Fertility outcomes after early-onset colorectal cancer: a matched cohort study using linked population-based data in England

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Background and Aim

Early-onset colorectal cancer (CRC) - CRC diagnosed in those under 50 years old - is rising. For women diagnosed with early-onset CRC, fertility after diagnosis is a key concern, yet robust, real-world evidence of fertility outcomes in this cohort remain limited. This study aims to understand the likelihood of live-birth post CRC diagnosis according to patient characteristics, to help inform patients and facilitate fertility preservation decisions.

Method

Study design

Population based matched cohort study using anonymised English electronic health record data from the Clinical Practice Research Datalink (CPRD) Aurum database, linked to:

- National Cancer Registration and Analysis Service (NCRAS)
- Hospital Episode Statistics Admitted Patient Care (HES APC)
- Systemic Anti-Cancer Therapy data set (SACT)
- Radiotherapy Data Set (RDTS)

Population and exposure of interest

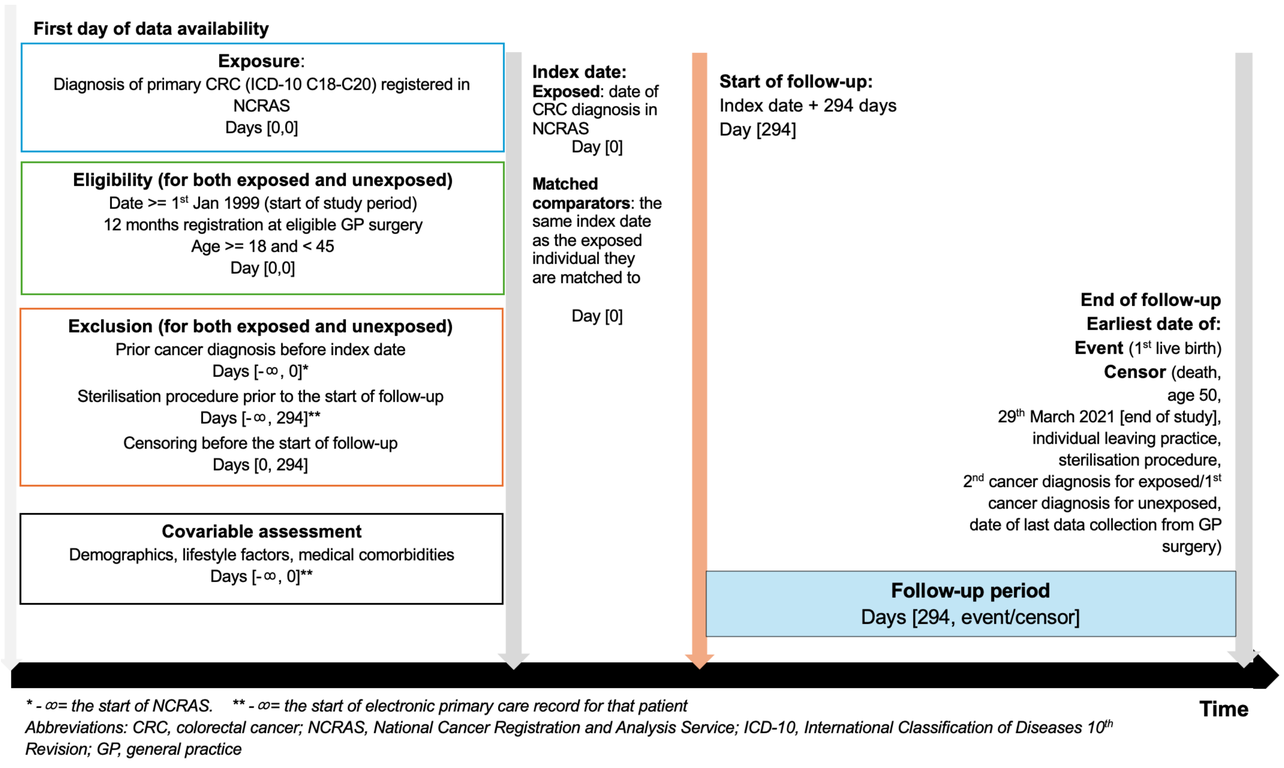
- Women with incident CRC diagnosed at ages 18-44 years during 1999-2018
- Identified from NCRAS using ICD-10 codes C18-C20
- Each matched to up to ten cancer-free comparators on age (±3 years, preference given to closer matches), general practice, and calendar time.

Outcome

- First live birth after 42-weeks post index date
  - Index date = date of diagnosis for cases; matched index date for comparators
- Ascertained from CPRD pregnancy register, supplemented by HES APC

Statistical analysis

- Cox proportional hazards models stratified on matched set with robust variance
- Adjusted for confounders: socioeconomic status, diabetes mellitus, inflammatory bowel disease, smoking, body mass index and high alcohol usage.
- Prespecified subgroup analyses with cancer-free comparators as baseline comparing:
  - Initial cancer treatment modality: surgery alone; surgery + systemic anti-cancer therapy [SACT]; surgery + SACT + radiotherapy
  - Tumour site: colon (ICD10 C18-19) vs rectum (ICD10 C20)
- Interactions with baseline age and prior live birth were also tested.



** - ∞= the start of NCRAS. ** - ∞= the start of electronic primary care record for that patient*
Abbreviations: CRC, colorectal cancer; NCRAS, National Cancer Registration and Analysis Service; ICD-10, International Classification of Diseases 10th Revision; GP, general practice

Figure 1. Study design diagram with inclusion and exclusion criteria, covariate assessment and follow-up window shown with respect to the timeframe of entry

Results

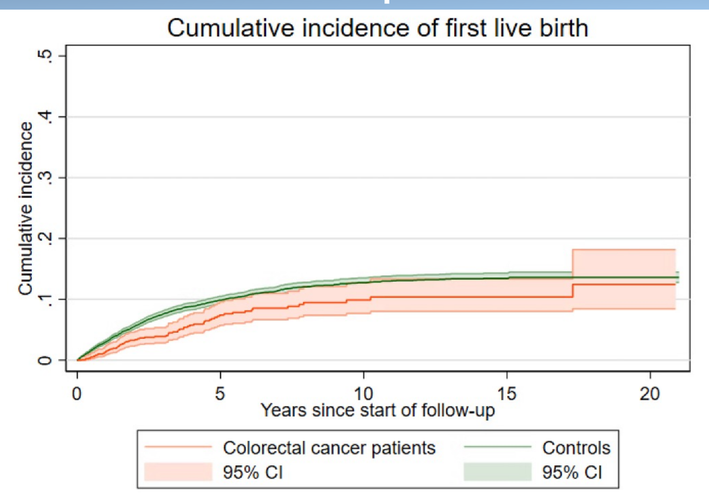
Cohort characteristics at index date

- 1,209 CRC patients and 11,035 comparators
- Median age
  - CRC cohort: 39.2 years
  - Comparators: 39.3 years
- Median follow-up: 3.6 years
- Comparators censored when their matched CRC patient censored
- Colorectal cancer stage at diagnosis:
  - I = 190 (15.7%)
  - II = 270 (23.3%)
  - III = 419 (34.7%)
  - IV = 138 (11.4%)
  - Missing = 192 (1.9%)
- Colon (C18) = 806 (66.7%) rectal (C19-20) = 33.3%)

Characteristics		CRC cohort (N=1,209)	Cancer-free cohort (N=11,035)
Age (years)	Mean (SD)	37.57 (6.10)	37.67 (6.02)
	Median (IQR)	39.18 (8.38)	39.25 (8.23)
	Min - Max	19.04 - 44.99	19.04 - 44.99
Index year group	1999 - 2005	263 (21.8%)	2,389 (21.7%)
	2006 - 2010	282 (23.3%)	2,579 (23.4%)
	2011 - 2015	417 (34.5%)	3,791 (34.4%)
	2016 - 2018	247 (20.4%)	2,276 (20.6%)
Socioeconomic status	1 (Least deprived)	269 (22.3%)	2,489 (22.6%)
	2	244 (20.2%)	2,403 (21.8%)
	3	218 (18.0%)	2,056 (18.7%)
	4	240 (19.9%)	2,119 (19.2%)
	5 (Most deprived)	238 (19.7%)	1,968 (17.8%)
Body Mass Index	Underweight	38(3.1%)	312 (2.8%)
	Normal	628 (51.9%)	5,768 (52.3%)
	Overweight	298 (24.7%)	2,696 (24.4%)
	Obese	245 (20.3%)	2,259 (20.5%)
Smoking status	Non-smoker	511(42.3%)	4,553 (41.3%)
	Ex-smoker	481 (39.8%)	4,286 (38.8%)
	Current smoker	217 (18.0%)	2,196 (19.9%)
History of alcohol misuse	No	1,173 (97.0%)	10,735 (97.3%)
	Yes	36 (3.0%)	300 (2.7%)
History of diabetes mellitus	No	1,170 (96.8%)	10,775 (97.6%)
	Yes	39 (3.2%)	260 (2.4%)
History of IBD*	No	1,104 (91.3%)	10,782 (97.7%)
	Yes	105 (8.7%)	253 (2.3%)
Prior birth	No	530 (43.8%)	4,889 (44.3%)
	Yes	679 (56.2%)	6,146 (55.7%)

Table 1. Baseline Characteristics of the study cohort * IBD = inflammatory bowel disease

Association between CRC and subsequent first live birth



Shaded areas represent 95% confidence intervals
Abbreviation: CI, confidence interval

Figure 2. Kaplan-Meier plot for the cumulative incidence of first live birth by exposure status

- Compared with cancer-free comparators, CRC was associated with a reduced likelihood of subsequent first live birth (adjusted HR 0.62, 95% CI 0.49-0.79; p<0.001).
- By treatment, compared to cancer-free comparators, HRs were 0.81 (CI 0.54-1.22) for those receiving surgery, 0.53 (CI 0.35-0.78) for surgery + SACT, and 0.09 (CI 0.01-0.68) for surgery + SACT + radiotherapy.
- By site, compared to cancer-free comparators, HR was lower for rectal (0.31, CI 0.17-0.56) than for colon cancer (0.76, CI 0.58-0.99).
- There was no statistical evidence that the association differed by prior live birth (p-value for interaction=0.50).
- In contrast, there was evidence of interaction with baseline age: HR 0.37 (CI 0.20-0.68) for >35 years vs 0.72 (CI 0.55-0.94) for ≤35 years (p-value for interaction=0.048).

Conclusion

Using electronic health record data, we showed that having a CRC diagnosis is associated with reduced likelihood of having a subsequent live birth, particularly in those older than 35, those with rectal cancer, or those receiving radiotherapy. Whether this is driven by lower fecundity following cancer, low survival or a change in fertility intentions is unclear. Nevertheless, our findings could contribute to personalised fertility counselling at diagnosis in UK clinics, tailored to specific cancer and patient characteristics; and facilitate local service planning.

Contact

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The presenting author does not have any conflict of interest

Ethical approval: CPRD study protocol was approved by CPRD's Research Data Governance group (Ref: 20_000268). Ethical approval was obtained from London School of Hygiene and Tropical Medicine Research Ethics Committee (Ref: 32266).