EUROPEAN JOURNAL OF CANCER 44 (2008) 522–527

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Review

The lifelong risk of metachronous colorectal cancer justifies long-term colonoscopic follow-up

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ARTICLE INFO

Article history:
Received 12 December 2007
Received in revised form
7 January 2008
Accepted 9 January 2008
Available online 5 February 2008

Keywords:
Colorectal cancers
Metachronous cancers
Registry
Epidemiology

ABSTRACT

Background: The aim of this study was to calculate the risk of metachronous colorectal cancers, to specify their characteristics and potential risk factors in a well-defined French population over a 27-year period.

Patients and methods: The 10,801 patients who had colorectal cancers totalled 61,879 person-years of follow-up. The actuarial method was used to obtain crude metachronous colorectal cancer rates. Standardised incidence ratios (SIRs) were calculated.

Results: The cumulative rate of metachronous colorectal cancer was 1.8% at 5 years, 3.4% at 10 years and 7.2% at 20 years. The incidence of metachronous colorectal cancer following a first colorectal cancer was higher than expected (SIR: 1.5 [1.3–1.7] $p < 0.001$). It remained greater throughout the study period, significantly only between the first and the fifth years following diagnosis (SIR: 1.9 [1.6–2.3] $p < 0.010$). As compared to solitary cancers, metachronous cancers were diagnosed at earlier stages (23.5% versus 40.9% were stage I, $p < 0.001$). None of the personal and tumour characteristics were predicting factors for the development of metachronous colorectal cancer.

Conclusion: Patients with colorectal cancer are at greater risk of developing a metachronous colorectal cancer. Among them, no predicting factors for the development of metachronous tumours were found. Thus lifelong colonoscopic surveillance is needed.

1. Introduction

Colorectal cancer is a major public health problem in France, as well as in many areas of the world. Around 37,000 new cases of colorectal cancer occur each year in France, representing 15% of all cancers[1] and among them approximately 85% were resected for cure.[2] Although the increased risk of developing metachronous colorectal cancer after a first one was identified some time ago,[1,3] there is a paucity of reports on their frequency, their epidemiological characteristics or their prognosis over time at a community level. Due to selection bias, hospital-based data cannot be used as reference values. This can explain why the frequency of multiple metachronous colorectal cancers varies between 2% and

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0959-8049/$ - see front matter
doi:10.1016/j.ejca.2008.01.007

12% in the literature.[3–6] Population-based studies are rare because they require an accurate follow-up of both the vital status and clinical events over a long period. Such data is important for defining screening strategies and adapting better surveillance schemes in order to improve survival of patients. The aim of this study was to determine the incidence of metachronous colorectal cancer in a well-defined French population over a 27-year period, to describe their characteristics, and to investigate whether specific factors were associated with the risk of metachronous colorectal cancer.

2. Material and methods

A population-based cancer registry records all digestive tract cancers in two administrative areas in Burgundy, France. These areas have a population of 1,101,000 according to the 1999 census. Cancer registration began in 1976. Information was regularly obtained from public and private pathologists, hospitals (university hospitals including the comprehensive cancer centre, general hospitals), private physicians (gastroenterologists, surgeons, oncologists and radiotherapists), general practitioners, as well as from the National Health Service and monthly review of death certificates. Due to the multiplicity of information sources, we assumed that nearly all newly-diagnosed cancers were recorded. The quality and comprehensiveness of registration is certified every 4 years by an audit of the National Institute of Health and Medical Research (INSERM) and of the National Public Health Institute (InVS).

Metachronous cancer was defined as a new cancer occurring at least 6 months after the initial colorectal cancer. So the risk of developing a metachronous cancer was only calculated for patients who survived at least 6 months after their first cancer. Recurrences, in particular anastomotic recurrences, were not included. All clinical and pathology reports were used to distinguish a recurrence or a colon metastasis from a new cancer. In case of difficulty the advice of an expert clinician involved in the registry was sought. Colorectal cancers that had developed in the context of inflammatory bowel diseases, hereditary non polyposis colorectal cancer or familial adenomatous polyposis were also excluded as well as anal cancers. The definitive cohort included 10,801 patients diagnosed with a first colorectal cancer between January 1976 and December 2002.

2.1. Studied variables

Demographic, clinical and tumour-related characteristics were routinely collected. Period of diagnosis of the first cancer was divided into four periods: 1976–1982, 1983–1989, 1990–1996 and 1997–2002. Occurrence time-lag between the first and second colorectal cancers was divided into four intervals: [6 months – 1 year], [1 year – 5 years], [5 years –10 years] and 10 years and over. Location of cancers was coded according to the ICD-O classification.[7] For analysis purposes, subsites were divided into right colon (caecum to transverse colon, C18.0 to C18.4), left colon (splenic flexure to rectosigmoïd junction, C18.5 to C19.9) and rectum ampulla (C20). Size of tumour was classified into '<3 cm', '3 to 5 cm' and '6 cm and over'. Macroscopic type of growth was classified into three categories: fungating tumours, ulcerofungating and ulcero-infiltrative tumours. Presence of associated adenomas was registered, as well as the existence of adenomatous remnants upon pathological examination of the resected specimen. Cancer extension at the time of diagnosis for resected cancers was classified according to the UICC classification.[8] Patients with visceral metastasis or who did not undergo resection were classified as having advanced stage disease.

2.2. Statistical methods

Cumulative metachronous colorectal cancer rates were calculated using the actuarial method and were expressed with standard errors. Patients who died were censored at time of death, and patients who developed a metachronous colorectal cancer were censored at time of recurrence. The expected number of metachronous colorectal cancers was obtained by multiplying the person-years at risk in each 5-year age group by the corresponding sex- and age-specific incidence rate. Person-years at risk were calculated from the date of first diagnosis of colorectal cancer until the date of death or to the date of the end of the follow-up (December 2005). The observed number of metachronous colorectal cancers was divided by the expected number to obtain a standardised incidence ratio estimate (SIR), and 95% confidence intervals (CI) were calculated assuming a Poisson distribution.

A non-conditional logistic regression was used to obtain odds ratio associated with the probability of developing a metachronous colorectal cancer according to the characteristics of the first cancer. Analyses were computed using the STATA 8 software.

3. Results

3.1. Epidemiological characteristics

The 10,801 patients diagnosed with a colorectal cancer totalled 61,879 person-years of follow-up. Among these patients, 216 (2.0%) presented a metachronous colorectal cancer (131 males and 85 females): 210 had one metachronous cancer, five had two, and one had three. The metachronous carcinoma was diagnosed 6 months to 1 year after the first carcinoma in 26 cases, 1 to 5 years later in 110 cases, 5 to 10 years later in 48 cases, and more than 10 years later in 32 cases. In 14 patients, two synchronous colorectal cancers were diagnosed before the occurrence of a metachronous cancer. The median age at the time of diagnosis of the first cancer was 71.1 years (interquartile: 21.0; 99.6). The median time-lag for the diagnosis of the second metachronous cancer was 42.7 months (interquartile: 6.5 to 270.6 months).

Characteristics of solitary colorectal cancers and of metachronous cancers are presented in Table 1. Metachronous cancers were almost 2-fold more often localised in the right colon than single cancers (52.6% versus 26.0%, $p < 0.001$) and appeared more often as fungating tumours (51.7% versus 36.3%, $p < 0.001$). They were smaller in size (less than 3 cm: 34.8% versus 17.0%, $p < 0.001$) and diagnosed at an earlier stage (stage I: 40.9% versus 23.5%, $p < 0.001$). Adenomatous remnants were present in 22.7% of metachronous cancers and in 14.9% of solitary cancers ($p < 0.001$) whereas the proportion of associated adenomas did not differ.

Table 1 – Characteristics of patients and cancer at time of diagnosis for solitary colorectal cancer and metachronous cancer

	Solitary colorectal cancer		Metachronous colorectal cancer			
			Index cancer		Second cancer	
	N	%	N	%	N	%
Sex						
Male	5867	**55.4**	131	**60.6**	131	**60.6**
Female	4718	**44.6**	85	**39.4**	85	**39.4**
						$p^a = 0.13$
Location						
Right colon	2743	**26.0**	56	**26.2**	113	**52.6**
Left colon	5067	**48.1**	111	**51.9**	65	**30.2**
Rectum	2722	**25.9**	47	**21.9**	67	**17.2**
						$p^a < 0.001$
Tumour size[b]						
<3 cm	1574	**17.0**	40	**19.8**	65	**34.8**
3–5 cm	5213	**56.5**	116	**57.4**	84	**44.9**
⩾6cm	2447	**26.5**	46	**22.8**	38	**20.3**
						$p^a < 0.001$
Growth features[b]						
Fungating	3302	**36.3**	79	**41.6**	90	**51.7**
Ulcero-fungating	2025	**22.3**	46	**24.2**	30	**17.3**
Ulcero-infiltrating	3762	**41.4**	65	**34.2**	54	**31.0**
						$p^a < 0.001$
Stage at diagnosis						
Stage I	2445	**23.5**	71	**33.3**	88	**40.9**
Stage II	3531	**33.9**	94	**44.1**	50	**23.3**
Stage III	2412	**23.2**	40	**18.8**	42	**19.5**
Advanced stage[c]	2021	**19.4**	8	**3.8**	35	**16.3**
						$p^a < 0.001$
Associated adenoma						
No	8363	**79.0**	156	**72.2**	168	**77.8**
Yes	2222	**21.0**	60	**27.8**	48	**22.2**
						$p^a = 0.66$
Adenomatous remnants[b]						
No	9004	**85.1**	169	**78.2**	167	**77.3**
Yes	1581	**14.9**	47	**21.8**	49	**22.7**
						$p^a < 0.001$

Number of cases unknown:
– colorectal location not otherwise specified, respectively 53, 2 and 1 cases.
– tumour size, respectively 510, 9 and 11 cases.
– growth features, respectively 656, 21 and 24 cases.
– stage, respectively 176, 3 and 1 cases.
a *Chi2 test comparing the characteristics of solitary colorectal cancer to that of the second metachronous cancer.*
b *Resected cases.*
c *TNM stage IV and no resected cases.*

3.2. *Incidence of metachronous cancers*

The overall cumulative rate of developing a metachronous colorectal cancer was 1.8% [95% CI: 1.5–2.2] at 5 years, 3.4% [2.9–4.0] at 10 years, 4.3% [3.6–5.2] at 15 years and 7.2% [5.6–9.3] at 20 years. Rates did not significantly vary according to the period of diagnosis, representing 2.0% at 5 years during the first 1976–1982 period and 2.3% during the last 1997–2002 period (Table 2).

As compared with the general population, the incidence of metachronous colorectal cancer for patients who survived at least 6 months after a resection of a first colorectal cancer was significantly greater (SIR: 1.5, $p < 0.001$) (Table 3). It tended to increase whatever the time-lag between the first and the second colorectal cancer but it was significant only between the first and the fifth year following diagnosis (SIR: 1.9 [CI 95% 1.6–2.3], $p < 0.01$). Beyond 5 years, excess risk was borderline significant. The frequency of metachronous colorectal cancer increased irrespective of sex, and size and growth features of the first colorectal cancer. The existence of a synchronous colorectal cancer increased the incidence of metachronous colorectal cancer (SIR: 2.6, $p < 0.001$). Both

Table 2 – Cumulative rates of metachronous colorectal cancers according to period of diagnosis

	1976–1982		1983–1989		1990–1996		1997–2002	
	%	95% CI	%	95% CI	%	95% CI	%	95% CI
1 year	0.0	–	0.3	[0.1–0.5]	0.2	[0.1–0.5]	0.4	[0.2–0.7]
3 years	0.8	[0.4–1.7]	1.1	[0.8–1.6]	1.0	[0.7–1.4]	1.0	[0.9–1.8]
5 years	2.0	[1.2–3.3]	2.0	[1.4–2.7]	1.4	[1.0–1.9]	2.3	[1.7–3.1]
10 years	3.1	[2.0–4.9]	3.1	[2.5–4.4]	3.3	[2.5–4.3]	–	–
20 years	6.7	[4.3–10.0]	7.9	[5.1–11.9]	–	–	–	–

Logrank test calculated using data up to 5 year follow-up: p value = 0.25.

Table 3 – Incidence of metachronous colorectal cancer after a first colorectal cancer

	Number of 2nd observed cancers (O)	Number of 2nd expected cancers (E)	SIR[a]	95% CI
Global	216	143.7	**1.5**[b]	[1.3–1.7]
Sex				
Male	131	100.6	**1.3**[c]	[1.1–1.6]
Female	85	54.6	**1.6**[b]	[1.3–1.9]
Delay of occurrence for metachronous cancer				
6 months to 1 year	26	22.5	**1.2**	[0.8–1.7]
1 year to 5 years	110	59	**1.9**[b]	[1.6–2.3]
5 years to 10 years	48	37.4	**1.3**	[1.0–1.7]
⩾10 years	32	24.7	**1.3**	[0.9–1.8]
Characteristics of the first cancer				
Size				
<3 cm	40	25.4	**1.6**[c]	[1.2–2.2]
3–5 cm	116	72.5	**1.6**[b]	[1.3–1.9]
⩾6 cm	46	32.1	**1.4**[c]	[1.1–1.9]
Growth features				
Fungating	79	53.5	**1.5**[b]	[1.2–1.8]
Ulcerofungating	46	27.9	**1.7**[b]	[1.2–2.2]
Ulceroinfiltrative	65	47.0	**1.4**[c]	[1.1–1.8]
Stage at diagnosis				
Stage I	71	44.8	**1.6**[b]	[1.3–2.0]
Stage II	94	58.6	**1.6**[b]	[1.3–2.0]
Stage III	40	26.7	**1.5**[c]	[1.1–2.0]
Advanced[d]	8	10.5	**0.8**	[0.4–1.5]
Synchronous colorectal cancer				
No	202	138.3	**1.5**[b]	[1.3–1.7]
Yes	14	5.4	**2.6**[b]	[1.5–4.4]
Associated adenomatous				
No	156	110.9	**1.4**[b]	[1.2–1.7]
Yes	60	32.8	**1.8**[b]	[1.4–2.4]
Adenomatous remnants				
No	169	116	**1.5**[b]	[1.3–1.7]
Yes	47	27.7	**1.7**[b]	[1.3–2.3]

a *Standardised incidence ratio, ratio O/E.*
b $p < 0.001$.
c $p < 0.05$, 95% *CI: 95% confidence interval.*
d *TNM stage IV and non resected cancers.*

associated adenomas and adenomatous remnants nearly doubled in its incidence. Due to a shorter survival period for advanced stages as compared to the earlier ones, the incidence of metachronous colorectal cancer significantly increased only for stages I, II or III.

Table 4 shows the relative risks of contracting a metachronous colorectal cancer according to the characteristics of the first colorectal cancer. None of the studied factors significantly influenced the risk of metachronous cancer. The presence of a synchronous colorectal cancer was associated with a risk of 1.78 ([0.95–3.05] $p = 0.054$) of developing a metachronous colorectal cancer, as compared to initial diagnosis without synchronous colorectal cancer.

Table 4 – Factors associated with the risk of presenting a metachronous colorectal cancer according to the characteristics of the first cancer

	RR	95% CI	P[a]
Sex			
Male	1		0.22
Female	1.20	[0.90–1.58]	
Characteristics of the first cancer			
Size			
<3 cm	1		0.82
3–5 cm	1.01	[0.74–1.40]	
⩾6 cm	0.94	[0.62–1.41]	
Growth features			
Fungating	1		0.66
Ulcerofungating	1.12	[0.76–1.65]	
Ulceroinfiltrative	0.94	[0.66–1.32]	
Stage at diagnosis			
Stage I	1		0.66
Stage II	1.01	[0.74–1.40]	
Stage III	0.94	[0.62–1.41]	
Advanced[b]	0.48	[0.20–1.00]	
Synchronous colorectal cancer			
No	1		0.05
Yes	1.78	[0.95–3.05]	
Associated adenomatous			
No	1		0.10
Yes	1.30	[0.95–1.76]	
Adenomatous remnants			
No	1		0.40
Yes	1.16	[0.82–1.62]	

Logistic regression model.
a *Likelihood ratio.*
b *TNM stage IV and non resected cancers.*

4. Discussion

Data from this study have the advantage of including all cases diagnosed in a well-defined French population over a long time period, together with strict criteria used to record a second primary cancer. Its aim was to provide non-biased statistics on the incidence and characteristics of metachronous colorectal cancers over a 27-year period. The multiplicity of information sources allowed all metachronous colorectal cancers to be recorded. This study was therefore carried out without the referral bias which often occurs in hospital-based series. One of the difficulties of assessing the frequency of metachronous cancers is that there is no consistent definition of the second event in published literature. We considered metachronous cancers to be those diagnosed more than 6 months after the first diagnosis.

Little is known about the cumulative risk of metachronous colorectal cancer. Our data indicates that it was 2% among 5-year survivors and 7% among 20-year survivors. These figures confirm the lifelong risk connected with the subsequent development of a new colorectal cancer. The 5-year cumulative rate remained stable over time. It can be hypothesised that most colorectal cancers diagnosed in the year following the first cancer had been missed. Yet, the very low 1-year cumulative rate suggested that, even at a population level, missed cancers are rare.

Five other population-based studies are reported in the literature. A 2- to 3-fold increased incidence was reported in Connecticut, Utah and Sweden,[9–11] and was limited to rectal cancers among those with a colon cancer in Finland.[12] The overall risk did not deviate from unity in England and Denmark.[13,14] The reasons for these discrepancies can be explained, at least partly, by differences in methods. In Connecticut, Utah or Sweden and in our study, hospital files were consulted. The registration of a second cancer in Denmark or England is uncertain, since the registration of a subsequent cancer within the same organ as the initial one was most of the time not registered. Misdiagnosed local recurrence or a rare colonic metastasis might contribute to the observed increased risk. However, 80% of recurrences are diagnosed within the 3 years following diagnosis. The persistent growing risk over time, although lower than during the 12–60 month period, suggests a true increased incidence of metachronous colorectal cancers. Colonoscopy surveillance can also affect the reported incidence of a second colorectal cancer. The excess incidence in our study was slightly lower than in other previous studies in Connecticut, Utah, Sweden or Finland covering a period when colonoscopy follow-up was less intensive. It can be hypothesised that detection and removal of adenomas prevented a number of cancers, explaining the smaller excess frequency reported in our survey. However, in the absence of data on colonoscopy follow-up, we cannot confirm this statement. As compared to the general population, the increased incidence of second colorectal cancer was significant only between the first and fifth year after surgery. However, the delay of occurrence varied from a few months to 25 years among the different studies[15–18] justifying a lifelong surveillance colonoscopy. The low frequency in advanced cancers is explained by the fact that these patients did not survive long enough to contract a second colorectal cancer.

Metachronous cancers were diagnosed at an earlier stage than the initial cancer or solitary cancers. Other series were in agreement with our results.[16,18,19] Endoscopic surveillance can explain the high proportion of TNM stage I among metachronous colorectal cancer. Metachronous colorectal cancers were also smaller in size and more often fungating or with adenoma remnants than colorectal cancers without metachronous colorectal cancer. There was a predominance of right-sided cancers among metachronous cancers compared to single colorectal cancers. The previous resection of index tumours that originated predominantly on the left side can explain this right-side shift as well as the development of total colonoscopy. The risk of developing a metachronous colorectal cancer was not influenced by the size, growth features, or existence of adenoma remnants or associated adenomas. Risk tended to be higher in the case of synchronous colorectal cancer. In conclusion, no significant predictive factors for the development of metachronous cancers were found. Due to the lifelong risk of subsequent metachronous colorectal cancer, long-term colonoscopic follow-up is needed. Because of the high incidence of right-sided tumours, colonoscopy needs to be complete.

Conflict of interest statement

None declared.

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