

# Survival of patients with colon and rectal cancer in central and northern Denmark, 1998–2009

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**Objective:** The prognosis for colon and rectal cancer has improved in Denmark over the past decades but is still poor compared with that in our neighboring countries. We conducted this population-based study to monitor recent trends in colon and rectal cancer survival in the central and northern regions of Denmark.

**Material and methods:** Using the Danish National Registry of Patients, we identified 9412 patients with an incident diagnosis of colon cancer and 5685 patients diagnosed with rectal cancer between 1998 and 2009. We determined survival, and used Cox proportional hazard regression analysis to compare mortality over time, adjusting for age and gender. Among surgically treated patients, we computed 30-day mortality and corresponding mortality rate ratios (MRRs).

**Results:** The annual numbers of colon and rectal cancer increased from 1998 through 2009. For colon cancer, 1-year survival improved from 65% to 70%, and 5-year survival improved from 37% to 43%. For rectal cancer, 1-year survival improved from 73% to 78%, and 5-year survival improved from 39% to 47%. Men aged 80+ showed most pronounced improvements. The 1- and 5-year adjusted MRRs decreased: for colon cancer 0.83 (95% confidence interval CI: 0.76–0.92) and 0.84 (95% CI: 0.78–0.90) respectively; for rectal cancer 0.79 (95% CI: 0.68–0.91) and 0.81 (95% CI: 0.73–0.89) respectively. The 30-day postoperative mortality after resection also declined over the study period. Compared with 1998–2000 the 30-day MRRs in 2007–2009 were 0.68 (95% CI: 0.53–0.87) for colon cancer and 0.59 (95% CI: 0.37–0.96) for rectal cancer.

**Conclusion:** The survival after colon and rectal cancer has improved in central and northern Denmark during the 1998–2009 period, as well as the 30-day postoperative mortality.

**Keywords:** neoplasms, survival, epidemiology, colorectal cancer

## Introduction

Colorectal cancer (CRC) is one of the most common malignancies in industrialized countries and one of the most common causes of cancer-related death.<sup>1,2</sup> In Denmark, approximately 4200 new cases of CRC are diagnosed each year,<sup>3</sup> with a 5-year survival of only 43%–49%.<sup>4,5</sup> Danish CRC survival is lower than in our neighboring counterparts and countries with similar health systems,<sup>6,7</sup> probably due to higher mortality in the first year after diagnosis.<sup>5,6,8</sup>

Similar to CRC, Denmark has lower survival for many other cancer sites.<sup>5,6,9</sup> Aiming to improve cancer control, the first National Cancer Plan was established in 2000.<sup>10</sup> The main topics were expansion of the diagnostic and nonsurgical treatment capacity, as well as establishment of multidisciplinary cancer groups and implementation of clinical databases in order to monitor quality of cancer treatment.

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In 2005, the second National Cancer Plan was launched<sup>11</sup> and concerned the reduction of diagnostic and treatment delays by organizing the cancer pathways, as well as strengthening the cancer surgery by centralization and in-service training. Although these different initiatives may have the potential of improving survival in CRC patients, no updated data on survival exist. We therefore conducted the present study to monitor survival and mortality in colon and rectal cancer patients using existing data from the central and northern Danish regions.

## Material and methods

We conducted this study in the central and northern Denmark regions with a combined population of 1.8 million persons. The National Health Service provides tax-supported health care for all inhabitants of Denmark, guaranteeing free access to general practitioners and hospitals.

### Identification of CRC patients

Through the Danish National Registry of Patients (DNRP), we identified all patients who had a first-time hospitalization with colon or rectal cancer between January 1, 1998 and December 31, 2009. The DNRP includes data on personal identification number, hospital, department, surgical and diagnostic procedures, and discharge diagnoses, as defined by the International Classification of Diseases 10th edition (ICD-10) by 1993.<sup>12</sup> The ICD-10 codes used to identify colonic cancer were C18–19 and rectal cancer C20–21.

### Survival

Since 1968, the Central Office of Civil Registration has assigned a unique 10-digit civil registration number to all Danish citizens,<sup>13</sup> which enables unambiguous data linkage between Danish registries. The Civil Registration System also contains information on vital status, date of death, and residence.

### Statistical analysis

We followed each patient from the date of colon or rectal cancer diagnosis until emigration, death, or June 25th 2010, whichever came first. To visualize crude survival we constructed Kaplan–Meier curves stratified according to periods of colon or rectal cancer diagnosis (1998–2000, 2001–2003, 2004–2006, and 2007–2009), estimating 1- and 5-year survival. In the latter periods we predicted 5-year survival using a hybrid analysis in which we included the

actual survival for as long as possible and then estimated the conditional probability of surviving thereafter based on the corresponding survival experience of patients in the previous period (ie, using a period analysis technique).<sup>14</sup> To compare mortality over time we used Cox proportional hazards regression analysis with 1998–2000 as a reference to estimate 1- and 5-year mortality rate ratios (MRRs) and the corresponding 95% confidence intervals (CIs) adjusting for age groups (15–64 years, 65–79 years, 80+ years) and gender. Additionally, analyses were stratified on age and gender. For the patients who underwent surgery, we likewise computed 30-day mortality rates for the four time periods. Surgery was defined as resection or first operative procedure, although the latter included resections if these were initially performed (see Appendix 1 for codes). First operative procedure also included defunctional procedures and/or definitive palliative procedures. Thus, a patient could enter both surgery groups in the case of an initial defunctional procedure and a resection hereafter. We used Cox proportional hazards regression analysis and estimated 30-day MRRs with 1998–2000 as a reference, adjusting for age and gender. Analyses were performed using SAS version 9.2 (SAS Institute Inc, Cary, NC).

## Results

### Colon cancer

A total of 9412 patients were diagnosed with colon cancer in the 1998–2009 period. The number of colon cancer patients increased from a total of 2097 in 1998–2000 to 2763 in 2007–2009 (Table 1), most pronounced among men (Table 2). At the same time median age at diagnosis declined from 73 years to 72 years. One-year overall survival improved from 65% to 70% over the study period, corresponding to an adjusted MRR of 0.83 (95% CI: 0.76–0.92) in 2007–2009 using 1998–2000 as a reference (Figure 1 and Table 1). Accordingly, the 5-year overall survival improved from 37% to predicted 43%, corresponding to a 5-year adjusted MRR of 0.84 (95% CI: 0.78–0.90) in 2007–2009 compared with 1998–2000. In general, in both genders and in all age groups the survival improved. Five-year survival improved particularly in men aged 15–64 and 80+ as well as in women aged 80+ (Table 2).

The 30-day postoperative mortality decreased during the study period; after resection from 9% in 1998–2000 to 7% in 2007–2009 (adjusted MRR 0.68 (95% CI: 0.53–0.87)) and after the first operative procedure from 11% to 8% (adjusted MRR 0.71 (95% CI: 0.57–0.88)) (Table 3).

**Table 1** One- and 5-year survival and MRRs (and 95% CIs) after colon and rectal cancer diagnosis according to the time periods

	Year of diagnosis			
	1998–2000	2001–2003	2004–2006	2007–2009
<b>Colon cancer</b>				
Number of cancer patients	2097	2160	2392	2763
Median age (years)	73	73	73	72
<b>1-year</b>				
Survival	65% (63%–67%)	67% (64%–68%)	69% (68%–71%)	70% (68%–71%)
MRR	1 (reference)	0.96 (0.87–1.06)	0.85 (0.77–0.94)	0.84 (0.76–0.93)
MRR <sup>a</sup>	1 (reference)	0.97 (0.88–1.08)	0.85 (0.77–0.94)	0.83 (0.76–0.92)
<b>5-year</b>				
Survival	37% (35%–39%)	40% (38%–42%)	43% (41%–45%) <sup>b</sup>	43% (41%–45%) <sup>b</sup>
MRR	1 (reference)	0.93 (0.86–1.00)	0.85 (0.79–0.92) <sup>b</sup>	0.84 (0.78–0.91) <sup>b</sup>
MRR <sup>a</sup>	1 (reference)	0.93 (0.86–1.00)	0.85 (0.78–0.91) <sup>b</sup>	0.84 (0.78–0.90) <sup>b</sup>
<b>Rectal cancer</b>				
Number of cancer patients	1336	1396	1399	1554
Median age (years)	71	70	69	69
<b>1-year</b>				
Survival	73% (70%–75%)	74% (72%–76%)	76% (73%–78%)	78% (76%–80%)
MRR	1 (reference)	0.94 (0.82–1.09)	0.89 (0.77–1.03)	0.77 (0.66–0.89)
MRR <sup>a</sup>	1 (reference)	0.97 (0.84–1.13)	0.91 (0.78–1.05)	0.79 (0.68–0.91)
<b>5-year</b>				
Survival	39% (36%–42%)	43% (40%–46%)	46% (43%–48%) <sup>b</sup>	47% (45%–50%) <sup>b</sup>
MRR	1 (reference)	0.90 (0.82–1.00)	0.84 (0.77–0.93) <sup>b</sup>	0.79 (0.72–0.88) <sup>b</sup>
MRR <sup>a</sup>	1 (reference)	0.92 (0.83–1.02)	0.85 (0.77–0.94) <sup>b</sup>	0.81 (0.73–0.89) <sup>b</sup>

**Notes:** <sup>a</sup>adjusted for age and gender; <sup>b</sup>predicted values.

**Abbreviations:** CI, confidence interval; MRR, mortality rate ratio.

## Rectal cancer

A total of 5685 patients were diagnosed with rectal cancer in the 1998–2009 period. The number of rectal cancer patients increased during the four time intervals from a total of 1336 to 1554 (Table 1), most pronounced among the youngest men and women (Table 2). At the same time, median age at diagnosis declined from 71 years to 69 years. The 1-year overall survival improved from 73% to 78%, corresponding to an adjusted MRR of 0.79 (95% CI: 0.68–0.91) in 2007–2009 using 1998–2000 as a reference (Figure 1 and Table 1). Accordingly, the 5-year survival improved from 39% 1998–2000 to the predicted 47% in 2007–2009, corresponding to an adjusted MRR of 0.81 (95% CI: 0.73–0.89). In general, improvements in survival were present in all age groups in both genders apart from 1-year survival in women aged 80+. Men aged 80+ showed remarkable improvements in 1- and 5-year survival, whereas 5-year survival also improved notably in both genders aged 65–79 (Table 4).

As for colon cancer patients, the 30-day postoperative mortality decreased for rectal cancer patients over the study period. After resection, 30-day mortality decreased from 5% in 1998–2000 to 3% in 2007–2009 (adjusted MRR of 0.59 (95% CI 0.37–0.96)), and after the first operative procedure

the 30-day mortality decreased from 7% to 4% (adjusted MRR of 0.61 (95% CI 0.41–0.89)) (Table 3).

## Discussion

In this large population-based study we found an improved survival in both colon and rectal cancer patients. Accordingly, the 30-day postoperative mortality also decreased for both cancer locations.

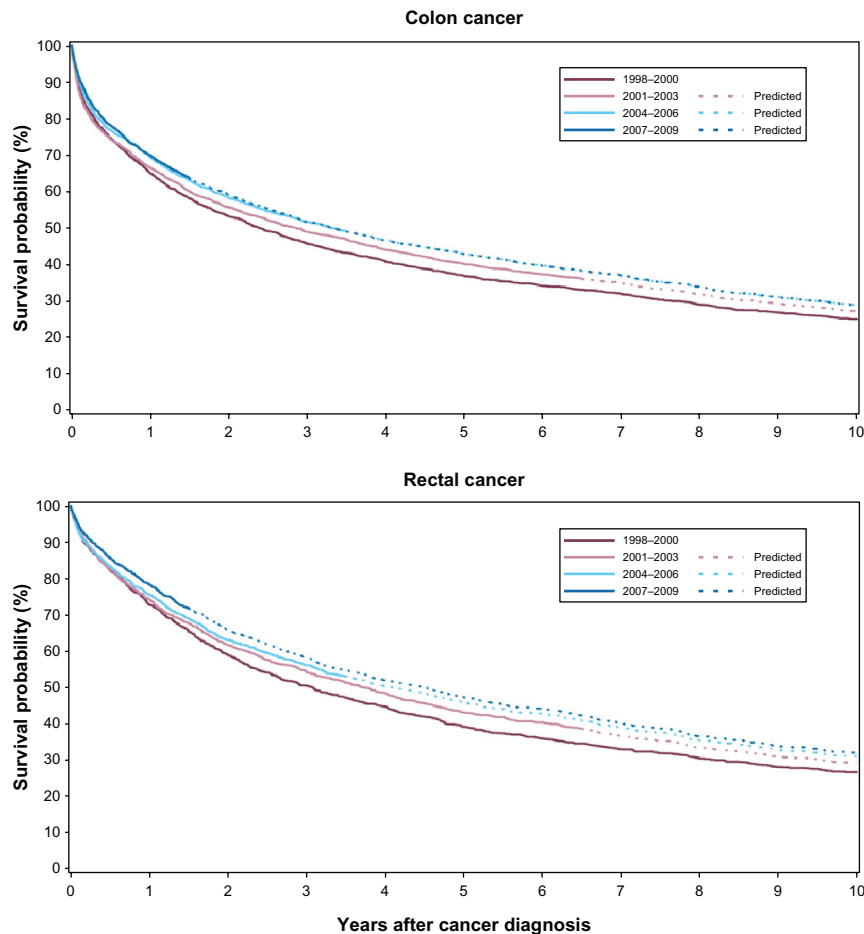
The main strength of this study is the population-based design with a large sample size covering about 30% of the Danish population and a complete hospital history. We had complete follow-up on all patients ensured by the Civil Registration System. These features minimize the risk of selection bias. We used the DNRP since it is continuously updated and has been demonstrated to be complete and valid.<sup>15,16</sup> We consider overall survival as a valid outcome measurement in this study of prognostic changes over time, rather than disease-specific survival, which may be affected by bias in classifying the cause of death. Such bias may be differential according to time period.<sup>17</sup>

Our study also had limitations. First, we had no data on cancer stage and thus were unable to evaluate whether the improvements in survival stemmed from better treatment or

**Table 2** One- and 5-year survival after colon cancer diagnosis according to age at diagnosis and time periods

Age (years)		Year of diagnosis			
		1998–2000	2001–2003	2004–2006	2007–2009
<b>Men</b>					
15–64	Number of cancer patients	282	323	346	401
	1-year survival	74% (69%–79%)	77% (72%–81%)	80% (75%–84%)	80% (76%–84%)
	5-year survival	45% (39%–50%)	45% (40%–50%)	54% (49%–59%) <sup>a</sup>	56% (50%–61%) <sup>a</sup>
65–79	Number of cancer patients	484	502	562	691
	1-year survival	66% (61%–70%)	64% (60%–68%)	70% (66%–73%)	70% (66%–73%)
	5-year survival	36% (32%–40%)	39% (35%–43%)	42% (38%–46%) <sup>a</sup>	41% (37%–45%) <sup>a</sup>
80+	Number of cancer patients	208	228	247	310
	1-year survival	49% (42%–56%)	54% (47%–60%)	59% (53%–65%)	57% (51%–63%)
	5-year survival	17% (13%–23%)	27% (21%–33%)	24% (19%–29%) <sup>a</sup>	22% (17%–27%) <sup>a</sup>
<b>Women</b>					
15–64	Number of cancer patients	294	314	300	395
	1-year survival	76% (71%–81%)	82% (77%–85%)	80% (75%–84%)	78% (73%–82%)
	5-year survival	48% (42%–53%)	53% (48%–59%)	57% (51%–63%) <sup>a</sup>	54% (49%–59%) <sup>a</sup>
65–79	Number of cancer patients	503	489	574	570
	1-year survival	68% (63%–71%)	68% (64%–72%)	74% (70%–77%)	73% (69%–76%)
	5-year survival	43% (38%–47%)	43% (38%–47%)	49% (45%–53%) <sup>a</sup>	48% (44%–52%) <sup>a</sup>
80+	Number of cancer patients	326	304	363	396
	1-year survival	52% (46%–57%)	51% (46%–57%)	50% (45%–55%)	55% (50%–60%)
	5-year survival	25% (21%–30%)	29% (24%–34%)	27% (22%–31%) <sup>a</sup>	31% (26%–36%) <sup>a</sup>

Note: <sup>a</sup>predicted values.



**Figure 1** Survival curves for patients with a first-time diagnosis of colon and rectal cancer.

**Table 3** Thirty-day mortality and 30-day MRRs (and 95% CIs) after resection or first surgical procedure in colon and rectal cancer patients

	Year of surgery			
	1998–2000	2001–2003	2004–2006	2007–2009
<b>Colon cancer</b>				
<b>Resection</b>				
Number of cancer patients	1471	1507	1674	1690
Median age (years)	73	72	72	72
30-day mortality	9% (8%–11%)	10% (9%–12%)	7% (6%–8%)	7% (5%–8%)
30-day MRR	1 (reference)	1.12 (0.89–1.41)	0.71 (0.55–0.91)	0.69 (0.53–0.88)
30-day MRR <sup>a</sup>	1 (reference)	1.14 (0.91–1.44)	0.71 (0.55–0.91)	0.68 (0.53–0.87)
<b>First surgical procedure</b>				
Number of cancer patients	1622	1615	1803	1880
Median age (years)	73	73	73	72
30-day mortality	11% (9%–12%)	12% (10%–13%)	8% (7%–10%)	8% (7%–9%)
30-day MRR	1 (reference)	1.09 (0.89–1.34)	0.74 (0.60–0.92)	0.71 (0.57–0.88)
30-day MRR <sup>a</sup>	1 (reference)	1.12 (0.91–1.38)	0.75 (0.60–0.93)	0.71 (0.57–0.88)
<b>Rectal cancer</b>				
<b>Resection</b>				
Number of cancer patients	865	852	773	890
Median age (years)	70	69	68	68
30-day mortality	5% (4%–7%)	5% (4%–7%)	5% (4%–7%)	3% (2%–4%)
30-day MRR	1 (reference)	0.95 (0.63–1.44)	1.00 (0.66–1.53)	0.54 (0.34–0.88)
30-day MRR <sup>a</sup>	1 (reference)	1.06 (0.70–1.61)	1.04 (0.68–1.58)	0.59 (0.37–0.96)
<b>First surgical procedure</b>				
Number of cancer patients	1025	1019	937	1087
Median age (years)	71	70	69	69
30-day mortality	7% (5%–8%)	6% (5%–8%)	7% (5%–9%)	4% (3%–5%)
30-day MRR	1 (reference)	0.95 (0.67–1.33)	1.02 (0.73–1.43)	0.56 (0.38–0.83)
30-day MRR <sup>a</sup>	1 (reference)	1.02 (0.73–1.43)	1.05 (0.75–1.48)	0.61 (0.41–0.89)

Note: <sup>a</sup>adjusted for age and gender.

Abbreviations: CI, confidence interval; MRR, mortality rate ratio.

**Table 4** One- and 5-year survival after rectal cancer diagnosis according to age at diagnosis and time periods

Age (years)		Year of diagnosis			
		1998–2000	2001–2003	2004–2006	2007–2009
<b>Men</b>					
15–64	Number of cancer patients	248	301	315	338
	1-year survival	84% (79%–88%)	82% (78%–86%)	83% (79%–87%)	89% (85%–92%)
	5-year survival	53% (47%–59%)	53% (47%–58%)	54% (48%–59%) <sup>a</sup>	58% (52%–63%) <sup>a</sup>
65–79	Number of cancer patients	343	367	383	427
	1-year survival	72% (67%–77%)	71% (66%–75%)	72% (68%–77%)	78% (74%–82%)
	5-year survival	37% (32%–42%)	40% (35%–45%)	42% (37%–47%) <sup>a</sup>	45% (40%–50%) <sup>a</sup>
80+	Number of cancer patients	133	117	128	146
	1-year survival	48% (39%–56%)	60% (50%–68%)	55% (46%–64%)	63% (54%–70%)
	5-year survival	14% (8%–20%)	24% (17%–32%)	22% (16%–30%) <sup>a</sup>	23% (16%–31%) <sup>a</sup>
<b>Women</b>					
15–64	Number of cancer patients	191	215	210	252
	1-year survival	82% (76%–87%)	89% (84%–92%)	91% (87%–95%)	87% (83%–91%)
	5-year survival	54% (46%–61%)	59% (52%–65%)	66% (59%–72%) <sup>a</sup>	63% (56%–68%) <sup>a</sup>
65–79	Number of cancer patients	292	267	229	256
	1-year survival	76% (71%–81%)	73% (67%–78%)	75% (69%–80%)	77% (71%–82%)
	5-year survival	40% (35%–46%)	43% (37%–49%)	48% (42%–54%) <sup>a</sup>	49% (43%–55%) <sup>a</sup>
80+	Number of cancer patients	129	129	134	135
	1-year survival	57% (48%–65%)	57% (48%–65%)	61% (52%–69%)	55% (46%–63%)
	5-year survival	19% (13%–27%)	20% (14%–27%)	25% (18%–32%) <sup>a</sup>	22% (15%–29%) <sup>a</sup>

Note: <sup>a</sup>predicted values.

diagnosis at an earlier stage. However, data on previous stage distribution in CRC reveal no substantial change during the 2001–2008 period,<sup>18</sup> thus speaking against major changes towards earlier diagnosis.<sup>19</sup> Length time and lead time biases are therefore unlikely.<sup>20</sup> Second, life expectancy has increased in the general population, particularly for men.<sup>21</sup> Therefore, our findings of improved survival being most pronounced among men aged 80+ may partly be attributable to a reduced mortality in general. Still, Coleman et al found that the 1-year relative survival of colorectal cancer in Denmark (ie, the ratio between observed survival and expected survival based on the background mortality) improved from 71.7% to 77.7% in the period 1995–2007.<sup>6</sup> This finding indicates that increased life expectancy in general is not solely responsible for the improved survival reported in our study.

A number of initiatives have been launched during the last decades to improve CRC prognosis. In 1998 the Danish Colorectal Cancer Group first published national clinical guidelines for diagnosis and treatment of CRC.<sup>22</sup> Furthermore, National Cancer Plans were introduced in 2000 and 2005 aiming also to improve health care organization and avoiding delay in cancer diagnostics and treatment. According to this, the surgical treatment of CRC patients has generally been centralized. However, evidence of the impact of high hospital procedure volume and high surgeon case volume on CRC prognosis is inconsistent, although some reviews have shown benefits.<sup>23–25</sup> Furthermore, in rectal cancer treatment, multidisciplinary teams comprising radiologists, pathologists, surgeons, and oncologists have been established.

In addition to these initiatives, refinements over time of diagnostic procedures and techniques, such as endoscopy, computerized tomography, magnetic resonance, ultrasonic scanning, and position emission tomography may also have played a role in improving CRC diagnosis by facilitating earlier and more accurate diagnosis. However, the similar stage distribution in CRC in Denmark in the period 2001–2008<sup>18</sup> indicates that these advances may only have played a minor role.

The surgical treatment of CRC has also developed over the study period, in at least three ways. First, total mesorectal excision technique was adapted in Denmark in 1996 in rectal cancer surgery. Improved survival by reduced local recurrence rate has been observed after implementation of this technique.<sup>26–28</sup> Second, treatment of cancer-related acute colonic obstruction by self-expanding metallic stents has been introduced.<sup>29</sup> This technique has the potential of converting emergent procedures into planned procedures,<sup>30</sup> which are associated with better

survival.<sup>31–33</sup> Third, laparoscopic surgery is now widely implemented.<sup>29</sup> Although randomized clinical trials on colon cancer tend to show improved short-term mortality by laparoscopic procedures compared with open surgery, long-term mortality does not differ significantly, and for rectal cancer, evidence on mortality improvements by laparoscopic surgery is less clear.<sup>34,35</sup> In addition to the potential improvements in surgical treatment, better perioperative care may also have contributed to the observed survival improvements. Furthermore, during the study period, an oxaliplatin-containing adjuvant chemotherapy regimen has been introduced in the treatment of colonic cancer<sup>36–38</sup> as well as biological monoclonal antibodies to selected patients with metastatic CRC.<sup>39,40</sup> For rectal cancer, preoperative radiotherapy with or without concomitant chemotherapy has been introduced. However, randomized clinical trials show lower local recurrence rate, but no effect on survival.<sup>41,42</sup>

The results from our study extend those from previous population-based studies based on data from the DNRP<sup>43</sup> and the Danish Cancer Registry.<sup>6,7,44</sup> Compared with our Nordic counterparts and countries with similar health systems, CRC survival in Denmark is still inferior despite the reported improvements.<sup>6,7</sup> This underlines the need of further initiatives, although we may await effects of the National Cancer Plans already implemented.

## Conclusion

In conclusion, survival after colon and rectal cancer has improved in central and northern Denmark during the 1998–2009 period. Accordingly, 30-day postoperative mortality after colon and rectal cancer has also improved.

## Disclosure

The authors report no conflicts of interest in this work.

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## Appendix I

Surgery codes for colon cancer resections were JFB20-97 and JFHxx, and for colon cancer first operative procedure, JFA68, JFA83-84, JFA96-97, JFCxx, JFF10-13, JFF20-31,

JFWxx. Similarly, surgery codes for rectal resections were JGB00-50 and JGB96-97, and for rectal, first surgical procedures were JGA32-52, JGA73-96, JGA98, JGWxx, JFF10-13, JFF20-31, and JFA68.

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