Risk of colorectal cancer following CT-verified acute diverticulitis: a nationwide population-based cohort study

N. Azhar*†, P. Buchwald*†, H. Z. Ansari‡, T. Schyman§, S. Yaqub¶, T. Øresland‡++ and J. K. Schultz‡

*Colorectal Unit, Department of Surgery, Skåne University Hospital, Malmö, Sweden, †Department of Clinical Sciences, Lund University, Malmö, Sweden, ‡Department of Digestive Surgery, Akershus University Hospital, Lørenskog, Norway, §Clinical Studies Sweden, Forum South, Skåne University Hospital, Lund, Sweden, ¶Department of Gastrointestinal Surgery, Oslo University Hospital, Oslo, Norway, and ++Faculty of Medicine, University of Oslo, Oslo, Norway

Received 27 October 2019; accepted 11 March 2020; Accepted Article online 16 April 2020

Abstract

Aim Routine colonoscopy to exclude colorectal cancer (CRC) after CT-verified acute diverticulitis is controversial. This study aimed to compare the incidence of CRC in patients with acute diverticulitis with that in the general population.

Method Patients with an emergency admission for diverticular disease to any Norwegian hospital between 1 January 2008 and 31 December 2010 were included through identification in the Norwegian Patient Registry using International Classification of Diseases (ICD-10) codes K57.1-9. To estimate the age-specific distribution of CT-verified acute uncomplicated diverticulitis (AUD) and acute complicated diverticulitis (ACD) in this nationwide study population, numbers from the largest Norwegian emergency hospital were used. Patients diagnosed with CRC within 1 year following their admission for acute diverticulitis were detected through cross-matching with the Cancer Registry of Norway. Based on both Norwegian age-specific incidence of CRC and estimated age-specific distribution of CT-verified diverticulitis, standard morbidity ratios (SMRs) were calculated.

Results A total of 7473 patients with emergency admissions for diverticular disease were identified (estimated CT-verified AUD $n = 3523$, ACD $n = 1206$); of these 155 patients were diagnosed with CRC within 1 year. Eighty had a CT-verified diverticulitis at index admission [41 AUD (51.3%); 39 ACD (49.7%)]. Compared with the general population, the SMR was 6.6 following CT-verified AUD and 16.3 following ACD, respectively.

Conclusion In the first year after CT-verified acute diverticulitis, especially after ACD, the risk of CRC is higher than in the general population. This probably represents misdiagnosis of CRC as acute diverticulitis. Follow-up colonoscopy should be recommended to all patients admitted with acute diverticulitis.

Keywords Colorectal cancer, acute diverticulitis, colonoscopy

What does this paper add to the literature? This paper shows that there is an increased risk of colorectal cancer within a year after diagnosis of CT-verified acute diverticulitis. This finding is probably due to misdiagnosis in both complicated and uncomplicated cases of diverticulitis. Examination of the colon should therefore still be recommended after an episode of acute diverticulitis.

Introduction

Several studies have shown an increasing incidence of diverticular disease in Western countries throughout the last century [1–3]. Approximately 30% of the population over 50 years and more than 65% above 70 years have diverticula in the colon [1–3]. It is believed that 4–15% of individuals with diverticulosis experience at least one episode of diverticulitis, the majority being acute uncomplicated diverticulitis (AUD) [1,2,4,5]. The accuracy of the clinical diagnosis is quite poor [6] and several cases have been described in which colorectal cancer (CRC) or advanced adenoma have been misdiagnosed as AUD [7]. Therefore, routine follow-up has been colonic examination of all patients a few weeks after the episode of suspected acute diverticulitis, either by colonoscopy or by CT-colonography [8].
A large nationwide Swedish case–control study found that patients hospitalized with diverticular disease had an increased risk of CRC in the first year after the admission compared with the background population, whereas in the following years the risk was equal [9]. That study was limited by the lack of differentiation of diverticular disease between AUD, acute complicated diverticulitis (ACD) or diverticular bleeding, and the uncertainty as to whether the diagnosis was based on clinical or radiological examination. Contrast-enhanced abdominal CT has become a regular supplement to clinical diagnosis in the work-up of left lower quadrant pain [2,8]. In Scandinavian institutions, most patients with a first episode of suspected acute diverticulitis are now investigated with an abdominal CT scan, and current practice is to perform a colonic examination a few weeks after the admission for acute diverticulitis.

Recently, several publications have challenged this practice for patients with a CT-verified episode of AUD [10–16]. In the two most recent meta-analyses, the prevalence of CRC was calculated to be 0.5% [17] or 1.3% [18] due to the inclusion of different studies. Whereas the first study [18] compared this prevalence only with screening populations (0.4–1%), the other study [17] compared it with screening populations (0.78%) and the age-adjusted incidence rate (0.046% according to SEER). These meta-analyses came to opposite conclusions concerning the usefulness of colonoscopy after CT-verified uncomplicated diverticulitis.

Routine examination of the colon is still recommended in most countries [8,19–21], although the latest Dutch guidelines have omitted this practice for asymptomatic patients after CT-verified AUD [22]. In Norway, the common practice has been to schedule a colon examination 6–8 weeks after discharge.

Colonoscopy and CT-colonography have small but not negligible risks of complication, may cause distress to the patient and are burdens on health economics. If the prevalence of misdiagnosed CRC in patients with CT-verified acute diverticulitis is similar to that in the general population, many patients might be spared an unpleasant and potentially hazardous colon examination. Since misdiagnosis of CRC after acute diverticulitis seems rare [10–12,23,24], a prospective trial addressing this issue would be difficult to pursue.

The aim of the present study was to compare the age-adjusted 1-year incidence of CRC in a large cohort of patients with CT-verified acute diverticulitis with that in the general population. The hypothesis was that CT diagnosis of acute diverticulitis has improved so much that misdiagnosis of CRC in patients with suspected acute diverticulitis has become rare.

Method

The study linked data between the Norwegian Patient Registry (NPR) and the Cancer Registry of Norway. The Cancer Registry of Norway records detailed information on every cancer diagnosed in Norway, including tumour location and morphology, and demographic information (including emigration status), retrieved from several sources (clinical and pathological reports, data from radiotherapy and death certificates). Since 2007 the NPR has recorded data for all patients treated at Norwegian hospitals and diagnoses are coded using the International Classification of Diseases, 10th revision (ICD-10).

All patients with an emergency admission to a Norwegian hospital between 1 January 2008 and 31 December 2010, discharged with a main diagnosis of diverticular disease (ICD code K57.1–9), were identified in the NPR and included in the study cohort. All included patients subsequently diagnosed with CRC within a year of the admission for diverticular disease were detected through cross-matching with the Cancer Registry of Norway. The medical charts of all patients with a CRC diagnosis within a year of a admission for diverticular disease were collected and reviewed (by HZA, NA, JKS). Patients without CT-verified acute diverticulitis at index admission and patients with suspicion of CRC or an additional finding on index CT leading to colon examination were excluded from further analysis. A 3-year period was chosen to reduce the risk of the incidence being skewed for one particular year.

To estimate the age-specific distribution of complicated and uncomplicated diverticulitis in the study population, and to assess the number of patients with a CT-verified episode of diverticulitis (population of interest), data from a consecutive series at Akershus University Hospital, investigating the in-hospital patients with acute diverticulitis for the study period, was used. During this period Akershus University Hospital covered approximately 7% of the Norwegian population. This was assumed a fair estimate, mirroring the rest of the country with regard to both incidence of diverticular disease and the use of diagnostic CT examination. To validate the completeness of the NPR a text search for the word ‘diverticulitis’ in all abdominal CT and discharge reports at Akershus University Hospital was conducted. The incidence of CRC in the Norwegian population between 2008 and 2010 was extracted from the Cancer Registry of Norway [25]. Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidance for reporting of observational studies was followed.
Statistical analysis
To investigate if CRC was more common among patients with acute diverticulitis than in the general population, the standardized morbidity ratio (SMR) was calculated, including the 95% confidence interval (CI) [26]. The SMR is the ratio between the actual number of CRC cases among patients with acute diverticulitis and the expected number of CRC cases among patients with acute diverticulitis, assuming the same incidence as in the Norwegian population, with standardization being done for age and sex. The expected number of CRC cases in patients with acute diverticulitis was calculated as the number of patients with acute diverticulitis in Norway multiplied by the proportion of people having CRC in the Norwegian population (Appendix S2 in the online Supporting Information). The actual number of patients with CT-verified acute diverticulitis was extrapolated from the number of CT-verified AUD and ACD among patients admitted with diverticular disease at Akershus University Hospital (Appendix S2). A SMR above 1 indicates a higher incidence of CRC in acute diverticulitis patients compared with the Norwegian population. SMRs were calculated for various age groups (20–39, 40–59, 60–79 and 80+ years) and an overall SMR was calculated by summarizing numbers for acute diverticulitis patients, person-years at risk, actual cases and expected cases from age groups. Statistical calculations were made using SAS 9.4 (SAS Institute Inc., Cary, North Carolina, USA).

Ethical considerations
This study has been approved by the Regional Ethics Committee South East Norway (no. 2011/2190).

Results
During a 3-year-period (2008–2010), 7473 patients had an emergency admission to Norwegian hospitals with any ICD-code for diverticular disease. By cross-matching the data with the Cancer Registry of Norway, 155 patients were identified who had been diagnosed with CRC within 1 year of an admission for diverticular disease. Five patient files could not be retrieved, despite several attempts. The review of the remaining 150 medical charts revealed 115 patients with CT-verified acute diverticulitis; of these 80 had acute diverticulitis without radiological suspicion of CRC or other colon pathology, 41 (51.3%) with AUD and 39 (49.3%) with ACD (Fig. 1). Mean age and the sex ratio were similar in both groups (Table 1). A previous episode of diverticulitis was more common in the AUD group. After both AUD and ACD, tumours were most commonly located in the rectosigmoid/sigmoid colon [33 (80.5%) and 30 (76.9%), respectively] (Table 1). Persistent symptoms were described in 40 (50.0%) and this information was missing in 32 (40.0%) patients. The tumour was located in the same colonic segment as the diverticulitis in 66 (82.5%) patients, most frequently in the sigmoid colon [31 (93.9%) following AUD], and for all of the ACD patients (n = 30). Three right-sided cancers were found in the AUD group, none of whom had right-sided diverticulitis. In the ACD group, two of the three patients with right-sided cancers had right-sided diverticulitis on CT. Sixty-two patients (67.5%) had a colonic examination after discharge, 34 (82.9%) in the AUD group and 20 (51.3%) in ACD group. For 10 patients this was not relevant as they had surgery during their admission and two patients were considered unfit for further investigation.

The review of patient charts at Akershus University Hospital during the study period revealed that 268 of 409 patients (65.5%) registered with an emergency admission with the primary diagnosis of diverticular disease (ICD-10 code K57) had CT-verified diverticulitis. Of these, 68 (25.4%) patients were diagnosed with ACD and 200 (74.6%) with AUD. The age distribution of patients with AUD and ACD is displayed in Appendix S1. The text search for the term ‘diverticulitis’ in CT and discharge reports revealed that all but one patient with a CT-verified diverticulitis during the study period were identified by the ICD-10 code K57.

During the study period, the extrapolated number of CT-verified cases of diverticulitis in the Norwegian population was 3523 for AUD and 1206 for ACD (Appendix S2). The SMR in the AUD group was 6.58 (95% CI 4.84–8.93) (Table 2) and 16.34 (95% CI 11.94–22.97) in the ACD group (Table 3). In both ACD and AUD, the highest SMR was observed in the youngest diverticulitis patients (40–59 years of age; Tables 2 and 3 and Fig. 2).

Discussion
Routine examination of the colon after an episode of diverticulitis, to rule out CRC at the same location, has long been standard in many countries. The present study demonstrates that the risk of being diagnosed with CRC after an episode of CT-verified acute diverticulitis is considerably higher than in the general population. The risk is highest after ACD, but also remarkably elevated after AUD. In the whole study population, 155 cancers were diagnosed within 1 year, making the incidence of CRC 2.0%, which is in line with previous studies (1.6–2.7%) [13,27–29]. This is the first study to
compare the age-specific incidence of CRC in patients diagnosed with acute diverticulitis with the age-specific incidence of CRC in the general population.

Previous studies have compared the prevalence of CRC among patients with diverticulitis with detection rates in screening studies with colonoscopy, and have been reported to be between 0.5% and 0.78% in meta-analyses [30,31]. Notably these detection rates only reflect the prevalence of undetected CRC in individuals participating in the colonoscopy screening program. Participation rates in screening programmes vary between 20% and 60% [31,32]. The detection rate of

**Figure 1** Study flowchart. CRC, Colorectal cancer; AUD, Acute uncomplicated diverticulitis; ACD Acute complicated diverticulitis; CT, Computed tomography## Patients admitted with ICD10-codes K57.1-K57.9## Estimates based on a cohort from Akershus University Hospital, see Supplement A. †† Crossmatch Norwegian Cancer Registry##All patients admitted to any Norwegian hospital 2008-2010 with diverticular disease were identified through ICD10-codes in the Norwegian Patient Registry. To estimate how many of those had a CT verified diverticulitis a cohort from the largest emergency hospital was used were 65.5% of patients registered with the ICD10-code K57 had a CT verified diverticulitis.
Table 1 Clinical characteristics of patients with cancer and CT-verified diverticulitis.

|                          | Total (n = 80) | AUD (n = 41) | ACD (n = 39) |
|--------------------------|---------------|--------------|--------------|
| Mean age, years (range)  | 71.9 (40–94)  | 72.0 (40–92) | 71.7 (47–94) |
| Female gender, n (%)     | 44 (55.0)     | 21 (51.2)    | 23 (59.0)    |
| Previous diverticulitis, n (%) | 12 (15.0) | 8 (19.5) | 4 (10.3) |
| Previous colonoscopy < 3 years, n (%) | 4 (5.0) | 2 (4.9) | 2 (5.1) |
| More than one admission, n (%) | 13 (16.3) | 7 (17.1) | 6 (15.4) |
| Persistent symptoms, n (%) | 40 (50.0) | 19 (46.3) | 21 (53.8) |
| Diverticulitis location, n (%) | 37 (90.2) | 34 (87.2) | 34 (87.2) |
| Sigmoid                  | 71 (88.8)     | 37 (90.2)    | 34 (87.2)    |
| Left colon               | 6 (7.5)       | 3 (7.3)      | 3 (7.7)      |
| Transverse colon         | 0 (0)         | 0 (0)        | 0 (0)        |
| Right colon              | 3 (3.8)       | 1 (2.4)      | 2 (5.1)      |
| Cancer location, n (%)   | 63 (78.8)     | 33 (80.5)    | 30 (76.9)    |
| Rectum                   | 7 (8.8)       | 2 (4.9)      | 5 (12.8)     |
| Rectosigmoid/sigmoid     | 3 (3.8)       | 3 (7.3)      | 0 (0)        |
| Transverse colon         | 1 (1.3)       | 0 (0)        | 1 (2.6)      |
| Right colon              | 6 (7.5)       | 3 (7.3)      | 3 (7.7)      |
| Colonic examination < 8 weeks from discharge | 32 (40.0) | 18 (43.9) | 14 (35.9) |
| Yes                      | 32 (40.0)     | 18 (43.9)    | 14 (35.9)    |
| > 8 weeks                | 22 (27.5)     | 16 (39.0)    | 6 (15.4)     |
| No                       | 14 (17.5)     | 4 (9.6)      | 10 (25.6)    |
| Not applicable           | 12 (15.0)     | 3 (7.3)      | 9 (23.1)     |
| Colonic examination as planned | 6 (10.1) | 1 (2.9) | 5 (25.0) |

ACD, acute complicated diverticulitis; AUD, acute uncomplicated diverticulitis.

*Patients who had emergency surgery during admission or were considered unfit for further investigation.

Table 2 Colorectal cancer standard morbidity ratio (SMR) after CT-verified acute uncomplicated diverticulitis.

| Age interval (years) | AUD Norway | Cases | Person-years at risk | Expected cases | Actual cases | SMR     |
|----------------------|------------|-------|----------------------|----------------|--------------|---------|
| 0–19                 | 0          | 5     | 3 694 133           | 0.00           | 0            | NA      |
| 20–39                | 243        | 155   | 3 833 950           | 0.01           | 0            | NA      |
| 40–59                | 1517       | 1752  | 3 889 549           | 0.68           | 8            | 11.71 (5.85;23.41) |
| 60–79                | 1391       | 6126  | 2 318 743           | 3.68           | 18           | 4.90 (3.09;7.77)  |
| 80+                  | 371        | 3307  | 658 247             | 1.87           | 15           | 8.04 (4.85;13.34) |
| Overall              | 3523       | 11 345| 14 394 622         | 6.23           | 41           | 6.58 (4.84;8.93)  |

SMR (actual cases/expected cases) regarding colorectal cancer in different age intervals comparing patients admitted to Norwegian hospitals in 2008–2010 with acute uncomplicated diverticulitis (AUD) diagnosed with colorectal cancer within 1 year of admission with the age-standardized incidence of colorectal cancer in the general Norwegian population.

NA, not applicable.

*Estimated number of K.57 patients with AUD in Norway 2008–2010: (AUD Akershus/K.57 Akershus) × K.57 Norway.
†New cases of colon cancer in Norway (sum of the years 2008–2010).
‡Person-years at risk in the Norwegian population 2008–2010.
§Expected cases of colon cancer among AUD patients: (cases/person-years) × AUD Norway.
¶Observed cases of colon cancer among AUD patients.
**Note that this is a sum of the numbers above and not calculated separately.
CRC in screening programmes is likely to be lower with 100% participation, as asymptomatic individuals are less likely to participate [31].

The risk of CRC in AUD patients in the present study was between five and eleven times higher in the younger age groups compared with that in the background population. However, the highest risk was found in patients with ACD – 11–20 times higher depending on the age group. This is in accordance with previous studies [13,33]. A recent meta-analysis on colonoscopy in patients after diverticulitis showed a similar risk for CRC as in screening populations, but their calculated risk for AUD patients was lower than in the present study [13]. Our findings are slightly surprising compared with those of previous studies [10–15,23,34,35], but consistent with the study by Meyers et al. [36] which showed a 44-fold higher risk of CRC after an episode of acute diverticulitis compared with the reference population. Since diverticulitis is not a risk factor for the development of CRC, the elevated risk can only be attributed to CRC being misdiagnosed as acute diverticulitis [37]. This is strengthened by the fact that the majority of patients were diagnosed with CRC at the same location as the previous diverticulitis, mainly in the sigmoid colon. Data from the Cancer Registry of Norway during the study period show almost equal numbers of rectal cancers, right-sided colon cancers and left-sided colon cancers in the Norwegian population. The fact that only very few rectal and right-sided tumours were found in this cohort further supports our findings (Appendix S3).

There are several limitations to this study which warrant further comment. The study was an observational retrospective cohort study and the data were nonrandomized. The data can only be as reliable as the registries. The high validity of the Cancer Registry of Norway has been shown [38], while the NPR has yet to be validated. However, the data from the prospective cohort, and from the text search at Akershus University Hospital, showed high validity of the NPR data.

During the study period (2008–2010), 65.5% of patients with diverticular disease (K57) admitted to Akershus University Hospital had CT-verified acute diverticulitis. The estimate of CT-verified AUD and ACD in the whole population was based on these numbers, which account for 7% of the Norwegian population. The uncertainty about these estimates involves a risk for proportion skewness. It is possible that the

Table 3 Colorectal cancer standard morbidity ratio (SMR) after CT-verified acute complicated diverticulitis (ACD).

| Age interval | ACD Norway† | Cases‡ | Person-years at risk§ | Expected cases¶ | Acutal cases** | SMR |
|--------------|-------------|--------|-----------------------|-----------------|---------------|-----|
| 0–19         | 0           | 5      | 3 694 133             | 0.00            | 0             | N.A.|
| 20–39        | 70          | 155    | 3 833 950             | 0.00            | 0             | N.A.|
| 40–59        | 434         | 1752   | 3889549               | 0.20            | 4             | 25.61 (10.66; 61.52) |
| 60–79        | 563         | 6126   | 2 318 743             | 1.49            | 27            | 18.14 (12.44; 26.45) |
| 80+          | 139         | 3307   | 658 247               | 0.70            | 8             | 10.00 (4.77; 20.99) |
| Overall††    | 1206        | 11 345 | 14 394 622            | 2.39            | 39            | 16.34 (11.94; 22.37) |

SMR, Standard Morbidity Ratio (Actual cases/Expected cases).
†Estimated number of K.57 patients with ACD in Norway 2008-201: (AUD Ahus/K.57 Ahus)*K.57 Norway.
‡New cases of colon cancer in Norway (sum of the years 2008–2010).
§Person-years at risk in the Norwegian population 2008–2010.
¶Expected cases of colon cancer among ACD patients: (Cases/Person-years)*ACD Norway.
**Observed cases of colon cancer among ACD patients.
††Note that this is a sum of the numbers above and not calculated separately.

Figure 2 Standard morbidity ratio (SMR) graph. Risk for colorectal cancer expressed as SMR following acute diverticulitis compared with the general population (dashed line). Graphs show SMR for different age groups and overall mean (95% CI).
proportion of CT-verified diverticulitis in diverticular disease patients was different in the rest of Norway. However, all cancer cases included were CT-verified according to the medical records, and the only uncertainty lies in the estimated denominator. We calculated that 1.2% (41 of 3523) of AUD patients and 3.2% (39 of 1206) ACD patients were diagnosed with CRC (Fig. 1). If in reality the number of patients with CT-verified diverticulitis was lower than estimated (<3523 for AUD or <1206 for ACD) the proportions would be higher than 1.2% and 3.2%, respectively. Only if we underestimated the number CT-verified AUD and ACD cases in the whole population would the proportion be lower. In the unlikely event that 4100 of 7473 patients diagnosed with K.57 had a CT-verified AUD, the proportion of CRC after AUD would still be 1% (41/4100), thus considerably higher than the annual incidence of CRC in the general population. Furthermore, the use of CT for diagnosis of acute diverticulitis has increased, as CT is now recommended in most modern guidelines [39].

In the AUD group there were three right-sided cancers, but none of these patients had right-sided diverticulitis and this might contribute to the elevation of CRC risk in the AUD group.

It has been suggested that individuals who are symptom-free after AUD can have follow-up colonoscopy omitted [18]. This study shows an elevated risk of CRC after an episode of AUD compared with the general population. One may argue that many of the included patients might have been diagnosed due to ongoing symptoms in any case. Ongoing symptoms were unfortunately unknown to a large extent in this cohort (40%), but other studies have shown persisting symptoms in up to 50% of AUD patients without cancer [40,41]; thus this may not be a useful discriminating characteristic. In this study, the majority of patients (67.5%) were diagnosed with CRC by a colonic examination. In 97.1% of AUD patients, a colonic examination was planned at discharge, consequently these CRCs may have remained undetected.

This study is an attempt to examine the ‘true’ age-specific risk of misdiagnosing CRC as acute diverticulitis, by comparing the incidence of CRC in patients with CT-verified acute diverticulitis with that in the general population in Norway using accurate cancer registry data. In addition, the retrieval of patient charts was achieved from nearly all Norwegian patients diagnosed with CRC within 1 year after an episode of diverticulitis, which makes the data for these patients very reliable. Furthermore, these data are likely to be generalizable to other Western populations, where incidences of CRC and diverticulitis are similar to those found in Norway.

However, although the study gives a good estimate of the incidence of CRC in patients with CT-verified diverticulitis, it does not answer the question of what the effect of omitting routine colonoscopy in these patients would be. Only a prospective randomized trial would be able to fully estimate the risk of missing a curable cancer when omitting colonoscopy.

Conclusion

Compared with the general population, a CRC diagnosis is far more frequent in the first year after an episode of CT-verified acute diverticulitis. Although the highest risk was observed in the ACD group, the increased risk in the AUD group cannot be neglected. This study indicates that abdominal CT in the acute setting does not prevent misdiagnosis of CRC and cannot replace routine follow-up colonic examination, particularly in younger patients (40–59 years) and ACD patients. The continued practice of follow-up colonoscopy is therefore recommended for all patients with acute diverticulitis. Further studies using better diagnostic tools and risk stratification are to be encouraged.

Conflicts of interest

None declared.

Funding

The study was funded by the South-Eastern Norway Regional Health Authority (PNR 2719011) and with research funding from Akershus University Hospital, which covered running expenses (PNR 265956). Accepted Article online 16 April 2020

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**Supporting Information**

Additional Supporting Information may be found in the online version of this article:

- **Appendix S1.** Age distribution of CT-verified acute uncomplicated diverticulitis at Akershus Hospital between 2008 and 2010.
- **Appendix S2.** Summary of data used and analyses performed.
- **Appendix S3.** New colorectal cancer cases in Norway between 2008 and 2010 based on cancer location. Numbers were provided by the Norwegian Cancer Registry.