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Original Paper

Incidence of Second Primary Cancers in Three Italian Population-based Cancer Registries

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This is the first population-based study carried out in a southern European region to evaluate the risk of a cohort of cancer patients for developing further cancers. The Tuscany Tumour Registry, the Ragusa Cancer Registry and the Cancer Registry of Romagna, three of the 14 population-based cancer registries active in Italy, were involved in the present study. Overall, 19252 incident cases of cancer of the female breast, and of the colon, rectum, lung and stomach were followed-up for 48 358.3 person-years. Only second metachronous cancers were considered. Controlateral breast cancers were analysed separately. Multiple primaries (MPs) were defined according to the IACR-IACR rules. The observed (O) numbers of MPs were compared with those expected (E) from age-, sex- and registry-specific incidence rates. Overall, 463 MPs were diagnosed (O/E = 0.87, $P < 0.001$). The O/E ratios for cancers of the colon (O/E = 0.66), rectum (O/E = 0.72) and all sites combined (O/E = 0.78) in males were significantly lower than expected. The deficit of observed MPs was significant during the first period (2–12 months) and increased over time. Patients over 65 years of age had a significant lower risk of MP, whereas young cancer patients had significantly higher risks for all cancers and for female breast cancer. Male lung cancer patients had a significantly reduced O/E ratio for stomach cancer (O/E = 0.21). Rectal cancer patients had reduced risks of developing stomach cancer and tumours of all sites combined and a 3-fold increased risk of kidney cancers. Colon cancer patients had an overall reduction in risk of MPs, but female colon cancer patients had a significantly increased risk for tumours of the ovary and small intestine; no significant results were found for primary stomach cancers. Female breast cancer patients had a significantly increased risk of rectal cancer (O/E = 1.97), and when synchronous and bilateral breast cancers were considered, significant overall increases in risk were seen for all cancer sites (O/E = 1.6) and for rectal (O/E = 2), and especially for breast cancers (O/E = 3). The cohort analysed had a lower risk of developing further independent tumours than the general population. Several artefacts may have biased these results: the exclusion of synchronous cancers greatly reduced the overall MP risk, and the age-related differences may have been due to reduced medical surveillance and diagnostic aggressiveness. We have confirmed the increased risk for kidney cancers in rectal cancer patients and the association between cancers of the colon and ovary. The significantly increased risk for rectal cancer in female breast cancer patients is probably due to hormonal and dietary factors. For female breast cancer patients, controlateral breast cancer represented the highest risk. The increased risk of cancer of the small intestine in patients with colon cancer may be due to overdiagnosis within increased medical surveillance. © **1997 Elsevier Science Ltd.**

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INTRODUCTION

In 1889, Billroth first described the occurrence in the same patient of multiple independent cancers (multiple primaries, MPs) [1], and since then several clinical case series of MPs have been reported and various definitions for MPs proposed [2, 3]. The first population-based studies on the incidence of MPs were carried out by cancer registries of long-standing [4] and in the national setting [5, 6]. More recently, other registries have contributed results [7-9].

As MPs are rare, many person-years of observation may be required before they are diagnosed. The populations observed and the length of follow-up period in the Italian registries are relatively limited; therefore, in the present study, the case series of three Italian population-based cancer registries were pooled.

This descriptive study was designed to evaluate the risk of developing further cancers in a cohort of cancer patients. It is the first such study carried out in a southern European region, where the cancer risks and associations may be different from those in the geographic areas where previous population-based studies have been performed.

MATERIALS AND METHODS

The registries involved in the study are three of the 14 population-based cancer registries active in Italy. They have been described fully elsewhere [10]. Some of their characteristics are as follows:

— the Tuscany Tumour Registry (RTT), active since 1984 in the Province of Florence (central Italy) with a resident population of 1 164 141;

— the Ragusa Cancer Registry (RTR), active since 1981 in the Province of Ragusa (southern Italy), 284 238 inhabitants;

— the Cancer Registry of Romagna (RTRo), active since 1985 in the Provinces of Fòrlí and Ravenna (central Italy), with 958 074 inhabitants.

The inclusion criteria for this cohort study were patients resident in the areas covered by the three registries who had cancer of the female breast or of the colon, rectum, lung or stomach in the period 1981–1989 for RTR patients and in 1985–1989 for patients in the RTT and RTRo. Each patient was followed up until death, 31 December 1991 (for RTT patients) or 31 December 1992 (for RTRo and RTR patients), or diagnosis of a second primary cancer, whichever came first. Person-years were calculated using each day of observation from the incidence date (day, month, year) to the end date (day, month, year). In order to avoid over-diagnosis and lead-time anticipation, due to a second diagnosis during ascertainment and treatment of first cancer, the first two months after the first cancer diagnosis were excluded from the analysis and only metachronous cancers were considered [5, 11].

The number of MPs attributed to a cancer case series can vary greatly according to the rules used to define MPs [12]. The three registries routinely used different local rules; however, as in a previous study good reproducibility among coders of the three registries has been described in the use of the IARC–IACR rules [13, 14]. MPs were defined according to those rules in the present study. These rules define MPs as two or more tumours arising at different sites (defined by the first three digits of the ICD-O topography code) [15] or at the same site when histological characteristics according to Berg's classification [16] are different. Only one tumour can be counted in paired organs or for systemic diseases unless the histological characteristics differ. For female breast cancer patients, however, both synchronous and contralateral breast cancers were analysed.

An average of 72.3% of the first primary cancers were verified histologically, the percentage varying slightly from one registry to another, but differing notably for different sites, from 87.3% for breast cancer to 55% for lung cancer. Approximately 92% of the second primary cancers were verified histologically.

The expected numbers of MPs were calculated by multiplying the age-, sex- and registry-specific incidence rates by the same categories of age, sex and registry person-years. The observed second primary cancers were compared with those expected by standardised morbidity rates (O/E). Assuming that MPs are independent events, a Poisson distribution was assumed for the small number of observed cases. The statistical significance of any deficit or excess of observed cases was assessed accordingly.

The relative risks for second primary cancers were evaluated as overall risks and as the risks specific for the first cancer site, and for sex, age and second cancer site. The effect of time from the first cancer diagnosis (less than 1 year, 1–5 years, more than 5 years) was also evaluated. When single sites were considered, only significant results, incidence of at least five observed MPs (excluding skin carcinomas) or known associations are reported.

RESULTS

4275 patients were observed for less than 2 months and therefore excluded. Among these, 4088 died within this period (95.6%), 112 were lost to follow-up (2.6%) and 75 had a second cancer diagnosis (1.8%). Therefore, the analysis comprised 19 252 subjects. The distribution of the cases by site, age at first cancer diagnosis, person-years of obser-

Table 1. Number of patients by site of first cancer, mean age at first cancer diagnosis, number of person-years, mean person-years of observation for first cancer site, number of metachronous MPs observed (Obs) and O/E (observed/expected) ratios

First cancer site	Number of cases	Age (years)	Person-years of follow-up	Mean length of observation (years)	Obs.	O/E
Breast	5237	61.3	20 537.0	3.9	144	1.04
Colon	3244	68.6	8883.4	2.7	98	0.77*
Rectum	1994	68.6	5472.7	2.7	65	0.78*
Stomach	4239	70.2	8057.8	1.9	101	0.87
Lung	4538	65.4	5407.4	1.2	55	0.78
All sites	19 252	66.1	48 358.3	2.5	463	0.87*

*$P < 0.05$.

Table 2. Distribution of metachronous MPs observed and observed/expected (O/E) ratios by first cancer and sex

First cancer site	Sex	No. observed	O/E
Stomach	M	71	0.91
	F	30	0.78
Colon	M	51	0.66*
	F	47	0.96
Rectum	M	41	0.72*
	F	24	0.92
Lung	M	50	0.81
	F	5	0.58
Breast	F	144	1.0
All sites	M	213	0.78*
	F	250	0.96

M, males; F, females. *$P < 0.05$.

vation (overall, 48 358.3), mean length of observation by site (mean, 2.5 person-years), observed cases and observed/expected ratios are presented in Table 1. As expected, the length of observation was longer for cancers with a better prognosis (female breast then colo-rectum). Altogether, 463 (2.4%) second primary cancers were diagnosed over the periods considered while 533.5 were expected (O/E = 0.87, $P < 0.001$). There were significant deficits of MPs for patients with colon (O/E = 0.77) and rectum (O/E = 0.78) cancers. The O/E ratios were significantly lower than expected only for males with cancers of the colon (O/E = 0.66) or rectum (O/E = 0.72) and for all sites combined (O/E = 0.78), and non-significantly lower ratios were seen for female stomach and lung cancers (Table 2).

A total of 12 899.9 person-years were accrued for 2–12 months after first cancer diagnosis, 31 203.1 from 1 to 5 years and 4255.5 after five years. When analysed by time since first cancer diagnosis (Table 3), the deficits of observed MPs for patients with stomach, colon, rectum and lung cancer were significant only during the first period (2–12 months). The O/E ratio increased over time, for all sites combined (beta = 0.21, $P = 0.004$) and for specific cancer sites, except for female breast cancers for which the ratio was stable.

Synchronous cancers were also evaluated for RTT patients (data not shown): during the first 2 months after first cancer diagnosis, the O/E was significantly increased (overall O/E = 1.9) for all sites except lung.

Table 4 shows the results of the analysis by age at the time the first cancer was diagnosed (less than or more than 65 years). Older patients showed a significant lower risk of MPs for colon, lung and all sites, while younger patients had significantly higher risks both overall and female breast cancers.

Table 3. Distribution of metachronous MPs observed (Obs) and of observed/expected ratios (O/E) by first cancer site and time since first cancer diagnosis

	Time since first cancer diagnosis (months)					
	2–12		13–60		61	
First cancer	Obs	O/E	Obs	O/E	Obs	O/E
Stomach	25	0.67*	68	0.96	8	0.95
Colon	16	0.49*	71	0.85	11	1.03
Rectum	12	0.55*	45	0.82	8	1.27
Lung	12	0.38*	39	1.00	4	1.21
Breast	30	1.09	101	1.06	13	0.84
All sites	95	0.63*	324	0.94	44	1.00

*$P < 0.05$.

Table 4. Distribution of metachronous MPs observed and of observed/expected ratios (O/E) by site of first cancer and age at first cancer diagnosis (less than and more than 65 years)

First cancer	Age (years)	Observed	O/E
Stomach	<65	22	1.17
	≥65	79	0.81
Colon	<65	21	1.02
	≥65	77	0.72*
Rectum	<65	12	0.84
	≥65	53	0.77
Lung	<65	22	1.19
	≥65	33	0.64*
Breast	<65	63	1.58*
	≥65	81	0.82
All sites	<65	140	1.25*
	≥65	323	0.76*

$P < 0.05$.

Table 5 shows the incidences of selected second primary cancers for each primary site. Male lung cancer patients had a significantly reduced risk of stomach cancer (O/E = 0.21). Risks that might have been expected to be increased, such as those for tobacco-related cancers (e.g. oral cavity and pharynx O/E = 5.02; kidney and other urinary organs, 1.6; oesophagus, O/E = 1.67; larynx, O/E = 1.89), were greater than 1.0 but not significant.

Rectal cancer patients had reduced risks of developing cancers at all sites combined and in the stomach, while there was a 3-fold increased risk for kidney cancers. Colon cancer patients had a reduced overall risk, which was significant for males; female patients showed a significantly increased risk for ovarian cancer. Moreover, there was an increased risk for cancer of the small intestine, especially for females. No significant deviations from unity were seen in the O/E ratios for patients whose first cancer was in the stomach.

Female breast cancer patients had a significantly increased risk of rectal cancer (O/E = 1.97). Of the sites previously reported to be associated with second primary cancers, colon, corpus uteri, melanoma and thyroid gland showed non-significantly increased risks, while there was a reduced risk of ovarian cancer. The analysis for breast cancer patients, including both synchronous and bilateral breast cancers, is presented in Table 6. Significantly increased overall risks were seen for all cancer sites (O/E = 1.6) and for cancers of the rectum (O/E = 2) and breast (O/E = 3). During the first 2 months after diagnosis, increased risks were also seen for cancers of the salivary glands, gum, stomach and pancreas. The risk for a contralateral breast cancer was increased during the first 2 months, by approximately 37 times the risk of the general population. The risk was around 1 during the subsequent 10 months and then increased significantly from 1 to 5 years after first diagnosis.

DISCUSSION

A second primary cancer occurred in 2.4% of the 19 252 cancer patients analysed, but overall they had a reduced risk of developing further independent tumours in comparison

Table 5. Selected MPs observed (O) and corresponding standardised incidence ratios (O/E) for males and females by site of first cancer

Site of second primary cancer	Males		Females		Males and females	
	O	O/E	O	O/E	O	O/E
Site of first cancer: lung						
Any site	50	0.81	5	0.58	55	0.78
Stomach	2	0.21*	1	0.93	3	0.28*
Colon	6	1.17	0	0	6	0.99
Larynx	5	1.92	0	0	5	1.89
Prostate	6	0.91				
Bladder	5	0.64	0	0	5	0.62
Kidney	4	1.73	0	0	4	1.61
Endocrine gland	0	0	1	182*	1	17.0
Oral cavity and pharynx	1	5.30	0	0	1	5.02
Oesophagus	1	1.79	0	0	1	1.67
Site of first cancer: rectum						
Any site	41	0.72*	24	0.92	65	0.77*
Lung	5	0.49	2	1.67	7	0.61
Prostate	9	1.45				
Kidney	5	3.07	2	4.10	7	3.27*
Colon	1	0.24	3	1.04	4	0.57
Stomach	3	0.38	1	0.29	4	0.35*
Breast, female			4	0.76		
Site of first cancer: colon						
Any site	51	0.66*	47	0.78	98	0.77*
Stomach	5	0.45	8	1.11	13	0.71
Small intestine	1	6.23	2	13.56*	3	9.74*
Rectum	2	0.49	3	1.11	5	0.73
Lung	10	0.70	0	0	10	0.60
Skin melanoma	2	3.65	1	1.64	3	2.59
Prostate	9	1.05				
Bladder	5	0.60	2	1.23	7	0.70
Ovary			5	3.48*		
Breast, female			8	0.78		
Site of first cancer: stomach						
Any site	71	0.91	30	0.78	101	0.86
Rectum	6	0.98	0	0	6	0.92
Colon	6	1.39	4	0.83	10	0.91
Lung	12	0.77	0	0	12	0.68
Prostate	10	1.10				
Bladder	11	1.23	0	0	11	1.07
Lymphomas	6	1.86	1	0.50	7	1.34
Breast, female			6	0.76		
Site of first cancer: female breast						
Any site			144	1.04		
Rectum			16	1.97*		
Stomach			15	0.77		
Colon			19	1.12		
Lung			9	1.18		
Cervix uteri			6	1.28		
Corpus uteri			10	1.10		
Bladder			5	1.06		
Kidney			5	1.59		
Lymphomas			9	1.18		
Ovary			3	0.53		
Skin melanoma			3	1.26		
Thyroid gland			3	1.70		

*$P < 0.05$.

with the general population. This reduction was significant for patients with cancers of the colon or rectum.

These findings could, however, be due to artefacts. The trend of risk for all synchronous and metachronous MPs over time since diagnosis of the first primary is similar to that for screening, being greater than 1 at time zero (screening time), less than 1 immediately afterwards and increasing thereafter. A similar effect may occur after a cancer diagnosis, when a series of examinations is often performed to evaluate the behaviour and extent of disease. This can result in the diagnosis of occult tumours (the risk for MPs observed during the first 2 months at the RTT was approximately 2), accounting for a cancer incidence lower than that expected during the subsequent 10 months due to diagnos-

Table 6. Female breast cancer patients. Distribution of metachronous and synchronous MPs observed (O) and of the observed/expected ratios (O/E) by second cancer site. Controlateral breast cancers were considered among the MPs

	Time since first breast cancer diagnosis (months)									
	0–2		3–12		13–60		61		Total	
Second cancer	O	O/E	O	O/E	O	O/E	O	O/E	O	O/E
Salivary gland	1	70.7*	0	0	0	0	0	0	1	3.1
Gum	1	374*	0	0	0	0	0	0	1	13.6
Oesophagus	0	0	0	0	1	2.0	0	0	1	1.4
Stomach	4	5.5*	4	1.1	8	0.6	1	0.6	17	0.9
Colon	2	3.2	4	1.3	14	1.4	0	0	21	1.34
Rectum	1	3.3	4	2.8	9	1.8	1	1.6	15	2.0*
Liver	0	0	0	0	0	0	1	4.7	1	0.39
Biliary tract	0	0	1	1.8	1	0.5	0	0	2	0.7
Pancreas	2	11.2*	0	0	0	0	2	0.44		
Lung	0	0	0	0	7	1.4	2	3.1	9	1.2
Thymus	0	0	0	0	1	18.2	0	0	1	13.1
Skin melanoma	1	10.9	1	2.2	2	1.3	0	0	4	1.7
Breast										
Contralateral	55	36.9*	7	1.0	41	1.7*	3	1.0	106	3.0*
Uterus (NOS)	0	0	0	0	2	6.2	0	0	2	4.2
Cervix	0	0	0	0	2	6.2	0	0	2	4.2
Corpus	2	6.3	2	1.3	6	1.2	1	1.5	11	1.4
Ovary	0	0	1	1.0	1	0.3	0	0	2	0.4
Bladder	0	0	1	1.1	3	1.0	0	0	4	0.9
Kidney	0	0	4	6.7*	1	0.5	0	0	5	1.6
Brain	0	0	0	0	2	1.5	0	0	2	1.0
Thyroid	0	0	0	0	2	1.7	1	6.7	3	1.8
Endocrine glands	0	0	0	0	1	13.0	0	0	1	8.6
111 defined sites	0	0	0	0	1	3.9	0	0	1	2.6
Leukaemias	0	0	0	0	0	0	1	3.5	1	0.3
Lymphomas	0	0	2	1.5	7	1.5	0	0	9	1.3
Overall	75	11.5*	36	1.1	134	1.2*	14	1.90	259	1.6*

*$P < 0.05$.

tic anticipation. In fact, the risk increased significantly over time (RR = 0.63, 0.94 and 1, respectively) from 2 months to 5 years and more after the diagnosis of the first primary ($P < 0.05$).

Interestingly, the risk varied according to the age of the patients, being lower for the elderly and higher for younger patients. This is probably due to the fact that further investigations of aged cancer patients are not considered useful, and symptoms due to the second cancers tend to be attributed to the previously diagnosed cancer. For younger patients, further efforts are made to identify and treat new neoplasms.

The analysis by sex showed risks lower than those expected except for cancer of the breast; the risks for cancer of the colon and rectum in males were significantly decreased. No difference in the distribution of person-years since first diagnosis was seen by sex. The significant differences may be due partially to the fact that men were diagnosed at a significantly younger age than women.

The reduced risk of rectal cancer patients for cancer at any site and for stomach cancer have been documented previously in Denmark [5] and Finland [6].

Some of the positive associations have been documented previously, such as the increased risk of kidney cancer in rectal cancer patients [17], and the association between cancers of the colon and ovary, the former probably being caused by the same hormonal factors as the latter. The significantly increased risk of cancer of the rectum in female breast cancer patients has not previously been documented, although non-significantly increased risks have been reported [18, 19]. The same hormonal factors that are associated with the increased risk of colon cancer may also be involved in rectal cancers. The risk of contralateral breast cancer was the highest of all risks for further neoplasms, as reported previously [18, 20], reinforcing the need for close surveillance of the remaining breast. Finally, an increased risk of cancer of the small intestine in patients with colon cancer was demonstrated, as shown in other population-based studies [21]. Carcinoid tumours (two of the three tumours of the small intestine observed in the present study), which are highly prevalent in the general population and have a relatively good prognosis, may have a high probability of diagnosis during follow-up investigations for colon cancer.

Even when the case series of the three registries were pooled, the number of MPs at single cancer sites was rather low. This may be due to relatively recent activation of Italian cancer registries and the consequently short period of follow-up. In order to increase the power of this study and to extend the analysis to other possible assocations, including bidirectional associations, other Italian registries are being included.

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