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Risk of diabetes in subjects with positive fecal immunochemical test: a nationwide population-based study

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Abstract

Risk of diabetes in subjects with positive fecal immunochemical test: a nationwide population-based study

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Background & aims: Positive fecal immunochemical test (FIT) result has been recently suggested as a risk factor for systemic inflammation besides colorectal cancer (CRC) screening. Diabetes can induce inflammation including gastrointestinal tract, but the etiology is unclear. We investigated the association between the FIT results and diabetes incidence.

Methods: From National Cancer Screening Program database, 7,946,393 individuals aged ≥50 years who underwent FIT for

CRC screening from January, 2009 to December, 2012 were enrolled. Primary outcome was the newly diagnosed diabetes on the basis of the International Classification of Disease 10th revision codes and administration of anti-diabetic medication during the follow-up period.

Results: During a follow-up of mean 6.5 years, the diabetes incidence were 11.97, 13.60, 14.53, and 16.82 per 1,000 person-years in the FIT negative, one-positive, two-positive, and three-positive groups, respectively. The HRs for diabetes incidence were 1.14 {95% confidence interval (CI) 1.12-1.16}, 1.21 (95% CI 1.16-1.27), and 1.40 (95% CI 1.28-1.55) in one-positive, two-positive, and three-positive FIT groups in comparison with FIT negative group, respectively. The impact was consistent in individuals without dyslipidemia {adjusted hazard ratio (aHR) 1.50 vs. 1.10, p for interaction =0.002} and those with normal FBG (aHR 1.60 vs. 1.17, p for interaction <0.001).

Conclusions: Positive FIT results are associated with significantly higher risk of diabetes. These results suggest that FIT can play a role not only as a screening tool of CRC, but also

as a surrogate marker of systemic inflammation, thus in increasing the diabetes risk.

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Keywords : fecal immunochemical test, diabetes, inflammation, surrogate marker, nationwide, population-based, cohort

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목 차

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Introduction

A positive test result of blood in feces implies a risk of developing colorectal cancer (CRC) or precancerous lesion such as adenomas (1). Fecal immunochemical test (FIT) is one of the tests that applies antibodies against human hemoglobin (Hb) and provides the evidence of occult blood in feces (2). It is widely used for CRC screening because of its convenience in numbers of test needed to confirm and preparation for test (3). It is well known that CRC screening with FIT reduces both incidence and mortality of CRC (4). In Korea, the National Cancer Screening Program (NCSP) had been developed in 2002 and offered an annual FIT to all Korean men and women over 50 years of age since 2004 (5).

As FIT has been proceeded for many years worldwide, positive FIT result has recently suggested as a risk factor for systemic inflammation besides colorectal neoplasia (6, 7). Diabetes is a serious and long-term disease, which is one of ten most common causes of death in adults. Prevalence of diabetes has increased, which 475 million people in worldwide had in 2017 (8). There are many risk factors for diabetes, such as family history, presence of abnormal immune system, age, obesity, physical inactivity, hypertension, and dyslipidemia. Diabetes is suggested to be associated with inflammation

including gastrointestinal tract, but the etiology of inflammation is still unclear (7). In addition, there is little research assessing the relationship between positive FIT result and the incidence of diabetes. Therefore, we investigated the association between the FIT results and diabetes risk in Korean general population.

Methods

Data sources and study population

The National Health Insurance Service (NHIS) is a public health insurance system that support most of Korean general population (approximately 97%). The database of the NHIS includes demographics, diagnosis of disease, medical treatment, laboratory data and so on.

We conducted a retrospective, nationwide population-based cohort study, using data from NCSP in NHI database. From this database, 7,946,393 individuals aged ≥50 years who underwent FIT for CRC screening from January 2009 to December 2012 were enrolled. Then, participants who did not undergo consecutive CRC screenings at least every 2 years, those with missing data, and those with fasting blood glucose (FBG) ≥ 126 mg/dL at health check-up database or diagnosed with diabetes prior to enrollment were excluded. A total of

1,193,149 participants were finally included as the study population and followed up until diabetes was diagnosed or December 2017. This study was approved by the Institutional Review Board of Seoul National University Hospital (IRB number, E-1906-008-1036).

Data collection

Data were investigated including age, sex, smoking status, alcohol consumption, income level, physical activity, presence of diabetes, hypertension, dyslipidemia, metabolic syndrome, lipid level, glucose level, body mass index (BMI), waist circumference, glomerular filtration rate (GFR).

Detailed information regarding smoking status, alcohol consumption, and physical activity of study participants was assessed via standardized self-reported questionnaires. Smoking status were classified as current, ex-, and non-smoker. Heavy drinkers were defined if the amount of alcohol exceeding 30g per day. Exercise was defined as 'yes' in case of moderate intensity for 30 minutes per day, at least 5 days per week or vigorous intensity for 20 minutes per day, at least 3 days per week.

Normal range of waist circumference was defined as less than 90 cm in men and 85 cm in woman. Obesity was defined as over 25kg/m2 in BMI according to the Asia-Pacific BMI criteria established by the Western Pacific Region of the World Health

Organization (9). Hypertension or dyslipidemia was diagnosed using laboratory data (systolic blood pressure ≥140 mm Hg and diastolic blood pressure ≥90 mm Hg; total cholesterol levels ≥240 mg/dL) or ICD code (ICD-10 code I10 to I15; or E78) with the list of prescribed medicine. Metabolic syndrome was defined as a combination of followings; hyperglycemia, central obesity, atherogenic dyslipidemia, and hypertension according to the National Cholesterol Education Program Expert Panel and Adult Treatment Panel III criteria.

FIT measurements

Subjects who underwent CRC screening sampled their stool as either a qualitative or a quantitative 1-day sampling method. They were educated to avoid contact with urine or water before sampling the stool. After sampling, the subjects submitted the sampled stool immediately or keep them in a refrigerator shortly before submission if they could not submit the samples immediately. There were various data of hospitals and the detailed kit were different. OC-Hemocatch Light kits (Eiken Chemical, Co., Tokyo, Japan) with a cut-off value as 50 nanograms of hemoglobin per milliliter of buffer (ng Hb/ml); FOB test kits (Humasis, Co., Seoul, Korea) with a cut-off value as 50 ng Hb/ml; ASAN Easy Test FOB kits (Asan Pharm, Co., Seoul, Korea) with a cut-off value as 50 ng Hb/ml; and SD Bioline FOB kits (SD, Co., Seoul, Korea) with a cut-off value as

30 ng Hb/ml were used for the qualitative method. OC-Sensor DIANA kits (Eiken Chemical, Co.) with a cut-off value as 100 ng Hb/ml; Hemo Tech NS-1000 kits (Alfresa Pharma, Co., Osaka, Japan) with a cut-off value as 40 ng Hb/ml; and Medex HM-JACK kits (Kyowa Chemical Industry, Co., Kagawa, Japan) with a cut-off value as 30 ng Hb/ml, were used for the quantitative method. The positivity of FIT results was defined with cut-off value of each test kit, as positive for above the point and negative for below the point (10).

Study endpoints

The primary outcome was the newly diagnosed diabetes which was identified on the basis of the International Classification of Disease 10th revision (ICD-10) codes E11, E12, E13, or E14 and administration of anti-diabetic medication during the follow-up period. The operational definition of diabetes as above was validated in previous study (11). Subjects who were diagnosed diabetes within 1 year from the index date were excluded because of the possibility not causally related to positive FIT results.

Statistical analysis

Data were analyzed using the Student's t-test for continuous variables with normality assumption and $\chi 2$ test for categorical variables. The incidence rate was calculated as the

number of newly diagnosed diabetes cases per 1000 person-years. The hazard ratio for the risk of diabetes in the positive FIT group was calculated after adjusting age, sex, smoking status, alcohol consumption, regular exercise, BMI, and FBG with Cox-proportional hazard models. The incidence rate of diabetes among each group was estimated with Kaplan-Meier analysis and the log-rank test. A p-value less than 0.05 was considered statistically significant. SAS version 9.3 (SAS institute, Cary, NC, USA) and SPSS version 25.0 (SPSS Inc, Chicago, IL, USA) were used for statistical analyses.

Results

Baseline characteristics of study population

Of a total of 1,193,149 individuals, 171,105 patients (14.3%) showed positive FIT results and were divided into 4 groups according to the number of positive FIT results: negative (n=1,022,044), one-positive (n=146,394), two-positive (n=20,895), and three-positive (n=3,816). The baseline characteristics are shown in Table 1. Participants with higher number of positive FIT results are more likely to be older, male, current smoker, and heavy alcoholics, have a higher value of BMI, weight, height, and waist circumference, and have lower rates of low income (all $p < 0.001$). In addition,

they tended to have more comorbidities, such as hypertension, dyslipidemia, and metabolic syndrome (all $p < 0.001$). However, subjects who exercise regularly were significantly lower in higher number of positive FIT results ($p < 0.001$).

Incidence of diabetes according to the number of positive FIT results

During a mean follow-up of 6.5 years, 94,635 incident cases of diabetes (7.9% of the total study population) were identified. The incidence rate of diabetes were 11.97, 13.60, 14.53, and 16.82 per 1,000 person-years in the FIT negative, one-positive, two-positive, and three-positive groups, respectively (Table 2). The cumulative risk of diabetes was gradually increased as the number of positive FIT results increased, and there was a significant different risk according to the frequency of FIT positivity (Figure 1).

The HRs for diabetes incidence were 1.14 (95% CI 1.12 – 1.16), 1.21 (95% CI 1.16 – 1.27), and 1.40 (95% CI 1.28 – 1.55) in one-positive, two-positive, and three-positive FIT groups in comparison with FIT negative group, respectively (log-rank $p < 0.001$, Table 2). Higher number of FIT positive results were significantly associated with the incidence of diabetes. Moreover, similar significant associations were also observed between the number of FIT positive results and diabetes incidence after adjusting for age, sex, smoking, alcohol

consumption, regular exercise, BMI, and FBG.

Subgroup analysis of diabetes incidence

In subgroup analysis, the trend of increase in incidence of diabetes with the increased number of FIT positive results was consistently observed in all subgroups. Among them, the impact of positive FIT results on the development of diabetes was more prominent in individuals without dyslipidemia (aHR 1.50 vs. 1.10, p for interaction = 0.002), those with normal FBG (< 100 mg/dL) (aHR 1.60 vs. 1.17, p for interaction <0.001) (Table 3).

As the FIT results and diabetes are both associated with malignancy such as colorectal cancer, we further stratified the total population according to the presence of cancers (all cancers including CRC), and analyzed the association between positive FIT results and the incidence of diabetes (Table 4). However, there was no significant effect of cancer on the diabetes incidence as the number of positive FIT results increased (p for interaction = 0.486).

Discussion

In this population-based study, we found that positive FIT

results were associated with significantly increased risk of diabetes and there was a linear relationship between the number of FIT positivity and incidence of diabetes. These results were consistent even after adjusting for well-known risk factors for diabetes including age, sex, and obesity. Our study also demonstrated a greater impact of positive FIT results on the incidence of diabetes in individuals with normal range of FBG and those without dyslipidemia.

The prevalence of diabetes is rapidly increasing in Asia-Pacific region which mainly attributed to a global increase in obesity (12). It has become a medical concern due to its long-term complications and economic burden. Recently, FIT, generally used as a tool for CRC screening, has been demonstrated to reflect colonic mucosal inflammation in inflammatory bowel disease, as well as systemic inflammation related to all-cause mortality (13, 14). Diabetes is also related to a chronic inflammatory environment, however, there were a few studies whether positive FIT results are correlated with diabetes risk and the results were inconsistent. A Japan cross-sectional study found that positive FOBT group had significantly higher HbA1c level than that of negative FOBT group even in subjects not receiving anti-diabetic medications (6). Another Taiwan cross-sectional study showed an increased tendency for FIT positivity in diabetic group compared to nondiabetic group (7). Our study, to the best of our knowledge, is the first

study to clarify the effect of positive FIT results on the development of diabetes in general population.

Several possible mechanisms might be involved in the associations between FIT positivity and diabetes incidence. First, hyperglycemia and advanced glycation end-products, which is one of by-product from hyperglycemia, can cause predisposing micro-/macroangiopathy. They can inhibit the synthesis of nitric oxide and induce oxidative stress(15). Increased levels of TNF-α, a key factor of angiogenesis, other cytokines including IL-1 and IL-6, and C-reactive protein are found in diabetes.(16) These series of changes in gastrointestinal tract consequently elicit microhemorrhage and make FIT results positive (17, 18). These findings suggest that diabetes itself can be a factor of systemic inflammation, especially in gut, by inducing generalized colonic inflammation (19) and a positive FIT result has a possibility to be a marker reflecting systemic inflammation.

Gut microbiome might provide another potential link between positive FIT results and diabetes. There are some studies that diabetes has significant effect on gut microbiome and gut barrier integrity (20, 21). Studies have shown that gut microbiota is significantly different between diabetic patients and healthy individuals that the proportion of *Firmicutes* and *Clostridium* was reduced and the levels of *Bacteroides*, *Escherichia coli* were increased in diabetic group (22).

Dysbiosis observed in type 2 diabetes patients activates low-grade chronic inflammation of islets, which may cause damage and dysfunction of islet β-cells (23). In addition, the metabolites from the gut microbes contribute to the gut barrier integrity. A compromised barrier leads to leakage of inflammatory mediators into systemic circulation and, therefore, increases insulin resistance (21).

On the other hand, many epidemiological studies reported an increased risk of cancer including stomach, colorectum, liver, pancreas, and kidney cancer in patients with diabetes (24). Hyperinsulinemia, hyperglycemia, and chronic inflammation have been implicated in increasing cancer risk through their influence on neoplastic process (25). Especially, type 2 diabetes significantly increased the risk for CRC (26) and higher HbA1c was associated with a higher prevalence of colorectal neoplasia (7). However, when we conducted subgroup analysis according to the presence of cancers, the increased risk for diabetes development showed consistent results regardless of the presence of all cancers including CRC. We could postulate that, besides CRC, FIT positivity itself could be an independent predictor for diabetes.

The most intriguing finding in this study was that the effect prediabetes and obesity on diabetes incidence in FIT positive populations were different. Prediabetes and obesity are two predominant risk factors for the diabetes development (27).

The association between FIT positivity and diabetes development was more prominent in those with normal FBG which could be explained that in subjects who already have prediabetes, the effect of high FBG is dominant compared to the effect of FIT positivity. In other words, baseline FBG has a stronger influence than positive FIT results on diabetes development. While, positive FIT results were consistently associated with diabetes risk in both obese and non-obese subgroups. Further studies are required to reveal the different impact of FIT positivity on the relationship between well-known risk factors and diabetes.

However, this study has some limitations. First, as the diagnosis of diabetes was defined only by ICD-10 codes and administration of anti-diabetic medications, subjects who satisfy postprandial diagnostic criteria for diabetes or did not visit a hospital during the study period could have been missed from our data. Second, we could not evaluate the correlation between positive FIT results and the HbA1c levels of diabetic populations, as the NHIS database did not provide the HbA1c levels. In addition, we could not obtain data regarding endoscopic findings or pathologic findings. Instead, all cancers including CRC could be identified using ICD-10 codes. Finally, due to its nature of a retrospective epidemiological study, it was not possible determine a causal relationship accurately.

Conclusion

In conclusion, participants with positive FIT results have significantly higher risk of diabetes compared with those with negative FIT results, after adjusting conventional risk factors. In addition, there was a dose-relationship between FIT positivity and incidence of diabetes. These results suggest that FIT can play a role not only as a screening tool of CRC, but also as a surrogate marker of systemic inflammatory condition and thus in increasing the diabetes risk.

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Table 1. Baseline characteristics of the study population

Characteristic	FIT negative (n=1022044)	FIT one-positive (n=146394)	FIT two-positive (n=20895)	FIT three-positive (n=3816)	p-value
Mean age (years)±SD	62.38±6.85	62.98±7.06	63.35±7.14	63.03±7.15	<0.0001
Male gender (%)	436025(42.66)	72789(49.72)	12153(58.16)	2551(66.85)	<.0001
Height (cm)	159.27±8.2	159.94±8.3	160.94±8.28	162.3±8.17	<.0001
Body weight (kg)	61±9.35	61.71±9.54	62.72±9.68	64.04±9.95	<.0001
BMI (kg/m^2)	24±2.86	24.08±2.88	24.16±2.88	24.25±2.93	<.0001
Waist circumference (cm)	81.49±8.06	82.24±8.09	83.08±8.1	83.72±8.12	<.0001
Smoking, current (%)	106631(10.43)	19239(13.14)	3308(15.83)	677(17.74)	<.0001
Alcohol consumption, heavy (%)	36054(3.53)	7058(4.82)	1360(6.51)	290(7.6)	<.0001
Exercise, regular (%)	517273(50.61)	71508(48.85)	10197(48.8)	2025(53.07)	<.0001
Hypertension (%)	426864(41.77)	66144(45.18)	10060(48.15)	1833(48.03)	<.0001
Dyslipidemia (%)	309576(30.29)	44993(30.73)	6468(30.95)	1220(31.97)	0.0002
Laboratory findings					
FBG (mg/dL)	94.99±10.9	95.23±11.24	95.42±11.56	94.62±12.47	<.0001
GFR (mL/min/1.73m^2)	84.97±31.82	84.45±29.61	84.22±26.67	84.76±36.28	<.0001
HDL (mg/dL)	54.83±14.81	54.51±14.97	54.29±14.86	55.03±15.5	<.0001
LDL (mg/dL)	120.66±33.74	119.51±34.35	118.03±34.9	117.73±34.55	<.0001
TG (mg/dL)	113.13±0.11	116.03±0.30	118.47±0.83	118.03±1.98	<.0001

FIT, fecal immunochemical test; SD, standard deviation; BMI, body mass index; FBG, fasting blood glucose; GFR, glomerular filtration rate; HDL, high density lipoproteins; LDL, low density lipoproteins; TG, triglyceride.

Table 2. Incidence of diabetes associated with fecal immunochemical test results

Number of positive FIT results	N	Diabetes	IR	HR (95%C.I)		
				Model 1 †	Model 2 ‡	Model 3 §
0	1022044	79399	11.97	1 ¶	1 ¶	1 ¶
1	146394	12876	13.60	1.14(1.12−1.16)	1.11(1.09−1.13)	1.08(1.06−1.10)
2	20895	1946	14.53	1.21(1.16−1.27)	1.17(1.11−1.22)	1.10(1.05−1.15)
3	3816	414	16.82	1.40(1.28−1.55)	1.35(1.23−1.49)	1.35(1.23−1.49)

FIT, fecal immunochemical test; N, number; IR, incidence rate (per 1000 person−years); HR, hazard ratio; CI, confidence intervals.
† not adjusted
‡ adjusted with age, sex
§ adjusted with age, sex, smoking status, alcohol consumption, regular exercise, body mass index, fasting blood glucose
¶ as reference value

Table 3. Subgroup analysis

Subgroup	Number of positive FIT results	HR(95%C.I)			p for interaction
		Model 1 †	Model 2 ‡	Model 3 §	
Age					0.0692
<65	0	1 ¶	1 ¶	1 ¶	
	1	1.14(1.11-1.16)	1.12(1.09-1.15)	1.08(1.06-1.11)	
	2	1.15(1.08-1.23)	1.11(1.04-1.18)	1.04(0.98-1.11)	
	3	1.39(1.22-1.59)	1.33(1.16-1.51)	1.28(1.12-1.46)	
≥65	0	1 ¶	1 ¶	1 ¶	
	1	1.10(1.07-1.13)	1.10(1.07-1.13)	1.07(1.04-1.10)	
	2	1.23(1.15-1.31)	1.23(1.15-1.31)	1.16(1.09-1.24)	
	3	1.38(1.20-1.59)	1.38(1.20-1.59)	1.42(1.24-1.64)	
Sex					0.2127
Male	0	1 ¶	1 ¶	1 ¶	
	1	1.12(1.10-1.15)	1.11(1.09-1.14)	1.08(1.05-1.11)	
	2	1.21(1.14-1.28)	1.20(1.13-1.27)	1.14(1.08-1.21)	
	3	1.31(1.17-1.48)	1.31(1.17-1.48)	1.32(1.17-1.48)	
Female	0	1 ¶	1 ¶	1 ¶	
	1	1.13(1.10-1.16)	1.10(1.07-1.13)	1.07(1.04-1.10)	
	2	1.16(1.08-1.24)	1.11(1.03-1.19)	1.04(0.96-1.12)	
	3	1.46(1.23-1.73)	1.43(1.21-1.69)	1.42(1.20-1.68)	
Obesity					0.0029
No	0	1 ¶	1 ¶	1 ¶	
	1	1.15(1.12-1.18)	1.11(1.08-1.14)	1.08(1.06-1.11)	
	2	1.30(1.22-1.38)	1.21(1.14-1.29)	1.17(1.10-1.25)	
	3	1.40(1.22-1.62)	1.30(1.13-1.50)	1.32(1.14-1.52)	
Yes	0	1 ¶	1 ¶	1 ¶	
	1	1.10(1.07-1.13)	1.09(1.06-1.12)	1.07(1.04-1.10)	
	2	1.09(1.03-1.17)	1.08(1.01-1.15)	1.03(0.97-1.10)	
	3	1.31(1.15-1.50)	1.30(1.14-1.49)	1.37(1.20-1.56)	
Hypertension					0.9756
No	0	1 ¶	1 ¶	1 ¶	
	1	1.11(1.08-1.15)	1.09(1.06-1.12)	1.06(1.03-1.09)	
	2	1.18(1.10-1.27)	1.13(1.05-1.22)	1.08(1.00-1.16)	
	3	1.44(1.23-1.67)	1.37(1.18-1.60)	1.35(1.15-1.57)	

Yes	0	1¶	1¶	1¶	
	1	1.11(1.08-1.14)	1.10(1.07-1.13)	1.08(1.05-1.10)	
	2	1.12(1.09-1.23)	1.14(1.08-1.21)	1.10(1.04-1.16)	
	3	1.30(1.15-1.47)	1.29(1.14-1.46)	1.32(1.17-1.50)	
Dyslipidemia					0.0016
No	0	1¶	1¶	1¶	
	1	1.16(1.13-1.18)	1.12(1.09-1.15)	1.09(1.06-1.11)	
	2	1.20(1.13-1.27)	1.13(1.06-1.20)	1.07(1.01-1.14)	
	3	1.59(1.41-1.79)	1.48(1.31-1.67)	1.50(1.33-1.70)	
Yes	0	1¶	1¶	1¶	
	1	1.10(1.07-1.13)	1.08(1.05-1.11)	1.05(1.02-1.08)	
	2	1.23(1.15-1.31)	1.18(1.10-1.26)	1.11(1.04-1.19)	
	3	1.13(0.97-1.33)	1.10(0.94-1.29)	1.10(0.93-1.29)	
FBG					<.0001
<100	0	1¶	1¶	1¶	
	1	1.18(1.14-1.21)	1.14(1.11-1.18)	1.13(1.09-1.16)	
	2	1.38(1.28-1.48)	1.31(1.22-1.41)	1.28(1.19-1.37)	
	3	1.67(1.44-1.94)	1.60(1.38-1.85)	1.60(1.38-1.86)	
≥100	0	1¶	1¶	1¶	
	1	1.07(1.04-1.09)	1.07(1.04-1.09)	1.04(1.02-1.07)	
	2	1.05(0.99-1.11)	1.05(0.99-1.11)	1.00(0.94-1.06)	
	3	1.19(1.05-1.35)	1.21(1.06-1.37)	1.16(1.03-1.33)	
Current Smoker					0.0299
No	0	1¶	1¶	1¶	
	1	1.12(1.10-1.15)	1.10(1.08-1.12)	1.07(1.04-1.09)	
	2	1.22(1.16-1.28)	1.18(1.12-1.24)	1.12(1.07-1.18)	
	3	1.43(1.28-1.59)	1.38(1.24-1.54)	1.38(1.24-1.54)	
Yes	0	1¶	1¶	1¶	
	1	1.15(1.09-1.20)	1.14(1.09-1.19)	1.13(1.08-1.18)	
	2	1.08(0.97-1.20)	1.07(0.96-1.19)	1.02(0.91-1.14)	
	3	1.17(0.94-1.46)	1.18(0.94-1.47)	1.23(0.99-1.54)	
Heavy Drinker					0.7656
No	0	1¶	1¶	1¶	
	1	1.13(1.11-1.15)	1.10(1.08-1.13)	1.07(1.05-1.09)	
	2	1.21(1.16-1.27)	1.16(1.11-1.22)	1.10(1.05-1.15)	
	3	1.40(1.27-1.55)	1.35(1.22-1.49)	1.36(1.23-1.51)	
Yes	0	1¶	1¶	1¶	

	1	1.17(1.08−1.26)	1.15(1.07−1.25)	1.12(1.03−1.21)	
	2	1.18(1.00−1.39)	1.16(0.98−1.37)	1.10(0.93−1.30)	
	3	1.30(0.93−1.83)	1.30(0.93−1.83)	1.23(0.88−1.72)	
Regular exercise					0.2294
No	0	1¶	1¶	1¶	
	1	1.12(1.09−1.15)	1.09(1.06−1.12)	1.06(1.04−1.09)	
	2	1.20(1.12−1.27)	1.15(1.08−1.22)	1.08(1.01−1.14)	
	3	1.50(1.31−1.71)	1.44(1.26−1.65)	1.42(1.25−1.62)	
Yes	0	1¶	1¶	1¶	
	1	1.15(1.12−1.18)	1.12(1.09−1.16)	1.09(1.06−1.12)	
	2	1.23(1.15−1.32)	1.18(1.11−1.26)	1.13(1.06−1.21)	
	3	1.32(1.15−1.52)	1.26(1.10−1.45)	1.28(1.11−1.47)	

FIT, fecal immunochemical test; N, number; IR, incidence rate (per 1000 person−years); HR, hazard ratio; CI, confidence intervals; FBG, fasting blood glucose.
† not adjusted
‡ adjusted with age, sex
§ adjusted with age, sex, smoking status, alcohol consumption, regular exercise, body mass index, fasting blood glucose
¶ as reference value

Table 4. Stratification according to history of malignancy

History of malignancy	Number of positive FIT results	N	Diabetes	IR	HR(95%C.I)			p for interaction
					Model 1 †	Model 2 ‡	Model 3 §	
No	0	988014	76426	11.89	1 ¶	1 ¶	1 ¶	0.4857
	1	140056	12242	13.47	1.13(1.11–1.15)	1.11(1.09–1.13)	1.07(1.05–1.09)	
	2	19896	1824	14.25	1.20(1.14–1.26)	1.15(1.10–1.21)	1.09(1.04–1.14)	
	3	3643	399	16.93	1.42(1.29–1.57)	1.37(1.24–1.51)	1.36(1.24–1.50)	
Yes	0	34030	2973	14.23	1 ¶	1 ¶	1 ¶	
	1	6338	634	16.52	1.16(1.07–1.27)	1.11(1.02–1.21)	1.07(0.98–1.16)	
	2	999	122	20.47	1.44(1.21–1.73)	1.33(1.11–1.59)	1.22(1.02–1.46)	
	3	173	15	14.45	1.02(0.61–1.69)	0.95(0.57–1.58)	1.01(0.61–1.68)	

FIT, fecal immunochemical test; N, number; IR, incidence rate (per 1000 person-years); HR, hazard ratio; CI, confidence intervals.

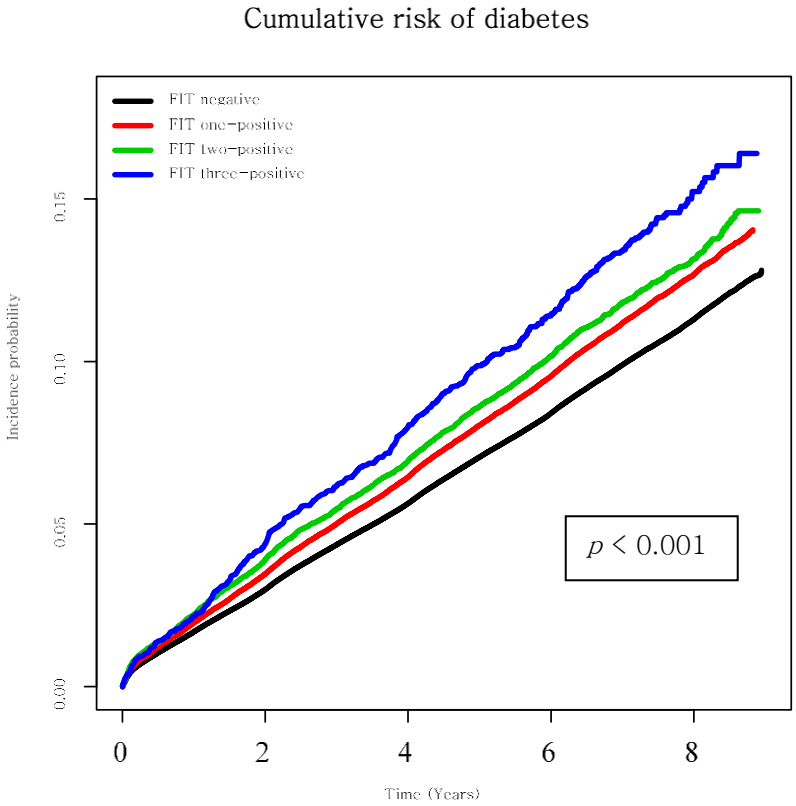
† not adjusted

‡ adjusted with age, sex

§ adjusted with age, sex, smoking status, alcohol consumption, regular exercise, body mass index, fasting blood glucose

¶ as reference value

Figure 1. Cumulative risk of diabetes associated with the number of fecal immunochemical test results



요약(국문초록)

목적: 최근 대변잠혈반응검사가 대장암의 선별검사로써의 역할 뿐 아니라 전신의 염증 상태를 나타내는 지표로써의 가능성도 제시되고 있다. 당뇨병은 장을 포함하여 신체 전반에 염증과 연관이 있다고 알려져 있지만, 그 원인은 뚜렷하게 밝혀지지 않았다. 이에 본 연구에서는 대변잠혈반응검사와 당뇨병 발병률 사이의 연관성을 조사하였다.

방법: 2009년 1월부터 2012년 12월까지 대장암 검진을 위해 대변잠혈반응검사를 시행한 50세 이상의 성인 7,946,393명의 자료를 국가암검진프로그램의 데이터베이스에서 추출하여 후향적으로 검토하였다. 당뇨병의 발병은 추적관찰기간 동안 국제질병분류 10차 개정코드에 근거하여 새로이 진단된 경우와 당뇨병약제를 투약한 경우로 평가하였다.

결과: 평균 6.5년의 추적 기간 동안 관찰한 당뇨병 발병률을 대변잠혈반응검사 결과의 양성 횟수에 따라 나누어 분석하였다. 대변잠혈반응검사의 결과가 음성, 1회 양성, 2회 양성, 3회 양성인 그룹으로 나누어 살펴보았을 때, 각각 1년에 1000명당 11.97, 13.60, 14.53, 16.82명 발병하였다. 각 그룹의 위험비는 음성인 그룹을 기준으로 하여 차례대로 1.14 (95% 신뢰구간 1.12-1.16), 1.21 (95% 신뢰구간 1.16-1.27), 1.40 (95% 신뢰구간 1.28-1.55)로 나타났다. 이러한 경향은 하위그룹 분석 시 이상지질혈증이 없는 군 (조정위험비 1.50 대 1.10, 교호작용의 p값 = 0.002)과 공복혈당이 정상인 군 (조정위험비 1.60 대 1.12,

교호작용의 p값 < 0.001)에서도 일관되게 관찰되었다.

결론: 대변잠혈반응검사가 양성인 경우, 높은 당뇨병 발병률과 유의한 관련이 있는 것으로 보인다. 이러한 결과는 대변잠혈반응검사가 대장암의 선별검사만이 아니라 더 나아가 전신적인 염증 상태를 나타낼 수 있는 대리지표가 될 수 있는 가능성을 시사한다.

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주요어 : 대변잠혈반응검사, 당뇨병, 염증, 대리지표, 전국인구기반, 코호트 연구.

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