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ORIGINAL ARTICLE

Influence of age on surgical treatment and postoperative outcomes of patients with colorectal cancer in Denmark and Yorkshire, England

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Abstract

Aim: Denmark and Yorkshire are demographically similar and both have undergone changes in their management of colorectal cancer to improve outcomes. The differential provision of surgical treatment, especially in the older age groups, may contribute to the magnitude of improved survival rates. This study aimed to identify differences in the management of colorectal cancer surgery and postoperative outcomes according to patient age between Denmark and Yorkshire.

Method: This was a retrospective population-based study of colorectal cancer patients diagnosed in Denmark and Yorkshire between 2005 and 2016. Proportions of patients undergoing major surgical resection, postoperative mortality and relative survival were compared between Denmark and Yorkshire across several age groups (18–59, 60–69, 70–79 and ≥80 years) and over time.

Results: The use of major surgical resection was higher in Denmark than in Yorkshire, especially for patients aged ≥80 years (70.5% versus 50.5% for colon cancer, 49.3% versus 38.1% for rectal cancer). Thirty-day postoperative mortality for Danish patients aged ≥80 years was significantly higher than that for Yorkshire patients with colonic cancer [OR (95% CI) = 1.22 (1.07, 1.38)] but not for rectal cancer or for 1-year postoperative mortality. Relative survival significantly increased in all patients aged ≥80 years except for Yorkshire patients with colonic cancer.

Conclusion: This study suggests that there are major differences between the management of elderly patients with colorectal cancer between the two populations. Improved selection for surgery and better peri- and postoperative care in these patients appears to improve long-term outcomes, but may come at the cost of a higher 30-day mortality.

KEYWORDS
colorectal cancer, elderly, mortality, surgical resection, survival

INTRODUCTION

Survival rates for patients with colorectal cancer have been shown to vary across Europe [1, 2]. In particular, it has been demonstrated that survival rates in Denmark and England were lower in the 1990s and early 2000s than in many other countries with comparable populations and health systems [2, 3]. In response, both these countries have instigated interventions to improve colorectal cancer outcomes.

While there are common areas in which interventions have been implemented in both countries, such as the introduction of, and training in, total mesorectal excision for rectal cancer [4, 5], there have been some differences in the approaches taken. In Denmark, these interventions have included detailed reviews of readily available observational data to quantify patterns of practice, identifying areas of concern and then focusing action to improve care [6]. There is strong evidence that this has radically changed practice and has coincided with improved outcomes. For example, 30-day postoperative mortality rates have fallen dramatically and survival rates are now more comparable with those of neighbouring Scandinavian countries [7]. Danish 5-year net survival improved from 49% to 66% for colonic cancer and from 48% to 69% for rectal cancer, compared with corresponding increases of 47% to 59% and 48% to 62% in the UK [8].

In 2016, a similar data-driven programme was implemented in Yorkshire, England. It aimed to quantify, in depth, the patterns of care and outcomes [9]. Interventions can then be developed and deployed by Yorkshire's clinical colorectal cancer community to try to eliminate any disparities in quality of care and improve outcomes. Understanding how the surgical management of patients in the region compares with that in populations with similar demographics is a key element of developing these interventions. The UK and Denmark have similar populations, life expectancy, Healthcare Access and Quality Index, smoking rates and alcohol consumption [10, 11].

Major surgical resection to remove the tumour and surrounding tissue, i.e. bowel resection including regional lymphadenectomy, is the mainstay of treatment for colorectal cancer. It has recently been suggested that observed survival differences may stem from differences in patient selection for surgical resection, especially in older age groups [12]; if more patients undergo a potentially curative treatment then this could lead to more patients surviving in the longer term. Although survival following surgery may be decreased in the older age groups, longer-term survival may be comparable to that of younger patients [13]. It has also been demonstrated in England that older rectal cancer patients selected for surgery have comparable outcomes to their younger counterparts [14].

Given the recent substantial improvements in survival that have been observed following the clinical interventions in Denmark, comparisons of surgical practice and postoperative outcomes between Denmark and Yorkshire should help to identify areas for improvement. Therefore, this study aimed to identify any differences in the approach to colorectal cancer resection according to patient age between Denmark and Yorkshire, and to investigate the potential impact of these on postoperative mortality and survival rates.

What does this paper add to the literature?

Age may influence the decision to surgically treat patients with colorectal cancer and therefore have an impact on overall survival rates. In this population-based study, we compared the use of major surgical resection and the impact this may have had on survival in different age groups over a 12-year period in two demographically similar regions of Europe.

METHOD

This was a retrospective population-based study, that included first-time primary colorectal cancers (ICD-10; C18–C20, excluding malignant neoplasm of the appendix C18.1), in patients aged ≥18 years and diagnosed between 1 January 2005 and 31 December 2016 in both Denmark and Yorkshire.

Data for Denmark were obtained from the Danish Colorectal Cancer Group (DCCG) database [15]. This database captures all colorectal cancer patients who have been diagnosed and/or treated at a surgical department in a Danish public hospital. The DCCG reports high ascertainment (95%–99%) when compared with the Danish National Patient Registry and the Danish Cancer Registry [15–17]. The DCCG captures the type of surgical procedure performed, if any, for all registered patients. Categorization of these procedures allows all patients who underwent a major surgical resection to be identified (Table S1 in the Supporting Information).

Like Denmark, the Yorkshire region has a total population of 5.7 million. The region accounts for approximately 10% of the colorectal cancer cases in England. The data for Yorkshire were sourced through the UK Colorectal Cancer Intelligence Hub's COloRECTal Repository (CORECT-R) [18]. Specifically, data from the cancer registry (National Cancer Registration and Analysis Service) were linked to hospital admission data (Hospital Episode Statistics) to identify all colorectal patients and those who underwent a major surgical resection, as described in CORECT-R's methodology [18]. The case ascertainment rate in the Yorkshire region was estimated to be 99% when compared with the Hospital Episodes Statistics dataset for the period 2001–2007 [19].

Patients were deemed to have undergone a major surgical resection if the operation date was within 1 month prior to, and up to 1 year after, the date of diagnosis. All analyses were performed separately for colon (C18–C19) and rectal cancer (C20), and further stratified by age group (18–59, 60–69, 70–79 and ≥80 years) and period of diagnosis (2005–2008, 2009–2012 and 2013–2016).

The observed percentage of patients treated with major resection in each stratum was calculated using the total number of cases

as the denominator, irrespective of treatment intent, which was not available across both datasets. Odds ratios (OR) and 95% confidence intervals (CI) were then calculated comparing Denmark with Yorkshire for each stratum and also combined for the whole study period using Mantel–Haenszel weights.

To investigate the factors associated with use of major resection, we modelled Danish and Yorkshire populations separately using logistic regression with the following covariates: age group, sex, stage of disease and study period. Stage of disease was missing for 11% and 19% of Danish and Yorkshire patients respectively. Therefore, we used ordered logistic imputation to impute missing values and estimated model coefficient and standard errors according to Rubin's combination rules (via the mi impute and mi estimate commands in Stata version 16).

To investigate the postoperative outcome following major resection, the proportion of deaths within 30 days of resection (30-day postoperative mortality) and within 1-year of resection (1-year postoperative mortality) were compared using ORs, with the same strata as before.

To investigate whether differences in the use of major resection may have an effect on overall outcome of colorectal patients in the two populations, we calculated 1-year survival estimates. We used relative survival using the strs [20] function in Stata to estimate survival and to control for any differences in background mortality between Denmark and Yorkshire. The background mortality of the general populations was estimated using life tables by sex, single year of age and calendar year. These were estimated over the three periods of diagnosis for all patients, and both resected and nonresected patients.

RESULTS

Colorectal populations

A total of 51,021 Danish and 39,456 Yorkshire patients with colorectal cancer were included. The age distribution of patients was broadly similar in the two populations at the beginning of the study; however, a higher proportion of patients in Yorkshire were aged ≥80 years during the most recent period for both colonic (30.9% vs 23.0%) and rectal (20.6% vs 16.5%) cancer (Table 1). An increase in the occurrence of Stage I colon cancers over time was observed in both populations, but comparisons between stage groups was difficult due to a differential rate of missing stage over the study period.

Colon cancer resections and outcomes

Overall, the proportion of colon cancer patients treated with major resection was higher in Denmark than in Yorkshire (77.3% vs 63.5%). This was consistent across all the periods of study and the difference in the use of major resections increased with age (70.5% vs 50.5% for the ≥80 years age group). After adjustment for covariates, the odds of resection for those aged ≥80 years compared with 60–69 years in Yorkshire were OR (95% CI) = 0.26 (0.23, 0.28), lower than the corresponding odds in Denmark [OR (95% CI) = 0.54 (0.50, 0.59)] (Table 2). The odds of resection were also lower in Stage III patients compared with Stage II patients in Yorkshire [OR (95% CI) = 0.54 (0.49, 0.60)] but not in Denmark [OR (95% CI) = 0.97 (0.82, 1.16)]. Additionally, a significant decrease in the use of resection was observed over the study period for both populations (Table 2).

Within patients aged ≥80 years, the use of resection decreased from 55.4% to 45.1% in Yorkshire. The corresponding decrease in Denmark was much smaller, from 70.9% to 68.5% (Figure 1A). Figure 2(A) shows that the use of major resection in Denmark compared with Yorkshire was significantly higher over all ages and study periods. Within the ≥80 years age group, the use of major resection in Denmark, compared with Yorkshire, also significantly increased over time from OR (95% CI) = 1.92 (1.71, 2.16) in 2005–2008 to OR (95% CI) = 2.63 (2.36, 2.93) in 2013–2016.

To investigate whether the differences in the use of resection across age groups had an effect on short-term outcomes, we compared 30-day postoperative mortality between the populations (Figure 1B, Table S3). A decrease in mortality was observed over time in all groups for both populations. Mortality was significantly higher in Denmark than in Yorkshire in the ≥80 years age group over the whole study period [OR (95% CI) = 1.22 (1.07, 1.38)]. When stratified by study period: Denmark had lower mortality than Yorkshire in 2013–2016 for all except the ≥80 years age group, significantly so for those aged 60–69 years.

To investigate longer-term differences, we compared 1-year postoperative mortality between the populations (Figures 1C and 2C). By the latest study period, there was no difference in the odds of death for Danish as compared with Yorkshire patients in the ≥80 years age group. Additionally, the odds of death were significantly lower in Denmark than Yorkshire in all the other age groups in 2013–2016.

Rectal cancer resections and outcomes

Overall, the proportion treated with major resection was higher in Denmark than in Yorkshire (71.2% vs 61.9%); this difference increased with age (Figure 1A, Table S2), with the largest difference in the ≥80 years age group (49.3% vs 38.1%, over the whole study period). Adjusted models showed similar results to those for colonic cancer, but with a stronger influence of age in both populations and no significant decrease over time in Danish patients (Table 2). Odds of resection were lower in Stage III patients compared with Stage II patients in Yorkshire [OR (95% CI) = 0.80 (0.68, 0.93)] but not in Denmark [OR (95% CI) = 1.04 (0.85, 1.28)]. However, unlike colon cancer, there was no large decrease over time in the observed proportion of resections for Yorkshire patients aged ≥80 years (33.3%–31.9%; Figure 1A).

The difference in use of major resection was significant in all age groups, with an increase in odds of major resection in Denmark

TABLE 1 Characteristics of patients diagnosed with colorectal cancer in Denmark and Yorkshire between 2005 and 2016

	Denmark, *N* (%)			Yorkshire, *N* (%)		
	2005–2008	2009–2012	2013–2016	2005–2008	2009–2012	2013–2016
Colon cancer						
Total	10186 (100.0)	10634 (100.0)	13321 (100.0)	8784 (100.0)	9628 (100.0)	9393 (100.0)
Age (years)						
18–59	1560 (15.3)	1486 (14.0)	1777 (13.3)	1241 (14.1)	1266 (13.1)	1325 (14.1)
60–69	2580 (25.3)	2909 (27.4)	3605 (27.1)	2020 (23.0)	2452 (25.5)	2215 (23.6)
70–79	3379 (33.2)	3545 (33.3)	4874 (36.6)	2994 (34.1)	3121 (32.4)	2947 (31.4)
≥80	2667 (26.2)	2694 (25.3)	3065 (23.0)	2529 (28.8)	2789 (29.0)	2906 (30.9)
Sex						
Male	4976 (48.9)	5229 (49.2)	6914 (51.9)	4737 (53.9)	5279 (54.8)	5144 (54.8)
Female	5210 (51.1)	5405 (50.8)	6407 (48.1)	4047 (46.1)	4349 (45.2)	4249 (45.2)
Stage						
Stage I	965 (9.5)	1095 (10.3)	1859 (14.0)	748 (8.5)	999 (10.4)	1307 (13.9)
Stage II	3173 (31.2)	3394 (31.9)	3737 (28.1)	2441 (27.8)	2503 (26.0)	2534 (27.0)
Stage III	2567 (25.2)	2486 (23.4)	3013 (22.6)	2180 (24.8)	2490 (25.9)	2379 (25.3)
Stage IV	2974 (29.2)	3054 (28.7)	3012 (22.6)	1692 (19.3)	1809 (18.8)	2409 (25.6)
Unknown	507 (5.0)	605 (5.7)	1700 (12.8)	1723 (19.6)	1827 (19.0)	764 (8.1)
Rectal cancer						
Total	5254 (100.0)	5449 (100.0)	6177 (100.0)	3732 (100.0)	4014 (100.0)	3905 (100.0)
Age (years)						
18–59	1110 (21.1)	1050 (19.3)	1139 (18.4)	732 (19.6)	764 (19.0)	843 (21.6)
60–69	1583 (30.1)	1782 (32.7)	1920 (31.1)	1024 (27.4)	1135 (28.3)	1063 (27.2)
70–79	1525 (29.0)	1611 (29.6)	2099 (34.0)	1167 (31.3)	1257 (31.3)	1196 (30.6)
≥80	1036 (19.7)	1006 (18.5)	1019 (16.5)	809 (21.7)	858 (21.4)	803 (20.6)
Sex						
Male	3115 (59.3)	3343 (61.4)	3845 (62.2)	2379 (63.7)	2648 (66.0)	2550 (65.3)
Female	2139 (40.7)	2106 (38.6)	2332 (37.8)	1353 (36.3)	1366 (34.0)	1355 (34.7)
Stage						
Stage I	963 (18.3)	1129 (20.7)	1181 (19.1)	453 (12.1)	728 (18.1)	911 (23.3)
Stage II	1232 (23.4)	1248 (22.9)	944 (15.3)	436 (11.7)	627 (15.6)	684 (17.5)
Stage III	1237 (23.5)	1180 (21.7)	1146 (18.6)	504 (13.5)	897 (22.3)	1343 (34.4)
Stage IV	1326 (25.2)	1367 (25.1)	1200 (19.4)	513 (13.7)	529 (13.2)	722 (18.5)
Unknown	496 (9.4)	525 (9.6)	1706 (27.6)	1826 (48.9)	1233 (30.7)	245 (6.3)

compared with Yorkshire with increasing age group (Figure 3A). Within the ≥80 years age group, the odds of resection in Denmark compared with Yorkshire increased, but not significantly, over time from OR (95% CI) = 1.75 (1.44, 2.13) to OR (95% CI) = 2.12 (1.74, 2.59).

Thirty-day mortality was similar across the majority of age groups (Figure 1B, Table S2) including in the ≥80 years age group [OR (95% CI) = 0.87 (0.64, 1.20)] over the whole study period. The only significant difference was observed in the 70–79 years age group during the last study period, with lower odds of death in Denmark than in Yorkshire. When comparing 1-year postoperative mortality, Denmark had significantly lower mortality than Yorkshire for the youngest age group in 2005–2008 and those aged 60–69 years in 2013–2016 (Figures 1C and 3C).

Impact on 1-year relative survival over time

For the entire cohort of patients with colonic cancer, relative survival in Denmark significantly improved over the study period for all patient age groups, including those aged ≥80 years (Figure 4A). Survival for patients with colonic cancer in Yorkshire showed a non-significant increase in all age groups. In nonresected patients, significant increases in relative survival were observed for all age groups ≥60 years in Denmark and for those aged ≥80 years in Yorkshire.

For the entire cohort of patients with rectal cancer, relative survival in Denmark displayed a consistent significant improvement over time in all ages (Figure 4B). Relative survival In Yorkshire did not significantly improve in patients <80 years, but a large significant

TABLE 2 Adjusted odds ratios (OR) and 95% confidence intervals (CI) for the use of major resection for patients diagnosed with colorectal cancer in Denmark and Yorkshire between 2005 and 2016

	Denmark, *N* (%)			Yorkshire, *N* (%)		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Colon cancer						
Age						
18–59	1.23	1.10–1.37	<0.001	1.36	1.21–1.53	<0.001
60–69	Ref.			Ref.		
70–79	0.92	0.84–1.00	0.046	0.72	0.66–0.79	<0.001
≥80	0.54	0.50–0.59	<0.001	0.26	0.23–0.28	<0.001
Sex						
Male	Ref.			Ref.		
Female	1.20	1.13–1.29	<0.001	1.11	1.04–1.18	0.002
Stage						
Stage I	0.27	0.23–0.33	<0.001	0.26	0.23–0.30	<0.001
Stage II	Ref.			Ref.		
Stage III	0.97	0.82–1.16	0.77	0.54	0.49–0.60	<0.001
Stage IV	0.03	0.02–0.03	<0.001	0.03	0.03–0.04	<0.001
Period						
2005–2008	Ref.			Ref.		
2009–2012	0.92	0.84–1.00	0.039	0.89	0.81–0.96	0.004
2013–2016	0.70	0.65–0.76	<0.001	0.74	0.68–0.80	<0.001
Rectal cancer						
Age						
18–59	1.25	1.09–1.43	0.001	1.31	1.13–1.51	<0.001
60–69	Ref.			Ref.		
70–79	0.70	0.62–0.78	<0.001	0.65	0.57–0.73	<0.001
≥80	0.25	0.22–0.29	<0.001	0.16	0.14–0.19	<0.001
Sex						
Male	Ref			Ref.		
Female	0.97	0.88–1.06	0.50	1.02	0.93–1.12	0.67
Stage						
Stage I	0.48	0.39–0.58	<0.001	0.40	0.33–0.48	<0.001
Stage II	Ref			Ref.		
Stage III	1.04	0.85–1.28	0.71	0.80	0.68–0.93	0.005
Stage IV	0.03	0.03–0.04	<0.01	0.06	0.05–0.07	<0.001
Period						
2005–2008	Ref.			Ref.		
2009–2012	1.09	0.98–1.22	0.12	0.85	0.76–0.95	0.006
2013–2016	1.02	0.92–1.14	0.72	0.67	0.60–0.76	<0.001

improvement was observed in those aged ≥80 years. Also of note was a particularly large increase in survival for nonresected patients for those aged 70–79 years in Denmark and those aged ≥80 years in Yorkshire.

DISCUSSION

This retrospective population-based study has shown a differing approach to surgical management of patients with colorectal cancer between Denmark and Yorkshire, especially in older age groups. A higher proportion of all patients underwent major surgical resection in Denmark and, of these patients, long-term postoperative mortality was as low as that in Yorkshire. High use of major resection in those aged ≥80 years in Denmark has been maintained while still increasing overall rates of survival, whereas decreasing use of resection in Yorkshire patients with colon cancer of the same age has coincided with a period of unchanging survival.

Although differences in the rates of use of resection for colonic cancer were found across all age groups, the most pronounced

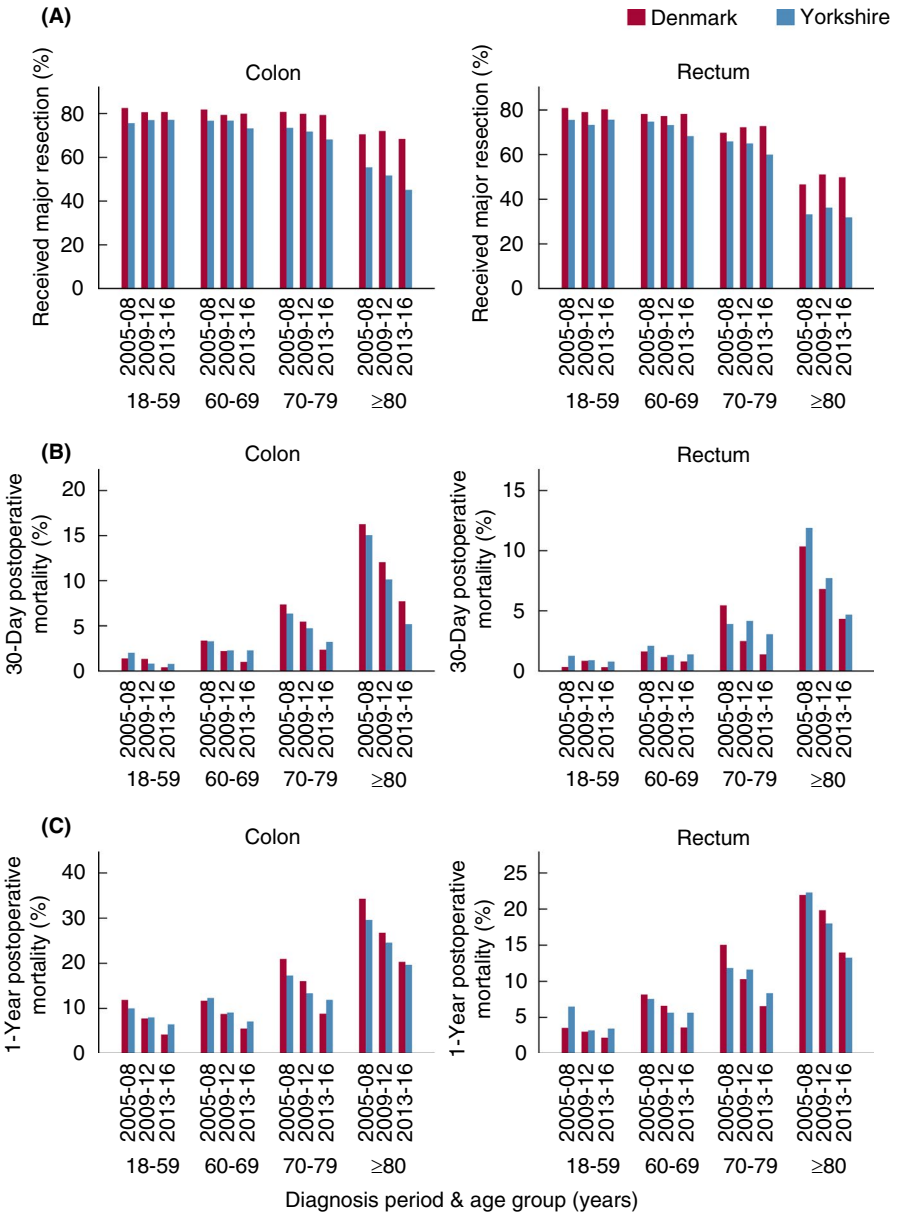

FIGURE 1 (A) Observed percentage of patients receiving major surgical resection, irrespective of intent, (B) death within 30 days of resection and (C) death within 1 year of resection for patients diagnosed with colorectal cancer in Denmark and Yorkshire between 2005 and 2016

difference was found in those aged ≥80 years, but also with noticeable differences in those aged 70–79 years. There is a concern that increased use of resection in older age groups will lead to a higher postoperative mortality as such patients are more likely to have existing comorbidity and frailty [13]. Some evidence for this was observed here, as there were increased odds of death within 30 days for Danish patients aged ≥80 years with colonic cancer. However, 1-year postoperative mortality in this age group in Denmark was equivalent to that observed in Yorkshire patients, and was actually lower for the latest study period in patients aged 70–79 years. The potential for a trade-off between increased short-term risk and longer-term benefit has been suggested previously when considering treatment of the older population [13]. It is also worth noting that 30-day postoperative mortality decreased sharply over time in both populations (16.2%–7.7% in Denmark, 15.1%–5.2% in Yorkshire), which suggests that patient care in the ≥80 years age group has improved considerably and needs to be considered when selecting patients for surgery.

Given that relative survival for resected patients aged ≥80 years with colonic cancer in Yorkshire improved over the study period, but not for all patients aged ≥80 years, it is possible that this could be due to a tendency to select fewer elderly patients for major resection. Whereas use of major resection in Yorkshire decreased over the study period, the Danish maintained relatively high use whilst still increasing 1-year relative survival. As more of the Danish patients aged ≥80 years received surgical resection, this could explain the substantial difference in relative survival between the two cohorts of patients in this age group.

Use of major resection was lower for rectal cancer in both countries. This is to be expected, since a number of patients will have alternative treatments including radiotherapy [21] and local surgical resection [22]. However, use of major resection was again higher in the Danish population. Unlike in colon cancer, the higher rate of resection did not coincide with a higher 30-day mortality for Danish patients aged ≥80 years compared with Yorkshire, and the mortality

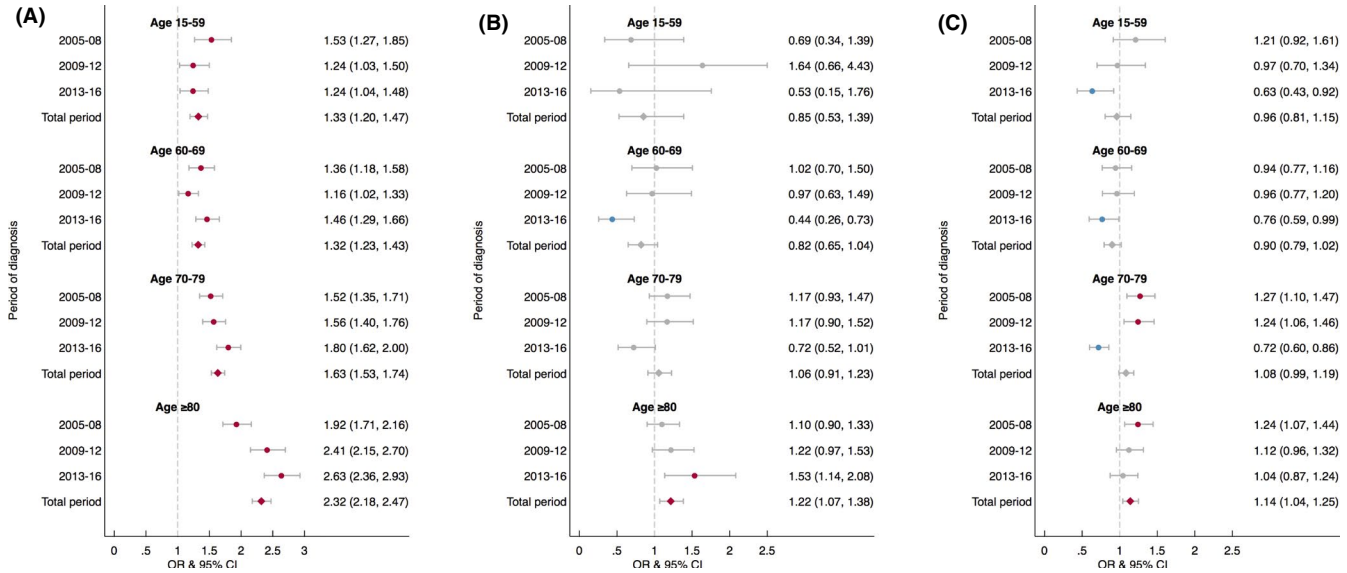

FIGURE 2 Odds ratios (OR) and 95% confidence intervals (CI) for (A) major surgical resection, (B) death within 30 days of resection and (C) death within 1 year of resection in Denmark compared with Yorkshire by age and period of diagnosis in colonic cancer. Significant results are indicated in red (increased odds in Denmark) and blue (increased odds in Yorkshire)

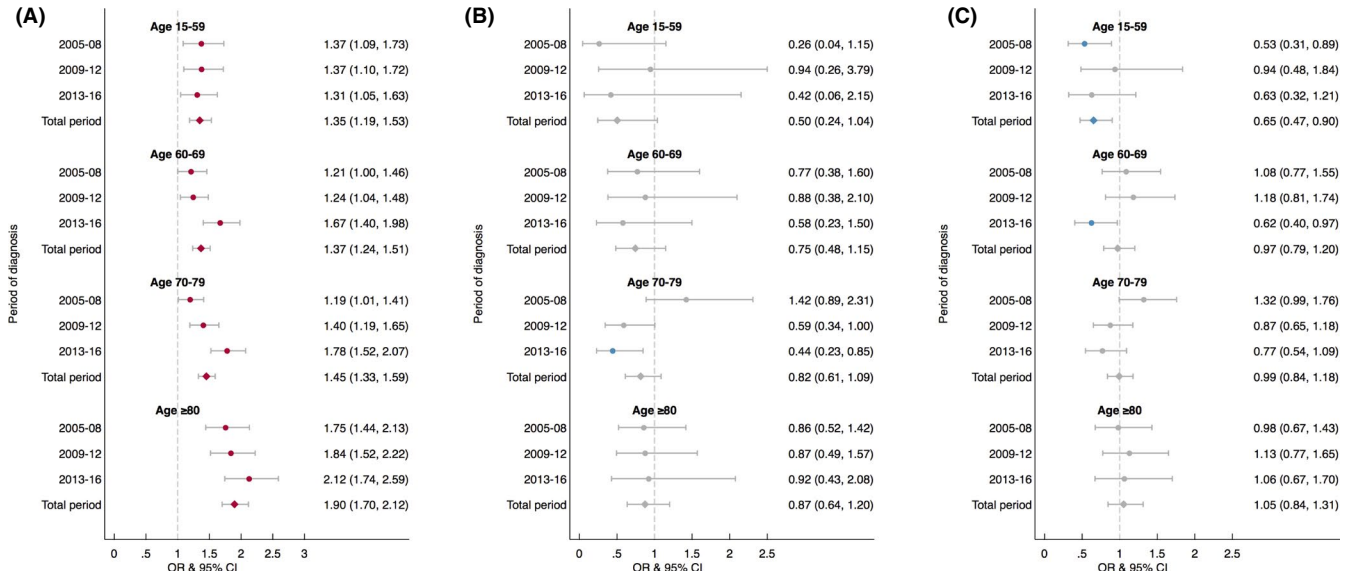

FIGURE 3 Odds ratios (OR) and 95% confidence intervals (CI) for (A) major surgical resection, (B) death within 30-days of resection and (C) death within 1 year of resection in Denmark compared with Yorkshire by age and period of diagnosis in rectal cancer. Significant results are indicated in red (increased odds in Denmark) and blue (increased odds in Yorkshire)

was significantly lower when comparing Danish and Yorkshire patients aged 70–79 years.

Whereas use of a major resection in Yorkshire for colonic cancer in patients aged ≥80 years decreased over time, the same was not true for the equivalent rectal cancer population. This coincided with an improvement in 1-year relative survival for Yorkshire patients of this age; this was, in fact, the only age group in Yorkshire to exhibit a significant improvement. As with colon cancer, relative survival steadily increased for the older age groups in both populations, suggesting an improvement in patient care. Interestingly, relative survival in the nonresected Danish patients aged <80 years improved dramatically from 2009–2012 to 2013–2016, which could possibly be due to increased survival for patients with metastatic disease.

Older patients are more likely to suffer from existing comorbidities and frailty. Therefore, it is an important issue to establish why the Danes appear more likely to operate in the older age groups than their counterparts in Yorkshire. Centralization of colorectal surgical

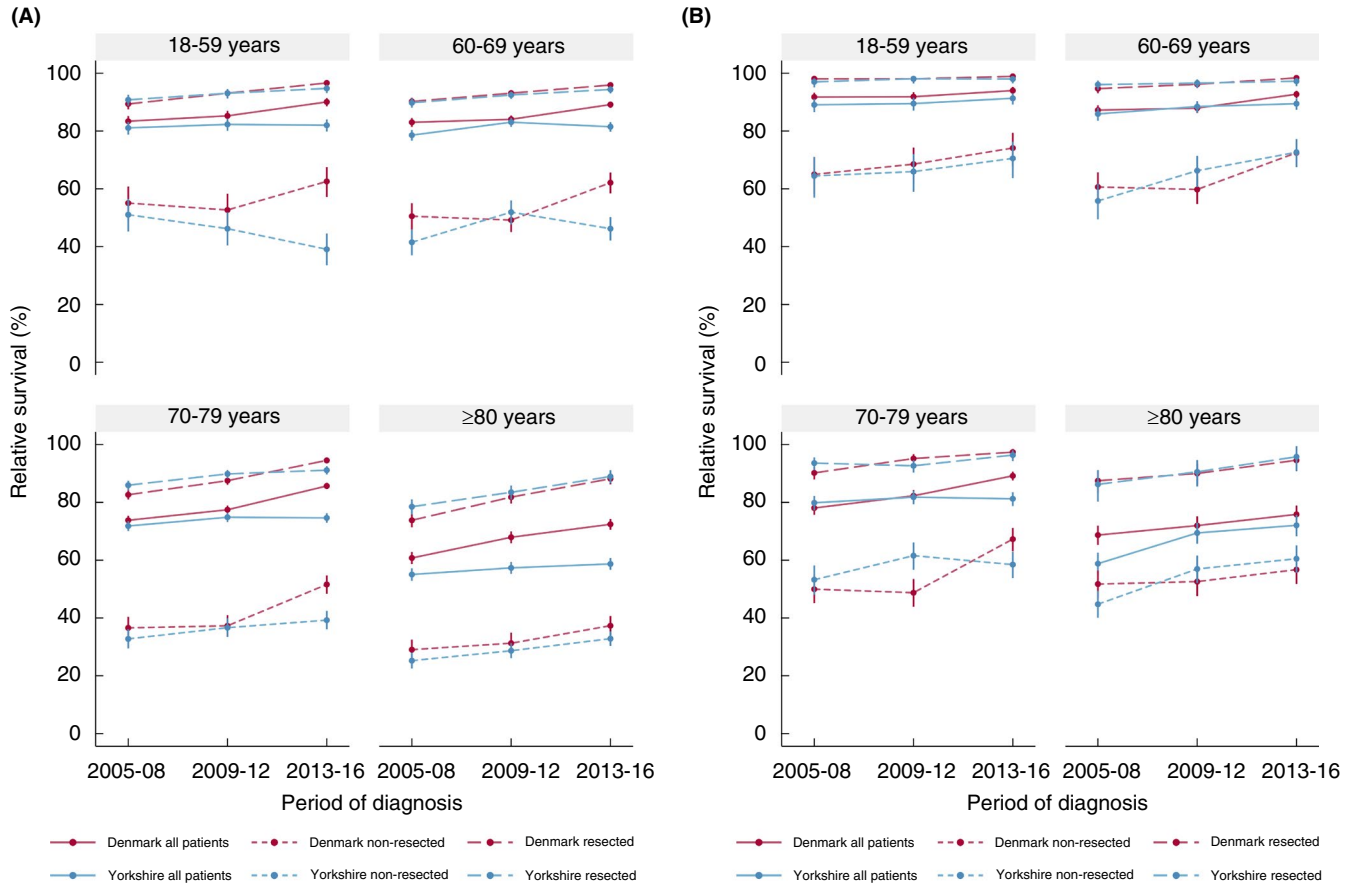

FIGURE 4 One-year relative survival and 95% confidence intervals stratified by age and period of diagnosis for all patients with colon cancer (A) and rectal cancer (B) in Denmark and Yorkshire, and by resection status

treatment was implemented in Denmark during the 2000s [4, 23], but the resulting number of centres is similar to that found in Yorkshire [9] with a population of equivalent size. The increased number of Danish cases shown in the last period of this study is almost certainly due to the later introduction of screening [24]. The impact of screening and centralization will have resulted in a higher number of cases per centre and, possibly, a higher per surgeon workload. Increased hospital and surgeon workload have shown associations with better outcomes in colorectal cancer [25, 26]. Preoperative and postoperative initiatives may also differ; for example, enhanced recovery after surgery (ERAS) has been adopted widely in Denmark [7] but not region-wide within Yorkshire. Since ERAS has been shown to lower the risk of postoperative complications and reduce recovery time [27], having such a policy in place may increase the willingness to operate. Additionally, Denmark is known to have a high uptake of laparoscopic surgery [6], which has been associated with reduced length of hospital stay and 30-day mortality compared with open surgery [28] and could be a contributing factor when considering patient recovery.

There are limitations in this study, and the implications of comparing the two datasets need to be considered. Potential disparities in case ascertainment may have a marginal effect on estimates of ORs when comparing proportions of resection between the two populations. However, we calculated that over 60% of colon cancer cases and over 40% of rectal cancer cases in Denmark would need to be missing in the ≥80 years age group in 2013–2016 for differences in ORs to be nonsignificant.

There are likely to be additional differences between the two datasets that may have an impact when investigating surgical management. The DCCG records the surgical procedure used at the time of operation, whereas the CORECT-R methodology uses an algorithm to retrospectively search hospital admission records and identify those patients who underwent a major resection. In addition, it is important to take into consideration that international comparison of survival estimates may be affected by differences in cancer registration practices [29]. This includes the completeness of the registration source [19, 30, 31] or errors in registration such as in the date of diagnosis [32]. However, this is unlikely to affect the survival estimates to the extent that it explains the observed differences [33].

The increased number of unknown stages in Denmark over time was largely down to revised TNM guidelines in 2014, in that some who were to receive neoadjuvant radio(chemo-)therapy may not have been given an initial stage due to the possibility of downstaging and thus classified as stage unknown. Conversely, staging information for Yorkshire patients improved over time. Thus, stratifying by stage groups may have resulted in spurious associations. Our stage-imputed models suggested differences in the use of resection according to stage. Stage III patients were less likely to have a major

resection than Stage II patients in Yorkshire, but not in Denmark. Further work investigating this using additional treatment information, or detailed TNM information, would improve stratification, allowing the impact of neoadjuvant radiotherapy in Stage III patients and use of local resections in Stage I patients to be assessed. Additionally, detailed comorbidity, performance status and lifestyle factors would all allow more detailed investigation of the differences shown in this study.

This study shows greater use of major resection in the older age groups for the Danish colorectal cancer population when compared with Yorkshire, corresponding to an increased short-term risk in colon cancer patients aged over 80 years but no increased risk in the longer term or in rectal cancer. If confirmed through further study, we should be able to identify more patients from Yorkshire who, with appropriate improvement in selection and improved peri- and postoperative care, are suitable for potentially curative surgery so improving long-term outcomes. It is important to appropriately communicate the risks of surgery, but it is also possible that many older patients in Yorkshire would benefit from consideration of a major resection.

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CONFLICT OF INTEREST

The authors declare there are no conflicts of interest.

AUTHOR CONTRIBUTIONS

John C. Taylor helped design the study, performed and interpreted the statistical analysis. Eva J. A. Morris, Philip Quirke, Lars Pedersen and Lene H. Iversen contributed to the design of the study, acquired and interpreted the data. Dermot Burke, Paul J. Finan, Simon Howell and Mark M. Iles interpreted the data. All authors contributed to the drafting of the article and approved the final version.

ETHICAL APPROVAL

The study was granted ethical approval (17/WM/0374) by the West Midlands – Solihull Research Ethics Committee in December 2017. The study was approved by the Health Research Authority and granted approval for inclusion in the National Institute for Health Research's portfolio of studies in December 2017 (project ID 227673).

DATA AVAILABILITY STATEMENT

The data used for this study are available from the National Cancer Registration and Analysis Service via application to the Public Helath England Office for Data Release and CORECT-R, and application to the DCCG, subject to relevant approvals.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of the article at the publisher's website.

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