PERGAMON

European Journal of Cancer 39 (2003) 1904–1911

European Journal of Cancer

www.ejconline.com

Familial relative risk of colorectal cancer: a population-based study

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Received 13 September 2002; received in revised form 28 February 2003; accepted 24 March 2003

Abstract

This study aimed to assess the familial relative risk for colorectal cancer (CRC) and its variation according to age and gender. A population-based family study was carried out in France, from 1993 to 1998, including 761 families. Familial CRC risks were estimated from a cohort analysis of the relatives. No obvious decrease in CRC risk was found with increasing age, except when either the proband, or the relative, were in the youngest age class. The effect of the relatives' and probands' ages on the CRC risk differed according to their gender. The cumulative risk of CRC increased at an earlier age in male relatives of probands younger than 60 years of age, than in female relatives. This result suggests that mechanisms specific to females, possibly interacting with genetic factors, explain the difference in the cumulative risks between families with male and female probands.

Keywords: Colorectal cancer; Family study; Relative risk

1. Introduction

Colorectal cancer (CRC) is the second most common cause of death from cancer in France, with approximately 33 400 new cases diagnosed per year [1]. As with many cancers, a family history (FH) of CRC has been shown to increase an individual's risk of developing the disease. The risk associated with a FH of cancer within the population has been estimated mainly from studies of first-degree relatives, and is usually estimated as a doubling of risk [2–4]. Other studies have concentrated on more selected populations (e.g. high-risk families), these have proved that some syndromes are inherited. Indeed, only a small fraction of CRC cases (less than 5%) are accounted for by the known inherited syndromes, familial adenomatous polyposis and hereditary non-polyposis colorectal cancer (HNPCC) [5]. Studies within high-risk families or the general CRC population have suggested heterogeneity in the familial risk. Indeed, some researchers have suggested that FH may have a greater impact on proximal tumours [6,7], others have shown that familial risk may be modified by exposure to hormones [7] or by diet [8]. A population-based family study, the CCREF (Calvados ColoREctal Family) study has been carried out in Calvados, France. The main aim of this study was to define the role of inherited factors in the transmission of CRC. This population-based family study allowed the evaluation of familial risk and its variation according to potential modifier factors. In this paper, we present estimates of the CRC familial relative risk and its variation according to age and gender.

2. Patients and methods

The CCREF study consisted of the collection of the CRC incident cases in the region served by the Calvados Cancer Registry. The local Research Ethics Committee in Calvados approved the study. All patients diagnosed with CRC between September 1993 and December 1998 were eligible for the study. Information on

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0959-8049/03/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/S0959-8049(03)00420-9

tumour histology was collected for all CRC cases. Patients' details were obtained from the pathology laboratories in the Calvados region, and the patients' general practitioners (GP) were contacted to obtain permission to contact the patient.

A trained interviewer asked all patients taking part in the study questionnaire on their FH of cancer and to provide a 20-ml blood sample. The FH questionnaire included details of spouses and all first- and second-degree relatives, including their date of birth, age at death if deceased, and any history of cancer, age at diagnosis and place of care. Information on all cancer cases in family members was verified through the local cancer registers, and medical care centres', GPs' or specialists' records.

2.1. Statistical methods

Familial cancer risks were estimated from a cohort analysis of the relatives of the CRC cases. At risk patients entered the cohort on 1 January 1970, or at birth if they were born after 1 January 1970, and were censored upon diagnosis of CRC if affected, upon death if deceased, on the date the FH questionnaire was completed if alive, or on the date of their first-degree relative's interview.

Relatives whose date of birth was unknown were given a fictitious date according to their position in the family. The date of birth was not known in approximately 20% of relatives. This missing information was mainly among grandparents, who accounted for very few person-years (≈0.6% of the total person-years). The expected numbers of cancers were calculated from Calvados age- gender- and period-specific (1978–1982, 1983–1987, 1988–1992, and 1993–1995) incidence rates. Familial relative risks (RR) were calculated from the ratio of observed number (O) to expected number (E) of cancers. Two-sided 95% Confidence Intervals (CIs) for RR estimates, heterogeneity and trend tests are based on the Poisson distribution [9]. We calculated incidence rates among relatives of CRC families by multiplying the familial RR of developing CRC by the incidence rate of CRC of general Calvados population in the corresponding period of time and 5-year age category.

3. Results

3.1. Study acceptability

Between September 1993 and December 1998, 1351 cases of CRC were diagnosed in the Calvados region. 34 cases were already deceased when the information of a CRC diagnosis was received. Thus, the GPs of 1317 cases were contacted to obtain permission to contact their patients. 94 of their patients died in the meantime (7.1%), 138 refused to allow us to contact their patients (10.5%) and 1085 gave us permission to contact their patients (82.5%). The most common reason for the GP's refusal was the patient's worsening health or, less frequently, the patient's mental status.

Of the 1085 patients for whom permission was obtained, 36 died during the time taken to get the GP's permission and the interviewer contacting them (3.3%), 282 CRC patients refused to participate (26.0%) and, therefore, 767 CRC patients agreed to participate (70.7%). Thus, 767 CRC patients out of 1351 incident cases (56.8%) were included in the CCREF study. The local Research Ethics Committee did not allow us to ask the CRC patients their reasons for refusing to participate in the study, thus causes of CRC patient refusal could not be studied. One CRC patient was excluded because of a lack of information about his family.

3.2. Comparison between participating and non-participating CRC cases

We compared the age at diagnosis of CRC and histological characteristics of participating and non-participating CRC tumours. Male and younger CRC patients (i.e. younger than 76 years) appeared to be slightly more willing to participate than the female ($P = 0.04$) and older ($P < 0.001$) CRC patients. There was no difference in the tumour site and type of cell differentiation between the two groups (Table 1). However, there was a significant difference in the invasive characteristics of the tumour like tissue invasion ($P < 0.001$), contiguous organ invasion ($P = 0.002$), and the regional lymph node and viscera metastasis invasion ($P < 0.001$) (data not shown). This reflects the GPs' refusal to interview CRC patients whose health was worsening. Familial risk of CRC was estimated according to a prognosis factor. Poor prognosis was determined as invasion of either the metastasis lymph nodes, viscera, or any contiguous organs. There was no difference in the familial risk estimates between good and poor prognosis (P of heterogeneity = 0.4) (data not shown). Thus, we analysed the familial risk of CRC in relatives of probands with pooled good and poor prognoses.

3.3. CRC case descriptions within families

The 766 probands belonged to 761 independent families, with five families containing two probands. There were 10 512 proband relatives. The number of relatives according to gender, relationship to the proband, and the mean age (at interview if alive, or age at death if deceased) per relationship category is shown in Table 2. The number of person-years per relationship category corresponds to the data follow-up from 1 January 1970.

Declared cancer cases were systematically verified. The mean percentage of confirmed CRC (colon or rectum) was 79.1% in all-degree relatives and 87.5% in

Table 1
Histopathological characteristics of the CRC tumours

Characteristics	Participating CRC cases or probands	Non-participating CRC cases	*P* values
	Number of tumours (%)	Number of tumours (%)	
Gender			
Males	447 (57.8)	314 (52.2)	*
Females	327 (42.2)	287 (47.8)	
Age at diagnosis (years)			
⩽45	25 (3.2)	9 (1.5)	
46–50	37 (4.8)	21 (3.5)	
51–55	39 (5.0)	16 (2.7)	
56–60	65 (8.4)	32 (5.3)	
61–65	105 (13.6)	59 (9.8)	**
66–70	144 (18.6)	86 (14.3)	
71–75	165 (21.3)	109 (18.1)	
76–80	79 (10.2)	77 (12.8)	
81–85	76 (9.8)	100 (16.6)	
⩾86	39 (5.0)	92 (15.3)	
Mean (S.D.)	68.5 (11.3)	73.3 (11.5)	***
Range	(25–95)	(39–103)	
Tumour site			
Caecum-ascending	119 (15.4)	96 (16.0)	
Transverse	85 (11.0)	68 (11.3)	0.33
Descending-sigmoid	253 (32.7)	166 (27.6)	
Rectum–RS junction	300 (38.8)	248 (41.3)	
Unknown	17 (2.2)	23 (3.8)	
Cell differentiation			
Undifferentiated	39 (5.0)	40 (6.7)	
Medium-differentiated	198 (25.6)	174 (29.0)	0.37
Well-differentiated	340 (43.9)	262 (43.6)	
Imprecise	197 (25.5)	112 (18.6)	
Unknown		13 (2.2)	

S.D., standard deviation; CRC, colorectal cancer.
*$P<0.05$; **$P<0.01$; ***$P<0.001$.

first-degree relatives. CRC cases were included in this analysis if they were diagnosed after 1 January 1970. Of the 107 cases considered to be CRC (Colon-Rectum and Intestine SAI), 78% were confirmed. Nearly 100% agreement between the case reports and the pathological report was found.

Considering all of the CRC cases (i.e. diagnosed either before or after 1 January 1970, and either first- or second-degree relationship with the proband), of the 761 families, 136 families included one other person with CRC (17.9%), 35 families included two other people with CRC (4.6%) and seven families included three or more other people with CRC (0.9%). Of the 250 CRC cases diagnosed in the proband relatives, 10.0% were diagnosed before the age of 50 years, and 4.0% before the age of 45 years. Only three families (0.4%) fulfilled the Amsterdam criteria [10] of 3 cases of CRC, of which 2 of the affected individuals are first-degree relatives of the third case, CRC occurring across two generations, plus 1 CRC case diagnosed under the age of 50 years. When the less strict criteria are considered (i.e. Amsterdam criteria II including the extracolonic cancers associated with HNPCC: endometrium, small bowel, ureter or renal pelvis) [11], the number of families fulfilling it is doubled (0.8%). However, few extracolonic cancers have been able to be confirmed. Indeed, only one family had endometrium and small bowel cancer verified by medical records; the other two families presented unconfirmed and imprecise uterine cancers.

Table 2
Distribution of relatives according to their relationship with the proband

Relationship with proband	No. of women	Mean age (S.D.)	No. of men	Mean age (S.D.)	Person-years (from 1 January 1970)
Children	1060	38.9 (12.8)	1068	37.0 (14.2)	45 701
Siblings	1266	57.5 (22.3)	1283	53.7 (22.1)	44 499
Parents	748	73.2 (16.2)	735	66.2 (15.6)	9137
Aunts–uncles	1413	68.1 (23.2)	1342	58.6 (23.4)	17 390
Grandparents	802	73.9 (15.4)	795	67.4 (15.3)	680
Total number	5289		5223		117 407

S.D., standard deviation.

3.4. Estimate of the familial risk

The risk of developing CRC associated with having a FH of CRC was 1.54 (95% CI: 1.26–1.86). The familial CRC risk appeared greater, but not significantly so, for first-degree relatives than second-degree relatives (RR = 1.71, 95% CI: 1.35–2.13 and RR = 1.22, 95% CI: 0.82–1.76, respectively). Although a few families had two or more relatives with CRC, the familial risk of CRC appeared to increase greatly when more family members had the disease. When two family members had the disease, the familial risk was 5.43 (95% CI: 4.28–6.78), when three or more family members had the disease, the familial risk was 8.52 (95% CI: 5.75–12.2) (data not shown).

Detailed information on colorectal tumours was only available for the probands, therefore familial CRC risk was estimated according to the proband's CRC localisation. There was a decrease in the point-estimated risk associated with localisation from 'caecum-ascending' colon (RR = 2.04; 95% CI: 1.24–3.15), 'transverse-descending-sigmoid' colon (RR = 1.65; 95% CI: 1.22–2.18) to gathered 'RSJ' (recto-sigmoid-junction) and rectum (RR = 1.26; 95% CI: 0.89–1.75). However, neither heterogeneity ($P = 0.20$) nor the trend test ($P = 0.07$) were significant (data not shown).

The familial CRC risk was estimated according to the gender and age of the relatives of the 761 probands (Table 3). There was no difference in the estimated risk between genders. Although neither heterogeneity nor the trend test were significant, there was a decrease in the point-estimated risk as the relative's age increased

Table 3
Relative risk of CRC in relatives according to their age and gender

Relative characteristics	O	E	RR	95% CI	*P* value	P_{trend}
Gender						
Female	53	34.11	1.55	(1.16–2.03)	0.002	
Male	54	35.28	1.53	(1.15–2.00)	0.002	NS
Age (years)						
⩽50	10	4.84	2.07	(0.99–3.80)	0.03	
51–60	17	10.16	1.67	(0.97–2.68)	0.03	NS
61–70 years	28	21.87	1.28	(0.85–1.85)	NS	
> 70	52	32.52	1.60	(1.19–2.10)	<0.001	
Gender and age (years)						
Female						
⩽50	4	2.32	1.72	(0.46–4.41)	NS	
51–60	5	4.49	1.11	(0.36–2.60)	NS	NS
61–70	14	9.80	1.43	(0.78–2.40)	NS	
> 70	30	17.49	1.72	(1.16–2.45)	0.004	
Male						
⩽50	6	2.52	2.38	(0.87–5.18)	NS	
51–60	12	5.66	2.12	(1.09–3.70)	0.01	NS
61–70	14	12.07	1.16	(0.63–1.95)	NS	
> 70	22	15.03	1.46	(0.92–2.22)	NS	

NS, non-significant; O, observed; E, expected; RR, relative risk; 95% CI, 95% Confidence Interval.

up to the age of 70 years (from 2.07 for relatives aged 50 years and less, to 1.28 for relatives aged between 61 and 70 years), followed by an increase in the estimated risk in the oldest age class (RR = 1.60). When the familial CRC risk was estimated according to the relative's age and gender, a similar trend was observed for male relatives. For female relatives, no clear pattern was observed. Although a higher risk of CRC was observed for the youngest females (RR = 1.72, 95% CI: 0.46–4.41), a similar point estimate was found among the eldest (RR = 1.72, 95% CI: 1.16–2.45).

The cumulative risk of developing CRC, according to gender, in the general Calvados population and in relatives of the CRC families was calculated (Fig. 1). The cumulative risk of CRC in men in the general population was 0.9% at 60 years, 2.9% at 70 years and 7.7% at 85 years. In men in CRC families, the CRC cumulative risk was 2% at 60 years, 4% at 70 years and 10% at 85 years. The cumulative risk of CRC in women in the general population was 0.7% at 60 years, 1.8% at 70 years and 4.6% at 85 years; in women in CRC families, it was 0.9% at 60 years, 2.3% at 70 years and 6.2% at 85 years.

To explore the effect of age on the familial CRC risk, relatives were classed according to their age and the proband's age at diagnosis (Table 4). A clear pattern of familial risk of CRC according to age was only observed in relatives of probands who were diagnosed before 50 years of age. Indeed, in this age-class, the familial CRC risk decreased from 5.17 (95% CI: 1.04–15.1) for relatives younger than or equal to 50 years, to 1.14 (95% CI: 0.31–2.92) for relatives aged over 70 years (*P* of trend = 0.03). In the other age-classes at diagnosis, the pattern of familial risk according to the relative's age is less clear, with an increase in familial risk among the oldest class of relatives. We observed a similar pattern of variation in familial risk according to the proband's age at diagnosis.

We calculated the cumulative risk of developing CRC in the CRC relatives according to the proband's age at diagnosis in two groups (proband age

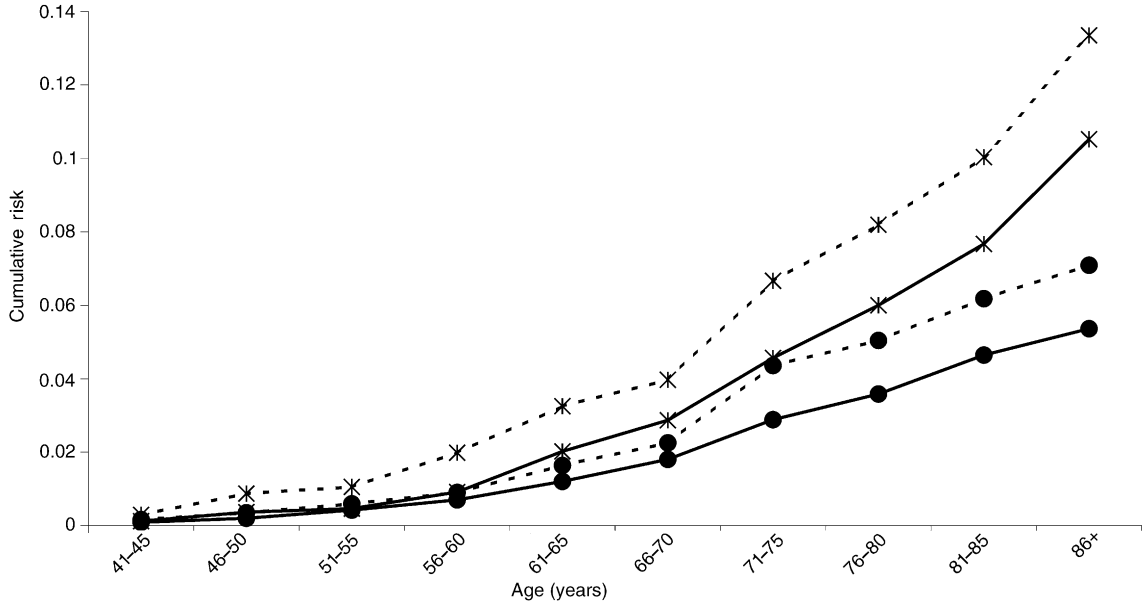

Fig. 1. Cumulative risk of colorectal cancer (CRC) in the general Calvados population and the Calvados colorectal family (CCREF) families. Dotted-starred line denotes the cumulative risk of CRC in male relatives of CCREF families. Starred line denotes the cumulative risk of CRC in men in the general Calvados population. Dotted-circled line denotes the cumulative risk of CRC in female relatives of CCREF families. Circled line denotes the cumulative risk of CRC in women in the general Calvados population.

Table 4
Relative risk of CRC in relatives according to their age and the proband's age at diagnosis

Age of relatives	Proband's age at diagnosis										
	⩽50 years		⩽60 years		⩽70 years		> 70 years		Total		
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	P_{trend}
⩽50 years	5.17	(1.04–15.1)	2.63	(0.30–9.50)	1.34	(0.15–4.85)	1.49	(0.30–9.50)	2.07	(0.99–3.80)	*
51–60 years	2.84	(0.76–7.26)	1.16	(0.13–4.20)	1.48	(0.48–3.46)	1.64	(0.13–4.20)	1.67	(0.97–2.68)	NS
61–70 years	1.69	(0.55–3.96)	1.50	(0.55–3.96)	1.26	(0.57–2.39)	1.03	(0.55–3.96)	1.28	(0.85–1.85)	NS
> 70 years	1.14	(0.31–2.92)	1.98	(1.02–3.45)	1.41	(0.79–2.32)	1.71	(1.02–3.45)	1.60	(1.19–2.10)	NS
Total	1.89	(1.08–3.08)	1.75	(1.10–2.65)	1.37	(0.93–1.94)	1.48	(1.10–2.65)	1.54	(1.26–1.86)	NS
P_{trend}		*		NS		NS		NS		NS	

*$P < 0.05$.

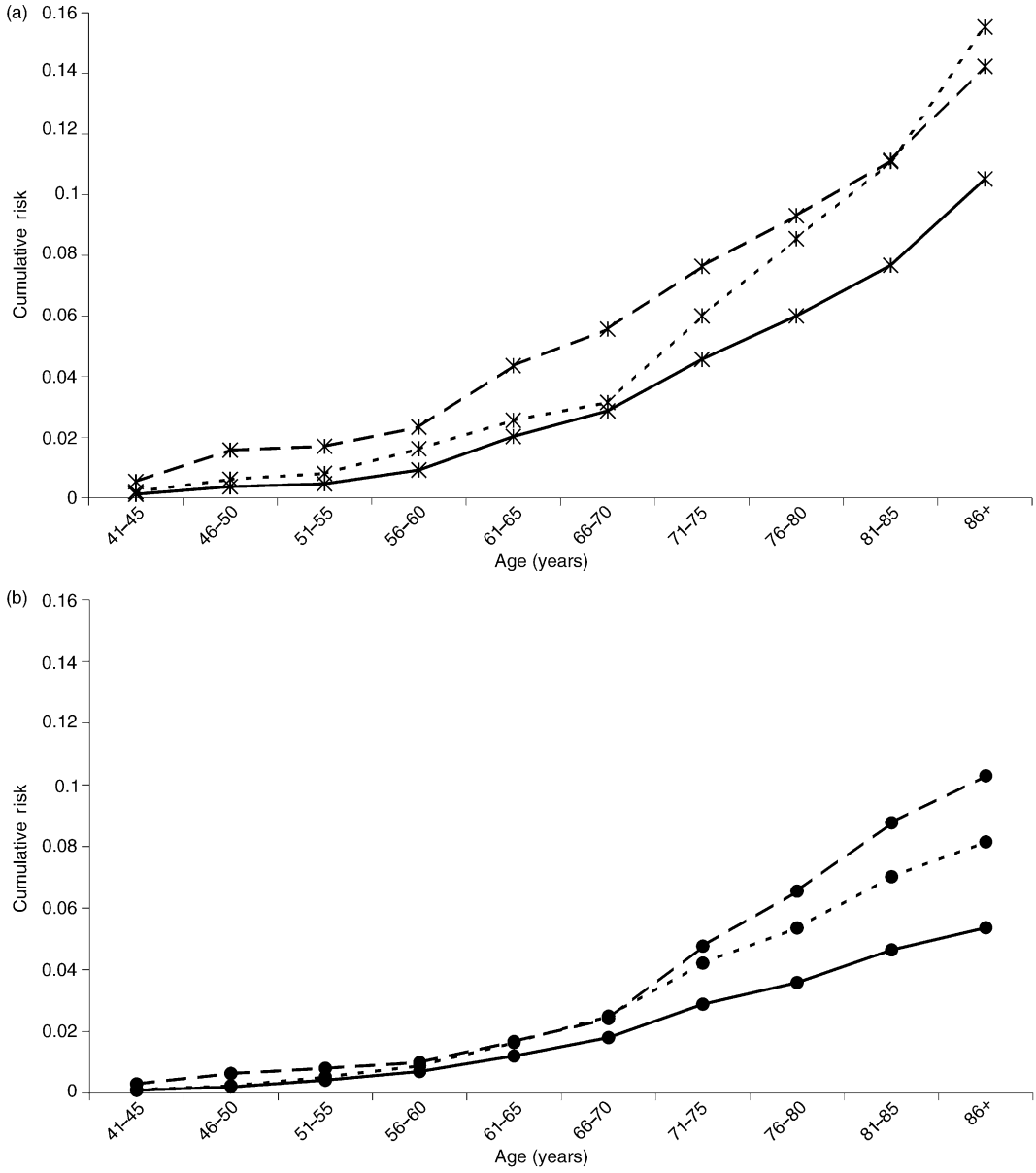

Fig. 2. Cumulative risks in Calvados colorectal family (CCREF) families according to the proband's age at diagnosis. (a) Starred lines denote the cumulative risk of colorectal cancer (CRC) in males, (b) bold-circled lines in females. Dotted lines denote the cumulative risk of CRC in relatives of CCREF families with probands older than 60 years, dashed lines with proband 60 years or younger, unbroken lines denotes the general Calvados population.

at diagnosis ⩽60 years and > 60 years) and according to the relative's gender (Fig. 2). In male relatives of probands with CRC diagnosed ⩽60 years (Fig. 2a, dashed-starred line), the cumulative risk of CRC increased at an early age. The cumulative risk of CRC was 1.6% compared with 0.4% for the general population at 50 years, 2.3% compared with 0.9% at 60 years, 5.6% compared with 2.9% at 70 years, and 11.1% compared with 7.7% at 85 years. In female relatives (Fig. 2b, dashed-circle line), the cumulative risk of CRC seemed to increase at a later age (the cumulative risk of CRC was 2.4% compared with 1.8% for the general population at 70 years, and 8.8% compared with 4.6% at 85 years). In male relatives with older probands (Fig. 2a, dotted-starred line), no clear pattern emerged. In female relatives with older probands (Fig. 2b, dotted-circle line), the cumulative risk of CRC also seemed to increase at a later age.

Familial CRC risk was estimated according to the proband's gender (Table 5). None of the *P* trends was significant. However, if the proband was male, the familial risk point estimate for both male and female relatives decreased as the proband's age at diagnosis increased (for male relatives, from 2.31, 95% CI: 0.84–5.02, if the proband was ⩽50 years old, to 1.15, 95% CI: 0.49–2.26 if the proband was > 70 years old; for female relatives, from 1.93, 95% CI: 0.62–4.51 if the proband was ⩽50 years old, to 0.96, 95% CI: 0.35–2.08 if the proband was > 70 years old). If the proband was female, there was no clear pattern in familial risk in male relatives according to the proband's age at diagnosis. However, there was a surprising increase in the familial risk point estimate in female relatives, from 1.55 (95% CI: 0.17–5.06) if the female proband was ⩽50 years old, to 2.34 (95% CI: 1.31–3.85) if the female proband was > 70 years old.

Table 5
Relative risk of CRC in relatives according to the proband's gender and age at diagnosis

Age of proband at diagnosis (years)	Gender of proband			
	Male		Female	
	RR	95% CI	RR	95% CI
Male relatives				
⩽50	2.31	(0.84–5.02)	1.53	(0.31–4.47)
51–60	1.90	(0.82–3.74)	1.64	(0.44–4.20)
61–70	1.57	(0.81–2.74)	1.17	(0.32–3.00)
> 70	1.15	(0.49–2.26)	1.49	(0.68–2.83)
Female relatives				
⩽50	1.93	(0.62–4.51)	1.55	(0.17–5.60)
51–60	1.79	(0.65–3.89)	1.57	(0.42–4.02)
61–70	1.01	(0.44–2.00)	2.05	(0.82–4.22)
> 70	0.96	(0.35–2.08)	2.34	(1.31–3.85)

4. Discussion

The CCREF study confirms that a family history of CRC increases one's risk of developing CRC (for example Refs. [3,10,12–13]) with estimations similar to those found in the Swedish family cancer database [14]. However, only 0.4% met the strict Amsterdam criteria I for HNPCC. This low prevalence estimate might be due to the inclusion of probands with *in situ* malignancies. However, when the 76 families of probands with *in situ* malignancy are excluded, the number of families fulfilling the Amsterdam criteria I or II remains approximately 0.4 and 0.8%, respectively. Previous estimates of the prevalence of HNPCC vary from less than 1%–13%. Our results are consistent with recent population-based studies (0.3% in [15]; 0.9% in [16]; and 1% in [17]).

Our study also found that the age of relatives and probands affects the CRC risk. No clear decrease in CRC risk was observed with increasing age, except if the proband was male and either the proband or the relative were in the youngest class. Indeed, if the proband was 50 years or younger, a significant decrease in familial risk of CRC was observed as the relatives' age increased. Similarly, if the relative was 50 years or younger, the CRC risk decreased significantly as the age of the proband increased. There are little data about the familial risk associated with early-onset disease outside of the colorectal cancer predisposition syndromes. However, our results are consistent with previous reports finding similar estimated risks [18–20]. Surprisingly, in most of the older age classes, an increase in CRC risk was observed. This increased risk may be due to the observed inverse effect of age on the familial risk in female relatives of female probands.

Since RRs according to age and gender are estimated on small numbers, we cannot exclude that the observed differences between RRs might be due to random variation. However, there are several suggested mechanisms on the association of female factors with CRC that may explain our findings [21–24]. Indeed, a study of trends in colon cancer mortality over time proposed that the generation of women that experienced both a substantial increase in fertility in the late 1950s and exposure to early high-dose oral contraceptives in the early 1960s subsequently experienced a transient decline in mortality from colon cancer [21]. Likewise, in England and Wales, trends in colorectal cancer incidence and mortality over time have found that the difference between the sexes is related to changes in female hormonal factors [25]. In several case–control and cohort studies, hormone replacement therapy has been found to be inversely associated with CRC [26], consistent with the hypothesis that female hormones may have a protective effect.

We suggest that specific female mechanisms, possibly interacting with genetic factors, may explain the

difference in the familial cumulative risks observed in this study. Indeed, environmental factors (e.g. hormonal factors) that women are exposed to when young, may protect them against the effects of genetic factors in the younger age classes. After exposure to these environmental factors has ended, the full effects of the genetic factors may emerge, resulting in a higher risk of CRC at a later age. Few studies have assessed the interactions between familial and hormonal risk factors [7,27,28]. Interaction studies are generally limited by statistical power [29]. Thus, no strong evidence for the consistent modification of the familial risk by exposure to hormones has resulted from these studies. Nevertheless, there have been some indications that the reduced risk of CRC, with higher parity, was prominent in women with a positive FH of CRC [7,28], and that a menopause at younger ages may lead to a greater risk of CRC in women with a FH of CRC [7].

Even if one cannot exclude that the observed differences between sexes might be due to random variation because of the small numbers in some subgroups, the difference in the cumulative familial risks observed in the CCREF study between families with either a male or a female proband suggests that there might be a gender-specific familial susceptibility. This difference only seemed to concern female relatives. Indeed, in male relatives, the gender of the proband did not seem to have any effect on the risk of CRC. Having a female relative affected by CRC seemed to increase women's lifetime risk of CRC more than having an affected male relative. Women generally have a higher percentage of proximal tumours than men. Moreover, it has been hypothesised [6] that proximal tumours have a stronger endogenous and genetic component than tumours in the distal colon which has also been observed in our study, although this difference was non-significant. This might partially explain the difference in familial risk in women according to the proband's gender. Unfortunately, detailed information on colorectal tumours was only available for a few relatives and, thus, the correlation between affected segments within families could not be measured.

Further studies are needed to confirm these results and to provide insight into the reasons for these differences in the familial risks between men and women. Moreover, screening protocols for CRC in first-degree relatives are still controversial in many countries. Precise and unbiased estimates of the risk of developing CRC are required for the determination of relevant guidelines. So far, most guidelines have been determined using the substantially high RR of CRC associated with being a first-degree CRC relative ($RR > 1.5$), without taking into account any potential variation in this relative risk. If our results were confirmed, it may be recommended to carry out an invasive screening method on people with a FH of CRC, depending on the age and gender of their affected relatives.

Acknowledgements

This study was made possible by the fruitful collaboration of general practitioners, anatomopathologists (Drs. J. Chasles, E. De Ranieri, P. Dupin, F. Galateau, B. Gallet, J. Jehan, A.-M. Mandard, D. Panthou, F. Petit, M. Rollet and P. Rousselot), gastro-enterologists, radiotherapists and surgeons of Calvados. This study was financed by la Fondation de France, la SNFGE, la Ligue Nationale Contre le Cancer, les ligues départementales: du Calvados, de l'Orne, de la Manche, des Yvelines, de l'Essonne et des Hauts-de-Seine, l'Institut Gustave Roussy, l'ARC, la MGEN and l'INSERM. We would like to thank S. Marlière, C. Pain, S. Iacobelli, C. Bégon and Mrs Ozanne for their technical help, Dr B. Guillois for his help with the collection of blood samples and Alex Edelman & Associates for language corrections.

References

1. Ménégoz F, Chérié-Challine L. *Le Cancer en France: Incidence et Mortalité*. Paris, France, Ministère de l'emploi et de la solidarité, 1999.
2. Goldgar DE, Easton DF, Cannon-Albright LA, Skolnick MH. Systematic population-based assessment of cancer risk in first-degree relatives of cancer probands. *J Natl Cancer Inst* 1994, **86**, 1600–1608.
3. Slattery ML, Kerber RA. Family history of cancer and colon cancer risk: the Utah Population Database. *J Natl Cancer Inst* 1994, **86**, 1618–1626.
4. Negri E, Braga C, La Vecchia C, *et al*. Family history of cancer and risk of colorectal cancer in Italy. *Br J Cancer* 1998, **77**, 174–179.
5. Potter JD. Colorectal cancer: molecules and populations. *J Natl Cancer Inst* 1999, **91**, 916–932.
6. Bufill JA. Colorectal cancer: evidence for distinct genetic categories based on proximal or distal tumour location. *Ann Intern Med* 1990, **113**, 779–788.
7. Newcomb PA, Taylor JO, Trentham-Dietz A. Interactions of familial and hormonal risk factors for large bowel cancer in women. *Int J Epidemiol* 1999, **28**, 603–608.
8. Sellers TA, Bazyk AE, Bostick RM, *et al*. Diet and risk of colon cancer in a large prospective study of older women: an analysis stratified on family history (Iowa, United States). *Cancer Causes Control* 1998, **9**, 357–367.
9. Breslow NE, Day NE. The design and analysis of cohort studies. In *Statistical Methods in Cancer Research*. Lyon, IARC, 1983, pp 89–99.
10. Vasen HF, Mecklin JP, Khan PM, Lynch HT. The International Collaborative Group on Hereditary Non-Polyposis Colorectal Cancer (ICG-HNPCC). *Dis Colon Rectum* 1991, **34**, 424–425.
11. Vasen HF, Watson P, Mecklin J-P, Lynch HT, the ICG-HNPCC. New clinical criteria for hereditary non-polyposis colorectal cancer (HNPCC, Lynch Syndrome) proposed by the International Collaborative Group on HNPCC. *Gastroenterology* 1999, **116**, 1453–1456.

12. Fuchs CS, Giovannucci EL, Colditz GA, Hunter DJ, Speizer FE, Willett WC. A prospective study of family history and the risk of colorectal cancer. *N Engl J Med* 1994, **331**, 1669–1674.
13. Burt RW. Familial risk and colon cancer. *Int J Cancer* 1996, **69**, 44–46.
14. Chuanhui D, Hemminki K. Modification of cancer risks in offspring by sibling and parental cancers from 2,112,616 nuclear families. *Int J Cancer* 2001, **92**, 144–150.
15. Evans DG, Walsh S, Jeacock J, *et al*. Incidence of hereditary non-polyposis colorectal cancer in a population-based study of 1137 consecutive cases of colorectal cancer. *Br J Surg* 1997, **84**, 1281–1285.
16. Peel DJ, Ziogas A, Fox EA, *et al*. Characterization of hereditary nonpolyposis colorectal cancer families from a population-based series of cases. *J Natl Cancer Inst* 2000, **92**, 1517–1522.
17. Aaltonen LA, Salovaara R, Kristo P, *et al*. Incidence of hereditary nonpolyposis colorectal cancer and the feasibility of molecular screening for the disease. *N Engl J Med* 1998, **338**, 1481–1487.
18. Le Marchand L, Zhao LP, Quiaoit F, Wilkens LR, Kolonel LN. Family history ans risk of colorectal cancer in the multiethnic population of Hawaii. *Am J Epidemiol* 1996, **144**, 1122–1128.
19. Johns LE, Kee F, Collins BJ, Patterson CC, Houlston RS. Colorectal cancer mortality in first-degree relatives of early onset colorectal cancer cases. *Dis Colon Rectum* 2002, **45**, 681–686.
20. Paraf F, Jothy S. Colorectal cancer before the age of 40: a case-control study. *Dis Colon Rectum* 2000, **43**, 1222–1226.
21. McMichael AJ, Potter JD. Reproduction, endogenous and exogenous sex hormones, and colon cancer: a review and hypothesis. *J Natl Cancer Inst* 1980, **65**, 1201–1207.
22. Potter JD, McMichael AJ. Large bowel cancer in women in relation to reproductive and hormonal factors: a case-control study. *J Natl Cancer Inst* 1983, **71**, 703–709.
23. Bjelke E. Colorectal cancer: clues from epidemiology. In *Proceedings of the Eleventh International Cancer Congress*. New York, Elsevier, 1975.
24. Wu AH, Paganini-Hill A, Ross RK, Henderson BE. Alcohol, physical activity and other risk factors for colorectal cancer: a prospective study. *Br J Cancer* 1987, **55**, 687–694.
25. Dos SSI, Swerdlow AJ. Sex differences in time trends of colorectal cancer in England and Wales: the possible effect of female hormonal factors. *Br J Cancer* 1996, **73**, 692–697.
26. Franceschi S, La Vecchia C. Colorectal cancer and hormone replacement therapy: an unexpected finding. *Eur J Cancer Prev* 1998, **7**, 427–438.
27. Slattery ML, Mineau GP, Kerber RA. Reproductive factors and colon cancer: the influences of age, tumour site, and family history on risk (Utah, United States). *Cancer Causes Control* 1995, **6**, 332–338.
28. Kampman E, Potter JD, Slattery ML, Caan BJ, Edwards S. Hormone replacement therapy, reproductive history, and colon cancer: a multicenter, case-control study in the United States. *Cancer Causes Control* 1997, **8**, 146–158.
29. Goldstein AM, Falk RT, Korczak JF, Lubin JH. Detecting gene-environment interactions using a case-control design. *Genet Epidemiol* 1997, **14**, 1085–1089.