Increasing colorectal cancer incidence in individuals aged

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Increasing colorectal cancer incidence in individuals aged <50 years – a population-based study

GRADUATE THESIS

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Abbreviations

CRC: Colorectal cancer

IRR: Incidence rate ratio

CI: Confidence interval

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Abstract

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Purpose: Data on the incidence of colorectal cancer (CRC) is conflicting, and it is unknown if the incidence is constant, declining, or increasing. Proximal colon cancer is considered to be more common among older individuals, but recent data have shown that rectal cancer and distal colon cancer have been increasing in the younger population. The aim of this study was to determine the trends regarding CRC incidence and tumour location in Sweden.

Methods: CRC statistics from the National Board of Health and Welfare 1995–2015 were used. CRC incidence rates by age group (<50 years, 50–79 years, ≥80 years), sex, and tumour localisation (proximal colon, distal colon, or rectum) were calculated and analysed using Poisson regression.

Results: The age-standardised incidence of CRC increased in Sweden during the study period. This increase was significant (P<0.0001) for colon cancer during the study period for all age groups regardless of tumour localisation. The greatest increase (27–52% per decade) in the colon cancer incidence rate was seen among men and women <50 years of age. The incidence rate for rectal cancer increased for men <50 years (P<0.0001), decreased for both men and women aged ≥80 years (P<0.005), and did not change for the remaining groups.

Conclusions: The CRC incidence in Sweden, in particular colon cancer, is increasing regardless of tumour localisation for individuals <50 years of age. This paper supports the implementation of population-based colorectal cancer screening. A diagnostic workup should be performed in symptomatic individuals <50 years of age.

Keywords: Colorectal cancer, incidence, Sweden, screening

Sažetak

Porast incidencije raka debelog crijeva kod osoba <50 godina – populacijska studija

Ida Gutlić

Svrha: Podaci o incidenciji kolorektalnog raka su proturiječni i nije poznato je li incidencija konstantna, opadajuća ili rastuća. Rak proksimalnog debelog crijeva smatra se češćim među starijim osobama ali nedavni podaci pokazuju da se rak stražnjeg debelog crijeva i rak distalnog debelog crijeva povećavaju u mlađoj populaciji. Svrha ovog istraživanja je bila odrediti trendove što se tiče incidencije kolorektalnog raka i lokacije tumora u Švedskoj.

Metode: Korišteni su statistički podaci kolorektalnog raka iz Naciolnalnog ministarstva za zdravlje i socijalnu skrb 1995-2015. Stopa incidencije kolorektalnog raka prema dobnoj skupini (<50 godina, 50-79 godina, ≥80 godina), spolu i lokaciji tumora (proksimalno debelo crijevo, distalno debelo crijevo ili stražnje debelo crijevo) su izračunati i analizirani pomoću Poissonove regresije.

Rezultati: Dobna standardizirana incidencija kolorektalnog raka povećala se u Švedskoj tijekom razdoblja istraživanja. Ovaj porast bio je signifikantan (P<0.0001) za rak debelog crijeva tijekom istraživanog razdoblja za sve dobne skupine bez obzira na lokaciju tumora. Najveći porast (27-52% /desetljeće) stope incidencije raka debelog crijeva viđen je među muškarcima i ženama mlađim od 50 godina. Stopa incidencije raka stražnjeg debelog crijeva porasla je za muškarce <50 godina (P<0.0001), smanjila se i za muškarce i za žene u dobi ≥80 godina (P<0.005) i nije se promijenila za preostale skupine.

Zaključak: Incidencija kolorektalnog raka u Švedskoj, posebno raka debelog crijeva, raste bez obzira na lokaciju tumora za osobe mlađe od 50 godina. Ova studija podržava uvođenje populacijski baziranog probira za kolorektalni rak. Diagnostičku obradu treba vršiti kod simptomatskih osoba mlađih od 50 godina.

Ključne riječi: kolorektalni rak, incidencija, Švedska, probir

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ORIGINAL ARTICLE

Increasing colorectal cancer incidence in individuals aged < 50 years—a population-based study

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Abstract

Purpose Data on the incidence of colorectal cancer (CRC) is conflicting, and it is unknown if the incidence is constant, declining, or increasing. Proximal colon cancer is considered to be more common among older individuals, but recent data have shown that rectal cancer and distal colon cancer have been increasing in the younger population. The aim of this study was to determine the trends regarding CRC incidence and tumour location in Sweden.

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Results The age-standardised incidence of CRC increased in Sweden during the study period. This increase was significant ($P < 0.0001$) for colon cancer during the study period for all age groups regardless of tumour localisation. The greatest increase (27–52% per decade) in the colon cancer incidence rate was seen among men and women < 50 years of age. The incidence rate for rectal cancer increased for men < 50 years ($P < 0.0001$), decreased for both men and women aged ≥ 80 years ($P < 0.005$), and did not change for the remaining groups.

Conclusions The CRC incidence in Sweden, in particular colon cancer, is increasing regardless of tumour localisation for individuals < 50 years of age. This paper supports the implementation of population-based colorectal cancer screening. A diagnostic workup should be performed in symptomatic individuals < 50 years of age.

Keywords Colorectal cancer · Incidence · Sweden · Screening

Introduction

Colorectal cancer (CRC) is the third most common malignancy in the world. It is considered to be a disease of the elderly population, and most cases occur after the age of 55 years [1]. However, the CRC incidence among younger individuals has been increasing over the last decades, particularly in countries with a western lifestyle [2–6]. The CRC incidence varies greatly globally, and the highest incidence is seen in more developed countries such as Australia and New Zealand (age-standardised rate 44.8/100,000 for men and 32.2/100,000 for women), while the lowest incidence is reported in Western Africa (age-standardised rate 4.5/100,000 for men and 3.8/100,000 for women) [7]. The CRC incidence has changed in high-risk countries over the past years, and it is either decreasing (USA), stable (France and Australia), or increasing (Norway, Finland, and Spain) [8]. The decreasing CRC incidence in the USA may partly be attributed to increased screening, but other factors may also play a role [9].

During the past decades, an increase in the colon cancer incidence in Sweden has been observed while the rectal cancer incidence has remained unchanged [10]. Most CRC cases occur in the older population; 9% of CRC diagnosed in Sweden in 2007–2011 was observed in individuals < 50 years whereas 53% was seen in those ≥ 80 years. The colon cancer

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crude incidence rate in 2007–2011 was 42/100,000 for both men and women, and the rectal cancer crude incidence rate was 25/100,000 for men and 17/100,000 for women during the same time period. A previous Swedish study on CRC incidence between 1959 and 1993 suggested an increase in CRC incidence, especially right-sided and rectum cancers, most likely explained by changes in lifestyle or carcinogenic exposures early in life. However, we lack knowledge about current CRC incidence trends in Sweden [11].

The aim of this study was to determine current trends for colon cancer (proximal and distal tumours) and the rectal cancer incidence regarding age and sex in Sweden.

Method

A population-based study on Swedish inhabitants was conducted. Population-based cancer incidence data for each year from 1995 to 2015 were obtained from the cancer statistics of the National Board of Health and Welfare. In this database, all primary, malignant tumours in Sweden have been registered since 1970. The data is obtained from the Swedish Cancer Registry and the Swedish Cause of Death Registry; consequently, all patients diagnosed with CRC are reported.

Age groups were as follows: < 50 years, 50–79 years, and ≥ 80 years. These cut-offs were chosen to be similar to recent studies published in order for the populations to be comparable. Cancer location was grouped into proximal (caecum, ascending colon, transverse colon, and splenic flexure), distal (descending colon, sigmoid colon), and rectal. Rectal cancers are defined as cancers < 15 cm from the anal verge. Only adenocarcinomas were included while carcinomas in the appendix, anus, and unspecified locations were excluded.

Statistical analysis

Age-adjusted incidence rates per 100,000 population were calculated using the European Standard Population 1976. The relationship between incidence and the co-variables age (< 50 years, 51–79 years, and ≥ 80 years), sex, tumour location (proximal, distal, and rectal), and year (1995–2015) was modelled using Poisson regression and expressed as incidence rate ratios (IRR) per decade with the corresponding 95% confidence interval (CI). Poisson regression was used for the analysis of data in this paper because it provides a good representation of how count data (IRR) depends on the co-variables (age, sex, tumour location, and time). If the co-variables are categorical, as is the case in this study, a contingency table is modelled. Poisson regression specifies which co-variables have a statistically significant effect on the count variable. SAS 9.4 (SAS Institute Inc., Cary, NC, USA) was used for statistical analysis. For illustrative purposes, CRC incidence rates were plotted for the three tumour locations during the study period. $P < 0.05$ was considered to be statistically significant.

Table 1 Colorectal cancer incidence

	1995	2000	2005	2010	2015
Population	8.837.496	8.882.792	9.047.752	9.415.570	9.851.017
New registrations	2112	2273	2488	2928	3090
Incidence (per 100,000 population)	48.10	51.26	55.13	62.49	63.80
Age 50–79 years					
% of population	29.35	31.00	31.62	31.96	32.78
% of new registrations	70.01	67.47	67.14	67.57	70.08
Age ≥ 80 years					
% of population	4.69	5.09	5.38	5.28	5.09
% of new registrations	26.18	28.24	29.18	27.92	26.19
Age-standardised incidence (per 100,000 population)*					
Total	33.37	34.81	36.61	40.75	40.09
Sex					
F	28.80	30.17	32.86	35.63	34.71
M	39.38	40.67	41.32	46.83	46.40
Tumour site					
Proximal	11.79	11.99	12.48	15.34	15.81
Distal	8.05	8.75	9.65	11.27	10.91
Rectal	13.53	14.07	14.52	14.12	13.83

*Standardised to the European Standard Population

Results

The Swedish population increased from 8,837,496 in 1995 to 9,851,017 in 2015, an increase of 11.5%. Individuals aged 50–79 years increased from 29.35% in 1995 to 32.78% of the total population in 2015. The age group ≥ 80 years grew from 4.67 to 5.09% of the population during the same time interval. The European Standard model for individuals aged 50–79 and ≥ 80 years is 27% and 2%, respectively. Consequently, both age groups are down-weighted when age-standardised incidence is calculated.

CRC incidence in Sweden is shown in Table 1. The number of new registrations in 1995 was 2112 (48.1 per 100,000 population) compared to 3090 (63.1 per 100,000 population) in 2015. This is equivalent to a crude incidence rate increase of 31% and a 46% increase in the number of new registrations. The age-standardised incidence rate in 1995 and 2015 was 33.37 compared to 40.09, respectively, corresponding to an age-standardised increase of 20%. The smaller increase in the age-standardised incidence rate (20%) compared to the crude incidence rate (31%) is a consequence of the increasing age of the Swedish population. Table 2 shows CRC incidence rates by age, sex, and tumour location.

Figure 1 shows the annual changes in the CRC incidence rate over time (1995–2015), which was estimated using Poisson regression. It is an illustrative representation of Table 3, where changes in the incidence rates per year can be followed throughout the studied period. The colon cancer incidence rate has increased for individuals irrespective of their age group while the rectal cancer incidence rate has either decreased (≥ 80 years) or remained relatively unchanged (50–79 years) during the study period.

Poisson regression modelling showed that the incidence rates increased significantly for colon cancer for all ages and locations ($P < 0.0001$). The proximal colon cancer incidence rate for all age groups increased, with the greatest increase seen in the youngest population for both sexes and in the oldest age group for men (Table 3).

The distal cancer incidence rate in the group aged < 50 years increased significantly per decade in both women (29% per decade, IRR = 1.29, 95% CI 1.14–1.45) and men (53% per decade, IRR = 1.53, 95% CI 1.34–1.74). The incidence rate for distal cancer in the two other age groups also showed an increase, but it was less pronounced.

The rectal cancer incidence rate increased by 30% per decade (IRR = 1.30, 95% CI 1.18–1.43) in men < 50 years, while it decreased for both women and men ≥ 80 years by 8% per decade for women (IRR = 0.92, 95% CI 0.88–0.96) and 7% per decade for men (IRR = 0.93, 95% CI 0.89–0.98). No change in the rectal cancer incidence rate was found in the age group aged 50–79 years and women < 50 years.

Table 2 Incidence by age, sex, and tumour location

	Incidence (per 100,000 population)				
	1995	2000	2005	2010	2015
Age < 50 years					
Women					
Proximal	0.91	1.19	0.93	0.97	1.65
Distal	0.98	1.12	1.00	1.25	1.31
Rectal	1.30	1.40	1.33	1.88	1.28
Men					
Proximal	0.97	1.03	0.96	1.79	2.15
Distal	0.77	0.79	0.93	1.20	1.47
Rectal	1.14	1.31	1.31	1.96	1.95
Age 50–79 years					
Women					
Proximal	39.18	37.43	41.39	49.33	51.37
Distal	25.55	24.67	28.69	32.30	30.14
Rectal	36.28	35.95	36.38	35.19	33.92
Men					
Proximal	41.62	37.75	35.70	48.16	48.52
Distal	30.40	31.42	34.34	42.61	43.85
Rectal	58.45	57.12	58.40	56.77	60.17
Age ≥ 80 years					
Women					
Proximal	104.83	112.33	126.89	155.19	169.41
Distal	45.14	54.43	55.21	62.39	53.12
Rectal	75.73	79.74	82.01	64.63	62.19
Men					
Proximal	136.71	148.63	146.82	163.83	166.32
Distal	87.88	94.18	93.69	113.04	93.85
Rectal	124.85	124.29	121.69	134.34	112.62

Discussion and conclusions

The main finding of this study is an increase in the CRC incidence rate in Sweden during the study period. This increase is significant for colon cancer in all age groups regardless of the tumour location. General CRC screening was not implemented in Sweden during the study period. Furthermore, specific cancer pathways allowing earlier detection of CRC were not launched until after 2015. The greatest increase in the colon cancer incidence rate is seen in the youngest age group (< 50 years) for both women and men. In addition, the rectal cancer incidence rate increased for men < 50 years, decreased for both sexes ≥ 80 years, and remained unchanged in the remaining cases.

The increasing CRC incidence rate among younger patients reported in this paper is also observed in other countries that share the same westernised lifestyle [2, 4–6, 12, 13]. However, the cause remains unknown and additional research

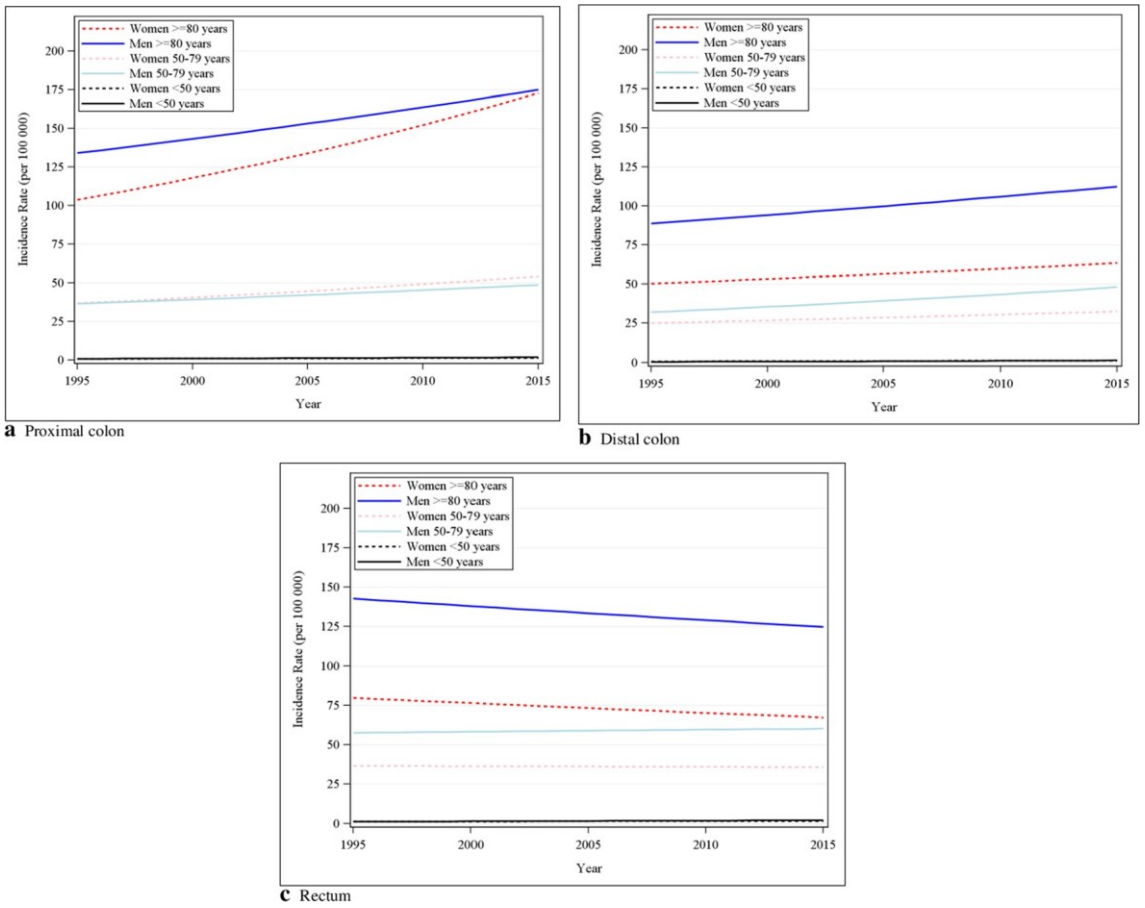

Fig. 1 Colorectal cancer rates in Sweden, 1995–2015, modelled by Poisson regression. Incidence rates by age, sex, and tumour location

is needed. Some evidence indicates that the increasing obesity rate is a contributing factor to the increasing incidence of CRC in the younger population [4]. In Sweden, the population became more obese during the study period, which may affect the CRC incidence [14, 15]. In addition, consumption of processed or red meat, a diet low in fibre, and physical inactivity may play a role in the increasing incidence. The effects of different risk factors also vary between colon and rectum cancers [16, 17].

Studies have shown that younger patients with CRC more often present with poorly differentiated tumours and a more advanced stage at the time of diagnosis compared to the elderly population [3, 6, 18]. The reasons behind these findings are unknown, but one explanation could be the earlier detection and prevention of CRC among older individuals in countries

Table 3 Incidence rate ratio of colorectal cancer over the interval 1995–2015

		Women		Men	
Age group	Tumour site	IRR (95% CI)	*P* value	IRR (95% CI)	*P* value
< 50	Proximal	1.27 (1.13; 1.44)	< 0.0001	1.41 (1.26; 1.58)	< 0.0001
	Distal	1.29 (1.14; 1.45)	< 0.0001	1.53 (1.34; 1.74)	< 0.0001
	Rectal	1.07 (0.96; 1.19)	0.21	1.30 (1.18; 1.43)	< 0.0001
50–79	Proximal	1.21 (1.18; 1.25)	< 0.0001	1.15 (1.12; 1.19)	< 0.0001
	Distal	1.14 (1.10; 1.18)	< 0.0001	1.23 (1.19; 1.26)	< 0.0001
	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)	< 0.0001	1.14 (1.09;1.19)	< 0.0001
	Distal	1.12 (1.06; 1.19)	< 0.0001	1.13 (1.07; 1.19)	< 0.0001
	Rectal	0.92 (0.88; 0.96)	0.0005	0.93 (0.89; 0.98)	0.0051

with organised screening programs [19]. However, a delayed diagnosis in younger patients with CRC could be another cause for the advanced disease in this population [3]. This delay may be a result of either physician- or patient-related factors. A study in patients with young-onset CRC with no known genetic predisposition showed that majority of patients were symptomatic at the time of diagnosis [20]. Our findings of an increased incidence of CRC in the younger population suggest that awareness of symptoms, on both the clinician's and patient's part, is important for early prevention of CRC in young adults.

Several studies have reported a left-to-right shift in the location of CRC among older individuals in the USA [21]. This relative increase in proximal colon cancers compared to distal cancers may partly be attributed to CRC screening, which may detect distal CRCs more effectively than proximal CRCs. The results obtained from this study indicate a greater increase in proximal tumours for individuals ≥ 80 years, in contrast to a decline in rectal tumours. An explanation as to why proximal colon cancer is more common than rectal cancer in the elderly is discussed in an article by Chouhan et al. [22]. Right-sided colon cancer is usually characterised by CpG island hypermethylation and BRAF mutations, which tend to accumulate with age. Conversely, young-onset colorectal cancers showed no CpG island hypermethylation, which suggests that there may be another underlying cause for the increase in proximal colon cancer in younger individuals seen in this paper. Brändstedt et al. [23], however, found an association between obesity, measured as different anthropometric factors. They found an increased risk of rectal cancer in women and an increase in colon cancer related to obesity in men. However, other studies have shown a positive correlation between the risk of rectal cancer and obesity in men [24, 25]. Thus, the CRC risk associated with obesity and genetic factors may vary by location and sex; obesity might have a stronger correlation with distal CRC while proximal tumours seem to be more associated with genetics.

The strength of this paper is that the entire Swedish population is considered over a period of 20 years. Every primary, malignant tumour since 1970 is documented in the cancer statistics of the National Board of Health and Welfare, from which the data were collected. Thus, we have a complete presentation of the incidence in the Swedish population. A limitation is that our data do not provide the underlying mechanisms. Although there is a great relative increase in the CRC incidence rate among younger patients, the increase in absolute numbers is relatively small (Table 2). The relative increase might be a result of natural variation over time. However, as mentioned previously, earlier studies in other countries also show similar trends.

Further research is needed to explain why the incidence rate of CRC in Sweden is increasing significantly, particularly in the younger population. Tumour biology, presenting symptoms, and risk factors in patients < 50 years need further investigation. The observation that > 90% of CRC cases occur in individuals > 50 years contradicts the implementation of screening for individuals < 50 years. However, the increase in CRC among young individuals, observed in multiple developed countries, may indicate that the threshold for CRC screening could be lowered.

The increase in CRC, especially colon cancer among younger individuals, suggests that increased attention should be paid to patients < 50 years of age who present with common symptoms of CRC. More studies are needed to establish the causes for the observed trends. This paper supports the implementation of a population-based CRC screening.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interests.

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Biography

Ida Gutlić was born in 1996 in Sweden. She was influened by the medical profession from an early age. During her teenage years she was a competetive swimmer and also swam for the Swedish Youth National Team. Her academic studies began in Malmö, Sweden, where she finished a science-oriented high school. During this time her interest for medicine grew stronger and in 2015 she started her studies at the Univeristy of Zagreb School of Medicine in English.