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Descriptive Epidemiology of Colorectal Cancer in Italy: The 6-year Experience of a Specialised Registry

Maurizio Ponz de Leon, Romano Sassatelli, Alessandra Scalmati, Carmela Di Gregorio, Rossella Fante, Gianni Zanghieri, Luca Roncucci, Milena Sant and Andrea Micheli

The Colorectal Cancer Registry of Modena recorded 838 malignancies of the large bowel between 1984 and 1989. Crude Incidence rates were 59.5 new cases per 100 000 per year in men and 47.4 in women (age-standardised values 33.1 and 20.6, respectively). 35 incident cases (4.2%) had multiple colorectal tumours, whereas 42 (5.1%) had extraintestinal malignancies (mainly breast, endometrium and stomach). Although 90.5% of the patients underwent surgery, this was "curative" in 634 (77.6% of the total), while 105 individuals (12.8%) had palliative operations; 78 patients (9.5%) were not operated, mainly because of metastatic disease or poor clinical condition. Finally, emergency operations—due to intestinal obstruction, perforation or massive bleeding—were carried out in 46 patients (6.1%). A total of 659 tumours (79%) were accurately staged. Among first-degree relatives of the registered patients a significant excess of cases of colorectal cancer was found in each year of the study. 5-year survival was evaluated in 132 (out of 140) patients registered in 1984 and followed-up until 1989. Overall 5-year survival was 37%, but rose to 43% when only colorectal cancer related deaths were taken into consideration. As expected, survival was strongly influenced by stage ($P < 0.0001$ by log-rank test). In conclusion, this study confirms previously reported data about incidence and mortality rates for colorectal cancer in northern Italy. The particular approach—limited to the large bowel—allowed the evaluation of the frequency of multiple tumours and of the marked aggregation of cancer among first-degree relatives. Finally, survival figures are comparable to those of many other studies and confirm that the clinical outcome of this neoplasm remains unfavourable in more than 50% of the affected patients.
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INTRODUCTION

COLORECTAL CANCER is still one of the major causes of neoplastic morbidity and mortality in all Western countries [1]. This is discouraging if one considers that unlike other tumours, in which the underlying biology is virtually unknown (i.e. pancreas and brain), for colorectal cancer several genetic and environmental factors have recently been defined and a risk profile can tentatively be traced [2]. One of the most promising approaches towards the control of this tumour type is through the systematic registration of all cases occurring in a geographically defined area. Besides general registries, which record cancer of all sites, it is worth emphasising the relevance of specialised registries, in which the investigation is limited to cancer of one or few organs.

In 1984 a specialised colorectal cancer registry was instituted in the health care district of Modena, Italy, with well-defined objectives already discussed in previous reports [3–5]. The purpose of the present study was to analyse the data of a 6-year registration period (1984–1989). Our interest was focused on incidence and mortality rates, TNM stage, type of surgery, familial aggregation of tumours and survival.

Correspondence to M. Ponz de Leon, Istituto di Patologia Medica, Policlinico, via del Pozzo 71, 41100 Modena, Italy.
M. Ponz de Leon, R. Sassatelli, A. Scalmati, G. Zanghieri and L. Roncucci are at the Istituto di Patologia Medica; C. Di Gregorio and R. Fante are at the Istituto di Anatomia Patologica, Università di Modena, Modena and M. Sant and A. Micheli are at the Istituto Nazionale per lo Studio e la Cura dei Tumori, Divisione di Epidemiologia, Milan, Italy.
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MATERIALS AND METHODS

Each of the 20 regions of Italy is divided in several health care districts. In the Region Emilia-Romagna, District 16 includes Modena and 10 smaller towns for a total of 262 332 residents (males: 126 036; females: 136 296; 1981 census and subsequent 1986 estimate). Patients were usually contacted and interviewed during hospitalisation. Besides personal data, a family tree—with the main causes of morbidity and mortality of first-degree relatives—was traced for almost all patients [3–5]. Errors due to under- or over-registration of cases should be very low in a registry owing to: (a) covering a very small geographic area; (b) data limited to a single neoplasm; (c) with histological verification in 90–95% of cases. DCO (death certificates only) were not included in the incidence rates. However, the percentages of DCO were calculated for 2 years in the registration period: they were 9.0% in 1986 and 6.3% in 1989. During the first 3-year registration period, each incident case was matched to a control of the same sex and age (±5 years). These were patients hospitalised in the local health district during the same period but not for neoplastic or gastrointestinal diseases. An accurate genealogical tree—limited to first-degree relatives (as for incident cases)—was also traced for each control.

For 132 of the patients registered in 1984 a 5-year follow-up was completed within December 1989. This accurate follow-up

enabled us to evaluate mortality due to metastatic or recurrent disease as well as deaths unrelated to colorectal cancer. In addition, the prognostic significance of several clinical and morphological parameters could be investigated [6].

Colorectal tumours were classified according to the International Classification of Diseases for Oncology (ICD-O) [7]. Severe dysplasia and carcinoma *in situ* were not classified as incident cases. As far as multiple tumours are concerned, we considered new incident cases of all colorectal cancers which appeared simultaneously (synchronous) or at various intervals of time (metachronous) in two different segments (4th digit ICD-O) of the large bowel. Local recurrences were not considered as new incident cases [6]. Staging of colorectal tumours was carried out with the TNM system [8] which closely corresponds to the Dukes' classification in four categories.

Crude, age-specific, age-standardised incidence (and mortality) rates were calculated following the guidelines of the International Agency for Research on Cancer [9] and using the standard age-structure of the World population. The statistical significance in the occurrence of neoplasms among first-degree relatives of cases and controls was assessed with the Mantel–Haenszel estimator and with a statistic test, proposed by Liang, which does not rely on the binomial assumption [10–12]. For patients registered in 1984, overall and colorectal cancer specific survival were evaluated with the Kaplan–Meier method [13].

RESULTS

Crude, age-standardised incidence rates, cumulative rate, crude and age-standardised mortality rates of colorectal cancer are shown in Table 1. The observed rates were in the range of values of western and industrialised countries and indicate that about three individuals out of 100 will develop cancer of the large bowel between 0 and 74 years. As for other neoplasms of the digestive organs, the observed incidence rates increased with age in both sexes, though rectal cancer remained appreciably higher in men in virtually all age-classes. Table 2 shows crude incidence rates of colonic and rectal cancer by location and by sex. As expected, tumours were unevenly distributed in the various intestinal segments and more than 70% of all neoplasms were localised between the splenic flexure and the rectum; consequently, crude incidence rate increased sharply in the most distal portions of the large bowel. Again, the results were consistent with most of the published series. The very low number of colon NOS (not otherwise specified) tumours reflects the accuracy of diagnosis, which was based on endoscopy and/or X-ray in more than 90% of cases.

Table 1. Number of cases, crude (CIR), age-standardised (ASIR, world population) incidence rates, cumulative rate (CR, 0–74), number of deaths, crude (CM), age-standardised (ASM, world population), mortality rates and mortality/incidence ratio (M/I) of colorectal cancer by sex, during the period 1984–1989

	Men	Women	Total
No. of cases	450	388	838
CIR*	59.5	47.4	53.4
ASIR*	33.1	20.6	26.9
CR(%)	4.1	2.4	3.2
No. of deaths	254	254	508
CM*	41.9	38.7	40.3
ASM*	22.2	15.2	18.7
M/I	0.73	0.75	0.74

*Per 100 000 person per year.
M/I = mortality/incidence ratio.

During the registration period, the number of incident cases ranged between 135 and 145 per year, and crude incidence between 50.8 and 54.4/100 000 [mean (S.D.), 52.6 (1.4)]. Only minor fluctuations were seen in the fraction of neoplasms in each of the three main anatomical subsites (right colon: caecum, ascending, transverse and flexures; left colon: descending, sigmoid and rectosigmoid junction; rectum: rectum + anus) in the 6 years of registration. This suggests that the frequently reported [14] trend to a gradual increase of proximal colonic cancer is probably a very slow event, which can presumably be appreciated over longer periods of observation.

Table 3 shows the frequency of multiple tumours (either colorectal or of other organs), TNM staging of registered tumours and type of surgery carried out in incident cases. As far as TNM staging is concerned, malignant polyps were considered stage I lesions. Nx represent cases in whom no lymph nodes were found in the resected colorectal specimen. The fraction of cases with histological verification was 93.5%.

Among the registered patients, 739 out of 817 (90.4%) underwent various types of operation, the most frequent being segmental resection, hemicolectomy, and abdomino-perineal (Miles) surgery. 78 patients (9.6%) were not operated for various reasons: 37 (47.4%) because of unresectable metastases; 18 (23%) owing to poor clinical conditions (including heart failure); 8 (10.2%) because of advanced age, whereas 3 patients refused surgery. Among other less frequent reasons: liver cirrhosis, neoplastic fistulas, synchronous neoplasms of other organs and sudden death immediately after diagnosis. Finally, 46 of the 739 patients (6.2%) underwent emergency operations, mostly due to intestinal obstruction, perforation or massive bleeding.

The frequency of malignancies among first-degree relatives of the registered patients is shown in Table 4, for the first and second 3-year period. The results are compared with those of a control group defined on the main clinical features of patients registered in 1984–1986. In this period, 89 cases of colorectal neoplasms were referred among case relatives versus 19 among control relatives ($P < 0.001$) [12]. An equivalent 4-fold excess (77 vs. 19) was reported for case relatives in 1987–1989. Moreover, in each 3-year period, the excess of malignancies among relatives was more marked in siblings (60 and 46, respectively, vs. 7 in controls). Besides colorectal cancer, no other tumour appeared to be significantly more frequent among case relatives.

Among the 132 patients registered in 1984 and who completed a 5-year follow-up, 83 (62.9%) died during the study period (50 of advanced or metastatic cancer, 23 of recurrences and 10 for causes unrelated to the neoplasm) and 49 (37.1%) were alive. Thus, overall 5-year survival was 37%, but actually increased to 43% by considering only colorectal cancer specific survival. Among the 113 patients who were operated, 10 (8.8%) died within 30 days after surgery and, with some approximation, this can be taken as a measure of the operative mortality. Apparently curative surgery was carried out in 86 patients, but in 26 (30.2%) recurrent or metastatic disease developed, mainly within the first 24 months after the operation. Among the various clinical and morphological variables evaluated, only TNM staging maintained an independent prognostic significance [6].

Table 2. Crude incidence rates (CIR) and confidence intervals (CI, in parentheses) of colon and rectal cancer by site and sex

	Men		Women		Total	
	CIR	CI	CIR	CI	CIR	CI
Colon (ICD-O 153)						
153.0 Hepatic flexure	2.4	(0.3–8.1)	1.8	(0.1–7.1)	1.9	(0.1–7.3)
153.1 Transverse colon	3.8	(0.9–10.2)	2.0	(0.2–7.1)	2.4	(0.4–8.6)
153.2 Descending colon	3.7	(0.8–10.0)	3.4	(0.7–9.6)	3.2	(0.7–9.7)
153.3 Sigmoid colon	13.5	(7.1–23.1)	14.4	(7.8–24.2)	15.1	(8.5–25.4)
153.4 Cecum	5.0	(1.5–11.9)	5.0	(1.5–11.9)	5.0	(1.5–11.9)
153.6 Ascending colon	4.3	(1.1–10.9)	2.6	(0.4–8.6)	3.3	(0.6–9.6)
153.7 Splenic flexure	2.4	(0.3–8.1)	1.8	(0.1–4.4)	0.2	(0.2–4.4)
153.9 Colon NOS	0.1	(0.5–4.2)	0.2	(0.3–4.4)	0.2	(0.3–4.4)
Total	35.2	(24.3–49.2)	31.1	(21.1–44.6)	33.1	(23.9–48.6)
Rectum (ICD-O 154)						
154.0 Rectosigmoid junction	8.7	(3.8–16.9)	5.1	(1.6–12.0)	6.9	(2.6–14.5)
154.1 Rectum	15.3	(8.5–25.4)	10.6	(5.1–19.4)	13.0	(6.8–22.5)
154.3 Anus	0.3	(0.2–4.6)	0.6	(0.05–5.1)	0.4	(0.1–4.7)
Total	24.3	(15.4–36.3)	16.3	(9.2–26.6)	20.3	(12.3–31.5)

DISCUSSION

The main findings of the present investigation can be summarised as follows:

(1) the incidence of colorectal cancer in our health care district—representative of the wealthy and industrialised northern Italy—remains stable and is comparable to that reported in many other Western countries [4, 20, 22].
(2) Multiple tumours (either site-specific or of other organs) can be observed in approximately 10% of the registered patients.
(3) Although the large majority of patients with colorectal malignancies undergoes surgery, the fraction of unoperated patients + palliative resections is still considerable; moreover, total (or sub-total) colectomy is extremely infrequent in our experience.
(4) First-degree relatives of patients with colorectal neoplasms show a 3–4-fold excess of these tumours when compared to a control population [3, 12].
(5) Five-year survival is strongly related to stage and is comparable to that of other population-based reports [15–16].

The incidence rates of colorectal cancer observed in this study are similar to the values reported by other registries in northern Italy, but appreciably higher than those observed in the central and southern areas of our country [17]. A similar north–south gradient has previously been reported for mortality rates. Since the various registries showed the same degree of accuracy—at least for this neoplasm—it is likely that these differences are true and, thus, dependent upon biological factors (diet, genetic background, physical activity).

The tendency to multiple and/or recurrent tumours is one of the most striking features of colorectal neoplasms and bears a direct relationship to the type of surgery, the extent of resection, the choice of adjuvant chemo- and radiotherapy and the follow-up of operated patients. Several studies showed that the prevalence of synchronous and metachronous colorectal cancer is in the order of 4–12% of all cases [18]. The high frequency of multiple malignancies together with the frequent simultaneous presence, or subsequent development, of adenomatous polyps—estimated in the order of 30% of all cases—led various surgeons to recommend a more radical approach (subtotal colectomy) to colorectal cancer. Moreover, simultaneous and metachronous tumours are a clinical feature of Lynch syndrome (hereditary non-polyposis colorectal cancer—HNPCC), which represents approximately 5% of all colorectal cancers, and in which subtotal colectomy has also been suggested [19]. In our 6-year experience we found 35 multiple colorectal cancers (4.2% of the total) which is close to the lowest values reported in the literature; moreover, one or more adenomatous polyps were found in 172 out of 817 registered patients (21%). The fact that only 4 total or subtotal colectomies were carried out (out of 634 curative resections, Table 4) can be interpreted, in our opinion, by assuming that the risk of multiple tumours (and thus the biological features of HNPCC) is probably under-estimated by many surgeons. Finally, our findings show that multiple tumours of other organs (especially breast, endometrium and stomach) are relatively frequent among patients with colorectal cancer (42, 5.1% of total). This is particularly interesting since these (and other) types of cancer aggregate in families with HNPCC [19].

Table 3. Patients with multiple tumours; TNM staging of registered cancers and type of surgery carried out in incident cases (period 1984–1989)

	No.	%
Patients with multiple tumours		
Of the large bowel	35	4.2
Synchronous	17	
Metachronous	18	
Of other organs*	42	5.1
Synchronous	6	
Metachronous	36	
TNM staging		
Stage I	122	14.5
Stage II	224	26.7
Stage III	150	17.9
Stage IV	163	19.5
Nx	58	6.9
Not staged	121	14.5
Total	838	100
Type of surgery		
No surgery	78	9.5
Palliative	105	12.9
Curative		
Resection or hemicolectomy	499	61.1
Subtotal colectomy	4	0.5
Miles + Hartman	103	12.6
Endoscopy	27	3.3
Unknown	1	0.1
Total	817	100

*The most frequent extracolonic cancers were in the following organs: endometrium (12 cases); breast (10); stomach (6); ovary (3); thyroid (2); larynx (2); small bowel (2); prostate (2).

Table 4. Frequency of malignant tumours among first-degree relatives of patients with colorectal cancer registered in 1984–1986 and in 1987–1989 (versus a control group matched to patients registered in 1984–1986). The data refer to 389 of 407 patients in the first 3-year period and to 372 of 412 in the second period

	1984–1986	Controls	1987–1989
Number of patients	389	389	372
Number of total relatives	2851	2662	2654
Number of parents	778	778	744
Number of siblings	1415	1227	1332
Number of colorectal cancers			
Among relatives	89*	19	77
Among parents	27*	12	31
Among siblings	60*	7	46
Among offspring	2	0	0
Number of cancers of other sites among relatives			
Stomach	38	40	33
Breast	23	32	23
Uterus, ovary	20	23	15
Liver, biliary tree	19	15	21
Lung	17	32	31
Brain	13	6	12
Bladder, kidney	10	6	6
Lymphatic	9	9	9
Prostate	7	7	5
Larynx	8	5	10
Bone, cartilage	5	3	4
Pancreas	4	2	3
Other sites	33	35	38

*$P < 0.001$, < 0.01 and < 0.001, respectively (Mantel–Haenszel summary estimates [12]).

Familial aggregation of tumours among relatives of incident cases has been extensively treated in previous reports [3, 12]. and is at present under active investigation with the main objectives of establishing the frequency of HNPCC in our population and of testing alternative hypotheses of genetic transmission in families not fulfilling the clinical criteria of HNPCC. In the present study we simply confirm the excess of colorectal malignancies among first-degree relatives of patients registered in the 3-year period 1987–1989. Moreover, once again no other tumour aggregates specifically in case families (Table 4).

One of the most discouraging findings of the study was that the annual proportion of stage IV + unstaged patients was in the order of 30–35% of total, with no tendency to a decrease of this fraction with time. In other words, in 1/3 of the registered patients the disease was so advanced it effectively prevented all therapeutical approaches. This bleak outlook may be due to the fact that patients usually seek medical advice upon the appearance of symptoms which are late events in the natural history of colorectal cancer. The distribution of patients among the various TNM classes is similar to that described in other investigations [20], whereas for unknown reasons other authors have reported a more favourable pattern of distribution [21]. The gradual decline of Nx (from 7.6% in 1984 to 1.3% in 1989) may reflect the tendency to a more radical approach in the surgical treatment of these neoplasms (data not shown).

Five-year survival, only fully evaluated for patients registered in 1984, was in the order of 40% and was therefore consistent with other large-scale investigations which failed to show any improvement in the treatment of colorectal cancer over the past 3 decades [15].

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In situ Hybridisation for Cytokine Gene Transcripts in the Solid Tumour Microenvironment

Domenico Vitolo, Anisa Kanbour, Jonas T. Johnson, Ronald B. Herberman and Theresa L. Whiteside

To determine if mononuclear cells (MNC) infiltrating various types of human solid tumours express genes for cytokines, *in situ* hybridisation with ^{35}S-labelled cDNA antisense probes for interleukin 2 (IL2), interferon gamma (IFN-γ), tumour necrosis factor alpha (TNF-α), interleukin 1-beta (IL1-β), transforming growth factor beta (TGF-β) and interleukin 2-receptors (IL2R) was performed. Fresh-frozen tissue samples of ovarian carcinomas (n=13), breast carcinomas (n=12), and squamous cell carcinomas of the head and neck (SCCHN, n=7) were evaluated for the presence and localization in the tumour of MNC positive for cytokine genes. In ovarian tumours and those breast carcinomas producing little or no mucin, only rare positive MNC were observed. In contrast, breast carcinomas producing mucin and all SCCHN contained numerous MNC expressing gene transcripts for IL2, IFN-γ, TNF-α, IL2R as well as TGF-β. In tumour-involved lymph nodes of patients with SCCHN, MNC expressing genes for cytokines were found around tumour metastases but not in non-involved areas. These data suggest that tumours expressing immunogenic antigens (e.g. mucin) contain many activated MNC, while other tumours either fail to activate or suppress functions of infiltrating MNC. In SCCHN or tumour-draining lymph nodes, local down-regulation of antitumour responses might be mediated by TGF-β produced by activated tumour-infiltrating MNC.
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INTRODUCTION

HUMAN MONONUCLEAR cells (MNC) have been most often studied in the peripheral blood, where their phenotypic and functional characteristics can be easily determined both in health and disease. Peripheral blood MNC can be serially monitored to detect disease- or therapy-related changes. However, peripheral blood MNC represent about 2% of those present in the body, and their characterisation does not reflect functional or phenotypic properties of tissue-infiltrating MNC [1, 2]. To study MNC in tissue, histological and immunohistological techniques have been used [3, 4], which provide information about location, distribution, intensity and phenotype of these cells, but not about the state of their activation or function in the local microenvironment. Yet, local interactions between tissue cells