

Risk analysis of colorectal cancer in women with endometrial carcinoma

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Abstract. Endometrial carcinoma (EC) and colorectal cancer (CRC) are closely linked in a well-documented, predominantly inherited cancer syndrome known as hereditary non-polyposis colorectal cancer (HNPCC). Epidemiological studies report that women with EC have a 1.5- to 3-fold increased risk of developing CRC. However, this elevated risk could be the consequence of genetic confounding. In order to plan a proper CRC prevention program, we sought to verify and quantify this risk, first estimating it in 697 women with EC who received treatment and follow-up in one health care district between 1986 and 2000. The standardised incidence ratio (SIR), which compares observed with expected cases of CRC in the general population, was calculated. Multiple logistic regression analysis was used to estimate the odds ratio and 95% confidence interval of a dependent variable, second primary CRC, as a function of clinical and pathological features. Multiple primary tumours were observed in 6.7% of the patients, with CRC being the second most frequently occurring type of cancer. The estimated overall risk for CRC was slightly higher than that observed in the general population, but was nonetheless not statistically significant. Multivariate analysis revealed a family history of CRC to be a risk factor for developing the disease as a second primary cancer. A BMI ≤ 25 and the pathological spectrum of EC were clinical and pathological features associated with CRC development, but were without statistical significance. MSH2 and MLH1 mutational screening confirmed genetic involvement in most of the CRCs observed in the cohort. Overall, the data show that women with EC have a CRC risk similar to that of the general population, and should therefore be screened on the basis of risk factors for CRC.

Introduction

Colorectal cancer (CRC) is the second leading cause of cancer-related morbidity and mortality among women in Italy. A personal history of gynaecological cancer is recognised as a risk factor for developing a second primary malignancy in the colon-rectum (1-4), with a 3-fold increased risk (2) in women who have previously had early-onset endometrial carcinoma (EC). In 1998, the European Panel on the Appropriateness of Gastrointestinal Endoscopy (EPAGE) established that the degree of risk related to a personal history of EC was similar to that conferred by having a first-degree relative with CRC, and the adoption of the same schedule of screening was suggested (5). However, when evaluating the risk of CRC in women who have previously had EC, the role of genetic factors - which lead to an increased risk of up to 25% in a minority of these women - must be taken into account. In fact, EC and CRC are closely linked in a well-documented, predominantly inherited cancer syndrome: hereditary non-polyposis colorectal cancer (HNPCC), also known as Lynch Syndrome. Two different types of HNPCC have been described; type I is characterised by the tendency to develop several CRCs, while type II includes people at high risk of developing endometrial, gastric and, of equal concern, ureteral and renal tumours. These conditions are determined by cancer-susceptibility genes of DNA mismatch repair.

Within the HNPCC family, EC is the most frequently-occurring extracolonic cancer. It has a 20% incidence rate in patients aged 70 years, although it develops at a significantly earlier age. In >50% of cases, a second primary tumour - usually of the CRC variety - occurs (6-8). The aim of the present study was to establish whether women with EC are at an increased risk of developing CRC, and whether they display any clinical risk factors for it.

Materials and methods

This hospital-based study on second primary malignancies in women with EC was conducted in Pordenone Province, a health care district of 270,000 inhabitants in Northeastern Italy. All members of the study population permanently reside

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in and originate from this district, and diagnostic and therapeutic facilities are locally available. As the area is covered by the Friuli-Venezia Giulia (FVG) Regional Cancer Registry, data on incident ECs are easily accessible. The registry covers the period from January 1, 1995 to December 31, 2001, and has archived data from six health care districts in the region, of which Pordenone is one.

In the present study, 697 patients (average age 62 years, range 32-81) with histologically-confirmed EC were treated and followed-up between 1986 and 2000. Analysis was conducted, taking into consideration three separate outcomes: i) patients developing CRC as a second primary tumour; ii) patients developing other malignancies as a second primary tumour; iii) patients developing no types of cancer.

The standardised incidence ratio (SIR) - the expected number of CRC cases - was calculated using age-specific incidence rates from the FVG Regional Cancer Registry. Each stratum-specific incidence rate was applied to the corresponding stratum-specific person-time experience of the study group to calculate the incidence rate without age as a confounding factor.

Multiple logistic regression analysis was used to estimate the odds ratio (OR) and the 95% confidence interval (CI) of the dependent variable, second primary CRC, as a function of independent clinical and pathological variables. The following information related to these variables was collected and included separately: age at menarche, menopausal status at diagnosis of EC, parity, BMI (Quetelet index, weight/height²), pathological features of EC (histology, grade, stage) and radiotherapy. Histology was stratified in the endometrioid tumours and in other carcinomas, such as endometrioid carcinoma with papillary serous and/or clear cell carcinoma components. Stage was defined according to the International Federation of Gynaecology and Obstetrics (FIGO) classification, 1988. Features of synchronous and metachronous neoplasms were collected, with a tumour being defined as synchronous when diagnosed within six months of EC diagnosis.

Family histories of cancer encompassing three generations, as well as information on demographic factors and anthropometrical characteristics, were additionally recorded. Histories reported by patients were verified by a review of medical or pathological records and classified into three groups: i) negative, no relative with cancer; ii) non-specific cancer aggregation, relatives with heterogeneous types of malignancies with no feature of hereditary cancer in the family; iii) CRC, at least one first-degree relative with CRC. Cases were defined as HNPCC when their family history fit the Amsterdam criteria: of three relatives with colon cancer, two were first-degree relatives of the third, all were without polyposis or diseases related to HNPCC, at least one had been diagnosed with cancer at <50 years of age), and at least two successive generations had been affected.

Genetic counseling and mismatch repair (MMR) gene (MLH1, MSH2, MSH6) mutation screening were conducted in the women with a family history of HNPCC or in those with multiple cancers and a family history of CRC. Of the 697 patients, 127 were not available for follow-up. We compensated for the resulting lack of data by cross-linking their names and dates of birth with the regional administrative health care database, in which all hospital admissions, pathological

Table I. Distribution of metachronous second primary cancer in 47 patients after diagnosis of endometrial carcinoma.

Site	Distribution no. (%)	
Breast	22	(3.15)
Colon-rectum	6	(0.86)
Bladder	4	(0.57)
Lung	4	(0.57)
Sarcomas	2	(0.28)
Skin	2	(0.28)
Liver	2	(0.28)
Thyroid	1	(0.15)
CNS	1	(0.15)
Pancreas	1	(0.15)
Lymphoma	1	(0.15)
Melanoma	1	(0.15)
Kidney	1	(0.15)
Stomach	1	(0.15)

CNS, central nervous system.

reports, treatments, and deaths either from neoplastic or non-neoplastic diseases have been registered since 1983.

Results

The mean duration of follow-up was ~6.5 years. Of the 697 patients, 433 (62.1%) continue to undergo follow-up without evidence of disease recurrence, 172 (24.7%) died of EC, and 92 (13.2%) died of intercurrent illness. Fifty-nine second primary malignancies were diagnosed in 47 of the 697 (6.7%) patients. The most frequently-occurring tumours were breast cancers (22 cases in 20 patients; 2.8%) and CRCs (6 cases in 6 patients; 0.8%). Synchronous ovarian cancers were diagnosed in 31 patients (4.4%). The second primary malignancies observed are summarised in Table I. Of the 6 CRC cases, 4 were located in the right colon and 2 in the rectum. They were diagnosed within an average of 54 months (range 36-96 months) following EC diagnosis. Of the 6 cases, 4 had a family history indicative of HNPCC.

Genetic counseling and mutation screening for MMR were performed in 7 patients; 4 of these had, as mentioned above, a family history indicative of HNPCC, and developed CRC during follow-up. Two had a synchronous ovarian cancer and a family history of CRC; one, with a family history including only one first-degree relative with CRC, developed the tumour. Of these 7 patients, 4 were carriers of MMR defects: MLH1 (aberrant splicing IVS7-2A→G), and MSH2 (frame shift mutation 399 del C, aberrant splicing IVS6-2A→C, stop codon Q824X) (9). All 4 of these developed CRC.

Six cases of CRC were observed rather than the estimated number of 5 (SIR=1.20, 95% CI 0.04-2.16). The annual age-standardised ratio (world population) for CRC in the female general population of the health care district studied was 29.2 per 100,000 in 1995-2001, with a 3.2% risk of developing CRC between the ages of 30 and 80 years.

Table II. Distribution no. (%) of patients according to characteristics, family history of cancer, endometrial carcinoma features and radiotherapy.

Features	Colorectal cancer (n=6)	Second primary cancer (n=42)	No second primary cancer (n=649)	Total (n=697)
Age at diagnosis (years)				
<50	1 (16.7)	4 (9.5)	79 (12.2)	84 (12.1)
≥50	5 (83.3)	38 (90.5)	570 (87.8)	613 (87.9)
Age of menarche (years)				
<14	3 (50.0)	23 (54.8)	413 (63.6)	439 (62.9)
≥14	3 (50.0)	19 (45.2)	236 (36.4)	258 (37.1)
Menopausal status				
Pre-menopausal	2 (33.3)	5 (11.9)	121 (18.6)	128 (19.4)
Post-menopausal	4 (66.7)	37 (88.1)	528 (81.4)	569 (81.6)
Parity				
Nulliparous	0 (0.0)	21 (50.0)	230 (35.4)	251 (36.1)
Parous	6 (100.0)	21 (50.0)	419 (64.6)	446 (63.9)
BMI ^a				
<25	3 (50.0)	7 (16.7)	196 (30.2)	206 (29.6)
≥25	3 (50.0)	35 (83.3)	453 (69.8)	491 (70.4)
Family history of cancer				
Negative	1 (16.7)	28 (66.7)	412 (63.5)	441 (63.3)
Non-specific	0 (0.0)	14 (33.3)	204 (31.4)	217 (31.1)
CRC	5 (83.3)	0 (0.0)	33 (5.1)	39 (5.6)
Histology				
Endometrial carcinoma	5 (83.3)	39 (92.9)	555 (85.5)	599 (85.9)
Other carcinomas ^b	1 (16.7)	3 (7.1)	94 (14.5)	98 (14.1)
Grade				
G1+G2	4 (66.7)	33 (78.6)	453 (69.8)	490 (70.3)
G3+G4	2 (33.3)	9 (21.4)	196 (30.2)	207 (29.7)
Stage				
IA+IB	5 (83.3)	29 (69.0)	337 (51.9)	371 (53.2)
IC	0 (0.0)	8 (19.0)	106 (16.9)	114 (16.3)
II	1 (16.7)	3 (7.1)	76 (11.7)	80 (11.4)
III+IV	0 (0.0)	2 (4.8)	130 (20.0)	132 (18.9)
Radiotherapy				
No	3 (50.0)	16 (38.1)	261 (40.2)	280 (40.2)
Yes	3 (50.0)	26 (61.9)	388 (59.8)	417 (59.8)

^aBMI, body mass index (weight/height²). ^bIncluding papillary serous and clear cell carcinomas.

Table II lists the distribution of cases according to the clinical and pathological features of the three subgroups of our three cohorts. The ORs for second primary CRC according to clinical and pathological features are shown in Table III. We observed a slightly decreased, though not statistically significant, risk of developing CRC in patients with a BMI ≤25 (OR=0.43; 95% CI 0.03-5.51). A 200-fold increased risk of CRC (OR=207.06; 95% CI 8.04-5327.89) was observed in patients with a family history of CRC.

Discussion

In our cohort, the 6.7% frequency of second primary malignancies was slightly lower than the range previously reported (7.1-22.7%); however, most studies have also included patients with metachronous cancers diagnosed prior to EC (9,10). The most frequently-occurring second primary cancer was breast cancer, with a percentage of 2.8 rather than 6%. Fewer than 1% of our patients developed CRC as a second primary

Table III. Odds ratio and 95% confidence interval for second primary colorectal cancer according to patient characteristics, family history of cancer, endometrial carcinoma features and radiotherapy.

Features	Absence of 2nd primary cancer (n=649) vs. 2nd primary CRC (n=6)	
	OR	95% CI
Age at diagnosis (years)		
<50	1.00	
≥50	4.67	0.14-150.71
Age of menarche (years)		
<14	1.00	
≥14	8.64	0.57-130.32
Menopausal status		
Pre-menopausal	1.00	
Post-menopausal	0.11	0.004-3.32
Parity		
Nulliparous	1.00	
Parous	∞	0.00-∞
BMI ^a		
<25	1.00	
≥25	0.43	0.03-5.51
Family history of cancer		
Negative	1.0000	
Non-specific	0.0004	0.00-∞
CRC	207.0600	8.04-5327.89
Histology		
Endometrial carcinoma	1.00	
Other carcinomas ^b	11.48	0.43-302.05
Grade		
G1+G2	1.00	
G3+G4	0.38	0.02-6.24
Stage		
IA+IB	1.0000	
IC	0.0000	0.00-∞
II	2.5300	0.08-74.57
III+IV	0.0002	0.00-∞
Radiotherapy		
No	1.00	
Yes	0.58	0.04-8.17

^aBMI, body mass index (weight/height²). ^bIncluding papillary serous and clear cell carcinomas. CRC, colorectal cancer; OR, odds ratio; CI, confidence interval.

cancer. The risk of CRC was enhanced by the number of cases, but did not reach statistical significance (SIR=1.20, 95% CI 0.04-2.16), perhaps due to the small size of the sample; despite the long follow-up period, the cohort remained small.

Although the present study has the limitation of being a hospital-based study, it bears the features of a population-based study, including patients with EC diagnosed and treated at the same facility available in the one area being studied. Previous studies have resulted in greatly varied reports of CRC risk in EC patients. In agreement with the results of the present study, one study reports a risk that did not reach statistical significance; in others, the risk ranged between 20 and 40% (1-4).

The CRC cases observed were diagnosed after a relatively short latency period (on average 4 years) from the initial diagnosis of EC. It is likely that this lag-time is too short for the induction of *de novo* CRC. Disease development can instead be attributed to common factors, including environment and mutations in similar predisposing genes, which play a predominant role in the aetiology of the two cancers (4).

Multivariate analysis indicated that familial clustering of CRC represents a strong risk factor for CRC, as reported in the literature (11,12). In particular, a family history indicative of HNPCC seemed to be a causative factor associated with risk, as 4 of the 6 cases with CRC as a second primary cancer displayed the clinical criteria necessary for a diagnosis of HNPCC. MSH2 and MLH1 screening mutation confirmed the clinical diagnoses and, therefore, the common genetic aetiology linking CRC and EC.

Regarding the other clinical features of women with CRC as a second primary cancer, several parameters were observed that may confirm the genetic pathogenesis of the disease. A BMI ≥25 appears to be a protective factor for CRC. Of the patients with EC and CRC, 50% did not exhibit obesity, the major risk factor for EC. This finding can be explained by the apparent involvement of genetic rather than common risk factors in the development of EC. The best-established risk factor for EC, second only to obesity, is chronic exposure to estrogens. Genetic involvement was observed in a small percentage of normal or overweight young women with EC, but not in obese patients (13).

A more variable histological spectrum of EC (endometrioid carcinoma with clear cell and papillary serous carcinoma components) was observed in the CRC cases. This feature implies the involvement of genetic factors in the pathogenesis of the CRC cases studied. Indeed, this has already been reported in patients carrying the MSH2 mutation (14).

Synchronous primary endometrial and ovarian cancers have been reported as features which might misleadingly result in the determination of HNPCC when a family history of CRC is involved. Although 2 of 31 patients (6.5%) reported having a first-degree relative with CRC, they did not meet the clinical criteria for HNPCC, nor were mutations observed in the MSH2, MLH1 and MSH6 genes (15-17).

In conclusion, our cohort of women with EC presented a slightly increased, but not statistically significant, risk of CRC. This elevated risk was related to HNPCC, which represents a confounding risk factor. Women with EC should therefore be screened for CRC in the same way that the general population is, stratifying them on the basis of risk factors such as age ≥50 years and a family history of cancer (18). Particular attention should be paid when collecting family history. Patients with a family history of cancer must be referred for genetic counseling and gene testing to rule out HNPCC.

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