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Adenoma, advanced adenoma and colorectal cancer prevalence in asymptomatic 40 to 49-year-olds with a first-degree family history of colorectal cancer

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ABSTRACT

Background:. First-degree relatives (FDR) of patients with colorectal cancer (CRC) have an increased CRC risk. Few studies have addressed if adenoma and advanced adenoma risk is increased among individuals with family history of CRC aged 40-49 years.

Aim: To define prevalence and location of adenoma, advanced adenoma and CRC according to age in asymptomatic individuals with family history of CRC.

Methods: Retrospective study of asymptomatic FDR of CRC patients, aged 40 to ≥70 years, undergoing first screening colonoscopy over a three year period .

Results: Among 464 individuals studied, adenoma and advanced adenoma prevalence was 18.1% and 6.4%, respectively. According to age intervals, prevalence of adenoma and advanced adenoma was 14% and 3.5% in 40-49 age group, 14.4% and 6.3% in 50-59 age group, 27% and 8% in 60-69 age group, 25% and 14% in ≥70 age group, with no significant difference among the four groups. No difference in lesion location was found, with similar numbers of pre-neoplastic lesions was found in right and left colon. CRC was diagnosed in three subjects (0.64%), one of them in 40-49 age group.

Conclusion: In our population of FDR of CRC patients aged 40-49 years, prevalence of adenoma and advanced adenoma was similar to that observed in older subjects with the same CRC risk. Our data support the current indication to perform screening colonoscopy earlier than 45 years in subjects at high CRC risk.

Keywords: adenoma, advanced adenoma, colonoscopy, colorectal cancer, screening colonoscopy.

What is new in this paper:

This study found adenoma and advanced adenoma prevalence in patients aged 40-49 years was similar to that in patients aged 50-59 years. This study also found a high prevalence of adenoma (18.1%) and advanced adenoma (6.4%) in FDRs of CRC patients, which were frequently detected in the proximal colon. Screening colonoscopy should be considered as procedure of choice in subjects with CRC family history starting at age 40.

INTRODUCTION

Colorectal Cancer (CRC) is the second most common cause of cancer-related death in men and women living in Western Countries(1). Screening with fecal occult blood test, sigmoidoscopy and colonoscopy have all been shown to reduce mortality and morbidity due to CRC (2, 3). Colonoscopy is an accepted screening tool in the average risk population aged >50 years, due to it's high sensitivity, specificitiy, cost-effectiveness and the ability to reduce CRC incidence and mortality (4-9). First degree relatives (FDR) of patients with CRC have a 3-6 fold increased risk of developing CRC, screening colonoscopy has therefore been recommended in this cohort.(10-13). Moreover, the age at diagnosis of CRC of the FDR has been reported to strongly influence the risk, raising from 2.2 when malignancy is diagnosed at age 45-59 to 3.8 at age <45 years. A similar increased risk has been reported, from 2.18 in FDR aged over 50 to 3.55 in FDR aged <50 (14). Therefore, current guidelines recommend screening colonoscopy at age 40 or 10 years younger than the age of the relative at diagnosis in patients having a FDR with CRC or adenoma at age <60 (8, 9, 15). The rationale for beginning screening at age 40 is that occurrence of CRC in such individuals parallels the risk in persons with no family history, but precedes it by about 10 years (11). However, data available regarding an increased incidence of adenoma and advanced

adenoma in <50 year-old subjects having FDR with CRC at age 60 are scarce and partially conflicting (12, 16-20).

This study aimed to assess the prevalence of adenoma and advanced neoplasia in asymptomatic 40-49 years old individuals undergoing first colonoscopy due to a family history of CRC.

METHODS

Study design

The study was a retrospective analysis of asymptomatic patients undergoing screening colonoscopy between January 2006 and December 2008. Of 8992 colonoscopies performed in our centre during the study period, 7937 (88%) had a diagnostic indication, while 1055 (12%) were for a screening purpose. Among the 1055 subjects who underwent screening colonoscopy, 591 (56%) did not have a family history of CRC. The remaining 464 subjects (44%) had at least one FDR affected by CRC and fulfilled the study inclusion criteria (Figure 1).

Collection of data and selection of patients

Colonoscopy reports were reviewed from an electronic database (Endobase, Olympus). Demographic information, indication for colonoscopy (symptoms, average risk screening or high risk screening for family history), clinical features, endoscopic findings including quality of bowel preparation, use of drugs during examination were available. All asymptomatic subjects having at least one FDR with CRC aged from 40 to ≥70 years were included in the study. Exclusion criteria were: previous colonoscopy for any reason; presence of symptoms possibly related to neoplasia, such as rectal bleeding, change in bowel habit, abdominal pain, anemia or unexplained weight loss; a history of inflammatory bowel disease,

hereditary non-polyposis CRC (HNPCC) or familial adenomatous polyposis; bowel resection for CRC or any other non neoplastic condition; incomplete endoscopic assessment due to inadequate bowel cleansing or lack of caecum intubation.

Colonoscopy

All individuals underwent colonoscopy following a standard oral bowel preparation with polyethylene glycol solution or oral phosphosoda. Sedation with intravenous midazolam and/or propofol plus fentanyl was used as requested. Expert gastroenterologists performed colonoscopy using high-resolution video-colonscopes (Olympus, Exera II System, CFQ165I).

At the end of the examination, quality of bowel cleansing and endoscopic findings, including number, size, morphology and location of polyps, were recorded in individual patient files. All polyps were removed at diagnosis or on later colonoscopy if any contraindications were present, and collected for histopathological assessment. Adenoma was classified according to current World Health Organization criteria (21) as tubular, tubulovillous, or villous and dysplasia as low- or high-grade. Advanced adenoma was defined as an adenoma measuring > 1 cm in diameter and/or containing villous component and/or with high-grade dysplasia.

Analysis of data and statistical evaluation

Overall prevalence and odds ratio of adenoma, advanced adenoma and CRC were defined. Prevalence in 40-49 age group was also calculated and compared with those in 50-59, 60-69 and ≥70 age groups. Fisher exact tests and χ^2 test were used to compare categorical variables. A P value <0.05 was considered to be statistically significant. Statistical analysis was performed by using MedCalc®11.5 software.

RESULTS

Study population

A total of 464 subjects, 273 females and 191 males (median age: 54 years; range: 41-78), with at least one FDR affected by CRC represented our study population (Figure 1). Subjects were stratified in four age groups: 143 individuals were in 40-49 age group, 173 in 50-59 age group, 112 in 60-69 age group and 36 in ≥70 age group. Female/male ratio in each age group was similar ($P = 0.79$).

Prevalence and location of adenoma, advanced adenoma and colorectal cancer

Endoscopy and histology findings are shown in Table 1. A total of 128 out of 464 (27.5%) subjects were found to have at least one lesion at screening colonoscopy. Three CRCs were detected (prevalence 0.65%), one in 40-49 age group and two in 50-59 age group, two located in sigmoid colon and one in right colon. All CRCs were invasive, one staged as T1N0 and two as T2N0.

A total of 183 polyps were removed in 125 subjects at the time of diagnosis or in a subsequent session, 118 (64%) adenoma and 65 (36%) hyperplastic polyps. Of 118 adenoma, 38 (32%) were classified as advanced adenoma: 27 (23%) were ≥1 cm, 14 (12%) showed villous component and 10 (8.5%) high-grade dysplasia. Overall, prevalence of adenoma and advanced adenoma was 18.1% and 6.4% respectively.

Distribution of adenoma in different colonic tracts is shown in Table 2. The number of adenoma and advanced adenoma located in right colon was similar to that found in recto-sigmoid tract ($P = 0.88$). Of the 30 subjects with advanced adenoma, 11 (37%) had the lesion located in the right colon in absence of polyps in the left colon.

Adenoma and advanced adenoma according to age

Prevalence of adenoma in 40-49 age group was similar to that in 50-59 age group, but significantly lower than in 60-69 age group as expected (14 *versus* 27%, χ^2: 5.74, 95% CI: 0.23 – 0.83; $P = 0.01$). Prevalence of advanced adenoma also appeared to increase with age: 3.5% in 40-49, 6.3% in 50-59, 8% in 60-69 and 14% in ≥70 age group; however, no significant difference was found except when subjects aged <50 years were compared with those aged ≥70 years ($P = 0.03$, 95% CI: 0.06 - 0.82). (Figure 2).

Sub-stratifying subjects <50 years in two groups, 40-44 and 45-49 years, a similar prevalence was found either for adenoma (12.7% versus 14.7%, P=0.92) either for advanced adenoma (3.6% *versus* and 3.4%, P=1.00).

Prevalence of adenoma, advanced adenoma and CRC according to gender

Males and females showed a similar prevalence of adenoma (22 *versus* 15.4%, respectively, p=0.07, Table 3), while prevalence of advanced adenoma was significantly higher in males than in females (8.9% *versus* 3.8%, respectively; p=0.03, 95% CI: 1.149-5.744). No difference of prevalence of CRC was found.

DISCUSSION

CRC represents a major public healthcare issue in Europe, with 280.000 new cases/year and 145.000 deaths (22). In Italy, about 46.000 new cases/year and >16.000 deaths from CRC have been estimated for the year 2005 (23). Screening programs have been introduced, which aim to diagnose and treat adenoma before malignant transformation or CRC at an early stage. Whilst the appropriateness of starting screening colonoscopy at age 50 in average risk subjects has been well demonstrated, there is disagreement about the age to start screening

colonoscopy in FDR of patients with CRC. The question was raised following the evidence by Fuchs et al. (11) that showed the cumulative incidence of CRC reported in FDR at age 40 was similar to that in those without CRC family history at age 50.

Our study has shown a high overall prevalence of adenoma (18.1%) and advanced adenoma (6.4%) in FDRs of CRC patients. These figures are in keeping with previous data (10-12, 24-27), and confirm a high risk of advanced neoplasia in subjects with a family history of CRC. Males were found to be at higher risk (OR 2.26), as previously reported (24-27).

Current recommendations (8, 9, 15) suggest starting screening colonoscopy, in people having FDR with CRC, at age 40 or 10 years younger than the age of the relative at diagnosis. Such a policy seems to be appropriate on the basis of our results, which found adenoma in 14% and advanced neoplasia in 4.2% of asymptomatic subjects aged 40-49 having FDR with CRC. Our figures are consistent with those reported by Menges et al. (25) who found in 40-49-year-old FDRs of CRC patients an incidence of adenoma and advanced adenoma of 18.9 and 5.3%, respectively, significantly higher than those in age-matched controls (8.2 and 2.3%, respectively). Furthermore, in a recent uncontrolled study (12) a prevalence of 16.3% of advanced neoplasia was detected in <50 years old FDRs of CRC patients. Other studies f FDRs of CRC patients have shown variability the prevalence of adenoma and advanced adenoma (Table 4). Several reasons may be hypothesized to explain this discrepancy. Lack of definition of villous morphology and high-grade dysplasia at histology may have led to underestimate true prevalence of advanced adenoma (20). Low quality of colonoscopy (<90% of caecal intubation) (27), gender and regional differences may also explain the variation in the reported studies. Finally, age intervals were not homogeneously defined (12,

16, 17, 25, 27), reporting prevalence of precancerous lesions in FDR aged between 40 and 65 years. In light of our and previous data we believe that screening colonoscopy should be started at age 40 in FDRs of CRC patients.

About one-third of preneoplastic lesions in our series were located in right colon with no lesion distal lesions beyond this. This finding is in agreement with previous investigations (28, 29) and may explain the occurrence of CRC in right colonic sites in about 30-40% of subjects with a family history (FH) of CRC (30, 31). Thus, a full colonoscopy should be preferred to sigmoidoscopy to screen individuals who have a FH of CRC.

Screening colonoscopy from age 40 in persons with a family history of CRC would mean a large increase in the number of examinations to be performed. This would have associated clinical and economical implications. The cost-effectiveness of such a policy has not yet been assessed. However, screening programs with colonoscopy, in average risk population, have been found to be cost-effective, and have reduced the number of expected CRC cases by around 20% and reduced the related costs for diagnosis and treatment (32). A prospective study on screening colonoscopy on FDRs aged 40-50 (33) and an analysis based on a microsimulation model (34) suggest early screening colonoscopy in subjects with family history of CRC may be cost-effective, especially if participation is high (33).

Our study has several limitations. Investigation includes only FDR without controls and was based on a retrospective review of colonoscopy records. Indeed, selection of controls is probably the most difficult problem in a screening study on risk of CRC in young FDRs based on colonoscopy, as people aged 40-45 do not routinely undergo colonoscopy except

when they are symptomatic. Another limitation is the lack of data regarding risk factors influencing the development of adenoma and CRC.

In conclusion, the present study confirms that advanced neoplasia risk in FDRs of CRC patients is high, especially in men. A relevant risk is evident in subjects <50 years and seems to justify starting screening before than 45 years. As advanced neoplasia frequently develops in the proximal colon, full early colonoscopy should be considered as the procedure of choice for screening in subjects with a family history of CRC .

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Table 1 Endoscopic/histological findings in 464 first-degree relatives of patients with colorectal cancer screened by colonoscopy.

Findings	Subjects	(%)	95% CI
Cancer	3	(0.6)	0.13 – 1.89
Advanced (high-risk) Adenoma	30	(6.4)	4.36 – 9.23
≥10 mm	27	(6)	4.01 – 8.72
Villous component	11	(2.3)	1.18 – 4.24
High-grade dysplasia	8	(1.7)	0.74 – 3.39
Low-risk Adenoma	54	(11.6)	8.74 – 15.18
Hyperplastic Polyp	41	(9)	6.52 – 12.23
No lesion	336	(72.4)	64.88 – 80.59
Total	464	(100)	

CI: Confidence Interval

Table 2 Distribution of adenoma and advanced adenoma along the colon and rectum in 464 first-degree relatives of patients with colorectal cancer.

Lesion	n	Right Colon n	(%)	Transverse n	(%)	Descending Sigma-Rectum n	(%)
Adenoma	118 (15)	41 46	(35) (39)	13	(11)	18	
Advanced Adenoma	38 (18)	14 14	(37) (37)	3	(8)	7	

Right colon includes caecum, ascending colon and hepatic flexure

Descending colon includes splenic flexure

Table 3. Prevalence of adenoma, advanced adenoma and colorectal cancer in study population according to gender.

	Subjects					
	Males (n=191)		Females (n=273)			
Lesion	n	(%)	n	(%)	*P*	Odds Ratio (95% CI)
Adenoma	42	(22)	42	(15.4)	= 0.07	1.55 (0.96 - 2.49)
Advanced Adenoma	18	(9.4)	12	(4.3)	= 0.03	2.26 (1.06 - 4.81)
Colorectal Cancer	1	(0.5)	2	(0.7)	= 0.78	0.71 (0.06 - 7.92)

CI: Confidence Interval

Table 4. Adenoma and advanced adenoma in first-degree relatives of patients with CRC estimated in different studies.

				Estimated Prevalence (%)			
				Any Age		40-49 Age	
Author (Ref.)	Year	Type of study	FDRs/Controls	A	AA	A	AA
Pariente (24)	1998	Prospective	185/370	23.2/17.3	10.8/4.9	n.d.	n.d.
Menges (25)	2006	Prospective	228/220	-	-	18.9/5.3	8.2/2.3
Bujanda (28)	2007	Prospective	107/ -	n.d.	8.4	n.d.	n.d.
Pezzoli (26)	2007	Prospective	562/ -	21.7	13.3	n.d.	n.d.
Puente Gutierrez (12)	2011	Prospective	263/ -	24.7	17.1	n.d.	16.3
Tsai (17)	2011	Prospective	643/4324	n.d.	5.9/4.9	n.d.	n.d.
Gupta (20)	2011	Retrospective	640/ -	-	-	15.4	3.3
Armelao (27)	2011	Prospective	1252/765	22.1/24.0	11.3/6.5	n.d.	n.d.
Castiglione (30)	2012	Retrospective	578/4051	6.9/6.4	35.6/26.5	n.d.	n.d.

FDR = First-Degree Relative; A = Adenoma, AA = Advanced Adenoma; n.d. = not defined

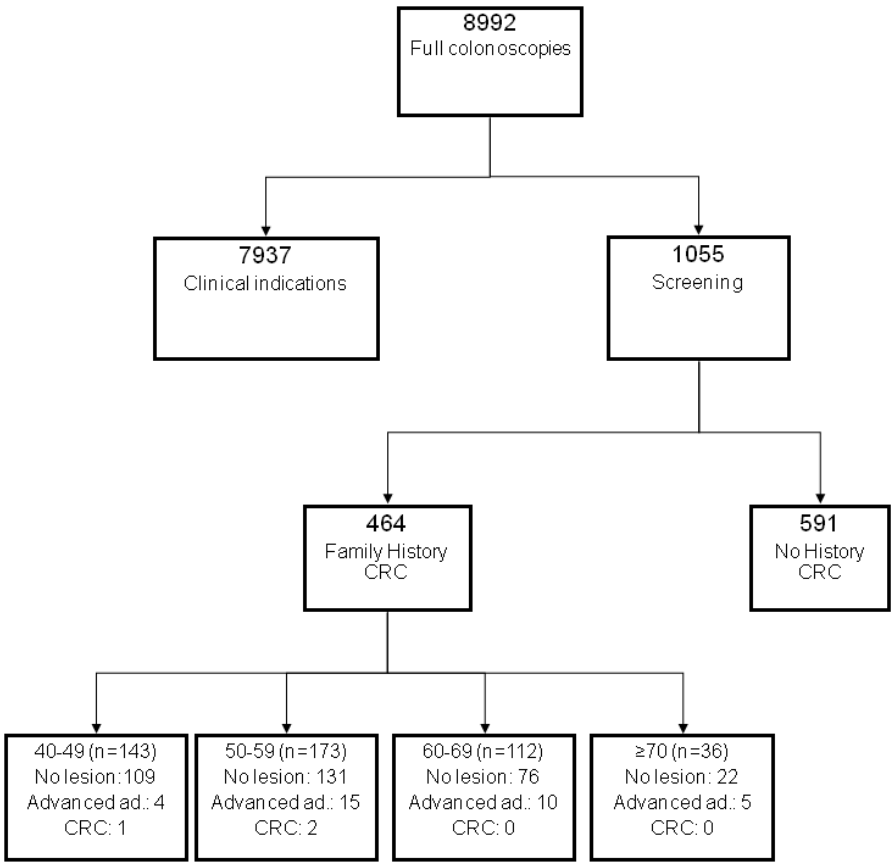

Figure 1. Flow diagram of all patients undergoing colonoscopy in the study period. Asymptomatic patients undergoing screening colonoscopy due to a family history of CRC were stratified in four age groups.

CRC: colorectal cancer

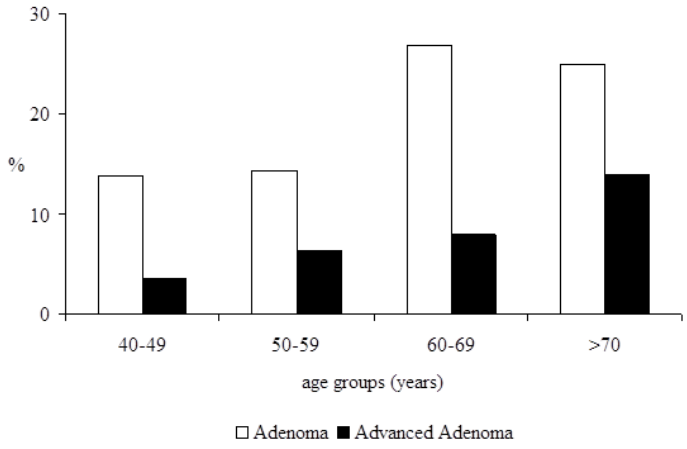

Figure 2. Prevalence of adenoma and advanced adenoma in different age groups