# Risk of recurrence in early-onset versus late-onset non-metastatic colorectal cancer, 2004–2019: a nationwide cohort study

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## Summary

**Background** The incidence of colorectal cancer (CRC) in individuals younger than 50 years of age (early-onset CRC) is increasing. Early-onset CRC often present at advanced stage, suggesting a more aggressive cancer course compared to late-onset CRC (age 50–79). This nationwide cohort study estimates the incidence of recurrence following early-onset CRC and late-onset CRC.

**Methods** The study included all Danish patients <80 years old operated for first-time Union for International Cancer Control (UICC) stage I–III CRC between January 2004 and December 2019. Recurrence status was determined by applying a validated algorithm to individual-level data from nationwide health registries. The 5-year cumulative incidence functions (CIF) of recurrence were reported for early-onset versus late-onset CRC. The difference in time to recurrence was estimated as a time ratio (TR) using an accelerated failure time model.

**Findings** Among 25,729 CRC patients, 1441 (5.6%) had early-onset CRC. Compared to late-onset CRC, early-onset was associated with advanced disease stages and higher treatment intensity. The 5-year CIF of recurrence was 29% (95% CI: 26%–31%) in early-onset versus 21% (95% CI: 21%–22%) in late-onset CRC. The higher CIF of recurrence for early-onset patients persisted in stage-stratified analysis. Time to recurrence was shorter in early-onset versus late-onset patients with TR = 0.76 (95% CI: 0.67–0.85). The 5-year CIF of recurrence decreased from 2004 to 2019 for both early- and late-onset patients–most prominent for early-onset patients.

**Interpretation** Early-onset CRC was associated with higher incidence of recurrence at all disease stages. Indicating that the increased risk is not explained by delayed diagnosis. The excess risk diminished from 2004 to 2019, suggesting that early-onset CRC may achieve a similar recurrence risk as late-onset CRC in a contemporary setting.

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**Keywords:** Colorectal cancer; Early-onset; Disease recurrence; National health care data registries

## Introduction

The average colorectal cancer (CRC) patient is diagnosed at the age of 72 years,[1] but when diagnosed at an age younger than 50 years, the disease is defined as early-onset CRC.[2] Early-onset CRC has gained interest as an increase in incidence has been observed in the United States and Europe over the past decades.[3–5] Consequently, early-onset CRC now accounts for approximately 10% of all first-time CRC cases.[1]

Survival following CRC has improved in recent decades,[6] but remains strongly associated with disease recurrence. Approximately 20% of patients experience

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## Research in context

### Evidence before this study

We searched PubMed for publications with no language restrictions from Jan 1, 2014, to August 14, 2024, using search terms "colorectal cancer" AND ("early-onset" OR "Young adults") AND "recurrence" to identify relevant publications. We found two pooled analysis of clinical trials (high risk stage II and stage III CRC) and four cohort studies (stage I–IV) that reported on recurrence among early-onset colorectal cancer (CRC) patients, here defined as <50 years of age at diagnosis. The pooled analysis of RCTs from the International Duration Evaluation of Adjuvant Chemotherapy (IDEA) database found no difference in DFS but reported a higher 3-year CIF of recurrence among early-onset CRC. The pooled analysis of stage III colon cancers from 25 randomized studies in the Adjuvant Colon Cancer Endpoint (ACCENT) database found early-onset patients associated with better DFS and survival after recurrence. Two cohort studies reported higher risk of recurrence among stage I–IV early-onset CRC. One cohort study reported worse RFS in male early-onset patients but not in female early-onset patients. The largest cohort study including three national registries reported better prognosis in early-onset patients but included patients from 1972 to 2013, hence it may not be reflective of modern CRC management. No nationwide (population-based) studies with a modern and contemporary cohort were identified.

### Added value of this study

In this Danish nationwide cohort study using health data registries, we comprehensively evaluated the risk of recurrence among early-onset CRC patients and compared this to late-onset CRC patients. Our population-based cohort include all cancers diagnosed from 2004 to 2019, consequently, we can report temporal changes in the risk of recurrence in early-onset CRC patients. Our study shows that early-onset CRC has increased risk of recurrence, and further an accelerated time to recurrence. From 2004 to 2019 the excess risk of recurrence in early-onset CRC diminished, and in the latest of our calendar periods from 2014 to 2019 there was only a marginal difference between early- and late-onset.

### Implications of all the available evidence

Along with existing evidence, our findings suggest that despite excess risk of recurrence, patients with early-onset CRC may potentially achieve a similar prognosis compared to late-onset CRC when treated according to modern guidelines. These findings provide useful and encouraging information for patients with early-onset CRC and their physicians. Intensive treatment algorithms based on age at diagnosis alone may not be warranted. However, further research is needed to evaluate if early-onset patients may benefit from intensified surveillance during the first postoperative year, as this study suggests an accelerated time to recurrence in early-onset patients.

recurrence despite curatively intended treatment, which is why guidelines recommend postoperative surveillance. Over the last decades the risk of recurrence has decreased for all disease stages.[7] Unfortunately, early-onset CRC patients are often diagnosed with advanced disease stage,[8] raising the question of whether early-onset CRCs have a particularly aggressive tumor biology[9] or their diagnosis is delayed.[10] Excess mortality has been reported among early-onset CRC in unadjusted analysis,[11] potentially due to increased risk of recurrence as a consequence of advanced disease at diagnosis.

Furthermore, as 50 years has been set as a cut-off for average-risk screening in many countries,[12] the stage-migration from CRC screening may have led to an increased difference in recurrence risk between early-onset and late-onset CRC in recent years.

The aim of this study was to estimate incidence of recurrence and time to recurrence in patients diagnosed with early-onset CRC (age <50 years at CRC diagnosis) compared to late-onset patients (aged 50–79 years) in a nationwide cohort of stage I–III CRC patients who underwent surgery with curative intent. Secondary aims were to explore changes in incidence of recurrence from 2004 to 2019, to explore differences in surveillance intensity between early-onset and late-onset patients, and to estimate potential differences in post-recurrence mortality.

## Methods

This nationwide cohort study was approved by the Danish Data Protection Agency (Central Denmark Region, J. no. 1-16-02-274-19). All Danish patients younger than 80 years at curative intended surgical resection for UICC TNM stage I–III CRC between January 2004 and December 2019 were included. The patients were identified from the Danish Colorectal Cancer Group (DCCG) database.[13]

To include first-time CRC patients, patients with a history of any cancer other than non-melanoma skin cancer (NMSC) or metastases of unknown origin any time prior to primary CRC surgery were excluded; this because the algorithm can not determine if metastases represent a CRC recurrence or a recurrence from previous non-CRC tumors. A diagnosis of CRC within 180 days from date of surgery was allowed, as neoadjuvant therapy is offered to some patients. Patients with a diagnosis of hereditary CRC including familial adenomatous polyposis (FAP) and hereditary nonpolyposis colorectal cancer (HNPCC) were excluded, as these patients follow different screening, treatment, and surveillance protocols.[14] Finally, patients who emigrated, were diagnosed with a second primary cancer, or died within 180 days postoperative were excluded. A diagnosis of metastases within 180 days postoperative is

interpreted as synchronous metastases by the algorithm, hence this reclassifies the patient as UICC stage IV and results in exclusion from this study.

For detailed motivations for the exclusion criterias see the Supplementary eResults.

### Data sources and identification of recurrence

Individual-level data were obtained from Danish health care registries[15] including the Danish Cancer Registry (DCR), the Danish National Registry of Patients (DNPR), and the Danish Pathology Registry (DPR). Data records were linked using the unique 10-digit civil registration number assigned by the Danish Civil Registration System (completeness ~100%[16]), and recurrence status was determined using a validated algorithm[17,18] defining recurrence as the earliest of the following indicators:

1) Metastasis (International Classification of Diseases [ICD]-10; DC76-DC80) in the DNPR or the DCR,
2) Treatment with chemotherapy (BWHA1-2, BOHJ17 or BOHJ19B1) registered by an oncological department in the DNPR 60 or more days from last cytostatic therapy code,
3) SNOMED combinations in the DPR, or
4) Local recurrence in the DNPR (ICD-10; DC189X, DC209X or DC991).

Cause of death was obtained from the Danish Register of Causes of Death, and ICD-10 DC18 or DC20 was defined as CRC-related death.

### Covariates

The dates of surgery were grouped into 3 calendar periods: 2004–2008, 2009–2013, and 2014–2019 based on changes to the management of CRC in Denmark.[7] The latter period coincides with the introduction of the National Danish Colorectal Cancer Screening Program in 2014.

Eligible patients were categorized by sex (male or female), pathological UICC stage of the primary CRC (pUICC I, II, or III according to UICC TNM classification 5th edition[19]), Charlson comorbidity Index score (CCI; 0, 1, 2, or ≥3),[20] location of primary CRC tumor (proximal colon, distant colon and rectum), surgical approach (laparoscopy, laparotomy, robot-assisted, and other), and surgical priority (emergency or elective). Histology was classified as adenocarcinoma, mucinous adenocarcinoma and signet-ring cell carcinoma. Mismatch repair gene status was categorized in proficient (pMMR) and deficient (dMMR).

### Statistical method

Absolute numbers and percentages were presented for categorical variables and medians with interquartile ranges (IQRs) for continuous variables. The study cohort was stratified by age at CRC diagnosis (early-onset and late-onset) and subgroup analyses were performed by age-groups; <40 years early-onset, 40–49 years early-onset, 50–59 years late-onset (*reference group*), 60–69 years late-onset and 70–79 years late-onset.

Patients were followed from 180 days (6 months) after curative surgery until whatever came first; recurrence (event), death (competing event), or second primary cancer other than NMSC (competing event), emigration (censoring), 5 years after surgery (censoring), or at the end of follow-up on January 1st 2024 (censoring). Second primary cancer was defined as ICD-10 code other than CRC (DC18 or DC20) or NMSC (DC44) registered in the DCR 180 or more days after surgery.

Incidence of recurrence was presented as a 1-, 3-, and 5-year cumulative incidence function (CIF) with death and second primary cancer as competing events. Cumulative incidence curves were constructed using the Aalen-Johansen estimator for visualization.

Cause-specific hazard ratios (HR) with 95% confidence intervals (95%CI) for recurrence was estimated using Cox proportional hazards regression treating death and second primary cancer as censoring events. Estimates were adjusted for sex, CCI score, tumor site, pUICC stage, and surgical priority. The proportional hazards assumption was assessed by plotting scaled Schoenfeld residuals. Due to differences in incidence of competing events between early-onset and late-onset CRC,[21] a sensitivity analysis was conducted by changing the effect estimate to subdistribution hazard ratios (sHR) of recurrence using Fine–Gray regression treating death and second primary cancer as competing risks.[22] In the subdistribution hazard model the patient remains at risk after a competing event occurs, and hence it provides a way to incorporate the effect of covariates on the CIF that may be more reflective of a real world setting in which the patients may experience competing events.

Difference in time to recurrence was estimated as time ratio (95% CI) using an accelerated failure time (AFT) model including sex, CCI score, tumor site, pUICC stage, and surgical priority, and treating death and second primary cancer as censoring events. A model was fitted for the following distributions of survival time: exponential, Weibull, log-logistic, and log-normal. The log-normal model was selected based on the lowest Akaka's information criteria (AIC) value, and Q–Q plots were used to check the suitability of the AFT-model with the log-normal baseline.

Differences in surveillance intensity were reported as number of CT scans per 1000 person years (PY) and compared between early- and late-onset with incidence rate ratio (IRR) and its 95% CI. Median time to first CT scan was reported.

The changes in incidence of recurrence from 2004 to 2019 was analyzed by stratifying according to calendar periods (2004–2008, 2009–2013, and 2014–2019 after the implementation of a national CRC FIT-based

screening program in 2014[23]). A sensitivity analysis was performed by stratifying the 2014–2019 group in screening-detected (SD) and non-screening detected (NSD) patients.[7]

Post-recurrence mortality was evaluated with all patients followed from date of recurrence until death or right-censored at the end of follow-up on January 1st 2023. Cumulative CRC-related mortality was visualized using the Aalen Johansen estimator. Cox proportional hazards regression was used to calculate hazard ratios (HRs) for CRC-specific death after early-onset and late-onset recurrence and was adjusted for sex, CCI score at recurrence, tumor site, and pUICC stage. Deaths from other causes were considered competing events and were censored on the date of death.

No hypothesis testing was executed in this observational study.[24]

Statistical analyses were carried out between September 2023 and April 2024 using R (https://www.r-project.org/) and Rstudio (RStudio, PBC, Boston, MA, http://www.rstudio.com/).

### Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

## Results

We identified 33,402 Danish patients younger than 80 years who underwent curative surgical resection for first-time UICC TNM stage I–III CRC between January 2004 and December 2019, Fig. 1. After applying exclusion criteria (approximately 23% of patients excluded; for detailed explanation of the exclusion criteria see Supplementary eResults), the final cohort consisted of 25,729 patients (median [IQR] age: 68 [61–73] years; 14,437 males [56%]), with 1441 (5.6%) who were diagnosed before the age of 50 years (early-onset CRC), Table 1. The early-onset group was associated with low CCI score, advanced UICC stage, and rectal tumor location. In subgroup analysis with patients stratified by age-groups the youngest subgroup aged <40 years was associated with increasing UICC stage and emergency surgery, Supplementary eTable 1.

### Recurrence in early-onset versus late-onset CRC

Within 5 years after surgery, recurrence was observed in 411 early-onset patients and 5150 late-onset patients for the entire period of inclusion from 2004 to 2019. In a competing risk model, the 5-year CIF of recurrence was 29% (95% CI: 26%–31%) in early-onset versus 21% (95% CI: 21%–22%), Fig. 2. The stage-specific 5-year CIFs of recurrence were higher for early-onset CRC

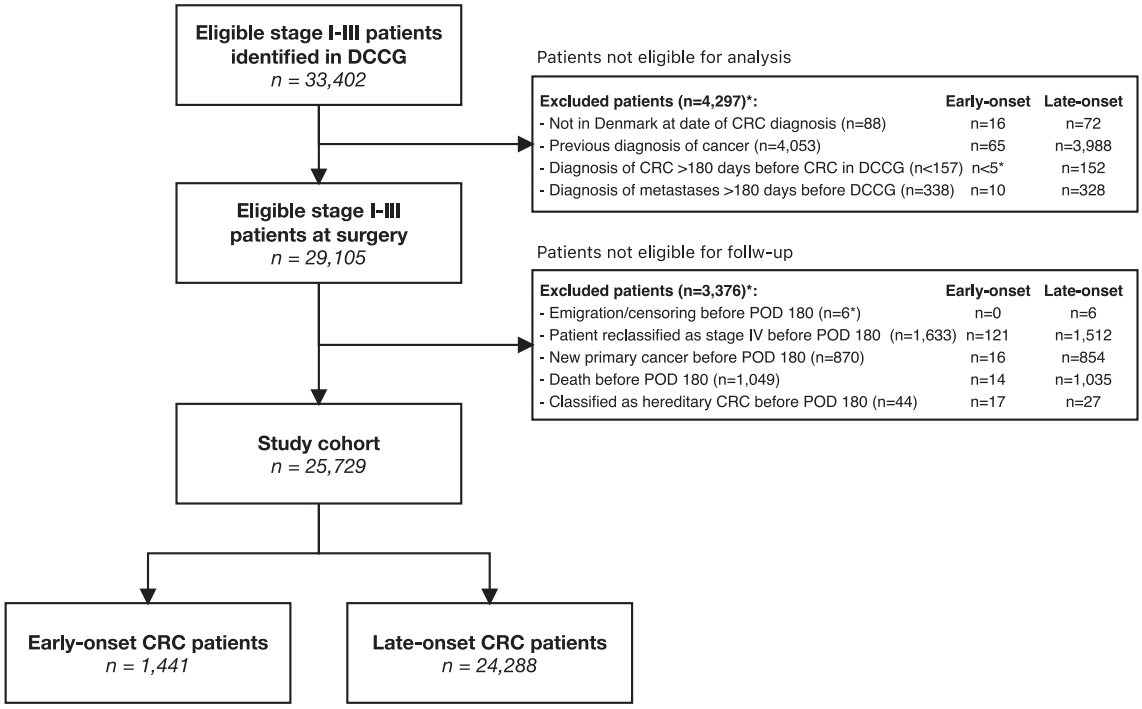


***Fig. 1:*** Flowchart of Cohort Selection. Patients aged < 80 years at curative surgery with resection of UICC TNM stage I–III CRC in Denmark from 1st January 2004, through 31st December 2019 were eligible for inclusion. Patients were excluded if they did not fulfill the requirements of the colorectal cancer recurrence algorithm. *Patients may be excluded due to more than one criterion. Cell-sizes < 5 are reported in aggregate to reduce identification of individuals in the data. Abbreviations: DCCG, Danish Colorectal Cancer Group; CRC, Colorectal cancer; POD, Postoperative day.

patients, Fig. 3A. For both early- and late-onset, the 5-year CIFs were higher for rectal cancers compared to colon cancers, Fig. 3B. When adjusted for sex, CCI score, tumor site, pUICC stage, and surgical priority, the hazard ratio of recurrence in early-onset CRC versus late-onset was 1.27 (95% CI: 1.15–1.41). Fine-Gray hazards regression provided a similar adjusted hazard ratio of 1.31 (95% CI: 1.18–1.45).

In subgroup analysis with patients stratified by age-groups, the risk of recurrence was highest for the <40 years early-onset group with a 5-year CIF of 31% (95% CI: 26%–37%) compared to 28% (95% CI: 26–31%) in the 40–49 years early-onset group and 23% (95% CI: 22%–24%) in the 50–59 years late-onset group, Fig. 3C.

For both early- and late-onset, the 5-year CIFs were higher for pMMR cancers compared to dMMR cancers, Fig. 3D, but MMR-status was missing for 26% of patients.

### Time to recurrence and surveillance intensity

Early-onset patients had accelerated time-to-recurrence with a median of 14.5 months (95% CI: 13.8–16.5) compared to 17.5 months (95% CI: 17.0–18.2) for late-onset patients corresponding to a time ratio of 0.75 (95% CI: 0.67–0.85) in adjusted analysis, Fig. 4A. Differences in surveillance patterns were observed between the two groups with a higher frequency of CT-scans among early-onset patients with 808 versus 738 CT-scans per. 1000 PY (IRR = 1.09, 95% CI: 1.06–1.13), and a shorter time from surgery to first CT scan in early-onset patients with a median time of 7.4 months (95% CI: 7.0–8.1 months) versus 10.9 months (95% CI: 10.6–11.1 months) for late-onset patients, Fig. 4B.

To explore if the observed accelerated time-to-recurrence for early-onset CRC patients were driven by early-onset patients being scanned sooner than late-onset, we stratified the analysis by timing of the first scan. For patients with an early first CT scan (<month 12) the median time-to-recurrence in early-onset versus late-onset was 14.1 months (95% CI: 12.4–17.1) versus 14.9 months (14.2–15.8), corresponding to a time ratio of 0.86 (95% CI: 0.71–1.05), Fig. 4C. For patients with first CT scan at 12 months the median time-to-recurrence was 18.4 months (95% CI: 15.0–24.1) versus 20.9 months (95% CI: 19.8–22.6), corresponding to a time ratio of 0.88 (95% CI: 0.73–1.05), Fig. 4D.

### Changes in incidence of recurrence from 2004 to 2019

Changes in characteristics among early-onset patients from 2004 to 2019 are given in Supplementary eTable 2. No evident stage migration was observed among early-onset CRC patients. However, early-onset CRC was associated with a higher treatment intensity with a larger fraction of the stage II and III patients receiving neoadjuvant or adjuvant oncological treatment compared to late-onset during all three calendar periods, Fig. 5.

| Variable | Overall, N = 25,729 | Onset of CRC | |
|---|---|---|---|
| | | Early, N = 1441 | Late, N = 24,288 |
| Age, median (IQR) | 68 (61–73) | 45 (41–48) | 68 (62–73) |
| **Sex, n (%)** | | | |
| Female | 11,292 (44%) | 683 (47%) | 10,609 (44%) |
| Male | 14,437 (56%) | 758 (53%) | 13,679 (56%) |
| **Charlson Comorbidity Index score, n (%)** | | | |
| CCI 0 | 17,601 (68%) | 1274 (88%) | 16,327 (67%) |
| CCI 1 | 5318 (21%) | 126 (8.7%) | 5192 (21%) |
| CCI 2 | 1531 (6.0%) | 23 (1.6%) | 1508 (6.2%) |
| CCI ≥ 3 | 1279 (5.0%) | 18 (1.2%) | 1261 (5.2%) |
| **UICC stage, n (%)** | | | |
| I | 6011 (23%) | 270 (19%) | 5741 (24%) |
| II | 10,329 (40%) | 516 (36%) | 9813 (40%) |
| III | 9389 (36%) | 655 (45%) | 8734 (36%) |
| **Tumor site, n (%)** | | | |
| Proximal colon | 7930 (31%) | 362 (25%) | 7568 (31%) |
| Distal colon | 9034 (35%) | 502 (35%) | 8532 (35%) |
| Rectum | 8748 (34%) | 577 (40%) | 8171 (34%) |
| **Tumor histology, n (%)** | | | |
| Adenocarcinoma | 23,479 (92%) | 1294 (90%) | 22,185 (92%) |
| Mucinous adenocarcinoma | 2036 (7.9%) | 125 (8.7%) | 1911 (7.9%) |
| Signetring cell carcinoma | 136 (0.5%) | 19 (1.3%) | 117 (0.5%) |
| **Mismatch Repair status, n (%)** | | | |
| dMMR | 2984 (12%) | 201 (14%) | 2783 (11%) |
| pMMR | 16,090 (63%) | 931 (65%) | 15,159 (62%) |
| Missing[a] | 6655 (26%) | 309 (21%) | 6346 (26%) |
| **Surgical approach, n (%)** | | | |
| Laparoscopy | 13,951 (54%) | 731 (51%) | 13,220 (54%) |
| Laparotomy | 9628 (37%) | 594 (41%) | 9034 (37%) |
| Robot-assisted | 1885 (7.3%) | 95 (6.6%) | 1790 (7.4%) |
| Other/missing[a] | 265 (1.0%) | 21 (1.5%) | 244 (1.0%) |
| **Surgical priority, n (%)** | | | |
| Elective | 24,280 (94%) | 1328 (92%) | 22,952 (94%) |
| Emergency | 1449 (5.6%) | 113 (7.8%) | 1336 (5.5%) |

CRC, colorectal cancer; CCI, Charlson Comorbidity Index; UICC, Union for International Cancer Control; dMMR, deficient mismatch reparir; pMMR, proficient mismatch repair. [a]Missing from both the Danish National Patient Registry and the Danish Pathology Registry.

*Table 1:* **Patient and surgical treatment characteristics stratified by age of colorectal cancer onset.**

From 2004 to 2019 stage-specific 5-year CIF of recurrence decreased in both stage I, II, and III early-onset patients (Supplementary eTable 3), with the largest reduction observed for stage I. Consequently, the difference in 5-year CIF of recurrence between early-onset and late-onset CRC decreased from 2004 to 2019, Table 2. The adjusted HR of recurrence among early-onset patients, with late-onset patients as reference, declined gradually from 1.37 (95% CI: 1.17–1.60) in 2004–2008 to 1.28 (95% CI: 1.08–1.53) in 2009–2013, and as low as 1.07 (95% CI: 0.88–1.31) in 2014–2019. Fine-Gray hazards regression provided similar hazard ratios, Table 2.

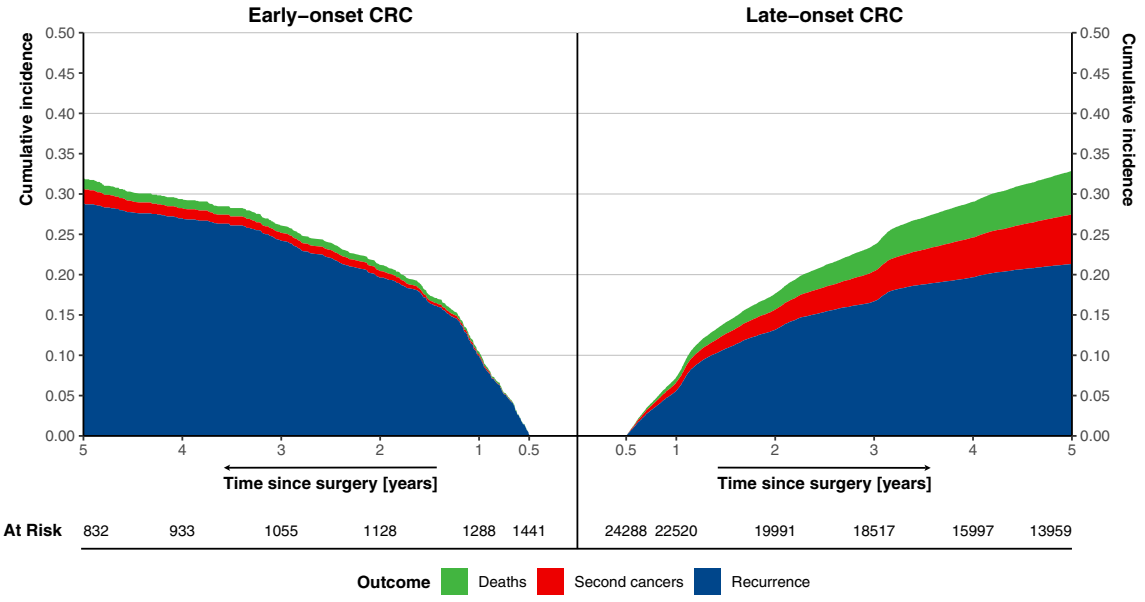


*Fig. 2:* Competing risk models of recurrence, death and second primary cancer in early-onset and late-onset CRC patients within 5 years after surgery.

In subgroup analysis, the excess risk of recurrence observed for the <40 years early-onset group compared to the 40–49 years early-onset group diminished in the 2014–2019 calendar period, Supplementary eTable 4. And when excluding the late-onset CRC patients from 2014 to 2019 who were identified by screening (restricted to 50–74 years of age), we found that the risk of recurrence in early-onset CRC was similar to the risk of recurrence in non-screening detected late-onset CRC with a HR of 1.00 (95% CI: 0.82–1.23), Supplementary eTable 5.

### Post-recurrence mortality in early-onset versus late-onset CRC

Among the 411 recurrence patients in the early-onset group, 162 (39%) died within 5 years after recurrence, and here of 143 (88%) of CRC-specific causes. Among the 5150 recurrence patients in the late-onset group, 2836 (55%) died within 5 years, and here of 2294 (81%) of CRC-specific causes. The 5-year CIF of post-recurrence CRC-specific mortality was 37% (95% CI: 32%–42%) in early-onset versus 50% (95% CI: 48%–52%) in late-onset. When adjusted for sex, CCI score, tumor site, and pUICC stage, the hazard ratio of post-recurrence CRC-specific mortality in early-onset CRC versus late-onset was 1.45 (95% CI: 1.23–1.72), Supplementary eFig. 1.

## Discussion

This nationwide cohort study of CRCs diagnosed from 2004 to 2019 shows that the cumulative incidence of recurrence among early-onset CRC patients is higher compared to late-onset patients with a 1.27-fold higher hazard of recurrence when adjusted for patient characteristics (other than age) and risk factors of recurrence. In subgroup analysis, the youngest of the early-onset patients (<40 versus 40–49) had the highest risk of recurrence.

Although a specific age threshold has not been found to divide CRC based on biological or pathological characteristics,[9] 50 years has been set as a cut-off for average-risk screening in many countries.[12] In 2014 CRC screening was implemented in Denmark for individuals aged 50–74, resulting in ~20% of all screening-eligible late-onset cancers being diagnosed through screening. The initial screening rounds of these screening programs have introduced stage-migration towards low stage disease with lower risk of recurrence.[7,25] Early-onset patients are not eligible for screening; hence they progress to the symptomatic phase before diagnosis. Consequently, we do not see evident stage-migration from 2004 to 2019 among early-onset patients. However, we conducted a sensitivity analysis, and found that risk of recurrence of early-onset patients was indifferent from that non-screening detected late-onset CRC patients.

Diagnosis, staging, and surgery was improved from 2004 to 2019, which decreased the risks of recurrence for early-as well as late-onset patients.[7] Over the period from 2004 to 2019 the use of oncological therapy was intensified, more prominently for early-onset than late-onset patients, which may be part of the explanation why the decrease in recurrence risk was more prominent for early-onset than late-onset patients. These findings suggest that early-onset CRC patients may

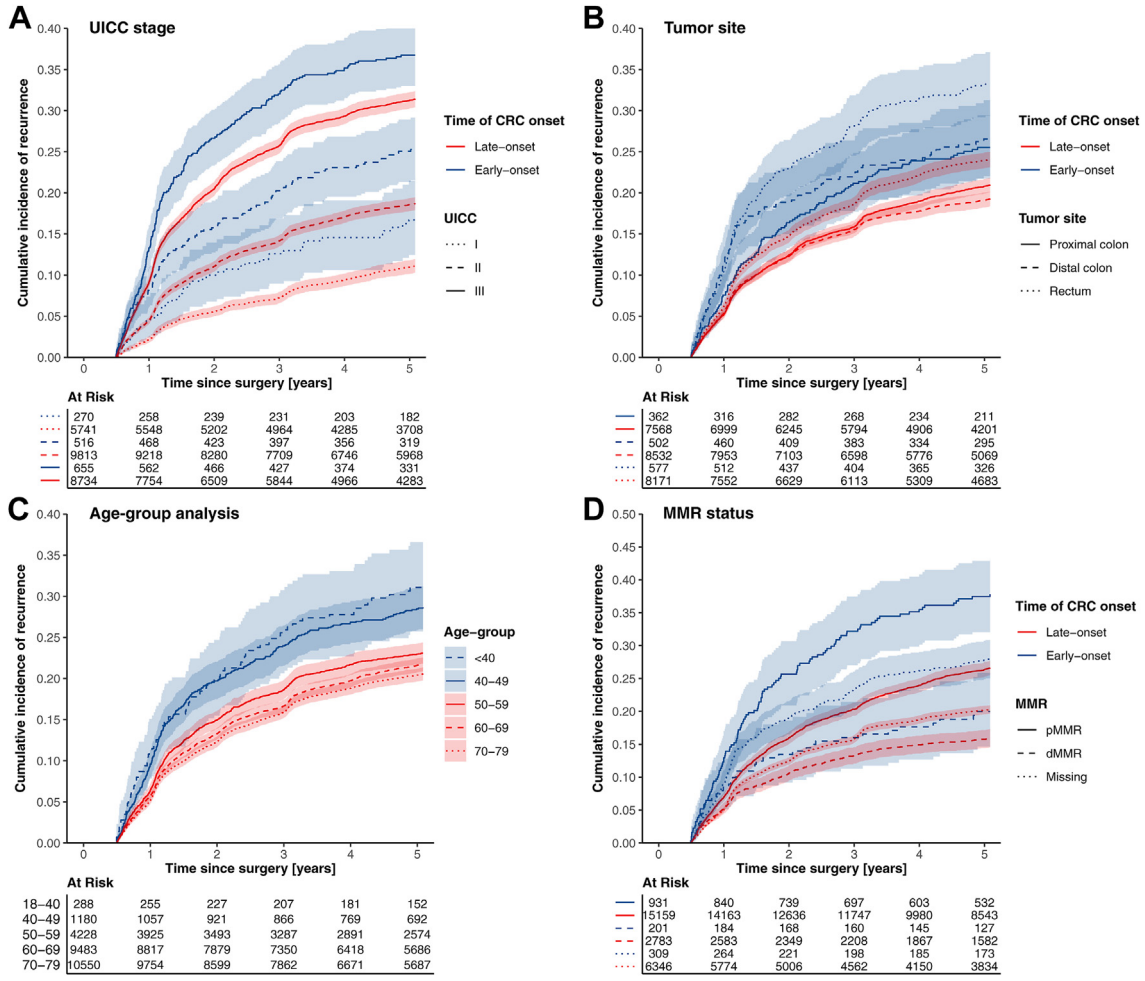


***Fig. 3:*** 5-year cumulative incidence of recurrence according to covariate. **A)** Stage-stratified 5-year cumulative incidence of recurrence in early-onset and late-onset colorectal cancer. **B)** 5-year cumulative incidence of recurrence in early-onset and late-onset colorectal cancer stratified by site of the primary CRC tumor. **C)** Cumulative incidence of recurrence by age-group at CRC onset. **D)** 5-year cumulative incidence of recurrence in early-onset and late-onset colorectal cancer stratified by MMR-status. Patients with missing MMR-status is shown. Constructed using the Aalen-Johansen estimator with death and second primary cancers as competing events. The filled areas represent 95% confidence intervals. All estimates are crude.

achieve a prognosis, in terms of recurrence risk, similar to that of late-onset patients if they are treated according to modern guidelines.[7] The effect may be complex and multifactorial. Firstly, a better general health in younger patients with fewer age-related comorbidities may allow for a better tolerance of oncological treatment,[26] although the higher treatment intensity has been associated with only minimal gain in survival.[27] Secondly, younger patients may have a larger immune repertoire, hence being able to initiate a stronger treatment response.[28] This has been reported for the addition of oxaliplatin to ACT in MSI stage III early-onset patients.[29] However, increased treatment intensity may represent overly aggressive treatment regimens, as no survival benefit has been found for early-onset CRC when treated with higher intensity.[30]

Our findings suggest that early-onset CRC has an accelerated time to recurrence with a higher risk of recurrence during the first postoperative year compared to late-onset CRC. We report a higher frequency of CT-scans among early-onset patients during the first 5 postoperative years, with distinct differences in timing of the first CT scan. A shorter time to recurrence among early-onset patients could be explained by earlier and more intensive surveillance. However, the overall rate of CT scans was only marginally elevated in early-onset patients and, importantly, we observed a shorter time to recurrence in early-onset compared to late onset also when restricting to patients who received the first CT scan at ~12 months. Therefore, a shorter time to recurrence among early-onset patients cannot be explained by surveillance bias alone. However, these

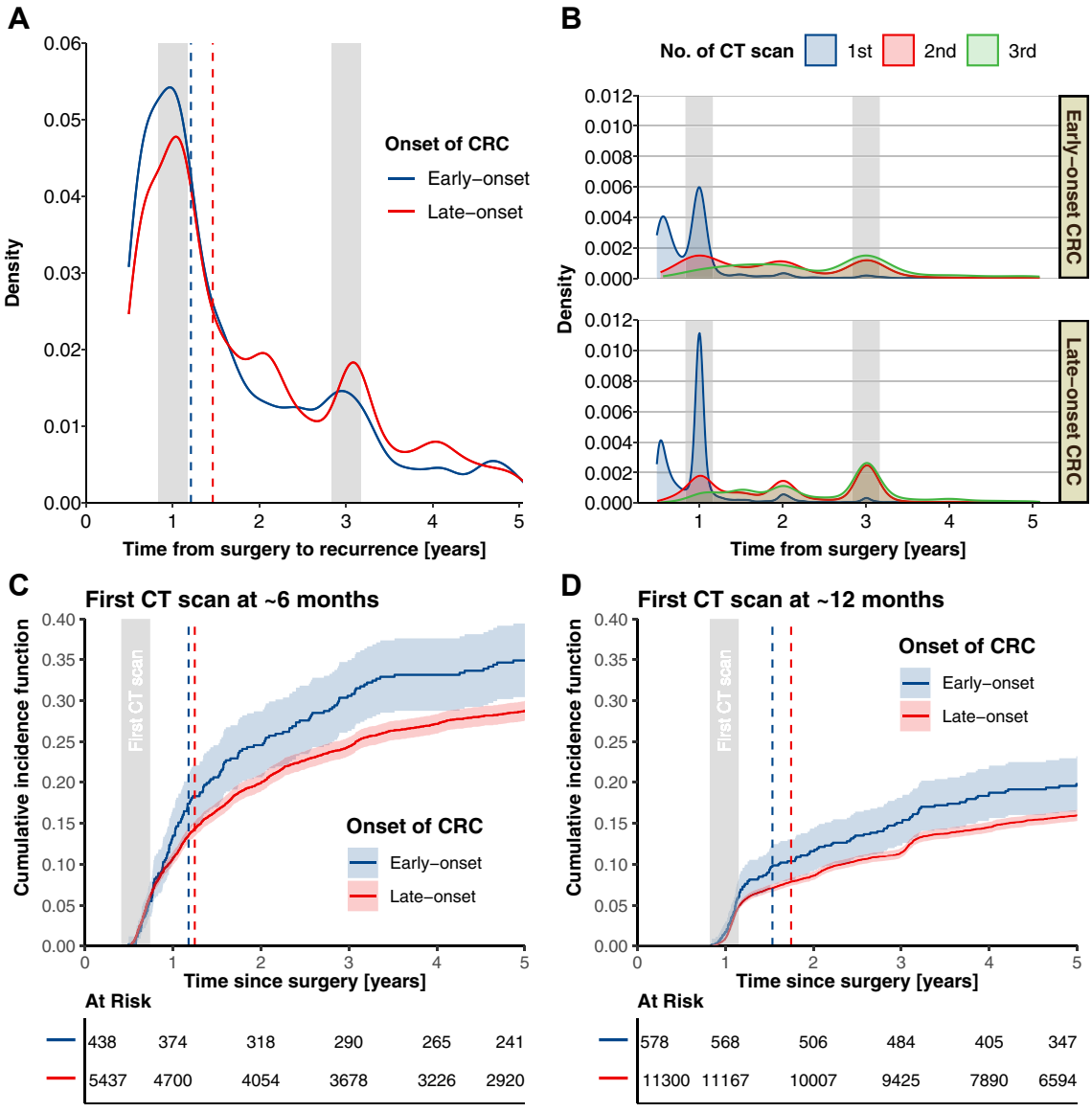


*Fig. 4:* Time to recurrence and surveillance intensity in early-onset versus late-onset colorectal cancer. **A)** Time from surgery to colorectal cancer recurrence by age at onset of colorectal cancer. Vertical dashed lines represent median time from curative surgery to recurrence. Shaded areas represent time points of surveillance imaging at 12 and 36 months after surgery (as per Danish guidelines since 2009). **B)** Pattern of CT scans by age at onset of colorectal cancer. Shaded areas represent time points of surveillance imaging at 12 and 36 months after surgery (as per Danish guidelines since 2009). **C)** Cumulative incidence of recurrence by age-group at CRC onset restricted to patients with an early first CT scan. Stratified by early onset versus late onset patients (illustrated by color). Constructed using the Aalen-Johansen estimator with death and second primary cancers as competing events. The filled areas represent 95% confidence intervals. Vertical dashed lines represent median time to recurrence. **D)** as panel 'C' but restricted to patients with the first CT scan timed at the 12-month postoperative time point.

findings may not be generalizable as a substantial variation has been found between national surveillance guidelines,[31] and Denmark follows a low intensity surveillance protocol due to the international multicenter randomized COLOFOL trial.[32] A Cochrane Review suggests no overall survival benefit for intensifying the follow-up of patients after curative surgery for CRC.[33] Surveillance strategies towards early-onset CRC patients remain unexplored, and future studies are warranted to address if early-onset patients may benefit from intensified surveillance during the early postoperative period.[32,33]

The Delphi Initiative for Early-Onset Colorectal Cancer (DIRECt) International Management Guidelines

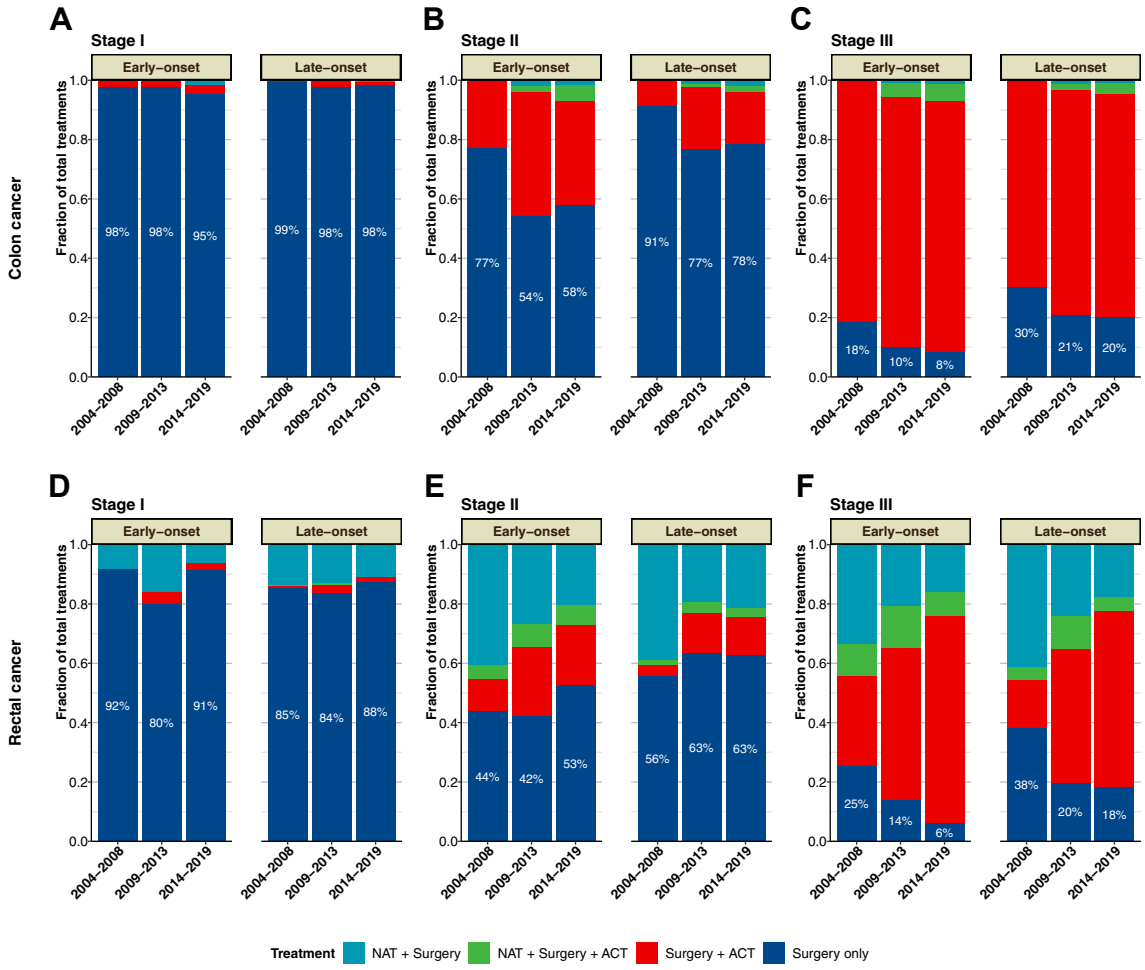


*Fig. 5:* Distribution of treatment regimes in early-onset colorectal cancer compared to late-onset colorectal cancer from 2004 to 2019. Stratified by tumor site and UICC stage. NAT = Neoadjuvant chemo- and/or radiotherapy, ACT = Adjuvant chemotherapy.

advise caution regarding termination of surveillance 5 years after surgery in early-onset CRC patients.[34] We have previously reported very low rates of late recurrence 5–10 years after surgery in early-onset CRC patients, why we found a 5-year period of investigation appropriate for this study.[35]

The main strength of this study is its nationwide approach, its reflection of the real-life CRC management, and the large sample size. Many studies on CRC recurrence are based primarily on intensive follow-up of clinical trial cohorts or cohorts from individual centers. Here we applied an algorithm to registry data to obtain recurrence status, which we recently validated to perform very well (sensitivity = 94%, specificity = 99%, positive predictive value = 94% and negative predictive value = 99%) on contemporary registry data.[18] Also, the registry data needed for the algorithm is available for the entire cohort with complete follow-up. The difference in risk of competing events between early-onset and late-onset CRC remains a statistical challenge. We present very similar outcomes of the cause-specific proportional hazards regression and the subdistribution hazards regression. From these we interpret that early-onset CRC patients have a higher risk of recurrence compared to late-onset patients, and that the difference cannot be explained by differences in risk of competing events.[21]

It can be considered a limitation that we excluded approximately 23% of patients, particularly geriatric patients, and patients with previous cancers, as the algorithm cannot determine the primary cancer of recurrence. Although this exclusion may have affected the generalizability of the study, we decided to exclude these patients to improve the internal validity and accuracy of recurrence rates. Another limitation is that the algorithm does not diagnose recurrence within 180 days from surgery. This quarantine is to allow for completion of primary treatment with up to 6 months of ACT and to

| Variable | Cumulative incidence function[a] | | | | | Fine–Gray[b] | | Cox PH[b] | |
|---|---|---|---|---|---|---|---|---|---|
| | N | N Event | 1-year CIF | 3-year CIF | 5-year CIF | sHR | CI | HR | CI |
| **All** | | | | | | | | | |
| Early-onset CRC | 1441 | 411 | 11% (95% CI: 9.9%–13%) | 25% (95% CI: 22%–27%) | 29% (95% CI: 26%–31%) | 1.31 | 1.18, 1.45 | 1.27 | 1.15, 1.41 |
| Late-onset CRC | 24,288 | 5150 | 7.1% (95% CI: 6.7%–7.4%) | 17% (95% CI: 17%–18%) | 21% (95% CI: 21%–22%) | *1* | *Reference* | *1* | *Reference* |
| **2004–2008** | | | | | | | | | |
| Early-onset CRC | 438 | 169 | 15% (95% CI: 12%–18%) | 33% (95% CI: 28%–37%) | 38% (95% CI: 34%–43%) | 1.43 | 1.21, 1.68 | 1.37 | 1.17, 1.60 |
| Late-onset CRC | 6584 | 1851 | 8.5% (95% CI: 7.8%–9.2%) | 22% (95% CI: 21%–23%) | 28% (95% CI: 27%–29%) | *1* | *Reference* | *1* | *Reference* |
| **2009–2013** | | | | | | | | | |
| Early-onset CRC | 449 | 135 | 12% (95% CI: 9.2%–15%) | 25% (95% CI: 22%–30%) | 30% (95% CI: 26%–34%) | 1.31 | 1.10, 1.57 | 1.28 | 1.08, 1.53 |
| Late-onset CRC | 6829 | 1564 | 8.0% (95% CI: 7.3%–8.6%) | 19% (95% CI: 18%–20%) | 23% (95% CI: 22%–24%) | *1* | *Reference* | *1* | *Reference* |
| **2014–2019** | | | | | | | | | |
| Early-onset CRC | 554 | 107 | 8.3% (95% CI: 6.2%–11%) | 18% (95% CI: 15%–21%) | 20% (95% CI: 17%–23%) | 1.10 | 0.90, 1.34 | 1.07 | 0.88, 1.31 |
| Late-onset CRC | 10,875 | 1735 | 5.6% (95% CI: 5.2%–6.1%) | 14% (95% CI: 13%–14%) | 16% (95% CI: 16%–17%) | *1* | *Reference* | *1* | *Reference* |

Cumulative incidence of colorectal cancer recurrence treating death and second primary cancer (other than colorectal cancer or non-melanoma skin cancer) as competing event. Reference level for each variable is marked in italics. CIF, Cumulative incidence function; sHR, Subdistribution hazard ratio; HR, Hazard ratio; CI, Confidence Interval. [a]Cumulative incidence estimates are crude estimates. [b]Subdistributional hazards by Fine–Gray regression and cox proprtional hazards adjusted for sex, Charlson Comorbidity Index score, tumor site, UICC stage and surgical priority.

***Table 2:*** **Risk of recurrence in early-onset versus later-onset UICC stage I–III colorectal cancer patients.**

avoid diagnosing synchronous metastases as a recurrence. Registration of MMR-status has not been part of national guidelines prior to 2013, which is why we report it missing for 49% of 2004–2008 patients and refrained from including MMR-status in our analyses. Despite adjusting for relevant covariates, there is always a risk of residual confounding by unmeasured covariates in observational studies. If data were available, it could have been relevant to adjust for VELIPI status and molecular subtypes of CRC.[36] Data on race and ethnicity is not available in Danish registries, but Denmark is mainly Caucasian.

In conclusion, our study suggests that early-onset CRC patients had a higher risk of recurrence compared to late-onset CRC from 2004 to 2019 for all disease stages indicating that delayed diagnosis is not the sole explanation for the higher risk. Nevertheless, an increased awareness towards early-onset CRC in general practice and by gastroenterologists may still promote earlier diagnosis and prognosis in these patients.

The excess risk was diminished in recent years, potentially due to more extensive treatment of younger and healthier early-onset patients that is, to date, not yet recommended by guidelines.[34]

The study provides some reassurance to early-onset patients and their treating clinicians that despite a more advanced disease stage at diagnosis, it may be possible to achieve a similar risk of recurrence as late-onset patients, when early-onset patients are treated according to modern guidelines.

### Contributors

All the authors made significant contributions to the completion of this study. Jesper Nors, Kåre Andersson Gotschalck, Rune Erichsen, and Claus Lindbjerg Andersen designed and conceptualized the study, contributed to data collection, formal analysis, and review and editing of the manuscript. Jesper Nors wrote the original draft and contributed to data visualization. Claus Lindbjerg Andersen contributed to funding acquisition and resources. Jesper Nors and Claus Lindbjerg Andersen were project administrators. Kåre Andersson Gotschalck, Rune Erichsen and Claus Lindbjerg Andersen contributed to project supervision.

### Data sharing statement

The data and code for data cleaning and analysis that support the findings of this study are available from Danish Health care registries and upon reasonable collaboration with a Danish Research Institution. Please see https://sundhedsdatastyrelsen.dk/da/english/health_data_and_registers/research_services for further details. Further information is available from the corresponding author upon request.

### Declaration of interests

The author(s) have no affiliations or financial involvement with any organization or entity with a financial interest or financial conflict with the study subject or materials discussed in the manuscript.

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### Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanepe.2024.101093.

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