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Colorectal cancer: no longer the issue in familial adenomatous polyposis?

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Abstract Familial adenomatous polyposis (FAP) is a dominantly inherited colorectal cancer (CRC) syndrome with an untreated lifetime prevalence of CRC close to 100% and extracolonic manifestations (ECM) of increasing clinical significance. This study examined the effect of systematic callup and prophylactic colectomy on FAP survival. Patients diagnosed, treated and followed-up at our institution were analysed. 'Callups' were those identified via the callup system; 'probands' were those identified by other means. Proportions were analysed by Chi-squared or Fischer's exact test. Mortality rates were indirectly standardised to the UK population. Survival curves from birth were estimated by Kaplan–Meier. A total of 439 patients (293 callups, 146 probands) were analysed. Crude mortality rates (CMRs) of callups and probands were 4.85 per 1,000 person years (PY) and 9.71 per 1,000 PY, respectively—a rate ratio of 0.50 (95% CI 0.34–0.72, $P = 0.0001$). The standardised mortality ratio (SMR) of callups was non-significantly lower than probands (4.12 vs. 4.70). Callups experienced non-significantly lower age-band specific SMR up to 45 years. More probands died of CRC (42.4 vs. 22.5%, $P = 0.025$), whereas more callups died of ECM (30.6 vs. 13.4%, $P = 0.027$). Median survival was 64 years for callups and 60 years for probands; survival curves did not differ significantly ($P = 0.253$). The crude mortality rate of callups is approximately half that of probands. As fewer callups die of CRC, a greater proportion die of ECMs. Callups experienced non-significantly reduced mortality up to 45 years. Whilst the FAP callup system reduces CRC risk, mortality attributable to ECMs needs to be addressed.

Keywords Cause of death · Colorectal cancer · FAP · Extracolonic manifestations · Survival

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Abbrevations

APC	Adenomatous polyposis coli (gene)
CI	Confidence interval
CMR	Crude mortality ration
CRC	Colorectal cancer
ECM	Extracolonic manifestations
FAP	Familial adenomatous polyposis
NHS	National health service (UK)
OR	Odds ratio
PY	Person-years
RR	Relative risk
SMR	Standardised mortality ratio

Introduction

In 2006, there were 37,514 new cases of colorectal cancer (CRC) in the UK, occurring at a rate of 45.3 per 100,000 population [1]. Familial adenomatous polyposis (FAP) accounts for less than 1% of these [2].

FAP is estimated to occur at a frequency of around 1 in 10,000 live births [3] with an estimated prevalence of 1 in

5,000 to 1 in 10,000 [4]. Mutations in the adenomatous polyposis coli (*APC*) gene [5–7] are identified in 65–95% of FAP cases; of these, 75–80% are inherited in an autosomal dominant manner, with the remaining 15–20% resulting from de novo mutations [5]. There is evidence of genotype-phenotype correlation in FAP with respect to severity of the colorectal polyposis and risk of formation of desmoid tumour, an extra-intestinal manifestation of the condition.

The principal clinical characteristic of FAP is the development of precancerous colorectal adenomatous polyps, with more than 100 considered pathognomic of the condition [8]. Development of CRC is a virtual inevitability unless prophylactic colectomy is undertaken, with total polyp counts greater than or equal to 1,000 conferring a relative risk (RR) for CRC of 2.3 [9]. In classical FAP, the median age of identification of polyposis is 17 years (although it is now clear that polyps are often present from late childhood) with a median age of onset of CRC of 40 years; the penetrance of CRC is 100% [3, 10].

To reduce the risk of progression from colorectal polyposis to CRC, individuals with FAP must be identified early—ideally through systematic screening—to enable prophylactic treatment. Removal of the colon in early life whilst polyps are at a pre-malignant stage largely ameliorates the morbidity and mortality attributable to CRC in FAP patients. This approach fails if either an at-risk member of a family with FAP does not attend for surveillance or treatment for a variety of reasons, or in the case of de novo mutation, where there will be no family history. Under these circumstances patients present much later, with symptomatic large polyps or established CRC.

In addition to CRC, there are also a number of extracolonic manifestations of FAP which are responsible for a considerable and increasing degree of morbidity and mortality (Table 1).

The current system whereby individuals from an affected pedigree are 'called up' for screening and offered prophylactic colectomy is primarily aimed at reducing the incidence of CRC in FAP patients. It seems logical, therefore, that as the rate of CRC decreases by virtue of early detection and prophylactic treatment, patients are more likely to survive to an age where extracolonic manifestations will develop and become important causes of morbidity and mortality. Indeed, the ratio of deaths attributable to extracolonic manifestations of FAP versus CRC was 0.15 in the 1960s—by the 1990s, this ratio was estimated to be 1.0 [11].

This study examines the effect that the 'callup' system has had on the mortality rates of FAP patients served by St Mark's Hospital Polyposis Registry and the attributable causes of death by callup status and age at death.

Table 1 Extracolonic manifestations of FAP [8, 14]

System	Feature	Frequency (%)
Upper gastrointestinal tract	Upper gastrointestinal adenomas [8]	95
	Upper gastrointestinal carcinomas [8]	5
	Fundic gland polyps [8]	40
	Pancreatic cancer [14]	1
Connective tissue	Osteomas [14]	20
	Desmoids [14]	20
Dental	Dental abnormalities [14]	17
Cutaneous	Epidermoid cysts [8]	50
Endocrine	Adrenal tumours [14]	7–13
	Papillary thyroid carcinoma [14]	1–2
Hepatobiliary	Biliary tract carcinoma [8]	<1
	Hepatoblastoma [14]	1–2
Central nervous system	Congenital hypertrophy of the retinal pigment epithelium (CHRPE) [8]	75
	Brain tumours (especially medulloblastoma) [14]	1–2

Methods

Study design

The programme of screening and prophylactic surgery was considered as a combined intervention; thus, 'callups' were considered as the treatment arm and 'probands' as the control arm, with the endpoint of this study being death. Follow-up on all patients continued until the first of notified date of death or 27th July 2009 (the date of data collection).

Patient inclusion criteria

In order to be included in this study, patients had to meet two criteria:

1. Confirmation of FAP:
   - *EITHER* identification of an *APC* mutation
   - *OR* 100 or more colorectal adenomas with no evidence of *MYH* mutation.
2. Primary surgery and all follow-up to date at St Mark's Hospital

The differing diagnostic criteria for FAP result from changing diagnostic methods over time and the fact that not all FAP patients or pedigrees have a demonstrable *APC* mutation. Deciding to limit the cohort to those that underwent primary surgery and all follow-up to date at St Mark's was taken as a quality control measure—as the Registry often depends on notification of death from other

healthcare organisations or family members, there would have been potential for ascertainment bias with respect to capturing the occurrence and date of death for those patients followed-up outside of St Mark's.

Patients were classed as 'callups' if they were diagnosed with FAP through the screening programme. Patients diagnosed with FAP outside of the screening programme were classed as 'probands'.

Data acquisition and collection

Data on eligible patients were collected from the St Mark's Hospital Polyposis Registry database, which contains details on all polyposis patients known to St Mark's Hospital since the inception of the Registry in 1924. St Mark's Polyposis Registry utilises a custom-made database for the purposes of registering and tracking patients. The database was created using Filemaker 10 for Windows and is maintained by Registry staff.

Data on all new clinical encounters and outcomes are entered prospectively by medical, nursing and clerical staff in tandem with standard clinical record keeping. Data preceding the implementation of the database were entered retrospectively from existing clinical records. Genealogical data are also entered into and available on the database. The majority of the data recorded on the database are derived from clinical records, but the Registry may rely on patients or relatives to provide information about changes of address and date and cause of death.

Cause of death was classified as to whether or not death was attributable to FAP and, where appropriate, whether death resulted from the colonic or extracolonic manifestations of FAP or from an unrelated cause. Coding of cause of death was undertaken by DCG, SKC and AS. Where there was disagreement, categorisation of causes of death was made by consensus.

Data analysis

Data was analysed with STATA 10.1/IC for Mac OS X. Assessment of normality of continuous variables was by quantile–quantile plot and the Shapiro–Wilk normality test; comparisons of continuous variables between two groups were made by unpaired *t* test or by Mann–Whitney U test depending on whether the variable in question was normally distributed.

Comparisons in proportions between groups were assessed using χ^2 for groups unless otherwise stated; Fisher's exact test was utilised for comparisons between groups with a sample size less than 40 or for whom the smallest expected value was less than 5.

Survival curves and life table data were calculated by the Kaplan–Meier estimate of the survivor function, with comparison of equality of survival curves by log-rank test. Crude mortality rates were derived from person-years of observation. Adjustment of crude mortality rates for potential confounders, assessment of the significance of rate ratios and assessment of effect modification were performed using Mantel–Haenszel methods (Mantel–Haenszel χ^2 (χ^2_{MH}) and χ^2 test for effect modification, respectively); terms were added in a stepwise manner. Standardised mortality ratios (SMRs) were calculated for our FAP cohort as a whole and by age-band by indirect standardisation, utilising the mortality rates of the 2001 UK population as a reference.

Statistical significance was assumed at $\alpha = 0.05$ for all analyses.

Results

A total of 439 patients (293 callups and 146 probands) were eligible for inclusion in this study. The median observation period was 42 years (IQR 24, range 14–86). A total of 125 patients died during the observation period, of which 56 (45%) were callups and 69 (55%) were probands. Clinical details of patients are summarised in Table 2. Males were over-represented in the proband group (59%) relative to the callup group (51%), but this difference was non-significant ($P = 0.111$).

The age at which patients were first seen was not normally distributed ($P < 0.00001$); callups were seen at a significantly younger age than probands, at median ages of 16 years (IQR 11, range 1–59) and 32, respectively (IQR 16, range 4–66) ($P < 0.0001$).

The distribution of polyp load was not normal ($P < 0.00001$); there was no significant difference in the polyp loads of callups and probands, with median polyp loads of 800 (IQR 975, range 3–8,000) and 1,000 (IQR 1,439, range 41–10,800), respectively ($P = 0.0950$). Despite there being no significant differences in polyp loads between the two groups, a significantly higher proportion of probands had cancer histologically identified in their primary operative specimen in comparison to probands (34 vs 5%, $P < 0.001$).

There were no significant differences between callups and probands in the proportion of patients in whom the *APC* mutation location was known with a genotype predicting a severe colorectal phenotype (18 vs. 25%, $P = 0.213$), attenuated phenotype (23 vs. 13%, $P = 0.094$) or classical phenotype (53 vs. 47%, $P = 0.382$). A significant difference in the proportion of patients with a desmoid-prone genotype was noted between callups and probands (6 vs. 15%, $P = 0.028$, Fisher's exact). The *APC* mutation locations for attenuated phenotype, classical phenotype, desmoid-prone genotype and severe colorectal phenotype where defined as

Table 2 Patient characteristics

	Callup	Proband	Overall
n	293	146	439
Sex (%)	Males: 149 (51%)	Males: 86 (59%)	Males: 235 (54%)
	Females: 144 (49%)	Females: 60 (41%)	Females: 204 (46%)
Median year of birth (IQR; range)	1968 (24; 1908–1994)	1949.5 (37; 1889–1993)	1963 (28; 1889–1994)
Patient ethnicity (%)	Caucasian: 214 (73%)	Caucasian: 110 (75%)	Caucasian: 324 (74%)
	Afro-Caribbean: 12 (4%)	Afro-Caribbean: 2 (1%)	Afro-Caribbean: 14 (3%)
	Indo-Asian: 11 (4%)	Indo-Asian: 2 (1%)	Indo-Asian: 13 (3%)
	Missing: 56 (19%)	Missing: 32 (22%)	Missing: 88 (20%)
Median age first seen (IQR; range)	16 (11; 1–59)	32 (16; 4–66)	20 (18; 1–66)
Median total polyps (IQR; range)	800	1,000	860
	(975; 3–8,000)	(1,439; 41–10,800)	(1,110; 3–10,800)
	[n = 268]	[n = 133]	[n = 401]
Cancer in operative specimen (%)	Yes: 15 (5%)	Yes: 49 (34%)	Yes: 64 (15%)
	No: 278 (95%)	No: 97 (66%)	No: 375 (85%)
APC mutation classification in patients with known mutation site	Attenuated: 45 (23%)	Attenuated: 8 (13%)	Attenuated: 53 (21%)
	Classical: 102 (53%)	Classical: 28 (47%)	Classical: 130 (52%)
	Severe: 31 (18%)	Severe: 15 (25%)	Severe: 49 (19%)
	Desmoid-Prone: 11 (6%)	Desmoid-Prone: 9 (15%)	Desmoid-Prone: 20 (8%)
Ever been a trial Participant (%)	Yes: 154 (53%)	Yes: 46 (32%)	Yes: 200 (46%)
	No: 139 (47%)	No: 100 (68%)	No: 239 (54%)
Dead (%)	56 (19%)	69 (47%)	125 (28%)
Median age of death (IQR; range)	49	52	49
	(24.5; 19–77)	(24; 24–85)	(24; 19–85)
	[n = 56]	[n = 69]	[n = 125]
Median age at end of follow-up period for survivors (IQR; range)	37	48	39
	(19; 14–86)	(21; 16–84)	(21; 14–86)
	[n = 237]	[n = 77]	[n = 314]

codons 5′ of codon 450, between codons 450–1,249, between codons 1,250–1,399 and 3′ of codon 1,399, respectively.

Age of death was not normally distributed ($P = 0.04$); there was no significant difference in the ages of death between callups and probands, with median ages of death of 49 years (IQR 24.5, range 19–77) and 52 years (IQR 24, range 24–85), respectively ($P = 0.0738$).

Crude mortality rates

Mortality rates were expressed as deaths per 1,000 person-years (PY) of observation. Overall, the mortality rate of the cohort of FAP patients in this study was 6.70 per 1,000 PY (95% CI 5.62 per 1,000 PY–7.99 per 1,000 PY), with a median survival time of 63 years.

Callups were subject to a crude mortality rate of 4.85 per 1,000 PY (median survival 64 years); probands experienced a crude mortality rate of 9.71 per 1,000 PY (median survival 60 years). The difference in crude mortality rate between callups and probands was significant, equating to a rate ratio of 0.50 (95% CI 0.34–0.72, $P = 0.0001$). The effect of potential confounders, added in a stepwise manner, was also assessed (Table 3), with callups experiencing a significantly lower mortality rate in comparison to probands up to a model controlling for sex, trial participation, total polyp count (by quartile) and patient ethnicity, with a rate ratio of 0.60 (95% CI 0.41–0.88, $P = 0.0081$).

Standardised mortality ratios (indirectly standardised to the 2001 UK population)

For the purposes of comparison, the mortality rate for the United Kingdom is utilised as a reference and, therefore, is equal to 1.0. Overall, the FAP patients in this cohort were subject to a significantly higher mortality rate than that of the UK population, with a SMR of 4.42 (95% CI 3.71–5.27).

The SMRs for callups and probands were both significantly higher than that of the 2001 UK population,

Table 3 Crude mortality rate ratios adjusted for confounders

Model adjusting for:	Rate ratio (Callups vs. Probands)	95% CI	*P*
None	0.50	0.35–0.71	0.0001
Sex	0.50	0.35–0.71	0.0001
Sex + Trial Participation	0.58	0.41–0.83	0.0025
Sex + Trial Participation + Polyps (by Quartile)	0.60	0.42–0.88	0.0073
Sex + Trial Participation + Polyps (by Quartile) + Ethnicity	0.60	0.41–0.88	0.0081

although not significantly different from one another; the SMR for callups was estimated at 4.12 (95% CI 3.17–5.36), with the SMR for probands estimated at 4.70 (95% CI 3.72–5.96).

The age-band-specific SMRs for callups and probands are shown in Fig. 1. Although the calculated age-band-specific SMRs for callups and probands do not differ significantly at any age, callups appear to have a lower SMR than probands until the 45–54 year age bracket, after which the age-band-specific SMRs are roughly equivalent.

Causes of death by age-band

A total of 115 (92%) of deceased patients had sufficient data from which cause of death could be classified: 49 (88%) of deceased callups and 66 (96%) of deceased probands were able to have cause of death determined and classified. Coding of causes of death and the proportions of deaths by each category of cause of death by age-band and callup status are shown in Tables 4 and 5 respectively.

Overall, a significantly greater proportion of probands' deaths were attributable to a cause of death classified as 'FAP—colonic' ($P = 0.025$). The proportion of deaths classified as 'FAP—colonic' was significantly greater for probands in the 15–34 year age band ($P = 0.040$, Fisher's Exact); observed differences in other age bands did not reach statistical significance.

A significantly greater proportion of observed deaths in the callup group were attributable to a cause of death classified as 'FAP—extracolonic' ($P = 0.027$). The proportion of deaths classified as 'FAP—extracolonic' was significantly greater for callups in the 15–34 year age band ($P = 0.008$, Fisher's Exact); observed differences in other age bands did not reach statistical significance.

There was no significant overall difference in the proportion of observed deaths classified as 'potentially FAP related' by callup status; however, a significantly greater proportion of probands aged 55–74 died of causes 'potentially FAP related' ($P = 0.038$, Fisher's Exact). The differences in the proportion of patients dying from diseases classified 'unrelated to FAP' was insignificant between callups and probands both overall and by age band.

Survival analysis

The Kaplan–Meier estimates of the survival curve for callups and probands (observed from birth) iare shown in Fig. 2. The median survival time for callups was 64 years compared to a median of 60 years for probands; the median survival time for all FAP patients was 63 years. There was no significant difference between the estimated survival curves (observed from birth) for callups and probands in this cohort of patients ($P = 0.2534$).

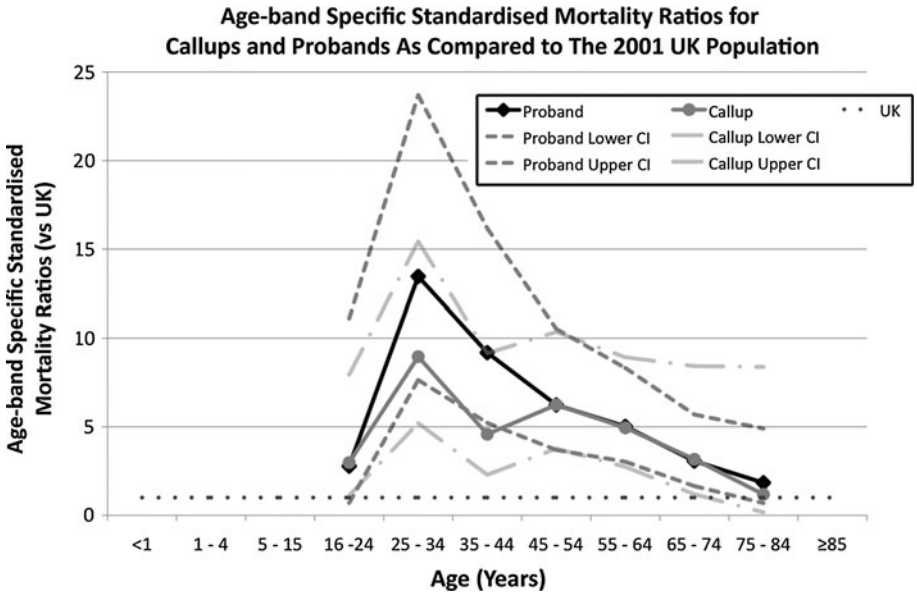

Fig. 1 Age-band specific standardised mortality ratios for callups and probands

Table 4 Coding of causes of death

FAP Related—Colonic	FAP Related—Extracolonic	Potentially Related to FAP	Unrelated to FAP
Bowel cancer	Glioblastoma multiforme	'Brain tumour' (no further information)	Accident
Bowel cancer colon	Cancer duodenum	Cancer multiple sites (no further information)	Bone cancer
Bowel cancer rectum	Cancer ileum	Cancer site unknown	Breast cancer
Cancer rectum	Cancer jejunum	Cancer UGI site unknown	Cerebral haemorrhage
Post-operative death (multi-organ failure following anastamotic breakdown)	Desmoid	Carcinomatosis (no further information)	Eye cancer
Post-operative death (intra-operative haemorrhage during IRA)	Desmoid haemorrhage	Gastric cancer	'Heart' (no further information)
	Duodenal cancer	Ischaemic small bowel (secondary to adhesions)	Leukaemia
	Gall bladder cancer	Oesophageal cancer	'Lung disease'
	Pancreatic cancer	Post-operative death (following polypectomy)	Blood transfusion mismatch
	Periampullary cancer	Pancreatitis	'Suspicious circumstances'
	Post-operative death (massive haemorrhage post-desmoidectomy)	Peritonitis	Ovarian cancer
	Post-operative death (post-Whipple's for duodenal cancer)	Post-operative death (no further information)	Pneumonia
			Post-operative death (pulmonary embolism 2 years after last operation)
			Pulmonary embolism (5 years after last operation)
			Road traffic accident
			Suicide
			Tetanus
			'Thrombosis'

Table 5 Causes of death by age-band

	15–34	35–54	55–74	≥75	All deaths
Callups					
FAP—Colonic	3 (18.75%)	5 (25%)	3 (23.08%)		11 (22.45%)
FAP—Extracolonic	8 (50%)	2 (10%)	5 (38.46%)		15 (30.61%)
Potentially FAP-Related	4 (25%)	5 (25%)	0 (0%)		9 (18.37%)
Unrelated to FAP	1 (6.25%)	8 (40%)	5 (38.46%)		14 (28.57%)
Total	16 (100%)	20 (100%)	13 (100%)		49 (100%)
Probands					
FAP—Colonic	7 (63.64%)	13 (46.43%)	7 (29.17%)	1 (33.33%)	28 (42.42%)
FAP—Extracolonic	0 (0%)	4 (14.29%)	5 (20.83%)	0 (0%)	9 (13.64%)
Potentially FAP-Related	3 (27.27%)	3 (10.71%)	7 (29.17%)	1 (33.33%)	14 (21.21%)
Unrelated to FAP	1 (9.09%)	8 (25.57%)	5 (20.83%)	1 (33.33%)	15 (22.73%)
Total	11 (100%)	28 (100%)	24 (100%)	3 (100%)	66 (100%)

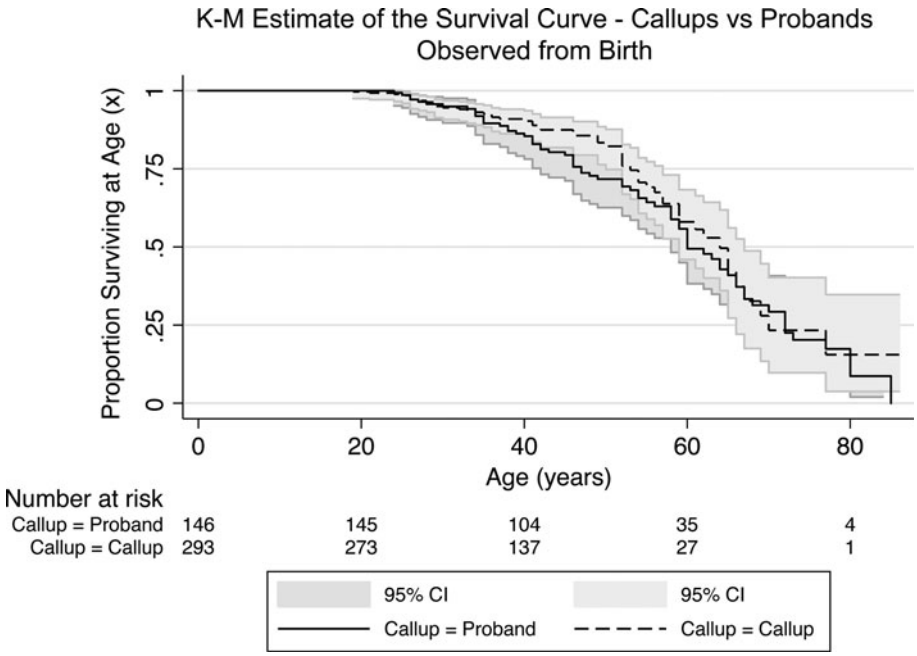

Fig. 2 Kaplan-Meier estimate of the survival curve for callups and probands (observed from birth)

Discussion

Since the inception of St Mark's Hospital Polyposis Registry, there have been significant improvements in surgical and medical care in tandem with general improvements in public health—all of which have led to improvements in life expectancy and quality of life. Therefore, it is highly likely that the efficacy of screening, diagnostics, prophylactic colectomy and post-operative care have changed over the observation period. That notwithstanding, callups have all been exposed to an intervention that is primarily aimed at reducing the incidence of CRC and improving life expectancy whereas probands have not.

Callups experience a crude mortality rate that is roughly half that of probands—a significant difference that persists when adjusting for the effects of sex, trial participation, polyp count and ethnicity. However, once the effect of age is taken into account (via SMRs), differences in survival between callups and probands, although favouring callups, become non-significant. When interpreting this result, one has to be mindful that the median age of survivors at the endpoint of this study was only 39 years (38 years for callups, 48 years for probands), meaning that the contribution of mortality rates from older age-bands to the overall SMR for callups may be relatively imprecise.

It is of note, however, that callups appear to be subject to a non-significantly reduced age-band specific SMR than probands up to the age of 45 years. It is likely that this difference is due to the reduction in incidence of CRC in callups attributable to prophylactic colectomy. Taking the reduction in colorectal deaths in callups and the similarity in SMRs past the age of 45 years into account, it is likely that reducing the incidence of CRC through prophylactic surgery reduces FAP related mortality up to the 4 to 5th decade of life but that the callup system, at the present time, is not able to reduce mortality attributable to extracolonic manifestations of FAP and non-FAP related deaths, the incidence of which are unaffected by prophylactic colectomy.

Comparing callups to probands, the odds ratio (OR) of CRC in the operative specimen in this study was 0.10 (95% CI 0.06–0.20, $P < 0.0001$). The crude mortality rate for FAP patients who had cancer in their operative specimen was 15.38 per 1,000 person-years compared to a rate of 4.87 per 1,000 person-years for those who did not; this difference is highly significant with a rate ratio of 3.155 (95% CI 2.206–4.513, $P < 0.0001$). The difference in crude mortality rates associated with a patient having cancer is somewhat attenuated by controlling for callup status (perhaps due to diagnosis at an earlier stage), but remains significant with a rate ratio of 2.73 (95% CI 1.82–4.08, $P < 0.0001$).

The estimates of the survival curves, as with the SMRs, indicate that callups have trend towards improved survival relative to probands up until approximately the 5th decade of life. The lack of significance in the difference between the survival of callups and probands may seem somewhat surprising in the context of existing literature [12, 13], but one needs to consider the methodology of previous studies when interpreting their results.

Bülow et al. [12] and Heiskanen et al. [13] commenced their periods of observation from time of diagnosis of FAP and time from primary operation, respectively; both studies concluded that callups experienced significantly improved survival compared to probands. These approaches, whilst

seemingly intuitive from the point of view of commencing follow-up from the time of proactive intervention, are highly prone to bias. In our dataset, callups were first seen at a median age of 16 years and probands at a median age of 32 years; if, as is likely, the probabilities of death or developing CRC are functions of time, the methodologies of previous studies will favour callups if for no other reason than the fact they are able to access treatment at an earlier age, hence allowing factors such as the probability of developing CRC to confound estimations of survival—a fact that is not taken into account by commencing follow-up from the time of diagnosis or primary surgery.

For the purposes of illustration, if follow-up is commenced from the time of diagnosis (Fig. 3) or primary surgery (Fig. 4) in our dataset, then callups appear to have significantly improved survival relative to probands ($P < 0.0001$ and $P < 0.0001$, respectively). The effect of bias is particularly evident when evaluating crude mortality rates: following patients from the time of diagnosis leads to a crude mortality rate of 9.67 per 1,000 PY for callups versus 21.58 per 1,000 PY for probands, (rate ratio 0.35, $P < 0.0001$), and if observation is commenced from the time of primary surgery then callups are subject to a crude mortality rate of 11.92 per 1,000 PY compared to 29.41 per 1,000 PY for probands (rate ratio 0.41, $P < 0.0001$).

The lack of significance in the differences in estimated survival (when observed from birth) and SMR may potentially result from a number of factors—in particular the relatively small sample size and number of deaths that limit the power of this study. The dataset utilised consists of longitudinal data on all FAP patients who were (and are) known to and had their follow-up provided by St Mark's Hospital Polyposis Registry—the range of year of birth of patients is 1889–1994, with the median year of birth of deceased patients being 1935. It is highly likely that there have been substantial changes in diagnostic, surgical and medical care over this period, notably the establishment of the UK National Health Service (NHS) in 1948. Prior to the NHS, it is possible that only those patients who could afford to privately fund their own healthcare would be able to avail themselves of the callup programme, introducing the potential for selection bias in those callups born or diagnosed with FAP before 1948.

The fact that this dataset is largely comprised of relatively 'young' patients—the median age of survivors at the end of the observation period is 39—would imply that the estimates of survival and mortality experienced by this cohort arguably reflect the outcomes and efficacy of surgical and medical practice that may no longer be considered contemporary. As such, this study may underestimate the true potential of the modern callup programme insofar as improved survival and reduced mortality are concerned—in order to do so, another 30–40 years of observation would be needed.

This study also indicates that, whilst non-significant, the callup system exerts the greatest benefit up to approximately the 5th decade of life—consistent with the timing of excess deaths attributable to the colonic manifestations of FAP—after which point callups and probands are subject to a SMR that is roughly equivalent, perhaps reflecting a stage in life where patients are at greater risk of extracolonic manifestations of FAP and diseases unrelated to FAP.

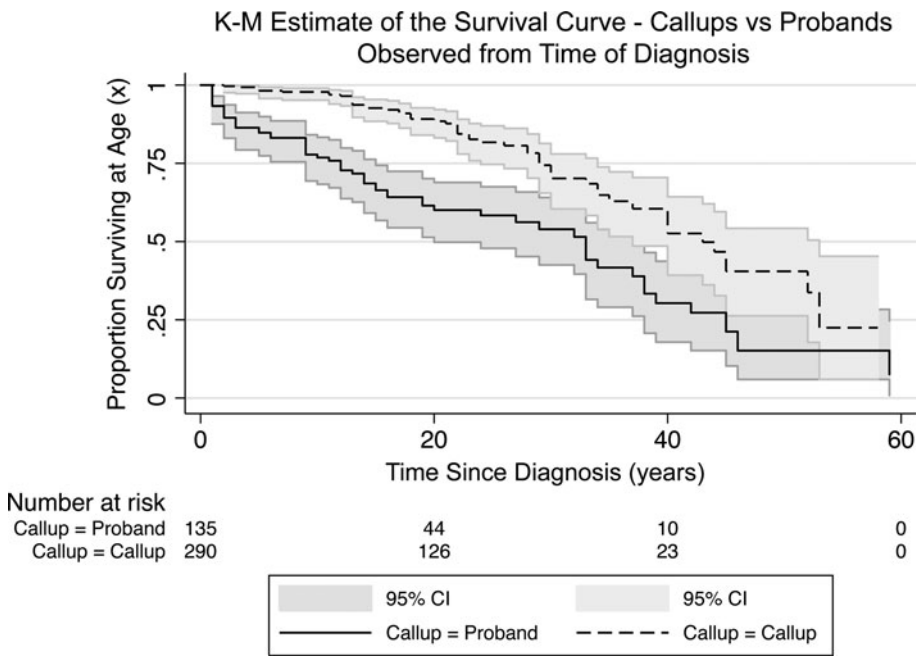

Fig. 3 Kaplan-Meier estimate of the survival curve for callups and probands (observed from time of diagnosis)

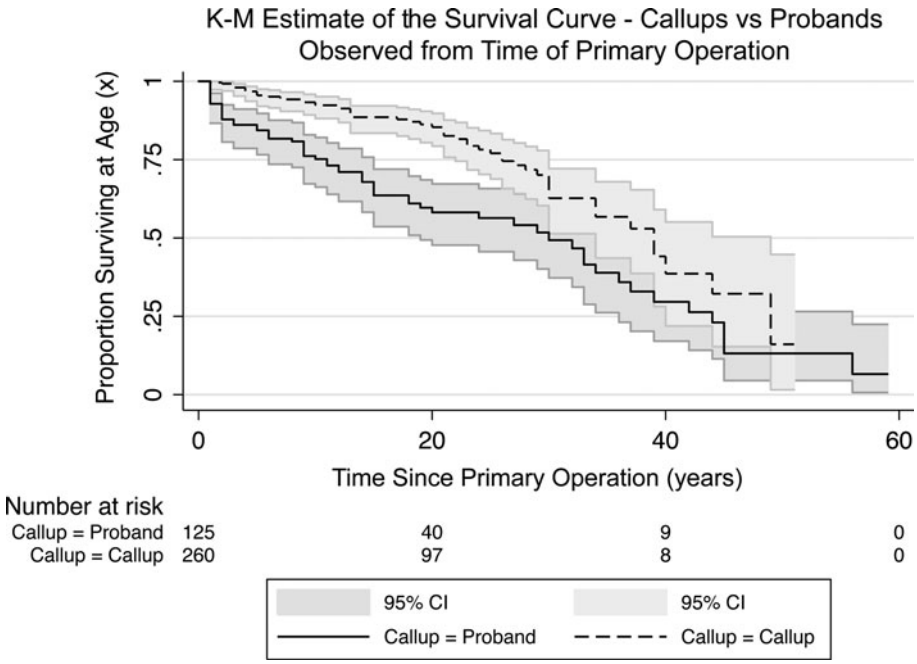

Fig. 4 Kaplan-Meier estimate of the survival curve for callups and probands (observed from time of primary operation)

At the present time, the callup system appears effective in reducing the prevalence of CRC at the time of primary operation, as evidenced by a 90% reduction in the odds of CRC being detected in the operative specimen of callups. However, in callups, the majority of deaths are attributable to the extracolonic manifestations of FAP—this finding represents a potential shortcoming in the contemporary management of FAP patients. For any patient that has undergone colectomy—and has no evidence of CRC at the time of primary operation—the priority of their continuing care has to be reducing the risk of extracolonic manifestations.

Our ability to successfully mitigate the risks of desmoid tumours and upper gastrointestinal polyposis and cancer is lagging behind that of CRC. Indeed, unless further research into risk stratification and treatment for extracolonic manifestations of FAP is undertaken, it is possible that the callup programme may—to some extent—become a victim of its own success, merely enabling patients to survive to a point past which we are unable to exert any meaningful control over the manifestations of FAP and commensurately reduce associated morbidity and mortality.

Successfully managing the extracolonic manifestations of FAP represents a significant challenge, but is one that be considered a priority if we are to make further progress in reducing morbidity and mortality attributable to FAP. It could be argued that the life-course of FAP can be split into three phases—an 'early life' phase where patients are most at risk from CRC, a 'mid-life' phase where patients are most at risk of the extracolonic manifestations of FAP and a 'late life' phase where survivors are subject to the same spectrum of disease as the general population.

Over the past 60 years, through screening and prophylactic colectomy, we have made significant inroads into the 'early life' phase of FAP, but unless we are able to harness a greater understanding of the pathogenesis of and develop effective treatments for the extracolonic manifestations of FAP, we will struggle to ensure the survival of FAP patients past the 'mid-life' phase of the disease.

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Conflicts of interest None declared.

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