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ORIGINAL ARTICLE

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Prescribed drugs in 27 000 individuals after diagnosis of colorectal cancer: A population-based cohort study

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Abstract

Background: The prevalence of prescribed drugs in survivors of colorectal cancer (CRC) was evaluated.

Methods: Data from the Cancer Registry of Norway were linked to the Norwegian Prescription Database for a study population of 3.52 million individuals. Prevalence ratios (PRs) with 95% confidence intervals (CIs) of prescribed drugs in CRC-survivors compared to the cancer-free population, were estimated by log-binomial regression, adjusting for age and education.

Results: Almost 27 000 individuals, aged 20 to 84, were diagnosed with CRC during 2005 to 2014. The first year after diagnosis, the prevalence of prescribed drugs was higher in CRC-survivors compared with the cancer-free population, especially drugs for anxiety and tension, and steroid-responsive conditions. PRs for several drugs, especially drugs used for mental and behavioural disorders, decreased with time since diagnosis. The prevalence of drugs used for anxiety and tension was elevated 10 years after diagnosis; PRs the first year after diagnosis were 20 (95% CI: 18-22) in males and 17 (16-18) in females. Ten years after diagnosis PRs were 5.0 (3.1-7.9) and 2.0 (1.0-3.8), respectively. In absolute numbers, the largest increase, compared to the cancer-free population, was in drugs used for gastric acid disorders and pain. The prevalence of neuromodulatory drugs was higher in CRC-survivors.

Conclusions: The prevalence of several drugs was higher in CRC-survivors than in the cancer-free population 10 years after diagnosis. The largest absolute excess in prevalence was for gastric acid disorder and pain medications, while the relative

Abbreviations: ATC, Anatomical Therapeutic Chemical; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CRC, colorectal cancer; CRN, Cancer Registry of Norway; CVD, cardiovascular disease; DDD, Defined Daily Doses; ICD, International Classification of Diseases; NNED, Norwegian National Education Database; NorPD, Norwegian Prescription Database; PR, prevalence ratio.

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prevalence of drugs used for anxiety and tension was high in CRC-survivors. Long persisting neuropathia was indicated.

KEYWORDS
chronic diseases, colorectal cancer, drugs, medication, pharmacoepidemiology, population-based

1 | INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer in men (11% of all cancers worldwide) and the second in women (9.5%).[1,2] Norway has the highest incidence of CRC among the Nordic countries.[3]

Comorbidities in individuals diagnosed with cancer have recently been examined in a Danish study; 55% had comorbidities at diagnosis.[4] In CRC-survivors, approximately one-third suffer from severe comorbidities at the time of cancer-diagnosis.[5] A recent large British study showed that survivors of most site-specific cancers had increased risk of one or more cardiovascular disease (CVD) outcomes[6]; the CRC-survivors had increased risks of venous thromboembolism and pericarditis.

Adverse long-term effects of CRC and its treatments include sensory neuropathy after oxaliplatin, gastrointestinal problems, urinary incontinence, sexual dysfunction, fatigue, anxiety and fear of recurrence, sleeping problems and depression.[7,8] However, their frequency throughout CRC survivorship needs to be properly quantified for implementing appropriate preventive strategies.

This study aimed to examine the prevalence of prescribed drugs, as a proxy for chronic diseases, in survivors of adult-onset CRC (≥20 years) in Norway during 2005 to 2014 relative to the cancer-free population.

Key Points

- Up to 12 years after diagnosis, the use of several drugs, particularly drugs for anxiety and tension, and steroid-responsive conditions, was higher in colorectal cancer (CRC) survivors than in the cancer-free population.
- In absolute terms, the use of drugs for gastric acid disorders and pain was high.
- The prevalence in use of drugs for cardiac arrhythmias was higher in male CRC-survivors over 60 years than in younger males, comparing the cancer-free population.
- The prevalence in use of drugs for anxiety and tension, and for pain was higher for survivors of non-localised than localised CRC.
- There was a higher prevalence of neuromodulatory drugs among the CRC-survivors.

2 | MATERIAL AND METHODS

Using unique national ID-numbers, we performed a comprehensive linkage of records from nationwide databases in Norway (a population of approximately 5.2 million in 2016); the National Population Registry (1954-2016),[9] the Cancer Registry of Norway (CRN) (1953-2014),[10] the Norwegian Prescription Database (NorPD) (2004-2016),[11,12] and the Norwegian National Education Database (NNED) (2004-2014).[13] The registries and the classification systems used are described in the Supplementary Material.

2.1 | Study population

In all, 3.66 million individuals born during 1920 to 1990 were living in Norway on January 1st, 2005. Of these, 145 030 were excluded because they had a history of cancer prior to 2005 and 1737 because they developed cancer, died, or emigrated before reaching age 20 years (Figure 1). Thus, the final study population comprised 3.52 million individuals who were followed up for dispensed drug prescriptions from age 20 or January 1st, 2005, whichever occurred latest, until emigration (n = 53 129), a cancer-diagnosis other than CRC (n = 181 853), age 85 years (n = 182 181), death (n = 174 751) or December 31st, 2016 (n = 2 925 627), whichever occurred earliest.

2.2 | Drugs and diseases

Reimbursed drugs (any reimbursement code; drugs used for chronic diseases with documented effects) were used as a proxy for the diseases/conditions listed in Table 1,[14] which were grouped into five major categories:

1. Cardiovascular diseases (CVDs)
2. Endocrine, nutritional, and metabolic diseases
3. Diseases of the nervous system
4. Mental and behavioural disorders
5. Other conditions

The selection of drugs examined in this study was primarily based on a study by Sarfati et al,[14] who developed and validated a pharmacy-

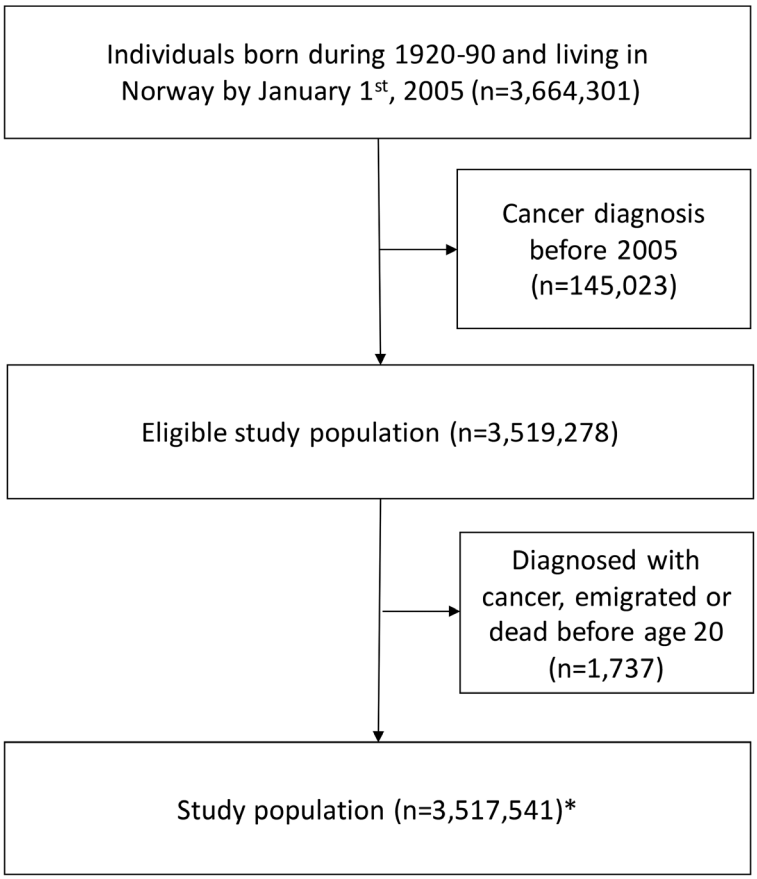

FIGURE 1 Selection of the study population, Norway 2005 to 2016

based comorbidity-index in cancer patients. In addition, two more classes of drugs (sex hormones and urologicals) were included based on mapping of comorbidities in CRC-patients.[7,8,15]

2.3 | Statistical analysis

One-year prevalence, hereafter termed prevalence, of drug use ('use' defined as dispensed drugs within the period studied irrespective of prior medication use) within each calendar year 2005 to 2016 was calculated.

Prevalence ratios (PRs) with 95% confidence intervals (CIs) of specific reimbursed drugs among CRC-survivors (defined as individuals alive after a CRC-diagnosis), compared to the cancer-free population for each calendar year (2005-2016), were estimated using log-binomial regression.

In the analyses, the calendar years for cancer-survivors were categorised into one-year intervals as (<1, 1, 2, …, 9, and ≥10 years) according to time from cancer-diagnosis to January 1st the actual year. The year in which the cancer was diagnosed was not included in any category to ensure that the drugs were used after the cancer-diagnosis. The year in which the follow-up ended was included only if the follow-up ended in the second half of that calendar year, but was excluded if it ended in the first half as individuals would have been 'under risk' of using drugs for less than half a year (see Supplementary Material). The statistical models included adjustments for the potential confounding effects of age (in 5-year categories: 20-24, 25-29, …, and 80-84 years) and educational level (compulsory (<10 years), intermediate (10-12 years) and tertiary (≥13 years)). For the latter variable, the NNED data for the years 2004, 2009, and 2014 were used, respectively, for the calendar years 2005-2008, 2009-2013, and 2014-2016. Further adjustment for country of birth (categorised as Norway, other high-income countries and low-income countries according to the Global Burden of Diseases, Injuries, and Risk Factors Study[16] did not change the estimates, and was consequently not included in the final models. PRs in patients stratified by stage of disease at diagnosis (localised and non-localised), age at diagnosis (<60 and ≥60 years) and subtype of CRC (colon and rectum) were also calculated.

In addition, age-standardised 1-year prevalence for males and females was computed for each drug group for the cancer-free population (averaged over the study period) and for the CRC-survivors 1 year before and 5 years after the CRC-diagnosis. We used direct standardisation with the Scandinavian standard population in 5-year age groups as reference population.[17]

The statistical analysis was performed in Stata version SE 15.0, using the cluster command to account for multiple observations per individual.

TABLE 1 Diseases/conditions studied, adapted from Sarfati et al[14]

Diseases/condition	Drug name	ATC-code
Cardiovascular diseases (CVDs)		
Cardiac arrhythmias	Cardiac glycosides Antiarrhythmics, class I and III	C01A C01B
Coronary heart disease	Vasodilators used in cardiac diseases	C01D
Ischemic heart disease/ hypertension	Antihypertensives Diuretics Beta blocking agents Calcium channel blockers Agents acting on the renin-angiotensin system	C02 C03 C07 C08 C09
Congestive heart failure	Diuretics	C03
Thromboembolism	Antithrombotic agents	B01
Endocrine, nutritional, and metabolic diseases		
Diabetes mellitus	Drugs used in diabetes	A10
Hyperlipidaemia	Lipid modifying agents	C10
Hypothyroidism	Thyroid preparations	H03A
Diseases of the nervous system		
Epilepsy	Antiepileptics	N03A
Parkinson disease	Anti-Parkinson drugs	N04
Mental and behavioural disorders		
Psychotic illness	Antipsychotics	N05A
Anxiety and tension	Anxiolytics Hypnotics and sedatives	N05B N05C
Depression	Antidepressants	N06A
Other conditions		
Gastric acid disorders	Drugs for acid related disorders	A02
Anaemia	Antianaemic preparations	B03
Steroid-responsive conditions	Corticosteroids for systemic use	H02
Osteoporosis/Paget disease	Drugs affecting bone structure and mineralisation	M05B
Pain	Analgesics Antiinflammatory and antirheumatic products, nonsteroids	N02 M01A
Chronic obstructive pulmonary disease (COPD)	Drugs for obstructive airway diseases	R03
Sex hormones and modulators of the genital system	Sex hormones and modulators of the genital system	G03
Urologicals	Urologicals	G04

2.4 | Ethics approval

The study was approved by the Regional Committee for Medical and Health Research Ethics (REC South East; no. 2010/131).

3 | RESULTS

Most (91%) of the eligible study population were born in Norway, and 24% had tertiary education in 2005 (increasing to 32% in 2014) (Table 2). Altogether 26 691 individuals were diagnosed with CRC (age 20-84 years) during 2005 to 2014; 21% of the cancers were localised at diagnosis. The number of CRC-survivors by time since diagnosis is given in Figure 2.

On average, 41% of males and 47% of females in the cancer-free population aged 30-84 years used at least one of the examined drugs (with reimbursement) during one calendar year in the study period (Table 3). The prevalence in CRC-survivors was higher than in the cancer-free population both in the year prior to the CRC-diagnosis and 5 years thereafter. The absolute excess in prevalence in CRC-survivors compared to the cancer-free population was especially large for drugs used for gastric acid disorders and for pain. The prevalence was highest in individuals with low education (data not shown), especially for drugs used for psychotic illness.

Table 3 also gives prevalence of drugs in patients with localised and non-localised CRC 5 years after diagnosis. The prevalence of drugs used for anxiety and tension was higher in patients with non-localised CRC than in patients with localised CRC. The proportions of individuals with use of two or more of the drug groups explored, were higher in CRC-survivors (31.3 in males and 32.3 in females) than in the cancer-free population (23.5 in males and 26.2 in females). Male CRC-survivors aged 60 or above had higher prevalence of drugs in general than those diagnosed before age 60, mostly due to drugs used for cardiac arrhythmias (Table S1).

3.1 | The first year after CRC-diagnosis

CRC-survivors had a higher prevalence of drugs in the first year after diagnosis for all the main drug groups examined (Figure 3), except for the group of drugs used for endocrine, nutritional, and metabolic diseases. The increased PR of drugs used for CVDs was mainly due to drugs used for thromboembolism, but prevalence was also higher, although to a lesser extent, for cardiac arrhythmias and congestive heart failure (Figure S2). In contrast, the prevalence of drugs for coronary heart disease was lower in CRC-survivors than in the cancer-free population. The prevalence of drugs for endocrine, nutritional, and metabolic diseases was slightly lower among CRC-survivors than in the cancer-free population, reflecting a lower prevalence of drugs for hyperlipidaemia (Figure S3). The higher prevalence of drugs for diseases of the nervous system among CRC-survivors was driven by the higher prevalence of drugs used for epilepsy, including neuromodulatory drugs

TABLE 2 Characteristics of the eligible study population and colorectal cancer patients diagnosed during 2005 to 2014

Characteristic	Number of individuals	%
Sex		
Male	1 758 395	50.0
Female	1 760 883	50.0
Year of birth		
1920-1939	504 226	14.3
1940-1959	1 089 696	31.0
1960-1990	1 925 356	54.7
Country of birth[a]		
Norway	3 211 102	91.2
Other high-income countries	123 941	3.5
Low-income country	182 772	5.2
Missing	1463	0.0
Education[b]		
Compulsory (<10 years)	1 074 170	30.5
Intermediate (10-12 years)	1 535 940	43.6
Tertiary (≥13 years)	836 718	23.8
Missing	72 450	2.1
Total	3 519 278	100.0
Colorectal cancer patients (n = 26 691)		
Age at diagnosis (years)		
20-39	530	2.0
40-59	5195	19.5
60-69	7864	29.5
70-84	13 102	49.1
Stage		
Localised	5638	21.1
Non-localised	20 503	76.8
Unknown	550	2.1
Type of cancer (ICD-10 code[c])		
Colon (C18)	17 514	65.6
Rectum and rectosigmoid (C19-20)	9177	34.4

[a]Categorisation based on the classification used in the Global Burden of Diseases, Injuries, and Risk Factors Study.[16]
[b]Categorisation based on information from Statistics Norway.[13] Information from 2004 was used for individuals born before 1989, and information from 2009 was used for individuals born 1989 to 1990.
[c]International Classification of Diseases, version 10.

such as carbamazepine, gabapentin, and pregabalin, but there was a lower prevalence of drugs for Parkinson disease (Figure S4). Altogether 6.4% used gabapentin, pregabalin or carbamazepine more than 5 years after diagnosis, and 87% of those not in combination (dispensed within 30 days) with other strong analgesics (opioids). Raised PRs were also observed for drugs used for several mental and behavioural disorders, particularly for anxiety and tension (more than 96% of the drugs were anxiolytics (Anatomical Therapeutic Chemical [ATC]-code: N05B)); the PRs were 20 (95% CI: 18-22) in males and 17 (16-18) in females (Figure S5). Among drugs for other conditions, a higher prevalence was seen for drugs used for gastric acid disorders, anaemia, steroid responsive conditions, pain, sex hormones and modulators of the genital system (females) and urologicals (males) in the CRC-survivors (Figure S6).

3.2 | Ten years after CRC-diagnosis

Ten years after CRC-diagnosis, the prevalence of drugs used for CVDs overall remained high in CRC-survivors, reflecting mainly use of drugs for thromboembolism, whilst the prevalence of drugs used for coronary heart disease was still lower than in the cancer-free population. The overall prevalence of drugs for diseases of the nervous system was higher in CRC-survivors compared to the cancer-free population, driven by drugs for epilepsy. The PRs were increased for drugs for mental and behavioural disorders in general. The largest relative increase was seen in drugs for anxiety and tension (PR = 5.0 (3.1-7.9) in males and 2.0 (1.0-3.8) in females).

In the drug group for other diseases/conditions, high PRs were seen for drugs used for gastric acid disorders, anaemia, steroid responsive conditions, pain and urologicals (males).

3.3 | Sex-differences

The total prevalence of drugs was about equal in males and females (Table S2). However, there were some differences for particular drugs. The prevalence of drugs used for cardiovascular diseases was lower in females than in males, whereas the prevalence of drugs used for hypothyroidism, psychotic illness, depression, osteoporosis/Paget disease and pain was higher in females. The PRs for drugs used for pain were higher in males than in females.

Sex hormones and modulators of the genital system were more often used by female CRC-survivors, especially females with rectal cancer (Table S3), than females in the cancer-free population. In male CRC-survivors, the prevalence of sex hormones and modulators of the genital system was increased 2 to 8 years after diagnosis (Figure S6). The PRs of use of urologicals were elevated in male CRC-survivors until at least 10 years after diagnosis (Figure S6).

3.4 | Localised vs non-localised cancer

The difference between survivors with localised and non-localised CRC was especially large during the first 5 years after diagnosis. The PRs of drugs used for anxiety and tension, and for pain (Figure S7, Table S4) were higher for survivors of non-localised than localised CRC. In females, the PRs were also higher for sex hormones in individuals with non-localised CRC.

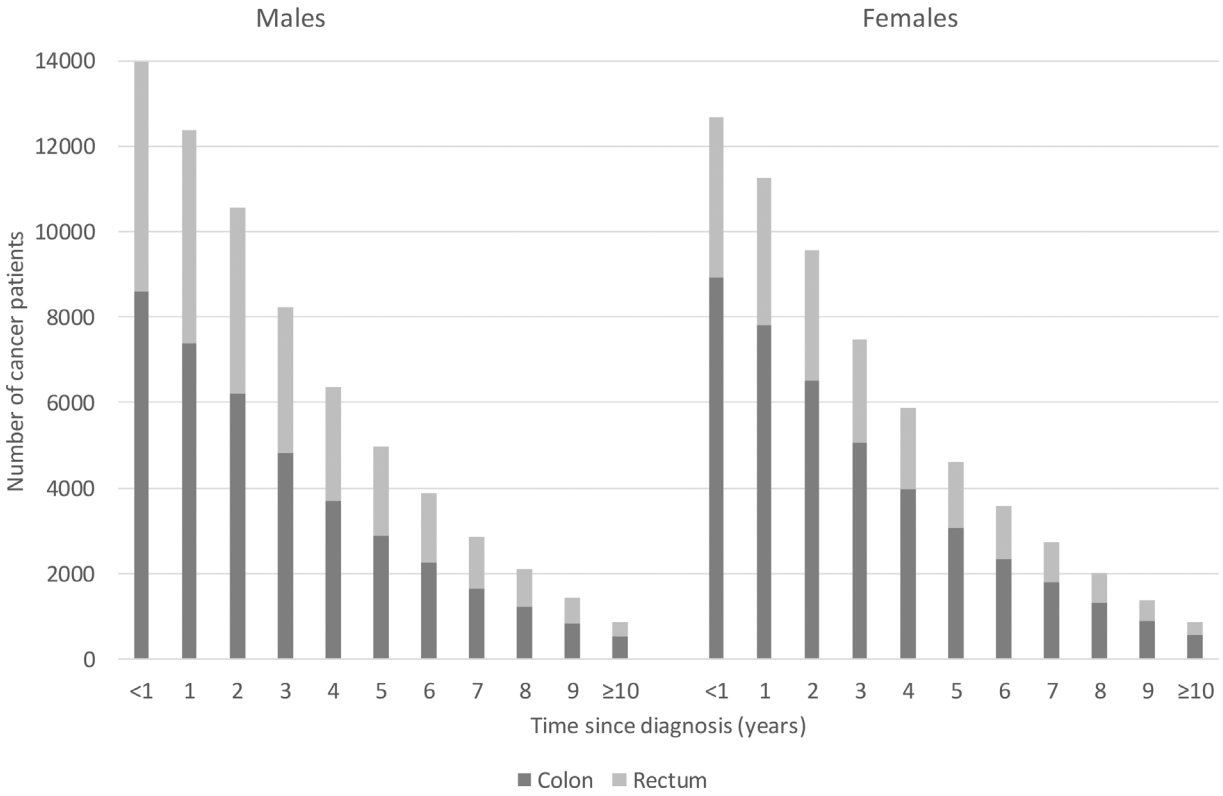

FIGURE 2 Colon and rectal cancer patients under observation by time since diagnosis, Norway 2005 to 2016

PRs were higher for drugs used for anxiety and tension in individuals with localised rectal than localised colon cancer.

4 | DISCUSSION

In this nationwide cohort study, we examined the use of drugs, as a proxy for chronic diseases, in survivors of CRC up to 12 years after diagnosis. The prevalence of many drugs was elevated in CRC-survivors the first year after diagnosis. Ten years after diagnosis, the prevalence was still elevated.

4.1 | Comparisons with other studies

A literature review in 2013 by Mitchell et al concluded that anxiety may be a problem in long-term cancer-survivors.[18] This accords with our results, which show an elevated prevalence of drugs used for anxiety and tension more than 10 years after the CRC-diagnosis, especially in males.

In a Danish study, Kjaer et al focused on risk of incident hospitalisation for somatic diseases in cancer-survivors diagnosed at age 40 years or above.[19] Colon cancer-survivors had an increased risk of hospitalisation in most of the diagnostic groups considered. Instead of hospitalisation, we focused on the prevalence of drugs dispensed outside institutions by time since diagnosis. Both studies, however, used population-based registries. Kjaer et al observed that cancer patients had higher risk of a range of somatic diseases requiring hospitalisation compared to the cancer-free population. In the first 5 years after diagnosis, colon cancer patients had an increased risk of hospitalisation due to diseases of the digestive system. We found a higher prevalence of drugs used for gastric acid disorders in CRC-survivors compared to the cancer-free population, even more than 10 years after diagnosis. Colon cancer patients had a higher prevalence than rectal cancer patients.

Fredheim et al compared the prevalence of analgesics and benzodiazepines in individuals with cancer 10 years after diagnosis with the prevalence in the cancer-free population, in a cross-sectional study from 2019, using the same data linkage as used in our study.[20] They found that cancer patients in general had a moderately higher prevalence of analgesics use 10 years after diagnosis, while in individuals diagnosed with cancers of the lower gastrointestinal tract (here CRC) the use was more similar to the cancer-free population. In our study, we observed an increase both in drugs used for anxiety and tension (including benzodiazepines) and pain (including analgesics) in CRC-survivors compared to the cancer-free population.

In 2019, Hawkins et al found an increased risk of endocrine/metabolic disorders in CRC-survivors.[21] Unfortunately, we did not have BMI-measurements in our data. However, we observed an increased prevalence of drugs used for diabetes mellitus (indicated by prescription of anti-diabetics [ATC: A10]) in CRC-survivors compared to the cancer-free population many years after diagnosis.

Sexual dysfunction and urinary incontinence are common among CRC-survivors.[7,8] According to a review by Panjari et al (2012),[22]

TABLE 3 One year prevalence (%) of different groups of drugs (dispensed and reimbursed) in the cancer-free Norwegian population during 2005 to 2016, in addition to the prevalence in colorectal cancer (CRC) patients (at diagnosis[a] and the fifth year after CRC-diagnosis, both for patients with localised and non-localised disease)

	Males					Females				
		CRC					CRC			
			Five years after diagnosis					Five years after diagnosis		
Disease/condition	Cancer-free	One year before diagnosis	Alla	Localised	Non-localised	Cancer-free	One year before diagnosis	Alla	Localised	Non-localised
Cardiovascular diseases (CVDs)	**23.0**	**24.8**	**27.1**	**26.5**	**27.6**	**20.5**	**21.7**	**24.6**	**22.9**	**25.3**
Cardiac arrhythmias	0.9	1.2	1.3	3.5	0.8	0.4	0.6	0.3	0.3	0.3
Coronary heart disease	2.0	2.1	1.5	1.8	1.3	1.2	1.3	1.0	1.3	0.9
Ischemic heart disease/ hypertension	21.7	23.4	24.9	24.5	25.3	19.3	20.8	20.6	20.8	20.6
Congestive heart failure	3.9	4.5	4.0	3.5	4.2	4.9	6.2	5.5	4.3	6.1
Thromboembolism	5.0	5.2	7.2	7.7	7.1	2.9	2.8	8.1	4.6	9.4
Endocrine, nutritional, and metabolic diseases	**17.8**	**17.8**	**17.7**	**16.4**	**18.1**	**18.7**	**19.5**	**21.3**	**28.4**	**19.7**
Diabetes mellitus	4.8	5.3	5.9	4.4	6.5	3.3	3.8	3.4	2.3	3.9
Hyperlipidaemia	14.8	14.5	13.8	13.6	13.8	11.3	11.8	13.4	14.4	12.8
Hypothyroidism	1.6	1.7	1.6	1.5	1.6	7.9	7.8	9.9	15.7	8.8
Diseases of the nervous system	**2.2**	**2.5**	**5.7**	**3.1**	**6.3**	**2.6**	**2.7**	**4.7**	**2.9**	**5.5**
Epilepsy	1.9	2.3	5.4	2.5	6.1	2.3	2.5	4.4	2.7	5.2
Parkinson disease	0.4	0.3	0.3	0.6	0.3	0.3	0.3	0.2	0.2	0.3
Mental and behavioural disorders	**6.7**	**6.6**	**9.4**	**7.6**	**10.0**	**11.2**	**10.4**	**12.3**	**10.3**	**13.5**
Psychotic illness	2.0	2.3	1.2	1.0	1.4	2.3	1.9	2.4	1.2	3.0
Anxiety and tension	0.3	0.3	2.7	0.8	3.2	0.5	0.5	3.4	1.1	4.3
Depression	5.3	5.4	6.8	6.4	7.0	9.8	9.3	9.2	9.7	9.3
Other diseases/ conditions	**19.6**	**19.2**	**31.2**	**35.7**	**28.1**	**26.2**	**25.2**	**33.6**	**32.3**	**35.0**
Gastric acid disorders	6.4	6.4	11.7	12.1	11.6	6.4	5.7	10.5	10.6	10.7
Anaemia	1.6	1.6	5.1	6.7	3.6	2.9	2.9	4.7	3.2	5.4
Steroid-responsive conditions	2.6	3.5	6.5	7.6	5.3	3.4	4.3	6.3	4.3	7.3
Osteoporosis/Paget disease	0.3	0.4	0.5	0.5	0.5	2.1	2.1	2.5	2.6	2.5
Pain	5.2	4.0	12.1	13.2	11.0	11.1	8.9	14.6	12.7	15.9
Chronic obstructive pulmonary disease (COPD)	6.4	6.6	5.9	7.6	5.7	8.5	8.4	7.4	8.2	7.2
Sex hormones and modulators of the genital system	0.2	0.1	1.1	0.5	1.2	0.3	0.5	4.2	4.4	4.3
Urologicals	2.6	1.9	3.6	4.2	3.4	1.6	1.4	2.4	2.1	2.6
At least one above (%)	**41.4**	**42.7**	**52.3**	**56.0**	**49.2**	**47.3**	**47.8**	**54.0**	**56.0**	**54.9**
At least two above (%)	**23.5**	**24.4**	**31.3**	**29.8**	**31.1**	**26.2**	**26.7**	**32.3**	**30.8**	**33.3**
Mean number	**0.9**	**0.9**	**1.2**	**1.2**	**1.2**	**1.0**	**1.0**	**1.3**	**1.3**	**1.4**

Note: The prevalence is age-standardised according to the Scandinavian standard population for ages 30 to 84 years.[17]

[a]The prevalence of a specific drug for all CRC-survivors is mostly between the prevalence in survivors in the groups having localised and non-localised disease. However, in some cases the prevalence in CRC-survivors in total is not between the prevalence in individuals with localised and non-localised disease due to different survival in patients with localised, non-localised and unknown stage of disease.

female rectal cancer patients have sexual function problems. In our study, the prevalence of sex hormones and modulators of the genital system was higher in female rectal cancer patients than in the cancer-free population, and higher PRs were seen in female than in male rectal patients. The prevalence of urologicals was more common in male CRC-survivors compared to the cancer-free male population.

In a large British population-based cohort study published in 2019, Strongman et al found that survivors of most site-specific cancers had increased risk of one or more CVD outcomes.[6] They used data from primary care and hospitals to look at the risk of getting various diseases, whereas we explored the prevalence of diseases measured by drug use. For CRC-patients, Strongman et al found an increased risk of venous thromboembolism and of pericarditis even 10 years after diagnosis. In our study, including almost twice as many CRC-survivors, the prevalence of drugs used for thromboembolism was still elevated more than 10 years after diagnosis. In patients with cancer and venous thromboembolism, lifelong treatment is often considered, explaining some of the elevated prevalence of drugs for thromboembolism many years after diagnosis.[23]

Oxaliplatin is a central chemotherapeutic drug in the treatment of CRC but is rarely recommended to patients above 75 years of age, and recently also rarely above 70. One of its dominating side effects (peripheral neuropathy) is caused by neurotoxic effects on the peripheral sensory nervous system. This chemotherapy-induced peripheral neuropathy reveals symptoms of paresthesia and dysesthesia, neuropathic pain, and numbness.[24] These symptoms usually decline with time, but the duration of symptoms has varied between studies.[25] A recent study has shown that up to a quarter of patients suffered chemotherapy-induced peripheral neuropathy 5 years after the end of chemotherapy.[26] Neuromodulatory drugs such as antiepileptics like carbamazepine, gabapentin, and pregabalin have demonstrated some activity in the prophylaxis and treatment of oxaliplatin-induced acute neuropathy. In our study, the majority of patients (87%) using neuromodulatory drugs were not combining these with other strong analgesics, indicating that the majority of the CRC-survivors were not using antiepileptics for pain caused by the cancer itself. These observations, together with the fact that the increased prevalence of drugs for diseases of the nervous system in CRC-survivors compared to the cancer-free population persisted up to 10 years after diagnosis, may indicate persistent neuropathy.

4.2 | Study strengths and limitations

The health care system in Norway covers the entire population, independently of socioeconomic status. In 2016, reimbursed drugs constituted 87% (measured in DDDs) of all prescribed drugs and included in the NorPD.[27]

Even though we know when the drugs were dispensed and to whom, we do not know when or whether the dispensed drugs were actually used. However, the fact that the drugs were dispensed with reimbursement indicates an underlying chronic disease. As we were using drug dispensing as a proxy for chronic diseases, it was irrelevant whether the drugs were taken or not.

We used population-based registries to explore the prevalence of drug use in all individuals diagnosed with CRC in Norway (2005-2014) prospectively up to 12 years after diagnosis. Reporting to the nationwide registries is mandatory. The completeness and quality of the NorPD and CRN are high,[10,12] and only 1.5% of the study population emigrated during follow-up. Hence, this study includes an unselected group of CRC-patients.

The drugs examined in this study might have been dispensed for diseases other than those investigated here, or for a combination of diseases. These drugs may also have been used to prevent certain conditions (ie, prophylactic treatment preoperatively with heparin [LMWH]), or when immobilised or together with chemotherapy.

We had no information on specific cancer treatment for the CRC-survivors and were thus unable to link adverse health effects to specific treatments. The main aim of our study was, however, to explore the prevalence of prescribed drugs, as a proxy for chronic diseases, in survivors of adult-onset CRC, rather than to examine the complicated associations between treatment and later health effects. The impact of different treatments on later health problems must be thoroughly explored in other studies.

Another limitation is the lack of information on possible confounders such as diet, smoking and alcohol consumption. However, we used information on education as an indicator of socioeconomic status. Information on cancer incidence was not available after 2014. Hence, among those regarded as 'cancer-free' after 2014, some individuals were diagnosed with cancer (estimates from current material indicate that about 1.5% of those at risk on January 1st, 2015 would have been diagnosed with cancer during 2015-2016). If the lack of information on cancer diagnoses had any impact on the study results, it would only influence the PRs in the first 2 years after diagnosis.

Many of the above-mentioned studies examined incidence of different diseases and hospital admissions, while we examined the prevalence of drug use. The studies are thus not directly comparable. Our study may detect milder cases, not leading to hospital visits. However, since NorPD does not contain medications dispensed at hospitals on an individual level, we may underestimate the total disease burden in the population. Data from the Norwegian Patient Registry could have been used for validating of the NorPD data. However, such a validation was beyond the aim of the present study.

In this study, we estimated the prevalence of drug use a specific year for distinct drugs, disregarding whether the individuals had used the drugs previously. Since only about 70% of the individuals diagnosed with CRC survive 5 years after diagnosis, this group of CRC patients differ from the total group diagnosed with CRC, not only by being 5 years older, but also because a larger proportion of those with advanced stage of cancer at diagnosis have died.

We explored the prevalence of 'use' of several specific drugs in the CRC patients, and the large number of tests were considered

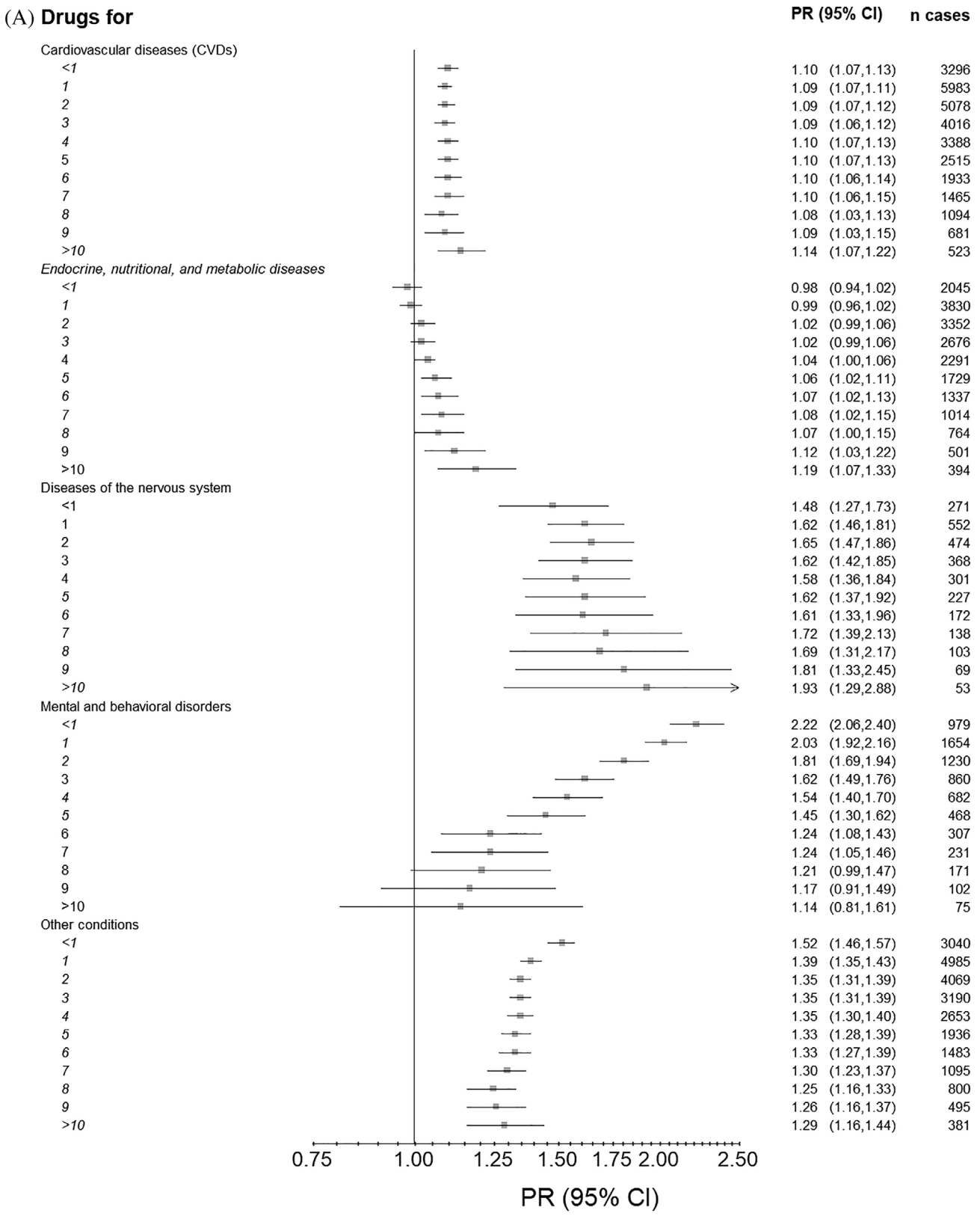

FIGURE 3 Prevalence ratios* (PRs) for reimbursed drugs in the five main groups** in patients with colorectal cancer compared to the cancer-free population by time since diagnosis, Norway 2005 to 2016. A, Males; B, Females. *Estimated by log-binomial regression, adjusted for age and education. **Main groups: 1. Cardiovascular diseases (CVDs) (Cardiac arrhythmias, Coronary heart disease, Ischemic heart disease/hypertension, Congestive heart failure, Thromboembolism). 2. Endocrine, nutritional, and metabolic diseases (Diabetes mellitus, Hyperlipidaemia, Hypothyroidism). 3. Diseases of the nervous system (Epilepsy, Parkinson disease). 4. Mental and behavioural disorders (Psychotic illness, Anxiety and tension, Depression). 5. Other conditions (Gastric acid disorders, Anaemia, Steroid-responsive conditions, Osteoporosis/Paget disease, Pain, Chronic obstructive pulmonary disease [COPD], Sex hormones and modulators of the genital system, Urologicals)

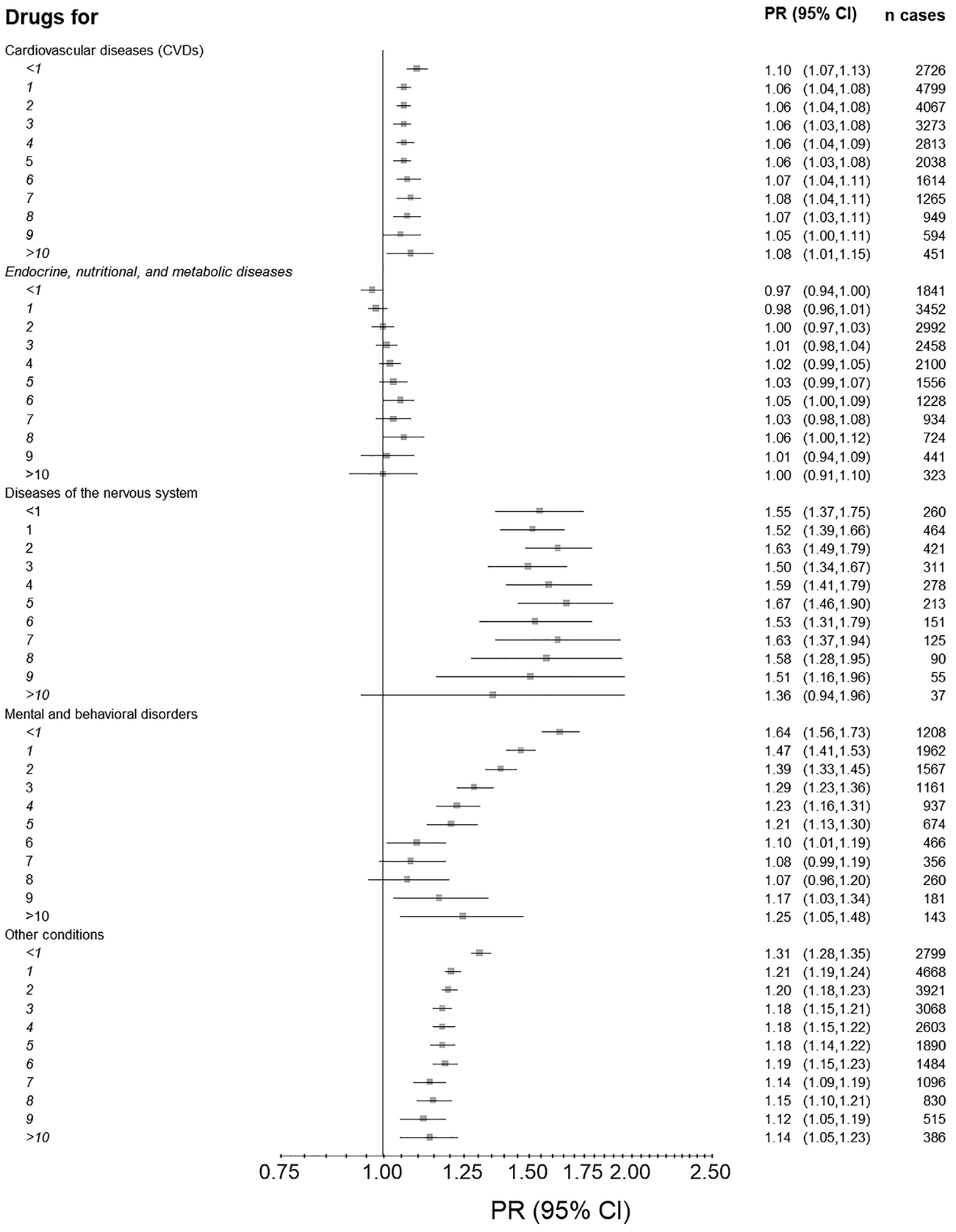

FIGURE 3 (Continued)

while interpreting the results. Due to the huge size of the dataset, the power was large resulting in narrow confidence intervals. Hence, we also considered the absolute level of the drug use.

In conclusion, the prevalence of different drugs was higher in CRC-survivors than in the cancer-free population, especially drugs used for anxiety and tension, and for steroid-responsive conditions. The absolute excess in prevalence was especially large for drugs used for gastric acid disorders and for pain, even a decade after CRC-diagnosis. The prevalence of neuromodulatory drugs such as gabapentin and pregabalin, was higher in the CRC-survivors than in the cancer-free population, indicating long persisting neuropathia. Altogether, our results emphasise the necessity of special monitoring of CRC-survivors.

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CONFLICT OF INTEREST

The authors have no conflicts of interest and no financial relationships relevant to this article to disclose.

ETHICS STATEMENT

The study was approved by the Regional Committee for Medical and Health Research Ethics (REC South East; no. 2010/131).

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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