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ORIGINAL ARTICLE

Colonoscopy screening for individuals aged 40–49 years with a family history of stomach cancer in Korea

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Abstract
Background For asymptomatic individuals aged 40–49 years, screening for colorectal cancer is recommended only if individuals are at an increased risk. A family history of colon cancer (FHCRC) is considered to increase risk, however, whether family history of stomach cancer (FHSC) increases the risk of adenoma is not well known. We aimed to see whether FHSC increases the risk in asymptomatic individuals aged 40–49 years in Korea.
Methods Among asymptomatic individual aged 40–49 years who underwent colonoscopy screening, risk of adenoma was assessed according to FHCRC or FHSC.
Results Of 3,160 individuals, male comprised 1,602 individuals (50.7%). FHCRC and FHSC was noticed in 163 (5.2%) and 227 (7.0%) individuals, respectively. Prevalence of adenoma was 31.9 %, 28.8%, and 22.3% for individuals with FHCRC, individuals with FHSC, and individuals without family history of cancer, respectively. FHSC was an independent risk factor for adenoma (odds ratio, 1.38; 95% confidence interval, 1.02–1.87, P=0.039) in asymptomatic individuals aged 40–49 years. Compared with individuals with FHCRC, individuals with FHSC showed no difference in risk for adenoma (P=0.347).
Conclusions As with individuals with FHCRC, individuals with FHSC might need to be considered as an individual with increased risk for adenoma. Therefore, earlier screening might be needed for asymptomatic individuals aged 40–49 years with FHSC in Korea.

Keywords Adenoma · Screening · Family history of stomach cancer

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Introduction

First-degree relatives of individuals with colorectal cancer (CRC) are known to have an increased risk of CRC [1–4]. Thus, screening for CRC is currently recommended to begin at age 50 years in populations at average risk, but individuals with a family history of CRC (FHCRC) are recommended to begin at age 40 years or 10 years before the youngest case in the immediate family [5].

Familial clustering may be due to a combination of environmental and genetic factors [6, 7]. While inheritance can determine the individual susceptibility to cancer, the environmental factor can influence expression or site of the cancer [2, 8]. A study of Korean and Dutch families with hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome) found a high frequency of stomach cancer and a lower incidence of endometrial cancer in the Korean HNPCC families compared with the Dutch families, which suggests that even strong genetic effect might be modified by environmental factors [8]. This finding implies that, although inherited susceptibility is important in the pathogenesis of colorectal neoplasia, local environmental factors should be considered in assessing the risk of CRC in families with cancer.

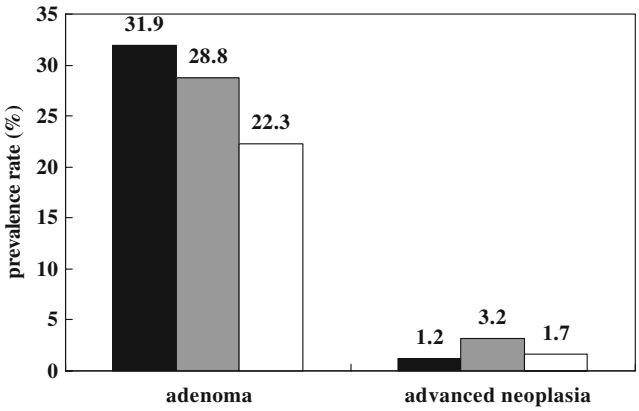

Fig. 1 Prevalence rate of adenoma and advanced neoplasia among three groups. Prevalence of adenoma in individuals with FHSC was higher when compared with individuals without FHC (P=0.025) and was not different when compared with individuals with FHCRC (P=0.516). There was no difference in incidence rate of advanced neoplasia among three groups (P=0.228). *Black*, *gray*, and *white* represent individuals with FHCRC, individuals with FHSC, and individuals without FHC, respectively

The incidence rate of CRC in Korea is increasing while stomach cancer is decreasing, which can be attributed to changes in environmental factors during the same time period [9]. But still, the stomach is the first commonest cancer site for men and the second commonest cancer site for women [9]. CRC is the fourth commonest cancer for men and the third commonest cancer for women [9]. In Korea, many individuals present with a family history of stomach cancer (FHSC). However, whether we should consider FHSC in assessing the risk of CRC or adenoma is not well known.

In this study, we aim to assess whether FHSC increases the risk of colonic neoplasia in asymptomatic individuals aged 40–49 years. We specifically focused on individuals aged 40–49 years because we wanted to find out whether individuals aged 40–49 years with FHSC would need earlier screening as in individuals with FHCRC. To address this issue, we compared the risk of colonic neoplasia among individuals with FHCRC, individuals with FHSC, and individuals without family history of colon or stomach cancer (FHC).

Methods

Study setting

Individuals enrolled in this study were selected from a total of 13,001 individuals who underwent screening colonoscopy at the endoscopy unit, Daehang Hospital, Seoul, Korea, between January 2007 and March 2008.

Three thousand one hundred sixty individuals aged 40–49 years were analyzed from those who successfully underwent total colonoscopy (defined as the insertion of the colonoscope to the cecum, by noting anatomic landmarks, ileocecal valve, and appendiceal orifice). We excluded individuals with hematochezia, sudden change in bowel habit, positive fecal occult blood test, anemia, and previous CRC screening history. We also excluded individuals with inflammatory bowel disease, evidence of familial polyposis or HNPCC, two or more first-degree relatives with cancer, one first-degree relative with cancer, other than colon or stomach cancer.

Just before the colonoscopy, individuals were asked to complete a questionnaire which also included information of cancer history on their relatives. A specialized nurse checked the questionnaires to eliminate errors, inconsistencies, and misunderstandings. Information regarding second-degree relatives was also collected. However, we only used family history regarding first-degree relatives because many did not know the actual site of cancer in their second-degree relatives. Thus, individuals with a first-degree relative with CRC or stomach cancer were regarded as having FHCRC or FHSC in this study.

Colonoscopy was performed after standard bowel preparation by participants at home. The colonoscopist recorded the extent of the examination and the quality of the bowel preparation. The size of polyps was estimated visually in situ. The findings on colonoscopy were categorized on the

Table 1 Baseline characteristics

	With HFCRC (N=163)	With HFSC (N=227)	Without HFC (N=2,770)	P value
Age (mean ± SD)	44.4±3.0	45.6±2.8	45.1±2.8	0.001
Sex (male/female)	89:74	124:98	1,389:1,386	0.15
Colonic neoplasia				
Tubular adenoma	52 (31.9%)	64 (28.2%)	618 (22.3%)	0.001
Advanced adenoma	2 (1.2%)	7 (3.1%)	46 (1.7%)	0.23
Colon cancer	0 (0%)	1 (0.4%)	2 (0.1%)	0.19

FHCRC Family history of colorectal cancer in first-degree relatives, *FHSC* family history of stomach cancer in first-degree relatives, *FHC* family history of cancer in first-degree relatives

Table 2 Independent risk factors with colonic neoplasia in individuals aged 40–49 years

Variables	Adenoma		Advanced neoplasia	
	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
Male sex	1.63 (1.38–1.93)	<0.001	1.85 (1.05 – 3.23)	0.032
FHCRC	1.61 (1.14–2.27)	0.007	0.72 (0.17–2.98)	0.648
FHSC	1.38 (1.02–1.87)	0.039	1.87 (0.83–4.20)	0.129

basis of the most advanced lesion identified. Advanced colonic neoplasia was defined as cancer or adenoma that was at least 10 mm in diameter, had high-grade dysplasia, had villous or tubulovillous histologic characteristics [10].

Statistical analysis

The chi-square test was used to assess difference of incidence rate between the three groups: individuals with FHCRC, individuals with FHSC, and individuals without FHC. Multivariate analysis was performed with the multiple logistic regression model. In our study, age, sex, FHCRC, and FHSC were considered independent variables. The presence or absence of adenoma or advanced colonic neoplasia was considered as a dependent variable. First, we analyzed whether FHSC is an independent risk factor for colonic neoplasia in asymptomatic individuals aged 40–49 years. Next, we assessed estimated odds ratio (OR) for FHSC and compared it to OR of individuals with FHCRC. *P* value of less than 0.05 was considered significant.

Results

Baseline characteristics

Of a total of 3,160 individuals, male comprised 1,602 (50.7%) individuals. Mean age was 45.1 years (standard deviation, 2.8). FHCRC was noticed in 163 (5.2%) individuals, and FHSC was noticed in 222 (7.0%) individuals. There was no difference in proportion of men in the prevalence of advanced adenoma and colon cancer among individuals with FHCRC, FHSC, and without FHC. Statistical difference was noticed for age (44.4±3.0, 45.6±2.8, and 45.1±2.8; $P=0.001$) and the incidence rate of tubular adenoma (31.9%, 28.2%, and 22.3%; $P=0.001$) for individuals with FHCRC, FHSC, and individuals without FHC, respectively.

Incidence of colonic neoplasia

Adenoma was found in 734 (23.2%) individuals. Advanced colonic neoplasia was found in 55 (1.7%) individuals, and three of 55 advanced neoplasias were cancer. Adenoma (27.5% vs. 18.8% for men vs. women, $P<0.001$) or advanced neoplasia (2.2% vs. 1.2% for men vs. women, $P=0.029$) was noticed more frequently in men than women.

Figure 1 shows the incidence rate of adenoma and advanced neoplasia among three groups. Adenoma was found more frequently in individuals with FHCRC ($P=0.004$) or in individuals with FHSC ($P=0.025$) compared with individuals without FHC. There was no difference in incidence rate of adenoma in individuals with FHSC compared with individuals with FHCRC ($P=0.516$). There was no difference in incidence rate of advanced colonic neoplasia among three groups ($P=0.228$; Table 1).

FHSC in assessing risk of colonic neoplasia

Male sex, FHCRC, and FHSC were independent risk factors for adenoma (Table 2). Male sex was only an independent factor associated with advanced adenoma. Compared with individuals with FHCRC, individuals with FHSC showed no difference in OR for adenoma or advanced adenoma, while individuals without FHC showed decreased OR for adenoma (Table 3).

Discussions

FHCRC is one of the well-known risk factors for colonic neoplasia [11–13]. However, limited data are available for risk of colonic neoplasia in families with history of other cancer. In studies performed in Norway and Poland, family history of other cancers (other than CRC) was not associated with adenoma occurrence, growth, or recurrence

Table 3 Difference in odds ratio of individuals compared with individuals with FHCRC

Variables	Adenoma		Advanced neoplasia	
	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
Individuals with FHSC	0.81 (0.51–1.26)	0.347	2.07 (0.42–10.3)	0.374
Individuals without FHC	0.59 (0.42–0.84)	0.003	1.30 (0.31–5.43)	0.717

[14, 15]. However, although exact cancer sites for other cancers were not presented in these studies, other cancers consisted of cancers of any kind. Therefore, clinical importance of family history of other cancers from one specific site, especially cancer from gastrointestinal tract such as stomach cancer, may need further clarification.

In this study, we specifically focused on FHSC. The reason was that stomach cancer is prevalent cancer in Korea [9], and stomach cancer was more prevalent in Korean HNPCC families compared with Dutch families [8]. Our hypothesis was that (1) familial clustering can be influenced by environmental factors [7, 8], (2) environmental factors which caused stomach cancer in their parents' generation may cause colonic neoplasia in next generation, since the incidence rate of CRC is increasing in Korea while stomach cancer is decreasing [9], therefore, (3) individuals with inherited susceptibility might develop colorectal neoplasia earlier in their life for nowadays, whereas they might have developed stomach cancer if they were born a decade earlier.

In this study, we noticed that an FHSC was an independent risk factor for adenoma in asymptomatic individuals aged 40–49 years. The incidence rate of adenoma was higher than asymptomatic individuals aged 40–49 years at average risk (individuals without FHC) and was not different from asymptomatic individuals aged 40–49 years with increased risk (individuals with FHCRC). These findings suggest that asymptomatic individuals aged 40–49 years with FHSC are at increased risk for colonic neoplasia, and hence, earlier screening might be needed for them. Our findings also suggest that, in assessing the risk of colonic neoplasia, local environmental factors might need to be considered.

There was no difference in the risk for advanced neoplasia in regard to FHCRC and FHSC. However, the actual prevalence of advanced neoplasia in this study was very low (1.7%), making it statistically low-powered. A measure of caution is needed in interpreting this result. In our study, we also found that men were more likely to have adenoma or advanced neoplasia, which was consistent with other studies [15–17]. The prevalence of adenoma (23.2%) was higher than prevalence of adenoma in the USA (12%) [18], Poland (9.5%) [15], and Korea (9.5%) [17] in the same age group. However, inclusion criteria differed from one study to other. Study from the USA or Korea included only average-risk individuals [17, 18], and a study from Poland only included individuals with family history of cancer of any kind [15]. In the study from Korea, adenoma prevalence was adenoma of more than 5 mm of size, while we included adenoma of any size. Prevalence of advanced neoplasia in our study (1.7%) was slightly lower than in these studies (2%~3.4%) [15, 17, 18].

There are several limitations in interpreting our results. First, most of studied individuals were individuals who did not meet current recommendation for screening colonoscopy. The most common reasons for colonoscopy in this study were patient-wanted procedures or subtle symptoms that did not meet the exclusion criteria in this study. Individuals in our study can be highly selected individuals, so our results cannot be generalized to population-based screening programs. Second, we did not collect several known risk factors for adenoma such as smoking, alcohol, diet, medications, metabolic syndrome, and body mass index [17, 19]. High prevalence of adenoma in our study does not exclude a possibility that individuals in our study are selected individuals who have higher risk for adenoma in terms of smoking, alcohol, diet, etc. These uncontrolled risk factors could have biased our results. Nevertheless, our study is a relatively large-sized study, from which one would not expect there to be a large difference of these risk factors between three groups that would have a substantial impact on our findings.

In summary, among individuals aged 40–49 years, FHSC was an independent risk factor for adenoma, and individuals with FHSC had no difference in the risk for adenoma compared with individuals with FHCRC. As with individuals with FHCRC, individuals with FHSC might need to be considered as an individual with increased risk in Korea, and, hence, earlier screening might be needed. Further studies are warranted.

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