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Equivalency of Fecal Immunochemical Tests and Colonoscopy in Familial Colorectal Cancer Screening

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This article has an accompanying continuing medical education activity on page e16. Learning Objective: Upon completion of this test, successful learners will be able to identify individuals at higher risk of colorectal cancer (CRC) according to their family history and select the appropriate screening test.

Podcast interview: www.gastro.org/gastropodcast. Also available on iTunes.

BACKGROUND & AIMS: Colonoscopy is the recommended screening procedure for first-degree relatives of patients with colorectal cancer (CRC), but few studies have compared its efficacy for CRC detection with that of other screening strategies. We conducted a controlled randomized trial to compare the efficacy of repeated fecal immunochemical tests (FITs) and colonoscopy in detecting advanced neoplasia (advanced adenoma or CRC) in family members of patients with CRC. **METHODS:** In a prospective study, 1918 first-degree relatives of patients with CRC were randomly assigned (1:1 ratio) to receive a single colonoscopy examination or 3 FITs (1/year for 3 years; OC-Sensor; cutoff $\geq$10 μg hemoglobin/g feces, corresponding to 50 ng hemoglobin/mL buffer). The strategies were considered to be equivalent if the 95% confidence interval of the difference for the detection of advanced neoplasia was ±3%. Follow-up analyses were performed to identify false-negative FIT results and interval CRCs. **RESULTS:** Of all eligible asymptomatic first-degree relatives, 782 were included in the colonoscopy group and 784 in the FIT group. In the intention-to-screen analysis, advanced neoplasia was detected in 33 (4.2%) and 44 (5.6%) first-degree relatives in the FIT and colonoscopy groups, respectively (odds ratio = 1.41; 95% confidence interval: 0.88–2.26; $P = .14$). In the per-protocol analysis, 28 first-degree relatives (3.9%) in the FIT group and 43 (5.8%) in the colonoscopy group had advanced neoplasia (odds ratio = 1.56; 95% confidence interval: 0.95–2.56; $P = .08$). FIT missed 16 of 41 advanced adenomas but no CRCs. The FIT strategy required endoscopic evaluation of 4-fold fewer individuals to detect 1 advanced neoplasia than the colonoscopy strategy. **CONCLUSIONS:** Repeated FIT screening (1/year for 3 years) detected all CRCs and proved equivalent to colonoscopy in detecting advanced neoplasia in first-degree relatives of patients with CRC. This strategy should be considered for populations where compliance with FITs is higher than with colonoscopy. ClinicalTrials.gov number: NCT01075633 (COLONFAM Study).

Keywords: Familial Colorectal Cancer; Colon Cancer; Diagnostic Yield; Colonoscopy Resources.

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First-degree relatives of patients with nonsyndromic colorectal cancer (CRC) are at higher risk of developing CRC than the general population.[1,2] Personal risk in these individuals has mostly been related to the age of the index case at diagnosis, degree of kinship, and number of relatives affected. Having a first-degree relative with CRC diagnosed after the age of 60 years is associated with an almost 2-fold increase in personal risk,[3] and this increases to 4-fold when CRC in the index case is diagnosed before the age of 55 years.[1,4] In addition, the risk of developing advanced adenoma or CRC is about 3-fold higher if a sibling is affected[5,6] and even higher when there are 2 or more first-degree relatives with CRC,[1,2] regardless of age at diagnosis. Based on this evidence, current practice guidelines recommend that subjects with CRC familial aggregation should be subject to more intensive screening strategies than the average-risk population. Although there is no uniform approach among scientific societies, most

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Abbreviations used in this paper: CI, confidence interval; CRC, colorectal cancer; FIT, fecal immunochemical testing; Hb, hemoglobin; OR, odds ratio.

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recommend colonoscopy every 5 years, starting at the age of 40, or 10 years younger than the index case at diagnosis.[7–10] These recommendations are based on empirical evidence, as no study has clearly demonstrated the efficacy of this policy to reduce CRC mortality or incidence in this population. However, the efficacy of colonoscopy screening in asymptomatic first-degree relatives of patients with CRC is clearly hampered by suboptimal compliance.[11] Two major factors contribute to this low screening uptake. First, screening in these individuals is mostly opportunistic, as they are currently excluded from population-based programs in most countries; and second, there is ample evidence showing underutilization of colonoscopy at the recommended intervals in this population.[12–17]

Tentative solutions to improve screening uptake in familial CRC include incorporating these individuals in average-risk population-based programs, as recently recommended by the European Guidelines,[18] and/or offering them alternative screening strategies with inferior detection yield but better acceptance than colonoscopy. In this regard, observational studies have shown that fecal immunochemical testing (FIT) has acceptable performance for detecting colorectal neoplasia in asymptomatic first-degree relatives of patients with CRC. Although randomized controlled trials on the efficacy of FIT vs colonoscopy in familial CRC are lacking, observational studies suggest that FIT has acceptable performance for detecting advanced neoplasia (advanced adenoma or CRC) in asymptomatic first-degree relatives of patients with CRC.[19,20] In addition, a recent study suggested that using FIT in the intervals of surveillance colonoscopies is useful to detect missed or rapidly developing colorectal neoplasms in this moderate-risk population.[21] All together, these data support the notion that FIT screening could be an alternative strategy to colonoscopy in the familial-risk population, with better screening uptake and acceptable performance.

We hypothesized that repeated FIT screening is equivalent to one-time colonoscopy for detecting advanced colorectal neoplasms in familial CRC. We therefore conducted a controlled randomized trial to compare the efficacy of annual FIT vs one-time colonoscopy for detecting advanced neoplasia in asymptomatic first-degree relatives of patients with CRC.

Methods

Study Population

Between January 2006 and December 2010, consecutive first-degree relatives (parents, siblings, or offspring) of patients with nonsyndromic CRC referred for screening to the high-risk CRC clinic of the University Hospital of the Canary Islands, were assessed for enrollment. This outpatient clinic coordinates the diagnosis and surveillance of patients with hereditary CRC syndromes, screening of first-degree relatives of nonsyndromic index cases and surveillance of patients with advanced colorectal neoplasia in a health area serving approximately 375,000 inhabitants. Therefore, first-degree relatives referred for screening came either from family doctors or gastroenterologists attending the reference health area or from the admissions department of the reference hospital, which provided an appointment for CRC index cases after surgical or oncologic treatment.

First-degree relatives and index cases were personally interviewed by a gastroenterologist (MC, AZG, MH, or IA) and completed a questionnaire about demographic data, their own medical history, and their family history of cancer (ie, number of affected relatives, age, sex, place of residence, and Amsterdam II criteria).[22] The enrollment criteria were asymptomatic first-degree relatives aged 40 years or older or 10 years younger than the youngest case in the family, confirmed CRC diagnosis of the index cases and their respective relatives by written (endoscopic, histopathologic, or clinical) report or documented by their family doctors, and having signed the informed consent form. Exclusion criteria were having previously undergone CRC screening, belonging to a high-risk group due to hereditary CRC syndrome, having a personal history of inflammatory bowel disease or colorectal neoplasia (any adenoma or CRC), having symptoms suggestive of colorectal disease (ie, rectal bleeding, altered frequency of bowel movements, constitutional symptoms, and anemia), and suffering from a serious illness (disease with a mean life expectancy of <5 years or chronic disease with performance status ≥ 2).

Eligible first-degree relatives and index cases were given a leaflet with detailed information about the study and were asked to invite any first-degree relatives older than 18 years to participate in the study. We encouraged them to pass on to their first-degree relatives the leaflet about the study and to stimulate their participation. For this purpose, a contact telephone number was given to arrange appointments with the study coordinator.

All authors had access to the study data and reviewed and approved the final manuscript. The Clinical Research Ethics Committee of our center approved the study protocol, on condition that colonoscopy was offered to all subjects with a negative FIT result over 36 months. The trial, registered as ClinicalTrials.gov number NCT01075633, was checked for compliance with the CONSORT (Consolidated Standards of Reporting Trials) checklist.

Randomization and Masking

To ensure that all first-degree relatives of each index case received the same screening strategy, families were randomly assigned to receive annual FIT and colonoscopy in case of a positive result or one-time colonoscopy in a 1:1 ratio, using a computer-generated list, concealed in sequentially numbered, sealed, opaque envelopes. Randomization was performed before signed informed consent was obtained. Eligible first-degree relatives received detailed written and verbal information about the screening strategy to which they were assigned. The study design allowed for crossover between the 2 screening strategies in the event of participant disagreement with their initial group assignment.

Fecal Immunochemical Testing

Individuals assigned to the FIT group were provided with a single OC-Sensor (Eiken Chemical Co., Tokyo, Japan) kit per year during 3 consecutive years with automated analysis of results, as described previously.[23] No specific indications on diet or medication were given. Participants were asked to keep fecal samples at 4°C and return them within 5 days after sampling. The cutoff to indicate colonoscopy was established at ≥ 10 μg hemoglobin