Colorectal cancer in patients < 50 years

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Colorectal cancer in patients < 50 years

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Abstract

Background: Colorectal cancer (CRC) is the third most common malignancy in Sweden after breast and prostate cancer. It is considered a disease that affects the older population. However, the incidence of CRC in Sweden is increasing in individuals < 50 years, a subgroup commonly referred to as early-onset CRC (EOCRC). This thesis aimed to study CRC from an age perspective, as few studies focus on CRC among young individuals.

Paper I analyses population-based CRC-incidence by age (< 50, 50-79, and ≥ 80 years), gender, tumor localization, and time period 1995-2015. The age-standardized incidence rate of colon cancer increased during the study period for all age-groups; the greatest increase was seen in the youngest age-group, < 50 years, regardless of tumour localization and gender ($p < 0.001$). The incidence of rectal cancer increased for men < 50 years ($p < 0.001$), decreased for both men and women aged ≥ 80 years ($p < 0.005$), and did not change for the remaining groups.

Paper II analyses postoperative 30-day complications and the rate of emergency surgeries in CRC-patients < 50 years at diagnosis compared with older age-groups (50-79 and ≥ 80 years), between 2010-2018. In total, 33,320 patients were included. CRC-patients <50 years had a higher proportion of surgical complications regarding anastomotic leakage, intra-abdominal infections and wound infections, but lower overall postoperative complications. Surgical emergencies were highest among patients ≥ 80 years, but after adjustment for confouncers, the odds were highest among patients < 50 years.

Paper III analyses 2,509 patients randomized to high-frequency follow-up computed tomography (CT) of the thorax and abdomen and a carcinoembryonic antigen (CEA) test at 6, 12, 18, 24, and 36 months versus low-frequency follow-up (CT and CEA at 12 and 36 months) after curative resection surgery for CRC between 2006-2010 stratified by age-groups ≤ 50, 51-70 and > 70 years. Among individuals ≤ 50 years with stage II-III CRC, there was no reduction in overall mortality, cancer-specific mortality, and cancer-specific recurrence with the more intensive follow-up regimen.

Paper IV analyses the role of YAP1 in EOCRC through transcriptomic and functional analyses. YAP 1 was overexpressed in EOCRC compared with LOCRC, with elevated levels associated with increased mitochondrial activity and a poorer prognosis, particularly in the CMS4 mesenchymal subtype. Pharmacological and genetic inhibition of YAP1 in EOCRC-like cells revealed its regulation of mitochondrial biogenesis and dynamics, including decreased TFAM expression and increased mitochondrial fragmentation.

Key words: Colorectal cancer, Sweden, incidence, complications, follow-up, molecular characteristics, early-onset colorectal cancer

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To my family

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Medicinae doctores in chirurgia

List of scientific papers

This thesis is based on the following articles, referred to in the text by their Roman numerals.

I. **Gutlic I**, Schyman T, Lydrup ML, Buchwald P. Increasing colorectal cancer incidence in individuals aged < 50 years – a population-based study. *Int J Colorectal Dis* 2019;7: 1221-6. doi: 10.1007/s00384-019-03312-3.

II. **Gutlic I**, Saraste D, Nordenvall C, Martling A, Lydrup ML, Buchwald P. Postoperative complications and emergency surgeries in colorectal cancer patients < 50 years – a national cohort study. *Colorectal Dis* 2024;26(7):1397-404. doi: 10.1111/codi.17058. Epub 2024 Jun 10.

III. **Gutlic I**, Veres K, Horváth-Puhó E, Lydrup ML, Buchwald P. Follow-up intensity after colorectal cancer surgery in patients aged ≤ 50, 50-70 and > 70 years – an analysis within the COLOFOL randomized clinical trial. *Int J Colorectal Dis* 2026;41(1):47. doi: 10.1007/s00384-026-05096-9.

IV. **Gutlic I**, Thokozile Nduku Y, Sjölander A, Lydrup ML, Buchwald P, Ranjan Satapathy S. YAP1 drives mitochondrial reprogramming in early-onset colorectal cancer cells through TFAM regulation. *(manuscript)*

Thesis overview

Title	Aim	Method	Results/conclusion
Paper I Increasing colorectal cancer incidence in individuals aged < 50 years – a population-based study	To analyze age-specific trends in colorectal cancer incidence and tumor localization in Sweden comparing the age groups < 50, 50-79, ≥ 80 years.	Population-based, nationwide data between 1995-2015 from the Swedish Cancer Registry was used. Poisson regression models assessed the trends in CRC incidence, adjusted for age, sex, and tumor location.	Age-standardized CRC incidence increased between 1995 and 2015. Poisson regression showed a sinificant increase in CRC incidence, particularly in colon cancer in patients <50 years (27-52% per decade).
Paper II Postoperative complications and emergency surgeries in colorectal cancer patients < 50 years – a national cohort study	To compare 30-day postoperative complications and emergency surgery rates between colorectal cancer patients < 50, 50-79, ≥ 80 years.	National cohort data from Swedish Colorectal Cancer Registry (2010-2018) was used. Logistic regression assessed the association between age and postoperative complications and emergency surgery adjusting for sex, tumor location, ASA score, neoadjuvant chemoradiotherapy.	Patient < 50 years had fewer overall complications but higher rates of specific surgical complications (e.g., anastomotic leakage, intra-abdominal infections, wound infections). Patients < 50 also had higher odds of emergency surgeries after adjusting for confounders.
Study III Follow-up intensity after colorectal cancer surgery in patients aged ≤ 50, 50–70 and > 70 years – a subgroup analysis within the COLOFOL randomized control trial	To assess wheather high-frequency postoperative follow-up after colorectal cancer surgery reduces overall 5-year mortality, cancer-specific mortality, and recurrence in patients ≤ 50 years.	Data from the COLOFOL RCT, including 2,509 patients were used. Patients were randomized to receive high-frequency (6, 12, 18, 24, 36 months) or standard (12, 36 months) follow-up, including CEA & CT.	High-frequency follow up did not significantly reduce overall- and cancer-specific mortality in patients ≤ 50 years (8.3% vs. 8.4%, 7.1% vs 7.4% p=NS), or significantly affect cancer-specific recurrence (12.9% vs 21.0%, p=NS).
Study IV YAP1 drives mitochondrial reprogramming in early-onset colorectal cancer cells through TFAM regulation	To assess YAP1 expression in EOCRC versus LOCRC and its link to mitochondrial oxidative phosphorylation (OXPHOS), consencus molecular subtype (CMS), and survival, with experimental validation in vitro.	Bulk RNA-sequencing data from three GEO cohorts (n=811) were analyzed to compare YAP1 expression between EOCRC and LOCRC. Functional validation was conducted in EOCRC-like and LOCRC-like cell lines using pharmacological and genetic YAP1 inhibition.	YAP1 was differentialy expressed in EOCRC than LOCRC and was significantly correlated with OXPHOS. EOCRC was enriched in CMS4, where high YAP1 levels were associated with worse survival. Functional validation showed that YAP1 inhibition led to mitochondrial fragmentation and reduced TFAM levels.

CRC, colorectal cancer; RCT, randomized controlled trial; CEA, carcinoembryogenic antigen; CT, computed tomography; EOCRC, early-onset CRC; LOCRC, late-onset CRC; NS, non-significant.

Abbreviations

ASA	American society of anesthesiologists (physical status classification)
ATCC	American type culture collection
CEA	Carcinoembryonic antigen
CI	Confidence interval
CMS	Consensus molecular subtype
CRC	Colorectal cancer
CT	Computed tomography
CTH	Chemotherapy
EOCRC	Early-onset colorectal cancer
FDR	False Discovery Rate
GEO	Gene expression omnibus
GSEA	Gene set enrichment analysis
HR	Hazard ratio
ICU	Intensive care unit
IRR	Incidence rate ratio
LOCRC	Late-onset colorectal cancer
MSI	Microsatellite instability
MsigDB	Molecular signatures database
NES	Normalized enrichment score
OR	Odds ratio
pTNM	Pathological tumour stage (pathological tumour-node-metastasis)
RT	Radiotherapy
SCRCR	Swedish colorectal cancer registry
siRNA	Small interfering ribonucleic acid
SMD	Standardized mean differences
TAZ	Transcriptional co-activator with PDZ-binding motif
TFAM	Mitochondrial transcription factor A
YAP1	Yes-associated protein 1

Introduction

Background

Early-onset colorectal cancer

Colorectal cancer (CRC) has traditionally been regarded as a disease predominantly affecting older adults, and population-based screening programs and clinical awareness have therefore primarily targeted individuals aged 50 years or above. However, in recent decades, the incidence of CRC in individuals younger than 50 years has increased, prompting increasing recognition of "early-onset colorectal cancer" (EOCRC) as a distinct and emerging clinical entity.

Although the age threshold of 50 years remains a practical distinction based on past screening guidelines, emerging evidence suggests that EOCRC differs from LOCRC across multiple domains. These differences encompass epidemiological patterns, tumor distribution, histopathological features, molecular profiles, and treatment-related considerations. Furthermore, younger patients face distinct survivorship challenges, including fertility preservation, long-term treatment toxicity, psychological burden, and extended life expectancy after diagnosis (1). Despite growing awareness, the underlying drivers of the increasing EOCRC incidence remain incompletely understood. Improved understanding of these mechanisms and differences may help inform future screening strategies, diagnostic pathways, therapeutic approaches, and postoperative follow-up protocols for younger patient populations.

Epidemiology

CRC ranks the third most prevalent malignancy and second leading cause of cancer-related mortality worldwide, representing a substantial portion of the global cancer burden. According to recent estimates, more than 1.9 million new CRC cases and over 930.000 CRC-related deaths occurred globally in 2020, reflecting significant morbidity and mortality across both high-income and low-income regions (2).

CRC incidence varies considerably by geography, partly reflecting differences in socioeconomic development, demographic structure, lifestyle exposures, and

degree of "westernization" (*Figure 1*). The highest rates of CRC are observed in westernized regions such as Australia, New Zealand, North America, and Western Europe, where age-standardized incidence rates commonly exceed 30-40 per 100.000 (3, 4). These high-incidence regions also correspond to countries with a high Human Development Index (HDI), suggesting that higher socioeconomic development, along with western dietary patterns, higher prevalence of obesity, and historically older population structures contribute to elevated CRC risk (5). In contrast, substantially lower incidence rates are observed in Africa, South-Central Asia, and parts of Latin America, where age-standardized incidence rates range from 5 to 15 per 100.000, reflecting lower HDI, differing lifestyle patterns, and less widespread adoption of westernized diets (6).

However, within these broad regions, considerable heterogeneity in CRC incidence exists between countries and subregions. For example, incidence rates in Northern and Southern Africa are somewhat higher than in Western or Eastern Africa, while several rapidly developing Asian countries, including South Korea, China, and Singapore, now report incidence rates approaching those of traditionally high-incidence Western countries (7). Over recent decades, a pronounced epidemiological shift has occurred in many middle-income countries where CRC incidence is rising sharply in parallel with economic development and changes in diet, physical activity, and obesity prevalence. Consequently, regions such as Eastern Asia now account for the largest absolute number of CRC cases globally, driven by both population size and rising incidence (8).

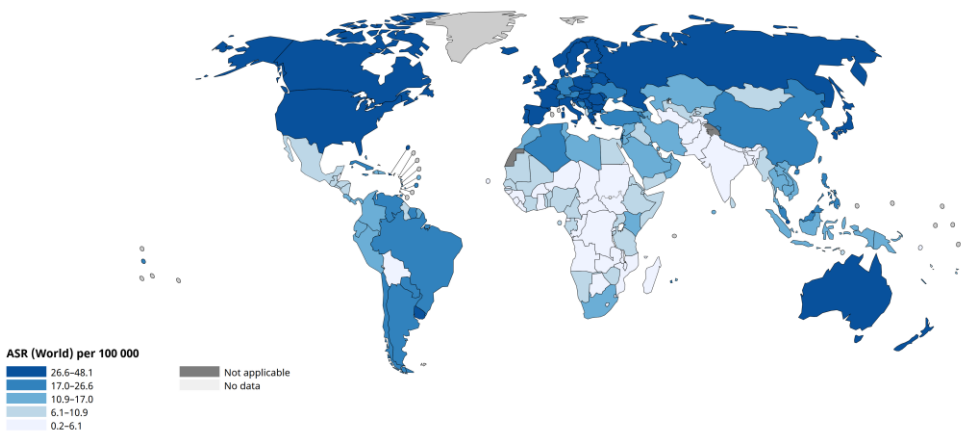

Figure 1. Age-standardized incidence rate (world) per 100,000 for colorectal cancer, 2022. Data source: GLOBOCAN 2022 (version 1.1), International Agency for Research on Cancer. Available from: Cancer today (http://gco.iarc.who.int/today). Accessed January 2026.

CRC incidence rises sharply with age, with the majority of cases (approximately 88-90 %) occurring in individuals older than 50 years old (9). In many high-income

countries, the incidence among older adults has stabilized or declined, largely attributed to the implementation of organized screening programs, the removal of premalignant lesions, and improved risk awareness. In contrast, rates among EOCRC have increased in at least 27 out of 50 countries worldwide over the past years (10-13). Since the early 1990s, the number of younger adults diagnosed with CRC in Sweden has increased two- to three-fold, where the incidence of EOCRC has grown by approximately 2% per year for rectal cancer, 2.41% for left-sided colon cancer, and 2.46 % for right-sided colon cancer (*Figure 2*) (14). Similar patterns have been observed in other high-income and westernized countries, but even more rapid annual increases over recent years have been reported in England (about 3.6%), Chile (around 4%), Japan (about 4.69%), New Zealand (around 4 %), Puerto Rico (3.8%) (13). Some analyses have reported the steepest increases in Brazil with annual percent changes approaching 9% (15). Notably, these rising EOCRC trends have been observed in some countries across successive generations since the 1960s, with more recent cohorts demonstrating progressively higher incidence than earlier cohorts, a phenomenon known as the birth-cohort effect (16, 17). This observation supports the hypothesis that early-life (childhood, adolescence, and early adulthood) or cumulative generational exposures, rather than aging alone, may play an important role in the observed rise. Within the EOCRC population, the highest absolute incidence rates are observed among individuals aged 45-49 years. However, the most pronounced relative rise in incidence over time have been reported in younger ages, particularly those aged 20-29 years, raising concern about shifting disease dynamics in increasingly younger populations (18).

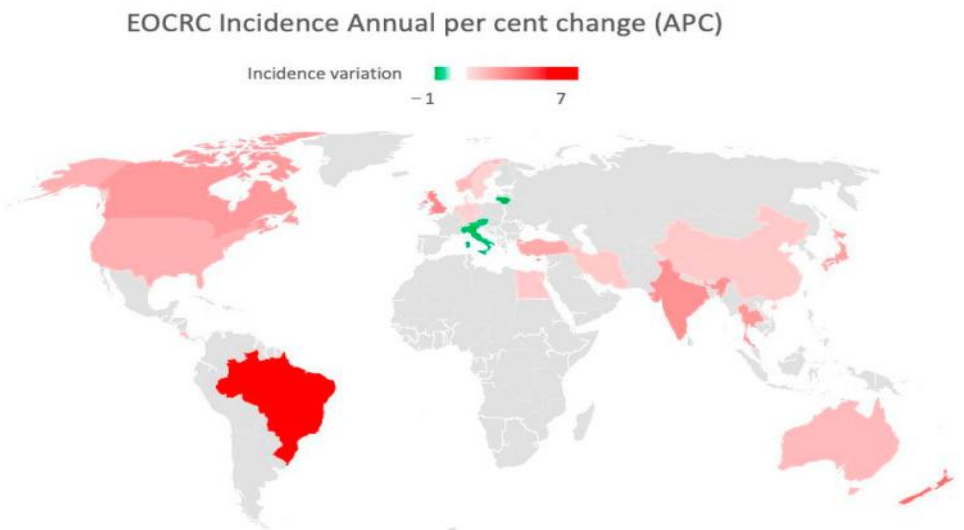

Figure 2. Annual percent change (APC) in incidence of EOCRC by country over various periods during recent decades. Data source: Medici et al. *Cancers.* doi: 10.3390/cancers15133509. Available at: https://pubmed.ncbi.nlm.nih.gov/37444619/.

Mortality trends partly mirror the success of screening, early detection and therapeutic advances. In many high-income countries, CRC mortality has steadily declined over the past several decades due to widespread implementation of fecal occult blood testing, colonoscopy, and advances in multimodal therapy. In contrast, mortality remains disproportionately high in low-resource regions where screening is limited and access to multimodal treatment is constrained (3). Global disparities in access to screening, diagnostic services, and treatments continue to shape survival outcomes. Importantly, recent epidemiologic analyses from the United States demonstrate that EOCRC has become a leading cause of cancer-related mortality among adults younger than 50 years, ranking first among men and second among women in this age group, where mortality, similar to incidence, continues to rise in patients under 50 years during the last decades (19, 20).

Taken together, CRC epidemiology patterns reveal a complex interplay between demographic aging, socioeconomic transition, lifestyle exposures, screening implementation, and generational effects. Understanding these patterns provides essential context for interpreting the clinical and biological differences between EOCRC and LOCRC, and for informing hypotheses regarding underlying etiological mechanisms.

Etiology

The etiology of CRC is multifactorial and complex. The majority of CRC cases, approximately 75 percent, are sporadic, arising from the accumulation of somatic mutations, while a smaller proportion, 10-30 percent, involves a family history of CRC and pathogenic variants in genes that account for about 5-6 percent of all CRC cases (21).

CRC develops through distinct molecular pathways, most commonly the adenoma-carcinoma sequence, also called the chromosomal instability (CIN) pathway, which accounts for approximately 85 % of cases (*Figure 3*). In this model, benign precancerous lesions (adenomas) gradually accumulate genetic alterations in key driver genes such as adenomatous polyposis coli (*APC*), *KRAS*, *SMAD4*, and *TP53* as CIN increases, ultimately driving the transition to invasive carcinoma (22). Beyond the conventional adenoma-carcinoma sequence, CRC also arises through a distinct serrated neoplasia pathway, which accounts for approximately 10-20 percent of CRCs and less frequently through the microsatellite instability (MSI) pathway (23). A total of 80-85% of CRCs are MSS, 10-16% MSI, and 1-2% ultra-mutated due to *POLE* mutations (24).

Progression from adenoma to carcinoma usually takes several years, often 10-15 years, highlighting the window for prevention by detection and removal of adenomas (25). Adenomas are highly prevalent in Western populations, with about one in four adults developing at least one adenoma during their lifetime, and their

frequency increases markedly with age (26, 27). Because of this stepwise progression, risk factors that promote adenoma formation or accelerate progression are central to CRC etiology.

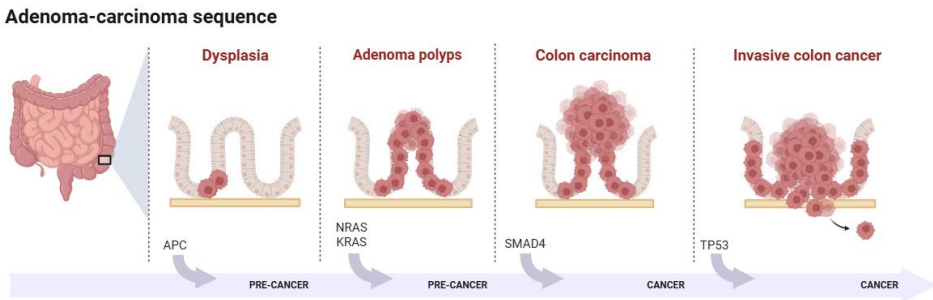

Figure 3. The adenoma-carcinoma sequence in colorectal tumorigenesis. Created in https://BioRender.com.

Risk factors

Since the majority of CRCs are sporadic rather than hereditary, identifying modifiable risk factors is essential to reduce exposure and limit disease incidence. Lifestyle-related factors appear to play a big role in the rising incidence of EOCRC, although they do not fully explain it (28, 29). The exposome refers to the totality of all environmental and internal exposures from conception onward, presenting a framework for understanding how these factors accumulate over a lifetime. The exposome is commonly divided into three interrelated components: the wider external environment, the specific external environment (e.g., diet, smoking, alcohol, antibiotics), and the internal environment (e.g., gut microbiota) (30). While specific data on EOCRC are limited, considering these cumulative exposures may help explain unique drivers of EOCRC. Similar risk factors influence both EOCRC and LOCRC, but the exposome perspective highlights the potential role of early-life and lifelong exposures in the rising incidence among younger adults (*Figure 4*).

Although EOCRC is rising, increasing age remains one of the most significant risk factors for CRC (31, 32). Other so-called non-modifiable risk factors include the male gender, a family history of CRC, colorectal polyps, and chronic inflammatory bowel disease (ulcerative colitis and Crohn's disease), all of which have been shown to increase the risk of CRC, including EOCRC (33, 34).

Modifiable risk factors, including environmental factors, such as dietary patterns, also contribute markedly to a large proportion of CRC (35). There is a recognized association between alcohol consumption and a higher risk of developing CRC, as well as EOCRC, with evidence suggesting a dose-dependent increase in risk of CRC

mortality as alcohol intake rises (36, 37). Cigarette smoking has been associated with CRC, as well as EOCRC, where studies have shown a moderate but significant increase in CRC risk (36, 38, 39).

Obesity is widely recognized as a significant risk factor for the development of several malignancies, including CRC, and its impact appears to be relevant in EOCRC as well. Excess body weight, especially central or abdominal obesity, has been associated with a marked increase in risk, with some studies indicating a stronger effect when obesity develops at a very young age (40, 41). Some studies show that persistent metabolic syndrome is also linked to elevated risk of CRC among individuals aged 20-49 years, with a stronger association observed for rectal cancer (42, 43). Lack of physical activity is widely acknowledged as a risk factor for CRC overall; its specific contribution to EOCRC is still debated (44). While some studies report a positive association between physical inactivity and EOCRC, particularly for rectal tumors, others have failed to confirm this relationship, potentially due to confounding variables like obesity and metabolic dysfunction (45).

In recent years, the gut microbiome has emerged as an important area of interest due to its involvement in cancer development and tumor progression, as well as response to therapy and prognosis in various cancers (46). Studies have consistently shown that the gut microbial composition of individuals with CRC differs markedly from that of healthy individuals, commonly described as dysbiosis (47). CRC tumor tissue is shown to have a relative abundance of potentially pro-carcinogenic bacteria, including Fusobacterium, Escherichia coli, Bacteroides, Enterococcus, Porphyromonas, and Peptostreptococcus species. In contrast, other bacteria have been thought to have protective effects, including Roseburia, Clostridium, Faecalibacterium, and Bifido-bacterium (48-51). High intake of processed meat has been identified as an established risk factor for CRC, whereas that of red meat has been identified as a probable risk factor for CRC (52, 53). Additional factors that may influence CRC risk through microbiome modulations include prolonged antibiotic exposure, which has been linked to a higher risk of colon cancer but not to rectal cancer (54). The specific impact of antibiotic usage on EOCRC remains conflicting (55, 56). Some evidence suggests that females born by cesarean section have an increased risk of EOCRC, which is believed to alter early-life microbial colonization (57). High intake of sugar-sweetened beverages and low vitamin D have also been shown to be risk factors for EOCRC (58, 59). Newer data also suggest a possible association between low milk consumption and EOCRC, although this requires further investigation (60).

As mentioned, there has been a steady increase in EOCRC across successive birth cohorts since the 1960s, suggesting that shared generational exposures, including modifiable environmental and lifestyle factors such as dietary changes and obesity, may play a role in this trend, many of which have increased since the 1950s (61). Environmental and lifestyle exposures may, in turn, influence the gut microbiome,

and emerging evidence suggests that EOCRC and LOCRC may not only differ in epidemiological and clinical characteristics but also in their microbial, metabolic, and host-environment interactions (62-64).

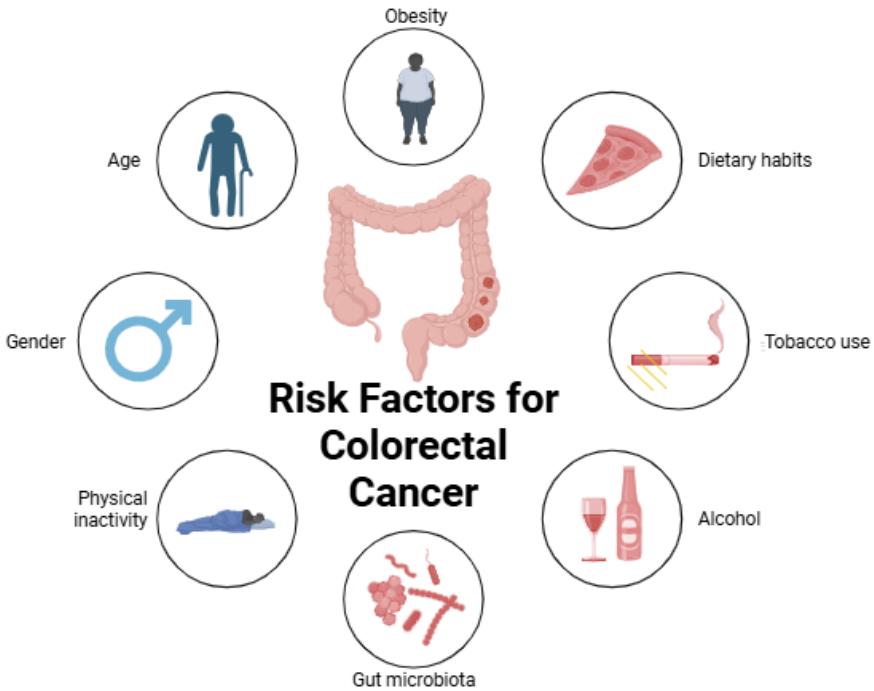

Figure 4. Risk factors for colorectal cancer. Created in https://BioRender.com.

Prevention

Primary prevention of CRC includes reducing risk factors mentioned previously, such as the intake of processed meat, red meat, alcohol, and smoking, as well as increasing known protective factors such as physical activity, intake of fiber, fruits, and vegetables (65). Some drugs that have shown to be protective factors for CRC are ASA (acetylsalicylic acid), postmenopausal hormone therapy, and Metformin; however, there are no current recommendations for chemoprevention today (66-68). Low-dose ASA has also recently been shown to decrease CRC recurrence when used as adjuvant therapy in patients with mutations in the PI3K signaling pathway, which is present in approximately 30-40% of all CRC patients (69).

Secondary prevention includes CRC screening, which aims to reduce mortality by detecting disease at an earlier stage and removing premalignant polyps.

Additionally, early detection may also reduce morbidity by decreasing the need for extensive surgery and oncological treatment. The main methods for screening are the fecal occult blood test (FOBT), either the guaiac test or the immunological fecal immunochemical test (FIT). In Sweden, and most other countries, the FIT test is used because it is easier for patients to use, less affected by diet, requires only one stool sample, and has higher sensitivity. Those with a positive FOBT are referred for further investigation with colonoscopy. This evidence-based screening method has been recommended by the European Union since 2003. In Sweden, the National Board of Health and Welfare issued the same recommendation in 2014 (70-73). In 2018, a workgroup within the Regional Cancer Centers in Sweden proposed a national screening program, with every region committing to implement it by 2026, offering screening every 2 years for individuals aged 60-74 years. Despite recent recommendations from clinicians in the workgroup within the Regional Cancer Centers to lower the screening age to 50 years, in line with European guidelines, the Swedish National Board of Health and Welfare has decided to maintain the starting age at 60 years. Individuals with one first-degree relative diagnosed with CRC before the age of 50 or with two affected first-degree relatives are recommended to have a one-time colonoscopy starting 5-10 years before the youngest age at diagnosis or at the age of 50 years, whichever comes first. Individuals with three affected first-degree relatives are recommended colonoscopy every 5 years (74).

Almost all countries in the European Union, 20 out of 27, have implemented population-based CRC screening programs, while Cyprus, Romania, and Lithuania are in the process of implementing population-based screening programs. The screening programs in Austria and Latvia are not population-based but opportunistic, while Greece and Bulgaria lack organized CRC screening programs. In countries outside of the European Union, such as Iceland, population-based screening programs are being implemented, while England, as a part of the United Kingdom, has already established population-based screening (75). The most common age-interval for CRC screening is 50-74 years.

Outside Europe, several countries are also introducing screening programs, although coverage and implementation vary widely. Population-based programs are mainly implemented in high-income countries, while many middle-income countries rely on opportunistic or pilot initiatives (76). In North America, Canada has a population-based screening program, while the USA relies mainly on opportunistic screening. In South America, only a few countries, such as Argentina, Brazil, Chile, and Uruguay, are testing population-based pilot programs while most others, like Cuba, Mexico, Colombia, Ecuador, and Puerto Rico, rely on national opportunistic programs. In Asia and Oceania, a mix of national population-based and opportunistic approaches is used in countries such as Japan, South Korea, Taiwan, Singapore, Thailand, and Australia. New Zealand is implementing national population-based screening, and China has initiated urban population-based pilot

programs. In Africa, Morocco is the only country with a pilot research project promoting voluntary screening (77).

In response to the rising disease burden, the United States Preventive Services Task Force (USPSTF) revised its screening guidelines in 2021 to recommend that routine CRC screening begin at age 45 years rather than 50 (78). However, these recommendations are primarily based on predictive models and on the observation that CRC risk in 45-49-year-olds now resembles that of 50-54-year-olds in the early 1990s, given the lack of sufficient empirical data. It is also important to bear in mind that, despite the large relative rise in EOCRC over the last decades, there has been a relatively small absolute increase in CRC incidence during the same period. Lowering the screening age could potentially overwhelm screening capacity and divert resources from older adults who are at higher risk. A decline in EOCRC incidence has been reported only in three countries – Italy, Austria, and Lithuania (11). In Austria and Italy, where screening programs for CRC began in the early 1980s at ages 40 and 45, respectively, the reduction in EOCRC has been largely limited to the 40-49 age group (79). These results imply that earlier screening could be effective in counteracting the trend of increasing CRC incidence among younger adults. Precision cancer screening, which integrates family history, environmental, and lifestyle factors, could be used to more accurately identify the optimal screening age and method for each individual, which offers a more effective and tailored approach than traditional age-based guidelines.

Characteristics

Anatomy & clinical presentation

The colorectal canal, approximately 150 cm long and 5-7 cm wide, extends from the ileocecal valve in the right lower abdomen to the anal canal (*Figure 5*). It consists of the caecum (with the appendix), ascending colon, transverse colon, descending colon, sigmoid colon, and rectum. The caecum, transverse colon, and sigmoid colon are intraperitoneal, while the ascending and descending colons are retroperitoneal. The rectum, typically 12-15 cm long, begins at the rectosigmoid junction. In the upper third of the rectum, the anterior and lateral surfaces are covered with peritoneum. In the middle third, peritoneal coverage is limited to the anterior surface, while the distal third is extraperitoneal, surrounded by mesorectal fascia, and forms the rectal ampulla. The definition of the rectum, debated recently, is important clinically and for research. In Sweden, the rectum is still defined as the last 15 cm of the large bowel, which is 15 cm from the anal verge as seen by, for example rigid rectoscopy (80). However, international consensus now defines the rectum as the sigmoid take-off, which is the junction between the sigmoid

mesocolon and the mesorectum as it elongates away from the sacrum, visible on imaging technologies such as computed tomography (CT) and magnetic resonance imaging (MRI) (81). The anal canal, 3-5 cm in length, transitions histologically from cylindrical epithelium in the rectum to squamous epithelium at the dentate line. In clinical practice, the puborectalis muscle is often used as the border between the rectum and the anal canal.

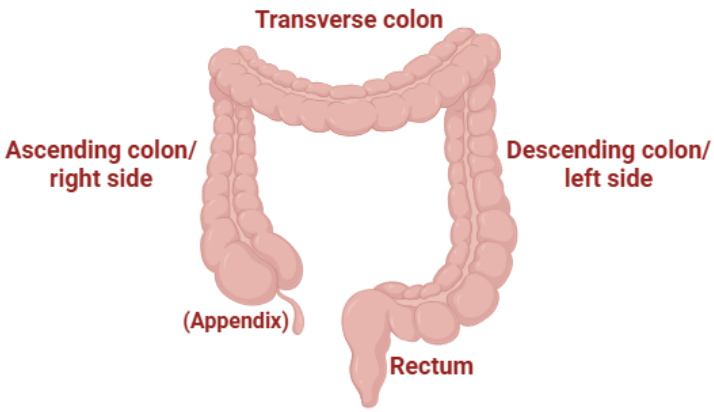

Figure 5. Schematic drawing of the colon and rectum. Created in https://BioRender.com.

CRC often has an insidious onset, and patients may be asymptomatic in early stages when the tumor burden is small (82). As the disease progresses, symptoms typically reflect tumor size, growth pattern, and anatomical localization within the colon or rectum. Right-sided colon cancers frequently present with iron-deficiency anemia caused by chronic occult bleeding, leading to nonspecific symptoms such as fatigue and reduced capacity for physical activity. In contrast, left-sided and rectal tumors more commonly cause alterations in bowel habits, such as constipation, diarrhea, or alternating stool consistency, as well as visible blood or mucous mixed with the stool. Rectal tumors may produce urgency and a sensation of incomplete evacuation of stool (tenesmus) due to local irritation. Abdominal pain is generally a later manifestation and may indicate luminal obstruction or locally advanced disease with invasion of adjacent structures. Symptoms of bowel obstruction, such as progressive constipation, colicky pain, and abdominal distension, can occur when the tumor causes significant luminal narrowing, and approximately one-fifth of all patients present acutely with large bowel obstruction. Systemic symptoms may include weight loss, anorexia, and ascites, which are more suggestive of advanced or metastatic disease (83, 84).

Rectal bleeding and alterations in bowel habits are generally regarded as high-risk symptoms, and the presence of multiple symptoms increases the likelihood of CRC, with the highest positive predictive value for non-metastatic disease observed when blood in the stool is combined with altered bowel habits (85, 86). According to previous studies, EOCRC may present differently and with a more delayed diagnosis than CRC in older patients with symptoms like hematochezia and abdominal pain, as well as changed bowel habits, being the most common in EOCRC (87). This symptom pattern may reflect that EOCRC more often manifests in the distal colon or rectum, leading to different clinical presentations. Additionally, a delayed diagnosis in EOCRC could be related to the tendency for symptoms to be misattributed to less serious conditions, such as hemorrhoids or irritable bowel syndrome, resulting in advanced disease at diagnosis.

Diagnosis

Colonoscopy with histopathological assessment is the first-line diagnostic method for suspected CRC. It allows biopsy of detected tumors and removal of incidental polyps with recommended endoscopic tattooing to aid lesion localization for future colonoscopies and surgery. If colonoscopy is incomplete, CT colonography may be used as a complementary investigation, as it has comparable diagnostic accuracy for tumors and polyps larger than 10 mm, whereas smaller polyps are rarely clinically relevant in symptomatic patients (88). Contrast-enhanced CT of the thorax and abdomen is performed pre-therapeutically to assess the extent of the primary tumor, detect involved lymph nodes, and detect possible distant metastases. In rectal cancer, pelvic MRI is the standard method for local staging and treatment planning, while MRI of the primary tumor in colon cancer is reserved for selected cases of suspected locally advanced disease (89-91). Endoscopic or transrectal ultrasound may provide additional information in specific situations, particularly for low rectal tumors or suspected invasion of colonic tumors on adjacent upper abdominal organs such as the ventricle or duodenum. If CT reveals suspected liver metastases in patients considered for curative treatment, liver MRI is recommended (92). PET-CT may be used when conventional imaging does not clearly determine whether the disease is potentially curable or palliative, especially in patients with suspected extra-pelvic spread. Routine blood tests, including carcinoembryonic antigen (CEA), are obtained (93). Following the initial workup, all patients are discussed at a multidisciplinary team conference, involving all specialties managing the patient, and treatment decisions are made in collaboration with the patient.

Prior to the multidisciplinary team conference, a TNM (Tumor, Node, Metastasis) classification of the tumor is determined based on the UICC (Union for International Cancer Control) TNM classification system *(Table 1)* (94).

Table 1. TNM classification system

T	Tumor
T0	No tumour
Tis	Carcinoma in situ (invasion of mucosal lamina propria)
T1	Invasion into submucosa
T2	Invasion into muscularis propria
T3	Invasion into subserosa/perirectal tissue; a. <1mm b. 1-5mm c. >5-15mm d. >15mm
T4	a. Perforation of visceral peritoneum b. Invasion of adjacent organs/tissues
N	**Node**
N0	No regional lymph node metastases
N1	1-3 regional lymph node metastases
N2	≥4 regional lymph node metastases
M	**Metastasis**
M0	None
M1	a. to one organ b. to more than one organ c. to peritoneum

While the TNM classification describes the anatomical extent of CRC, another staging system, based on the UICC TNM classification, can group TNM categories into clinically meaningful prognostic classes *(Table 2)*. The two classification systems are used together to guide treatment decisions in CRC.

Table 2. Staging according to the UICC TNM classification

Stage	T	N	M
0	Tis	N0	M0
I	T1-T2	N0	M0
II	T3-T4	N0	M0
III	T1-T4	N1-N2	M0
IV	Any T	Any N	M1 a-c

The stage at diagnosis is the strongest predictor of survival. Localized CRC (stage I-II) has a relatively high 5-year overall survival rate of around 90 %. However, recurrence can still occur, particularly in high-risk patients. For stage III CRC, the 5-year overall survival rate is about 70 %, with recurrence in 30-40 % of cases within 5 years. In stage IV CRC, the 5-year overall survival rate is approximately 14% (95-97). Survival data for EOCRC remains inconsistent. While some studies suggest a worse prognosis for younger patients, others report similar or even better outcomes compared to older individuals. EOCRC often presents at a more advanced stage than LOCRC (98-101). Although younger patients are more likely to receive more intensive neoadjuvant or adjuvant chemotherapy at all stages, these treatments do not seem to result in significantly better outcomes compared to older patients (98, 102). This raises concerns about whether young patients are being overtreated without clear benefits, as well as the effectiveness of these treatments in this group.

Molecular features

CRC develops through three principal molecular pathways; the CIN pathway, the serrated neoplasia pathway, and the microsatellite instability (MSI) pathway. Each pathway is characterized by a distinct initiating event, a specific type of genomic instability, and distinct pattern of tumor progression. While these classifications are distinct by definition, they often overlap within CRC tumorigenesis (103, 104).

The CIN pathway is the most common mechanism of colorectal carcinogenesis, responsible for approximately 70-90% of all CRCs. It is initiated by loss of the adenomatous polyposis coli (*APC*) tumor suppressor gene, leading to dysregulated Wnt/β-catenin signaling and the formation of conventional adenomas (105). Germline mutations in *APC* cause familial adenomatous polyposis (FAP), a hereditary form of CRC, while somatic *APC* mutations are found in approximately 70-90% of sporadic CRCs; both follow the CIN pathway (106). As adenomas enlarge, activating mutations in *KRAS* promote further proliferation and survival. Progressive chromosomal instability, characterized by aneuploidy (abnormal number of chromosomes) and loss of heterozygosity (loss of the remaining normal allele of a gene), results in the accumulation of additional genetic alterations. Late loss of tumor suppressors such as *TP53* and *SMAD4* permits invasion and malignant transformation, leading to microsatellite-stable (MSS) CRC (107). Tumors arising from the CIN pathway are often localized in the distal colon (108).

The serrated neoplasia pathway arises from serrated polyps, most often sessile serrated lesions, and accounts for approximately 10-20% of sporadic CRCs (105). The initiating event is typically an activating *BRAF* mutation, which drives aberrant MAPK/ERK signaling and promotes epigenetic dysregulation. Unlike the CIN pathway, where tumor progression is driven by DNA mutations, deletions, and gains (changes in DNA sequence and chromosome numbers), the serrated pathway relies heavily on epigenetic alterations (such as DNA hypermethylation) rather than structural DNA changes. This leads to the CpG island methylator phenotype (CIMP), characterized by widespread promoter hypermethylation and transcriptional silencing of tumor suppressor genes. When methylation of the MLH1 promoter occurs, mismatch repair is lost, leading to sporadic microsatellite instability (MSI)-high CRC (23). Although most serrated pathway CRCs become MSI-high due to MLH1-methylation, a minority remain MSS, even though they still harbour *BRAF* mutations and CIMP-high features. This occurs because the MLH1 gene is not methylated in these tumors, despite the presence of other molecular markers typical of the serrated pathway (109). Tumors arising from the serrated neoplasia pathway are frequently localized in the proximal colon and may progress more rapidly than those in the CIN pathway (110).

The MSI pathway accounts for 2-4% of CRCs and primarily refers to Lynch syndrome, caused by germline mutations in genes of the DNA mismatch repair (MMR) pathway, including MLH1, MSH2, MSH6, or PMS2 (111). In these cases,

a second somatic hit inactivates the remaining functional allele, resulting in complete loss of MMR. Although the MSI (Lynch syndrome) pathway accounts for only a small fraction of CRCs, it is considered a separate pathway since it has a distinct hereditary cause, unique molecular features, and important clinical and therapeutic implications. Defective MMR leads to microsatellite instability, causing accumulation of insertion-deletion mutations in repetitive DNA sequences of key genes such as TGFBR2 (growth regulator) and BAX (apoptosis regulator), disrupting normal growth control and cell death, allowing rapid progression from adenoma to carcinoma, resulting in MSI-high CRC (112).

In Sweden, all CRCs are routinely tested at diagnosis for MMR or MSI status. This information serves as both a prognostic and predictive biomarker, helping identify patients with Lynch syndrome. Tumors showing loss of MMR function are classified as MMR-deficient (dMMR) while those with normal MMR function are considered proficient (pMMR). If MLH1 loss is detected, additional testing for *BRAF* mutations is performed to help distinguish sporadic tumors from those associated with Lynch syndrome. Tumors with *BRAF* mutation are usually sporadic, while those without *BRAF* mutation warrant further genetic testing. Cases with loss of other MMR proteins (MSH2, MSH6, PMS2) are referred directly for genetic counseling regardless of BRAF status. For patients with metastatic or locally advanced CRC, molecular tumor analysis should include *KRAS*, *NRAS*, and *BRAF* mutations, including BRAF V600, to guide treatment decisions (80).

The molecular pathways of CRC development are complex and often overlap, but *Figure 1* provides a simplified representation highlighting the most common events in each pathway.

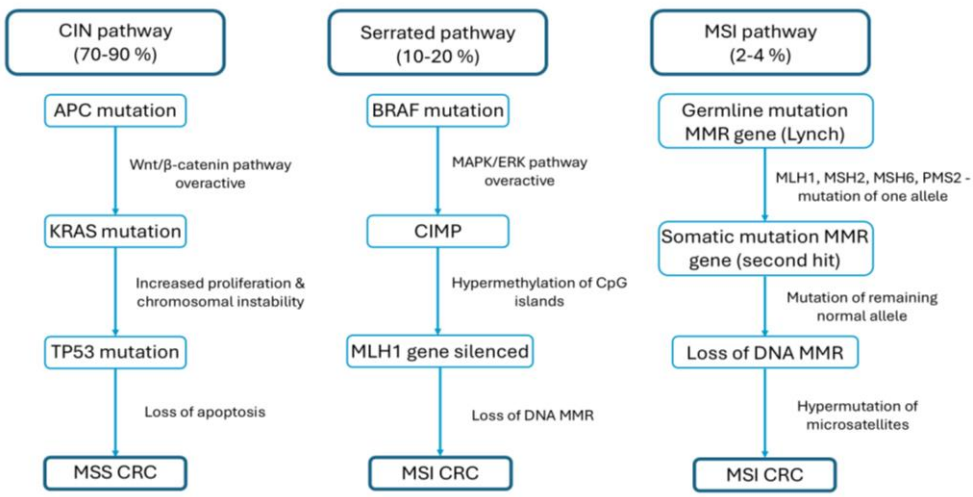

Figure 6. Major molecular pathways driving colorectal cancer development

Since CRC shows substantial molecular diversity, gene expression-based subtyping has emerged as an essential tool for understanding the heterogeneity of CRC. The Consensus Molecular Subtypes (CMS) classification system stratifies CRC into four major subtypes based on gene expression patterns, each associated with distinct molecular features, clinical outcomes, and responses to therapies (113-115).

CMS1, known as the MSI immune subtype, is characterized by MSI, a high mutation burden, and frequent *BRAF* mutations. The CMS1 tumors show strong immune activation and are often associated with a favorable prognosis at early stages, but poorer survival after disease relapses.

CMS2, the canonical subtype, accounts for the largest proportion of CRC cases. It is characterized by CIN and activation of Wnt and Myc signaling pathways. The CMS2 tumors typically display epithelial differentiation, often respond more favorably to conventional chemotherapy, and are associated with better overall survival compared to the other subtypes.

CMS3, the metabolic subtype, is defined by metabolic dysregulation and frequent *KRAS* mutation. CMS3 tumors exhibit altered cellular metabolism, intermediate clinical outcomes, and are less well understood than other subtypes.

CMS4, known as the mesenchymal subtype, is characterized by prominent stromal infiltration, activation of transforming growth factor-β (TGF-β) signaling, angiogenesis, and epithelial-mesenchymal transition. CMS4 tumors are associated with aggressive tumor behavior, increased risk of metastasis, and poor prognosis.

Although CMS classification is not yet routinely used in clinical practice, it represents a valuable tool for research and development of targeted therapies (115).

EOCRC exhibits several distinct molecular characteristics compared with LOCRC. MSI and dMMR are more common in EOCRC (116). EOCRC also shows a higher frequency of *TP53*, *KRAS*, and beta-catenin 1 (*CTNNB1*) mutations but lower rates of *BRAF* mutations and CIMP compared with LOCRC (117-119).

The Hippo pathway

The Hippo signaling pathway plays a crucial role in cell growth, differentiation, and tissue homeostasis, primarily by regulating the transcriptional co-activators YAP1 (Yes-associated protein 1) and TAZ (Transcriptional co-activator with PDZ-binding motif). Under normal conditions, Hippo signaling limits YAP1/TAZ activation by promoting their phosphorylation, thereby retaining them in the cytoplasm. When the Hippo pathway is disrupted, YAP1 and TAZ are dephosphorylated, translocate to the nucleus, and stimulate the transcription of genes that support cell proliferation, survival, and metastasis. This dysregulation of the Hippo-YAP1 pathway has been

linked to a variety of malignancies, including CRC, where it contributes to tumorigenesis, aggressiveness, and poor prognosis (120).

The Hippo-YAP1 pathway interacts with several key signaling pathways in CRC. One of the most significant interactions occurs within the Wnt/β-catenin pathway, which is frequently activated in CRC, by stabilizing β-catenin, promoting cell cycle progression, and tumor growth. Conversely, Wnt signaling can regulate components of the Hippo pathway, thereby affecting YAP1 activity (121, 122). This crosstalk is essential for preserving the balance between proliferation and differentiation in CRC cells. Similarly, PI3K-Akt-mTOR signaling regulates YAP1, promoting cell survival and metabolic reprogramming, supporting tumor growth (123). YAP1 also interacts with TGF-β and Notch signaling, promoting epithelial-to-mesenchymal transition and maintaining cancer stem cells in CRC, thereby contributing to tumor aggressiveness and therapy resistance (124).

Histopathological features

Histopathological evaluation remains central to the diagnosis, prognostication, and treatment decision-making in CRC, providing critical information on tumor type, grade, stage, and molecular correlates (125).

More than 90% of all CRCs are adenocarcinomas, originating from glandular epithelium. Conventional adenocarcinoma is characterized by malignant glands infiltrating the bowel wall, often showing irregular architecture, nuclear atypia, and mitotic activity. Although the majority of cases are diagnosed as adenocarcinoma Not Otherwise Specified (NOS), several other histological variants of adenocarcinomas are recognized, each having distinct clinicopathological features. Mucinous adenocarcinoma is defined by extracellular mucin comprising more than 50 % of the tumor volume. These tumors are more commonly associated with MSI and tend to occur in the proximal colon (126). Signet ring cell carcinoma constitutes a rare and aggressive subtype, characterized by intracellular mucin displacing the nucleus peripherally, giving a signet ring appearance. This subtype is linked to a poor prognosis and advanced stage at diagnosis (127). Other less common variants include medullary adenocarcinoma, often associated with MSI (dMMR) status, and serrated adenocarcinoma, which shows features similar to serrated polyps.

Histological grading of CRC is primarily based on the degree of gland formation. Tumors are classified as low grade (well to moderately differentiated) when more than 50% of glandular structures predominate and high grade (poorly differentiated) when less than 50 % of glandular structures are present. Lymphovascular invasion, perineural invasion, tumor budding, and tumor deposits represent adverse histological features and are recommended for routine reporting in CRC pathology (125). The host immune response, assessed histologically, has been shown to have

prognostic implications where a prominent tumor-infiltrating lymphocyte response has been associated with improved outcomes and MSI status (128).

EOCRC has been shown to be more frequently associated with poorly differentiated tumors, mucinous or signet-ring cell histology, and lymphovascular and perineural invasion than LOCRC. These histopathological differences may contribute to the more aggressive clinical behavior and a higher likelihood of advanced disease (stage III-IV) at diagnosis, often observed in EOCRC (116, 117, 129).

Treatment

Neoadjuvant treatment – colon cancer

The standard treatment for stage I-III colon cancer is upfront surgery. Historically, neoadjuvant therapy has played a limited role, however this approach has been partly revised following the FOxTROT trial. In patients with locally advanced yet operable pMMR (MSS) colon cancer, particularly radiological T4 and/or N2 disease, short-course neoadjuvant oxaliplatin-based chemotherapy can be considered in individuals with good performance status (WHO 0-1) and no obstructive symptoms of the tumor (130). Other studies of T3-T4 colon cancer have confirmed histological tumor downstaging after neoadjuvant chemotherapy, although without consistent improvement in disease-free or overall survival (131, 132). For resectable dMMR (MSI) colon cancer, upfront surgery remains standard. Although the NICHE-2 study reported high pathological complete response rates following short-course neoadjuvant immunotherapy, long-term outcomes and randomized evidence are lacking, which is why immunotherapy should currently be restricted to clinical trials in these patients (133).

In locally advanced colon cancer where radical resection is unlikely (conversion setting) and shrinking of the tumor is needed, neoadjuvant chemotherapy is recommended for pMMR (MSS) tumors with or without the addition of EGFR- or VEGF-targeted agent. In conversion settings with dMMR (MSI) tumors, neoadjuvant immunotherapy may be discussed at a multidisciplinary team conference.

Radiotherapy has been far less extensively studied in colon cancer than in rectal cancer and has no proven benefit in operable disease. However, limited registry data suggest improved R0 resection rates and survival in cT4 tumors, and despite weak evidence, preoperative chemoradiotherapy may be considered in selected cases of locally advanced, non-metastatic colon cancer with invasion of adjacent unresectable structures (134).

Neoadjuvant treatment – rectal cancer

In localized rectal cancer, neoadjuvant treatment is tailored according to the estimated risk of local and distant recurrence, primarily based on MRI-staging. In early rectal cancer, where the risk of local recurrence with surgery alone is ≤ 5-6 %, upfront surgery without neoadjuvant therapy is recommended in Sweden. For intermediate-risk disease, defined by an estimated local recurrence risk of ≥ 6-8 % but without markedly increased risk of distant metastases, short-course radiotherapy (SCRT: 5 Gray x 5 days) followed by surgery is recommended, either with immediate resection or with a delay of 4-8 weeks.

In locally advanced rectal cancer, where tumor downstaging is required to facilitate radical resection or where the risk of distant metastases is high, total neoadjuvant therapy (TNT) is now recommended. In Sweden, TNT most commonly consists of SCRT followed by 12-18 weeks of combination chemotherapy, reflecting a shift of systemic treatment from a postoperative to the preoperative setting. In patients who are not candidates for combination chemotherapy, SCRT followed by delayed surgery remains the standard approach. The rationale for neoadjuvant therapy includes tumor downstaging, reduction of locoregional recurrence, early treatment of micrometastatic disease, and, in selected cases, the possibility of organ preservation (80).

Multiple randomized clinical trials have shown that neoadjuvant radiotherapy significantly reduces the risk of local recurrences in rectal cancer, with SCRT reducing the relative risk by approximately 50-70%, independent of surgical technique (135, 136). Radiotherapy has shown to be more effective when delivered preoperatively than postoperatively (137). Randomized clinical trials have also shown that conventional fractionated radiotherapy (1,8-2 Gray daily up to 45-50.4 Gray for 5-6 weeks) combined with concurrent chemotherapy (5-Fluorouracil or capecitabine), so-called conventional chemoradiotherapy (CRT), has shown improved local control and likely survival compared with radiotherapy alone in locally advanced disease (138, 139). However, comparisons between conventional fractionated radiotherapy combined with concurrent chemotherapy versus SCRT alone in cT3-T4 tumors have not demonstrated significant differences in local control, disease-free survival, or overall survival (140, 141).

A total neoadjuvant therapy strategy has been evaluated in several clinical trials. The RAPIDO study showed that SCRT followed by neoadjuvant capecitabine and oxaliplatin (CAPOX) chemotherapy significantly increased pathological complete response rates and reduced distant metastases compared with neoadjuvant conventional CRT followed by selective use of adjuvant chemotherapy in selected patients, although no overall survival benefit was observed and a higher rate of locoregional recurrence was reported at five years (142, 143). Other studies have similarly demonstrated improved tumor response and reduced distant failure with

total neoadjuvant therapy (144, 145). In patients with a complete clinical response after neoadjuvant treatment, a “watch-and-wait” strategy may be considered in experienced centers, provided informed consent is obtained (146, 147).

Overall, SCRT followed by neoadjuvant chemotherapy (TNT) has become the preferred standard treatment for locally advanced rectal cancer in Sweden, while conventional CRT remains an alternative, particularly when maximal tumor regression or organ preservation is prioritized. Despite the more widespread use of conventional CRT worldwide, randomized studies have not demonstrated superior local control or survival compared to SCRT with neoadjuvant chemotherapy. Routine adjuvant chemotherapy after surgery is generally not recommended, as systemic treatment is now predominantly administered in the neoadjuvant setting.

The presence of dMMR (MSI) can guide treatment decisions in localized rectal cancer. Phase II studies have reported remarkably high clinical complete response rates following neoadjuvant PD-1 blockade in locally advanced disease. Although this approach has not yet been approved by the Food and Drug Administration (FDA) or European Medicines Agency (EMA), the 2025 National Comprehensive Cancer Network (NCCN) guidelines recommend six months of PD-1-directed immunotherapy as the preferred primary treatment for patients with dMMR (MSI) rectal cancer staged T3-4 or N1-2 (148, 149).

After completing neoadjuvant therapy, patients undergo restaging with CT scans and pelvic MRI (for rectal cancer) to evaluate tumor response, including any downstaging of the TNM stage. This assessment informs the planning of the subsequent step, which is typically surgical resection.

Surgical treatment

Surgery remains the primary curative treatment for CRC and aims to achieve complete tumor removal with negative resection margins (R0). At the beginning of the surgical procedure, the abdominal cavity is systematically explored to identify previously undetected metastatic disease or locally advanced tumor growth, which may alter the surgical strategy. Surgical resection is performed along anatomical planes with the removal of the intact mesentery and associated lymphatic drainage. In colon cancer, this approach is referred to as complete mesocolic excision (CME) and involves resection of the tumor-bearing bowel segment together with its mesocolon and central vascular ligation, whereas surgical treatment of rectal cancer follows the principles of total mesorectal excision (TME). Adequate longitudinal and circumferential margins, as well as removal of lymph nodes, are essential for oncological radicality (150, 151).

Minimally invasive surgery, including laparoscopic and robot-assisted techniques, is recommended as first-line treatment when feasible. Compared with open surgery, minimally invasive approaches provide equivalent oncological outcomes while offering advantages in terms of faster recovery, reduced postoperative pain, shorter hospital stay, and fewer abdominal wall complications (152, 153).

The extent and type of resection depend on tumor location, stage, and patient-related factors. Segmental colectomy is generally sufficient for most colon cancers, while rectal cancer is treated with anterior resection or abdominoperineal excision, depending on tumor height, sphincter involvement, and the possibility of achieving adequate margins. Temporary or permanent stoma formation may be required in some cases.

Locally advanced CRC, where standard resection cannot achieve clear margins, requires a multidisciplinary approach. To obtain oncological radicality (R0), en bloc multivisceral resection of involved organs or structures may be required, as dissection through tumor-adjacent adhesions is linked to an increased risk of residual disease and local recurrence (154). Due to technical complexity, such cases should be treated at specialized high-volume centers (155). Similarly, patients with local recurrence should be referred to high-volume centers as radical resection offers the best chance for long-term survival despite increased surgical complexity (156).

Adjuvant treatment

Adjuvant chemotherapy is administered after curative-intent surgery in CRC to reduce the risk of recurrence. The main agents used are fluoropyrimidines (5-FU or capecitabine) either as monotherapy or in combination with oxaliplatin. The choice to initiate adjuvant therapy should consider recurrence risk and be individualized through shared decision-making with the patient.

For colon cancer, fluoropyrimidine monotherapy typically requires six months of treatment, while combination therapy with oxaliplatin can often be limited to three months, particularly for lower-risk stage III disease. High-risk stage II patients, defined by risk factors such as pT4 tumors or tumor perforation, may also benefit from adjuvant therapy. The addition of oxaliplatin further increases disease-free survival by approximately 20 % in stage III colon cancer but has not demonstrated a clear benefit in stage II cases (157, 158). Adjuvant therapy should begin as soon as possible after surgery, ideally within six weeks and no later than eight weeks, as delayed initiation beyond 12 weeks compromises efficacy (159). Age and comorbidity influence the treatment choice. Patients aged $\geq$ 70 years may benefit less from oxaliplatin and have a higher risk of toxicity, which is why monotherapy

with fluoropyrimidine is often preferred, although combination therapy can be considered in biologically fit older patients (160, 161).

The duration of adjuvant chemotherapy has been evaluated in the IDEA collaboration, which demonstrated that shorter treatment durations are associated with substantially reduced toxicity. In patients with lower-risk stage III tumors (T1-3, N1), three months of capecitabine and oxaliplatin (CAPOX) appears to provide comparable disease control compared to six months, whereas evidence supporting three months of 5-FU and oxaliplatin (FOLFOX) is less robust. In patients with higher-risk disease or when monotherapy with fluoropyrimidines is used, six months of treatment remains the standard (162).

In rectal cancer, adjuvant chemotherapy is more selectively applied due to evolving preoperative treatments. Patients treated with TNT or conventional CRT may not require additional postoperative chemotherapy, as the full adjuvant effect is considered achieved. Decisions should also be guided by postoperative pathological assessment and the presence of risk factors (142-144).

Tumors with dMMR (MSI) are associated with a favorable prognosis (163). In stage II colon cancer, fluoropyrimidine monotherapy has not demonstrated a clear benefit in dMMR tumors and is therefore generally not recommended (164). In patients with high-risk stage II and stage III dMMR tumors, combination chemotherapy including oxaliplatin may be considered, as there is insufficient data to support the use of monotherapy alone (165). Despite its clinical relevance, MMR status should be interpreted in conjunction with pathological risk factors when deciding on adjuvant treatment. Emerging biomarkers, such as circulating tumor DNA (ctDNA) and tumor immunoprofiles, show promise for tailoring adjuvant therapy, but standardized and clinical implementation is pending (166).

Postoperative outcomes & follow-up

Postoperative complications

Postoperative complications remain a major contributor to morbidity, mortality, and reduced quality of life following CRC surgery (167, 168). The development of these complications is affected by a combination of patient-related, tumor-related, and perioperative factors. General preoperative risk factors often include advanced age, sex, impaired nutritional status, obesity, the presence of comorbidity and systemic inflammatory responses, all of which may negatively affect postoperative recovery (169). Tumor-specific characteristics also play a role in postoperative complication

risk. Advanced tumor stage, large tumor size, invasion of adjacent structures, and acute presentation such as bowel obstruction, bleeding, or perforation are associated with increased surgical complexity and a higher rate of postoperative complications (170-172).

Early postoperative complications are particularly relevant as they are linked to increased short-term mortality and may also affect long-term oncological outcomes. Surgical complications, such as anastomotic leakage, postoperative bleeding, and infection are among the most serious adverse events following CRC resection. These complications commonly occur within the first 1-2 postoperative weeks following surgery and may substantially increase the need for additional treatment and follow-up care (173).

Anastomotic leakage represents a critical complication resulting from impaired healing at the anastomotic site and is associated with severe intra-abdominal infection and increased mortality. Its occurrence is influenced by preoperative patient-related factors such as advanced age, smoking, obesity, metabolic disorders, impaired immune status, history of radiotherapy, as well as by tumor characteristics, emergency presentation, and technical aspects of surgery (174).

Postoperative infections, including surgical site infections and intra-abdominal infections, represent another major category of complications following CRC surgery. Risk factors include, for example, obesity, diabetes mellitus, male sex, stoma formation, smoking, emergency surgery, and prolonged operative time (175).

Intra-abdominal bleeding is a serious postoperative complication that may result from vascular injury, inadequate hemostasis, or coagulopathy. Although relatively uncommon, it often requires urgent intervention and is associated with increased morbidity, longer hospital stays, and a higher risk of mortality. Risk factors include extensive surgery, emergency procedures, presence of comorbidities such as heart and kidney disease, as well as preexisting coagulation disorders (176).

Stoma formation is associated with a distinct spectrum of early postoperative complications. These include peristomal skin irritation, mucocutaneous separation, and ischemia or necrosis of the stoma. Such complications may result from patient-related factors such as advanced age, obesity, corticosteroid use, as well as technical factors, impaired blood supply, or excessive tension on the bowel (177).

EOCRC patients generally tend to have fewer age-associated comorbidities, including pulmonary and cardiovascular disease, which is associated with a lower baseline risk to develop medical complications compared to LOCRC. However, EOCRC may experience a greater functional and psychological impact from postoperative complications due to longer life expectancy, work and family

responsibilities, as well as higher expectations for postoperative quality of life, even after uncomplicated surgery.

Functional & psychological outcomes

The impact of CRC extends beyond its physical aspects, significantly affecting functional and psychological outcomes that can influence quality of life. Surgical treatment for CRC can lead to lasting changes including stomas (temporary or permanent), diarrhea, constipation, incontinence or altered bowel functions, with possible complications such as anastomotic leaks, infections or delayed healing, further worsening symptoms. These issues often disrupt daily activities, social participation, and return to work which can profoundly affect a patient's sense of independence and normalcy. Pelvic surgeries, particularly in rectal cancer, can also impair sexual and urinary functions with complications like urinary retention, fistulas, or nerve injury exacerbating the adverse symptoms.

The long-term effects of chemotherapy or radiotherapy also contribute to functional outcomes. Chemotherapy-induced peripheral neuropathy, fatigue, and muscle weakness can hinder patients' ability to perform basic daily tasks, while radiotherapy can lead to intestinal dysfunction, causing chronic pain, bloating, and bowel obstruction.

CRC diagnosis and treatment can also lead to significant psychological challenges, including stress, anxiety, depression, and fear of recurrence. Concern about stomas or long-term bowel dysfunction may affect self-esteem, body image, and social relationships. Post-traumatic stress is also common, particularly after intensive treatments or surgical complications, with some patients experiencing chronic symptoms such as intrusive thoughts, hyperarousal, and avoidance behaviors.

Strong social support from family, friends, or support groups is critical for coping with the psychological impact of CRC. Targeted interventions like rehabilitation programs, counseling, and cognitive-behavioral therapy can help manage anxiety, depression, and stress, improving overall quality of life.

Postoperative surveillance

Postoperative follow-up after curative surgery for CRC aims to detect potentially treatable recurrences and metachronous neoplasia. Surveillance strategies are therefore directed at patients considered fit for further oncological or surgical intervention in the event of disease recurrence.

For patients with radically resected stage II-III CRC without metastases, routine follow-up with contrast-enhanced CT of the thorax and abdomen combined with

carcinoembryonic antigen (CEA) testing at 12 and 36 months postoperatively is recommended in Sweden. Patients with radically resected stage I tumors have a low risk of recurrence, and routine surveillance with CT imaging and CEA testing is not recommended in this group. Adequate staging at the time of primary treatment is essential to identify synchronous metastases. If a complete, high-quality colonoscopy was not performed preoperatively, it should be performed as soon as possible after surgery, no later than six months postoperatively. Long-term surveillance of metachronous adenomas and tumors is recommended with colonoscopy at three years after surgery and subsequently every five years, provided the patients remain eligible for intervention. Follow-up may be omitted or discontinued in patients with significant comorbidity who are unlikely to tolerate treatment for recurrence (80).

Follow-up after resection of metastases varies between guidelines and clinical practice. The European Society for Medical Oncology (ESMO) recommends relatively intensive surveillance during the first years, with follow-up every three months for two years and every six months thereafter, although these recommendations are largely based on expert consensus rather than evidence (178). In Sweden follow-up after radical resection of metastases is typically less intensive, with follow-up every six months for two years and an additional control at three years. For patients undergoing cytoreductive surgery with HIPEC for peritoneal carcinomatosis, as well as selected patients after liver or lung metastases resection, follow-up continues annually for one to three years after the initial two-year period, with additional follow-up at four and five years (80).

The scientific evidence supporting different follow-up strategies is limited. Early studies evaluating survival outcomes were heterogeneous and underpowered, and their relevance is further reduced by major advances in imaging and treatment of metastatic disease over the past two decades. CT of the thorax and abdomen combined with CEA testing constitutes the preferred surveillance modality. CEA should not be used as a standalone test but interpreted in conjunction with imaging findings and longitudinal trends (179). There is no evidence to support routine use of MRI or PET imaging (180, 181). Circulating tumor DNA is a promising marker for recurrence risk but is not yet sufficiently validated for routine clinical use (182-184). Large, randomized control trials, including COLOFOL, FACS, and GLIDA, have consistently shown that more intensive follow-up does not improve overall or cancer-specific survival despite higher detection rates or presence of operable recurrences (185-187). Consequently, intensified surveillance is not routinely recommended.

The concept of individualized follow-up based on a patient´s risk profile is appealing, yet the scientific evidence supporting the need for more frequent follow-up in high-risk patients remains insufficient. While current surveillance guidelines

are largely based on LOCRC, EOCRC may require more tailored approaches because of the distinct features and risk profiles of younger patients. Early recurrence patterns in EOCRC suggest the need for careful monitoring, with potential for intensified or personalized surveillance in high-risk groups (188). Additionally, younger patients may require more personalized follow-up to address functional, psychological, and fertility concerns as well as quality-of-life concerns.

Aims

Paper I

The aim was to examine trends of CRC incidence and tumor localization comparing age-groups < 50, 50-79, and ≥ 80 years in Sweden.

Paper II

The aim was to examine whether postoperative 30-day complications and the rate of emergency surgery differed between CRC patients < 50 years compared with those diagnosed at older ages.

Paper III

The aim was to evaluate whether high-frequency follow-up after CRC surgery is associated with reduced 5-year overall mortality, cancer-specific mortality, and recurrence among patients ≤ 50 years.

Paper IV

The aim was to investigate age-related differences in YAP1 expression in CRC and to examine its association with mitochondrial oxidative phosphorylation, molecular subtype, and prognosis, with functional validation in EOCRC-like (≤ 50 years) versus LOCRC-like cells (> 50 years).

Methods

Overview of methods

Table 3. Overview of methods in the included studies

	Paper I	Paper II	Paper III	Paper IV
Title	Increasing CRC incidence in individuals aged < 50 years – a population-based study	Postoperative complications and emergency surgeries in CRC patients <50 years – a national cohort study	Follow-up intensity after CRC surgery in patients aged ≤50, 50–70 and >70 years – a subgroup analysis within the COLOFOL randomized control trial	YAP1 drives mitochondrial reprogramming in early onset CRC cells through TFAM regulation
Study design	Observational cohort study	Observational cohort study	Subgroup analysis of a randomized control trial	Transcriptomics datasets analyses with in vitro functional validation
Study population	CRC <50, 50-79, ≥80 years in Sweden	CRC <50, 50-79, ≥80 years in Sweden	CRC ≤50, 51–70, >70 years in Denmark, Sweden & Uruguay	CRC ≤50 & >50 years
Study period	1995-2015	2015-2018	2006-2010	2025-2026
Data sources	SCR	The Swedish Colorectal Cancer Registry	COLOFOL trial cohort	Gene Expression Omnibus datasets & American Type Culture Collection
Outcome	Incidence rate	Postoperative 30-day complications & emergency resections	5-year overall mortality, cancer-specific mortality rate, 5-year cancer-specific recurrence rate	YAP1-mediated metabolic and prognostic features in EOCRC

CRC, colorectal cancer; EOCRC, early-onset colorectal cancer; SCR, The Swedish Cancer Register; RCT, Randomized control trial; SCRCR, The Swedish Colorectal Cancer Registry

Paper I

Study population

The study was a nationwide, population-based observational study conducted in Sweden. The study population comprised all individuals diagnosed with CRC during the period from 1995-2015. Analyses were performed at the population level, using national registry data. The study population comprised individuals diagnosed with CRC adenocarcinoma, whereas cancers of the anus, appendix, and tumors with unspecified locations were excluded.

Data sources & data collection

Data were obtained from the national health registers administered by the Swedish National Board of Health and Welfare. Information on CRC incidence was retrieved from the Swedish Cancer Registry (SCR), a compulsory nationwide registry established in 1958 to monitor cancer incidence and survival trends in Sweden. The register captures approximately 80,000 new malignant tumors per year (excluding basal cell carcinoma) and records detailed information on tumor type, morphology, date of diagnosis, patient demographics, and tumor extent. Tumors are coded according to successive versions of the International Classification of Diseases (ICD and ICD-O). The SCR is highly complete and provides the foundation for official cancer statistics and epidemiological research in Sweden (189). Mortality data from the Swedish Cause of Death Register (SCDR) were available through registry linkage but were not analyzed as outcome in this study.

Statistical analysis

CRC incidence rates were computed overall and stratified by age-group, sex, and tumor localization. Temporal trend analyses were performed using Poisson regression models to evaluate changes in incidence over time. Statistical significance of observed trends was assessed using estimates from the Poisson regression models and their 95% confidence intervals (CIs). Results were presented as age-standardized incidence rates and relative changes across the study period.

Paper II

Study population

This study was a national, population-based cohort analysis including all individuals in Sweden who underwent surgical resection for stage I-III CRC between 2010-2018, as recorded in the Swedish Colorectal Cancer Registry (SCRCR). The cohort comprised 33,320 patients. Excluded from the study were patients who did not undergo abdominal surgical resection, those with carcinoma of the appendix, and patients with missing key data required for analysis (11,896).

Data sources and data collection

Data were obtained from the SCRCR, a national quality registry that prospectively collects detailed clinical information on all diagnosed colorectal adenocarcinomas in Sweden. The register includes two components: one for rectal cancer (recorded from 1995) and one for colon cancer (recorded from 2007) (190, 191). Reporting to the registry is nearly complete, with coverage between 2008 and 2015 of 98-99%, and most cases are reported within 12 months of diagnosis (192). The SCRCR contains information on patient demographics, tumor characteristics, preoperative staging, radiology, perioperative and postoperative surgical details, pathology reports, and follow-up. Data are registered continuously during treatment and follow-up, and the number of variables has expanded over time to address evolving clinical research questions. The registry supports quality improvement, evaluation of national care guidelines, and research to improve treatment outcomes and reduce regional differences in care.

Statistical analysis

Patient characteristics, tumor characteristics, surgical details, and outcomes were compared across age groups using bivariate analyses. The analysis of variance (ANOVA) method was employed for continuous variables, and the chi-square test was used for categorical variables. To assess the association between age group and postoperative 30-day complications, a multivariable logistic regression model was used which estimates the odds of experiencing any postoperative 30-day complication. The model was adjusted for potential cofounders including sex, tumor localization, neoadjuvant (chemo)radiotherapy, and American Society of Anesthesiologists (ASA) score. Adjusted odds ratios (ORs) with 95% CIs were reported.

Paper III

Study population

The study is a subgroup analysis of patients enrolled in the COLOFOL randomized trial, a multicenter study conducted at 24 hospitals in Sweden, Denmark, and Uruguay between 2006 and 2010. A total of 2,509 patients were included in the intention-to-treat analysis. Eligible patients had undergone surgical resection with curative intent (R0 resection) for colorectal adenocarcinoma, with or without neoadjuvant treatment according to national guidelines. Inclusion criteria comprised stage II or stage III disease, age < 76 years at the time of surgery, and confirmation of a neoplasia-free colon and rectum within three months post-surgery. All participants were required to have preoperative imaging of the liver and lungs. Carcinoembryonic antigen (CEA) levels were measured one month after surgery, and patients with elevated postoperative values were included only after exclusion of residual or metastatic disease. Exclusion criteria included local resection only, known hereditary CRC syndromes, limited life expectancy due to comorbidity, inability to provide informed consent or adhere to follow-up, participation in conflicting clinical trials, or history of malignancy other than non-melanoma skin cancer.

Data sources and data collection

Data for the study were obtained from the COLOFOL randomized trial, in which patients were allocated in a 1:1 ratio to low-frequency or high-frequency postoperative follow-up after curative CRC surgery (185). The present study is a post hoc subgroup analysis performed within the established trial cohort and was not part of the original protocol. Clinical data were prospectively collected according to the trial protocol and included patient demographics, tumor characteristics, treatment details, and follow-up investigations.

Follow-up procedures differed by randomization group. Patients in the high-frequency group underwent contrast-enhanced CT of the thorax and abdomen and serum CEA at 6, 12, 18, 24, and 36 months post-surgery, while those in the low-frequency group were assessed at 12 and 36 months. Surveillance data were obtained through scheduled clinical visits and included imaging results, CEA levels, symptom reporting, and documentation of recurrence and survival outcomes. Follow-up continued for three years, with recurrence and mortality outcomes tracked up to five years.

Statistical analysis

Baseline patient, tumor, and treatment characteristics were summarized using descriptive statistics and compared across predefined age groups. The incidence of the outcomes 5-year overall mortality, cancer-specific mortality rate, and 5-year cancer-specific recurrence rate was analyzed using time-to-event methods, accounting for competing risks when applicable. Risk differences were assessed using appropriate statistical tests, and effect estimates were reported with 95% CIs.

Associations with outcomes were evaluated using multivariable regression models, adjusting for age at surgery, sex, stage, tumor localization, planned postoperative chemotherapy, history of diabetes, cardiovascular disease, cerebrovascular disease, pulmonary disease, and smoking. The proportional hazards assumption was assessed, and because it was not fully met, the reported hazard ratios are interpreted as average effects over the follow-up period. To account for differences across participating centers, additional models including center-level random effects were applied.

Paper IV

Study population

Three independent CRC cohorts from the publicly available Gene Expression Omnibus (GEO) were included in the bulk RNA-sequencing data analysis, comprising a total of 811 patients along with a gene set from the Molecular Signature Database (MSigDB), containing 200 genes. For functional validation, four human CRC cell lines (three EOCRC-like and one LOCRC-like) were obtained from the American Type Culture Collection (ATCC).

Data sources and data collection

Bulk RNA-sequencing data

Gene expression data from three GEO cohorts (GSE39582 [n=579], GSE17536 [n=177], and GSE17537 [n=55]) were retrieved from publicly available research databases, which contain anonymized tumor samples and molecular data collected and used in previous CRC studies. Available clinical variables, including sex, tumor stage, and MSI status, were obtained from dataset annotations and original publications.

The hallmark oxidative phosphorylation (OXPHOS) gene set was obtained from the MSigDB, a publicly available, validated database of predefined gene sets

representing established biological pathways. No new patient data or biological material were collected for the bulk RNA-sequencing data.

Functional validation

Human CRC cell lines were obtained from the ATCC, a certified international cell bank of authenticated cell lines originally derived from surgically resected human tumors. Cell lines derived from patients aged ≤ 50 years (**HT-29**, ATCC® HTB-38™; **SW480**, ATCC® CCL-228™; **HCT116**, ATCC® CCL-247™) were classified as EOCRC-like, whereas the cell line derived from a patient < 50 years (**Caco-2**, ATCC® HTB-37™) was classified as LOCRC-like. The HT-29 cell line was derived from a 44-year-old female with colonic adenocarcinoma; SW480, from a 50-year-old male with colonic adenocarcinoma; HCT116, from a 48-year-old male with colonic adenocarcinoma; and Caco-2, from a 72-year-old male with colonic adenocarcinoma. Cells were grown under standard conditions as recommended by the supplier. All experiments were conducted using cells at low passage numbers, meaning they had been sub-cultured only a few times since being obtained from ATCC, and all cultures were confirmed to be free of mycoplasma.

Non-targeted and YAP1-targeted small interfering RNAs (siRNAs) were purchased from Dharmacon, a commercial supplier of synthetic RNA molecules for gene silencing (catalog numbers: D-001206-13-20 and M-012200-00-0010).

The YAP1 inhibitor Verteporfin was obtained from Sellack Chemicals. All antibodies were purchased from commercial suppliers: Cell Signaling Technology (YAP, TFAM), Santa Cruz Biotechnology (GAPDH, β-actin), Thermo Fisher (Goat anti-Rabbit IgG (H+L), Alexa Fluor™ 488, Goat anti-Mouse IgG (H+L), Alexa Fluor™ 555), Sigma (DAPI), and Dako (Goat Anti-Rabbit Immunoglobulins/HRP, Goat Anti-Mouse Immunoglobulins/HRP). These antibodies and inhibitors were ordered from their respective suppliers' websites.

Bulk RNA-sequencing data analysis

Differential gene expression analysis

To identify genes differentially expressed between EOCRC and LOCRC, the Linear Models for Microarray Data (limma) package in R was used. Linear models were applied to gene expression data from each GEO cohort, with age-group as the primary variable of interest. Where available, models were adjusted for potential confounders including sex, tumor stage, and MSI status. To improve the accuracy and statistical power of the results, empirical Bayes moderation was applied, to stabilize variance estimates across genes. The Benjamini-Hochberg method was used to control for multiple testing across all genes, and genes with an adjusted p-value (false discovery rate, FDR) < 0.05 and an absolute log2 fold change > 0.5 were considered significantly differentially expressed.

To confirm the reliability of the findings, the primary analyses were repeated across three independent GEO cohorts. A meta-analysis was conducted using random-effects models in the metafor package (v 4.4-0) to combine effect sizes from the individual datasets. The degree of heterogeneity between studies was assessed using I^2 statistics and Cochran's Q test. Effect sizes and their corresponding confidence intervals for each cohort, as well as pooled estimates, were visualized using forest plots.

Gene set enrichment & correlation analysis

To identify biological pathways associated with YAP1 expression, gene set enrichment analysis (GSEA) was performed using gene expression data from each GEO dataset. Genes were ranked by their Spearman correlation with YAP1 expression. Enrichment was assessed using four gene set categories: (1) Hallmark pathways from MSigDB, (2) Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways including a custom set of 60 core genes involved in OXPHOS, (3) genes regulating mitochondrial biogenesis (TFAM, NRF1, PPARGC1A, PPARGGC1B), and (4) a YAP1 target gene set (CTGF, CYR61, ANKRD1, AREG). Except for the Hallmark OXPHOS gene set obtained from the MSigDB, the other gene sets were selected based on prior biological knowledge and published studies. Enrichment analysis was performed using the fgsea package in R with 10,000 permutations, and pathways with an FDR < 0.05 and normalized enrichment score (NES) > 1.5 were considered significantly enriched.

To examine the relationship between YAP1 expression and OXPHOS pathway activity, Spearman correlation analysis was performed using the same GEO datasets. OXPHOS activity was estimated for each tumor sample in the GEO datasets by calculating the mean expression of the 200 genes in the Hallmark OXPHOS gene set from MSigDB, generating a single pathway activity score per sample (higher scores indicate higher OXPHOS activity). Correlation analyses were conducted separately for EOCRC and LOCRC groups, and statistical significance was assessed using permutation testing.

Consensus molecular subtype classification

To examine potential differences in CRC subtypes between EOCRC and LOCRC, CMS classification was performed on gene expression data from the GSE39582 dataset from GEO using the CMScaller algorithm. This tool applies a random forest classifier to assign each tumor sample to one of four CMS based on their gene expression profiles: CMS 1 (MSI Immune), CMS2 (Canonical), CMS3 (Metabolic), and CMS 4 (Mesenchymal). Prior to classification, gene expression data were converted from gene symbols to Entrez IDs using the org.Hs.eg.db annotation package to ensure consistency. The CMScaller algorithm was then applied to assign each tumor sample with the closest CMS subtype. Samples for which the algorithm

was uncertain about the classification were excluded from further subtype-specific analyses.

Functional validation analysis

To experimentally validate the findings from the bulk RNA sequencing analysis, functional validation was conducted using both pharmacological and genetic silencing of YAP1.

YAP1 inhibition – pharmacological silencing

The drug Verteporfin was used on HT-29 and SW480 cells (EOCRC-like), as well as Caco-2 cells (LOCRC-like) to assess the effects of pharmacological YAP1 silencing on mitochondrial morphology (via mitochondrial visualization) and protein expression levels (via Western blotting).

siRNA transfection – genetic silencing

Non-targeted or YAP1-targeted siRNA (Dharmacon) was transfected into HT-29 and SW480 cells (EOCRC-like) using standard transfection protocols. The siRNA molecules were designed to specifically bind to the mRNA of the YAP1 gene, leading to genetically silencing of YAP1 and inhibition of protein production. This approach was used to further assess the effect of genetic YAP1 silencing on mitochondrial morphology (via mitochondrial visualization), protein expression levels (via Western blotting), and protein localization (via immunofluorescence).

Mitochondrial visualization

Mitochondrial morphology was assessed to determine how YAP1 silencing (pharmacologically and genetically) affects mitochondrial dynamics, particularly fission and fusion. Under stress conditions, such as those in cancer, mitochondrial dysfunction can lead to excessive fragmentation, elongated tubular structures becoming punctate, spherical organelles, resulting in the loss of interconnected reticular architecture of the mitochondria. These morphological changes can affect cellular energy production and contribute to disease progression. MitoTracker™ Red CMXRos stain was used to stain mitochondria, enabling visualization of structural mitochondrial changes in cells. Following treatment of cells with the drug Verteporfin or siRNA targeting YAP1, mitochondria were labeled and analyzed to observe any alterations in shape or structure. Imaging was performed using confocal microscopy, and changes in mitochondrial morphology were quantified using imageJ software.

Western blotting

Western blotting was used to investigate protein levels of key markers following both pharmacological and genetic YAP1 silencing in HT-29 and SW480 cells (EOCRC-like) and in Caco-2 cells (LOCRC-like). This technique detects and

quantifies specific proteins of interest, providing insight into the effects of YAP1 inhibition on downstream cellular processes, particularly those related to mitochondrial function and energy metabolism.

After YAP1 silencing, protein extracts were prepared from treated cells, and the protein concentration was determined. The same quantities of protein were loaded onto SDS-PAGE gels, transferred to PVDF membranes, and probed with primary antibodies targeting the protein of interest. Secondary antibodies allowed chemiluminescent detection, and protein bands were visualized and quantified using a ChemiDoc imaging system. Densitometric analysis was performed, and protein levels were normalized to corresponding loading controls for reliable comparisons across experimental conditions.

Immunofluorescence

Immunofluorescence staining was employed to visualize the subcellular location and expression of specific proteins following genetic YAP1 depletion in SW480 cells (EOCRC-like). This provides valuable insight into how YAP1 silencing affects mitochondrial dynamics and function. Cells were fixed and made permeable to enable antibody access to intracellular structures. Primary antibodies targeting proteins of interest were applied, followed by secondary antibodies labeled with fluorescent dyes for detection. Fluorescently labeled antibodies were then visualized using confocal microscopy, and images of specific regions of interest were captured. Fluorescence intensity was quantified using ImageJ software, enabling assessment of changes in protein distribution between experimental conditions.

Statistical analysis

Statistical analyses for both bulk RNA-sequencing data and functional validation were conducted using R (v4.3.0) and Graphpad Prism (v10.0), respectively. Limma was used to find all genes differentially expressed between EOCRC and LOCRC groups. Parametric tests, non-parametric tests and meta-analysis were performed to focus on YAP1 across independent cohorts. Parametric tests (Student's t-test, ANOVA) were used when data met normality assumptions, and non-parametric tests (Mann-Whitney U, Kruskal-Wallis) were used when these assumptions were not met. For RNA-sequencing data, more detailed statistical analyses, including methods for normalization and correction for multiple testing, are described above. For all tests, p-values < 0.05 were considered statistically significant. In cases of multiple comparisons, appropriate corrections (e.g., Bonferroni or FDR) were applied where necessary.

Definitions

Age-groups were used to stratify CRC cases into predefined age categories: < 50 years, 50-79 years and ≥ 80 years at diagnosis (papers I and II). In paper III, age-groups were defined as ≤ 50 years, 51-70 years, > 70 years, and in paper IV as EOCRC (ages ≤ 50 years) and LOCRC (ages > 50 years).

Tumor location was classified by primary site: proximal colon cancer (caecum, ascending colon, transverse colon, splenic flexure), distal colon cancer (descending colon, sigmoid colon) and rectal cancer (< 15 centimeters from the anal verge) (papers I, II, III, IV). In paper II, for tumors spanning multiple segments, the location was defined by the tumor center or deepest invasion according to T stage.

Emergency surgery was defined as a non-elective resection performed due to acute presentation (e.g., obstruction, perforation/abscess, or bleeding) (paper II).

Postoperative 30-day complications were characterized as any surgical or medical adverse events requiring treatment that occurred during the index hospital stay or within 30 days after CRC surgery, including events after discharge to home (paper II).

Cardiovascular disease included a diagnosis of acute myocardial infarction, hypertension or other heart diseases (paper III).

CRC-like cells are cell lines derived from CRC patient tumor tissue and cultured in the laboratory under optimal conditions. These cells retain molecular and genetic characteristics of the original tumor (paper IV).

Ethical considerations

For study I, data were obtained from the SCR, a publicly available database that registers all primary malignant tumors in Sweden. As a health data register, the SCR operates under the Health Data Register Act (1998:543) and associated regulations (2001:709), which govern the types of information that can be included and the obligations of healthcare providers to submit data. The registry is regulated by the Swedish National Board of Health and Welfare, which ensures that the necessary ethical guidelines are followed. Since the data used in this study is fully anonymized and publicly available, no additional ethical approval or informed consent was required.

For study II, data were obtained from the SCRCR, which collects data that is gathered with the patient's permission. The study was approved by the Stockholm Regional Ethical Review Board, Sweden (Dnr: 2017/2295-32).

For study III, ethical approval was obtained by the Uppsala Regional Ethical Review Board, Sweden (Dnr: 2004 M-453), the Frederiksberg and Copenhagen Scientific Committee (KF 01-194/04), and the Ethics committee of the Faculty of Medicine at the University of the Republic, Uruguay (Exp. No. 074140-094530-06). All participants provided written informed consent following their primary surgical CRC resection.

For study IV, ethical approval was not required, as this study used publicly available data and commercially sourced reagents. The GEO and MSigDB datasets used in this study contain anonymized data from previous research, with no personal or identifiable information involved. The ATCC cell lines were obtained from publicly available repositories, where cell lines are typically immortalized or established from human tissues. These cell lines have been ethically sourced by the suppliers, and the necessary informed consent and ethical approval were obtained by the institutions that originally collected the biological material. Additionally, reagents from Dharmacon, Selleck Chemicals, Cell Signaling Technology, Santa Cruz Biotechnology, Thermo Fisher and Dako are laboratory products and do not include the collection of human samples.

Main results

Paper I

Crude & age-standardized incidence

- A significant overall increase in CRC incidence was observed in Sweden, with the crude incidence rate (unadjusted for confounders) rising by 31%, from 48.1 per 100,000 in 1995 to 63.1 per 100,000 in 2015.
- The age-standardized incidence rate increased by 20 % from 33.37 to 40.09 per 100,000 between the same years. The smaller increase compared with the crude rate reflects the ageing Swedish population, yet it still indicates a true rise in incidence beyond demographic changes.
- When comparing the crude incidences between the year 1995 and 2015 we can observe an increased crude incidence rate of CRC across all age-groups, tumor locations, and both sexes, except for rectal cancer in women of all ages and men ≥ 80 years. The largest relative increases were observed in individuals < 50 years (*Table 4*).

Table 4. Crude incidence rate of CRC between 1995 and 2015

		Women	Men
Age group	Tumor Site	Crude incidence rate	Crude incidence rate
<50	Proximal	1.81	2.22
	Distal	1.34	1.91
	Rectal	0.98	1.72
50-79	Proximal	1.31	1.17
	Distal	1.18	1.44
	Rectal	0.93	1.03
≥80	Proximal	1.62	1.22
	Distal	1.18	1.07
	Rectal	0.82	0.90

Data source: Adapted from Gutlic et al. International Journal of Colorectal Disease. doi: 10.1007/s00384-019-03312-3.

Outcome & Poisson Regression

- Colon cancer: Poisson regression modelling adjusted for age, sex, tumor location and time showed significant increases in colon cancer incidence across all age groups, with the most pronounced increases in individuals < 50 years (*Table 5*).
    - Among men < 50 years, proximal colon cancer increased by 41% per decade (IRR 1.41, 95% CI 1.26-1.58), and distal colon cancer by 53% per decade (IRR 1.53, 95% CI 1.34-1.74).
    - Among women < 50 years, proximal colon cancer increased by 27% per decade (IRR 1.27, 95% CI 1.13-1.44), and distal colon cancer by 29% per decade (IRR 1.29, 95% CI 1.14-1.45).
    - Among women ≥ 80 years, a substantial increase of proximal colon cancer by 29% per decade was also observed (IRR 1.29, 95% CI 1.25-1.34).
- Rectal cancer: Poisson regression modelling showed varying trends in rectal cancer (*Table 5*).
    - Among men < 50 years, rectal cancer increased by 30% per decade (IRR 1.30, 95% CI 1.18-1.43).
    - Among women ≥ 80 years, rectal cancer decreased by 8% per decade (IRR 0.92, 95% CI 0.88-0.96) and in men ≥ 80 years by 7% per decade (IRR 0.93, 95% CI 0.89-0.98).
    - No significant changes in rectal cancer incidence were observed for women < 50 years or for individuals aged 50-79 years.

Table 5. Incidence rate ratio of CRC over the time period 1995-2015

		Women		Men	
Age group	Tumor Site	IRR (95 % CI)	p-value	IRR (95 % CI)	p-value
<50	Proximal	1.27 (1.13 ; 1.44)	<.0001	1.41 (1.26 ; 1.58)	<.0001
	Distal	1.29 (1.14 ; 1.45)	<.0001	1.53 (1.34 ; 1.74)	<.0001
	Rectal	1.07 (0.96 ; 1.19)	0.21	1.30 (1.18 ; 1.43)	<.0001
50-79	Proximal	1.21 (1.18 ; 1.25)	<.0001	1.15 (1.12 ; 1.19)	<.0001
	Distal	1.14 (1.10 ; 1.18)	<.0001	1.23 (1.19 ; 1.26)	<.0001
	Rectal	0.99 (0.96 ; 1.02)	0.46	1.02 (0.10 ; 1.05)	0.08
≥80	Proximal	1.29 (1.25 ; 1.34)	<.0001	1.14 (1.09 ; 1.19)	<.0001
	Distal	1.12 (1.06 ; 1.19)	<.0001	1.13 (1.07 ; 1.19)	<.0001
	Rectal	0.92 (0.88 ; 0.96)	0.0005	0.93 (0.89 ; 0.98)	0.0051

Data source: Adapted from Gutlic et al. International Journal of Colorectal Disease. doi: 10.1007/s00384-019-03312-3.

Paper II

Descriptive analysis

- A total of 33,320 CRC patients who underwent surgical resection between 2010 and 2018 were included: 1557 (4.7%) were < 50 years, 23,582 (70.8%) were 50-79 years, and 8,181 (24.6%) were ≥ 80 years.
- Patients < 50 years were more likely to present with rectal and distal colon cancer, had a higher proportion of obesity (body mass index > 30 kg/m^2), lower ASA scores (I-II), more advanced pTNM stage (III), were more likely to receive preoperative chemoradiotherapy, had longer operating times, and were more likely to receive a temporary stoma compared to patients aged 50-79 and ≥ 80 years (p<0.001).
- Patients < 50 and 50-79 years were more likely to undergo minimally invasive surgery (28.1% and 28.6% respectively), compared to those ≥ 80 years (25.5%). Patients < 50 years underwent a higher proportion of left hemicolectomies and anterior resections, reflecting the predominance of distal and rectal cancer in this age-group. Colectomies were also more common in the youngest age group (p<0.001).

Outcomes

- Patients < 50 years had fewer overall postoperative 30-day complications (p=0.050) and less emergency resections (p<0.001) compared with the two older age-groups.
- Despite lower overall complications, both patients < 50 and 50-79 years had higher proportions of surgical complications compared to patients ≥ 80 years (16.5% and 16.9%, versus 14.1% respectively, p<0.001).
- Anastomotic leakage and intra-abdominal infections were more frequent in patients < 50 years (5.7% and 3.5%, respectively) than in the 50-79 and ≥ 80 age-groups (<0.001). Wound infections were also more common in patients < 50 and 50-79 years (5.3%) compared to the oldest age-group (3.7%)(p<0.001).

Logistic Regression

- Logistic regression, if not adjusting for confounders, showed 32% lower odds of emergency surgeries in patients < 50 years compared with those ≥ 80 years (crude OR 0.68, 95% CI 0.56-0.83) (*table 6*).

Table 6. Logistic regression comparing age group vs emergency surgeries

Age group	Crude OR (95% CI)	P value
< 50	0.68 (0.56; 0.83)	<0.001
50-79	0.59 (0.54; 0.64)	<0.001
≥ 80 years	1.00	<0.001

- Logistic regression adjusting for gender, tumor location, neoadjuvant chemoradiotherapy, ASA score, BMI, and pTNM stage showed 28% higher odds of emergency surgeries in patients < 50 years compared with those ≥ 80 years (adjusted OR 1.28, 95% CI 1.02-1.60) (*Table 7*).

Table 7. Logistic regression comparing age group vs emergency surgeries adjusted for gender, tumor location, neoadjuvant chemoradiotherapy, ASA score, BMI, and pTNM stage.

Age group	Adjusted OR (95% CI)	P value
< 50	1.28 (1.02; 1.60)	0.037
50-79	0.89 (0.80; 0.98)	0.029
≥ 80 years	1.00	0.001

- Logistic regression, if not adjusting for confounders, showed 13% lower odds of overall postoperative 30-day complications in patients < 50 years compared with those ≥ 80 years (crude OR 0.87, 95% CI 0.77-0.98) (*Table 8*).

Table 8. Logistic regression comparing age group vs postoperative 30-day complications

Age group	Crude OR (95% CI)	P value
< 50	0.87 (0.77; 0.98)	0.024
50-79	0.96 (0.91; 0.98)	0.045
≥ 80 years	1.00	0.050

- Logistic regression adjusting for gender, tumor location, neoadjuvant chemoradiotherapy, ASA score, BMI, and pTNM stage showed 18% lower odds of overall postoperative 30-day complications in patients < 50 years compared with those ≥ 80 years (adjusted OR 0.82, 95% CI 0.71-0.94) (*Table 9*).

Table 9. Logistic regression comparing age group vs postoperative 30-day complications adjusted for gender, tumor location, neoadjuvant chemoradiotherapy, ASA score, BMI, and pTNM stage.

Age group	Adjusted OR (95% CI)	P value
< 50	0.82 (0.71; 0.94)	0.003
50-79	0.87 (0.82; 0.93)	<0.001
≥ 80 years	1.00	<0.001

Paper III

Descriptive analysis

- A total of 2,509 patients with stage II-III CRC who underwent curative surgery were included, of whom 183 were aged ≤ 50 years, 1,714 were aged 51-79 years, and 612 were aged > 70 years.
- Intensive follow-up (high-frequency CT and CEA measurements) did not significantly reduce 5-year overall mortality for patients ≤ 50 years compared with standard follow-up (8.3% vs. 8.4%; risk difference 0.2%, 95% CI -8.0% to 8.3%).
- Similarly, cancer-specific mortality was not reduced by high-frequency follow-up in patients ≤ 50 years (7.1% vs. 7.4%; risk difference 0.3%, 95% CI -7.4% to 8.0%).
- The 5-year cancer-specific recurrence risk for patients ≤ 50 years was lower in the high-frequency group (12.9%) than in the standard group (21.0%), but this difference was not statistically conclusive (risk difference 8.1%, CI -2.6% to 18.7%).

Outcomes and Cox Regression

- In Cox regression analyses adjusting for sex, age at surgery, tumor location, stage, planned postoperative chemotherapy, smoking, and comorbidities, there were no significant differences between high- and low frequency follow-up in overall mortality (adjusted Hazard Ratio [HR] 1.2, 95% CI 0.4-3.5), cancer-specific mortality (adjusted HR 1.3, 95% CI 0.4-4.4), or cancer-specific recurrence-risk (adjusted HR 0.7, 95% CI 0.3-1.5) for patients ≤ 50 years. Similarly, lack of benefit from intensified follow-up was observed in patients aged 51-70 and > 70 years (Table 10).

Table 10. Intention-to-treat: Cox regression analyses

Outcome	Age-group	Adjusted HR high-frequency group (95% CI)
Overall mortality	≤ 50 years	1.2 (0.4; 3.5)
Overall mortality	51-70 years	0.9 (0.7; 1.2)
Overall mortality	> 70 years	0.8 (0.6; 1.2)
Cancer-specific mortality	≤ 50 years	1.3 (0.4; 4.4)
Cancer-specific mortality	51-70 years	0.9 (0.7; 1.2)
Cancer-specific mortality	> 70 years	0.9 (0.6; 1.4)
Cancer-specific recurrence risk	≤ 50 years	0.7 (0.3; 1.5)

Cancer-specific recurrence risk	51-70 years	1.3 (1.0; 1.6)
Cancer-specific recurrence risk	> 70 years	1.1 (0.7; 1.5)

Data source: Adapted from Gutlic et al. International Journal of Colorectal Disease. doi: 10.1007/s00384-026-05096-9.

Paper IV

Bulk RNA-sequencing data

Differential gene expression analysis

- YAP1 mRNA expression was consistently higher in EOCRC (≤ 50 years) than LOCRC (> 50 years) across all three GEO datasets; statistical significance was reached only in the GSE39582 dataset (p=0.011), containing the largest number of patients (EOCRC n=78; LOCRC=506) (*Figure 7*).
- Combined analysis of all 797 patients (EOCRC n=103; LOCRC=694) confirmed a modest but statistically significant elevation of YAP1 (EOCRC median 7.92 vs LOCRC median 7.84, p=0.024.
- Random-effects meta-analysis confirmed a consistent positive direction of effect across all three datasets, demonstrating higher YAP1 expression in EOCRC compared to LOCRC in each cohort. The pooled effect size was small (standard mean difference=0.30) and did not reach statistical significance (p=0.30). However, the absence of meaningful heterogeneity between studies (I^2=0), indicates that the observed pattern was reproducible across independent patient cohorts.
- Overall, YAP1 is modestly but consistently elevated in EOCRC, supporting an age-associated trend.

Gene set enrichment analysis

- OXPHOS was the most prominently enriched metabolic pathway in the Hallmark analysis, showing the strongest statistical significance and the highest proportion of genes correlated with YAP1 among Hallmark pathways.
- KEGG analysis independently confirmed OXPHOS enrichment as the top YAP1-correlated pathway, supporting mitochondrial reprogramming as a consistent YAP1-driven feature in EOCRC.

Survival analysis

- Patients were divided into high- and low-YAP1 expression groups based on the median value. High YAP1 expression was associated with significantly reduced overall survival across two independent probe sets targeting different regions of the YAP1 transcript (224894_at: HR 1.64, p=0.00027; 213342_at: HR 1.42, p=0.0031) (*Figure 8*).

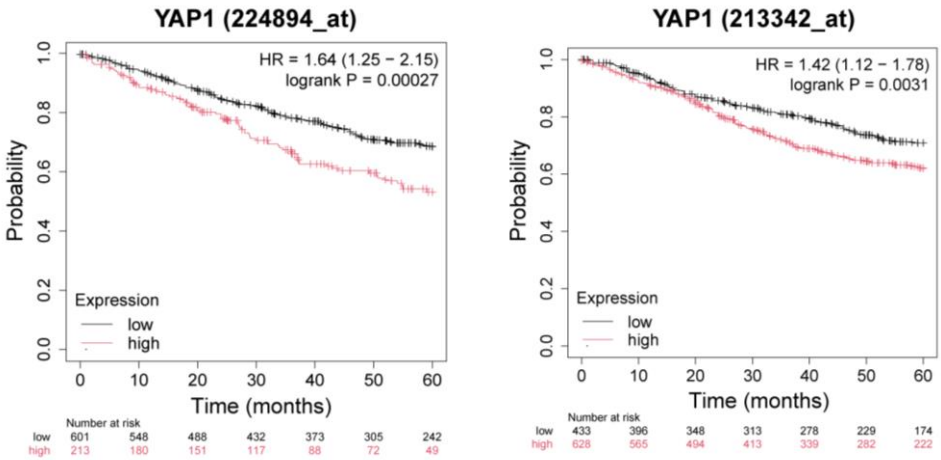

Figure 8. Kaplan-Meier survival curves stratified by YAP1 expression levels using two different probe sets. Data source: From the author's unpublished manuscript.

CMS classification

- EOCRC showed enrichment for the CMS4 mesenchymal subtype (~45%) compared with LOCRC (~35%), accompanied by a relative reduction in CMS2 canonical epithelial tumors.
- Within EOCRC, YAP1 expression did not differ significantly between CMS subtypes (ANOVA p=0.14), indicating that elevated YAP1 is not restricted to a specific CMS group.
- Survival analysis restricted to CMS4 tumors revealed that CMS4 with high YAP1 expression conferred markedly worse prognosis than in unselected CRC (probe 224894_at: HR 2.18, 95% CI 1.44-3.29, p=0.00015; probe 213342_at: HR 1.67, 95% CI 1.11-2.22, p=0.011) (*Figure 9*).

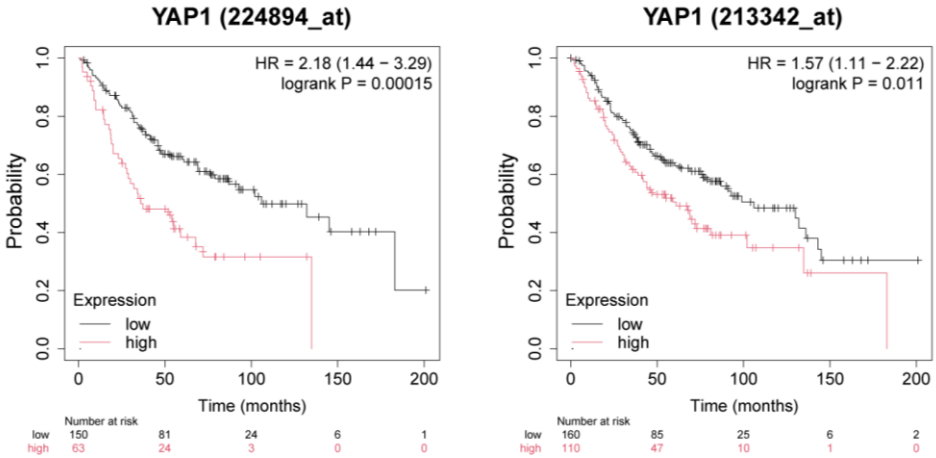

Figure 9. Kaplan-Meier survival curves restricted to CMS4 colorectal cancer stratified by YAP1 expression levels using two independent probe sets. Data source: From the author's unpublished manuscript.

Functional validation

Pharmacological inhibition of YAP1

- Western blot analysis demonstrated higher YAP1 protein levels in SW480 and HT-29 cells (EOCRC-like) than in Caco-2 cells (LOCRC-like).
- Treatment with Verteporfin dose-dependently suppressed TFAM (mitochondrial transcription factor A) protein levels in HT-29 cells (p=0.004), whereas Caco-2 cells showed minimal TFAM changes, indicating a stronger YAP1-TFAM coupling in EOCRC-like cells (*Figure 10*).

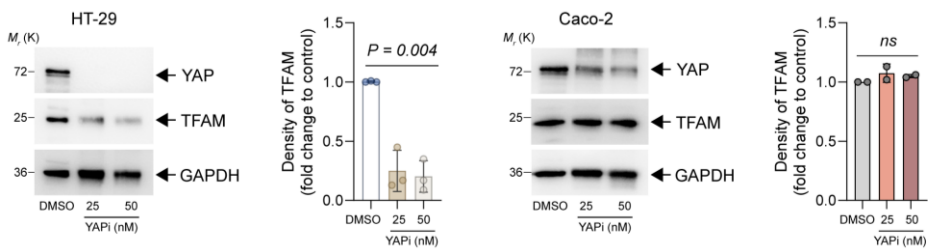

Figure 10. Western blot analysis and denistometric quantification demonstrating pharmacological YAP1 inhibition effects on TFAM protein abundance in HT-29 and Caco-2 cells. Data source: From the author's unpublished manuscript.

- Confocal imaging of MitoTracker-stained cells revealed that YAP1 inhibition induced mitochondrial fragmentation, converting tubular networks into punctate spherical organelles ($p<0.001$), suggesting that YAP1 regulates both mitochondrial biogenesis and network architecture.

Genetic inhibition of YAP1

- RNA interference-mediated YAP1 depletion in HT-29 and SW480 (EOCRC-like) cells significantly reduced TFAM protein levels (HT-29: $p=0.005$; SW480: $p=0.002$), recapitulating effects seen with pharmacological inhibition and confirming YAP1 as a transcriptional regulator of mitochondrial biogenesis.
- Confocal imaging revealed that YAP1 knockdown induced profound mitochondrial fragmentation ($p<0.001$), similar to that induced by Verteporfin treatment. Quantitative analysis showed reduced mitochondrial length, branching, and network complexity, consistent with the fragmented phenotype (*Figure 11*).

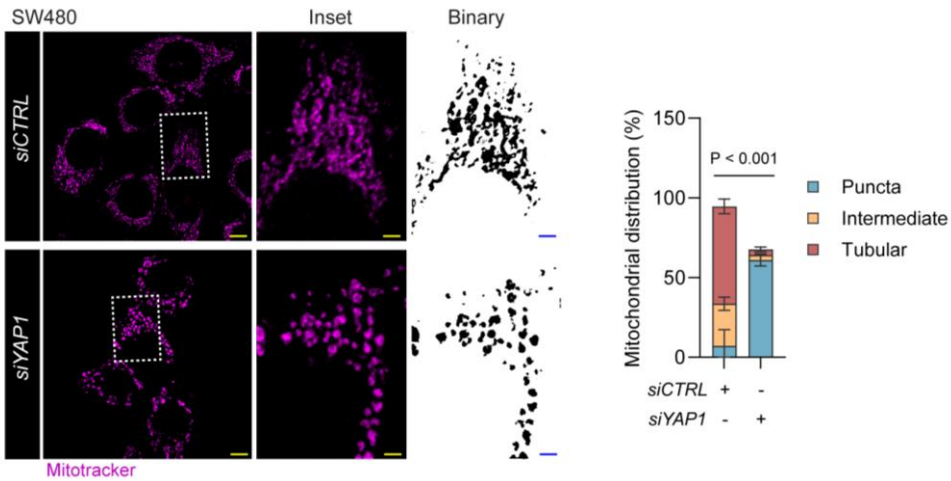

Figure 11. Confocal microscopy imaging and morphometric quantification of mitochondrial architecture in SW480 cells following genetic siRNA-mediated YAP1 knockdown. Data source: From the author's unpublished manuscript.

- Dual-channel immunofluorescence (TFAM and TOMM20) showed that YAP1 depletion reduced TFAM colonization within mitochondria, causing aberrant cytoplasmic distribution and impaired mitochondrial import ($p=0.002$), suggesting that YAP1 regulates both TFAM abundance and mitochondria's ability to transcribe genes needed for energy production.

Discussion

General discussion

Increasing incidence of EOCRC

The population-based study demonstrated a significant increase in the incidence of CRC in Sweden between 1995 and 2015. The crude incidence rate of CRC rose by 31%, while the age-standardized incidence increased by 20% during the study period. While the smaller increase in the age-standardized rates compared to the crude rates reflects the ageing of the Swedish population, the fact that the age-adjusted incidence still rose suggests a genuine increase in CRC incidence beyond demographic shifts.

A key finding of this study is the considerable increase in EOCRC, particularly in the colon. This rise is consistent with recent global trends indicating a similar pattern of increasing CRC incidence among younger populations (11). The significant increase in CRC among younger individuals could be partly attributed to potential changes in risk factors, including increasing rates of obesity, physical inactivity, and unhealthy dietary habits.

Interestingly, the incidence of rectal cancer showed mixed trends. While men < 50 years experienced a 30% increase in rectal cancer incidence rate per decade, the incidence rate in those ≥ 80 years declined by 7-8% per decade. This divergence might reflect differences in diagnostic practices or access to healthcare. Specifically, the observed decline in rectal cancer incidence in older populations could be due to improvements in healthcare availability, including more proactive diagnostic measures and early detection efforts. Although a national screening program was not yet fully implemented in Sweden during the study period, studies have demonstrated the efficacy of screening in reducing CRC burden (72, 73). The lack of significant changes in rectal cancer incidence among women < 50 years and individuals aged 50-79 years suggests that the incidence is not uniform across all subgroups.

These findings highlight the importance of public health addressing the rising incidence of EOCRC through targeted prevention strategies and the consideration of earlier screening. They also point out the need for increased symptom awareness in younger populations, alongside the role of lifestyle factors such as diet and physical activity.

Impact of neoadjuvant therapy on postoperative complications

In study II, patients < 50 years had fewer overall postoperative 30-day complications compared with older age-groups. However, they demonstrated higher rates of specific surgical complications, particularly anastomotic leakage, intra-abdominal and wound infections. This suggests that while younger patients have fewer medical comorbidities and better overall physiological reserve, they may be at increased risk for certain surgery-related adverse events.

One possible explanation is the higher proportion of more advanced stage at diagnosis in younger patients, frequently necessitating more aggressive treatments, such as neoadjuvant chemotherapy and radiotherapy. The greater use of neoadjuvant treatment in this group may negatively affect tissue quality, potentially increasing the susceptibility to impaired anastomotic healing and infectious complications. These findings highlight the need to consider treatment-related tissue effects when evaluating postoperative risk in EOCRC patients.

Tumor location and surgical complexity

Younger patients more frequently presented with rectal and distal colon cancers, consistent with previous trends (193). These tumor locations often require more complex resections, which may explain the longer operation times observed in the younger age group. In rectal cancer, anastomotic leakage occurred more often in younger patients (7.3%) than in the oldest age-group (4.8%), although this difference was not statistically significant (p=0.084). For colon cancers, younger patients had a statistically higher anastomotic leakage rate (5%) compared with patients aged 50-79 years (4.3%) and > 80 years (3.4%)(p=0.004).

Although minimally invasive surgery was more common in younger patients – an approach generally associated with reduced postoperative morbidity – the higher proportion of advanced disease, greater use of neoadjuvant therapy, and predominance of left-sided and rectal tumors may collectively contribute to increased surgical complexity and specific complication risks. This underscores the importance of individualized perioperative risk assessments and surgical planning in patients with EOCRC.

The role of obesity in postoperative complications

Additionally, younger patients had a higher proportion of obesity, which may have contributed to the increased proportion of anastomotic leakage, intra-abdominal infections and wound infections. Obesity is a well-known risk factor for postoperative complications, as it can substantially impair tissue healing and increase the risk of complications (194). Obesity reduces blood flow to tissues, impair oxygenation, and nutrient delivery, which can slow wound healing and increase the risk of postoperative complications like anastomotic leakage and infections. Moreover, the chronic low-grade inflammation associated with obesity weakens immune responses, making it harder to control infections after surgery.

Given these risks, preoperative optimization strategies, including weight management and prehabilitation, are crucial in reducing complications and improving surgical outcomes in this population.

Advanced tumor stage and emergency surgery

In unadjusted analyses, older patients had higher rates of emergency surgeries, potentially reflecting delayed presentation or age-related factors. However, after adjustment for potential confounders, including gender, tumor location, neoadjuvant therapy, ASA score, BMI, and tumor stage, patients < 50 years had higher odds of undergoing emergency surgeries.

The apparent discrepancy suggests that although emergency procedures were numerically more common in older individuals, younger patients were at increased relative risk once differences in baseline characteristics were accounted for. A potential explanation is the higher prevalence of advanced stage at diagnosis among younger patients, which may reflect more aggressive tumor biology or diagnostic delay. Such a factor could increase the likelihood of acute presentations requiring urgent surgical intervention.

High-intensity follow-up & CRC recurrences

Previous research have suggested that younger patients with CRC tend to present with more aggressive disease and may experience higher risk of recurrence compared to older adults (188). This raises the question whether intensive surveillance could yield survival benefits for this population. However, the findings of study III indicated that high-frequency follow-up, including more intensive CT imaging and CEA measurements, did not significantly improve overall mortality, cancer-specific mortality, or cancer-specific recurrence compared to standard follow-up for patients ≤ 50 years. Similar findings were noted across older age groups as well.

The lack of observed benefits in our study could be a result of several factors. First, while high-frequency follow-up did show a lower recurrence rate in patients < 50 years (12.9% vs. 21.0%), the difference was not statistically significant. This suggests that the observed reduction in recurrence could be due to random variation rather than a true effect. Additionally, the sample size and follow-up duration in our study may not have been sufficient to detect a more substantial impact. Studies with smaller sample sizes are often underpowered, which can obscure meaningful differences. Further research with a larger cohorts may be needed to more accurately assess the potential benefits of intensive follow-up in younger CRC patients.

Furthermore, the lack of significant benefit from high-intensity follow-up may be explained by the timing of CRC recurrences. Most recurrences typically occur within the first two or three years following surgery, and many might be detected by symptoms prior to next scheduled follow-up. In such cases, intensive follow-up may offer limited advantages particularly if the recurrence is symptomatic, occurs

in a location difficult to visualize with standard imaging, or is too small to detect. This highlights the need for more nuanced approach to follow-up that accounts for the clinical presentation and the timing of recurrence, as well as the imitations of imaging for early detection.

Stage II versus stage III & follow-up intensity

Younger patients more frequently present with stage III disease, and it is plausible that those patients might have higher baseline risk of recurrence. Although tumor stage is a central prognostic factor and could plausibly modify the effect of surveillance intensity, our study did not include a stratified analysis comparing stage II and stage III disease within the age groups. Importantly, even if such analysis had been performed, the relatively small number of younger patients in our cohort would likely have limited the statistical power to detect meaningful differences between follow-up strategies. Consequently, it remains uncertain whether surveillance intensity should be tailored according to age. Larger studies are needed to determine whether selected high-risk subgroups, such as younger patients with stage III disease, drive benefit from intensified surveillance.

During the initial period of the COLOFOL trial there was no national surveillance program in Sweden, and follow-up regimens varied widely, ranging from no follow-up to annual check-ups for five years. In 2016, Swedish national guidelines were updated to recommend a low-frequency follow-up regimen similar to that used in the COLOFOL-trial (80). However, it is noteworthy that this regimen is less intense than those recommended by international guidelines such as those from the National Comprehensive Cancer Network (NCCN) and the American Society of Clinical Oncology (ASCO), which might advocate for more frequent follow-up assessments especially in high-risk patients such as younger individuals (195-197).

YAP1 and its role in EOCRC

In study IV, we explored the molecular underpinnings of EOCRC, focusing specifically on the role of YAP1, a critical regulator of the Hippo pathway that influences cellular proliferation, survival, and metabolism, which may play an important role in the pathogenesis of EOCRC. We found that YAP1 expression was significantly elevated in EOCRC compared to LOCRC. Previous studies have suggested a link between YAP1 overexpression and aggressive cancer phenotypes (198). Notably, the higher levels of YAP1 in EOCRC-like cells are consistent with previous observations that EOCRC tends to be diagnosed at a later stage and with more aggressive disease (116). Moreover, we observed a higher prevalence of the CMS4 mesenchymal subtype compared with LOCRC, which is associated with more advanced disease and poorer prognosis. CMS4 tumors are typically more aggressive due to features such as stromal activation, epithelial-mesenchymal transition (EMT) and metabolic reprogramming that support tumor invasion and therapy resistance (113). These results suggest that YAP1 promotes more aggressive

disease, potentially through its regulation of mitochondrial function and the OXPHOS pathway.

YAP1 and metabolic reprogramming in EOCRC

GSEA identified OXPHOS as the top metabolic pathway associated with YAP1 expression in EOCRC. Recent studies have emphasized the importance of mitochondrial metabolism in cancer progression, and its association with Hippo signaling (199, 200). Our data suggests that YAP1 regulates mitochondrial biogenesis, as evidenced by TFAM expression upon YAP1 inhibition. This indicates that YAP1 may drive mitochondrial dysfunction, supporting cancer cell survival and proliferation in EOCRC.

Implications of YAP1 as a prognostic biomarker

Elevated YAP1 was associated with poorer overall survival in CRC patients, consistent with prior research linking YAP1 overexpression to worse prognosis (201). Interestingly, we observed that the prognostic impact of YAP1 was particularly pronounced in the CMS4 mesenchymal subtype, underscoring its role in driving aggressive tumor behaviors, such as metastasis and therapeutic resistance. Given these findings, YAP1 emerges as a potential prognostic biomarker and therapeutic target in EOCRC, particularly through its regulation of mitochondrial pathways such as OXPHOS and TFAM, which may offer promising therapeutic strategies in EOCRC.

Methodological considerations

Overall methodology

In study II, crude rates initially that patients < 50 years had fewer emergency surgeries compared to older age groups. However, after adjusting for gender, tumor location, ASA score, neoadjuvant chemoradiotherapy, BMI and pTNM stage, logistic regression revealed that patients < 50 years had significantly higher odds of emergency surgery compared with patients ≥ 80 years. This phenomenon, known as Simpson's paradox or confounding reversal, occurs when a crude association appears protective, but adjustment for relevant confounders uncovers the true direction of risk.

Protective factors in younger patients, such as lower ASA score (indicating better overall health), predominance of distal or rectal tumors (may be less likely to present emergently), were counterbalanced by risk factors including more advanced tumor stage and higher BMI. Consequently, despite their generally heathier profile, patients < 50 years are at disproportionately higher risk of emergency surgery once

these confounders are accounted for. The apparent decrease in crude odds reflect the masking effect of advanced-stage disease in younger patients, highlighting the aggressive nature of EOCRC. In contrast, patients 50-79 years still had slightly lower odds of emergency surgery compared to the oldest age group when adjusting for confounders, which is consistent with the general pattern that very elderly patients are more likely to present emergently due to frailty and comorbidities.

In study III, the selection of the survival endpoint is a critical methodological consideration, particularly in age-stratified analyses. Five-year overall survival reflects mortality from any cause and provides a comprehensive and objective measure that does not rely on accurate classification of cause of death. It is therefore robust and clinically meaningful, especially in real-world population-based studies. However, 5-year overall survival may be substantially influenced by competing mortality risks, particularly in older populations with a higher prevalence of comorbidities. In contrast, cancer-specific survival measures deaths attributed to CRC and aims to isolate the oncological impact of the disease. This endpoint may be particularly informative when comparing outcomes across age groups, as it reduces bias introduced by non-cancer-related mortality.

When studying EOCRC, cancer-specific survival may therefore provide a clearer assessment of tumor-related prognosis, whereas overall survival captures the overall clinical burden of disease. Ideally, both endpoints should be reported to allow comprehensive interpretation of age-related survival differences.

Internal validity

Internal validity is the degree to which a study accurately establishes a cause-and-effect relationship between variables, without being influenced by confounding factors or biases.

In study I, internal validity is strong because it uses nationwide, population-based data from the SCR, which is comprehensive, highly reliable, and provides high-quality data on CRC cases diagnosed between 1995 and 2015. This enhances the internal validity of the study, as it reduces the likelihood of selection bias, given that the entire population of CRC patients within the study period is included, regardless of healthcare availability, socioeconomic status, and other additional factors that might influence diagnosis. Regarding confounders, the study used Poisson regression to adjust for key variables such as age, sex, tumor location, and time. This helps control for potential confounding effects of these factors on the observed trends in CRC incidence.

As in study I, the internal validity of study II is strengthened by the use of a large, population-based cohort from the SCRCR, which includes comprehensive, high-quality data on patient demographics, tumor characteristics, treatment, and surgical outcomes. This dataset allows for reliable conclusions regarding the association

between age, treatment strategies, and surgical outcomes. Applying multivariable logistic regression to account for potential confounders additionally improves the study's internal validity. However, residual confounding cannot be fully excluded, as some unmeasured factors may influence postoperative outcomes.

Study III was initially conducted as a randomized controlled trial, the gold standard for establishing causal relationships. Randomization minimizes selection bias, ensuring that the groups receiving high-frequency follow-up versus low-frequency follow-up were compatible at baseline. Data collection was prospectively planned and standardized, ensuring consistency in how follow-up was carried out. The protocol for follow-up assessment was meticulously defined, reducing variability in follow-up procedures. The study adjusted for several potential confounders, which also strengthens internal validity. However, in spite of these strengths, the post hoc nature of the subgroup analysis may introduce limitations to internal validity. Since the analysis was not part of the original protocol, it was not prespecified, making it more prone to Type I error (false positives) and potentially overfitting in statistical models due to a relatively small sample size in some subgroups (e.g., patients ≤ 50 years). These issues may limit the robustness of the findings, and further confirmatory studies would be necessary to draw definitive conclusions.

In study IV, internal validity is generally strong due to the use of well-established in vitro models, such as EOCRC-like (SW480, HT-29) and LOCRC (Caco-2) cell lines. These cell lines enable controlled experiments, ensuring that the observed effects are directly attributed to specific manipulation of YAP1. Additionally, the study employed both pharmacological and genetic silencing of YAP1, which strengthens the findings by validating the results through independent methods. The combination of multiple methods, including Western blotting, immunofluorescence, and mitochondrial visualization, further strengthens the study's internal validity by reducing the likelihood that the observed effects were due to a single method's limitations.

External validity

External validity indicates how well the results of a study can be applied or generalized to other populations, settings, or conditions outside the study.

The external validity of Study I is strong, as it includes a comprehensive, nationwide cohort. However, these results may not be directly generalizable to other countries with different healthcare systems, screening programs, or risk factors.

Likewise, the external validity or generalizability, of study II is high due to the population-based nature of the cohort, which includes a large, nationally representative sample of CRC patients from Sweden. As a result, the findings can be applied to the broader population of CRC patients undergoing surgery, especially in countries with similar health care systems and cancer management practices.

However, the results may not be directly applicable to regions with significantly different treatment protocols, healthcare infrastructure, or population demographics.

Study III included patients from multiple countries, improving its generalizability across different healthcare systems and populations. The study population was drawn from a large, real-world trial (COLOFOL), which increases applicability to routine clinical practice. However, the study focused on patients with stage II-III CRC who underwent curative surgery, and the findings may not apply as well to patients with more advanced stages of cancer. In addition, the study did not include patients > 75 years, which may limit the generalizability of the results to older populations. While older adults are frequently underrepresented in clinical trials, it is important to note that many older individuals are fit and healthy.

Study IV's external validity has both strengths and limitations. The use of publicly available GEO datasets strengthens the generalizability of the findings to other CRC populations. However, the relatively small number of EOCRC patients in these datasets compared to older cohorts may affect the robustness of the results, especially for this age group. Additionally, since the GEO datasets combine data from multiple studies, the patient population may not fully represent the diverse real-world EOCRC population. Furthermore, while the gene expression data in GEO are highly valuable for identifying molecular signatures, these data often lack important demographic and clinical details (e.g., age, sex, geographic location, treatment regimens, disease staging), which limits the ability to fully interpret the biological findings in clinical contexts.

Strengths & limitations

Paper I

One of the limitations of this study is that it is observational in nature, which means it cannot establish causality between observed trends in CRC and potential risk factors. A key strength of this study lies in its use of comprehensive, nationwide registry data, which provides a large, representative sample of CRC cases across a 20-year period. The SCR is a well-established, high-quality dataset that captures nearly all cases of CRC in Sweden, assuring both broad coverage and generalizability within the Swedish population. Additionally, the use of Poisson regression models provided a reliable statistical framework used for analyzing temporal trends while adjusting for confounders, resulting in more accurate and reliable estimates of changes in CRC incidence.

Paper II

The study uses data from over 33,000 patients, which provides a robust sample size that enhances the precision and reliability of the findings. The large cohort also

lowers the risk of bias in participant selection and improves how well the study cohort reflects the broader population. The SCRCR is a well-established, high-quality registry with near-complete reporting, maintaining the accuracy and comprehensiveness of the data used in this study. The study employed logistic regression to control for key confounding variables, providing more accurate estimates of the associations found. However, there still might be unmeasured variables that could influence the outcomes. Despite the high quality and completeness of the SCRCR, there is always a possibility of underreporting or missing data, particularly for postoperative complications, which could introduce bias into the results. The study focuses on postoperative 30-day complications, which provides valuable insight into short-term outcomes but do not capture long-term complications or survival data, which are also critical for evaluating surgical success. While emergency surgeries were analyzed, the definition and categorization of "emergency" versus "elective" procedures may vary across institutions, producing potential inconsistencies in the data.

Paper III

The post hoc nature of this subgroup analysis introduces probable biases. This reduces the certainty with which conclusions can be drawn from the study, especially when interpreting results from smaller subgroups. The sample size of patients ≤ 50 years was relatively small (183 patients), which limits the statistical power of the analyses within this subgroup. Although the original study was randomized, it was not possible to blind physicians or patients, leading to detection bias. For instance, patients in the high-frequency follow-up group may have received more intensive care or attention, influencing both the detection of recurrences and reporting of clinical outcomes.

Paper IV

While this study provides important knowledge into the role of YAP1 in EOCRC, several limitations should be acknowledged. First, our findings are based on in vitro experiments, and the extent to which these translate to in vivo models remains to be established. Future studies could explore the role of YAP1 in preclinical animal models, which could help validate our findings and assess the therapeutic efficacy of YAP1 inhibitors. Additionally, while our survival analysis used publicly available data, the lack of detailed clinical annotations (such as treatment regimens and comorbidities) limits our ability to fully interpret the prognostic significance of YAP1 across different patient cohorts. Therefore, prospective clinical studies are necessary to further evaluate YAP1 as a prognostic biomarker and therapeutic target. Furthermore, while we focused on mitochondrial dysfunction, future research needs to explore the broader cellular processes regulated by YAP1 in EOCRC, including its impact on cellular adhesion, invasion, and resistance to chemotherapy. Investigating these processes could provide a deeper understanding

of how YAP1 may contribute to the aggressive nature of EOCRC and guide the development of targeted therapies.

One of the strengths of this paper is the use of large, publicly available datasets from the GEO, which allowed for an extensive and statistically robust comparison of gene expression between EOCRC and LOCRC. By analyzing three different GEO cohorts, the study was able to identify consistent patterns of YAP1 overexpression in EOCRC, increasing the reliability and generalizability of the findings. Another strength lies in the multi-faceted experimental approach, which combined bulk RNA sequencing, functional validation in EOCRC-like cell lines, and clinical survival analysis.

Conclusions

- CRC incidence in Sweden significantly increased between 1995-2015, particularly of colon cancer among individuals < 50 years, with rectal cancer also rising in men < 50 years.
- The rising trends in EOCRC emphasize the need for increased symptom awareness in younger populations and support consideration of earlier CRC screening in Sweden.
- Patients < 50 years with CRC are more likely to present with rectal and distal colon cancer, more advanced stages, and obesity.
- Despite experiencing fewer overall postoperative 30-day complications, patients < 50 years had higher rates of specific surgical complications, including anastomotic leakage, intra-abdominal infections, and wound infections.
- When adjusting for confounders, patients <50 had higher odds of undergoing emergency surgery compared with older patients, underscoring the complexity of EOCRC.
- Intensified follow-up with more frequent CT imaging and CEA measurements did not significantly improve overall survival, cancer-specific survival, or recurrence risk in patients ≤ 50 years, nor in older age groups.
- Elevated YAP1 expression in EOCRC was linked to mitochondrial reprogramming, particularly via oxidative phosphorylation and mitochondrial dynamics. Functional inhibition of YAP1 confirmed its regulatory role in mitochondrial function and morphology.
- High YAP1 expression was associated with poor prognosis in CMS4 mesenchymal tumors, highlighting YAP1's potential as a therapeutic target.

Future perspectives

The rising incidence of EOCRC in the Western world poses a major challenge in clinical practice and public health, highlighting the need for further research aimed at providing prevention, treatment, and surveillance strategies. This thesis sheds light on several key areas, particularly through the analysis of national registry data, population-based cohorts, clinical outcomes, and molecular analyses. While the current findings give important insights into incidence, surgical outcomes, follow-up, and molecular characteristics of EOCRC, several critical avenues remain for future research to gain deeper insight into understanding, preventing and treating this disease.

Paper I highlighted the significant rise of EOCRC incidence in Sweden. This trend calls for urgent attention to early detection methods, tailored prevention strategies, and the development of screening protocols targeted at younger individuals. Since EOCRC tends to present with more aggressive clinical features, future research needs to focus on refining risk stratification models to identify individuals at higher risk.

In paper II, we observed differences in surgical outcomes between EOCRC and LOCRC, including variations in postoperative complications and emergency surgeries. The younger cohort presented with more advanced tumors and higher rates of surgical complications, despite fewer overall complications. Research into tailored perioperative care and surgical approaches for EOCRC patients, considering their unique clinical profiles, will be critical for improving surgical outcomes.

The findings from paper III, suggested that intensified follow-up may not provide significant benefits for EOCRC patients in terms of survival or recurrence, raising the need for a more refined approach to surveillance. Future research should concentrate on determining which patient groups truly benefit from high-frequency follow-up and whether new biomarkers or imaging techniques could improve detection of recurrence in this group.

In paper IV, elevated YAP1 expression was linked to mitochondrial dysfunction and poor prognosis in EOCRC, particularly in the CMS4 subtype. Future studies should continue to focus on exploring the role of YAP1 in EOCRC, as well as other key molecular pathways, to identify potential therapeutic targets. Given the aggressive

nature of EOCRC, research into molecular stratification could enable more personalized treatment approaches and better survival outcomes.

Given the global increasing burden of EOCRC, international collaboration is essential. Multi-center studies and large-scale cohort data and collaborative efforts will help inform global strategies for better prevention, detection, and treatment of EOCRC. While substantial progress has been made, EOCRC remains a complex and evolving challenge. Continued research, focusing on early detection, personalized treatment, surveillance, and the molecular underpinnings of EOCRC, will play an important role in improving patient outcomes and addressing the rising incidence of EOCRC.

Populärvetenskaplig sammanfattning

Cancer i tjock- och ändtarmen (kolorektalcancer, KRC) är den tredje vanligaste och näst mest dödliga cancerformen i världen, inklusive Sverige. KRC kan uppstå var som helst i tjocktarmen (kolon) eller i den sista delen av tarmen (ändtarmen, rektum). Symptomen varierar beroende på tumörens placering och kan inkludera förändrade tarmvanor, blod i avföringen, magont, känsla av ofullständig tarmtömning, trötthet eller oförklarlig viktminskning. Många människor upplever dock inga symptom i de tidiga stadierna, vilket gör att sjukdomen upptäcks först när den är mer avancerad. Tack vare screening med avföringsprov samt koloskopi kan cancer upptäckas tidigare, ibland innan tumören ens har utvecklats till cancer. I Sverige har man nu infört befolkningsbaserad screening för åldrarna 60-74 år men detta inkluderar inte yngre patienter under 60 år.

Trots att majoriteten av fallen diagnosticeras hos äldre vuxna, har en oroande trend visat att yngre individer alltmer drabbas av KRC. De som är under 50 år vid diagnos benämns ofta ”Early-Onset Colorectal Cancer (EOCRC)”. Trots att EOCRC utgör en liten del av alla KRC-fall, har antalet fall ökat markant de senaste decennierna. I USA förutspås andelen av alla fall KRC-fall som gäller EOCRC överstiga 10% år 2030. Denna utveckling är fortfarande inte helt förstådd, och det finns ett växande behov av att undersöka de bakomliggande orsakerna. Tidigare forskning har främst fokuserat på äldre vuxna men denna avhandling undersöker den ökande trenden och de specifika egenskaperna hos EOCRC.

Det första delarbetet i avhandlingen fokuserade på incidensen av KCR under en period från 1995 till 2015 i Sverige. Studien visade att incidensen av KRC bland personer yngre än 50 år har ökat med hela 53% per decennium mellan 1995 och 2015, särskilt för tjocktarmscancer. Detta är en oroande trend, då den indikerar att fler unga drabbas jämfört med tidigare. Det är av stor vikt att förstå varför denna grupp ökar så dramatiskt, och delarbete I understryker behovet av riktad forskning för att få en djupare förståelse för EOCRC.

I det andra delarbetet undersöktes egenskaperna, behandlingen och komplikationer efter kirurgi hos EOCRC. Studieresultaten visade att yngre patienter (under 50 år) tenderade att ha mer avancerade stadier av cancer vid diagnos, och att de ofta fick mer cellgifts- och strålbehandling innan operation jämfört med äldre individer. Trots detta var de övergripande komplikationerna vid kirurgi färre bland yngre patienter, men en högre andel av de yngre patienter fick allvarliga kirurgiska komplikationer,

så som fler andel anastomotiska läckage av tarmkopplingen och infektion jämfört med äldre patienter. Att förstå dessa skillnader är viktigt för att kunna ge bättre kirurgisk uppföljning och behandling till denna specifika patientgrupp. Det är också viktigt att identifiera faktorer som bidrar till de högre kirurgiska komplikationerna hos unga för att förbättra behandlingsstrategier.

På senare år har stora framsteg gjorts både kirurgiskt och onkologiskt när det gäller behandlingen av återfall av KRC, vilket har ökat möjligheterna till bot och överlevnad. Det tredje delarbetet undersökte effekten av intensiv uppföljning efter kirurgi i en subgruppsanalys av patienter från COLOFOL-studien, en randomiserad multicenterstudie som jämförde effekten av hög- och lågfrekvent postoperativ uppföljning hos patienter med stadium II-III KRC. Resultaten visade att intensiv uppföljning, inte ledde till signifikant förbättrad överlevnad för patienter under 50 år, vare sig när det gällde total överlevnad eller cancerspecifik överlevnad. Man fann heller inget signifikant resultat när det gäller återfallsfrekvensen i den högfrekventa gruppen. Behov av vidare forskning behövs för att identifiera de mest effektiva metoderna för uppföljning.

I det fjärde delarbetet analyserades de genetiska och biologiska skillnaderna mellan KRC-tumörer hos unga och äldre patienter, med fokus på en specifik gen, YAP1. Resultaten visade att YAP1, som är en gen involverad i celltillväxt och överlevnad, uttrycks högre i tumörer från yngre patienter. Denna höjning av YAP1 kan spela en viktig roll i den ökade aggressiviteten hos dessa tumörer. Vidare analyser visade att YAP1:s aktivitet vad kopplad till en ökad aktivitet i de mitokondriella vägarna (oxidativ fosforylering), vilket tyder på att YAP1 inte bara är en regulator av tillväxt utan också kan påverka energiproduktionen i tumörceller. Dessa resultat öppnar för nya forskningsvägar kring behandlingsstrategier som kan förbättra och skräddarsy terapier för unga KRC-patienter, särskilt genom att fokusera på de specifika molekylära mekanismerna som driver tumörernas aggressivitet i denna åldersgrupp.

Sammanfattningsvis visar denna avhandling att KRC hos yngre individer är ett växande problem, och att det finns både kliniska och biologiska skillnader mellan unga och äldre patienter som behöver utforskas mer ingående. För att kunna ge dessa patienter bästa möjliga behandling och uppföljning krävs mer forskning som kan hjälpa oss att förstå sjukdomens unika egenskaper i denna åldersgrupp.

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References

1. Zaborowski AM, Abdile A, Adamina M, Aigner F, d'Allens L, Allmer C, et al. Characteristics of Early-Onset vs Late-Onset Colorectal Cancer: A Review. JAMA surgery. 2021;156(9):865-74.
2. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA: a cancer journal for clinicians. 2021;71(3):209-49.
3. Arnold M, Sierra MS, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global patterns and trends in colorectal cancer incidence and mortality. Gut. 2017;66(4):683-91.
4. Morgan E, Arnold M, Gini A, Lorenzoni V, Cabasag CJ, Laversanne M, et al. Global burden of colorectal cancer in 2020 and 2040: incidence and mortality estimates from GLOBOCAN. Gut. 2023;72(2):338-44.
5. Khazaei S, Rezaeian S, Khazaei S, Mansori K, Sanjari Moghaddam A, Ayubi E. Effects of Human Development Index and Its Components on Colorectal Cancer Incidence and Mortality: a Global Ecological Study. Asian Pacific journal of cancer prevention : APJCP. 2016;17(S3):253-6.
6. Darmadi D, Mohammadian-Hafshejani A, Kheiri S. Global Disparities in Colorectal Cancer: Unveiling the Present Landscape of Incidence and Mortality Rates, Analyzing Geographical Variances, and Assessing the Human Development Index. Journal of preventive medicine and hygiene. 2024;65(4):E499-e514.
7. Zhang T, Guo Y, Qiu B, Dai X, Wang Y, Cao X. Global, regional, and national trends in colorectal cancer burden from 1990 to 2021 and projections to 2040. Frontiers in oncology. 2024;14:1466159.
8. Wu S, Zhang Y, Lin Z, Wei M. Global burden of colorectal cancer in 2022 and projections to 2050: incidence and mortality estimates from GLOBOCAN. BMC cancer. 2025;25(1):1770.
9. Pan H, Zhao Z, Deng Y, Zheng Z, Huang Y, Huang S, et al. The global, regional, and national early-onset colorectal cancer burden and trends from 1990 to 2019: results from the Global Burden of Disease Study 2019. BMC public health. 2022;22(1):1896.
10. Siegel RL, Fedewa SA, Anderson WF, Miller KD, Ma J, Rosenberg PS, et al. Colorectal Cancer Incidence Patterns in the United States, 1974-2013. Journal of the National Cancer Institute. 2017;109(8).

11. Siegel RL, Torre LA, Soerjomataram I, Hayes RB, Bray F, Weber TK, et al. Global patterns and trends in colorectal cancer incidence in young adults. Gut. 2019;68(12):2179-85.
12. Kasi PM, Shahjehan F, Cochuyt JJ, Li Z, Colibaseanu DT, Merchea A. Rising Proportion of Young Individuals With Rectal and Colon Cancer. Clinical colorectal cancer. 2019;18(1):e87-e95.
13. Sung H, Siegel RL, Laversanne M, Jiang C, Morgan E, Zahwe M, et al. Colorectal cancer incidence trends in younger versus older adults: an analysis of population-based cancer registry data. The Lancet Oncology. 2025;26(1):51-63.
14. Barot S, Liljegren A, Nordenvall C, Blom J, Radkiewicz C. Incidence trends and long-term survival in early-onset colorectal cancer: a nationwide Swedish study. Annals of oncology : official journal of the European Society for Medical Oncology. 2025;36(11):1400-8.
15. Lui RN, Tsoi KKF, Ho JMW, Lo CM, Chan FCH, Kyaw MH, et al. Global Increasing Incidence of Young-Onset Colorectal Cancer Across 5 Continents: A Joinpoint Regression Analysis of 1,922,167 Cases. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2019;28(8):1275-82.
16. Downham L, Laversanne M, Perdomo S, Filho AM, Bray F, Brennan P. Increase of early-onset colorectal cancer: a cohort effect. Journal of the National Cancer Institute. 2025.
17. Gupta S, May FP, Kupfer SS, Murphy CC. Birth Cohort Colorectal Cancer (CRC): Implications for Research and Practice. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association. 2024;22(3):455-69.e7.
18. Chambers AC, Dixon SW, White P, Williams AC, Thomas MG, Messenger DE. Demographic trends in the incidence of young-onset colorectal cancer: a population-based study. Br J Surg. 2020;107(5):595-605.
19. Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. CA: a cancer journal for clinicians. 2023;73(1):17-48.
20. Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. CA: a cancer journal for clinicians. 2024;74(1):12-49.
21. Board PDQCGE. Genetics of Colorectal Cancer (PDQ®): Health Professional Version. PDQ Cancer Information Summaries. Bethesda (MD): National Cancer Institute (US); 2002.
22. Nguyen LH, Goel A, Chung DC. Pathways of Colorectal Carcinogenesis. Gastroenterology. 2020;158(2):291-302.
23. Leggett B, Whitehall V. Role of the serrated pathway in colorectal cancer pathogenesis. Gastroenterology. 2010;138(6):2088-100.
24. Li Q, Geng S, Luo H, Wang W, Mo YQ, Luo Q, et al. Signaling pathways involved in colorectal cancer: pathogenesis and targeted therapy. Signal transduction and targeted therapy. 2024;9(1):266.

25. Shussman N, Wexner SD. Colorectal polyps and polyposis syndromes. Gastroenterology report. 2014;2(1):1-15.
26. Heitman SJ, Ronksley PE, Hilsden RJ, Manns BJ, Rostom A, Hemmelgarn BR. Prevalence of adenomas and colorectal cancer in average risk individuals: a systematic review and meta-analysis. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association. 2009;7(12):1272-8.
27. Corley DA, Jensen CD, Marks AR, Zhao WK, de Boer J, Levin TR, et al. Variation of adenoma prevalence by age, sex, race, and colon location in a large population: implications for screening and quality programs. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association. 2013;11(2):172-80.
28. Akimoto N, Ugai T, Zhong R, Hamada T, Fujiyoshi K, Giannakis M, et al. Rising incidence of early-onset colorectal cancer - a call to action. Nature reviews Clinical oncology. 2021;18(4):230-43.
29. Stoffel EM, Murphy CC. Epidemiology and Mechanisms of the Increasing Incidence of Colon and Rectal Cancers in Young Adults. Gastroenterology. 2020;158(2):341-53.
30. Wild CP. Complementing the genome with an "exposome": the outstanding challenge of environmental exposure measurement in molecular epidemiology. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2005;14(8):1847-50.
31. Wu S, Powers S, Zhu W, Hannun YA. Substantial contribution of extrinsic risk factors to cancer development. Nature. 2016;529(7584):43-7.
32. Roshandel G, Ghasemi-Kebria F, Malekzadeh R. Colorectal Cancer: Epidemiology, Risk Factors, and Prevention. Cancers. 2024;16(8).
33. Hu Y, Kharazmi E, Liang Q, Brenner H, Sundquist J, Sundquist K, et al. Risk of colorectal cancer by family history of both colorectal carcinomas and colorectal polyps: a nationwide cohort study. Cancer communications (London, England). 2025;45(11):1407-16.
34. Jess T, Rungoe C, Peyrin-Biroulet L. Risk of colorectal cancer in patients with ulcerative colitis: a meta-analysis of population-based cohort studies. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association. 2012;10(6):639-45.
35. Veettil SK, Wong TY, Loo YS, Playdon MC, Lai NM, Giovannucci EL, et al. Role of Diet in Colorectal Cancer Incidence: Umbrella Review of Meta-analyses of Prospective Observational Studies. JAMA network open. 2021;4(2):e2037341-e.
36. Hua H, Jiang Q, Sun P, Xu X. Risk factors for early-onset colorectal cancer: systematic review and meta-analysis. Frontiers in oncology. 2023;13:1132306.
37. Cai S, Li Y, Ding Y, Chen K, Jin M. Alcohol drinking and the risk of colorectal cancer death: a meta-analysis. European journal of cancer

prevention : the official journal of the European Cancer Prevention Organisation (ECP). 2014;23(6):532-9.
38. Bai X, Wei H, Liu W, Coker OO, Gou H, Liu C, et al. Cigarette smoke promotes colorectal cancer through modulation of gut microbiota and related metabolites. Gut. 2022;71(12):2439-50.
39. Botteri E, Iodice S, Bagnardi V, Raimondi S, Lowenfels AB, Maisonneuve P. Smoking and colorectal cancer: a meta-analysis. Jama. 2008;300(23):2765-78.
40. Safizadeh F, Mandic M, Hoffmeister M, Brenner H. Colorectal Cancer and Central Obesity. JAMA network open. 2025;8(1):e2454753.
41. Liu PH, Wu K, Ng K, Zauber AG, Nguyen LH, Song M, et al. Association of Obesity With Risk of Early-Onset Colorectal Cancer Among Women. JAMA oncology. 2019;5(1):37-44.
42. Jin EH. Alteration of metabolic syndrome and the risk of colorectal cancer in individuals younger than 50 years. Journal of Clinical Oncology. 2024;42(3_suppl):81-.
43. Jin EH, Han K, Lee DH, Shin CM, Lim JH, Choi YJ, et al. Association Between Metabolic Syndrome and the Risk of Colorectal Cancer Diagnosed Before Age 50 Years According to Tumor Location. Gastroenterology. 2022;163(3):637-48.e2.
44. Keum N, Bao Y, Smith-Warner SA, Orav J, Wu K, Fuchs CS, et al. Association of Physical Activity by Type and Intensity With Digestive System Cancer Risk. JAMA oncology. 2016;2(9):1146-53.
45. Nguyen LH, Liu PH, Zheng X, Keum N, Zong X, Li X, et al. Sedentary Behaviors, TV Viewing Time, and Risk of Young-Onset Colorectal Cancer. JNCI cancer spectrum. 2018;2(4):pky073.
46. Janney A, Powrie F, Mann EH. Host-microbiota maladaptation in colorectal cancer. Nature. 2020;585(7826):509-17.
47. Olesen SW, Alm EJ. Dysbiosis is not an answer. Nature microbiology. 2016;1:16228.
48. Wong SH, Yu J. Gut microbiota in colorectal cancer: mechanisms of action and clinical applications. Nature reviews Gastroenterology & hepatology. 2019;16(11):690-704.
49. Wirbel J, Pyl PT, Kartal E, Zych K, Kashani A, Milanese A, et al. Meta-analysis of fecal metagenomes reveals global microbial signatures that are specific for colorectal cancer. Nature medicine. 2019;25(4):679-89.
50. Brennan CA, Garrett WS. Gut Microbiota, Inflammation, and Colorectal Cancer. Annual review of microbiology. 2016;70:395-411.
51. Öberg J, Buchwald P, Nilsson A, Nilson B, Inghammar M. Risk and prognosis of colorectal cancer following bacteraemia with Streptococcus bovis-Streptococcus equinus complex: A Swedish nationwide retrospective cohort study. Epidemiology and infection. 2025;154:e2.
52. Ungvari Z, Fekete M, Varga P, Lehoczki A, Munkácsy G, Fekete JT, et al. Association between red and processed meat consumption and colorectal

cancer risk: a comprehensive meta-analysis of prospective studies. GeroScience. 2025;47(3):5123-40.
53. Farvid MS, Sidahmed E, Spence ND, Mante Angua K, Rosner BA, Barnett JB. Consumption of red meat and processed meat and cancer incidence: a systematic review and meta-analysis of prospective studies. European journal of epidemiology. 2021;36(9):937-51.
54. Lu SSM, Mohammed Z, Häggström C, Myte R, Lindquist E, Gylfe Å, et al. Antibiotics Use and Subsequent Risk of Colorectal Cancer: A Swedish Nationwide Population-Based Study. Journal of the National Cancer Institute. 2022;114(1):38-46.
55. McDowell R, Perrott S, Murchie P, Cardwell C, Hughes C, Samuel L. Oral antibiotic use and early-onset colorectal cancer: findings from a case-control study using a national clinical database. British journal of cancer. 2022;126(6):957-67.
56. Nguyen LH, Cao Y, Batyrbekova N, Roelstraete B, Ma W, Khalili H, et al. Antibiotic Therapy and Risk of Early-Onset Colorectal Cancer: A National Case-Control Study. Clinical and translational gastroenterology. 2022;13(1):e00437.
57. Cao Y, Nguyen LH, Tica S, Otegbeye E, Zong X, Roelstraete B, et al. Evaluation of Birth by Cesarean Delivery and Development of Early-Onset Colorectal Cancer. JAMA network open. 2023;6(4):e2310316.
58. Hur J, Otegbeye E, Joh HK, Nimptsch K, Ng K, Ogino S, et al. Sugar-sweetened beverage intake in adulthood and adolescence and risk of early-onset colorectal cancer among women. Gut. 2021;70(12):2330-6.
59. Kim H, Lipsyc-Sharf M, Zong X, Wang X, Hur J, Song M, et al. Total Vitamin D Intake and Risks of Early-Onset Colorectal Cancer and Precursors. Gastroenterology. 2021;161(4):1208-17.e9.
60. Ramadan M. Assessing the contribution of nine preventable risk factors attributed to the burden of early onset colorectal cancer in Gulf Cooperation Council (GCC) countries. Preventive medicine reports. 2023;35:102389.
61. Juul F, Hemmingsson E. Trends in consumption of ultra-processed foods and obesity in Sweden between 1960 and 2010. Public health nutrition. 2015;18(17):3096-107.
62. Barot SV, Sangwan N, Nair KG, Schmit SL, Xiang S, Kamath S, et al. Distinct intratumoral microbiome of young-onset and average-onset colorectal cancer. EBioMedicine. 2024;100.
63. Adnan D, Trinh JQ, Sharma D, Alsayid M, Bishehsari F. Early-onset Colon Cancer Shows a Distinct Intestinal Microbiome and a Host-Microbe Interaction. Cancer prevention research (Philadelphia, Pa). 2024;17(1):29-38.
64. Kong C, Liang L, Liu G, Du L, Yang Y, Liu J, et al. Integrated metagenomic and metabolomic analysis reveals distinct gut-microbiome-derived phenotypes in early-onset colorectal cancer. Gut. 2023;72(6):1129-42.
65. Clinton SK, Giovannucci EL, Hursting SD. The World Cancer Research Fund/American Institute for Cancer Research Third Expert Report on Diet,

Nutrition, Physical Activity, and Cancer: Impact and Future Directions. The Journal of nutrition. 2020;150(4):663-71.
66. Gartlehner G, Patel SV, Reddy S, Rains C, Schwimmer M, Kahwati L. Hormone Therapy for the Primary Prevention of Chronic Conditions in Postmenopausal Persons: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. Jama. 2022;328(17):1747-65.
67. Rothwell PM, Wilson M, Elwin CE, Norrving B, Algra A, Warlow CP, et al. Long-term effect of aspirin on colorectal cancer incidence and mortality: 20-year follow-up of five randomised trials. Lancet (London, England). 2010;376(9754):1741-50.
68. Higurashi T, Hosono K, Takahashi H, Komiya Y, Umezawa S, Sakai E, et al. Metformin for chemoprevention of metachronous colorectal adenoma or polyps in post-polypectomy patients without diabetes: a multicentre double-blind, placebo-controlled, randomised phase 3 trial. The Lancet Oncology. 2016;17(4):475-83.
69. Martling A, Hed Myrberg I, Nilbert M, Grönberg H, Granath F, Eklund M, et al. Low-Dose Aspirin for PI3K-Altered Localized Colorectal Cancer. The New England journal of medicine. 2025;393(11):1051-64.
70. Swedish National Board of Health and Welfare. Recommendations for screening of Colorectal Cancer. https://wwwsocialstyrelsense/globalassets/sharepoint-dokument/dokument-webb/nationella-screeningprogram/screening-tjockandtarmscancer-rekommendationpdf. 2014.
71. Mandel JS, Church TR, Bond JH, Ederer F, Geisser MS, Mongin SJ, et al. The effect of fecal occult-blood screening on the incidence of colorectal cancer. The New England journal of medicine. 2000;343(22):1603-7.
72. Lindholm E, Brevinge H, Haglind E. Survival benefit in a randomized clinical trial of faecal occult blood screening for colorectal cancer. Br J Surg. 2008;95(8):1029-36.
73. Hewitson P, Glasziou P, Irwig L, Towler B, Watson E. Screening for colorectal cancer using the faecal occult blood test, Hemoccult. The Cochrane database of systematic reviews. 2007;2007(1):Cd001216.
74. Swedish Colorectal Cancer Registry. National guidlines for colorectal cancer screening in Sweden. https://kunskapsbankencancercentrumse/globalassets/kunskapsbanken/tjock--och-andtarmscancerscreening/nationellt-vardprogram-tjock-och-andtarmscancerscreeningpdf. 2022.
75. Commission OE. EU Country Cancer Profiles Synthesis Report 2025. OECD Publishing, Paris, https://doiorg/101787/20ef03e1-en. 2025.
76. Zhang L, Mosquera I, Lucas E, Rol ML, Carvalho AL, Basu P. CanScreen5, a global repository for breast, cervical and colorectal cancer screening programs. Nature medicine. 2023;29(5):1135-45.
77. IARC. International Agency for Research on Cancer. Working Group on the Evaluation of Cancer-Preventive Interventions. Colorectal cancer screening. Lyon (FR). Available from:

https://wwwncbinlmnihgov/books/NBK553200/pdf/Bookshelf_NBK553200pdf. 2019.
78. Davidson KW, Barry MJ, Mangione CM, Cabana M, Caughey AB, Davis EM, et al. Screening for Colorectal Cancer: US Preventive Services Task Force Recommendation Statement. Jama. 2021;325(19):1965-77.
79. Schreuders EH, Ruco A, Rabeneck L, Schoen RE, Sung JJ, Young GP, et al. Colorectal cancer screening: a global overview of existing programmes. Gut. 2015;64(10):1637-49.
80. Swedish Colorectal Cancer Registry. National guidlines in Sweden. https://kunskapsbankencancercentrumse/globalassets/cancerdiagnoser/tjock--och-andtarm-anal/vardprogram/nationellt-vardprogram-tjock-andtarmscancerpdf. Accessed May 13, 2025.
81. D'Souza N, de Neree Tot Babberich MPM, d'Hoore A, Tiret E, Xynos E, Beets-Tan RGH, et al. Definition of the Rectum: An International, Expert-based Delphi Consensus. Annals of surgery. 2019;270(6):955-9.
82. Holtedahl K, Borgquist L, Donker GA, Buntinx F, Weller D, Campbell C, et al. Symptoms and signs of colorectal cancer, with differences between proximal and distal colon cancer: a prospective cohort study of diagnostic accuracy in primary care. BMC family practice. 2021;22(1):148.
83. Dekker E, Tanis PJ, Vleugels JLA, Kasi PM, Wallace MB. Colorectal cancer. Lancet (London, England). 2019;394(10207):1467-80.
84. Argilés G, Tabernero J, Labianca R, Hochhauser D, Salazar R, Iveson T, et al. Localised colon cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of oncology : official journal of the European Society for Medical Oncology. 2020;31(10):1291-305.
85. Ewing M, Naredi P, Zhang C, Månsson J. Identification of patients with non-metastatic colorectal cancer in primary care: a case-control study. The British journal of general practice : the journal of the Royal College of General Practitioners. 2016;66(653):e880-e6.
86. Hamilton W. The CAPER studies: five case-control studies aimed at identifying and quantifying the risk of cancer in symptomatic primary care patients. British journal of cancer. 2009;101 Suppl 2(Suppl 2):S80-6.
87. Demb J, Kolb JM, Dounel J, Fritz CDL, Advani SM, Cao Y, et al. Red Flag Signs and Symptoms for Patients With Early-Onset Colorectal Cancer: A Systematic Review and Meta-Analysis. JAMA network open. 2024;7(5):e2413157.
88. Atkin W, Dadswell E, Wooldrage K, Kralj-Hans I, von Wagner C, Edwards R, et al. Computed tomographic colonography versus colonoscopy for investigation of patients with symptoms suggestive of colorectal cancer (SIGGAR): a multicentre randomised trial. Lancet (London, England). 2013;381(9873):1194-202.
89. Kijima S, Sasaki T, Nagata K, Utano K, Lefor AT, Sugimoto H. Preoperative evaluation of colorectal cancer using CT colonography, MRI, and PET/CT. World journal of gastroenterology. 2014;20(45):16964-75.

90. Dam C, Lindebjerg J, Jakobsen A, Jensen LH, Rahr H, Rafaelsen SR. Local staging of sigmoid colon cancer using MRI. Acta radiologica open. 2017;6(7):2058460117720957.
91. Fernandes MC, Gollub MJ, Brown G. The importance of MRI for rectal cancer evaluation. Surgical oncology. 2022;43:101739.
92. Zech CJ, Korpraphong P, Huppertz A, Denecke T, Kim MJ, Tanomkiat W, et al. Randomized multicentre trial of gadoxetic acid-enhanced MRI versus conventional MRI or CT in the staging of colorectal cancer liver metastases. Br J Surg. 2014;101(6):613-21.
93. Hall C, Clarke L, Pal A, Buchwald P, Eglinton T, Wakeman C, et al. A Review of the Role of Carcinoembryonic Antigen in Clinical Practice. Annals of coloproctology. 2019;35(6):294-305.
94. Brierley JD, Gospodarowicz MK, Wittekind C. TNM classification of malignant tumours. 8th ed ed: Wiley-Blackwell; 2017. xviii, 253 p. p.
95. Siegel RL, Miller KD, Goding Sauer A, Fedewa SA, Butterly LF, Anderson JC, et al. Colorectal cancer statistics, 2020. CA: a cancer journal for clinicians. 2020;70(3):145-64.
96. Swedish Colorectal Cancer Registry, Quality Report, Colon Cancer. https://cancercentrumse/download/1826c1f26f19a76a8084e5310a/1764084303862/kvalitetsregisterrapport%20tjocktarmscancer%202024pdf. 2024.
97. Swedish Colorectal Cancer Registry, Quality Report, Rectal Cancer. https://cancercentrumse/download/1826c1f26f19a76a8084e53213/1764085339315/kvalitetsregisterrapport%20%C3%A4ndtarmscancer%202024pdf. 2024.
98. Zaborowski AM, Murphy B, Creavin B, Rogers AC, Kennelly R, Hanly A, et al. Clinicopathological features and oncological outcomes of patients with young-onset rectal cancer. Br J Surg. 2020;107(5):606-12.
99. Kolarich A, George TJ, Jr., Hughes SJ, Delitto D, Allegra CJ, Hall WA, et al. Rectal cancer patients younger than 50 years lack a survival benefit from NCCN guideline-directed treatment for stage II and III disease. Cancer. 2018;124(17):3510-9.
100. Saraste D, Järås J, Martling A. Population-based analysis of outcomes with early-age colorectal cancer. British Journal of Surgery. 2020;107(3):301-9.
101. O'Connell JB, Maggard MA, Liu JH, Etzioni DA, Livingston EH, Ko CY. Do young colon cancer patients have worse outcomes? World journal of surgery. 2004;28(6):558-62.
102. Kneuertz PJ, Chang GJ, Hu CY, Rodriguez-Bigas MA, Eng C, Vilar E, et al. Overtreatment of young adults with colon cancer: more intense treatments with unmatched survival gains. JAMA surgery. 2015;150(5):402-9.
103. Fearon ER, Vogelstein B. A genetic model for colorectal tumorigenesis. Cell. 1990;61(5):759-67.
104. Pino MS, Chung DC. The chromosomal instability pathway in colon cancer. Gastroenterology. 2010;138(6):2059-72.
105. Parmar S, Easwaran H. Genetic and epigenetic dependencies in colorectal cancer development. Gastroenterology report. 2022;10.

106. Hankey W, Frankel WL, Groden J. Functions of the APC tumor suppressor protein dependent and independent of canonical WNT signaling: implications for therapeutic targeting. Cancer metastasis reviews. 2018;37(1):159-72.
107. Grady WM, Carethers JM. Genomic and epigenetic instability in colorectal cancer pathogenesis. Gastroenterology. 2008;135(4):1079-99.
108. Baran B, Mert Ozupek N, Yerli Tetik N, Acar E, Bekcioglu O, Baskin Y. Difference Between Left-Sided and Right-Sided Colorectal Cancer: A Focused Review of Literature. Gastroenterology research. 2018;11(4):264-73.
109. De Palma FDE, D'Argenio V, Pol J, Kroemer G, Maiuri MC, Salvatore F. The Molecular Hallmarks of the Serrated Pathway in Colorectal Cancer. Cancers. 2019;11(7).
110. Lee MS, Menter DG, Kopetz S. Right Versus Left Colon Cancer Biology: Integrating the Consensus Molecular Subtypes. Journal of the National Comprehensive Cancer Network : JNCCN. 2017;15(3):411-9.
111. Gómez-Molina R, Martínez R, Suárez M, Peña-Cabia A, Calderón MC, Mateo J. Lynch syndrome and colorectal cancer: A review of current perspectives in molecular genetics and clinical strategies. Oncology research. 2025;33(7):1531-45.
112. Randrian V, Evrard C, Tougeron D. Microsatellite Instability in Colorectal Cancers: Carcinogenesis, Neo-Antigens, Immuno-Resistance and Emerging Therapies. Cancers. 2021;13(12).
113. Guinney J, Dienstmann R, Wang X, de Reyniès A, Schlicker A, Soneson C, et al. The consensus molecular subtypes of colorectal cancer. Nature medicine. 2015;21(11):1350-6.
114. Dienstmann R, Vermeulen L, Guinney J, Kopetz S, Tejpar S, Tabernero J. Consensus molecular subtypes and the evolution of precision medicine in colorectal cancer. Nature reviews Cancer. 2017;17(2):79-92.
115. Ten Hoorn S, de Back TR, Sommeijer DW, Vermeulen L. Clinical Value of Consensus Molecular Subtypes in Colorectal Cancer: A Systematic Review and Meta-Analysis. Journal of the National Cancer Institute. 2022;114(4):503-16.
116. Tang J, Peng W, Tian C, Zhang Y, Ji D, Wang L, et al. Molecular characteristics of early-onset compared with late-onset colorectal cancer: a case controlled study. International journal of surgery (London, England). 2024;110(8):4559-70.
117. Willauer AN, Liu Y, Pereira AAL, Lam M, Morris JS, Raghav KPS, et al. Clinical and molecular characterization of early-onset colorectal cancer. Cancer. 2019;125(12):2002-10.
118. Lawler T, Parlato L, Warren Andersen S. The histological and molecular characteristics of early-onset colorectal cancer: a systematic review and meta-analysis. Frontiers in oncology. 2024;14:1349572.
119. Li J, Pan Y, Guo F, Wang C, Liang L, Li P, et al. Patterns in genomic mutations among patients with early-onset colorectal cancer: an international,

multicohort, observational study. The Lancet Oncology. 2025;26(8):1055-66.
120. Mohammadpour S, Torshizi Esfahani A, Sarpash S, Vakili F, Zafarjafarzadeh N, Mashaollahi A, et al. Hippo Signaling Pathway in Colorectal Cancer: Modulation by Various Signals and Therapeutic Potential. Analytical cellular pathology (Amsterdam). 2024;2024:5767535.
121. Park HW, Kim YC, Yu B, Moroishi T, Mo JS, Plouffe SW, et al. Alternative Wnt Signaling Activates YAP/TAZ. Cell. 2015;162(4):780-94.
122. Azzolin L, Panciera T, Soligo S, Enzo E, Bicciato S, Dupont S, et al. YAP/TAZ incorporation in the β-catenin destruction complex orchestrates the Wnt response. Cell. 2014;158(1):157-70.
123. Garcia KC, Khan AA, Ghosh K, Sinha S, Scalora N, DeWane G, et al. PI3K regulates TAZ/YAP and mTORC1 axes that can be synergistically targeted. bioRxiv : the preprint server for biology. 2025.
124. Zhang L, Zhang F, Liang H, Qin X, Mo Y, Chen S, et al. Hippo/YAP signaling pathway in colorectal cancer: regulatory mechanisms and potential drug exploration. Frontiers in oncology. 2025;15:1545952.
125. IARC. International Agency for Research on Cancer. Digestive System Tumours. WHO Classification of Tumours editorial board 5th ed 5th ed: World Health Organization (WHO). 2019.
126. Boland CR, Goel A. Microsatellite instability in colorectal cancer. Gastroenterology. 2010;138(6):2073-87.e3.
127. Hyngstrom JR, Hu CY, Xing Y, You YN, Feig BW, Skibber JM, et al. Clinicopathology and outcomes for mucinous and signet ring colorectal adenocarcinoma: analysis from the National Cancer Data Base. Annals of surgical oncology. 2012;19(9):2814-21.
128. Galon J, Costes A, Sanchez-Cabo F, Kirilovsky A, Mlecnik B, Lagorce-Pagès C, et al. Type, density, and location of immune cells within human colorectal tumors predict clinical outcome. Science (New York, NY). 2006;313(5795):1960-4.
129. Ionescu VA, Gheorghe G, Baban IA, Barbu A, Georgescu TF, Tiuca LC, et al. Prognostic Differences Between Early-Onset and Late-Onset Colorectal Cancer. Medicina (Kaunas, Lithuania). 2025;61(3).
130. Morton D, Seymour M, Magill L, Handley K, Glasbey J, Glimelius B, et al. Preoperative Chemotherapy for Operable Colon Cancer: Mature Results of an International Randomized Controlled Trial. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2023;41(8):1541-52.
131. Hu H, Zhang J, Li Y, Wang X, Wang Z, Wang H, et al. Neoadjuvant Chemotherapy With Oxaliplatin and Fluoropyrimidine Versus Upfront Surgery for Locally Advanced Colon Cancer: The Randomized, Phase III OPTICAL Trial. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2024;42(25):2978-88.
132. Jensen LH, Kjaer ML, Larsen FO, Hollander NH, Rahr HB, Pfeffer F, et al. Phase III randomized clinical trial comparing the efficacy of neoadjuvant

chemotherapy and standard treatment in patients with locally advanced colon cancer: The NeoCol trial. Journal of Clinical Oncology. 2023;41(17_suppl):LBA3503-LBA.
133. Chalabi M, Verschoor YL, Tan PB, Balduzzi S, Van Lent AU, Grootscholten C, et al. Neoadjuvant Immunotherapy in Locally Advanced Mismatch Repair-Deficient Colon Cancer. The New England journal of medicine. 2024;390(21):1949-58.
134. McLaughlin C, Kim NK, Bandyopadhyay D, Deng X, Kaplan B, Matin K, et al. Adjuvant radiation therapy for T4 non-rectal colon adenocarcinoma provides a cause-specific survival advantage: A SEER database analysis. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology. 2019;133:50-3.
135. Cedermark B, Dahlberg M, Glimelius B, Påhlman L, Rutqvist LE, Wilking N. Improved survival with preoperative radiotherapy in resectable rectal cancer. The New England journal of medicine. 1997;336(14):980-7.
136. Kapiteijn E, Marijnen CA, Nagtegaal ID, Putter H, Steup WH, Wiggers T, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. The New England journal of medicine. 2001;345(9):638-46.
137. Sauer R, Becker H, Hohenberger W, Rödel C, Wittekind C, Fietkau R, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. The New England journal of medicine. 2004;351(17):1731-40.
138. Bosset JF, Collette L, Calais G, Mineur L, Maingon P, Radosevic-Jelic L, et al. Chemotherapy with preoperative radiotherapy in rectal cancer. The New England journal of medicine. 2006;355(11):1114-23.
139. Braendengen M, Tveit KM, Berglund A, Birkemeyer E, Frykholm G, Påhlman L, et al. Randomized phase III study comparing preoperative radiotherapy with chemoradiotherapy in nonresectable rectal cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2008;26(22):3687-94.
140. Bujko K, Nowacki MP, Nasierowska-Guttmejer A, Michalski W, Bebenek M, Kryj M. Long-term results of a randomized trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer. Br J Surg. 2006;93(10):1215-23.
141. Ngan SY, Burmeister B, Fisher RJ, Solomon M, Goldstein D, Joseph D, et al. Randomized Trial of Short-Course Radiotherapy Versus Long-Course Chemoradiation Comparing Rates of Local Recurrence in Patients With T3 Rectal Cancer: Trans-Tasman Radiation Oncology Group Trial 01.04. Journal of Clinical Oncology. 2012;30(31):3827-33.
142. Bahadoer RR, Dijkstra EA, van Etten B, Marijnen CAM, Putter H, Kranenbarg EM, et al. Short-course radiotherapy followed by chemotherapy before total mesorectal excision (TME) versus preoperative chemoradiotherapy, TME, and optional adjuvant chemotherapy in locally advanced rectal cancer (RAPIDO): a randomised, open-label, phase 3 trial. The Lancet Oncology. 2021;22(1):29-42.

143. Dijkstra EA, Nilsson PJ, Hospers GAP, Bahadoer RR, Meershoek-Klein Kranenbarg E, Roodvoets AGH, et al. Locoregional Failure During and After Short-course Radiotherapy Followed by Chemotherapy and Surgery Compared With Long-course Chemoradiotherapy and Surgery: A 5-Year Follow-up of the RAPIDO Trial. Annals of surgery. 2023;278(4):e766-e72.
144. Jin J, Tang Y, Hu C, Jiang LM, Jiang J, Li N, et al. Multicenter, Randomized, Phase III Trial of Short-Term Radiotherapy Plus Chemotherapy Versus Long-Term Chemoradiotherapy in Locally Advanced Rectal Cancer (STELLAR). Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2022;40(15):1681-92.
145. Bujko K, Wyrwicz L, Rutkowski A, Malinowska M, Pietrzak L, Kryński J, et al. Long-course oxaliplatin-based preoperative chemoradiation versus 5 × 5 Gy and consolidation chemotherapy for cT4 or fixed cT3 rectal cancer: results of a randomized phase III study. Annals of oncology : official journal of the European Society for Medical Oncology. 2016;27(5):834-42.
146. van der Valk MJM, Hilling DE, Bastiaannet E, Meershoek-Klein Kranenbarg E, Beets GL, Figueiredo NL, et al. Long-term outcomes of clinical complete responders after neoadjuvant treatment for rectal cancer in the International Watch & Wait Database (IWWD): an international multicentre registry study. Lancet (London, England). 2018;391(10139):2537-45.
147. Appelt AL, Pløen J, Harling H, Jensen FS, Jensen LH, Jørgensen JC, et al. High-dose chemoradiotherapy and watchful waiting for distal rectal cancer: a prospective observational study. The Lancet Oncology. 2015;16(8):919-27.
148. Cercek A, Lumish M, Sinopoli J, Weiss J, Shia J, Lamendola-Essel M, et al. PD-1 Blockade in Mismatch Repair-Deficient, Locally Advanced Rectal Cancer. The New England journal of medicine. 2022;386(25):2363-76.
149. Cercek A, Sinopoli JC, Shia J, Weiss JA, Temple L, Smith JJ, et al. Durable complete responses to PD-1 blockade alone in mismatch repair deficient locally advanced rectal cancer. Journal of Clinical Oncology. 2024;42(17_suppl):LBA3512-LBA.
150. Heald RJ, Husband EM, Ryall RD. The mesorectum in rectal cancer surgery--the clue to pelvic recurrence? Br J Surg. 1982;69(10):613-6.
151. Hohenberger W, Weber K, Matzel K, Papadopoulos T, Merkel S. Standardized surgery for colonic cancer: complete mesocolic excision and central ligation--technical notes and outcome. Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland. 2009;11(4):354-64; discussion 64-5.
152. Veldkamp R, Kuhry E, Hop WC, Jeekel J, Kazemier G, Bonjer HJ, et al. Laparoscopic surgery versus open surgery for colon cancer: short-term outcomes of a randomised trial. The Lancet Oncology. 2005;6(7):477-84.
153. Bonjer HJ, Deijen CL, Abis GA, Cuesta MA, Pas MHGMvd, Klerk ESMdL-d, et al. A Randomized Trial of Laparoscopic versus Open Surgery for Rectal Cancer. New England Journal of Medicine. 2015;372(14):1324-32.

154. Mohan HM, Evans MD, Larkin JO, Beynon J, Winter DC. Multivisceral resection in colorectal cancer: a systematic review. Annals of surgical oncology. 2013;20(9):2929-36.
155. Archampong D, Borowski D, Wille-Jørgensen P, Iversen LH. Workload and surgeon's specialty for outcome after colorectal cancer surgery. The Cochrane database of systematic reviews. 2012;2012(3):Cd005391.
156. Nordkamp S, Voogt ELK, van Zoggel D, Martling A, Holm T, Jansson Palmer G, et al. Locally recurrent rectal cancer: oncological outcomes with different treatment strategies in two tertiary referral units. Br J Surg. 2022;109(7):623-31.
157. André T, Boni C, Mounedji-Boudiaf L, Navarro M, Tabernero J, Hickish T, et al. Oxaliplatin, Fluorouracil, and Leucovorin as Adjuvant Treatment for Colon Cancer. New England Journal of Medicine. 2004;350(23):2343-51.
158. Tournigand C, André T, Bonnetain F, Chibaudel B, Lledo G, Hickish T, et al. Adjuvant therapy with fluorouracil and oxaliplatin in stage II and elderly patients (between ages 70 and 75 years) with colon cancer: subgroup analyses of the Multicenter International Study of Oxaliplatin, Fluorouracil, and Leucovorin in the Adjuvant Treatment of Colon Cancer trial. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2012;30(27):3353-60.
159. Gögenur M, Rosen AW, Iveson T, Kerr RS, Saunders MP, Cassidy J, et al. Time From Colorectal Cancer Surgery to Adjuvant Chemotherapy: Post Hoc Analysis of the SCOT Randomized Clinical Trial. JAMA surgery. 2024;159(8):865-71.
160. Haller DG, O'Connell MJ, Cartwright TH, Twelves CJ, McKenna EF, Sun W, et al. Impact of age and medical comorbidity on adjuvant treatment outcomes for stage III colon cancer: a pooled analysis of individual patient data from four randomized, controlled trials. Annals of oncology : official journal of the European Society for Medical Oncology. 2015;26(4):715-24.
161. Dottorini L, Petrelli F, Ghidini A, Rea CG, Borgonovo K, Dognini G, et al. Oxaliplatin in Adjuvant Colorectal Cancer: Is There a Role in Older Patients? Journal of Clinical Oncology. 2023;41(18):3300-3.
162. André T, Meyerhardt J, Iveson T, Sobrero A, Yoshino T, Souglakos I, et al. Effect of duration of adjuvant chemotherapy for patients with stage III colon cancer (IDEA collaboration): final results from a prospective, pooled analysis of six randomised, phase 3 trials. The Lancet Oncology. 2020;21(12):1620-9.
163. Vilar E, Gruber SB. Microsatellite instability in colorectal cancer-the stable evidence. Nature reviews Clinical oncology. 2010;7(3):153-62.
164. Gkekas I, Novotny J, Fabian P, Nemecek R, Palmqvist R, Strigård K, et al. Mismatch repair status predicts survival after adjuvant treatment in stage II colon cancer patients. Journal of surgical oncology. 2020;121(2):392-401.
165. Cohen R, Taieb J, Fiskum J, Yothers G, Goldberg R, Yoshino T, et al. Microsatellite Instability in Patients With Stage III Colon Cancer Receiving Fluoropyrimidine With or Without Oxaliplatin: An ACCENT Pooled

Analysis of 12 Adjuvant Trials. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2021;39(6):642-51.
166. Kotani D, Oki E, Nakamura Y, Yukami H, Mishima S, Bando H, et al. Molecular residual disease and efficacy of adjuvant chemotherapy in patients with colorectal cancer. Nature medicine. 2023;29(1):127-34.
167. Khuri SF, Henderson WG, DePalma RG, Mosca C, Healey NA, Kumbhani DJ. Determinants of long-term survival after major surgery and the adverse effect of postoperative complications. Annals of surgery. 2005;242(3):326-41; discussion 41-3.
168. Giglia MD, Stein SL. Overlooked Long-Term Complications of Colorectal Surgery. Clinics in colon and rectal surgery. 2019;32(3):204-11.
169. van Rooijen S, Carli F, Dalton SO, Johansen C, Dieleman J, Roumen R, et al. Preoperative modifiable risk factors in colorectal surgery: an observational cohort study identifying the possible value of prehabilitation. Acta oncologica (Stockholm, Sweden). 2017;56(2):329-34.
170. Bot J, Piessen G, Robb WB, Roger V, Mariette C. Advanced tumor stage is an independent risk factor of postoperative infectious complications after colorectal surgery: arguments from a case-matched series. Diseases of the colon and rectum. 2013;56(5):568-76.
171. Yang KM, Jeong MJ, Yoon KH, Jung YT, Kwak JY. Oncologic outcome of colon cancer with perforation and obstruction. BMC gastroenterology. 2022;22(1):247.
172. Yasui M, Takemasa I, Miyake Y, Hata T, Ikeda M, Miyake Y, et al. Tumor Size as an Independent Risk Factor for Postoperative Complications in Laparoscopic Low Anterior Resection for Advanced Rectal Cancer: A Multicenter Japanese Study. Surgical laparoscopy, endoscopy & percutaneous techniques. 2017;27(2):98-103.
173. Huebner M, Hübner M, Cima RR, Larson DW. Timing of complications and length of stay after rectal cancer surgery. Journal of the American College of Surgeons. 2014;218(5):914-9.
174. McDermott FD, Heeney A, Kelly ME, Steele RJ, Carlson GL, Winter DC. Systematic review of preoperative, intraoperative and postoperative risk factors for colorectal anastomotic leaks. Br J Surg. 2015;102(5):462-79.
175. Cai W, Wang L, Wang W, Zhou T. Systematic review and meta-analysis of the risk factors of surgical site infection in patients with colorectal cancer. Translational cancer research. 2022;11(4):857-71.
176. Chen D, Afzal N, Sohn S, Habermann EB, Naessens JM, Larson DW, et al. Postoperative bleeding risk prediction for patients undergoing colorectal surgery. Surgery. 2018;164(6):1209-16.
177. Kwiatt M, Kawata M. Avoidance and management of stomal complications. Clinics in colon and rectal surgery. 2013;26(2):112-21.
178. Cervantes A, Adam R, Roselló S, Arnold D, Normanno N, Taïeb J, et al. Metastatic colorectal cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Annals of oncology : official journal of the European Society for Medical Oncology. 2023;34(1):10-32.

179. Treasure T, Monson K, Fiorentino F, Russell C. The CEA Second-Look Trial: a randomised controlled trial of carcinoembryonic antigen prompted reoperation for recurrent colorectal cancer. BMJ open. 2014;4(5):e004385.
180. Titu LV, Nicholson AA, Hartley JE, Breen DJ, Monson JR. Routine follow-up by magnetic resonance imaging does not improve detection of resectable local recurrences from colorectal cancer. Annals of surgery. 2006;243(3):348-52.
181. Sobhani I, Itti E, Luciani A, Baumgaertner I, Layese R, André T, et al. Colorectal cancer (CRC) monitoring by 6-monthly 18FDG-PET/CT: an open-label multicentre randomised trial. Annals of oncology : official journal of the European Society for Medical Oncology. 2018;29(4):931-7.
182. Tie J, Wang Y, Tomasetti C, Li L, Springer S, Kinde I, et al. Circulating tumor DNA analysis detects minimal residual disease and predicts recurrence in patients with stage II colon cancer. Science translational medicine. 2016;8(346):346ra92.
183. Callesen LB, Hansen TF, Andersen RF, Pallisgaard N, Kramer S, Schlander S, et al. OPTIMISE: Optimisation of treatment selection and follow-up in oligometastatic colorectal cancer - a ctDNA-guided phase II randomised approach. Study protocol. Acta oncologica (Stockholm, Sweden). 2022;61(9):1152-6.
184. Schraa SJ, van Rooijen KL, van der Kruijssen DEW, Rubio Alarcón C, Phallen J, Sausen M, et al. Circulating tumor DNA guided adjuvant chemotherapy in stage II colon cancer (MEDOCC-CrEATE): study protocol for a trial within a cohort study. BMC cancer. 2020;20(1):790.
185. Wille-Jørgensen P, Syk I, Smedh K, Laurberg S, Nielsen DT, Petersen SH, et al. Effect of More vs Less Frequent Follow-up Testing on Overall and Colorectal Cancer-Specific Mortality in Patients With Stage II or III Colorectal Cancer: The COLOFOL Randomized Clinical Trial. Jama. 2018;319(20):2095-103.
186. Primrose JN, Perera R, Gray A, Rose P, Fuller A, Corkhill A, et al. Effect of 3 to 5 years of scheduled CEA and CT follow-up to detect recurrence of colorectal cancer: the FACS randomized clinical trial. Jama. 2014;311(3):263-70.
187. Snyder RA, Hu CY, Cuddy A, Francescatti AB, Schumacher JR, Van Loon K, et al. Association Between Intensity of Posttreatment Surveillance Testing and Detection of Recurrence in Patients With Colorectal Cancer. Jama. 2018;319(20):2104-15.
188. Nors J, Gotschalck KA, Erichsen R, Andersen CL. Risk of recurrence in early-onset versus late-onset non-metastatic colorectal cancer, 2004–2019: a nationwide cohort study. The Lancet Regional Health - Europe. 2024;47.
189. Barlow L, Westergren K, Holmberg L, Talbäck M. The completeness of the Swedish Cancer Register: a sample survey for year 1998. Acta oncologica (Stockholm, Sweden). 2009;48(1):27-33.
190. Påhlman L, Bohe M, Cedermark B, Dahlberg M, Lindmark G, Sjödahl R, et al. The Swedish rectal cancer registry. Br J Surg. 2007;94(10):1285-92.

191. Kodeda K, Nathanaelsson L, Jung B, Olsson H, Jestin P, Sjövall A, et al. Population-based data from the Swedish Colon Cancer Registry. Br J Surg. 2013;100(8):1100-7.
192. Moberger P, Sköldberg F, Birgisson H. Evaluation of the Swedish Colorectal Cancer Registry: an overview of completeness, timeliness, comparability and validity. Acta oncologica (Stockholm, Sweden). 2018;57(12):1611-21.
193. Yeo H, Betel D, Abelson JS, Zheng XE, Yantiss R, Shah MA. Early-onset Colorectal Cancer is Distinct From Traditional Colorectal Cancer. Clinical colorectal cancer. 2017;16(4):293-9.e6.
194. Madsen HJ, Gillette RA, Colborn KL, Henderson WG, Dyas AR, Bronsert MR, et al. The association between obesity and postoperative outcomes in a broad surgical population: A 7-year American College of Surgeons National Surgical Quality Improvement analysis. Surgery. 2023;173(5):1213-9.
195. National Comprehensive Cancer Network. NCCN guidlines: colon cancer. https://wwwnccnorg/guidelines/guidelines-detail?category=1&id=1428. Accessed Feburary 18, 2025.
196. National Comprehensive Cancer Network. NCCN guidlines: rectal cancer. https://wwwnccnorg/guidelines/guidelines-detail?category=1&id=1461. Accessed February 18, 2025.
197. Meyerhardt JA, Mangu PB, Flynn PJ, Korde L, Loprinzi CL, Minsky BD, et al. Follow-up care, surveillance protocol, and secondary prevention measures for survivors of colorectal cancer: American Society of Clinical Oncology clinical practice guideline endorsement. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2013;31(35):4465-70.
198. Chen H, Shang Y, Li X, Wang R. YAP1 expression in colorectal cancer confers the aggressive phenotypes via its target genes. Cell cycle (Georgetown, Tex). 2024;23(1):83-91.
199. Zhang X, Fan Y, Tan K. A bird's eye view of mitochondrial unfolded protein response in cancer: mechanisms, progression and further applications. Cell death & disease. 2024;15(9):667.
200. Biswal P, Sahu MR, Ahmad MH, Mondal AC. The interplay between hippo signaling and mitochondrial metabolism: Implications for cellular homeostasis and disease. Mitochondrion. 2024;76:101885.
201. Poma AM, Torregrossa L, Bruno R, Basolo F, Fontanini G. Hippo pathway affects survival of cancer patients: extensive analysis of TCGA data and review of literature. Scientific reports. 2018;8(1):10623.

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1992 Magnus Bergenfeldt
1993 Anders Lundell
1993 Baimeng Zhang
1994 Staffan Weiber
1994 Stefan Matthiasson
1994 Björn Sonesson
1995 Jan Stewenius
1995 Björn Arnljots
1995 Jan Holst
1995 Leif Israelsson
1995 Per Jönsson
1996 Norman Jensen
1996 Jens Peter Game
1996 Hans Bohe
1997 Wayne Hawthorne
1997 Öyvind Östraat
1997 Yilei Mao
1998 Diya Adawi
1998 Liselotte Frost-Arner
1998 Martin Malina

1998 Thomas Björk
1998 Mats Hedberg
1998 Håkan Brorson
1998 Magnus Becker
1999 Zhonquan Qi
1999 Stefan Appelros
1999 Göran Ahlgren
1999 Håkan Weiber
2000 Ingvar Syk
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2001 Christer Svedman
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2001 Ursula Mirastschijski
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2003 Nina Kvorning
2003 Gudmundur Danielsson
2003 Fritz Berndsen
2003 Salathiel Mzezewa
2004 Marianne Starck
2004 Li Xiang
2004 Karl Malm
2004 Claes Jansen
2004 Peter Danielsson
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2005 Ann-Cathrin Moberg
2005 Anders Holmström
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2005 Carolin Freccero
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2005 Elzanaty Saad
2005 Björn Lindkvist
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2008 Martin Persson
2008 Sara Regnér
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2008 Asaduzzaman Muhammad
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2009 Martin Almquist
2009 Farokh Collander Farzaneh
2010 Dorthe Johansen
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2010 Patrik Velander
2010 Andrada Mihaescu
2011 Salma Butt
2011 Emma Hansson
2011 Aree Abdulla
2011 Darbaz Awla
2012 Martin Rehn
2012 Milladur Rahman
2012 Su Zhang
2012 Jan Slotta
2012 Åsa Olsson
2012 Martin Öberg
2012 Songen Zhang
2013 Zirak Hasan
2013 Karzan Hamad Palani
2014 Thordur Bjarnason
2014 Clara Påhlman
2014 Ada Tosovic
2015 Hannes Hartman
2015 Mohammed Merza
2015 Rundk Hwaiz
2015 Lingtao Luo
2015 Yongzhi Wang
2016 Fredrik Olofsson
2016 Jonas Roller
2016 Stina Klasson
2016 Andrea Polistena
2017 Ali Bagher
2017 Jenny Rystedt
2017 Peder Rogmark
2017 Hanna Sternby
2017 Ann Nozohoor Ekmark
2018 Jasmine Brandt Bratlie
2018 Mattias Hoffner
2018 Nihad Gutlic
2018 Amr Al-Haidari
2019 Artur Németh
2019 Linnea Huss
2019 Cecilia Dahlbäck
2019 Carl-Fredrik Rönnow
2019 Mia Stiernman
2019 Shabaz Majid
2020 Michael Rose
2020 Avin Hawez
2020 Raed Madhi
2020 Johan Linders
2021 Henrik Jutesten
2021 Najia Azhar
2021 Anwar Algaber
2021 Christina Stene
2021 Malte Sandsveden
2022 Feifel Du
2022 Zhiyi Ding
2022 Erik Agger
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2023 Örvar Arnarson
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2025 Allan Gutlic
2025 Charlotta L Wenzelberg
2025 Victoria Arthursson
2025 Mattias Lepseny
2025 Roberto Rosén
2025 Måns Cornefjord