Original article

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Trend of incidence, subsite distribution and staging of colorectal neoplasms in the 15-year experience of a specialised cancer registry

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Background: Two-thirds of colorectal malignancies are localised in the left colon and rectum. Recent studies suggest a trend towards an increase of right-sided tumours which might have important implications for screening and surveillance. A colorectal cancer registry was set up in Modena, northern Italy, with the purpose of examining incidence, subsite distribution and staging of colorectal malignancies over a 15-year period.

Patients and methods: From 1984 to 1998, 2517 tumours in 2462 patients were detected and staged with the tumour node metastasis (TNM) system. The 'right colon' was considered from caecum to splenic flexure; the 'left colon' included descending and sigmoid colon; and the 'rectum' included rectosigmoid junction, ampulla and anus.

Results: Cancer incidence showed an overall increase. Considering the various subsites, an increase of 33.7% in all colonic segments was shown whereas rectal tumours tended to decline. TNM staging showed a gradual increase of localised lesions (41.2% in 1984 versus 53.3% in 1998), with a proportional reduction of advanced tumours.

Conclusions: Our study indicates an increase of tumour incidence in all colonic segments more than a shift to the right colon. TNM staging tended to improve with an appreciable increase of localised lesions. These findings could be consequent to a more extensive use of colonoscopy.

Key words: cancer, colon, incidence, rectum, registry

Introduction

Cancer of the colon and rectum continues to be one of the leading causes of cancer-related morbidity and mortality in all parts of the western World [1], and there are reasons to believe that the progressive extension to other countries of western culture (the essence of 'globalisation') will lead to a rapid increase in the incidence of these neoplasms in the Third World. In the USA and western Europe, colorectal cancer constitutes approximately 10% of all malignancies, and in one series represents the second leading cause of death for tumours in both sexes [2, 3]. Despite new detection techniques and treatment modalities, death rates for colonic and rectal neoplasms have remained virtually unchanged over the past two or three decades [4, 5].

Subsite distribution of colorectal malignancies indicates that ~70% of them are localised in the distal or left large bowel, i.e. between the splenic flexure and the lower rectum [6]. Several studies, however, showed a tendency for a proximal shift of cancer distribution, with right-sided lesions becoming more and left-sided lesions less prevalent [7–11], but not without controversies [12–14]. It remains unclear if this is a true biological phenomenon or simply an artefact due to many reasons, including the lack of agreement on the most appropriate division of the colorectum into anatomical subsites [15, 16].

The debate is not only academic or theoretical, but may have important implications in the screening and surveillance of high-risk individuals. Indeed, it is usually assumed—by traditional teaching—that >50% of colorectal tumours can be detected with the flexible sigmoidoscope [17, 18]. If the 'rightwards shift' is a true phenomenon, this might represent one more argument for abandoning sigmoidoscopy and favouring pancolonoscopy as the technique of choice for screening individuals at risk of colorectal cancer. In a recent editorial [19] it has been stated that "relying on flexible sigmoidoscopy is as clinically logical as performing mammography of one breast to screen women for breast cancer".

A specialised colorectal cancer registry was instituted in the local health care district, in 1984 [20]. Through the data of this registry, we purposed to examine the pattern of incidence of these tumours, subsite distribution and staging over a 15-year period.

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Table 1. Main data of cancer registration in the whole period 1984–1998

ICD-O	Gender	Crude incidence rate[a]	Age-standardised incidence[a]		Cumulative risk 0–74 years (×1000)	Affected individuals
			World population	European population		
153-Colon	Male	45.7	24.1	35.8	30.3	850
	Female	40.6	16.9	25.1	20.6	814
154-Rectum	Male	23.8	12.9	18.8	17.2	448
	Female	17.3	7.4	11.0	9.0	350
Total	Male	69.5	37.0	53.9	47.5	1298
	Female	57.9	24.3	36.1	29.6	1164

[a]Number of new cases per 100 000 residents per year.
ICD-O, International Classification of Diseases for Oncology.

Patients and methods

Colorectal cancer registry

The general organisation of the specialised cancer registry has been described in detail elsewhere [20–22]. The district includes Modena and 10 surrounding communities made up of a total of 265 227 residents (128 228 men and 136 939 women) at the 1991 census. Modena is in northern Italy, 180 km south-east of Milan. The area is highly industrialised (textiles, motor cars and pottery, in particular), entirely flat, almost exclusively urban and with one of the highest levels of income per person in Italy.

Registration of all colorectal malignancies that developed in the resident population began in 1984; by the end of 1998, 2517 tumours in 2462 patients (1298 men and 1164 women) had been detected. Histological verification was obtained in 98.0% of cases, with an average mortality/incidence ratio of 0.65. Colorectal tumours were classified according to the International Classification of Diseases for Oncology (ICD-O) [23]. Ambiguous or unclear definitions—such as 'superficial cancerization', 'intraepithelial or glandular neoplasia', 'neoplastic foci' or '*in situ* carcinoma'—were not considered as cancer (and thus not included in the registration) unless there was a clear infiltration of the neoplastic tissue through the muscularis mucosae.

Tumours were classified with the tumour node metastasis (TNM) system, which closely corresponds with the Dukes' classification, into four main categories [24]. This procedure follows simple physiopathological considerations and eliminates—at least in part—ambiguities and confusion consequent to the numerous revisions of the Dukes' staging system. Thus, stage I (Dukes' A) defines a neoplasm confined within the muscular wall of the large bowel; this category can be subdivided into $T_1N_0M_0$, when tumours spread through the muscular mucosae into the submucosa, and $T_2N_0M_0$, when tumours have infiltrated the muscular wall. In stage II (Dukes' B), the tumour spreads beyond the smooth muscle ($T_3N_0M_0$), or may infiltrate perirectal or pericolic organs ($T_4N_0M_0$). In stage III (Dukes' C), there is the metastatic involvement of lymph nodes (C-1, $T_{1–4}N_1M_0$, if the involved nodes are up to three; C-2, $T_{1–4}N_2M_0$ when they are four or more), independently from the dimensions and the degree of infiltration of the primary tumour. In stage IV ($T_{1–4}N_{0–2}M_1$, corresponding to the 'D' category of other classifications), the tumour metastasises to the liver, lung or, more rarely, other organs.

For the purpose of the present study, 'right or proximal colon' was considered that part of the large bowel extending from the caecum (including the appendix) to the splenic flexure (included). 'Left or distal colon' included the descending and sigmoid colon; 'rectal' lesions were those located in the rectal ampulla, rectosigmoid junction and anus.

Statistical analysis

Crude, age-standardised (age-adjusted) incidence rates and cumulative risks were calculated following the general guidelines of the International Agency for Research on Cancer (IARC) [25], using the resident population at census 1991 as the denominator, and the age structure of the World population.

Poisson regression model (STATA 7 software package, Texas, USA) was used to evaluate the trends of incidence throughout the registration period. Statistical analysis was carried out by estimating a general model of regression in which sex, age at diagnosis and triennium of incidence were chosen as covariates. The trends of stage at diagnosis (TNM I versus II, III, IV or Nx) and of tumour location (right colon versus left colon or rectum) were estimated with a model of regression for every classification of stage and site using as in the previous general model sex, age at diagnosis and triennium of registration as covariate factors. Age at diagnosis was codified in to five classes: 0–49, 50–59, 60–69, 70–79 and 80+ years. As reference categories, the model considered male sex, younger age at diagnosis (≤49 years), first triennium of registration (1984–86) and Dukes' A tumours.

Results

Crude, age-standardised incidence rates and 0–74 years cumulative risks are shown in Table 1, while Table 2 shows the number of colorectal malignancies developed in the various anatomical subsites in each triennium of registration; by comparing the first and the last triennium, there was a 33.7% increase of cancer occurrence. Considering each anatomical subsite, the trends showed a gradually rising tumour incidence in all colonic segments, with values in the last triennium almost double those of the first triennium, and with a striking almost 4-fold increase of tumours in the ascending colon. In contrast, the number of rectal neoplasms showed only minor fluctuations throughout the registration period. Trends were similar when males and females were separately analysed (data not shown).

Figures 1 and 2 show the absolute and relative frequency of tumours in the right colon, left colon and rectum. The progressive rise of colonic lesions (both in the right and left colon) was clearly evident (Figure 1). As a proportion of total cases, rectal lesions accounted for 40% of all tumours in the first triennium, while their frequency fell to 25% in the period 1996–98 (Figure 2). This trend is further illustrated in Figure 3, which compares the relative dis-

Table 2. Number of cases of colorectal malignancies by anatomical sublocalisation (males and females considered together)

Site (ICD-O)	Years of registration						
	1984–86	1987–89	1990–92	1993–95	1996–98	Total	*P*
Caecum (153.4) + appendix (153.5)	33	45	51	46	51	226	NS
Ascending (153.6)	23	32	42	86	85	268	<0.001
Transverse (153.1) + flexures (153.0; 153.7)	53	57	62	61	84	317	0.04
Descending (153.2)	31	25	32	39	51	178	0.04
Sigmoid	106	111	126	178	192	713	<0.001
Rectum (154.1) + junction (154.0)	165	145	180	144	151	785	NS
Anus (154.3)	4	2	8	4	12	30	NS
Total	415	417	501	558	626	2517	–
Sex ratio (M:F)	1.09	1.18	1.04	1.05	1.21	1.12	–

NS, not statistically significant.
ICD-O, International Classification of Diseases for Oncology.

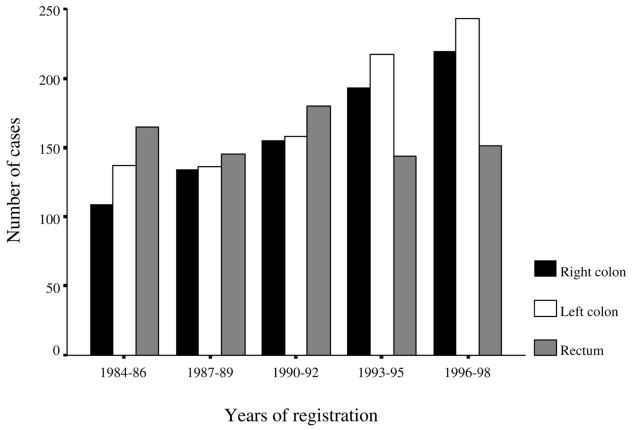

Figure 1. Frequency of tumours in the right colon, left colon and rectum (number of cases) in each triennium of registration.

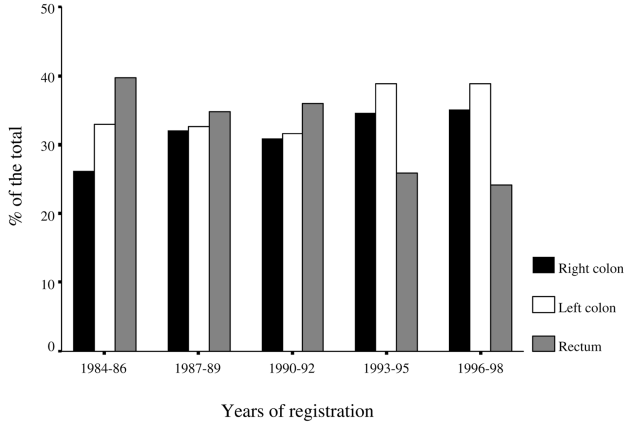

Figure 2. Relative frequency of tumours in the right colon, left colon and rectum (percentage of total) in each triennium of registration.

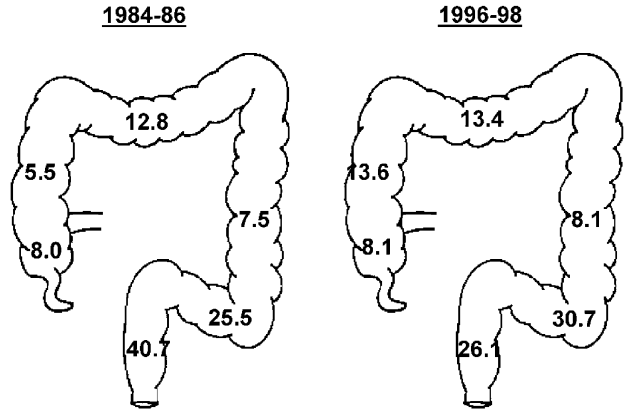

Figure 3. Tumour distribution in each colonic subsite in the first and last triennium of registration (percentage of total).

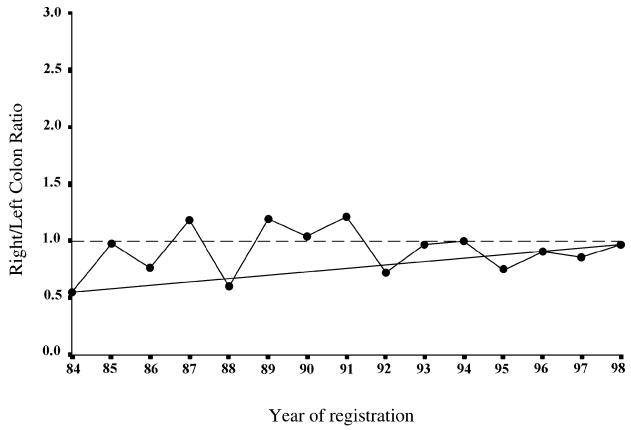

Figure 4. Ratio between number of right and left colonic tumours in each year of registration.

tribution of tumours in each colorectal subsite in the first and last 3-year period of registration. Moreover, Figure 4 shows the ratio between right-sided and left-sided lesions in each year of registration. The ratio showed some fluctuations, but on average, remained close to 1, thus indicating a balanced occurrence of tumours in these two subsites more than a 'shift' to the right.

Table 3. Percentage of total cases, by stage, in each year of registration, 1984–98 (for 2404 patients, including only adenocarcinomas)

Stage	Year															
	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	Total
I	8.1	14.4	8.5	9.9	12.2	10.7	15.9	9.2	17.8	15.0	7.7	16.7	15.8	22.5	16.8	13.8
II	33.1	22.7	29.5	38.2	28.2	35.0	31.6	41.7	32.0	35.9	37.4	40.1	35.5	32.1	36.5	34.4
III	14.0	16.7	20.2	19.1	19.8	21.4	29.0	22.1	20.6	26.9	29.6	28.1	26.1	21.9	23.4	23.0
IV	22.1	22.7	23.2	22.9	24.4	22.8	15.2	16.6	22.5	15.6	18.7	8.3	16.7	15.5	15.2	18.3
X[a]	6.5	8.3	14.0	3.8	6.9	1.5	2.1	1.8	3.0	3.0	–	2.6	1.5	–	–	3.2
Unstaged[b]	16.2	15.2	4.6	6.1	8.5	8.6	6.2	8.6	4.1	3.6	6.6	4.2	4.4	8.0	8.1	7.3
Total	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100

[a]X: each T, N_x, M_0.
[b]Not operated on for colorectal cancer but without a clear demonstration of metastasis.

Table 3 illustrates the TNM staging for the 2404 patients with colorectal carcinoma observed during the study period. The data are shown as percentages of the total. The trend showed a gradual but appreciable increase in localised lesions (stage I and II) and a proportional reduction of advanced and unstaged neoplasms; however, in absolute values, advanced tumours showed only minor changes throughout the study. Finally, Table 4 shows variations in staging of the three main anatomical subsites of the large bowel. Stage I tumours were less frequent in the right colon when compared with the left colon and rectum; however, the difference virtually disappeared when considering localised lesions together (stages I and II). Unstaged lesions were more prevalent in the rectum in almost all years of registration.

The results of Poisson regression analysis are summarised in Tables 5, 6 and 7. As a general phenomenon, the incidence of colorectal malignancies was lower in females throughout the registration period ($P < 0.05$). Trend analysis showed a significant rising incidence of cancer in all age groups (50–59, 60–69, 70–79, 80+ years) when compared with the reference category (0–49 years). As far as stage was concerned, stage I, II and III lesions showed a significant increase in incidence over time, which is particularly evident in the last triennium of registration. In contrast, the incidence of more advanced (stage IV) tumours tended to remain stable, whereas N_x lesions (i.e. cases with no lymph nodes in the resected specimen) showed a definite decline. Finally, both right and left-sided neoplasms tended to rise, the increase of incidence being particularly significant in the last two triennia of registration. At variance with these findings, rectal tumours remained stable until 1992, but showed a significant decline in the period 1993–1998.

Table 4. Staging of colorectal adenocarcinomas, by anatomical sublocalisation, in each triennium of registration. Data expressed as per cent of total cases.

Stage	Triennium					Total
	1984	1987	1990	1993	1996	
	1986	1989	1992	1995	1998	
Right Colon						
I	9.1	3.6	7.4	3.1	10.5	7.6
II	29.1	42.2	44.7	46.9	43.1	42.8
III	14.5	21.7	28.1	33.6	25.5	25.7
IV	30.9	26.5	18.2	11.7	15.7	17.8
X[a]	7.3	1.2	0.8	0.8	0	1.7
Unstaged[b]	9.1	4.8	0.8	3.9	5.2	4–5
Left Colon						
I	9.8	6.3	14.8	20.4	16.8	14.2
II	28.7	36.9	40.2	37.1	32.7	33.9
III	20.5	19.8	23.9	28.2	24.5	24.7
IV	20.5	30.7	16.2	12.1	19.4	18.8
X[a]	13.1	4.5	2.1	1.1	1.0	3.9
Unstaged[b]	7.4	1.8	2.8	1.1	5.6	4.4
Rectum						
I	12.0	15.7	16.7	17.3	32.3	19.3
II	30.9	28.1	30.9	26.4	24.6	26.2
III	12.8	20.7	21.0	21.5	16.9	19.0
IV	20.3	21.5	16.7	18.2	13.1	18.3
X[a]	12.0	3.3	3.1	2.5	0.8	4.1
Unstaged[b]	12.0	10.7	11.6	14.1	12.3	13.1

[a]X: each T, N_x, M_0.
[b]Unstaged: not operated on for colorectal cancer but without a clear demonstration of metastasis.

Discussion

The results of the present study can be summarised as follows. First, there was a general increase in the incidence of colorectal neoplasms during the registration period. This increase was observed in both sexes, though incidence rates in women remained significantly lower than in men. Secondly, tumours were appreciably more frequent over the age of 50 years, Thirdly, not only localised (stage I and II) but also metastatic (though resectable) tumours (stage III) showed a significant increase in incidence over time; this was in contrast with the stability of more severe (stage IV) lesions. Finally, there was a gradual increase in cancer incidence in all colonic segments, while rectal lesions tended to decline.

Table 5. Results of Poisson regression analysis: general population (variables investigated are gender, age and triennium of registration)

Variable	IRR (95% CI)
Gender	
Male	Reference category
Female	0.68 (0.62–0.73)
Age, years	
≤49	Reference category
50–59	4.67 (3.86–5.64)
60–69	9.44 (7.90–11.26)
70–79	17.27 (14.52–20.55)
≥80	20.06 (16.67–24.14)
Triennium	
1984–86	Reference category
1987–89	0.96 (0.83–1.10)
1990–92	1.07 (0.94–1.22)
1993–95	1.15 (1.01–1.30)
1996–98	1.21 (1.06–1.37)

CI, confidence intervals; IRR, incidence ratio rate.

Various studies—especially from North America—have suggested that colorectal malignancies have undergone a 'rightward shift' during the last three to four decades, with right-sided lesions becoming more and left-sided less prevalent [8–10, 26]. However, at variance with these reports, other investigators were unable to show a definite increase of right-sided tumours. Thus, in a study of 60 000 autopsies carried out between 1928 and 1972, Parkash [27] showed a gradual increase in the incidence of colorectal carcinomas, but this occurred throughout the large bowel, with no preferential location of the lesions in the right colon. Even in North America, Lanier et al. [12] found no increase in the incidence of right-sided neoplasms, while Vobecky et al. [13] showed a relatively stable rate of proximal lesions from 1967 to 1980. Finally, in more recent years, Crerand et al. [14] evaluated the distribution of colorectal carcinomas in a large series (n = 1553) of Irish patients over a 30-year period. Their results showed that the distribution among the various anatomical subsites changed very little during the study period.

The reasons for these conflicting results remain unclear, although they could also be attributed to different criteria adopted for the division of the colorectum into anatomical subsites [16]. Thus, in some studies the right colon included only the caecum, ascending colon and hepatic flexure [10], while other authors suggested that the proximal colon should be made up of the caecum through the descending colon [16]. The criteria that we and others [14] have adopted were to consider the right colon as the portion of large bowel including caecum, ascending colon, transverse colon and flexures (and left colon the portion including descending and sigmoid colon), as suggested by either epidemiological [28] or anatomical considerations.

Other possible explanations for the different distribution of colorectal malignancies into right and left colonic segments might include (i) the impact of environmental risk factors, such as diet and lifestyle [29]; (ii) a different frequency of hereditary colorectal neoplasms (which are characterised by an increased frequency of right-sided lesions) [30]; and (iii) a more or less extensive use of colonoscopy [31]. Despite the controversies, the issue of a possible

Table 6. Results of Poisson regression analysis: tumour location in the large bowel

Variable	IRR (95% CI)		
	Right colon	Left colon	Rectum
Gender			
Male	Reference category		
Female	0.78 (0.68–0.90)	0.69 (0.60–0.79)	0.58 (0.51–0.67)
Age, years			
≤49	Reference category		
50–59	2.66 (1.88–3.76)	3.11 (2.28–4.25)	2.90 (2.07–4.06)
60–69	5.52 (4.03–7.57)	5.52 (4.11–7.43)	6.20 (4.52–8.50)
70–79	12.71 (9.38–17.20)	9.32 (6.96–12.49)	9.93 (7.26–13.60)
≥80	15.62 (11.35–21.51)	11.53 (8.45–15.74)	10.50 (7.46–14.77)
Triennium			
1984–86	Reference category		
1987–89	1.10 (0.85–1.43)	0.89 (0.70–1.13)	0.85 (0.68–1.07)
1990–92	1.19 (0.92–1.53)	0.96 (0.76–1.21)	1.01 (0.82–1.24)
1993–95	1.41 (1.10–1.79)	1.22 (0.98–1.52)	0.78 (0.62–0.98)
1996–98	1.51 (1.19–1.91)	1.20 (1.05–1.61)	0.79 (0.64–0.99)

Table 7. Results of Poisson regression analysis: TNM stage of tumours

Variable	IRR (95% CI)				
	TNM I	TNM II	TNM III	TNM IV	N_x
Gender					
Male	Reference category				
Female	0.71 (0.56–0.89)	0.65 (0.57–0.74)	0.67 (0.57–0.79)	0.73 (0.60–0.88)	0.65 (0.41–1.03)
Age, years					
≤49	Reference category				
50–59	2.14 (1.25–3.68)	2.61 (1.86–3.68)	2.25 (1.56–3.26)	2.55 (1.63–3.98)	1.06 (0.23–4.92)
60–69	3.74 (2.23–6.26)	5.69 (4.14–7.83)	4.26 (3.02–6.01)	4.40 (2.88–6.72)	1.50 (0.33–6.87)
70–79	6.10 (3.69–10.08)	9.89 (7.21–13.55)	8.04 (5.74–11.25)	6.81 (4.47–10.38)	2.80 (0.65–12.14)
≥80	6.19 (3.48–10.99)	11.57 (8.28–16.16)	8.86 (6.12–12.81)	7.21 (4.54–11.47)	4.92 (1.11–21.78)
Triennium					
1984–86	Reference category				
1987–89	0.90 (0.56–1.44)	1.10 (0.86–1.41)	1.07 (0.78–1.49)	0.92 (0.69–1.22)	0.71 (0.40–1.25)
1990–92	1.35 (0.89–2.06)	1.30 (1.03–1.66)	1.32 (0.98–1.79)	0.80 (0.59–1.07)	0.50 (0.25 0.98)
1993–95	1.52 (1.01–2.28)	1.45 (1.16–1.82)	1.76 (1.32–2.35)	0.77 (0.57–1.04)	0.49 (0.22–1.08)
1996–98	1.96 (1.34–2.88)	1.39 (1.10–1.75)	1.56 (1.17–2.09)	0.83 (0.62–1.11)	0.38 (0.13–1.08)

[a]Numbers in bold are statistically significant.
CI, confidence intervals; IRR, incidence ratio rate.

increase over time of right-sided lesions remains of fundamental relevance, since it can be viewed as one of the main points in favour of colonoscopy as the technique of choice for exploring the large bowel in screening procedures [19].

The results of the present study show that incidence rates of colonic tumours are progressively rising, while the frequency of rectal lesions have tended to decline. This trend was associated with a sharp increase of localised lesions and with a significant improvement of 5-year survival (data not shown) [32]. However, the absolute numbers of advanced (stage IV and unstaged) lesions did not show any consistent decline throughout the observation period. Similar results have been reported by several other investigators [33–35]. Colonoscopy is requested more and more frequently than in the past; considering that symptoms due to colorectal lesions are often scanty, we might expect an increased detection of tumours only as a consequence of a more extensive use of endoscopy. Since women are more reluctant to undergo endoscopic examinations [36], this might particularly explain the lower incidence of cancer in females observed in this study.

Western populations continue to become older; since colorectal cancer shows a peak of incidence at ages 65–70, the gradual ageing of the population probably represents the main 'natural' factor predisposing to colorectal neoplasms. Thus, the significantly higher occurrence of colorectal cancer in the age groups 50–59, 60–69, 70–79 and 80+ (versus individuals in whom tumours occurred before the age of 50 years) is not surprising. Finally, there is no doubt that life has become more comfortable in all western countries; this has resulted in an increase in the availability of hypercaloric food and alcoholic beverages, and a greater amount of time spent in sedentary activity (for many individuals it is not unusual nowadays to spend 10–14 h watching a monitor, either computer or television). All of these factors (i.e. high intake of meat, animal fat and refined food, low intake of fibre and a tendency for low physical activity) have been associated with an increased risk of colonic tumours and, to a lesser extent, rectal neoplasms [29, 37, 38].

The more favourable staging at diagnosis (Tables 3 and 4) is presumably related to the wider use of colonoscopy, and this, in turn, can be attributed to an increased attention of patients and doctors towards the screening, early detection and symptoms of this common disease [32, 39]. However, the absolute numbers of advanced and unstaged lesions showed very little change during the registration period. This observation suggests that the more frequent use of endoscopy and the increased attention towards prevention and early diagnosis are not sufficient to induce a definite reduction in the rates of inoperable lesions and to reduce the absolute number of deaths [39]. Perhaps a vigorous promotion of lower endoscopy in the elderly population and large-scale research studies evaluating fecal occult blood testing might reveal valuable tools that may help to reduce the number of patients who present with advanced disease.

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