Demographic trends in the incidence of young-onset colorectal cancer in England: a population-based study, 1974-2015

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Disclaimer: No conflicts of interest

Authorship credit: All authors contributed to the conception and design; acquisition of data, analysis and interpretation of data; drafting the article or revising it critically for important intellectual content; and final approval of the version to be published.

Original Article: Presented in the 'Six of the best' BJS prize session at the ACPGBI conference in Dublin, 1st July, 2019.

Abstract

Background

Evidence is emerging that colorectal cancer (CRC) incidence is increasing in young adults, but the descriptive epidemiology required to better understand these trends is currently lacking.

Method

A population-based cohort study was carried out of all adults aged 20-49 years diagnosed with CRC in England between 1974 and 2015. Data were extracted from the NCRAS database using ICD9/10 codes for CRC. Temporal trends in age-specific incidence rates (IRs) according to gender, anatomical subsite, index of multiple deprivation (IMD) quintile and geographical region were analysed using Joinpoint regression.

Results

A total of 56 134 new diagnoses of CRC were analysed. The most sustained increase in IR was in the 20-29 age group which is mainly driven by a rise in distal tumours. The magnitude of IR increases was similar in both genders and across Index of Multiple Deprivation quintiles, although the most pronounced increases in incidence were in the southern regions of England.

Conclusion

CRC should no longer be considered a disease of older people: changes in incidence rates should be used to inform future screening policy, preventative strategies and research agendas, as well as increasing public understanding that younger people need to be aware of the symptoms of CRC.

Introduction

CRC is a major cause of cancer related mortality and is the third most common cause of cancer death in the UK.[1, 2] Advances in the surgical and oncological management of CRC are the most likely explanation for the UK age-standardised mortality rate reducing from 49 to 27 per 100 000 person-years over the past 40 years.[2]

Despite age-standardised incidence rates remaining static in the UK, as well as in other high human development index (HDI) nations,[3] there is increasing evidence that incidence rates are increasing in adults under 50 years of age. A US study, using SEER data, revealed a doubling in the incidence rate of both colon and rectal cancers in patients aged between 20 and 54 years since 1974.[4] Similar findings have been demonstrated in cohorts from Canada,[5, 6] Australia,[7] New Zealand,[8] and most recently Europe,[9] suggesting that the underlying risk of CRC is increasing in young people.

While males are well recognised to have a higher incidence of colon and rectal cancer in older age groups, there is little difference in the incidence rates between men and women in adults under 40 years of age [10, 11]. UK data have shown that males have a higher proportion of rectal tumours, but that females have a higher proportion of right-sided tumours [12]. However, data on anatomical subsite has not been linked to age-specific incidence trends in the UK population. Data from North America suggest that incidence rate increases have been driven by an increase in distal tumours,[4, 6] whereas European data suggest that incidence rate increases are more pronounced for colon cancer.

Socioeconomic status (SES) is associated with several important CRC risk factors. [13-15] In the UK, data from Northern Ireland have shown no difference in age-standardised incidence between deprivation deciles,[16] unlike in Scotland, where men from more deprived areas have been shown to have an increased incidence of CRC with evidence of an increasing deprivation gap over time. [17, 18] Previous studies have focused on SES as a risk factor for CRC incidence, but this has never been analysed in the context of recent changes in age-specific incidence trends in young adults. Significant variations in the burden of disease exist between the nine regions of England, including variation in the age-standardised rate of years of life lost to CRC. [19, 20] Understanding if there is a socioeconomic and regional variation in incidence rate trends in the young population could help elucidate potential aetiological factors.

While data from the UK has been incorporated in recent Europe-wide population-based studies,[9] a more detailed description of the epidemiology underlying the recent increase in CRC incidence in young adults trends is required. This is vital, as young adults typically present with more advanced tumours that carry a poorer prognosis and a more thorough knowledge of the descriptive epidemiology would help inform future preventative strategies. Therefore, the aim of this study was to determine temporal trends in incidence of colorectal cancer stratified by gender, anatomical subsite in the colorectum, socioeconomic status and geographical region of England.

105 **Methods**
106 **Data sources**
107 This study is reported according to the STROBE guidelines for epidemiological
108 studies. Data were obtained on all patients diagnosed with CRC aged 20 years and
109 above from 1974 to 2015 using data from the National Cancer Registration and
110 Analysis Service (NCRAS) (Request ID: ODR1718_067). NCRAS is a UK-wide
111 partnership operated by Public Health England (PHE) to collect data on all types of
112 cancer, including CRC, occurring in the English population.
113 **Procedures**
114 ICD codes were used to identify all diagnoses of CRC. ICD 9 codes [colon 153.0-153.9
115 (excluding 153.5 - appendix tumour) and rectum 154.0 and 154.1] for CRC were used
116 for diagnoses made between 1974 to 1994. ICD 10 codes [colon C18.0-C18.9
117 (excluding C18.1 – appendix tumour) and rectum C19 (recto-sigmoid) or C20 (rectum)]
118 were used for diagnoses made between 1995 to 2015 (appendiceal adenocarcinomas
119 were excluded and analysed separately - supplemental figure 1). For the purposes of
120 this study, young adults were defined as those aged 20-49 years with cases grouped
121 into three age groups based on age at diagnosis: 20-29 years, 30-39 years and 40-49
122 years.
123 Mid-year population estimates (MYPE) were obtained from the Office for National
124 Statistics (ONS) to provide population data stratified by age. MYPEs in conjunction
125 with the number of new diagnoses were used to calculate age-specific incidence
126 density rates per 100 000 person-years, referred to hereafter as the age-specific
127 incidence rate, for each age group using the formula given below.
128
129 Age-specific incidence rate =   Number of new cases in age group
130   Mid-year population estimate of age-group
131
132 The European Standard Population 2013 (ESP 2013) was then used to derive age-
133 standardised incidence rates for colon and rectal cancer for the overall dataset (20-
134 49 years), in accordance with the methodology for direct-standardisation by the
135 ONS.[21]
136
137 Age-standardised incidence rate =   ∑(ESP of age-group x age-specific rate)
138   ∑ ESP of age-group
139
140 CRC cases were further stratified by gender (using gender-specific population
141 estimates from the ONS as above), anatomical subsite: either proximal (caecum to
142 descending colon) and distal (sigmoid to rectum), geographical region (using region-
143 based population estimates from the ONS from 1981 onwards) and Index of Multiple
144 Deprivation (IMD) quintile (from 2001 onwards). IMD is an area-based metric that
145 combines weighted information from seven domains: Income (weighting 22.5%),
146 Employment (22.5%), Education (13.5%), Health (13.5%), Crime (9.3), Barriers to
147 housing & services (9.3%) and Living environment (9.3%). Lower-layer Super Output
148 Areas (LSOA; 32 844 in England) are given a value based on these domains. IMD

149 quintiles were calculated by ranking all LSOA from most to least deprived and then
150 splitting this ranking into five equal groups (each quintile has 20% of the ranked areas).
151 **Statistical analysis**
152 Data analyses were performed using Joinpoint Regression Program [22] (National
153 Cancer Institute (NCI), https://surveillance.cancer.gov/joinpoint/, version 4.7.0.0) to
154 analyse the magnitude and direction of temporal trends in age-specific incidence rates
155 according to gender, anatomical site, IMD quintile and geographical region.
156 Permutation analysis of the log transformed incidence rates was used to fit a series of
157 joined lines with a minimum of 0 and a maximum of 5 join points. A series of
158 comparisons among fitted models ranging from 0 to 5 join points was then undertaken
159 to select the best fit model. This procedure allowed estimation of the annual
160 percentage change (APC) in incidence. The squared correlation coefficient (R^2) was
161 used to estimate the goodness-of-fit of the Joinpoint regression models to provide an
162 indication of the extent of agreement between modelled and observed values.
163 Inspection of residuals under the models presented herein did not give cause for
164 concern, i.e. standard errors appeared homoscedastic, free from serial correlation and
165 without any unduly influential observations.
166 Age-period-cohort modelling (National Cancer Institute's Age Period Cohort web tool,
167 https://analysistools.nci.nih.gov/apc) was used to assess the independent effects of
168 age, period and cohort on CRC incidence rates.[23]. This was performed for all adults
169 aged above 20 years. Data were inputted using three ten-year age groups (20-29, 30-
170 39 and 40-49 for the Joinpoint regression modelling while four ten-year period groups
171 (1976-1985, 1986-1995, 1996-2005, 2006-2015) were used for the age-period-cohort
172 modelling as it was necessary to have age and time-period groups covering an equal
173 timespan. Therefore, there were 11 birth cohorts starting in 1886 through to 1986 in
174 ten-year bands. Reference values for the age-period-cohort model were arbitrarily
175 chosen from the first cohort analysed (1976-1985). Data presented from this model
176 were shown as incidence rate ratios (IRR) and 95 % confidence intervals (CI) to
177 assess cohort effects. Local drift was estimated by presenting age-specific net annual
178 percentage change in incidence rates.
179

Results

Of the 1 145 639 new cases of CRC diagnosed between 1974 to 2015 in adults aged over 20 years, there were 2594 cases in 20-29 year olds, 11 406 cases in 30-39 year olds, and 42 134 in 40-49 year olds.

Age-specific trends according to gender

Following an initial reduction in CRC incidence rates, there was a marked increase in rates among both 20-29 and 30-39 year olds. In 20-29 year-olds (figure 1A), incidence rate increases commenced earlier in females (APC=4.6% (95%CI 3.3 to 5.9%) from 1986) than in males (APC=5.1% (95%CI 3.7 to 6.5%) from 1992). In 30-39 year-olds (figure 1B), incidence rate increases commenced a decade later than in 20-29 year-olds with incidence rate increases again being observed earlier in females (APC=3.8% (95%CI 2.9 to 4.8%) from 1995) than in males (APC=6.0% (95%CI 4.4 to 7.6%) from 2002). The incidence rate trends observed in the younger age groups were more attenuated in 40-49 year olds (figure 1C), with small increases observed from 2003 onwards in both women (APC=1.5% (95%CI 0.5 to 2.5%)) and men (APC=0.8% (95%CI -0.1 to 1.6%)). These findings were suggestive of an age-cohort effect and assessed in more detail using age-period-cohort modelling applied to the entire adult population aged over 20 years. Using the 1926 birth cohort as the reference group, the incidence rate ratio (IRR) of CRC for cohorts born from 1886 to 1966 remained constant, following which there was a progressive increase in IRRs for successive birth cohorts (1976 cohort IRR=1.4, 95%CI 1.1 to 1.8; 1986 cohort IRR=2.2, 95%CI 1.3 to 3.8) (supplementary figure 1B-K).

Age-specific trends according to anatomical subsite

Increases in proximal cancer incidence rates were noted in 20-29 year olds (APC=4.4% (95%CI 2.3 to 6.5%) from 1995) and 30-39 year olds (APC=5.8% (95%CI 3.3 to 8.3%) from 2005), but with no observed effect in 40-49 year olds (APC=0.0% (95%CI -1.1 to 1.1%) from 2004) (figures 2A-C). The increase in proximal cancer age-standardised incidence rates among 20-49 year olds was predominantly driven by increases in the incidence of caecal and ascending colon cancers (supplemental figure 2). Age-specific incidence rate increases in distal cancers were more sustained and of a greater magnitude in comparison to proximal cancers among 20-29 year olds (APC=5.6% (95%CI 4.4 to 6.8%) from 1991) and 30-39 year olds (APC=3.3% (95%CI 1.0 to 5.7%) from 1995-2005 and APC=7.0% (95%CI 4.2 to 9.8%) from 2006). A less pronounced increase in distal cancer was also noted among 40-49 year olds (APC=1.4% (95%CI 0.7 to 2.1%) from 2001).

Age-standardised trends according to IMD quintile

The age-standardised incidence rates of distal cancers increased more rapidly than proximal cancers in all quintiles, except quintile 2 (supplemental figure 3A-E). There was no statistically significant difference in the magnitude of incidence rate increases across the quintiles for either proximal (p=0.110) or distal cancers (p=0.230).

Age-standardised trends according to geographical region

In 1985, age-standardised incidence rates of proximal cancers among 20-49 year olds were decreasing across all regions of England, except in London, with the greatest reduction observed in the South West (APC=-12.1%, 95%CI -20.3 to -3.1%) (figure 3).

224 By 2015, incidence rates were increasing the fastest in the south-eastern regions
225 (APC South East=7.4%, 95%CI 4.8 to 10.1%; London=6.5%, 95%CI 0.1 to 13.2%;
226 East of England=6.0%, 95%CI 2.5 to 9.7%). A similar, but more pronounced trend,
227 was noted for distal cancers (figure 4). By 2005, the most rapid increase in distal
228 cancer age-standardised incidence rates was noted in the South West (APC=10.1%
229 (95%CI 6.1 to 14.1%) with all other southern regions experiencing annual increases
230 of greater than 5%.

Discussion

232 This is the largest study based on a single, national population registry to describe
233 detailed epidemiological changes in CRC incidence in a young adult population. The
234 finding that CRC incidence is increasing rapidly in young adults supports recent
235 findings from other high HDI nations.[4-9, 24]. Rapid increases were observed in adults
236 aged 20-39 years, which appears to be driven by increases in the rate of distal
237 tumours. Incidence rate increases in the English population appear to be similar in
238 both genders and across all socioeconomic groups. Importantly, incidence rates are
239 increasing the fastest in the southern regions of England, particularly in the South
240 West where the incidence of distal cancers is now increasing by more than 10% each
241 year. A substantial birth cohort effect is observed with dramatic increases in IRRs from
242 the mid-1960s onwards, similar to the observations in North American studies,
243 although incidence rate ratio increases in these studies appear to have occurred in
244 birth cohorts born approximately 15 years earlier.[4, 6] This suggests that any exposure
245 to underlying risk factors may have occurred earlier in the North American population.
246 Tumours in young adults are thought to be sporadic in nature,[25] with environmental
247 factors likely playing a significant causative role. The rising incidence of CRC in young
248 adults coincides with several environmental changes most notably increasing
249 childhood and adult obesity rates.[26] It is recognised that early-life obesity leads to an
250 increased risk of developing CRC.[27, 28] Therefore the increases in CRC incidence in
251 young men and women may reflect the recent UK obesity prevalence trends, where
252 prevalence rates among adults aged 35-54 years have increased from 15.4% to 26.3%
253 in men and 17.9% to 24.5% in women, between 1993 and 2004.[29]

254 The more pronounced increase in the incidence rate of distal tumours compared to
255 proximal tumours contrasts findings from recent European data,[9] but is similar to the
256 results from several North American studies.[4, 6, 30] While risk factors associated with
257 an increased risk of CRC have been identified, the strength of their association with
258 tumour development at individual sites within the colorectum remains unclear.
259 Differences in the way environmental factors promote tumorigenesis at various sites
260 within the colorectum suggest that proximal and distal tumours may be biologically
261 distinct entities;[31] this may explain why the incidence in distal tumours from this English
262 cohort has increased more rapidly. The biological differences in early versus late onset
263 CRC have been explored by several studies: a recent large cohort study characterising
264 the clinical and molecular features of early-onset CRC demonstrated enrichment of
265 certain phenotypes such as consensus molecular subtype 1 (CMS1) in distal tumours
266 in adults under 50 years.[32, 33] Other work has shown low levels of microsatellite

267 instability (MSI) in CRC in young adults.[34, 35] Additionally, there is a prevalence of
268 mutations in genes such as β-catenin[34, 36] and KRAS.[37] Interestingly, the combination
269 of altered environmental exposures combined with the different tumour biology
270 suggests that young adult CRC may be a different disease to later onset disease.
271 This study showed no evidence for an association between SES and the rate of
272 increase in incidence of both proximal and distal tumours, contrary to previous studies
273 where higher incidence rates were observed in more deprived groups.[16-18] Although
274 factors associated with an increased risk of CRC, such as obesity, low fibre diet and
275 reduced physical activity, are known to be associated with lower SES,[13-15] changes in
276 obesity prevalence trends are actually similar between socioeconomic groups[38] and
277 may partly explain the lack of association between SES and CRC incidence rate
278 increases observed in this study. Additionally, obesity is one of many risk factors
279 associated with the development of CRC and is itself caused by several complex
280 societal, genetic and environmental interactions. It is perhaps not surprising that
281 understanding the causative effects of single environmental risk factors is
282 challenging.[39]
283 Geographical inequalities in health are well characterised in England with incidence
284 rates of all cancers noted to be higher in the North of England than in the South,
285 although there is minimal variation in colorectal cancer incidence by region.[40] In this
286 study we observed recent incidence rate increases in CRC across all English regions,
287 although the most marked increases were observed in the South of England. It is
288 difficult to explain why incidence rates are increasing more rapidly in young adults in
289 the South given that risk factors such as obesity are increasing faster in Northern
290 regions.[38] It is important to point out that the effect of regional variations in access to
291 healthcare/endoscopy services on CRC incidence rates remains unknown and it may
292 be that the observed incidence rate increases seen in the more affluent, southern
293 regions are driven by increased awareness and access to medical care.
294 The main strengths of this study are the size and completeness of the dataset. Data
295 were obtained from NCRAS, a nationally curated cancer registry, with 100% complete
296 data for 1974-2012 and 98.4% complete data for 2013-2015. Unfortunately, stage-
297 specific data were not routinely recorded until 2012, so further analysis of incidence
298 rate trends according to tumour stage could not be performed. It will be important to
299 know whether the increase in young-onset CRC was driven by an increase in the
300 detection of early stage disease, particularly in regions and socioeconomic groups that
301 may have increased health awareness and access to endoscopy services. Data
302 presented in this study are population-based in nature and specific causal inferences
303 cannot be made. In addition, IMD quintile and geographical region are group-level
304 metrics and are unable to account for individual level contextual effects that could have
305 affected the association between these variables and observed CRC incidence rates.
306 Finally, with the increasing of use of endoscopy in England,[41] it could be argued that
307 this accounted for the rising incidence of CRC. However, detection bias is unlikely as
308 incidence rates were decreasing until the 1990s, and the most rapid increases were
309 observed in the youngest age groups (the least likely to attend for endoscopic
310 examination).

311   In summary, the incidence rate of young-onset CRC cancer is increasing, particularly
312   among adults aged 20-39 years. This trend appears to be predominantly driven by a
313   rise in distal tumours. Incidence rate increases of a similar magnitude have been
314   observed in both genders and across IMD quintiles, but are most pronounced in the
315   South of England. Importantly, there is a strong birth cohort effect and it is likely that
316   the increased risk in the youngest cohorts will be carried forward as they age, which
317   will place a significant burden on future healthcare resources. The role of
318   environmental factors such as diet, obesity, physical exercise and the gut microbiota
319   in the development of young-onset CRC are incompletely understood and require
320   further research. Reducing the screening age below 50 years will have significant
321   resource implications in the current economic climate [42] and instead, there should be
322   more focus on risk stratifying symptomatic younger patients to further investigation
323   using tests such as quantitative faecal immunohistochemical testing.

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