PERGAMON

European Journal of Cancer 36 (2000) 95–99

European Journal of Cancer

www.elsevier.com/locate/ejconline

Comorbidity and colorectal cancer according to subsite and stage: a population-based study

M.F. De Marco [a, b], M.L.G. Janssen-Heijnen [c], L.H. van der Heijden [c], J.W.W. Coebergh [a, c,*]

[a] *Department of Epidemiology and Biostatistics, Erasmus University Medical School, Rotterdam, The Netherlands*
[b] *Institute of Health, University of Siena, Italy*
[c] *Comprehensive Cancer Centre South, PO Box 231, 5600 AE, Eindhoven, The Netherlands*

Received 29 January 1999; received in revised form 19 July 1999; accepted 20 August 1999

Abstract

In developed countries the growing proportion of elderly colorectal cancer patients with comorbidity will probably complicate clinical management. The aim of this study was to investigate the prevalence of prognostically relevant comorbidity in unselected colorectal cancer patients diagnosed in the Eindhoven Cancer Registry, according to age, gender and subsite and the association with stage of disease, treatment and short-term survival. Comorbid conditions were recorded, according to Charlson's index. The most common concomitant illnesses were cardiovascular diseases, previous cancers and hypertension. The prevalence of comorbidity, especially of cardiovascular disease, previous cancer and diabetes, was highest in the ascending colon. It was slightly higher in patients with Dukes' stage A, probably due to early detection because of regular monitoring for the comorbid condition. Comorbidity was not associated with the resection rate, but was negatively associated with short-term survival. Elder male colorectal cancer patients particularly suffer from substantial comorbidity, influencing the prognosis.

Keywords: Comorbidity; Colorectal cancer; Colon subsite; Dukes' stage

1. Introduction

Colorectal cancer, as in most Western countries is the third most common cancer in The Netherlands [1]. The male/female ratio generally increases up to 2-fold with increased age and from proximal to distal [2–5]. The proportion of elderly patients ($\geqslant$60 years of age) with colorectal cancer has increased up to 75% in most of these countries [6], together with the likelihood that patients also have other chronic disabling conditions [7]. Comorbidity, or the coexistence of various chronic illnesses, has an important impact on the management and prognosis of cancer patients [8]. Patients with prognostically relevant comorbidity are usually excluded from clinical trials, which affects external validity. The presence of comorbidity may also affect the presentation and recognition of symptoms and consequently the time of detection of cancer [8–10]. In this study, we investigated the prevalence of prognostically relevant comorbidity in unselected colorectal cancer patients according to age and gender and explored the pattern of occurrence according to subsite. In addition, we studied the association between comorbidity and time of detection of colorectal cancer and analysed the association between the presence of comorbidity and the resection rate, and short-term ($<$4 months) survival, according to age and stage of disease.

2. Patients and methods

The analyses are based on data on 3355 patients with colorectal cancer diagnosed in the period 1993–1995 and registered in the Eindhoven Cancer Registry. This registry covers a large part of the southeastern Netherlands and comprises approximately two million inhabitants since 1988. The registry is notified by six pathology departments, hospital medical record offices

* Corresponding author. Tel.: +31-40-2971616; fax: +31-40-297610.
E-mail address: jw.coebergh@ikz.nl (J.W.W. Coebergh).

0959-8049/00/$ - see front matter
PII: S0959-8049(99)00221-X

Table 1.
Classification of comorbidity, according to an adapted version of Charlson and colleagues [11]

Chronic Obstructive Pulmonary Disease (COPD) (medically treated)
Cardiovascular diseases:
Myocardial infarction, cardiac decompensation, angina pectoris
Peripheral arterial disease, intermittent claudication, abdominal aneurysm
Cerebrovascular diseases (cerebrovascular accident, hemiplegia)
Other malignancies (except basal cell skin carcinoma)
Hypertension (medically treated)[a]
Diabetes mellitus (medically treated)
Other:
Connective tissue diseases:
Besnier Boeck disease, Wegener's disease, SLE (systemic lupus erythematosus)
Rheumatoid arthritis (only severe)[a]
Kidney diseases (chronic glomerulonephritis, chronic pyelonephritis)
Bowel diseases (Crohn's disease, ulcerative colitis)[a]
Liver diseases (cirrhosis, hepatitis)
Dementia
Chronic infections

[a] Added to the list of Charlson and colleagues [11].

in 17 community hospitals and two large Radiotherapy Institutes. When recording the data on newly diagnosed cancer patients, mostly within 4–6 months after diagnosis, registrars also collected data on comorbidity for all patients diagnosed since 1993 directly from the medical records, using letters of referral from and discharge to general practitoners (GPs) and other consultants, the medical history and preoperative reports. The study population consisted of 1710 male and 1645 female patients.

Tumour site and morphology had been classified according to the International Classification of Diseases for Oncology (ICD-O); tumours of the descending colon were combined with those of the sigmoid colon, and tumours of the rectum with those of the rectosigmoid area [4]. Only adenocarcinoma was included in this study. Prognostically relevant concomitant conditions were recorded according to a slightly adapted version of the Charlson index [11] (Table 1). This index was developed in a series of 607 patients consecutively admitted to a medical service at a single medical centre and includes prognostic conditions based on relative 1-year all-cause mortality. It has been validated several times. During 1996 and 1997, the completeness and accuracy of extraction of comorbidity from the medical records by the registry personnel was checked by evaluating the medical records of a series of consecutive patients with lung ($n=125$), endometrial ($n=200$) and prostate cancer ($n=150$). Recording of comorbidity was correct for approximately 80% of patients with lung or prostate cancer and 90% of those with endometrial cancer [12–14]. Under-registration by registry personnel was found mainly for cardiac and other vascular diseases (20%), because isolated terms such as CABG (coronary artery bypass grafting), bypass and PTCA (percutaneous transluminal coronary angioplasty) had sometimes been disregarded. Since this was only corrected in the recording process of patients diagnosed since January 1997 we increased the prevalence of heart and vascular diseases recorded in the period 1993–1996 by approximately 20% of the originally recorded prevalence. Information on comorbidity was missing in 10% of (mainly younger) patients, most likely signifying the absence of comorbidity.

Tumour stage was determined according to Dukes' classification; patients with cancer of unknown stage who did not undergo surgery were included in Dukes' stage D. Incidence rates per 100 000 person-years, the male/female incidence ratio and stage-distribution have been calculated, according to subsite and age (Table 2). The prevalence of comorbidity was analysed (for males and females) according to age (<70 and $\geqslant 70$ years of age), subsite of colorectal cancer, and Dukes' stage. The association between comorbidity and resection rate and short-term survival was analysed, according to age and Dukes' stage.

Table 2.
Incidence rates, sex ratios and stage distribution of colorectal cancer, according to age and subsite (1993–1995)

Subsite	Incidence[a] per 10^5 person-years		Age (years)	Male/female ratio	n	Dukes' stage distribution (%)				Unknown
	Male	Female				A	B	C	D	
Ascending	11.8	10.5	<70	1.1	276	1.4	44	22	25	8
			$\geqslant 70$	1.2	404	2.5	46	21	16	15
Transversum	6.9	5.9	<70	0.9	178	1.7	37	21	33	8
			$\geqslant 70$	1.4	230	2.2	44	17	23	15
Descending + sigmoid	18.4	14.5	<70	1.2	486	11	37	21	18	13
			$\geqslant 70$	1.5	442	11	38	20	17	13
Rectosigmoid + rectum	26.4	14.9	<70	1.6	700	8.9	35	21	15	20
			$\geqslant 70$	2.1	526	7.2	39	14	13	26
Total[b]	65.2	47.5	<70	1.2	1702	7.3	37	20	19	16
			$\geqslant 70$	1.5	1653	6.4	41	18	17	19

[a] Adjustment to European Standard Population.
[b] Includes data of unknown/overlapping site for 47 male and 36 female patients.

3. Results

Incidence rates, according to subsite of all patients diagnosed during 1993–1995 show that the most frequent subsite was the rectum and the rectosigmoid junction (Table 2). The male/female incidence ratio increased with age at any subsite and from proximal to distal. The stage distribution improved from proximal to distal, being most favourable in the sigmoid, and this was also the case for the elderly ($\geqslant$ 70 years of ages).

Cardiovascular diseases, previously diagnosed cancers (both in the large bowel and elsewhere) and hypertension were the most common associated chronic diseases in both age groups and chronic obstructive pulmonary disease (COPD) and diabetes to a lesser extent (Fig. 1). Females had more hypertension than males. Below 70 years of age 51% of males and 59% of females did not suffer from any serious comorbid condition, whereas this was true for only 26% and 34%, respectively, in the group over 70 years of age. Among the previously diagnosed cancers the most common tumours among men were those of the urinary tract (20%), colon and rectum (18%), lung (18%) and prostate (15%). Among women the most common previously diagnosed tumours were those of the breast (39%), colon and rectum (18%) and female genital system (13%).

Overall a significant ($P = 0.006$) decrease in prevalence of comorbidity from proximal to distal cancer occurred (from 52% for the ascending colon to 44% for the rectum), especially in the younger male group (from 48% for the ascending colon to 31% for the rectum). The prevalence of cardiovascular diseases among males < 70 years of age declined from proximal to distal colon cancer from 20 to 11%, the prevalence of previous

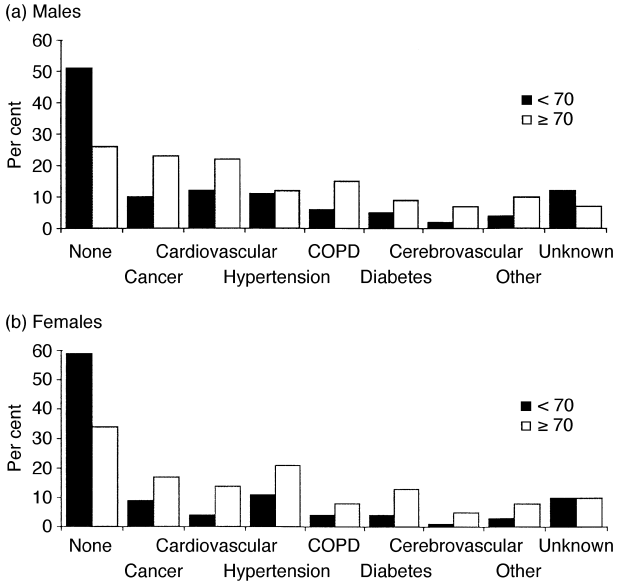

Fig. 1. Prevalence of comorbidity in colorectal cancer patients. COPD, chronic obstructive pulmonary disease.

Table 3
Prevalence (%) of comorbidity, according to subsite

	% Ascending		% Transverse		% Descending + sigmoid		% Rectum + rectosigmoid	
Age (years)	< 70	⩾70	< 70	⩾70	< 70	⩾70	< 70	⩾70
Male ($n = 1652$)								
Comorbidity[a]	($n = 141$)	($n = 167$)	($n = 86$)	($n = 110$)	($n = 249$)	($n = 208$)	($n = 421$)	($n = 270$)
None	44	27	47	26	44	27	59	26
Previous cancers	16	22	8.1	32	10	25	7.6	19
Cardiovascular	20	34	20	24	16	25	11	24
Hypertension	11	12	8.1	10	14	16	9.5	9.3
COPD	8.5	17	8.1	11	7.2	14	4.5	18
Diabetes	9.2	10	4.7	6.4	3.6	8.7	3.8	10
Cerebrovascular	2.1	8.4	5.8	2.7	2.0	7.2	1.7	6.7
Other	5.0	9.6	0	16	3.6	6.7	5.2	10
Unknown	8.5	4.2	15	9.1	14	7.2	10	7.8
Female ($n = 1590$)								
Comorbidity[a]	($n = 135$)	($n = 237$)	($n = 92$)	($n = 120$)	($n = 237$)	($n = 234$)	($n = 279$)	($n = 256$)
None	55	38	59	26	59	36	61	32
Previous cancers	8.9	20	11	22	5.5	16	11	13
Cardiovascular	9.7	16	1.3	16	5.5	16	3.8	19
Hypertension	10	17	11	23	13	18	9.7	27
COPD	3.0	3.4	0	7.5	3.8	10	5.0	11
Diabetes	4.4	13	7.6	14	4.2	15	3.2	13
Cerebrovascular	3.0	4.6	0	5.0	0.8	4.3	1.1	5.9
Other	5.9	6.3	5.4	11	1.7	8.5	3.2	7.8
Unknown	9.6	11	7.6	12	12	9.8	8.6	8.2

[a] Some patients reported more than one co-morbid condition.
COPD, Chronic obstructive pulmonary disease.

Table 4
Prevalence (%) of comorbidity in patients with colorectal cancer, according to Dukes' stage and age

Age (years)	% Dukes' A		% Dukes' B		% Dukes' C		% Dukes' D	
	<70	⩾70	<70	⩾70	<70	⩾70	<70	⩾70
Male ($n=1492$)								
No. of diseases	($n=65$)	($n=56$)	($n=352$)	($n=314$)	($n=180$)	($n=130$)	($n=205$)	($n=190$)
None	40	25	51	32	55	22	51	24
⩾1	51	66	37	62	32	70	37	68
Unknown	9	9	12	6	13	8	12	8
Female ($n=1435$)								
No. of diseases	($n=60$)	($n=50$)	($n=272$)	($n=356$)	($n=164$)	($n=160$)	($n=164$)	($n=209$)
None	57	34	60	33	62	40	54	28
⩾1	32	64	30	59	31	48	31	59
Unknown	12	2	9	8	7	11	15	13

cancers from 16 to 7.6% and the prevalence of diabetes from 9.2 to 3.8% (Table 3).

In patients with a Dukes' A stage tumour the prevalence of comorbidity (especially previously diagnosed cancer and cardiovascular disease) was slightly higher for men younger than 70 years and for women over 70 years of age (Table 4).

After adjustment for age and Dukes' stage, comorbidity did not affect the resection rate, being over 95% for patients with Dukes' A to C tumours, 64% for patients younger than 70 years with Dukes' D tumour and 47% for patients over 70 years with Dukes' D tumour. Table 5 shows that serious concomitant diseases negatively affected short-term survival in patients with Dukes' A to C tumours, especially in patients over 70 years of age. It had less influence on survival for patients with Dukes' D tumours.

4. Discussion

We studied the prevalence of prognostically relevant comorbidity in unselected colorectal cancer patients, for males and females in two age groups, according to anatomic subsite, and Dukes' stage, and the influence of comorbidity on resection rate and short-term survival. Approximately 35% of patients below 70 years of age and 61% of patients over 70 years of age had serious comorbidity, these proportions being higher for males than for females. The most frequent concomitant diseases were cardiovascular diseases, previous cancers (diagnosed less than 10 years ago) and hypertension. The under-reporting of comorbidity in the cancer registry was limited, due to preoperative screening and the experience of the medical record abstractors. None the less, the recording process exhibited a learning curve.

Despite obvious biases with respect to detection we compared our population-based prevalence rates with those obtained in Dutch general practice. Our prevalence rates were approximately the same as the 4-year prevalence rates of visits in general practices [15], except for previously detected (and in part possibly cured) cancer, of which the prevalence in our study of colorectal cancer patients was 50% higher. In contrast with other studies [16] the prevalence of diabetes mellitus did not seem much higher than in the general population.

Except for women aged 70 years or older, there was a clear decrease in the number and types of associated chronic illnesses (particularly for cardiovascular diseases and diabetes) from the proximal to the distal large bowel, and this was more striking in males than in females. Considering the subsite- and gender-specific incidence rates (Table 2), showing higher incidence for males at more distal locations, and the rising trends in

Table 5
Four-month mortality of newly diagnosed patients with colorectal cancer, according to age, number of concomitant diseases and Dukes' stage

	n	Age <70 years		P value	n	Age ⩾70 years		P value
		Number of concomitant diseases (%)				Number of concomitant diseases (%)		
		0	⩾1			0	⩾1	
Dukes'								
A	111	0	4		101	0	4	
B	553	2	4	0.08	625	7	12	0.03
C	309	1	6	0.04	262	6	16	0.03
D or unknown	529	12	17	0.14	524	22	30	0.05
All	1502	5	9	0.004	1512	11	19	0.001

sigmoid cancer in males [17] we would have expected the reverse. The subsite-specific occurrence of cardiovascular diseases, albeit relevant for the testing of lifestyle related hypotheses on the risk of colon and rectum cancer, was not reported in other studies [18–20]. If the presence of certain comorbid conditions like diabetes and vascular diseases implies common risk factors and/or pathophysiological pathways (for example dietary habits and microvascular disease), our findings suggest different factors to be involved in the development of cancer at different subsites [21, 22]. Our study showed a slightly higher prevalence of comorbidity in earlier stages of colorectal cancer. This has also been observed in patients with breast cancer [9]. The higher prevalence of comorbidity in Dukes' A patients can probably be explained by a detection bias: regular monitoring of people with a serious concomitant condition can accelerate the diagnosis of colorectal cancer [10].

In spite of the high mean age, the resection rate exceeded 95% in patients with Dukes' A to C cancer and ranged between 47 and 64% in those with Dukes' D cancer. The resection rate for this group of patients in The Netherlands was relatively high within Europe [23]. Because resection is often crucial to prevent bowel obstruction and anaemia due to chronic blood loss, comorbidity does not seem to be a firm contra-indication. Although not influencing the resection rate, comorbidity negatively influenced short-term survival, especially in patients over 70 years of age. The negative effect of comorbidity, especially high impact heart problems, COPD, renal failure and thyroid/glandular disease, on the survival of colon cancer patients was also found in an American study with National Institute of Aging (NIA), National Cancer Institute (NCI) and Surveillance Epidemiology and End Results (SEER) data [24].

To conclude, our findings show a high prevalence of prognostically relevant comorbid conditions, especially in elderly males. Medical care for these patients must be reasonably complex and tailor-made. The differing prevalence rates according to gender and subsite illustrate variation in the aetiology of colorectal cancer, with a marked influence of cardiovascular risk factors for cancers in the ascending colon. Short-term survival of colorectal cancer is worse in the presence of comorbid conditions

References

1. Black R, Bray F, Ferlay J, Parkin DM. Cancer incidence mortality in the European Union: cancer registry data estimates of national incidence for 1990. *Eur J Cancer* 1997, **33A**, 1075–1107.
2. Devesa SS, Chow WH. Variation in colorectal cancer incidence in the United States by subsite of origin. *Cancer* 1993, **71**, 3819–3826.
3. Jensen OM. Different age and sex relationship for cancer of subsites of the large bowel. *Br J Cancer* 1984, **50**, 825–829.
4. Levi F, Randimbison L, La Vecchia C. Trend in subsite distribution of colorectal cancer and polyps from the Vaud Cancer Registry. *Cancer* 1993, **72**, 46–50.
5. de Jong UW, Day NE, Muir CS, *et al*. The distribution of cancer within the large bowel. *Int J Cancer* 1972, **10**, 463–477.
6. Monfardini S, Yancik R. Cancer in the elderly: meeting the challenge of an aging population. *J Natl Cancer Inst* 1993, **85**, 532–538.
7. Havlik R, Yancik R, Long S, Ries L, Edwards B. The National Institute on aging and the National Cancer Institute SEER collaborative study on comorbidity and early diagnosis of cancer in the elderly. *Cancer* 1994, **74**, 2101–2106.
8. Feinstein AR. The pre-therapeutic classification of comorbidity in chronic disease. *J Chron Dis* 1970, **23**, 455–468.
9. Satariano WA. Comorbidity and functional status in older women with breast cancer: implications for screening, treatment, and prognosis. *J Gerontol* 1992, **47**, 24–31.
10. Mor V, Guadagnoli E, Masterson-Allen S, *et al*. Lung, breast, and colorectal cancer: the relationship between extent of disease and age at diagnosis. *J Am Geriatr Soc* 1988, **36**, 873–876.
11. Charlson ME, Pompei P, Ales KL, Mackenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chron Dis* 1987, **40**, 373–383.
12. Janssen-Heijnen MLG, Coebergh JWW, Razenberg PPA. *Validation Study of Comorbidity in Lung Cancer Patients Diagnosed in 1995*. Eindhoven Cancer Registry, Internal report, 1997.
13. Janssen-Heijnen MLG, Coebergh JWW, Razenberg PPA. *Validation Study of Comorbidity in Patients with Endometrial Carcinoma Diagnosed in 1994 and 1995*. Eindhoven Cancer Registry, Internal report, 1997.
14. Post PN, Janssen-Heijnen MLG, Coebergh JWW, Razenberg PPA. *Validation Study of Comorbidity in Prostate Cancer Patients Diagnosed in 1995*. Eindhoven Cancer Registry, Internal report, 1997.
15. Groen ASM, Hofmans-Okkes IM, Lamberts H. Different figures for frequencies of diseases in health surveys and morbidity in studies in general practice (in Dutch). *Ned Tijdschr Geneeskd* 1997, **141**, 634–639.
16. Weiderpass E, Gridley G, Nyrén O, Ekbom A, Persson I, Adami H-O. Diabetes mellitus and risk of large bowel cancer. *J Natl Cancer Inst* 1997, **89**, 660–661.
17. Damhuis RAM, Coebergh JWW, Driessen WMM, van der Heijden LH. Increasing incidence of cancer of the sigmoid and ascending colon for men in south-east Netherlands. *Eur J Cancer* 1995, **31A**, 2116–2117.
18. La Vecchia C, D'Avanzo B, Negri E, Franceschi S. History of selected diseases and the risk of colorectal cancer. *Eur J Cancer* 1991, **27A**, 582–586.
19. Kune GA, Kune S, Watson LF. Colorectal cancer risk, chronic illnesses, operations, and medications: case control results from the Melbourne Colorectal Cancer study. *Cancer Res* 1988, **48**, 4399–4404.
20. Payne JE, Meyer HJ. The influence of other diseases upon the outcome of colorectal cancer patients. *Aust NZ J Surg* 1995, **65**, 398–402.
21. Bufill JA. Colorectal cancer: evidence for distinct genetic categories based on proximal or distal tumor location. *Ann Intern Med* 1990, **113**, 779–788.
22. McMichael AJ, Potter JD. Do intrinsic sex differences in lower alimentary tract physiology influence the sex-specific risks of bowel cancer and other biliary and intestinal diseases? *Am J Epidemiol* 1983, **118**, 620–627.
23. Gatta G, Sant M, Coebergh JWW, Hakulinen T, and the EUROCARE Working Group. Substantial variation in therapy for colorectal cancer across Europe: EUROCARE Analysis of Cancer Registry data for 1987. *Eur J Cancer* 1996, **32A**, 831–835.
24. Yancik R, Wesley MN, Ries LAG, *et al*. Comorbidity and age as predictors of risk for early mortality of male and female colon carcinoma patients: a population-based study. *Cancer* 1998, **82**, 2123–2134 .