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Colorectal cancer survival trends in Norway 1958–1997

E. Angell-Andersen[a,*], S. Tretli[a,b], M.P. Coleman[c], F. Langmark[a], T. Grotmol[a]

[a]*Cancer Registry of Norway, Institute of Population-based Cancer Research, Montebello, N-0310 Oslo, Norway*
[b]*The Norwegian University of Science and Technology, Trondheim, Norway*
[c]*London School of Hygiene and Tropical Medicine, London WC1E 7HT, UK*

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Abstract

The purpose of this study was to examine the pattern of survival for colorectal adenocarcinoma (CRC), and to investigate the prognostic factors for the disease. In the analysis, 50 993 cases of CRC aged 40–84 years, diagnosed between 1958 and 1997 in Norway, were included. Esteve's relative survival method was used, together with a time trend analysis, conducted by least-squares linear regression. Cox proportional hazards regression analysis was used to examine cause-specific mortality. Five-year relative CRC survival has increased by an estimated 3% per 5-year diagnostic period. In 1958–1962, relative survival was about 40% for both males and females, and increased to 56 and 60%, respectively, in 1993–1997. Rectal cancer had a higher cause-specific mortality (RR 1.26, 95% CI 1.22–1.30) than proximal colon (reference) and distal colon (RR 0.97, 95% CI 0.93–1.00 cancers), while females had a lower cause-specific mortality than males (RR 0.88, 95% CI 0.86–0.90). The increase in the relative survival rate in Norway is probably due to improved treatments and advanced diagnostics. Norway has a higher CRC survival rate than the EUROCARE average.
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1. Introduction

Colorectal cancer is the second most common type of cancer among both males and females in Norway, with a world standardised age-adjusted incidence rate in 1993–1997 of 40 per 100 000 for males, and 33 per 100 000 for females [1]. In 1958–1962, the incidence was 17 per 100 000 for males and 15 per 100 000 for females. Thus, there has been more than a doubling of incidence in the period between 1958 and 1997. This incidence trend has increased significantly more than in the other Nordic countries during the same time period. However, the reasons for this are still obscure [2]. Currently, Norway has the highest incidence of colorectal cancer in this region. Accordingly, it is of interest to see whether the relatively high increase in the incidence of colorectal cancer has affected survival rates in the period between 1958 and 1997.

In 1985–1989, the 5-year relative survival for colorectal cancer in Europe was, on average, 47%, but the differences between countries ranged from 25 to 59% for males, and 23 to 56% for females [3]. Most of the variation in survival between the countries is thought to be due to differences in tumour stage at diagnosis [4]. The EUROCARE relative survival average has increased steadily over the past decades, with the risk of dying from this cancer form going down approximately 20% from 1978–1980 to 1987–1989 [4]. Survival has also increased in countries where it was initially high, indicating that even where diagnosis and treatment are good, survival can be improved [5]. Norway has not previously participated in the EUROCARE study. It is, therefore, of interest to compare the Norwegian data with this study.

The prognosis of colorectal cancer is first, and above all, dependent on the stage of the disease at diagnosis, but also on treatment (surgery and adjuvant therapy). In addition, factors related to the tumour and the host (patient) may also be important. No consensus exists as to whether the anatomical location of the tumour is important for the probability of survival. Some have

* Corresponding author. Tel.: +47-2333-3968; fax: +47-2245-1370.
E-mail address: elisabeth.andersen@kreftregisteret.no (E. Angell-Andersen).

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noted significantly better survival for cancer of the proximal and distal colon versus rectum after 5 years [3,6], while others have seen no significant difference [7]. There is also controversy about other prognostic factors, such as gender and age with proponents both for [8,9], and against [5,6,10] their role.

The population-based Norwegian Cancer Registry was used to study the three aims mentioned above, namely to examine the patterns of relative survival for colorectal cancer for patients diagnosed in the period 1958–1997, to compare colorectal cancer survival in Norway with the EUROCARE countries, and to study the prognostic factors for cause-specific mortality for colorectal cancer.

2. Patients and methods

2.1. Study population

Currently, Norway has a population of 4.5 million (2002), whereas its population in 1958 was 3.3 million. Norway has free access to health care, and has an egalitarian system of health.

Since 1952, Norway has had a complete population-based cancer registry. Notification of cancer cases is statutory. The notification includes a unique identification number, anatomical location (based on International Classification of Disease, version O (ICD-O)), stage of disease at time of diagnosis (the rules of the Surveillance, Epidemiology and End-Results (SEER) programme), histological findings, and basis for diagnosis. Previous ICD versions were converted to ICD-O. For colorectal cancer, 97% of the cases among males, and 94% among females are histologically-verified [1]. The Cause of Death Registry at Statistics Norway registers all deaths, based upon death certificates issued by physicians. The underlying cause of death is recorded for all cases.

This study includes all cases of colorectal adenocarcinoma diagnosed in Norway from 1958 to 1997. The study population was aged between 40 and 84 years at the time of diagnosis. The inclusion and exclusion criteria for the present study are the same as those used in our examination of trends in incidence of colorectal cancer in Norway in the period from 1958 to 1997 [2].

Tumours localised in the caecum, ascending and transverse colon (ICD-O C18.0, C18.2–C18.6, C18.8) were defined as proximal colon cancers, while distal colonic cancer constitutes cancers of the descending and sigmoid colon, and rectosigmoid junction (ICD-O C18.7, C19). Rectal cancers (ICD-O C20) were included as one group. Sub-site information (ICD-O C18.9) was lacking for 996 persons (2.0%), and these were excluded in the sub-analyses.

Only the first tumour in the colorectal area was included, as patients with previous cancer are likely to have a poorer than average survival, leading to the exclusion of 1682 cases (3.0%). For death certificate only (DCO) and autopsy only cases, the month of diagnosis and death is the same. These cases must be excluded, since their true date of diagnosis is unknown, leading to the exclusion of 1327 cases (2.5%).

2.2. Statistical analysis

2.2.1. Relative survival

There are primarily three ways of measuring survival: crude survival, cause-specific survival, and relative survival [11]. Relative survival is the 'method of choice' for most cancer registries [12], as it is accurate even for analyses on patients over 75 years of age [13] and as no information on the cause of death is required. Relative survival is the ratio of the observed survival in the study group to the survival expected if the cases were following the mortality rates of the general population from which they arise.

The Estève method was used to estimate relative survival. This model is based on individual data and a maximum likelihood approach (proportional hazards model) [14]. STATA statistical package was used for this analysis, using the STREL algorithm described by Coleman and colleagues [11]. The STREL algorithm is widely used, and is found to give stable estimates [11].

The life table used for the expected mortality of the general population was supplied by Statistics Norway, with all-cause death rates for each 5-year period by single year of age and gender. End of follow-up was set to 1 April 2002, as Statistics Norway had complete vital status registration to that date when the analyses were conducted.

The relative survival rates were age-standardised using the direct method with the EUROCARE standard for colorectal cancer used as weights [15], adjusted for the difference in age groups between EUROCARE and this study. The weights are the same for males and females. This allows direct comparison with EUROCARE data.

A test of trend was conducted to examine the average increase in 5-year relative survival over the 40-year period. The average change in survival between successive 5-year periods was estimated by fitting a least-squares linear regression to the age-standardised survival rates for the eight diagnostic periods, for colorectal overall and for each of the sub-sites, separately for males and females. The assumption of linearity was verified by assessing the plots.

2.2.2. Cox regression analysis

The Cox proportional hazards model was used to perform a multivariate analysis to estimate the influence of the predictor variables (gender, age at diagnosis, period of diagnosis, anatomical location) after control-

ling for stage, on cause-specific (colorectal cancer) mortality. The assumption of proportional hazard for the variables was verified by performing log-minus-log plot of the covariates versus the mortality rates. The endpoint for the Cox regression was cause-specific mortality in the first five years of observation. A 'forward' fitting strategy was used to select the variables that contributed significantly to the final model, the level of significance was defined as $P < 0.05$.

More than 500 deaths in both the first and last diagnostic period 20% and 5% of the patients, respectively, had no cause of death specified. Therefore, these two periods were excluded from this analysis.

3. Results

3.1. Characteristics

A total of 50 993 patients were included in the analysis: 25 816 males and 25 177 females. Table 1 shows the characteristics of the participants. The age distribution was similar for males and females, with the median age being 70 years for both genders. The age distribution has shifted over the past 40 years, with the median age increasing from 67 years for men and 66 years for women in the period 1958–1962 to 71 and 72 years in the period 1993–1997, respectively. As Table 2 shows, the stage-specific distribution for all sub-sites has also changed the proportion of localised cancers has decreased between 50–70% in the 40-year study period.

Table 1
Characteristics and percentage distribution of the 50 993 Norwegians diagnosed with colorectal cancer between 1958 and 1997

Variable	Male	Female
	n (%)	*n* (%)
Age at diagnosis (years)		
40–44	416 (2)	504 (2)
45–49	823 (3)	849 (3)
50–54	1402 (5)	1457 (6)
55–59	2299 (9)	2144 (9)
60–64	3572 (14)	3184 (13)
65–69	4689 (18)	3995 (16)
70–74	5255 (20)	4969 (20)
75–79	4575 (18)	4602 (18)
80–84	2785 (11)	3473 (14)
Period of diagnosis		
1958–1962	1265 (5)	1194 (5)
1963–1967	1773 (7)	1777 (7)
1968–1972	1775 (7)	1717 (7)
1973–1977	2455 (10)	2435 (10)
1978–1982	3649 (14)	3720 (15)
1983–1987	4762 (18)	4612 (18)
1988–1992	5086 (20)	4875 (19)
1993–1997	5051 (20)	4847 (19)
Stage at diagnosis		
Localised	9771 (38)	9268 (37)
Regional	10 147 (39)	10 212 (41)
Distant	5401 (21)	5233 (21)
Unknown	497 (2)	464 (2)
Sub-site		
Proximal colon	7194 (28)	9426 (37)
Distal colon	8023 (31)	7807 (31)
Rectum	10 599 (41)	7944 (32)

3.2. 5-year relative survival

There has been a clear increase in 5-year relative survival rates (subsequently referred to as 'survival'). Table 3 shows survival for males and females for each period of diagnosis and by sub-site, and the adjusted age-standardised survival rates. In 1958–1962, survival for colorectal cancer was around 40% for both males and females. Over the next 40 years, survival increased steadily for all sub-sites, and in 1993–1997 overall survival was 56% for males and 60% for females.

Fig. 1 presents the overall and stage-specific colorectal cancer survival rates from 1958–1962 to 1993–1997. For localised cancers, survival for males has increased from 59% in 1958–1962 to 84% in 1993–1997; while for females, the increase has been from 60 to 87%. The increase in survival has been of an even larger magnitude for cancers with a regional extent, with an increase from 28 and 37% in 1958–1962, to 64 and 65% in 1993–1997, for males and females, respectively. For patients with distant metastases, there has been no increase in survival for either gender over the 40-year period.

Table 2
Distribution of the 50 993 colorectal cases by stage at diagnosis and sub-location for three selected time periods of diagnosis

Sub-site	Stage at diagnosis	1958–1962 (%)	1973–1977 (%)	1993–1997 (%)
Proximal colon	Localised	44	34	24
	Regional	33	42	52
	Distant	21	23	22
	Unknown	3	1	1
	Total (*n*)	766	1489	3577
Distal colon	Localised	47	36	29
	Regional	32	36	48
	Distant	19	26	22
	Unknown	2	2	2
	Total (*n*)	840	1528	2992
Rectum	Localised	53	49	37
	Regional	28	31	43
	Distant	15	19	18
	Unknown	3	2	2
	Total (*n*)	853	1873	3332

Table 3
Five-year relative survival (%) (and 95% CI) of colorectal cancer by period of diagnosis

	Gender	Period of diagnosis							
		1958–1962	1963–1967	1968–1972	1973–1977	1978–1982	1983–1987	1988–1992	1993–1997
Colorectal (all)	M	38.7 (35.6–41.8)	40.5 (37.8–43.2)	38.3 (35.6–40.9)	43.0 (40.7–45.4)	47.3 (45.3–49.2)	49.6 (47.8–51.3)	51.0 (49.3–52.7)	56.3 (54.6–58.0)
	F	40.1 (37.0–43.2)	41.0 (38.4–43.5)	42.8 (40.2–45.4)	46.3 (44.1–48.6)	50.4 (48.5–52.2)	53.4 (51.7–55.1)	56.4 (54.8–58.0)	59.6 (57.9–61.2)
Proximal colon	M	45.0 (39.0–51.2)	50.0 (44.5–55.0)	48.1 (42.5–53.6)	50.4 (45.4–55.1)	50.3 (46.4–54.1)	51.0 (47.5–54.3)	51.0 (47.8–54.1)	54.9 (51.8–58.0)
	F	43.3 (37.9–48.6)	43.8 (39.4–48.1)	47.2 (42.4–51.7)	47.4 (43.5–51.1)	50.2 (47.1–53.2)	55.8 (53.0–58.5)	55.6 (52.9–58.2)	59.4 (56.8–61.8)
Distal colon	M	33.9 (31.6–42.3)	38.8 (34.2–43.3)	37.9 (33.1–42.6)	45.4 (41.0–49.6)	51.4 (47.7–55.1)	53.2 (50.0–56.3)	53.2 (50.2–56.3)	59.3 (56.1–62.3)
	F	39.0 (33.8–44.2)	42.9 (38.4–47.3)	43.8 (39.4–48.1)	47.6 (43.6–51.5)	51.6 (48.2–54.9)	54.2 (51.2–57.1)	57.9 (54.9–60.7)	58.9 (55.9–61.9)
Rectum	M	35.6 (31.6–40.5)	35.2 (31.1–39.4)	32.7 (28.7–36.6)	37.4 (34.0–40.8)	42.8 (39.9–45.7)	46.2 (43.6–48.9)	49.4 (46.8–52.1)	55.2 (52.4–57.9)
	F	38.2 (32.6–43.8)	35.7 (31.2–40.2)	37.4 (32.8–41.9)	44.0 (40.1–47.9)	49.4 (46.2–52.5)	50.0 (47.0–52.9)	56.1 (53.2–58.9)	60.5 (57.5–63.5)
Age-adjusted colorectal (all)	M	38.4	40.0	37.7	42.4	47.0	50.5	52.7	57.0
	F	39.1	40.8	44.0	46.3	50.7	54.1	56.8	59.7

M, male; F, female; 95% CI, 95% Confidence Interval.

Table 4
Estimated increase (%) in 5-year relative survival per 5-year diagnostic period for colorectal cancer in Norway 1958–1997

Sub-site	Gender	% increase (95% CI)	*P* value
Proximal colon	M	1.0 (0.5–1.7)	0.003
	F	2.4 (2.0–2.9)	<0.001
Distal colon	M	3.5 (2.6–4.4)	<0.001
	F	3.0 (2.5–3.6)	<0.001
Rectum	M	3.3 (2.5–4.1)	<0.001
	F	3.4 (2.8–4.4)	
Colorectal (all)	M	2.8 (2.1–3.6)	<0.001
	F	3.2 (2.7–3.7)	<0.001

Table 4 gives the estimated average increase in colorectal cancer survival between successive 5-year diagnostic periods. There was a significant increasing trend, both overall and for all sub-sites of the bowel. The smallest increase in survival was seen for proximal cancer in males where the estimated increase per 5-year diagnostic period was 1.0%. The largest increase in survival was seen for distal colon cancer for males and rectal cancer for females, with an increase of 3.5% per 5-year diagnostic period.

3.3. Comparison with EUROCARE

Table 5 shows the Norwegian age-standardised survival rate compared with the EUROCARE rate for 1985–1989 [5]. Table 5 shows that Norway has a significantly higher colorectal cancer survival than the EUROCARE average for both genders. Norwegian colorectal survival rates range between 47 and 55%, while EUROCARE rates range between 42 and 47%. Table 5 also gives the survival rates for colon and rectal cancer for the Nordic countries [5]. These survival estimates for both colon and rectum, for both genders are similar, with the exception of Denmark.

3.4. Cox regression analysis

Table 6 presents the crude and the adjusted relative risks (RR) for the covariates in the Cox regression analyses on cause-specific mortality. All covariates were found to contribute significantly to the final model. The most important prognostic variable for cause-specific mortality within the patient population was stage at diagnosis, with those being diagnosed with distant metastases having a more than 9 times higher cause-specific mortality than those with localised cancer. Females had significantly lower cause-specific mortality than males (RR 0.88, 95% CI 0.86–0.90). After similar analyses on all-cause mortality for the last two diagnostic periods only, females continued to have a lower relative mortality risk (RR 0.84, 95% CI 0.81–0.87)

Table 5
Comparison of 5-year relative survival for colorectal cancer between Norway, the Nordic countries and EUROCARE

Country	Colon		Rectum	
	Men survival (95% CI)	Women survival (95% CI)	Men survival (95% CI)	Women survival (95% CI)
Norway[a]	52 (50–54)	55 (53–57)	47 (44–49)	50 (47–52)
Sweden[b]	52 (48–56)	55 (52–57)	49 (45–54)	52 (47–57)
Finland[b]	48 (44–51)	50 (48–52)	49 (46–53)	46 (43–49)
Iceland[b]	44 (35–55)	52 (42–63)	N/A	53 (39–70)
Denmark[b]	39 (37–41)	43 (41–44)	38 (36–40)	41 (39–44)
EUROCARE[b]	47 (45–48)	46 (45–48)	42 (41–44)	43 (41–44)

N/A, not available.
[a] 1983–1987 age-standardised.
[b] 1985–1989 from the EUROCARE study [3].

Table 6
Crude and adjusted relative risks and 95%CI from Cox regression for cause-specific mortality for colorectal cancer diagnosed in 1963–1992 in Norway

Variable	*N*	Crude RR	Crude 95% CI	Adjusted RR[a]	Adjusted 95% CI[a]
Stage at diagnosis					
Localised	14 910	1	Reference	1.00	Reference
Regional	14 875	1.96	1.89–2.03	2.11	2.03-2.18
Distant	8129	8.66	8.33–8.99	9.26	8.92-9.62
Unknown	722	6.08	5.57–6.65	6.12	5.60–6.69
Age at diagnosis (years)					
40–44	691	0.85	0.76–0.96	0.83	0.74–0.93
45–49	1288	0.96	0.88–1.05	0.92	0.85–1.01
50–54	2152	0.93	0.87–1.00	0.90	0.84–0.97
55–59	3465	0.96	0.91–1.02	0.96	0.90–1.02
60–64	5249	1	Reference	1.00	Reference
65–69	6728	1.00	0.95–1.06	1.06	1.00–1.12
70–74	7653	1.18	1.12–1.24	1.25	1.19–1.31
75–79	6841	1.29	1.23–1.35	1.45	1.38–1.53
80–84	4569	1.55	1.47–1.63	1.85	1.76–1.95
Gender					
Male	19 500	1	Reference	1.00	Reference
Female	19 136	0.88	0.86–0.91	0.88	0.86–0.90
Period of diagnosis					
1963–1967	3550	1.43	1.36–1.51	1.61	1.52–1.69
1968–1972	3492	1.43	1.35–1.50	1.49	1.42–1.57
1973–1977	4890	1.29	1.23–1.35	1.30	1.24–1.36
1978–1982	7369	1.16	1.11–1.20	1.13	1.08–1.18
1983–1987	9374	1.07	1.03–1.11	1.07	1.03–1.11
1988–1992	9961	1	Reference	1.00	Reference
Sub-site					
Proximal colon	12 277	1	Reference	1.00	Reference
Distal colon	11 998	0.96	0.92–0.99	0.97	0.93–1.0
Rectum	14 361	1.08	1.04–1.11	1.26	1.22–1.30

RR, relative risk.
[a] Adjusted for each of the covariates in the table.

(data not shown). The risk associated with anatomical location was affected by the adjustment, with a high increase in risk for the rectum. After adjustment, rectal cancer had a higher cause-specific mortality (RR 1.26, 95% CI 1.22–1.30) than proximal colon (reference) and distal colon (RR 0.97, 95% CI 0.93–1.00). No difference in survival was seen between the proximal and distal colon. For the last two diagnostic periods on all-cause mortality, rectal cancer continued to have higher relative mortality risk (RR 1.10, 95% CI 1.05–1.15) (data

not shown). The earliest diagnostic periods had a higher risk of cause-specific mortality: those diagnosed in 1963–1967 had a 1.6-fold higher risk of cause-specific mortality compared with those diagnosed in 1988–1992. The cause-specific mortality for the age groups from 40–44 years to 60–69 years was roughly similar. Mortality was higher at older ages, for example the age group 75–79 years have a 45% higher risk of dying than the age group 60–64 years (reference). The trends for both period of diagnosis (RR 0.92, 95% CI 0.92–0.93) and age at diagnosis (RR 1.08, 95% CI 1.07–1.09) were significant.

4. Discussion

The 5-year relative survival rates (subsequently referred to as 'survival') of colorectal adenocarcinoma have shown an estimated average increase of around three percent between the successive five-year diagnostic periods over the past 40 years. In 1958–1962, survival was around 40% for males and females, but this has increased to 56 and 60%, respectively, in 1993–1997. This increase in survival has occurred in a period where colorectal cancer incidence has escalated dramatically in Norway. Thus, the healthcare system has apparently handled this increased number of patients satisfactorily.

There may be a number of reasons why survival has improved over time. Peri- and postoperative mortality for this group of patients has declined from approximately 10% around 1960, to the present figure of less than 5% [16]. This is due to the introduction of the prophylactic use of antibiotics in the 1980s, and better anaesthetic surveillance; improved surgical treatments may also have played a role. A small contribution to the improved survival may have resulted from the preoperative use of irradiation therapy against primarily inoperable rectal cancer [17], and the increased use of chemotherapy. In addition, a more aggressive surgical approach against local recurrence of the disease and distant metastasis may have contributed.

Although there is no direct evidence in favour of an earlier diagnosis of colorectal cancer during our study period, it is likely that establishing colonoscopy as a routine diagnostic tool in the 1980s has resulted in an increase in earlier diagnoses. Lead-time bias makes it difficult to assess the true effect of earlier diagnosis on survival. However, what the improved diagnostic techniques have led to is a more accurate staging over time. When the staging is more accurate, stage-specific, but

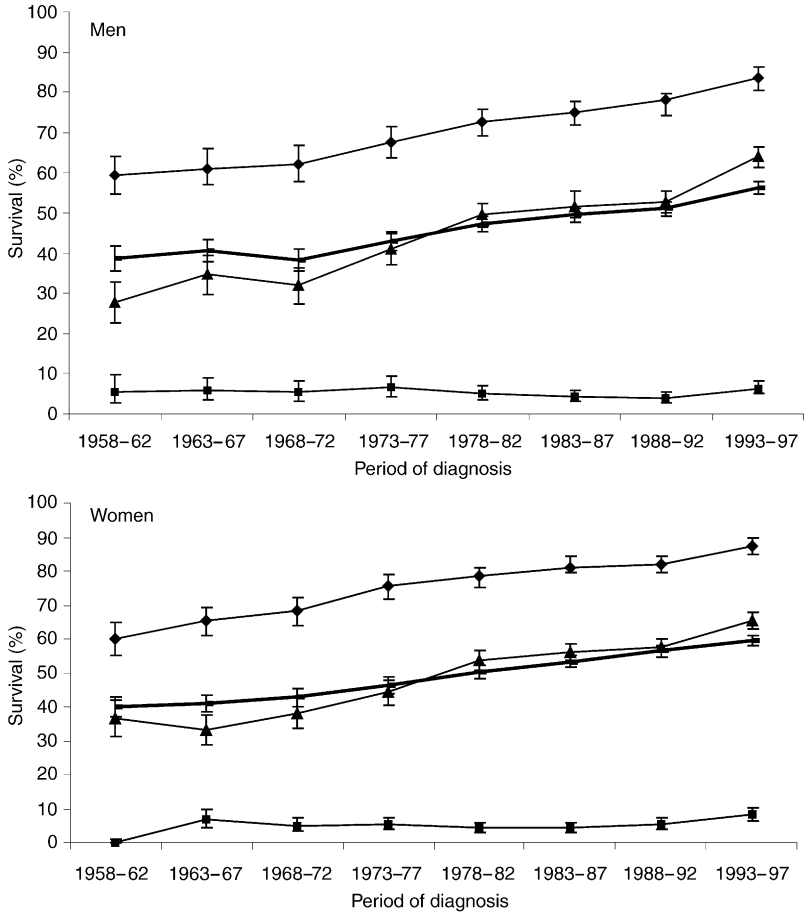

Fig. 1. Five-year relative colorectal cancer survival by stage of diagnosis (◆ localised, ▲ regional, ■ distant, ━ all stages).

not overall survival is influenced [18]. This is due to stage-migration: localised cancers are now to a higher extent 'true' localised cancers, while those diagnosed as advanced cancers in fact now also include the moderately advanced. Moreover, over time, stage-specific treatments will be improved due to more accurate staging, and this should improve the overall survival rates. Thus, comparing stage-specific survival estimates over time should be done with caution. The stage-specific survival of colorectal cancer has increased substantially from 1958 to 1997, and so has the proportion of moderately advanced tumours (with regional extent). A similar shift of stage-distribution has also been seen in Denmark [19]. Much of this shift is likely an artefact, due to stage-migration. This is supported by our data in that the survival of localised and regional cancers improved more than the overall survival rates during our study period, for both males and females (Fig. 1).

There is also another indication of an earlier detection of cancer over time. In a previous age–period–cohort analysis of Norwegian colorectal cancer incidence data covering the same time period, we have shown that for distal colon and rectum cancers, the period effect is more pronounced than the cohort effect in both males and females [2]. The opposite is suggested for proximal colon cancers. This indicates that for cancers localised in the distal part of the gastrointestinal tract, there may have been an improved early diagnostic yield over time, also influenced by a decrease in patient delay [20]. Although no organised screening programme has been implemented for colorectal cancer in this country so far, there has probably been an increased diagnostic activity in the colorectum (endoscopy, faecal occult blood test), and an increased awareness of symptoms [21]. Due to its easier access and earlier detection of symptoms, the distal part rather than the proximal part of the colon, has profited most from this, which has probably led to earlier detection of these cancers over time.

Registration practices may also have changed during the 40 years of our study. In 1958–1962, a tumour in the colorectal area may have been coded as 'unspecified location' in the abdomen or pelvis (ICD-O C 76.2/ICD-O C76.3). During the study period, improved diagnostics and the development of registration practices have led to more tumours being coded with a specified location. As an example, the age-adjusted incidence rates of this location (ICD-O C76.2) was 11.4 per 100 000 for males and 13.4 per 100 000 for females in 1958–1962, decreasing to around 2 per 100 000 for both genders in 1993–1997 (world standardised). The specific distribution of cancers in this location is not known, but most cancers probably have a true location in the pancreas or the liver, but also the colon, genitalia, intestines, and stomach are possible locations. The higher incidence seen in females 1958–1962 is probably related to a number of cancers of the ovaries. None the less, some cases from this category, and the other locations mentioned above, should, with today's standards, be classified as colorectal cancer. As survival of cancers with an 'unspecified location' is poor (approximately 5%), the decreasing use of this location suggests that the true survival in the earlier diagnostic periods may be lower, and therefore, the estimated increase over the 40-year period is probably higher than that reported here.

The Norwegian survival estimates for colorectal cancer were higher than the EUROCARE average, and equal to those of the Nordic countries. Gatta and colleagues [5] suggested that a likely explanation for the diverging EUROCARE survival estimates was differences in management, with an estimated 50% of the variability being attributed to variation in health spending. The Nordic countries are seen as a homogeneous group, as all countries have free access to health care. The Nordic countries have seen a widespread increase in colorectal incidence over the past 40 years, with Norway having the highest increase [22]. The mortality of colorectal cancer has been rather stable in all the Nordic countries, but again Norway has proven to be the exception with much higher increase being observed [22]. All countries, except Denmark, have similar survival estimates (Table 5). The lower survival in Denmark appears to be due to patients being diagnosed at a later stage compared with patients in the other Nordic countries [23].

However, one must be careful in the comparison between countries and registries, as the example about tumours with an unspecified location in the abdomen (ICD-O C76.2) has shown. This is also illustrated by comparison with data from the United States of America (USA), a country that has a higher survival average than Norway, with survival being close to 60% in 1985–1989 [24]. However, it is suggested that the SEER programme in the USA registers non-surgical cases to a lesser degree, and is also more likely to include small or clinically silent lesions [24]. This will make direct survival comparisons with a population-based registry problematic.

There has been some controversy as to whether age, gender or anatomical location are important prognostic factors [3,6–10]. Accordingly, as part of this study, a multivariate Cox regression analysis was performed. No difference in survival was detected between cancers of the proximal and distal colon, whereas cancers of the rectum had a worse prognosis than those of the colon. This is evidenced by the historically high local recurrence rate for rectal cancer [16], which may be due to both treatment and genetic factors. Technically, rectal cancers are more difficult to remove surgically, as they are situated low in the pelvic area [25]. It is also suggested that proximal cancers, in particular, have a better survival compared with rectal cancer due to a genetic advantage [26]. Females have a lower risk of cause-specific mortality, which may be due to females having a

broader sacrum [25], making surgery easier. Contrary to common belief, previous studies do not suggest that females are more prone than males to respond to cancer symptoms [27]. This study also found that only ages over 70 years have a higher cause-specific mortality compared with the younger age groups. As the median age is 72 years in 1993–1997, attention must be placed on improving detection and treatment at an older age.

This is a population-based study, with complete records of colorectal cancer patients, thus, most biases can be ruled out. However, selection bias can arise from the cases excluded as DCO and autopsy. In this study, this proportion was stable over time, and lower than that found in the survival analysis of England and Wales [11]. Thus, the proportion of DCO is unlikely to have any influence on the survival trends presented here.

In conclusion, this population-based study indicates that there has been a real increase in colorectal cancer survival in Norway between 1958 and 1997, during a period of increased incidence. The improvement in survival is probably due to advances in treatment, and possibly diagnostic methods. Improved patient delay and earlier diagnosis also cannot be ruled out. Norway has higher survival estimates than the EUROCARE average, probably due to an adequate healthcare system, including appropriate health spending. Females have lower cause-specific mortality than males, and rectal cancer has a higher mortality than colon cancer. Further attention should be focused on how Norway can continue to improve colorectal cancer survival. In addition, the criteria for survival comparison between countries ought to be standardised. It is important to ensure that the basis of registration is similar, therefore, survival comparison should ideally be limited to population-based registries. Future studies should also be aimed at exploring the reasons for the difference in cause-specific mortality between the genders and between cancers within the colorectum.

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References

1. The Cancer Registry of Norway. *Cancer in Norway 2000*. Oslo, Info Print As, 2003.
2. Svensson E, Grotmol T, Hoff G, Langmark F, Norstein J, Tretli S. Trends in colorectal cancer incidence in Norway by gender and anatomic site: an age-period-cohort analysis. *Eur J Cancer Prev* 2002, **11**, 489–495.
3. Gatta G, Faivre J, Capocaccia R, Ponz de Leon M. Survival of colorectal cancer patients in Europe during the period 1978–1989. *Eur J Cancer* 1998, **34**, 2176–2183.
4. Gatta G, Capocaccia R, Sant M, *et al*. Understanding variations in survival for colorectal cancer in Europe: a EUROCARE high resolution study. *Gut* 2000, **47**, 533–538.
5. Sant M, Capocaccia R, Coleman MP, *et al*. Cancer survival increases in Europe, but international differences remain wide. *Eur J Cancer* 2001, **37**, 1659–1667.
6. Fernandez E, Bosetti C, La Vecchia C, Levi F, Fioretti F, Negri E. Sex differences in colorectal cancer mortality in Europe, 1955–1996. *Eur J Cancer Prev* 2000, **9**, 99–104.
7. Ronucci L, Fante R, Losi L, *et al*. Survival for colon and rectal cancer in a population-based cancer registry. *Eur J Cancer* 1996, **32A**, 295–302.
8. Crocetti E, Barchielli A, Buiatti E, Castiglione ?, Zappa M. Colorectal cancer survival- population-based rates in the province of Florence. *Eur J Cancer Prev* 1996, **5**, 189–195.
9. Micheli A, Mariotto A, Giorgi Rossi A, Gatta G, Muti P, the EUROCARE working group. The prognostic role of gender in survival of adult cancer patients. *Eur J Cancer* 1998, **34**, 2271–2278.
10. Yeole BB, Sunny L, Swaminathan R, Sanjaranarayanen E, Parkin DM. Population-based survival from colorectal cancer in Mumbai (Bombai) India. *Eur J Cancer* 2001, **37**, 1402–1408.
11. Coleman MP, Babb P, Damiecki P, *et al*. *Cancer Survival Trends in England and Wales: Deprivation and NHS Region*. London, The Stationery Office, 1999.
12. Dickman P, Sloggett A, Hills M, Hakulinen T. Regression models for relative survival. *Stat Med* [in press].
13. Zahl PH. A proportional regression model for 20-year survival of colon cancer in Norway. *Stat Med* 1995, **14**, 1249–1261.
14. Estève J, Benhamou E, Croasdale M, Raymond L. Relative survival and the estimation of net survival: elements for further discussion. *Stat Med* 1990, **9**, 529–538.
15. Berrino F, Sant M, Verdecchia A, the EUROCARE working group. *Survival of Cancer Patients in Europe: The EUROCARE Study*. IARC Scientific Publication No. 132). Lyon, International Agency for Research on Cancer, 1995.
16. Wibe A, Møller B, Norstein J, *et al*. A national strategic change in treatment policy for rectal cancer—implementation of total mesorectal excision as routine treatment in Norway. A national audit. *Dis Colon Rectum* 2002, **45**, 857–866.
17. Horn A, Morild I, Dahl O. Tumour shrinkage and down staging after preoperative radiation of rectal adenocarcinomas. *Radiother Oncol* 1990, **18**, 19–28.
18. Feinstein AR, Sosin DM, Wells CK. The Will Rogers phenomenon. Stage migration and new diagnostic techniques as a source of misleading statistics for survival in cancer. *N Engl J Med* 1985, **312**, 1604–1608.
19. Johansen C, Soll-Johanning H, Kolstad H, Lynge E, Carstensen B. Digestive organs, Survival of Danish cancer patients 1943–87. *APMIS* 1993, **101**(Suppl. 33), 51–60.
20. Carter S, Winslet M. Delay in presentation of colorectal carcinoma: a review of causation. *Int J Colorectal Dis* 1998, **13**, 27–31.
21. Steine S, Lærum E. Referrals for radiological examination of the large bowel. Pre-radiological examinations, tests, and referral letters. *Fam Pract* 1994, **11**, 21–25.
22. Coleman MP, Esteve J, Damiecki P, Arslan A, Renard H. Trends in cancer incidence and mortality. *IARC Sci Publ* 1995, **132**, 225–237.
23. Engeland A, Haldorsen T, Dickman PW, *et al*. Relative survival of cancer patients: a comparison between Denmark and the other Nordic countries. *Acta Oncol* 1998, **37**, 49–59.

24. Gatta G, Capocaccia R, Coleman MP, *et al*. Toward a comparison of survival in American and European cancer patients. *Cancer* 2000, **89**, 893–900.
25. Cohen AM, Winawer SJ, Friedman MA, *et al*, eds. *Cancer of the Colon, Rectum, and Anus, Vol. 1,* 2nd edn. New York, McGraw-Hill, 1995.
26. Gryfe R, Kim H, Hsieh ETK, *et al*. Tumor microsatellite instability and clinical outcome in young patients with colorectal cancer. *N Engl J Med* 2000, **342**, 69–78.
27. Porta M, Gallen M, Malats N, Planas J. Influence of 'diagnostic delay' upon cancer survival: an analysis of five tumour sites. *J Epidemiol Comm Hlth* 1991, **45**, 225–230.