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Characterisation of Familial Colorectal Cancer Type X, Lynch syndrome, and non-familial colorectal cancer

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Background: Familial Colorectal Cancer Type X (FCCTX) is defined as individuals with colorectal cancer (CRC) who families meet Amsterdam Criteria-1 (AC1), but whose tumours are DNA-mismatch-repair-proficient, unlike Lynch syndrome (LS). FCCTX does not have an increased risk of extra-colonic cancers. This analysis compares epidemiologic and clinicopathologic features among FCCTX, LS, and 'non-familial' (non-AC1) CRC cases.

Methods: From the Colon Cancer Family Registry, FCCTX ($n=173$), LS ($n=303$), and non-AC1 ($n=9603$) CRC cases were identified. Questionnaire-based epidemiologic information and CRC pathologic features were compared across case groups using polytomous logistic regression.

Results: Compared with LS, FCCTX cases were less likely to be current (*vs* never) smokers; have a proximal subsite (*vs* rectal) tumour; or have mucinous histology, poor differentiation, or tumour-infiltrating lymphocytes. There were no observed differences in co-morbidities or medication usage.

Conclusions: FCCTX were less likely to be current tobacco users; other exposures were similar between these groups. Histopathologic differences highly suggestive of LS CRCs do not appear to be shared by FCCTX.

'Familial Colorectal Cancer Type X' (FCCTX) collectively describes cases of colorectal cancer (CRC) that meet clinical Amsterdam Criteria-1 (AC1) for Lynch syndrome (LS), but whose tumours are DNA-mismatch-repair-proficient as assessed by tumour immunohistochemistry (IHC) and/or microsatellite instability (MSI) testing (Vasen *et al*, 1991; Lindor *et al*, 2005). Approximately half of CRC cases who meet AC1 (three relatives with CRC across two successive generations (with one case being a first-degree relative of the other two), at least one case diagnosed before age 50, and the exclusion of familial adenomatous polyposis), are now classified as

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FCCTX (Lynch & de la Chapelle, 2003; Renkonen *et al*, 2003; Schiemann *et al*, 2004; Woods *et al*, 2005). FCCTX pedigrees show an autosomal-dominant inheritance pattern, but the genetic basis remains unknown, and may constitute more than one genetic aetiology.

Previous studies have indicated clinical and pathologic differences between FCCTX and LS (online Supplementary Table S1). Relative to LS, FCCTX is associated with lower predisposition to CRC (standard incidence ratio 2.3 *vs* 6.1), is not associated with extracolonic cancers (Lindor *et al*, 2005), has an older mean age at diagnosis (50–60 years *vs* 40 years), is more likely to be left-sided, and is less likely to be associated with synchronous or metachronous cancers. Histopathologically, FCCTX *vs* LS CRCs have more heterogeneous architecture, a predominant tubular growth pattern, less frequent mucinous histology, and less often with peritumoural or tumour-infiltrating lymphocytes (TIL) (Schiemann *et al*, 2004; Lindor *et al*, 2005; Llor *et al*, 2005; Mueller–Koch *et al*, 2005; Dove-Edwin *et al*, 2006; Valle *et al*, 2007; Chen *et al*, 2008; Koh *et al*, 2011; Klarskov *et al*, 2012).

To our knowledge, there have been no reports that compare epidemiologic characteristics across FCCTX, LS, and non-Amsterdam Criteria-1 (non-AC1) cases and there are few large studies that describe the breadth of histopathologic features in these groups. Our study aimed to describe the demographic, environmental, and tumour characteristics of FCCTX and determine how they compare with LS and non-AC1 cases within the Colon Cancer Family Registry (CCFR).

MATERIALS AND METHODS

As described elsewhere (Newcomb *et al*, 2007), the CCFR (http://coloncfr.org) is an international consortium of CRC cases and controls from population- and/or clinic-based sites in North America and Australasia. Recruited during 1998–2007, participants completed written informed consent for study enrolment; protocols were approved by local institutional review boards. Collection of epidemiologic and family history data and biospecimens was standardised across all centres.

The following tumour characteristics were abstracted from the clinical histopathology report and/or from pathologist review: location, size, nodal status, differentiation, histologic type, and presence/absence of peritumoural lymphocytes, Crohn's-like reaction, tumour-infiltrating lymphocytes, and venous invasion. MSI and/or IHC were performed on all tumour samples (Lindor *et al*, 2005; Newcomb *et al*, 2007).

Cases were allocated to one of the three groups: (1) 'LS' ($n = 312$) for cases meeting AC1 and whose tumours were classified as MSI (MSI-high and/or MMR-deficient), (2) 'FCCTX' ($n = 177$) for cases meeting AC1, but with non-MSI tumours, or (3) 'non-AC1' ($n = 12{,}175$) for the remainder of CRC cases whose family histories did not meet AC1. No more than one individual per family was included in the analysis. Restricting the analysis to available epidemiologic/tumour information, we included 173/146 FCCTX, 303/245 LS, and 9603/7878 non-AC1 CRC cases.

Statistical methods. Odds ratios (OR) with 95% confidence intervals were estimated using polytomous logistic regression

Table 1. Epidemiologic characteristics of FCCTX compared with Lynch syndrome and non-Amsterdam Criteria-1 colorectal cases in the Colon Cancer Family Registry

Characteristic, *n* (%)	FCCTX ($n = 173$)	Lynch ($n = 303$)	Non-AC1 ($n = 9{,}603$)	FCCTX *vs* Lynch[a] OR[b] (95% CI)	FCCTX *vs* non-AC1[a] OR[b] (95% CI)	Lynch *vs* non-AC1[a] OR[b] (95% CI)
Case characteristics[c]						
Age, mean (s.d.)	53.3 (11.3)	50.5 (11.4)	56.3 (12.0)	1.02 (1.00, 1.03)	0.99 (0.98, 1.00)	0.97 (0.96, 0.98)
Male gender	76 (44%)	149 (49%)	4797 (50%)	0.81 (0.56, 1.18)	0.80 (0.59, 1.09)	0.99 (0.79, 1.25)
BMI, mean (s.d.)	27.5 (6.6)	26.5 (5.8)	27.2 (5.8)	1.03 (0.10, 1.07)	1.02 (0.99, 1.04)	0.98 (0.96, 1.01)
Smoking						
Never	85 (49%)	148 (49%)	4252 (45%)	1 (Reference)	1 (Reference)	1 (Reference)
Former	74 (43%)	106 (35%)	4198 (44%)	1.17 (0.78, 1.76)	0.99 (0.72, 1.37)	0.85 (0.65, 1.11)
Current	13 (8%)	49 (16%)	1096 (11%)	0.48 (0.24, 0.94)	0.62 (0.35, 1.13)	1.30 (0.93, 1.83)
Co-morbidities (yes/no) (% yes)						
Diabetes	17/155 (9%)	20/283 (7%)	1154/8404 (12%)	1.48 (0.74, 2.94)	1.16 (0.69, 1.94)	0.78 (0.49, 1.25)
Hyperlipidemia	42/129 (24%)	79/222 (26%)	2995/6530 (31%)	0.84 (0.53, 1.31)	0.88 (0.61, 1.27)	1.05 (0.80, 1.39)
Aspirin	38/134 (22%)	68/231 (22%)	2771/6747 (29%)	0.83 (0.52, 1.34)	0.99 (0.68, 1.46)	1.19 (0.89, 1.60)
Acetaminophen	23/149 (13%)	51/250 (17%)	1469/8026 (15%)	0.72 (0.42, 1.23)	0.81 (0.52, 1.27)	1.13 (0.83, 1.55)
NSAIDs	31/141 (18%)	53/249 (17%)	1555/7910 (16%)	1.01 (0.62, 1.66)	1.16 (0.78, 1.73)	1.14 (0.84, 1.56)
Laxatives	39/133 (23%)	60/242 (20%)	2136/7375 (22%)	1.04 (0.65, 1.65)	1.04 (0.72, 1.51)	1.01 (0.75, 1.36)
Multivitamin	73/99 (42%)	131/171 (43%)	4829/4702 (50%)	0.88 (0.60, 1.31)	0.98 (0.71, 1.34)	1.10 (0.86, 1.41)
Folic acid	22/150 (13%)	39/261 (13%)	941/8528 (10%)	1.03 (0.58, 1.84)	1.13 (0.70, 1.80)	1.09 (0.76, 1.57)
Calcium	36/136 (21%)	59/244 (19%)	2507/7012 (26%)	0.84 (0.51, 1.38)	0.80 (0.54, 1.19)	0.95 (0.70, 1.30)
Female (yes/no) (% yes)						
Oral hormonal contraceptives	70/27 (72%)	115/39 (75%)	2783/1972 (58%)	0.93 (0.50, 1.72)	1.31 (0.81, 2.12)	1.41 (0.95, 2.09)
PMH with uterus intact	23/41 (36%)	48/67 (41%)	1041/1805 (36%)	0.44 (0.05, 3.92)	0.90 (0.12, 6.80)	2.04 (0.76, 5.42)
PMH with hysterectomy	6/12 (33%)	12/26 (32%)	314/471 (39%)	0.68 (0.35, 1.34)	1.19 (0.68, 2.09)	1.76 (1.17, 2.64)

Abbreviations: **AC1** = Amsterdam Criteria-1; BMI = body mass index; FCCTX = Familial Colorectal Cancer Type X; PMH = post-menopausal hormone use; s.d. = standard deviation.
[a]All models are adjusted for age at diagnosis, sex, and study site.
[b]OR per one unit increase in continuous variables (age at diagnosis and BMI). For binary variables, the reference group is those without the characteristic.
[c]Age = age at diagnosis (years); BMI = BMI two years prior to diagnosis (kg m^{-2}).

Table 2. Histopathologic characteristics of FCCTX in CCFR compared with Lynch syndrome and non-Amsterdam Criteria-1 colorectal cases

Characteristic, *n* (%)	FCCTX (*n* = 146)	Lynch (*n* = 245)	Non-AC1 (*n* = 7,878)	FCCTX *vs* Lynch[a] OR (95% CI)	FCCTX *vs* non-AC1[a] OR (95% CI)	Lynch *vs* non-AC1[a] OR (95% CI)
Cancer subsite						
Caecum	17 (12%)	55 (22%)	1034 (13%)	0.18 (0.09, 0.37)	0.95 (0.54, 1.67)	5.2 (3.32, 8.14)
Ascending	15 (10%)	64 (26%)	1129 (14%)	0.13 (0.06, 0.27)	0.66 (0.35, 1.22)	5.22 (3.37, 8.07)
Transverse	13 (9%)	31 (13%)	578 (7%)	0.27 (0.12, 0.59)	1.18 (0.63, 2.21)	4.44 (2.67, 7.41)
Descending	7 (5%)	14 (6%)	438 (6%)	0.38 (0.14, 1.08)	0.78 (0.35, 1.74)	2.03 (1.03, 3.99)
Sigmoid	37 (25%)	22 (9%)	1931 (25%)	1.02 (0.51, 2.04)	0.98 (0.63, 1.52)	0.96 (0.55, 1.66)
Rectum	50 (34%)	37 (15%)	2455 (31%)	1 (Reference)	1 (Reference)	1 (Reference)
Missing/other	7 (5%)	22 (9%)	313 (4%)			
T-stage						
T1	22 (15%)	27 (11%)	958 (12%)	1 (Reference)	1 (Reference)	1 (Reference)
T2	26 (18%)	48 (20%)	1328 (17%)	0.75 (0.35, 1.57)	0.78 (0.43, 1.40)	1.04 (0.64, 1.70)
T3	74 (51%)	127 (52%)	4242 (54%)	0.85 (0.45, 1.63)	0.65 (0.39, 1.07)	0.76 (0.49, 1.18)
T4	11 (8%)	9 (4%)	576 (7%)	1.75 (0.60, 5.05)	0.72 (0.34, 1.52)	0.41 (0.19, 0.89)
Missing	13 (8%)	34 (13%)	774 (10%)			
Differentiation						
Well	22 (15%)	21 (9%)	633 (8%)	1 (Reference)	1 (Reference)	1 (Reference)
Moderate	97 (66%)	127 (52%)	4712 (60%)	0.88 (0.45, 1.75)	0.62 (0.38, 1.02)	0.70 (0.43, 1.15)
Poor	16 (11%)	55 (22%)	1149 (15%)	0.33 (0.14, 0.78)	0.41 (0.21, 0.82)	1.25 (0.73, 2.14)
Missing/other	11 (8%)	42 (17%)	1384 (18%)			
Histology						
Adenocarcinoma	132 (90%)	191 (78%)	6771 (86%)	1 (Reference)	1 (Reference)	1 (Reference)
Mucinous	11 (8%)	41 (17%)	856 (11%)	0.39 (0.19, 0.80)	0.68 (0.36, 1.27)	1.72 (1.21, 2.45)
Signet ring	1 (1%)	4 (2%)	79 (1%)	0.38 (0.04, 3.44)	0.68 (0.09, 4.96)	1.79 (0.64, 5.07)
Missing/other	2 (1%)	9 (4%)	172 (2%)			
Additional features (yes/no) (% yes)[b]						
Peritumoural lymphocytes	23/57 (28%)	61/71 (46%)	954/1608 (37%)	0.49 (0.26, 0.90)	0.75 (0.45, 1.25)	1.54 (1.07, 2.23)
Crohn's-like lymphocytes	14/60 (19%)	61/70 (37%)	627/1843 (25%)	0.27 (0.14, 0.54)	0.78 (0.43, 1.41)	2.84 (1.97, 4.10)
Tumour-infiltrating lymphocytes	20/65 (24%)	98/43 (70%)	704/1920 (27%)	0.14 (0.07, 0.26)	0.89 (0.53, 1.50)	6.41 (4.40, 9.36)
Venous invasion	16/79 (11%)	9/135 (4%)	735/4027 (9%)	3.21 (1.35, 7.65)	1.27 (0.73, 2.21)	0.40 (0.20, 0.79)

Abbreviations: **AC1** = Amsterdam Criteria-1; FCCTX = Familial Colorectal Cancer Type X.
[a]All models are adjusted for age at diagnosis, sex, and study site. Reference group is those without the characteristic.
[b]These features were only collected at four of six study sites (Mayo Clinic, Australasia, UH, and CCO).

comparing case groups: FCCTX *vs* LS, FCCTX *vs* non-AC1, and LS *vs* non-AC1. ORs were adjusted for age at diagnosis, sex, and study site. Smoking history (ever/never smoked ≥ 1 cigarette a day for ≥ 3 months) was based on the history 1 year preceding diagnosis. Age at diagnosis and pre-diagnostic body mass index (BMI) were included in models as continuous variables. All other covariates were binary. Complete-cases analyses were conducted for all variables, with the exception of the histopathologic variables, which include those with missing and unknown as a separate category. Duplicates were removed for the limited number of participants ($n = 307$; 3.6%) who contributed more than one tumour sample. Analyses were performed using SAS 9.3 (Cary, NC, USA) and R 3.0.0 (Vienna, Austria). Reported *P*-values are two-sided; $P \leq 0.05$ was considered statistically significant.

RESULTS

FCCTX cases were slightly older at diagnosis than LS (mean 53.3 *vs* 50.5 years Table 1). By definition, all FCCTX and LS families met AC-1. In comparison, of the 9603 individuals who were classified as non-AC1, 33% were diagnosed before age 50, 5% had two or more first-degree relatives with CRC (13% had one first-degree relative), and 15% had MSI-high tumours.

The self-reported proportion of ever smokers was similar across the three groups, but FCCTX had the lowest prevalence of current smokers ($P = 0.03$ and 0.12 compared with LS and non-AC1, respectively). A higher proportion of FCCTX *vs* LS reported being former smokers. BMI and the prevalence of diabetes, hyperlipidemia, aspirin/NSAID and other medication usage, and gynaecologic history elements did not vary significantly between groups.

FCCTX CRCs were less often located in proximal subsites than LS (caecal, ascending, or transverse colon; all $P < 0.001$, Table 2); no subsite difference was observed for FCCTX *vs* non-AC1 tumours. Overall, the LS group had the lowest proportion of T4 tumours, but a statistically significant difference was observed only when comparing LS and non-AC1 CRCs. Nodal N-stage could not be reliably assessed owing to the variability in missing data between sites (data not shown).

FCCTX CRCs were more commonly poorly differentiated compared with LS/non-AC1 tumours, and were less often mucinous than LS tumours. FCCTX tumours had a smaller proportion of peritumoural lymphocytes, Crohn's-like reaction,

and TIL than LS CRCs, but there was no difference compared with non-AC1 tumours. Venous invasion was most commonly seen in FCCTX tumours.

DISCUSSION

This study evaluated epidemiologic and clinicopathologic data across FCCTX, LS, and non-AC1 cases of CRC. A statistically significant difference across these groups was noted for smoking history, whereas no differences were observed in co-morbidities, medication use, or gynaecologic history elements. Classic histopathologic features of LS CRCs were much less commonly observed in FCCTX CRCs. There were no clear distinguishing features for FCCTX *vs* non-AC1 tumours.

Comparison of FCCTX and LS. Individuals classified as FCCTX were less likely to be current smokers. Tobacco use is associated with a higher incidence of colorectal adenoma and invasive CRC in both the general population and in LS (Watson *et al*, 2004; Botteri *et al*, 2008; Pande *et al*, 2010). The difference in CRC prevalence between FCCTX and LS may be partially mediated by differences in tobacco use habits, although we cannot rule out that smoking has less effect in FCCTX than in LS.

In this comprehensive pathologic analysis, we confirmed the previously-reported left- *vs* right-sided predominance of FCCTX *vs* LS by subsite (Llor *et al*, 2005; Mueller-Koch *et al*, 2005; Valle *et al*, 2007). In the present analysis, there were also a greater proportion of large (T4) primary FCCTX tumours compared with LS CRCs. On histologic review, the mucinous histology, poor differentiation, and TIL features reported as characteristic of LS tumours (Jenkins *et al*, 2007) were not common in FCCTX CRCs. Prior studies have analysed some of these features, but with inconsistent results (Llor *et al*, 2005; Valle *et al*, 2007; Chen *et al*, 2008; Klarskov *et al*, 2011; Koh *et al*, 2011; Klarskov *et al*, 2012). FCCTX CRCs in our analysis also had a lower proportion for peritumoural lymphocytes and Crohn's-like reaction, but a significantly higher proportion had venous invasion relative to that observed in LS CRCs.

Comparison of FCCTX and non-AC1. Epidemiologic factors did not distinguish FCCTX and non-AC1 cases. FCCTX tumours had significantly lower frequency of poor differentiation than non-AC1 CRCs and a trend toward a higher proportion with venous invasion. Tumour subsite, T-stage, and tumoural lymphocytes were not observed to differ between FCCTX and non-AC1 tumours.

Strengths and limitations. This analysis benefits from a large, international cohort of patients with standardised data collection, providing the opportunity to compare FCCTX, LS, and non-AC1 CRCs in the first epidemiologic and in-depth clinicopathologic analysis. The epidemiologic features were assessed by a single baseline survey, as it is difficult to longitudinally evaluate any changes in these factors in such rare syndromes. To keep this analysis meaningful, we selected a classification based on the current information readily available to clinicians, namely personal and family history (the Amsterdam Criteria) and standard tumour analysis (MSI and/or MMR IHC). The non-AC1 cohort contains a mixture of sporadic MSI (typically due to *MLH1* promoter hypermethylation and associated sporadic *BRAF* mutations (Lynch *et al*, 2007)) and non-MSI cases. CRC is increasingly being recognised as genetically and epigenetically heterogeneous (Marisa *et al*, 2013), making selection of a true comparison group difficult. FCCTX is likely also genetically heterogeneous and would benefit from in-depth molecular characterisation (Abdel-Rahman *et al*, 2005; Sanchez-de-Abajo *et al*, 2007; Goel *et al*, 2010). It should also be noted that it is possible, given the multiple statistical comparisons performed in this analysis, that the noted associations could be chance findings. Thus, independent validation is needed.

CONCLUSIONS

This study compared FCCTX, LS, and non-AC1 CRC cases. FCCTX were less likely to be current tobacco users; other exposures were similar between these groups. Subsite analysis confirms the distal colonic predominance of FCCTX *vs* LS CRCs. Histopathologically, mucinous histology, poor differentiation, and TIL were strongly associated with LS, rather than FCCTX or non-AC1, tumours, whereas venous invasion was more commonly seen in FCCTX. Additional molecular analysis may eventually explain the observed histopathologic differences between FCCTX and LS tumours.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DISCLAIMER

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