Original article

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Clinicopathological differences between familial colorectal cancer type X and sporadic cancer in an isolated area of spain

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Abstract

Aim Very few studies have compared the epidemiological characteristics of patients with familial colorectal cancer Type X (FCCTX) with those of sporadic colorectal cancer (S-CRC). The aim of this study was to compare clinicopathological characteristics and survival between FCCTX and S-CRC in patients from a historically isolated geographical region.

Method A retrospective study was carried out of patients with S-CRC and FCCTX treated in the Canary Islands. Family and personal history of colorectal cancer (CRC) were recorded, together with genetic (microsatellite instability), immunohistochemical and clinical variables.

Results Forty-eight (10.6%) of 451 patients were classified as FCCTX and the remaining 403 (89.4%) as S-CRC. Age at the diagnosis of tumour was significantly lower in FCCTX than in S-CRC (64.06 ± 12.65 years *vs* 69.13 ± 10.80 years; $P = 0.01$; $Z = -2.48$). Patients with FCCTX had a larger number of synchronous tumours ($P = 0.09$). Recurrence was significantly higher in FCCTX than in S-CRC (18.7% *vs* 8.6%; $P = 0.01$). Survival correlated significantly with the number of first-degree and second-degree relatives with CRC ($P = 0.04$; OR: 1.368, 95% CI: 1.01–1.84, and $P = 0.04$; OR: 1.363, 95% CI: 1.08–1.65) and with the total number of cases of CRC in the immediate family ($P < 0.01$; OR: 1.377, 95% CI: 1.17–1.61). Recurrence-free time was significantly lower in patients with FCCTX (log-rank = 0.01).

Conclusion Significant differences were found in several demographic and clinicopathological variables between patients with FCCTX and patients with S-CRC. These included increased tumour presentation under the age of 50 years and a higher recurrence rate in patients with FCCTX, suggesting an increased risk of CRC in this group.

Keywords Colorectal cancer, familial colorectal cancer Type X, FCCTX, lymph node ratio, Lynch syndrome, sporadic colorectal cancer

What does this paper add to the literature?
Few studies have compared the epidemiological characteristics of patients with familial colorectal cancer Type X (FCCTX) and sporadic colorectal cancer (S-CRC). In an isolated geographical region, significant differences were found in several demographic and clinicopathological variables between patients with FCCTX and patients with S-CRC.

Introduction

Colorectal cancer (CRC) is the second leading cause of cancer-related mortality in the western world. Approximately 30% of CRC diagnoses show evidence of a familial component and approximately 5% of patients with CRC have well-known inherited mutations. Among the latter, familial adenomatous polyposis (FAP) and Lynch syndrome (LS) are the most frequent. Studies on LS have led to the discovery that approximately 40% of families meeting the Amsterdam criteria for the diagnosis of LS do not have microsatellite instability. This group of tumours is recognized as familial colorectal cancer Type X (FCCTX) [1]. FCCTX is clinically different from LS in that it has a lower incidence of CRC, a lower risk of extracolonic tumours and that tumours

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tend to develop at a later age [1–6]. In this respect, some specific molecular findings have begun to emerge [7–10] and further developments are to be expected in the near future. Current evidence indicates that families with FCCTX constitute a very heterogeneous group. The Amsterdam criteria I and II indicate that this disease is characterized by strong familial aggregation, so it is likely that certain cases of FCCTX are caused by high-penetrance mutations (i.e. with a monogenic component). No such genes have, however, yet been identified and it is likely that any genes identified in the future would only explain a small number of cases of FCCTX [5]. So, the genetic characteristics of FCCTX are not well defined and the genealogical study of patients to find families meeting the Amsterdam criteria, coupled with the study of microsatellite instability, are the only means of identifying and separating these families from those with sporadic CRC (S-CRC). Because of their greater susceptibility, early detection strategies are needed. Besides the family studies, it is important to identify clinical features that distinguish susceptibility to FCCTX and to S-CRC.

Given its historical geographical isolation until recent times, the island of Tenerife is a privileged environment for familial and genetic field studies. Family recruitment is relatively easy because most members still live on the island. The aims of this study were to identify families with FCCTX and to compare their clinicopathological characteristics and survival with patients with S-CRC without a familial history.

Method

Familial study

The study received Institutional Review Board approval from the Hospital Universitario de Canarias on 28 June 2012, with protocol number 2012/26. It included all patients diagnosed and treated at the University Hospital of Canarias for S-CRC between 2009 and 2010. We excluded patients from a family with known hereditary syndrome (LS or FAP) and nonresidents owing to the expected difficulties in follow up. The study included only patients diagnosed with sporadic colon cancer; familial cancers were excluded so patients were diagnosed in clinics or by screening of asymptomatic patients over 50 years old using immunochemical faecal occult blood testing, so there were no early family screening colonoscopies. The family tree of each patient allowed us to identify families that met the Amsterdam II criteria. In these families, tumours were tested for microsatellite instability, and those showing positivity were discarded. Immunohistochemistry of proteins of the mismatch repair {MMR} genes (*MSH2*, *MLH1*, *MSH6* and *PMS2*) allowed us to confirm the absence of mutations. A diagnosis of FCCTX was based on the fact that tumour showed estable microsatellites (MSS) and immunohistochemistry showed no abnormality in expression of MMR protein. Based on these criteria, the patients were divided into two groups: those who did not meet the Amsterdam II criteria, considered to have S-CRC; and those who did meet the Amsterdam II criteria, considered to have FCCTX.

These definitions created some problems with nomenclature because other authors have divided Amsterdam II tumours into two groups – LS (known MMR defects) and hereditary nonpolyposis colorectal cancer (HNPCC) – irrespective of the MSS/MSI status. The current evidence indicates, however, that families with FCCTX constitute a very heterogeneous group. The Amsterdam I and II criteria indicate that this disease is characterized by strong familial aggregation, so it is likely that some cases of FCCTX are caused by high-penetrance mutations (i.e. those with a monogenic component). No such genes have yet been identified, however, and it is likely that any gene identified in the future will only account for a small number of cases of FCCTX.

Details were obtained of the patient demographics, a familial history of CRC and other tumours and clinicopathological variables, including tumour location, carcinoembryonic antigen (CEA) level, synchronous or metachronous tumour, metastasis at diagnosis, recurrence and metastasis during follow up.

Histopathological study

The following histopathological variables were analysed: Dukes stage; degree of differentiation; lymphocyte infiltration; Crohn's-like lymphocytic reaction; mucinous/signet-ring differentiation; medullary growth pattern; vascular tumoral invasion; and the lymph node ratio (LNR). Histopathological study was conducted by an expert pathologist who was blinded to the tumour group in every case.

Microsatellite instability study

In all cases, DNA was amplified in a 25 μl volume containing 200 ng of tumour DNA, 0.5 μM of each primer, 1 × buffer, 1.5 mM $MgCl_2$, 200 μM dNTPs and 1U *Tth* DNA polymerase (Pacisa-Giralt, Madrid, Spain). To assess microsatellite instability we utilized the MSI ANALYSIS SYSTEM V 1.2 (Promega, Madison, Wisconsin, USA), which meets the recommendations proposed by the

National Cancer Institute [11]. Products were amplified in a Perkin Elmer Cetus 480.0 thermocycler (Perkin Elmer, Madrid, Spain), electrophoresed in nondenaturing 8–15% polyacrylamide gels and antigen-stained.

Immunohistochemistry

Immunohistochemistry was performed on formalin-fixed paraffin-embedded sections of tumour, after antigen retrieval in high-pH solution (Dako, Glostrup, Denmark), at 123°C for 1 min. Sections were treated with 0.1% Triton X-100 in phosphate-buffered saline (PBS), and then incubated with mouse monoclonal antibody, diluted 1:50 in 3% bovine serum albumin/PBS, against human MSH2 (clone G219-1129; BD PharMingen, San Diego, California, USA), MLH1 (clone G168-15; BD PharMingen), MSH6 (clone 44; BD Transduction Laboratories, San Jose, California, USA) and PMS2 (clone A16-4; BD PharMingen) proteins. After blocking endogenous peroxidase with 0.3% hydrogen peroxide (H_2O_2) in methanol, for 15 min, slides were washed three times (5 min each wash) with PBS and then incubated for 30 min with horseradish peroxidase-conjugated anti-mouse IgG (Dako). After another three washes in PBS, a DAB-H_2O_2 solution was used as chromogen, and sections were counterstained with haematoxylin. Adjacent normal tissue and surrounding tissue lymphocytes served as internal positive controls for each case. Nuclear staining of the tumour was scored as either present or absent compared with the corresponding internal control.

Statistical analysis

For qualitative variables we used frequency distributions and proportions expressed in percentages, and for dichotomous variables ORs were used. For quantitative variables, the mean, median, mode, SD, maximum and minimum and range were calculated. Kaplan–Meier curves were used to study survival, metastasis-free time and recurrence.

The statistical significance of differences between variables was estimated using Pearson's χ^2 or Fisher's exact tests, as appropriate, for qualitative variables. For quantitative variables, the Student's *t*-test was used for normal (parametric) and the Mann–Whitney *U*-test for abnormal (nonparametric) distributions, previously assessed using the Kolmogorov–Smirnov test.

The analysis of survival was performed using the log-rank or the Breslow test, as appropriate. Cox regression analysis was used for univariate and multivariate analysis of survival. All statistical calculations were performed using SPSS 15.0 (SPSS, Inc., Chicago, Illinois, USA), and a value of $P \leq 0.05$ was considered as significant for all variables.

Results

Of 525 patients recruited, 464 met the inclusion criteria. The family tree was incomplete in six, so they were excluded. Four-hundred and three of the remaining 458 patients with a complete family tree did not meet the Amsterdam criteria and were considered S-CRC. Of the remaining 55 (12%) who did meet the criteria, seven had a tumour with microsatellite instability and MMR. They were therefore considered to have LS and were excluded. The remaining 48 patients met the Amsterdam criteria, but their tumours exhibited microsatellite stability and were therefore considered to be FCCTX.

Table 1 summarizes the characteristics of the patients and the tumour. Age at diagnosis was significantly lower in patients with FCCTX than in patients with S-CRC (67 ± 12.58 years *vs* 70 ± 10.75 years; $P = 0.01$; $Z = -2.48$); this difference was unchanged on analysis according to gender. When patients were grouped according to a cut-off of 50 years (the recommended age for screening programmes for the general population) in patients with FCCTX the tumour was found to appear before the age of 50 years more frequently than in patients with S-CRC ($P < 0.01$). On stratification according to age above 50 years, no differences between these age groups were observed between FCCTX and S-CRC patients (Table 1).

There was no difference between patients with FCCTX and patients with S-CRC in the distribution of tumours according to gender ($P = 0.7$) or tumour location ($P = 0.2$). The results of predictors of survival in patients with FCCTX and patients with S-CRC are summarized in Table 2. There were no differences between the two groups in CEA levels, lymphocyte infiltration, Crohn's-like lymphocytic reaction, mucinous/signet-ring differentiation, medullary growth pattern, number of metastatic regional lymph nodes, LNR or the presence of polyps. However, tumour vascular invasion was significantly higher in patients with FCCTX than in patients with S-CRC (18.0% *vs* 8.9%, $P = 0.03$). No differences were observed in obstructing, perforated or metachronous tumours, but the number of synchronous tumours was higher in the FCCTX group ($P = 0.09$). There was no difference in tumour stage at diagnosis. Given the wide range in stage among the patients, tumour stage was classified in terms of survival at 5 years, in accordance with survival data published in the Surveillance, Epidemiology and End-Results (SEER) Cancer Statistics Review by the

Table 1 Characteristics and tumour location of patients with familial colorectal cancer type X (FCCTX) and sporadic colorectal cancer (S-CRC).

Variable	FCCTX (n = 48)	S-CRC (n = 403)	P
Age at diagnosis (years)*	67 ± 12.58	70 ± 10.75	0.01 (Z = −2.48)
Age (years)			
< 50 years	13 (27)	22 (5.4)	0.000
> 50 years	35 (73)	381 (94.5)	
Age groups (years) (< 50 years excluded)			
50–60 years	5 (13.8)	56 (14.5)	0.85
60–70 years	10 (27.7)	127 (32.9)	
70–80 years	17 (47.2)	154 (39.8)	
> 80 years	4 (11.2)	49 (12.8)	
Gender			
Male	30 (62.5)	262 (65)	0.7
Female	18 (37.5)	141 (35)	
Gender and age†			
Male	65.07 ± 11.39	69.3 ± 9.86	0.07 (Z = −1.78)
Female	62.3 ± 14.71	68.7 ± 12.39	
Tumour location			
Right-sided	10 (20.8)	109 (27)	0.22
Left-sided	26 (54.2)	165 (41)	
Rectum	12 (25)	128 (32)	

Values are given as median ± SE*, mean ± SE† or n (%).

American Joint Committee on Cancer [4]. If survival was over 50%, the stage was considered as favourable (Stages I, IIA, IIB and IIIA), and if below 50%, it was considered unfavourable (Stages IIC, IIIB, IIIC and IV). Comparison of favourable and unfavourable stages showed no significant differences between the two groups. There were no differences in the presence of metastasis at diagnosis, or during follow up, but recurrence was significantly higher in patients with FCCTX than in patients with S-CRC (18.7% *vs* 8.6%; P = 0.01). Univariate analysis of family history data (Table 3) showed that survival was significantly correlated with the number of first-degree relatives with CRC (P = 0.04; OR: 1.368, 95% CI: 1.01–1.84), the number of second-degree relatives with CRC (P = 0.04; OR: 1.363, 95% CI: 1.01–1.85), the total number of relatives with CRC (P < 0.01; OR: 1.377, 95% CI: 1.17–1.61), vascular invasion (P = 0.02; OR: 1.651, 95% CI: 1.08–2.51) and local recurrence (P < 0.01; OR: 0.582, 95% CI: 0.40–0.84). There were no significant differences in gender or age at diagnosis. Multivariate analysis showed only the total number of relatives with CRC to be a predictor of early mortality (Table 3). Kaplan–Meier curves of survival (Breslow = 0.17; Fig. 1) and metastasis-free interval (log-rank = 0.23; Fig. 2) showed no significant differences between FCCTX and S-CRC. However, the interval to recurrence was significantly shorter in patients with FCCTX (log-rank = 0.01; Fig. 3).

Discussion

FCCTX, described by Lindor *et al.* in 2005 [1], originally included patients who met the Amsterdam I criteria but whose tumours did not show microsatellite instability or mutations in MMR genes. Although many authors feel that the term FCCTX should not be used and does not represent a clinically meaningful stratification of the CRC population, approximately 40% of the families meeting the Amsterdam II criteria for a diagnosis of hereditary nonpolyposis CRC lack evidence of heritable defects in the MMR system. More specifically, these patients have no germline mutations in the MMR genes, no tumour microsatellite instability and no loss of immunohistochemical staining of the MMR proteins. Moreover, FCCTX is clearly clinically different from LS [5], so the identification of differences that distinguish patients presenting FCCTX from those with S-CRC should reinforce the existence of the syndrome but only the identification of the genes associated with FCCTX will facilitate the molecular diagnosis of the disease.

The Amsterdam criteria are not very sensitive or specific for LS, so it could be thought that our S-CRC group is likely to have contained a substantial number

Table 2 Predictors of survival in patients with familial colorectal cancer type X (FCCTX) and sporadic colorectal cancer (S-CRC).

Variable	FCCTX (n = 48)	S-CRC (n = 403)	P
CEA	122.08 ± 396.76	107.50 ± 744.66	0.46 (Z = −0.73)
Vascular invasion			
Yes	9 (18.7)	36 (8.9)	0.03
No	39 (81.3)	367 (91)	
Lymphocyte infiltration			
Yes	9 (18.7)	46 (11.4)	0.14
No	39 (81.3)	357 (88.5)	
Cell differentiation			
Well differentiated	15 (36.5)	98 (30.6)	0.21
Moderately differentiated	20 (48.7)	196 (61.2)	
Undifferentiated	6 (14.8)	26 (8.2)	
Mucinous/signet-ring differentiation			
Yes	3 (6.25)	47 (11.6)	0.25
No	45 (93.75)	356 (88.3)	
Crohn's-like lymphocytic reaction			
Yes	5 (10.4)	63 (15.6)	0.33
No	43 (89.5)	340 (84.3)	
Metastatic lymph nodes	2.53 ± 4.56	1.49 ± 2.50	0.18 (Z = −1.31)
LNR	0.21 ± 0.29	0.14 ± 0.24	0.22 (Z = −1.22)
Polyps present			
Yes	9 (18.7)	62 (15.3)	0.54
No	39 (81.3)	341 (84.7)	
Perforated tumour			
Yes	3 (18.7)	28 (6.9)	0.85
No	45 (81.3)	375 (93.1)	
Obstructing tumour			
Yes	10 (20.8)	69 (17.1)	0.52
No	38 (79.2)	334 (82.9)	
Metachronous tumour			
Yes	2 (4.1)	14 (3.4)	0.81
No	46 (95.9)	387 (96.6)	
Synchronous tumour			
Yes	6 (12.5)	42 (10.4)	0.09
No	25 (87.5)	378 (89.6)	
Tumour stage			
0	9 (18.9)	74 (18.5)	0.55
I	9 (18.9)	103 (25.7)	
IIA	0 (0)	7 (1.9)	
IIB	1 (2)	6 (1.6)	
IIIA	0 (0)	10 (2.6)	
IIIB	14 (29.2)	78 (19.3)	
IIIC	2 (4)	17 (4.2)	
IVA	5 (10.5)	61 (15.3)	
IVB	8 (16.5)	44 (10.9)	
Favourable stage			
Yes	19 (39.5)	200 (49.6)	0.17
No	29 (60.5)	203 (50.4)	
Metastasis at diagnosis			
M0	35 (72.9)	297 (73.6)	0.90
M1	13 (27.1)	106 (26.4)	

Table 2 (Continued).

Variable	FCCTX (n = 48)	S-CRC (n = 403)	P
Local recurrence			
Yes	9 (18.7)	35 (8.6)	0.01
No	39 (81.3)	368 (91.4)	
Metastasis during follow up			
Yes	17 (35.4)	110 (27.2)	0.22
No	31 (64.6)	293 (72.8)	

Values are given as median ± SE or n (%).
CEA, carcinoembryonic antigen; LNR, lymph node ratio.

Table 3 Univariate and multivariate analysis of variables related to survival in familial colorectal cancer type X (FCCTX).

Type of analysis	OR	95% CI	P
Univariate analysis			
Age at diagnosis	1.013	0.97–1.04	0.45
Gender	1.023	0.45–3.32	0.95
Number of relatives with CRC	1.377	1.17–1.61	< 0.01
Number of first-degree relatives with CRC	1.368	1.01–1.84	0.04
Number of second-degree relatives with CRC	1.363	1.01–1.85	0.04
Local recurrence	0.582	0.40–0.84	< 0.01
Vascular invasion	1.651	1.08–2.51	0.02
Multivariate analysis			
Local recurrence	1.523	0.52–4.39	0.43
Vascular invasion	2.004	0.63–6.30	0.23
Number of relatives with CRC	1.353	1.08–1.69	< 0.01
Number of first-degree relatives with CRC	0.915	0.60–1.37	0.67

CRC, colorectal cancer.

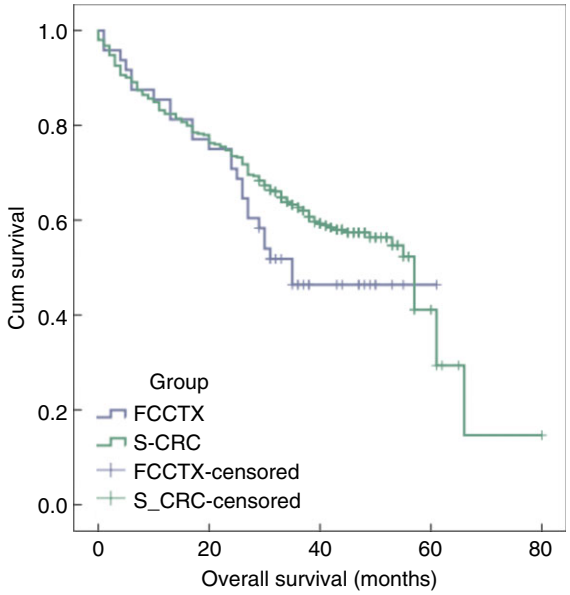

Figure 1 Kaplan–Meier plots showing survival of familial colorectal cancer type X (FCCTX) and sporadic colorectal cancer (S-CRC).

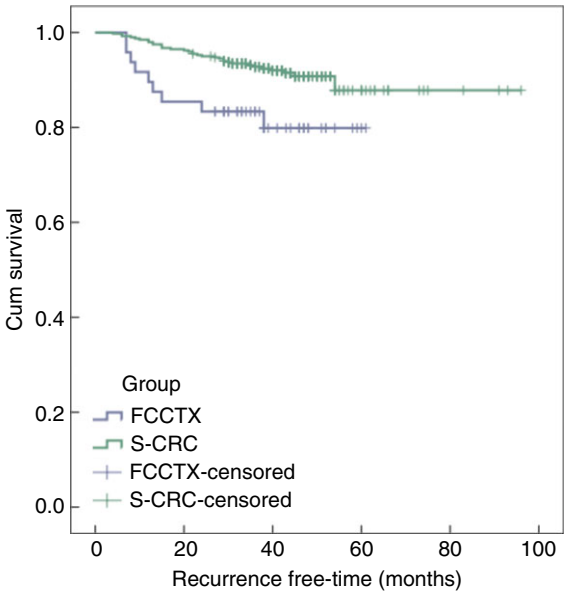

Figure 2 Kaplan–Meier plots showing recurrence-free time between familial colorectal cancer type X (FCCTX) and sporadic colorectal cancer (S-CRC).

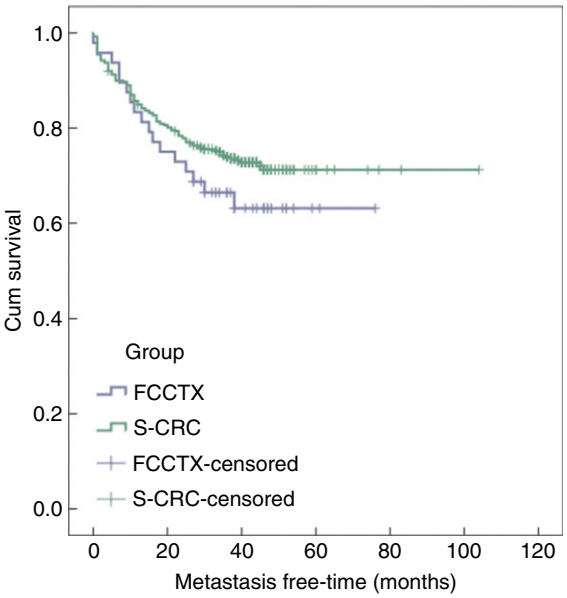

Figure 3 Kaplan–Meier plots showing metastasis-free time between familial colorectal cancer type X (FCCTX) and sporadic colorectal cancer (S-CRC).

of patients with LS. Our research team recently found, in this isolated area, a common mutation in families known to have LS [12] , allowing early identification and diagnosis. We are therefore confident that the presence of patients with LS in our S-CRC group was nonexistent or minimal.

This definition poses some problems, as some studies on FCCTX also include families meeting the Amsterdam II criteria and microsatellite stable tumours [6,10,13–15]. Furthermore, only 69% of patients with LS caused by *MSH6* mutations show microsatellite instability [16] and therefore some families with *MSH6* mutations and stable tumours could have been included in the FCCTX group. In this sense, the term 'Lynch-like syndrome' has recently been proposed [17,18]. Some molecular features specific to familial FCCTX tumors have, however, been reported. Significant, but mostly unsuccessful, efforts have been made to understand the genetic cause of FCCTX. Several dominant predisposition loci that have been mapped to different chromosomal regions, such as 3q13.31-q27.1, 3q22, q21.1, 5q14-q22, 7q31, 8q13.2, 9q22.2-31.2, 10p15.3-p15.1, 12q24.32 and 13q22.1-13q31.3, have been identified using genome-wide linkage studies in families with CRC but no causal genes have yet been identified [5]. Although several studies have described the FCCTX tumours and compared the clinical characteristics of FCCTX and LS [3–6,18], only one recent study [19] compared some epidemiological characteristics of patients with FCCTX and patients with S-CRC.

Although a comparison with patients with LS would be interesting (the study would therefore require three groups), FCCTX is clearly clinically different from LS. In particular, patients with FCCTX have a lower incidence of CRC and a lower risk of extracolonic tumors and they tend to develop cancer at a later age [3–6,18]. Therefore, we have preferred to focus on lesser-known differences between patients with FCCTX and patients with S-CRC. Our group has discovered a mutation of LS in this historically isolated geographical area [12], allowing early diagnosis of CRC in these patients, which reduces the unbiased comparison of survival with the other groups.

Knowledge of the differences between patients with FCCTX and patients with LS is of undoubted interest, but patients in both groups have a familial predisposition. The comparison between patients with FCCTX and patients with S-CRC is, however, paramount because among patients considered to have S-CRC it is necessary to identify those who are actually FCCTX and should therefore have strict monitoring and surveillance. For this we need to know the clinical and/or pathological data of the two types, as they can help to identify cases of FCCTX.

The analysis of epidemiological factors shows differences in age at diagnosis between patients with FCCTX and those with S-CRC, in contrast to the findings of Shiovitz *et al.* [19]. Mean age at diagnosis was noticeably lower in the FCCTX group than in the S-CRC group, in agreement with previous reports [19,20]. This is also reflected in the higher proportion of FCCTX patients, below the age of 50 years, with tumours. The finding of young age at diagnosis is not surprising in the FCCTX group, considering that age below 50 years is an Amsterdam II criterion, although this specifies 'at least one member' of the affected family with a tumour appearing below 50 years, but other affected members may be older than 50 years. This means that the mean age difference with respect to the S-CRC group is not large. Our findings confirm that differences in age not only allow a classification of FCCTX but also that the presence of affected members younger than 50 years of age was sufficiently high to result in a significant reduction in the mean age of the group with FCCTX.

This finding may be important because it implies the existence of a group of patients who, if not correctly classified as FCCTX, may present with tumours before they are included in a screening programme. The 12% proportion of families meeting the Amsterdam criteria II is unusually high but these populations have a demographic history of probable isolation since they first became established in the Canary Islands in 1500 AD. The isolation of these populations for several centuries

until well into the 20th century leads to speculation of considerable genetic drift occurring over 20 generations. Such genetic drift would have reduced the allelic variability before its more recent expansion. There is also a high degree of consanguinity because of the small number of founding settlers, making this population of great interest for genetic studies of complex syndromes such as LS and FCCTX [21]. Thus, populations with a degree of genetic isolation may show a different set of genes than other populations, which could explain some differences from other FCCTX studies.

As with other authors, we found no differences in presentation of cancer according to gender or tumour location [19]. Analysis of histopathological factors in patients with FCCTX showed a higher proportion of tumours with vascular invasion, as previously reported by Shiovitz *et al.* [19], but not a lower frequency of poorly differentiated tumours, which they found. Moreover, we did not observe differences in levels of CEA, lymphocytic infiltration, number of metastatic nodes, polyps, tumour stage at diagnosis or perforated, obstructed or metachronous tumours, but interestingly, patients with FCCTX tended to have a larger number of synchronous tumours than did patients with S-CRC ($P = 0.09$). No difference between the two groups was found in overall survival or in metastasis-free interval, but patients with FCCTX showed a greater incidence of local recurrence than did patients with S-CRC, shown by the shorter time to recurrence in the Kaplan–Meier survival curves.

Univariate analysis of familial cancer in patients with FCCTX showed that the number of first-degree and second-degree relatives with CRC was associated with increased mortality, as was the total number of relatives with CRC, but multivariate analysis showed only the total number of relatives with CRC to be an independent predictor of increased mortality (Table 3). These data suggest that in different families with FCCTX, the disease can have different degrees of manifestation according to the higher or lower accumulation of relevant mutations, although these remain unidentified. The island of Tenerife, given its geographical isolation until recent times, could have conditioned the founder effect of certain gene variants which, added to a high degree of consanguinity, could reinforce the importance of the number of relatives with CRC [12].

In conclusion, the present study confirms that in addition to family history, there are differences in demographic and clinicopathological variables between FCCTX and S-CRC. These include a higher rate of tumour presentation before 50 years of age, a higher proportion of synchronous tumours and a higher recurrence rate, thus confirming the increased risk of CRC in these patients. All this implies the need to monitor these patients and their families closely once the index case has been detected. The results also reinforce the importance of an accurate family tree to identify patients with probable FCCTX until a specific genetic test becomes available [22]. Individuals with the diagnosis of FCCTX syndrome should undergo screening for CRC cancer. The optimal interval for colonoscopic surveillance in individuals with FCCTX syndrome has not been established in randomized trials. As is carried out in individuals with LS, we believe that patients of families with FCCTX should undergo CRC screening with colonoscopy every 1–2 years beginning at age 20–25 years, or 2–5 years before the earliest age at diagnosis of CRC in the family, whichever comes first.

The small number of 48 patients with FCCTX in the present study may limit the usefulness of the analysis, but most previous studies have been larger and the small size of the island should also be taken into account. Nevertheless, the results lend support to the notion that FCCTX is an independent clinical entity, albeit with heterogeneous characteristics. The fact that FCCTX presents with features in common with LS (such as family history, younger age at diagnosis and greater number of synchronous tumours) and also with S-CRC (such as the predominance of left-sided tumours and less lymphocyte infiltration) raises the question of whether FCCTX is an 'intermediate syndrome' between LS and S-CRC. Further genetic and clinical studies could shed light on this point.

Conflicts of interest and Source of funding

The authors have no conflicts of interest in the manuscript, including financial, consultant, institutional and other relationships that might lead to bias.

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