tumour (T-stage). We tried to account for this by basing the stage on the postoperative histopathological stage when available for operated patients. According to the evaluation study of the SCRCR, postoperative histopathological stage is a variable with much higher validity. Nevertheless, our study demonstrated a relatively high rate of missing data on stage, probably as the result of incomplete staging of non-operated patients.

**Data from the surveillance registry at the Cancer Prevention Clinic**

The primary data source for Papers III and IV are the surveillance registry located at the Cancer Prevention Clinic at Umeå University Hospital. This registry is very small compared to the SCRCR and the validity depends on the accuracy of the colonoscopist and the staff handling the registry. If scheduled colonoscopies are not performed or results of performed colonoscopies are not reported, reminding letters to the affected endoscopy departments are sent from the Cancer Prevention Clinic. The system is well functioning as there were few missing data in the study. Although this study could not verify the validity of all findings at the colonoscopies, all study subjects were crosschecked with the Regional Cancer Registry. Since both cancers and adenomas with high-grade dysplasia are by law reported to the cancer registry, the validity of CRC cases found in surveillance is very high.
Data analysis

Analyzing risk for colorectal cancer

In Papers I and II, the comparisons of risk for CRC are based on incidence rates from the SCRCR. The comparison depends on the coverage and the validity of the data in the SCRCR, which has already been discussed.

In Papers III and IV, we compared observed cases of CRC during surveillance with an estimated number of cases without surveillance. From a methodological viewpoint, a control group with the same risk for CRC without surveillance would have been preferable rather than the performed cohort analysis of estimated cases of cancer. However, since our study population includes HCRC individuals with up to 80% lifetime risk for CRC, a control group without surveillance would have been ethically problematic. Furthermore, we wanted to study the effectiveness of an ongoing implanted surveillance program outside a controlled study’s efficacy setting. The early studies on the efficacy of colonoscopic surveillance in HCRC had control groups in terms of individuals who abstained surveillance. Modern studies of surveillance including HCRC have either refrained from controls or used cohort analysis to estimate cases. Recent randomised studies comparing different surveillance intervals have only been performed in patients with low risk for CRC—i.e., FCRC.

Survival analysis in colorectal cancer

There are different ways to measure and compare survival, each with their own advantages and disadvantages.

Observed all-cause (overall) mortality or survival refers to the probability of surviving all causes of death. In Sweden, thanks to an almost complete date of death records and personal identification numbers, all-cause survival is easy to measure with good validity. To measure the outcome of CRC, all-cause survival has the obvious drawback of including all competing risks for death among a group of patients who often are old and fragile. Consequently, comorbidity will be a major confounding factor for survival.

Cause-specific mortality or survival has a better potential to capture isolated CRC outcome. The information, however, depends on the validity of the death certificates. The validity of the CDR in Sweden has been estimated to approximately 90% for malignant disease. However, there can be differential bias regarding death certificate validity between different areas or group of patients. We used both all-cause and cause-specific survival as endpoints in Paper I because the differences in the outcome measures could help us interpret the results.
For the actual comparison of survival, we mainly used Cox regression analysis to calculate proportional hazard ratios. Cox regression analysis is one of the most common methods for survival analysis, because it accounts for each study subject’s observation time and incorporates and adjusts for variables affecting survival. An important part of Cox regression analysis is the proportional hazard assumption. It means that the hazard ratio between the studied groups should be constant over time, (e.g., the predictor value of the included variables should not vary over time) In survival studies in cancer, the variable age often causes a Cox model to violate the proportional hazard assumption as the risk of dying increases by age. We used the standard method of choice to meet the proportional hazard assumption: i.e., stratifying a Cox regression analysis by age. However, in the univariable survival analysis, additional weighted log rank analysis had to be performed.

**Analysing Socioeconomic status (SES)**

Socioeconomic status (SES) is often stated as one the strongest predictors of a person’s morbidity and mortality. But what is SES and how should it be measured? Most researchers agree that a person’s SES can depend on several factors, such as education, income, and occupation. In addition, SES has a relative dimension as a measure of one person’s status in a society is always related to the status of others. SES can be measured on an individual level, but also on a aggregated level (e.g., according to the population’s mean social deprivation in an area). All aggregated measurements can lose validity on SES in the individual study subject, but thanks to the linkage in Risk North we could measure individual SES in terms of educational level.

If one were to use only one measure for SES impact on health, educational level is perhaps the best proxy. Education level can easily be divided into different comparable levels, capturing the relative aspect of SES; in the Swedish context, education level is also one of the most common used measures of SES. However, in Sweden, many occupations that do not require higher education have a higher salary than occupations that do require a higher education. This might constitute a limitation in using educational level as the only measure of SES.

**Analysing travel time**

Thanks to the linkage to the GD, in Paper II we could precisely measure each patient’s travel time. We decided to measure travel time rather than distance as travel time includes the quality of the roads and speed limits, a more precise measurement of the travel burden.
Several previous studies have analysed travel time/distance as a categorical variable (i.e., according to quartiles or different cut of values).\(^{130,30,31}\) One of the reasons for categorising distance might be to pre-set a distance or travel time, which is thought to affect a person’s behaviour in health seeking. To avoid such preconceptions of our subjects’ behaviour, we choose to analyse travel time as a continuous variable.

**Cost-effectiveness analysis**

Health economics is an interdisciplinary science drawing on the health care sector and economics. From a health care perspective rooted in human biology research, health economics can seem unusual, with a lot of modelling based on estimations and assumption. Health economics, however, has its own framework for critical assessment that aims to enhance valid generalizable research results.\(^{104-106}\)

A basic requirement is that the health care intervention studied has a proved effect in its clinical setting; in our study, the cost-effectiveness analysis in Paper IV is based on the results in Paper III. Concerning the building of a model for costs of effects, the included variables should be accurately stated and measured with clear references to the sources of the information. This will facilitate a critical assessment of the modelling. The uncertainty of the estimations of costs and effects should be evaluated by a sensitivity analysis.

Ideally, a probabilistic sensitivity analysis is performed based on the probability distributions of the most important variables in a model. We chose a simplified approach in terms of a scenario sensitivity analysis, constructing best-case or worst-case scenarios for the cost-effectiveness of surveillance. Another simplification of our study deals with the discounting of future costs and effects. Discounting is based on the idea of positive time preference, meaning we prefer benefits today rather than tomorrow. The absence of discounting in Paper IV may influence the comparision with other studies. However, it would probably not affect the study’s overall conclusion, as the margin to current Swedish thresholds is large.

The comparability of our results is also influenced by the extent of the inclusion of societal costs. In an extended societal perspective, indirect costs regarding consumption and production due to gained life years are included beyond the duration of the study period – i.e., until the end of the study subject’s life.\(^{131}\) We did not use an extended societal perspective, but the National Board of Health and Welfare and the Dental and Pharmaceutical Benefits Agency (TLV) in Sweden often use this viewpoint in cost-effectiveness studies.\(^{61,105,110}\)
General discussion

**Sociodemographic differences in incidence of colorectal cancer**

In Paper I, we demonstrated an over 10% lower incidence in CRC in the Northern Health Care Region compared to the rest of the country. In the whole of Sweden, the incidence was higher in males, individuals with lower SES, and those living alone. However, these risk groups were more prevalent in northern Sweden, a finding that makes the lower incidence in the north more striking. Fundamentally, the reason for the differences in incidence can be found in two areas – in the genes and in the environment – neither of which we have information on in the Risk North database. The causality, however, can be discussed in relation to other studies.

From a genetic viewpoint, the population in northern Sweden differs from the rest of Sweden. A large part of the population in the north originates from a relatively small founder population living on coast in late 16th century. There are also important genetic contributions from Sami and Finnish ethnic groups. The overall impact on genetic differences within Sweden and CRC incidence has never been studied. However, many of the families with HCRC in Paper III (i.e., with a higher risk for CRC) originate from isolated river valleys in the north.

Furthermore, a trend in our findings suggests the environment (life-style) is the most interesting explanatory factor. In our studies, the largest difference in incidence was in our oldest study subjects (> 79 years), whereas the youngest (< 60 years), exhibited no significant differences in incidence. The reasons for these findings may be due to statistical power, since CRC is more unusual in the young, but one may speculate regarding differences in life-style related risk factors in the past.

Regional differences in cancer mortality in Sweden associated with dietary patterns were studied 1969-1978. A lower CRC mortality was found in northern Sweden, which was associated with a traditional diet of high intake of fibre and dairy products. CRC has a slow oncogenesis and dietary patterns earlier in life may influence the risk for CRC in the elderly today. Similarly, the more even risk for CRC in the younger patients could be associated with less regional differences in dietary patterns of today. With these assumptions, the pattern of difference in incidence for CRC between the north and the south is part of the global so-called cancer transition: the process of adapting to a more western lifestyle increases the risk for certain cancers. In northern Sweden, this cancer-transition may have been delayed, compared to the rest of the country, and associated with lower SES in the population.
Historically, low SES has been associated with lower risk for CRC in Europe and higher risk in the U.S. The paradox has been attributed to differences in dietary patterns and obesity between persons with low SES in the U.S. and Europe.\textsuperscript{24, 25, 136, 137} Until recently, low SES in Europe been associated with traditional diets and therefore low risk for CRC and low BMI, unlike the situation in the U.S. High SES in Europe has been associated with intake of more expensive foods such as red meat and alcohol, increasing the risk for CRC. In the U.S., unequal participation rates in CRC screening may further have increased the socioeconomic disparities.\textsuperscript{25} In Sweden, a study covering the years 1971 through 1998 showed a higher risk for colon cancer in males with high SES.\textsuperscript{129} The next Swedish study, covering 1993-2010, found no differences for colon cancer, but an increased risk for rectal cancer in persons with low SES.\textsuperscript{111} Finally, in our study, covering 2007-2013, the incidence for both colon and rectal cancer was higher in individuals with low SES. This overall trend in Sweden can be interpreted in the same cancer-transition framework, where historical life-style CRC risk patterns are changing. The trend also complicates the role of SES as a risk factor for CRC in Sweden. In the past, low SES may have been associated with protective life-style factors, but today low SES is associated with risk factors such as consuming processed meat, obesity, and low physical activity.\textsuperscript{138}

To conclude, the lower CRC incidence in northern compared to southern Sweden is a true difference in incidence, probably due to differences in life-style risk factors among the elderly.

**Sociodemographic differences in colorectal cancer survival**

*Overall socioeconomic disparities in colorectal cancer survival in Sweden*

The main research question regarding CRC survival in Paper I was to study differences in survival between northern and southern Sweden, especially with regards to underlying socioeconomic differences. In accomplish this study’s aim, we also had to examine some of the overall aspects in Sweden of socioeconomic and CRC.

The univariable analysis in Paper I demonstrated poorer outcome in CRC for males, lower SES, or living alone in all of Sweden. These findings are not new; the same associations have been shown both globally and in numerous Swedish studies.\textsuperscript{24, 25, 34-37} The effect size of demonstrated disparities in survival for CRC due to socioeconomics in Sweden is remarkable for a health care system that aims to provide equal health care.
In countries without a general public health care system (e.g., the U.S.), individual economic conditions affect a person’s health care in a direct way – both the access to care and the affordability of care. In settings with public health care system and universal coverage of all citizens, the causality between SES and CRC outcome is less obvious and understandable. A review by Wood et al. on the origins of socio-economic inequalities in cancer survival divided possible underlying causes into three groups: factors relating to the tumour, the patient, and the health care system. However, many of these factors may interact and a complete causal model for the association between SES and CRC survival is probably very complex. Figure 11 is an attempt to visualise such a model using a directed acyclic graph or a Bayesian network.

Advanced tumour stage at diagnosis, including an increased risk for emergency surgery, is probably the last mediating factor in a chain of causal factors related to less access to care. Access to care includes a person’s awareness, health-seeking behaviour, and participation in screening, as well as availability of the health care. Low SES can also be associated with competing risk factors for death in terms of life-style factors and co-morbidity.

Lacking social support from the patient’s family or close friends can affect health-seeking behaviour as well as the treatment being offered. In a Swedish study by Cavilli-Björkman et al., living alone was an independent risk factor for less treatment and worse outcome in metastatic CRC. Other Swedish studies on rectal cancer demonstrate the same trend with low SES and living alone associated with disparities in treatment and survival.
**Figure 11.** Graphic presentation of hypothetical causal pathways between SES and CRC survival.

Differences in colorectal cancer survival between the northern and the southern Sweden

To return to our research question of differences in survival between northern and southern Sweden, no differences were demonstrated in the univariable analysis, either for rectal or colon cancer or cause-specific or all-cause survival. The subsequent multivariable analysis was performed to explore any impact on survival of sociodemographic differences between northern and southern Sweden. The only regional difference in survival demonstrated in the analysis was an isolated finding of better all-cause survival in colon cancer in southern Sweden, HR 0.92[CI 95% 0.86 – 0.98]. No differences in cause-specific survival were demonstrated. A hazard ratio cannot be interpreted as a difference in relative risk for the entire study period; instead, it is a point estimate of the difference in the hazard for death at any point during the study period. Considering colon cancer is such a common disease, equalising outcome might improve survival for a significant number of people in northern Sweden.
Fundamentally, the reasons for the regional inequality in survival may be found in differences in treatment, other competing causes of death (co-morbidities), or life-style associated CRC prognostic factors. The combined findings of a regional difference in all cause survival, but not in cause-specific survival, may suggest underlying regional difference in other competing causes of death as an important factor. However, since Paper I did not include data on either the patients’ co-morbidities, treatment, or life-style associated prognostic factors, the regional difference in all-cause survival for colon cancer cannot be fully explained in this study. Differences in CRC treatment in Sweden are outside the scope of this thesis, not because treatment is unimportant, but deliberately left out as a subject for further studies from the Risk North database.

Another interesting finding is how the variables in multivariable model affected survival when they were added to the model one at a time. For colon cancer, no difference in all-cause survival was shown until m-stage was added to the model. M-stage in itself is the strongest prognostic factor in the model and about 1% more of patients in southern compared to northern Sweden had metastases at diagnosis. However, missing data on m-stage was 1% higher in the north. Consequently, the true proportion of metastatic disease might be similar in both areas, and the difference in all-cause survival for colon cancer could be confounded by differential bias of m-stage.
Travel time to care and colorectal cancer survival

Paper II examined another sociodemographic factor – travel distance to care – and its possible association to survival within the Northern Health Care Region. There are different opinions about whether distance to care directly affects access to care and thus survival or whether the association is a result of differences in sociodemographic prognostic factors between rural and urban populations.\textsuperscript{30-32, 144-147} Figure 12 presents possible causal pathways for an association between travel time and survival.

\textbf{Figure 12. Hypothetical causal pathways between travel time to care and CRC survival.} SES as a potential confounder is indicated in red colour.

In contrast to most previous studies, no association between travel time to the nearest hospital and cause-specific survival in CRC was found (Paper II). In studies proposing a direct travel time-survival effect, longer travel time has been associated with more advanced stages at diagnosis – stage acting as a mediator affecting survival.\textsuperscript{31, 147-149} Advanced stage, however, can be a result of lesser access to care for several reasons, not just distance to care (Figure 12).
In our study, no association between travel time to care and stage at diagnosis was demonstrated. This is a probably the most plausible explanation to the overall absence of association between travel time and survival in our study. In addition, risk for emergency operation or proportion of non-operated patients were not associated to travel time. However, like most prior studies, our study found that longer travel time was associated with negative prognostic factors such as older age, lower SES, and living alone. This raises questions whether the Swedish health care system manages to equalise risks associated with distance to care.

From a health care system viewpoint, one factor of interest is travel costs to care. In Sweden, the law regulates the right to free or subsidized travel regardless of the individual’s travel distance to care or level of income.\textsuperscript{150} A complete comparison of travel costs schemas in European countries is beyond the scope of this thesis. However, in Norway, which also has a generous system for travel costs compensations, a prior study demonstrated no association between travel time and CRC survival.\textsuperscript{151, 152}

Other distance-related barriers to care within a health care system could be dysfunctional referral pathways or centralised care far from the patient. Optimising referral pathways from GPs is one the reasons for standardised cancer care pathways in Sweden, known as Standardiserade vårdförlopp.\textsuperscript{71} Standardised cancer care processes had not been introduced during our study period. There is a trend towards centralising surgery, especially for rectal cancer. This trend was observed in the Northern Health Care Region during the study period. The local hospital could still diagnose CRC as most patients in our study lived rather close to the nearest hospital. In our sensitivity analysis, we analysed survival by travel time to the operating hospital – still without finding an association between travel time and survival.

To draw a summary conclusion regarding sociodemographic factors and CRC survival in this study: As with prior studies, low SES and living alone were associated with worse outcome for CRC patients in Sweden. In contrast to most previous studies, we found no association between travel time and survival. An isolated finding of lower all-cause survival for colon cancer in northern Sweden was demonstrated, a result that cannot be fully interpreted with the available data.
**Prevention of inherited colorectal cancer**

In contrast to life-style associated risk factors for CRC, an inherited risk for CRC cannot be modified, but the consequences may be reduced. In Paper III, we observed only one case of CRC during surveillance, instead of the 9.5 – 10.5 estimated cases without surveillance. This corresponds to an overall incidence rate of 1 per 1256 person years at risk. Direct comparisons of the cancer preventive effect in different studies are difficult as definitions for FCRC and HCRC vary according to underlying family risk for CRC. More recent studies on the surveillance report incidence rates (1.1 – 1.14/1000 person-years) about the same magnitude as in our study.69, 94 The recommended start of surveillance and intervals in our study for FCRC and HCRC seems to be a reasonably safe strategy to prevent CRC.

The preventive effect of a surveillance program also highly depends on the individual’s compliance to recommended surveillance. For colonoscopic surveillance of individuals with a family risk, participation rates vary from about 60% in the U.S. and U.K. to 98% in Finland and 90% in Sweden (as indicated in our study).101, 153, 154 These rates are high compared to uptake for CRC screening in the general population, probably because individuals with familial risk are more motivated to participate.66, 155 In both our study and the Finnish study, a centralised unit for genetic counselling and organisation of surveillance were combined with decentralisation of the colonoscopies to local hospitals.

In our study, the quality of the performed colonoscopies was not reported according to modern standards.67, 68 Furthermore, the quality indicators, which are reported, suggest a rather moderate quality. According to modern quality standards, the completeness of a colonoscopy should be described by a statement of the bowel’s cleanliness and if cecum was intubated. In our study, 10/597 examinations were reported incomplete due to inadequate bowel cleanliness. We have no information of the degree of incompleteness in these ten examinations or the cleanliness of the other 587 colonoscopies. However, our reported unadjusted caecal intubation rate of 90% is according to modern standards. The accuracy of a colonoscopy can be measured by the adenoma detection rate.156 Based on our colonoscopic findings, the adenoma detection rate was about 14%, compared to a preferable 25-35%.67, 68 Considering our study population should have a higher incidence of adenomas due to their familial risk, the observed adenoma detection rate is notably low. Other quality indicators such as withdrawal time, pain control, and polyp recovery rate were not reported. In addition, complications were not reported in a standardised way. The reported quality of colonoscopies during the study period probably reflects the fact that there were no formal competence requirements or quality standards in place for colonoscopies. However, in spite of low quality examinations, the surveillance program as a whole managed to prevent CRC.
One of the most important aims of evaluating surveillance is to optimize future surveillance with regards to start of surveillance and surveillance intervals. Analysing findings at the initial colonoscopy may help us find the appropriate age for starting surveillance, and surveillance intervals can be modelled from findings at the follow-up examinations. The present study’s small size limits the possibilities to draw such conclusions on how to optimise future surveillance, but the findings can be discussed within this context.

Ideally, surveillance should begin when the individual has reached an age associated with a “just enough” risk for CRC. A “just enough” risk for CRC could be translated to an increased incidence of precursor adenomas, but not for CRC - then surveillance would have started too late. An incidence of precursor adenomas in parity with a same aged group in the general population would instead indicate a too early start of surveillance or a non-increased risk for CRC in the studied group. In our study, about 6% of the study subjects had a high-risk adenoma (HRA) on their first examinations and no CRC was found. In a meta-analysis on advanced adenomas in the general population, the HRA rate was 3.8% in persons < 65 years (mean age at first colonoscopy in our study was about 53 years). During our follow-up colonoscopies, the total rate of HRA was a little more than 3%

Our findings of an increased rate of HRA and no CRC at the first examinations can be interpreted as proof of appropriate starting ages: age 25 for HCRC and 5-10 years before the age of the first diagnosed case in families with FCRC. The rate of HRA in the follow-up examinations could be interpreted as the study population thanks to surveillance at appropriate intervals has a risk for CRC in parity with the general population. One might argue that a HRA is a very late finding on the adenoma-carcinoma pathway, a lesion very close to becoming an invasive cancer. A safer strategy might be to intervene earlier in the pathway, before simple adenomas becomes high-risk adenomas. There is an uncertainty of the transition rates from adenomas over high-risk adenomas to cancer. In the general population, the annual transition rate is estimated to be about 2.5 – 6.3%, depending on age and gender. In inherited CRC, the transition is thought to be faster. To prevent all HRA and thus increase the safety margin, a more intensive surveillance program for CRC prevention can come at the price of high health care costs and increased discomfort of the individuals at risks. Consequently, the cost-effectiveness aspect of surveillance is important.
**Cost-effectiveness of colonoscopic surveillance**

A limited number of studies on the cost-effectiveness of colonoscopic surveillance or family history based screening have been performed.\(^{159-163}\) All earlier studies are completely based on simulations and vary regarding setting and risk for CRC in the studied group. Consequently, it is difficult to make a direct comparison of the earlier results, in terms of ICERs, to the results in the present study. All prior studies conclude that colonoscopic surveillance is cost-effective in preventing inherited CRC.

Comparisons with other health care interventions or thresholds for cost-effectiveness in a Swedish context might be more helpful for interpreting the results in Paper IV. Compared to Swedish thresholds, the ICER in our study (3596 €/QALY ≈ 36000 SEK/QALY) is a low-cost intervention in the base case and has a moderate cost-effectiveness in the worse-case scenario (33 779 €/QALY ≈ 340 000 SEK/QALY). In the best-case scenario, the ICER was negative; that is, with these assumptions, surveillance saves both lives and money.

A few years ago, the National Board of Health and Welfare in Sweden presented health economic evaluations of screening for breast cancer and CRC in the general population. The ICER, calculated in a societal perspective for the prior mammography screening program in Sweden for women age 50-69 years, was approximately 200 000 SEK/QALY compared to no screening at all.\(^{110}\) Compared to this evaluation of mammography, the cost-effectiveness of the colonoscopic surveillance in our study was higher.

In the evaluation of CRC screening for individuals 50-74 years, using biannual faecal immunochemical test (FIT), the ICER was approximately 20 000 SEK/QALY compared to no screening at all.\(^{61}\) Testing for blood in the stools has not been a valid alternative in surveillance for inherited CRC due to a low sensitivity for pre-malignant adenomas. However, the sensitivity for modern FIT to detect advanced adenomas is stated to be 20-30%.\(^{7}\) Considering the proposed accelerated adenoma-carcinoma pathway in inherited CRC, the almost 100% sensitivity of a high quality colonoscopy is still probably preferable to surveillance.\(^{56}\) The overall conclusion in Papers III and IV is that the colonoscopic surveillance program prevented CRC and is cost-effective in a Swedish health care context.
Conclusions

- Individuals living alone or with lower socioeconomic status have an increased risk for CRC. These risk groups are more prevalent in northern compared to southern Sweden; however, despite this, the incidence of CRC is lower in the north. The lower incidence in northern Sweden is probably due to differences in life-style risk factors among the elderly.

- In the survival analysis, adjusted for regional differences in sociodemographic prognostic factors, an isolated finding of lower all-cause survival for colon cancer in northern compared to southern Sweden was demonstrated. Consequently, differences in sociodemographic prognostic factors would not explain the regional difference in all-cause survival colon cancer.

- Analysis of travel time showed no association between travel time to the nearest hospital and CRC survival in northern Sweden.

- The underlying causes for the isolated finding of poorer all-cause survival for colon cancer patients in northern Sweden cannot be fully explained in this study and needs further investigations. These findings causes may lie in differences in treatment and co-morbidity or in methodological limitations in the present study.

- The colonoscopic surveillance programme for families in northern Sweden with inherited risk for CRC prevented cancer with a good cost-effectiveness. One of the factors for the success of the surveillance program may be the high compliance by the individuals at risk.
Future perspectives

As shown in this thesis and in numerous other studies, a person’s SES, including social support, has a great impact on CRC, both in terms of risk for disease and outcome. To equalize these conditions have proven to be a dilemma, even in an egalitarian country such as Sweden. One of the obstacles for successful interventions is the probably the complex association between SES and health outcomes. The exact causality and impact of e.g., for example, access to care, lower health awareness, health-seeking behaviour, and co-morbidity are difficult to account for, when studying a specific disease. Differences in treatment related to SES are easier to study and has perhaps therefore - received much attention. The Risk North database offers great opportunities for future studies in this complex area of research. The full potential of the Risk North database linking sociodemographic, health, and health care data has not yet been realized.

Regarding regional disparities in CRC, the Northern Health Care Region has been studied in this thesis on an aggregated level. The health care region consists of four county councils that all share some sociodemographic characteristics, but under different conditions independently provide the actual health care. Future studies within the Risk North project, especially regarding differences in CRC care, should be performed on a caregiver level in order to identify areas of improvement and intervention. One especially interesting area for future studies is disparities for oncological care in northern Sweden. The access to oncological care is very unequal within the region; one county council, is still without any permanent oncologist as of 2019.

An often-proposed way to equalise outcome in CRC regardless of SES is to increase health care personal awareness of treatment disparities. Considering the complex underlying mechanisms between SES and health, one must question if equalising treatment is the only solution. Theoretically, general screening in a population has the potential of equalising health outcomes by reaching all citizens, regardless of an individual’s awareness of somatic symptoms or help-seeking behaviour. Unfortunately, CRC screening seems to be another area of health care disparities as participation rates vary by SES. In Sweden, nationwide CRC screening will hopefully start during 2019. It is important that we manage to achieve equality of screening uptake in Sweden, otherwise screening will increase and not reduce disparities in CRC. The lack of association between travel time and survival presented in Paper II shows that it might be possible to compensate for negative sociodemographic prognostic factors on a health care system level.
It is also important that health care uses the tools that are already in place to prevent CRC. Familial risk for CRC is not one of most important risk factors for CRC, but it is easy to assess, basically by asking a patient about their family history. As shown in this thesis, once a familial risk for CRC has been identified, we have effective means to prevent CRC. These findings are strong reasons to emphasise the importance of collecting the family history for patients with CRC.
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