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Original Research

Incidence, treatment and relative survival of early-onset colorectal cancer in the Netherlands since 1989

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Abstract ***Aim:*** Previous studies showed that the incidence of early-onset colorectal cancer (EO-CRC, diagnosis <50 years) is rising in Western countries. Additionally, young patients present with more advanced disease. Integrated nationwide assessment of epidemiologically and clinically relevant trends would provide more insight into this specific group of patients with CRC. We aimed to provide an analysis of trends in age- and stage-specific incidence, characteristics, treatment and relative survival of patients with EO-CRC in the Netherlands and compare these with 50- to 59-year-old patients.

Methods: Data from 1989 to 2018 were retrieved from the Netherlands Cancer Registry. Non-standardised age-specific incidence rates were calculated, and trends were assessed using Joinpoint regression. Treatment and 5-year relative survival trends were provided and compared between EO-CRC and 50- to 59-year-old patients.

Results: The EO-CRC incidence annually increased with 0.7–2.1% over the last decades. CRC incidence for the 50- to 59-year-old population annually increased with 0.8–1.7% until 2006 and showed a major increase in incidence after the introduction of nationwide screening in 2014. Stage III and Stage IV CRC primarily increased across the studied age groups, while Stage I and Stage II CRC did not. Patients with EO-CRC received multimodal treatment more often than 50- to 59-year-old patients, but differences were minor. Relative survival increased over time and showed little differences between EO-CRC and 50- to 59-year-old patients.

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Concluding statement: Only few epidemiological and clinical differences were found between EO-CRC and 50- to 59-year-old patients; hence, the urge for a specific approach of EO-CRC in screening and treatment guidelines might be tempered.

1. Introduction

While the median age at diagnosis of patients with colorectal cancer (CRC) is 70 years [1], the incidence of early-onset colorectal cancer (EO-CRC)—presentation of disease before the age of 50 years—is reportedly increasing in several Western populations [2–9]. Not only is this increase in incidence unexplained, but also younger patients more often seem to have an advanced stage of disease at diagnosis [10]. Several risk factors have been associated with EO-CRC, such as smoking, consumption of alcohol, obesity, metabolic abnormalities and intake of sugar-sweetened beverages [11–15]. Also, pathogenic germline variants have been associated with CRC in young patients; however, no germline mutation can be identified in 80% of EO-CRC cases [16]. Yet, no consensus has been reached on a suiting explanation for the concerning increase in the incidence of EO-CRC.

Treatment guidelines do not differentiate between young and older patients, but the treatment of EO-CRC has been shown to differ from treatment of older patients with CRC [14]. Large population-based studies have shown that young patients receive more intensive treatment and achieve comparable or longer cancer-specific survival than older patients despite more morphologically unfavourable characteristics [17–19]. Contrastingly, a recent study concluded that there is no evidence that sporadic EO-CRC is biologically different from the presentation of CRC at an older age, advocating no clinically different approach of EO-CRC [19].

Many of the aforementioned findings have derived from studies with a focus on incidence, treatment or survival. Few studies have been performed incorporating a combination of epidemiological and clinical elements of EO-CRC, while differentiating between numerous age groups, cancer stages and time periods. The Netherlands Cancer Registry (NCR) has gathered data on all patients with CRC in the Netherlands since 1989. The availability of these high-quality nationwide real-world data allows for integrated analyses of epidemiological trends on incidence and characteristics in combination with clinical trends on treatment and relative survival. The comprehensive overview, which herewith would be provided, could improve our understanding of EO-CRC. Additionally, the comparison of EO-CRC trends with those of an older age group of patients with CRC would provide essential context to EO-CRC trends. As guideline non-adherence in the treatment of CRC increases with age [20], the youngest age group from the age of 50 years will likely be the most appropriate comparator. Therefore, the aim of this study is to provide a comprehensive analysis of trends in age- and stage-specific incidence, characteristics, treatment and relative survival in patients with EO-CRC in the Netherlands and to compare these trends with those of 50- to 59-year-old patients with CRC.

2. Materials and methods

2.1. Patients

Data were acquired through the NCR. This registry, managed by the Netherlands Comprehensive Cancer Organization, has been gathering data on all cancer cases in the Netherlands since 1989. NCR data managers retrieve general and tumour-specific data from the electronic patient records in the hospitals. Coincidentally detected tumours after obduction for another cause of death than CRC are not included in the registry. Tumour localisation and type were coded according to ICD-O-3 [21]. Topography codes C18.0 and C18.2–9 were classified as colon; C19.9 and C20.9 were classified as rectum. Tumour stage was classified following TNM Classification of Malignant Tumours of the Union for International Cancer Control valid at the time of diagnosis [22]. Pathological TNM classification was used as reference for cancer stage. When pathological TNM classification was not available or patients received neoadjuvant treatment, clinical TNM classification was used as reference. Data on disease recurrence and treatment of disease recurrence were not collected. Vital status is updated annually through linkage with the Dutch Personal Records Database, which contains personal details of all the citizens in the Netherlands. Consequentially, loss of follow-up on vital status is extremely low. Follow-up data were updated until 31 January 2019.

2.2. Study design

All patients diagnosed with CRC in the Netherlands between 1989–2018 aged <60 years were included in this retrospective cohort study. For analyses on incidence, treatment and relative survival, colon cancer (CC) and rectal cancer (RC) were separately assessed.

The study population was divided into two age groups: 0- to 49-year-old (i.e., EO-CRC) and 50- to 59-year-old patients. For the incidence trend analyses, the EO-CRC group was split into three groups: <40, 40–44 and 45–49 years. The 30-year time period between 1989–2018 was divided into six time periods of 5 years each. Cases were included in the incidence analyses if they met the criteria for inclusion of multiple primary tumours according to the rules of the International Association of Cancer Registries (IACR) [23]. Patients with Stage X disease or missing data on treatment were excluded from treatment analyses. Conventional, endoscopic and microscopic surgeries of the primary tumour were regarded as tumour resection.

2.3. Statistical analyses

Incidence rates were calculated for each of the four age groups as crude rates per 100,000 person-years. Additionally, stage-specific incidence rates were calculated for each age group. Joinpoint regression analysis was performed to test for trend changes and estimated average percentage of change (APC) [24].

Patient and tumour characteristics were tested for change over time using asymptomatic chi-square tests.

Treatment trends were presented as the percentage of total treatments given per stage for each time period. Treatment proportions were compared between EO-CRC and 50- to 59-year-old patients per time period using Fisher's exact tests.

Relative survival was estimated using the Pohar Perme method [25]. This method weighs a patient's contribution to the net survival based on the patient's expected survival for a healthy person in the population. Expected survival is based on demographic variables such as sex, age and calendar year [26]. Additionally, excess hazard ratios (EHRs) for the first 5 years after diagnosis were modelled using a full-likelihood approach, with 50- to 59-year-old patients as reference [27]. EHRs enable for the comparison of 5-year relative survival between the two age groups.

P-values <0.05 were regarded as statistically significant, and all statistical tests were two-sided.

All analyses were performed using SAS software, version 9.4, of the SAS System for Windows (SAS Institute Inc., Cary, NC, USA), except for identification of trend changes (Joinpoint Regression Program, version 4.8.0.1, April 2020; Statistical Methodology and Applications Branch, Surveillance Research Program, National Cancer Institute) and relative survival analyses (Stata Statistical Software, Release 16. College Station, TX: StataCorp LLC).

3. Results

3.1. Patient and tumour characteristics

Of all CRC cases in the NCR cohort between 1989–2018 (i.e., 329,023 CRC cases), 61,498 (18.7%) occurred <60 years and were included in this study. Of these 61,498 cases, 17,660 (28.7%) were patients with EO-CRC and 43,838 (71.3%) were 50- to 59-year-old patients (Supplementary table 1). Trend analyses of patient and tumour characteristics of both age groups are presented in Tables 1 and 2, respectively.

Table 1
Patient and tumour characteristics of patients with EO-CRC.

	1989–1993	1994–1998	1999–2003	2004–2008	2009–2013	2014–2018	Total	P-value
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N	
Gender								
Male	1393 (54.9)	1358 (52.0)	1421 (51.4)	1585 (52.0)	1777 (53.1)	1710 (51.0)	9244	
Female	1145 (45.1)	1256 (48.1)	1345 (48.6)	1462 (48.0)	1567 (46.9)	1641 (49.0)	8416	0.0498*
Localisation								
Colon	1529 (61.2)	1550 (60.3)	1606 (59.4)	1715 (57.6)	1943 (59.7)	1937 (59.7)	10280	
Rectum	968 (38.8)	1020 (39.7)	1097 (40.6)	1261 (42.4)	1311 (40.3)	1308 (40.3)	6965	0.1465
Stage								
I	414 (16.3)	454 (17.4)	412 (14.9)	438 (14.4)	445 (13.3)	448 (13.4)	2611	
II	760 (29.9)	729 (27.9)	727 (26.3)	735 (24.1)	719 (21.5)	602 (18.0)	4272	
III	701 (27.6)	727 (27.8)	854 (30.9)	961 (31.5)	1177 (35.2)	1239 (37.0)	5659	
IV	584 (23.0)	607 (23.2)	698 (25.2)	837 (27.5)	954 (28.5)	1045 (31.2)	4725	
X	79 (3.1)	97 (3.7)	75 (2.7)	76 (2.5)	49 (1.5)	17 (0.5)	393	<0.0001*
Morphology								
Non-mucinous adenocarcinoma	1988 (78.3)	2079 (79.5)	2249 (81.3)	2548 (83.6)	2876 (86.0)	2953 (88.1)	14693	
Mucinous adenocarcinoma	465 (18.3)	457 (17.5)	423 (15.3)	395 (13.0)	358 (10.7)	276 (8.2)	2374	
Signet cell carcinoma	51 (2.0)	48 (1.8)	64 (2.3)	66 (2.2)	76 (2.3)	70 (2.1)	375	
Other	34 (1.3)	30 (1.2)	30 (1.1)	38 (1.3)	34 (1.0)	52 (1.6)	218	<0.0001*

P-values were calculated for proportional changes over time using asymptomatic chi-squared tests.
*Indicates statistically significant differences.

Table 2
Patient and tumour characteristics of patients aged 50–59 years.

	1989–1993	1994–1998	1999–2003	2004–2008	2009–2013	2014–2018	Total	P-value
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N	
Gender								
Male	2538 (54.0)	3146 (56.6)	3889 (55.5)	4550 (55.3)	4729 (56.4)	5581 (56.1)	24433	
Female	2166 (46.1)	2413 (43.4)	3123 (44.5)	3676 (44.7)	3654 (43.6)	4373 (43.9)	19405	0.0619
Localisation								
Colon	2773 (59.5)	3273 (59.2)	3979 (57.2)	4714 (58.0)	4917 (59.4)	5914 (60.3)	25570	
Rectum	1889 (40.5)	2252 (40.8)	2975 (42.8)	3417 (42.0)	3365 (40.6)	3887 (39.7)	17785	0.0008*
Stage								
I	900 (19.1)	1057 (19.0)	1247 (17.8)	1423 (17.3)	1287 (15.4)	2188 (22.0)	8102	
II	1449 (30.8)	1602 (28.8)	1964 (28.0)	2056 (25.0)	1856 (22.1)	1879 (18.9)	10806	
III	1190 (25.3)	1545 (27.8)	1998 (28.5)	2422 (29.4)	2853 (34.0)	3343 (33.6)	13351	
IV	1000 (21.3)	1184 (21.3)	1662 (23.7)	2124 (25.8)	2270 (27.1)	2444 (24.6)	10684	
X	165 (3.5)	171 (3.1)	141 (2.0)	201 (2.4)	117 (1.4)	100 (1.0)	895	<0.0001*
Morphology								
Non-mucinous adenocarcinoma	3913 (83.2)	4693 (84.4)	5966 (85.1)	7107 (86.4)	7346 (87.6)	9092 (91.3)	38117	
Mucinous adenocarcinoma	694 (14.8)	768 (13.8)	909 (13.0)	887 (10.8)	807 (9.6)	607 (6.1)	4672	
Signet cell carcinoma	42 (0.9)	49 (0.9)	59 (0.8)	114 (1.4)	103 (1.2)	103 (1.0)	470	
Other	55 (1.2)	49 (0.9)	78 (1.1)	118 (1.4)	127 (1.5)	152 (1.5)	579	<0.0001*

P-values were calculated for proportional changes over time using asymptomatic chi-squared tests.
*Indicates statistically significant differences.

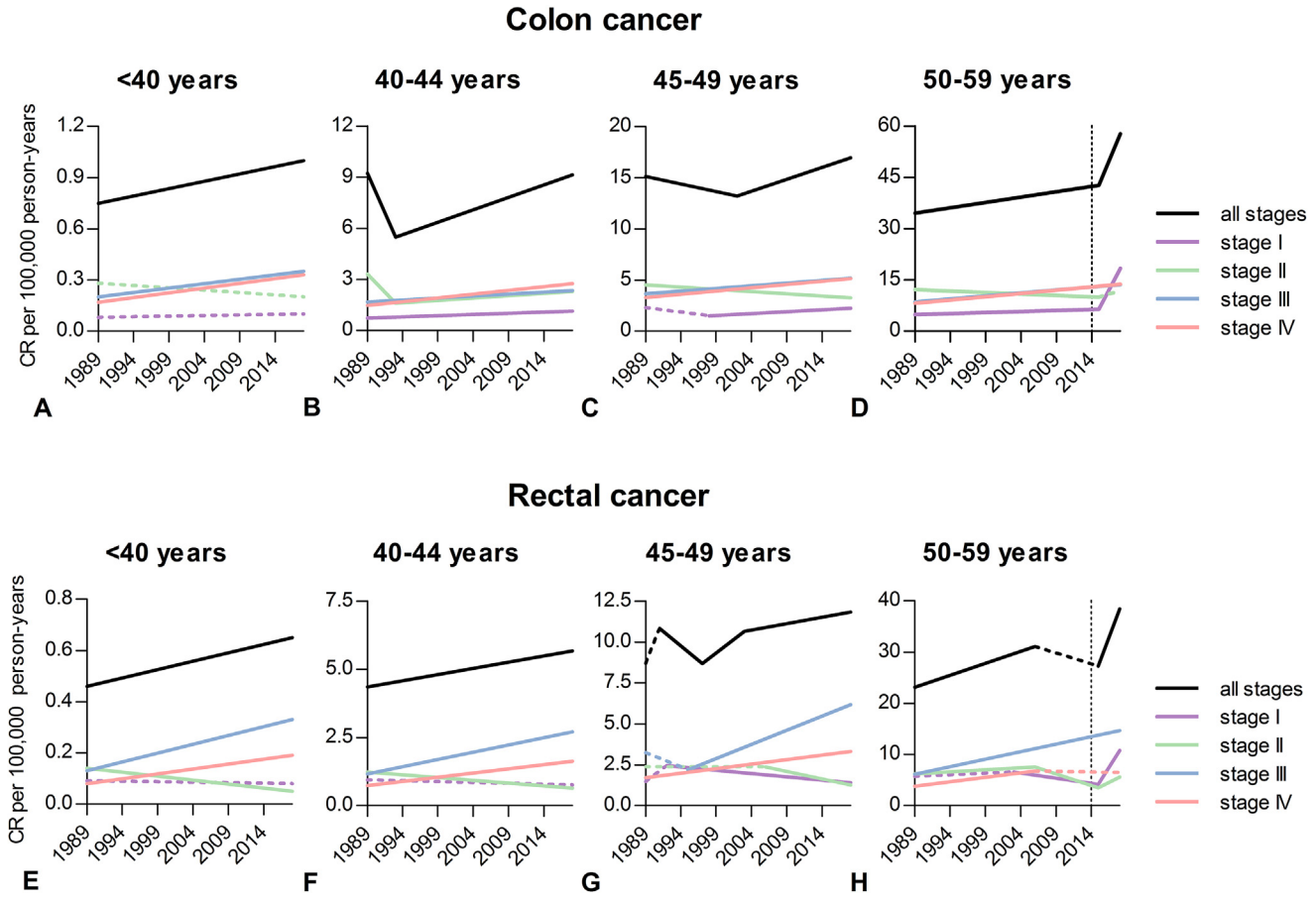

Fig. 1. Overall and stage-specific incidence trends of colorectal cancer in age groups below <60 years between 1989–2018. The introduction of nationwide screening for the 55- to 74-year-old population in 2014 is indicated with a vertical dotted line. Dotted trend lines represent insignificant trend changes, while solid trend lines represent significant trend changes.

3.2. Incidence trends

After the exclusion of cases not meeting IACR inclusion criteria (N = 807), 60,691 cases were included in the incidence trend analyses. Crude incidence rates are graphically presented in Supplementary Fig. 1.

Incidence trends are presented in Fig. 1. Corresponding average percentages of change (APCs) are displayed in Table 3.

3.3. Treatment

After the exclusion of cases with Stage X disease (N = 1,288) and patients without information on treatment (N = 140), 60,070 cases were included in treatment analyses. Distribution of these cases across the subsite, stages and time periods is outlined in Supplementary Table 2.

3.3.1. Stage I–III colon cancer

Patients with Stage I early-onset colon cancer (EO-CC) more often received additional treatment next to surgical resection than their 50- to 59-year-old counterparts in 2014–2018 (Fig. 2A). Patients with Stage II EO-CC received adjuvant treatment more often than 50- to 59-year-old patients with CC in four of the six time periods (Fig. 2B). In 1989–1993 and 1994–1998, adjuvant chemotherapy was also more often given to patients with Stage III EO-CC (Fig. 2C). This difference vanished thereafter. In 2009–2013 and 2014–2018, resection only was less often used for Stage III EO-CC than in their 50- to 59-year-old counterparts.

Table 3
Average percentages of change in colon and rectal cancer incidence.

	Colon cancer		Rectal cancer	
	Time period	APC (95% CI)	Time period	APC (95% CI)
<40 years				
All stages	1989–2018	1.0* (0.5, 1.5)	1989–2018	1.2* (0.6, 1.8)
Stage I	1989–2018	0.8 (−0.7, 2.5)	1989–2018	−0.6 (−2.3, 1.1)
Stage II	1989–2018	−1.2 (−2.5, 0.1)	1989–2018	−3.3* (−5.4, −1.1)
Stage III	1989–2018	1.9* (1.0, 2.7)	1989–2018	3.2* (2.5, 4.0)
Stage IV	1989–2018	2.3* (1.4, 3.2)	1989–2018	3.1* (1.5, 4.6)
40–44 years				
All stages	1989–1993	−12.2* (−20.9, 2.5)	1989–2018	0.9* (0.4, 1.4)
	1993–2018	2.1* (1.4, 2.7)		
Stage I	1989–2018	1.5* (0.3, 2.8)	1989–2018	−0.7 (−2.3, 0.8)
Stage II	1989–1993	−16.6* (−27.8, −3.6)	1989–2018	−2.3* (−3.3, −1.2)
	1993–2018	1.5* (0.5, 2.4)		
Stage III	1989–2018	1.1* (0.2, 2.1)	1989–2018	2.9* (2.0, 3.9)
Stage IV	1989–2018	2.2* (1.0, 3.3)	1989–2018	2.8* (1.4, 4.2)
45–49 years				
All stages	1989–2002	−1.0* (−2.0, −0.0)	1989–1991	11.7 (−4.0, 30.0)
	2002–2018	1.6* (0.8, 2.3)	1991–1997	−3.7* (−6.9, −0.3)
			1997–2003	3.5* (0.1, 7.1)
			2003–2018	0.7* (0.1, 1.3)
Stage I	1989–1998	−5.0 (−9.8, 0.2)	1989–1992	17.8 (−8.7, 51.9)
	1998–2018	2.2* (0.6, 3.6)	1992–2018	−2.1* (−3.0, −1.2)
Stage II	1989–2018	−1.1* (−1.7, −0.6)	1989–2006	−0.1 (−1.4, 1.3)
			2006–2018	−5.0* (−7.2, −2.9)
Stage III	1989–2018	1.2* (0.7, 1.7)	1989–1995	−6.1 (−12.9, 1.1)
			1995–2018	4.6* (3.6, 5.6)
Stage IV	1989–2018	1.5* (1.0, 2.1)	1989–2018	2.3* (1.3, 3.3)
50–59 years				
All stages	1989–2015	0.8* (0.6, 1.0)	1989–2006	1.7* (1.1, 2.4)
	2015–2018	10.6* (3.8, 17.8)	2006–2015	−1.5 (−3.3, 0.4)
			2015–2018	12.2* (3.0, 22.1)
Stage I	1989–2015	1.1* (0.5, 1.6)	1989–2003	1.0 (−0.9, 2.9)
	2015–2018	42.1* (22.4, 64.9)	2003–2015	−3.8* (−6.3, −1.2)
			2015–2018	37.4* (12.6, 67.8)
Stage II	1989–2015	−0.8* (−1.1, −0.4)	1989–2006	1.2* (0.3, 2.1)
	2015–2018	5.7 (−4.0, 16.4)	2006–2015	−8.2* (−10.8, −5.6)
			2015–2018	17.1* (2.7, 33.5)
Stage III	1989–2018	1.6* (1.3, 2.0)	1989–2018	3.0* (2.7, 3.4)
Stage IV	1989–2018	1.8* (1.4, 2.2)	1989–2006	3.5* (2.3, 4.7)
			2006–2018	−0.4 (−2.3, 1.6)

Stage-specific average percentages of change were calculated using Joinpoint regression analyses between 1989–2018 for different age groups <60 years.
*Indicates statistically significant trend changes.

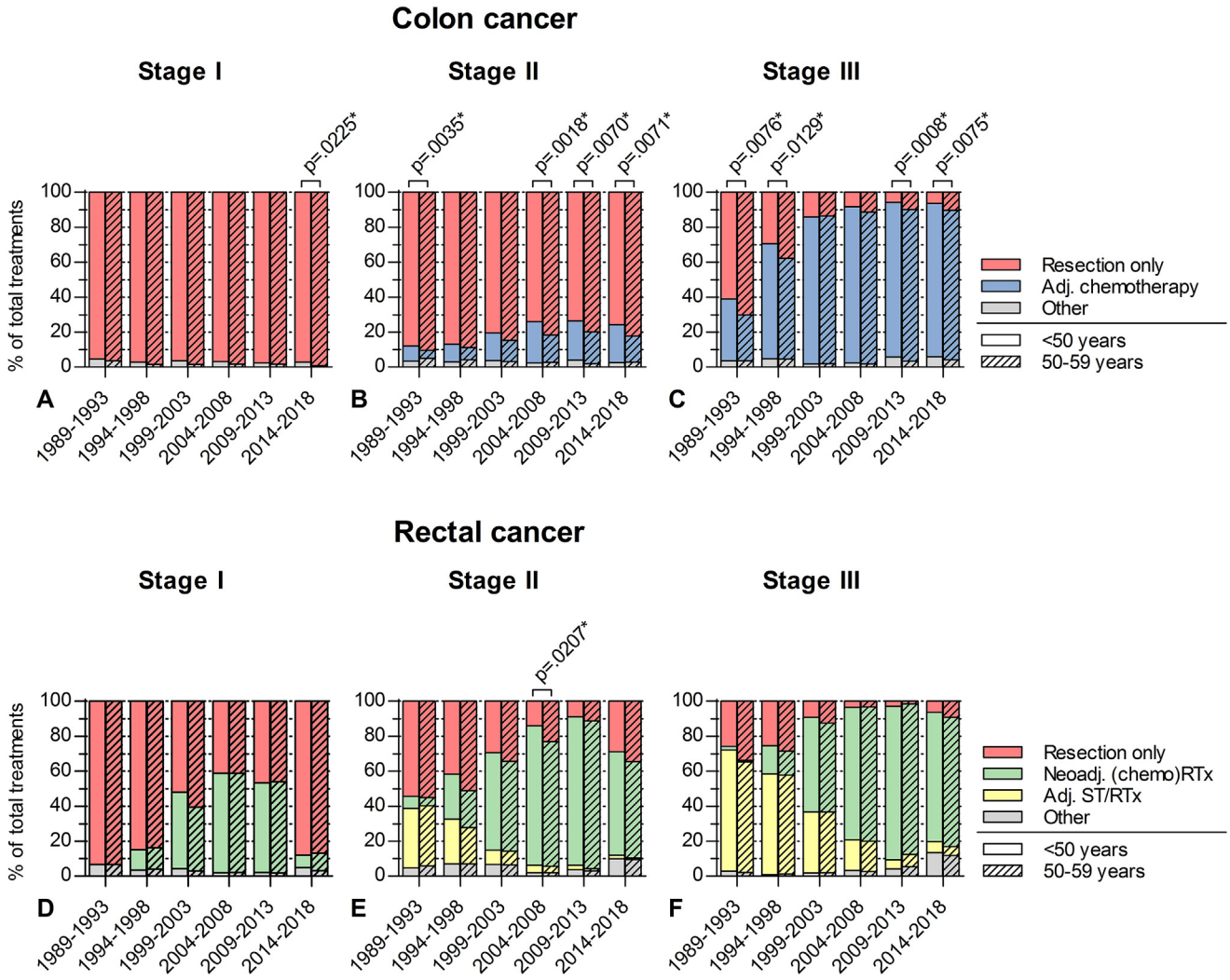

Fig. 2. Treatment trends of patients with Stage I–III colon and rectal cancer in the Netherlands between 1989–2018, categorised and presented as the percentage of total treatments given per 5-year time period. Adjuvant (adj.), neoadjuvant (neoadj.), radiotherapy (RTx) and systemic therapy (ST) were abbreviated. Systemic therapy included chemotherapy, targeted therapy and hormonal therapy. Treatment proportions were compared between the <50 and 50- to 59-year age groups using Fisher's exact test, and statically significant differences (*, $p < .05$) were indicated with the corresponding p-value.

3.3.2. Stage I–III rectal cancer

Treatment of early-onset rectal cancer (EO-RC) did not differ from treatment of 50- to 59-year-old patients with RC for disease Stage I and III (Fig. 2D and F). For Stage II disease, however, neoadjuvant (chemo)radiation was used more often in patients with EO-RC than in 50- to 59-year-old patients in 2004–2008 (Fig. 2E). Thereafter, this difference was no longer present.

3.3.3. Stage IV CC and RC

Primary tumour treatment of patients with Stage IV EO-CC and EO-RC differed from that of their 50- to 59-year-old counterparts in four time periods and one time period, respectively (Fig. 3A and C). For both subsites, early-onset patients were more often treated with the combination of resection and additional therapy, and the 50- to 59-year-old patients received no treatment more often.

Metastasectomy was performed more often for patients with EO-CC than for 50- to 59-year-old patients with CC in 2004–2008 (Fig. 3B). No differences in metastasectomy rates occurred between patients with EO-RC and 50- to 59-year-old patients with RC (Fig. 3D).

3.4. Relative survival

All cases were included in relative survival analyses (N = 61,498), but stage-specific analyses excluded Stage X cases (N = 1,288). Median follow-up to vital status was 4.8 years (interquartile range: 1.7; 12.6). Trends in CC and RC 5-year relative survival for the early-onset and 50- to 59-year-old age groups are displayed in Fig. 4. EHRs with corresponding 95% confidence intervals (CIs) of the 5-year relative survival estimate are presented in Fig. 5.

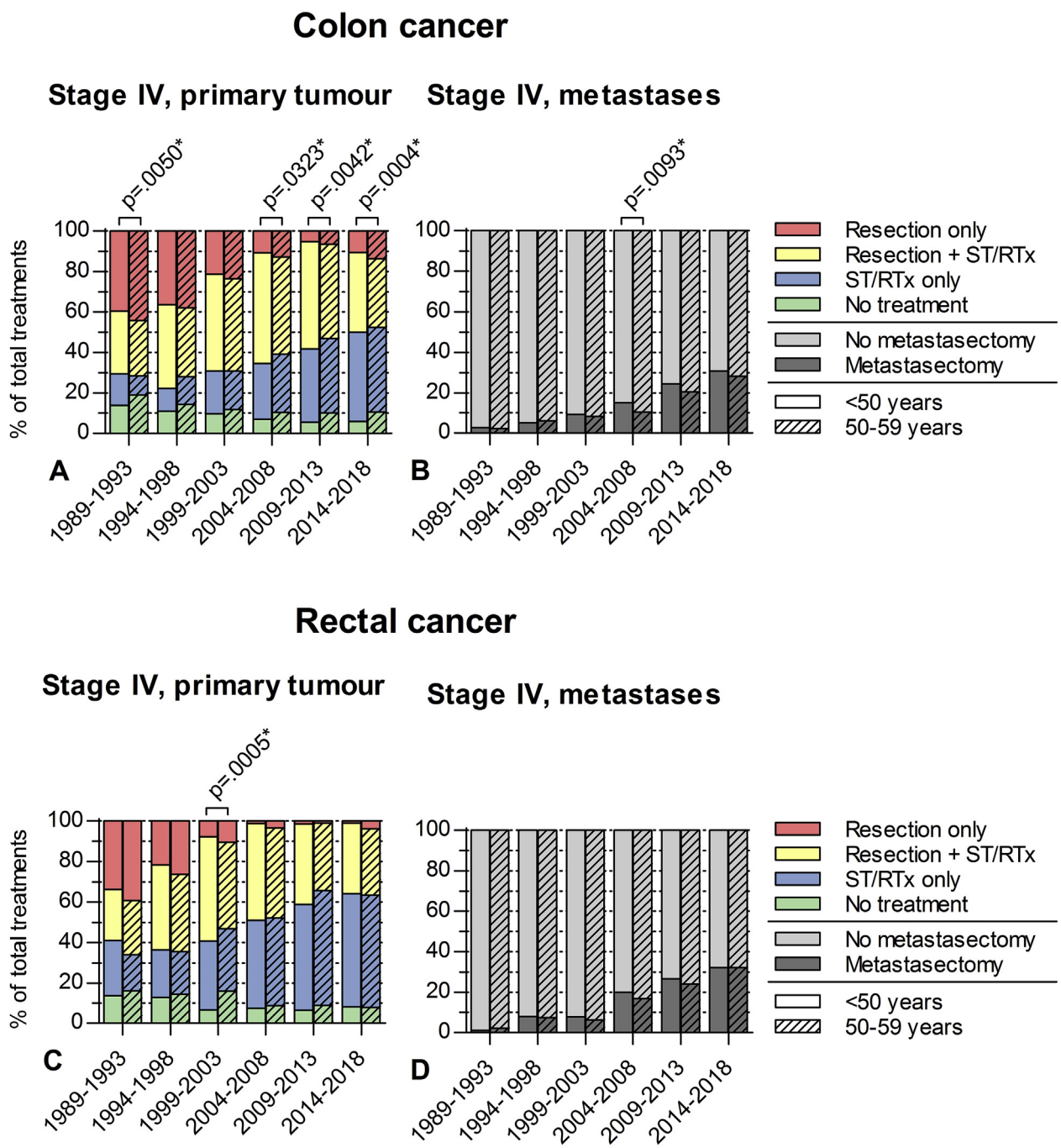

Fig. 3. Treatment trends of patients with Stage IV colon and rectal cancer in the Netherlands between 1989–2018, categorised and presented as the percentage of total treatments given per 5-year time period. Radiotherapy (RTx) and systemic therapy (ST) were abbreviated. Systemic therapy included chemotherapy, targeted therapy and hormonal therapy. Treatment proportions were compared between the <50 and 50- to 59-year age groups using Fisher's exact test, and statically significant differences (*, $p < .05$) were indicated with the corresponding p-value.

3.4.1. Colon cancer

The 5-year relative survival of Stage II–IV CC showed evident increases in 5-year relative survival over the studied time period for both age groups. Comparison of the 5-year relative survival between the early-onset and 50- to 59-year-old age groups showed that patients with EO-CC had a superior 5-year relative survival in the time periods between 1999-2013. This benefit switched between the age groups in 2014–2018. No differences in 5-year relative survival occurred between the two age groups for Stage I CC. For Stage II CC, early-onset patients had a better 5-year relative survival during four of the six time periods. Early-onset patients had a better 5-year relative survival as well for Stage III and Stage IV CC in 2009–2013.

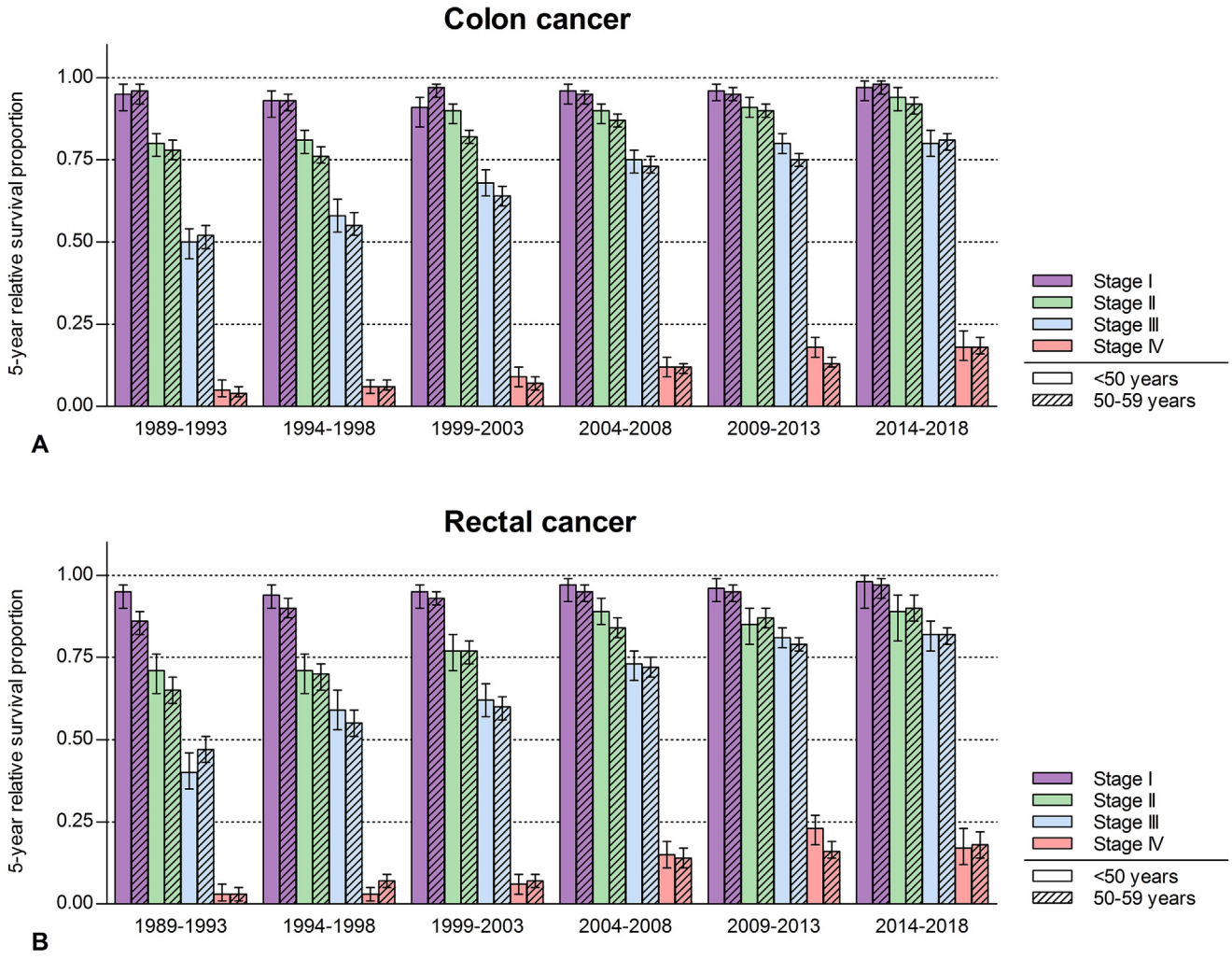

Fig. 4. Five-year relative survival trends for patients with colon (A) and rectal (B) cancer in the Netherlands between 1989–2018. Five-year relative survival proportions are presented per 5-year time period for the <50 and 50- to 59-year age groups. Error bars indicate the 95% confidence interval of the 5-year relative survival estimate.

3.4.2. Rectal cancer

Corresponding to CC trends, 5-year relative survival of Stage II–IV RC noticeably increased over 1989–2018. Between the early-onset and 50- to 59-year-old RC age groups, no difference in overall 5-year relative survival was present until 2014–2018, when 50- to 59-year-old patients with RC showed better 5-year relative survival. Patients with Stage I EO-RC displayed superior 5-year relative survival to 50- to 59-year-old patients with RC in the time periods between 1989–1998. Patients with Stage II and Stage IV EO-RC showed superior 5-year relative survival to their 50- to 59-year-old counterparts in 2004–2008 and 2009–2013, respectively.

4. Discussion

This large retrospective nationwide cohort study showed an annual increase of 0.7–2.1% in overall incidence of EO-CRC over the last decades. The 50- to 59-year-old population showed increasing incidence trends of comparable magnitudes between 1989–2006. Following the introduction of nationwide CRC screening for the population aged 55–74 years in 2014, Stage I and Stage II incidence increased, while Stage III and Stage IV remained comparable with EO-CRC. Treatment showed minor differences between patients with EO-CRC and 50- to 59-year-old patients over time, with patients with EO-CRC tending to receive multimodal treatment more often. Five-year relative survival showed an ongoing improvement over time, with only few differences between the two age groups.

Compared to other studies, this study showed comparable age-specific incidence rates of EO-CRC in the Netherlands. For the population aged <50 years, Siegel *et al.* reported APCs of 2.0 (95% CI: 1.6; 2.4) between 2003-2012. An APC of 1.1 (95% CI: 0.7; 1.6) was found for patients aged ≥50 years [8]. The studied trend was of a 10-year duration only, which is short in comparison with the 30-year time span of this study. Vuik *et al.* reported an APC between 2–3% for the age-standardised

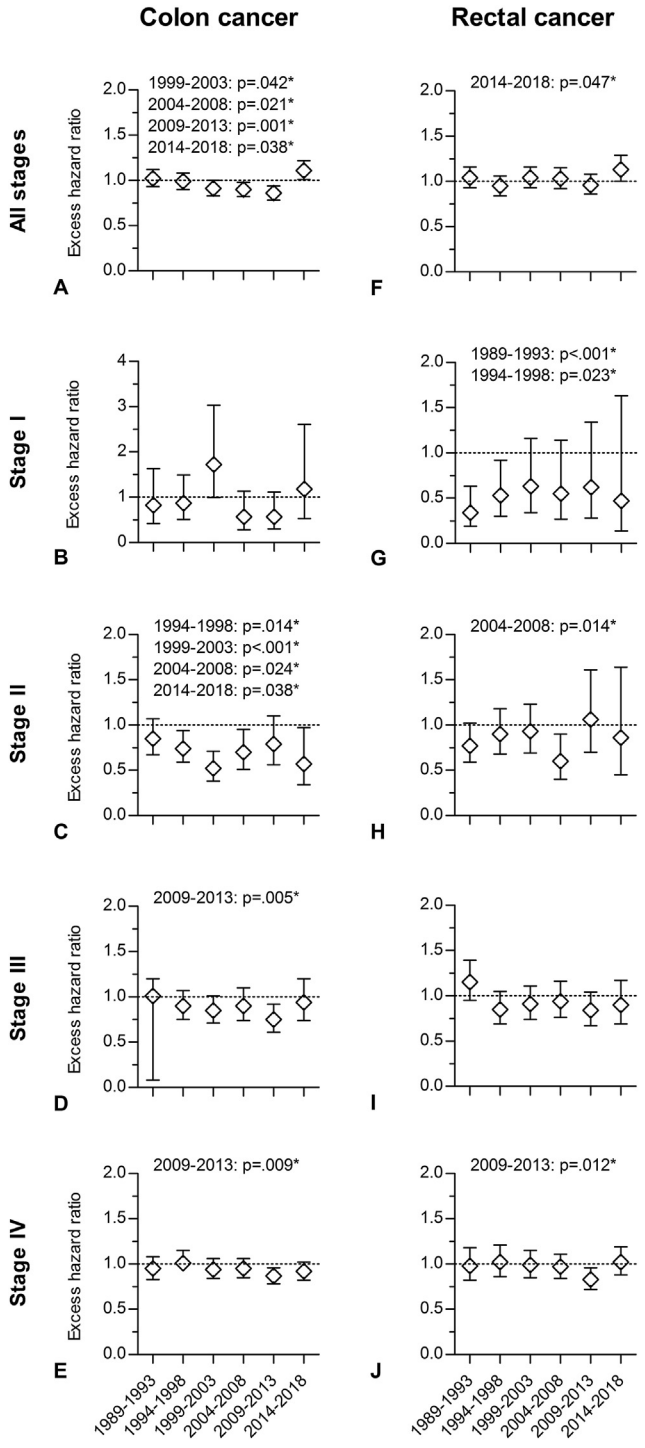

Fig. 5. Excess hazard ratios (EHRs) comparing 5-year relative survival between patients with early-onset and 50- to 59-year-old colon (A–E) and rectal (F–J) cancer in the Netherlands from 1989 to 2018. EHRs were calculated for 5-year relative survival estimates over 5-year time periods. Statistically significant differences were presented with corresponding p-values (*, $p < 0.05$). The EHR of the early-onset age groups is presented, with the 50- to 59-year-old age groups as reference of 1 (dotted line).

group of patients with CRC aged 20–39 years from 1990 to 2016 [9]. In the present study, EO-CRC age groups showed an APC of crude incidence rates between 0.7–2.1% over the last decennia. Siegel *et al.* used the world standard population, and Vuik *et al.* used a European standard population, that is, crude incidence rates were weighted with the age distribution of the global and European population, respectively. In the current study, crude incidence rates were not weighted with another population but presented as such. Consequentially, this study more accurately represents the nationwide situation. However, by not age-standardising our incidence analyses, the analyses are somewhat more difficult to directly compare with other countries.

The stage-specific incidence analyses reflect a pattern, in which Stage III and Stage IV diseases have primarily increased since 1995, while Stage I and Stage II diseases have showed more decreasing trend changes or no change at all. This pattern of increasing presentation of advanced staged disease is illustrated across all EO-CRC age groups, and in the 50- to 59-year-old age group before the introduction of nationwide screening. This makes it unlikely that this trend is EO-CRC-specific. A suiting explanation for this pattern lies in the principle of stage migration, in which enhanced diagnostic methods for locoregional and distant metastases and improved pathological techniques and quality standards after resection make it more likely that small metastases are identified. Consequentially, groups of patients migrate from lower stages to higher stages over time.

The treatment of CRC changed over the last decades with the introduction of multimodal treatment [28]. An increase in the use of multimodal treatment was noticed in this study—mainly for Stage II–III CRC. Also, an increase in metastasectomy was seen in both age groups. While CRC treatment guidelines in the Netherlands do not differentiate for age, multimodal treatment was used more often for patients with EO-CC and EO-RC than for 50- to 59-year-old patients. However, the differences between these age groups are minor in magnitude. An association of EO-CRC and the use of additional therapy has been described previously for other populations [17,29–32], while more aggressive treatments based solely on the age at CRC diagnosis are not warranted [19].

The effect of advancements in diagnosis and treatment on the relative survival is illustrated by the increase in relative survival of Stage II–IV CRC in both age groups. Stage-specific EHRs of patients with EO-CRC showed some differences over time, all resulting in better relative survival than 50- to 59-year-old patients. Most recently, only patients with Stage II EO-CC had better relative survival than 50- to 59-year-old patients; no other differences were found. This shows that patients with EO-CRC have very comparable relative survival outcomes to 50- to 59-year-old patients. This is in line with some previously conducted studies [18,30,32–34], while other studies reported slightly better survival outcomes for EO-CRC [17,29]. Interestingly, patients

with EO-CRC had overall worse relative survival than 50- to 59-year-old patients in the most recent time period, while this was not reflected in stage-specific outcomes. This disparity is most likely caused by the introduction of the nationwide screening programme in 2014: Stage I disease occurs more often in patients with screened CRC [35], and as a consequence, the overall group of screened patients has significantly better survival outcomes [36].

Owing to the high-quality data of the NCR, this study provides an accurate, comprehensive overview over EO-CRC in the Netherlands over the last decades. Nonetheless, this study has some limitations. First, this study was designed as a nationwide, retrospective cohort study. For this reason, the results from this study cannot be extrapolated directly to other populations. It is however likely that similar trends would also be present in other Western countries. Second, statistical significance is easily reached, even in subgroups of the total study population of more than 60,000 subjects. Small proportional differences should be interpreted with caution, as they will not always reflect clinically relevant differences.

5. Conclusions

In conclusion, this study shows that the crude incidence of EO-CRC in the Netherlands has increased with APCs of 0.7–2.1% over the last decades, but this increase is highly comparable to the trends of 50- to 59-year-old patients before the introduction of nationwide screening. The comparison of treatment and relative survival of EO-CRC with 50- to 59-year-old patients showed minor differences between the two groups. As only few epidemiological and clinical differences were found between patients with EO-CRC and 50- to 59-year-old patients, the urge for a specific approach of EO-CRC in screening and treatment guidelines might be tempered.

Author contributions

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Conflict of interest statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2022.01.029.

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