Occult Blood in Feces Is Associated with Increased Risk of Psoriasis

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\textbf{Keywords}
Fecal immunochemistry test · Fecal occult blood · Psoriasis · Population-based study

\textbf{Abstract}

\textbf{Background:} The fecal immunochemistry test (FIT) has been proposed as a surrogate marker of intestinal inflammation. Psoriasis is a chronic inflammatory skin disease that is linked to underlying systemic inflammatory conditions, including inflammatory bowel disease. \textbf{Methods:} We investigated the association between occult blood in feces and the risk of psoriasis using data from the National Health Insurance System. This study was conducted involving 1,395,147 individuals who underwent health examinations from January 2009 to December 2012 and were followed up until the end of 2017. \textbf{Results:} The incidence of psoriasis (per 1,000 person-years) was 3.76 versus 4.14 (FIT-negative versus FIT-positive group) during a median follow-up of 6.68 years. In the multivariable-adjusted model, the hazard ratios for psoriasis were 1.03 for one positive FIT result, 1.12 for two positive FIT results, and 1.34 for three positive FIT results compared with negative FIT results. \textbf{Conclusion:} The risk of psoriasis was significantly increased in patients with positive FIT results compared to the FIT-negative population.

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\textbf{Introduction}

The fecal occult blood test screens for colorectal cancer (CRC) by detecting small amounts of blood in the stool [1]. The fecal immunochemistry test (FIT), which uses antibodies against human hemoglobin (Hb) to estimate the fecal Hb concentration, is an increasingly popular method for CRC screening because of its effectiveness, high sensitivity, low cost, and convenience (it can be delivered by mail) [2, 3]. In South Korea, the National Cancer Screening Program (NCSP) offers an annual FIT to all individuals older than 50 years [4, 5]. A positive FIT result indicates a high risk of having or developing CRC or precancerous lesions. It follows that asymptomatic persons with positive FIT results have a higher risk of CRC mortality than those with negative results. The concentration of Hb in feces is reported to correlate with endoscopic inflammation in patients with Crohn’s disease or ulcerative colitis, suggesting that Hb in feces could be predictive of gut inflammation independently of its association with CRC [6, 7]. Furthermore, subclinical colonic inflammation reflects the systemic inflammatory status and can result in occult bleeding [8].

Psoriasis, which affects approximately 2–3% of the population [9], is a chronic inflammatory skin disease characterized by inflammatory reactions, immune ab-
normalities, and vascular abnormalities [10, 11]. It has been recognized as part of a systemic inflammatory condition linked to diabetes mellitus (DM), obesity, cardiovascular disease, and metabolic syndrome [12, 13]. A correlation between psoriasis and gastrointestinal disorders, particularly inflammatory bowel disease (IBD), has been frequently reported, and several studies have suggested a causal link between psoriasis and gut inflammation [14]. Until now, the relationship between occult blood in feces and skin disease has not been explored in detail. Therefore, we investigated the association between the FIT result and the risk of psoriasis in a South Korean population undergoing an annual health checkup using the database of the South Korean National Health Insurance System (NHIS).

Methods

Data Sources

This retrospective nationwide population-based study was performed using the NHIS database, which covers approximately 97.2% of the population of South Korea. The NHIS reviews in- and outpatient claims sent from healthcare institutions. The NHIS database includes information on patient age, sex, diagnoses, and comorbidities based on the International Classification of Diseases, tenth revision (ICD-10) as well as records of prescriptions, procedures, and prescribed drugs. Enrollees in the NHIS are assigned unique identification codes and are recommended to have a health checkup at least every 2 years.

Study Population

The NCSP provides a single annual FIT to all South Korean adults above 50 years of age, and subjects with a positive FIT result are recommended follow-up examination with either colonoscopy or double contrast barium enema [15]. From the NHIS database, we enrolled patients aged 50 years or older who underwent CRC screening as part of the NCSP from January 2009 to December 2012. We excluded subjects with missing data on at least one variable and those who did not undergo consecutive CRC screenings at least every 2 years. To avoid confounding by preexisting diseases, those with a history of psoriasis (based on the ICD-10 code) before the index year were also excluded. Finally, 1,395,147 subjects were included in the analysis. The study population was followed up until the end of 2017.

FIT Measurements

FITs were processed using a 1-day qualitative or quantitative sampling method. The participants were instructed to collect fecal samples before they contacted urine or water. The participants were also instructed to return the fecal samples immediately or to store them briefly in a home refrigerator before returning them. For the qualitative method, OC-Hemocatch Light kits (Eiken Chemical, Co., Tokyo, Japan), with a cutoff of 50 ng/mL, FOB test kits (Humasis, Co., Seoul, South Korea), with a cutoff of 50 ng/mL, ASAN Easy Test FOB kits (Asan Pharm, Co., Seoul, South Korea), with a cutoff of 50 ng/mL, and SD Bioline FOB kits (SD, Co., Seoul, South Korea), with a cutoff of 30 ng/mL, were used. For the quantitative method, OC-Sensor DIANA kits (Eiken Chemical, Co.), with a cutoff of 100 ng/mL, Hemo Tech NS-1000 kits (Alfresa Pharma, Co., Osaka, Japan), with a cutoff of 40 ng/mL, and Medex HM-JACK kits (Kyowa Chemical Industry, Co., Kagawa, Japan), with a cutoff of 30 ng/mL, were used [16]. The results of FITs were categorized as negative or positive according to the cutoff points of the test kits. The primary outcome was newly diagnosed psoriasis. The patients in the study group who had developed psoriasis for the first time were identified based on the World Health Organization ICD-10 codes that represented psoriasis (L40*). The primary outcome was newly diagnosed psoriasis. The patients in the study group who had developed psoriasis for the first time were identified based on the World Health Organization ICD-10 codes that represented psoriasis (L40*). As a covariate, DM was defined as the presence of ICD-10 code (E10–E14) and the prescription of antidiabetic medications, or a fasting glucose level >126 mg/dL. Hypertension (HTN) was defined as the presence of ICD-10 codes (I10 or I11) and the prescription of antihypertensive agents, or systolic/diastolic blood pressure ≥140/90 mm Hg. Dyslipidemia was defined as the presence of ICD-10 code (E78) and the prescription of a lipid-lowering agent or a total cholesterol level ≥240 mg/dL. Metabolic syndrome was diagnosed based on the revised National Cholesterol Education Program – Adult Treatment Panel III criteria [17].

Statistical Analysis

Continuous variables were compared by Student’s t test and categorical variables by χ² test. Uni- and multivariate Cox proportional hazard regression analyses were performed to evaluate the association between occult blood in stool and psoriasis. Multivariable adjusted hazard ratios (aHRs) were calculated after adjusting for age, sex, smoking, exercise, and income. The cumulative risk of psoriasis during follow-up was analyzed by the Kaplan-Meier method, and the log-rank test was used to examine the effect of repetitive positive FIT results on psoriasis development. We tested the normality assumption of the data, and when the distribution of the continuous data was nonnormal, log transformation was applied to make data conform to normality. A p value <0.05 was considered indicative of statistical significance. Statistical analysis was performed using the Statistical Analysis System version 9.3 software (SAS Institute, Cary, NC, USA).

Results

Characteristics of the Study Population

A total of 1,395,147 individuals were included in the study. Among them, 204,180 patients (14.6%) had positive FIT results during a median follow-up period of 6.68 years. The baseline characteristics of the study population are shown in Table 1. The patients in the FIT-positive group were more likely to be older, male, current smokers, and heavy drinkers and to have a higher value for body mass index (BMI) and waist circumference, lower frequency of regular exercise, and lower income. The co-
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**Effect of Occult Blood in Stool on Psoriasis Incidence**

The incidence of psoriasis was 3.76 per 1,000 person-years in the FIT-negative group and 4.14 per 1,000 person-years in the FIT-positive group. The crude incidence of psoriasis increased gradually as the number of positive FIT results increased (4.04, 4.58, and 5.61 per 1,000 person-years in the one-, two-, and three-positive FIT groups, respectively). Compared to subjects with a negative FIT result, the probability of psoriasis increased in proportion to the number of positive FIT results (log-rank test, \(p < 0.0001\); Fig. 1).

The unadjusted HRs for psoriasis for the one-, two-, and three-positive FIT groups in comparison with the FIT-negative group were 1.074 (95% confidence interval [CI] 1.042–1.108), 1.216 (95% CI 1.132–1.307), and 1.495 (95% CI 1.278–1.734), respectively. The significant association remained after adjusting for age, sex, BMI, smoking, alcohol consumption, regular exercise, HTN, DM, and dyslipidemia. The number of positive FIT results was significantly associated with psoriasis development (aHR 1.029, 95% CI 0.997–1.061 for one positive result; aHR 1.118, 95% CI 1.04–1.201 for two positive results; and aHR 1.342, 95% CI 1.157–1.557 for three positive results) (Table 2).

Further sensitivity analysis was performed according to the CRC development and significant associations between the number of positive FIT results and the risk of psoriasis remain robust in subjects without CRC (aHR 1.343 vs. 0.969). In addition, individuals without IBD showed a stronger association between positive FIT re-

**Table 1. Baseline characteristics of the study population**

| FIT number       | 0 (n = 1,190,967) | 1 (n = 174,194) | 2 (n = 25,304) | 3 (n = 4,682) | \(p\) value |
|------------------|------------------|----------------|---------------|--------------|------------|
| Age, years       | 62.72±6.89       | 63.32±7.06     | 63.64±7.16    | 63.24±7.12   | <0.0001    |
| Male sex         | 524,671 (44.05%) | 89,198 (51.21%)| 15,051 (59.48%)| 3,160 (67.49%)| <0.0001    |
| BMI, kg/m\(^2\)  | 24.13±2.91       | 24.23±2.94     | 24.31±2.94    | 24.39±2.96   | <0.0001    |
| Waist circumference, cm | 82.06±8.18     | 82.89±8.23     | 83.69±8.2     | 84.3±8.13    | <0.0001    |
| Systolic BP, mm Hg | 125.85±14.98    | 126.54±15.12   | 127.18±15.12  | 126.91±14.5  | <0.0001    |
| Diastolic BP, mm Hg | 76.8±9.68       | 77.23±9.78     | 77.58±9.81    | 77.73±9.57   | 0.0285     |
| Fasting glucose, mg/dL | 101.1±22.33    | 101.98±23.41   | 102.83±24.36  | 102.59±26.19 | <0.0001    |
| Total cholesterol, mg/dL | 198.76±37.59   | 197.94±38.16   | 197.08±38.3   | 196.78±38.21 | <0.0001    |
| LDL cholesterol, mg/dL | 118.48±34.45   | 117.17±35.02   | 115.91±35.54  | 114.82±35.35 | <0.0001    |
| HDL cholesterol, mg/dL | 54.24±14.82    | 53.9±14.97     | 53.74±15.33   | 54.3±15.36   | <0.0001    |
| Triglyceride, mg/dL | 115.75 (115.64–115.86) | 119.08 (118.79–119.37) | 121.69 (120.91–122.48) | 121.36 (119.49–123.25) | <0.0001    |
| Smoking          |                  |                |               |              |            |
| None             | 847,573 (71.17%) | 116,033 (66.61%)| 15,592 (61.62%)| 2,812 (60.06%)| <0.0001    |
| Ex-smoker        | 214,853 (18.04%) | 34,622 (19.88%)| 5,615 (22.19%)| 1,023 (21.85%)|            |
| Current smoker   | 128,541 (10.79%) | 23,539 (13.51%)| 4,097 (16.19%)| 847 (18.09%)  |            |
| Alcohol consumption |              |                |               |              | <0.0001    |
| None             | 822,727 (69.08%) | 112,849 (64.78%)| 15,368 (60.73%)| 2,727 (58.24%)|            |
| Mild             | 323,613 (27.17%) | 52,416 (30.09%)| 8,166 (32.27%)| 1,576 (33.66%)|            |
| Heavy            | 44,627 (3.75%)  | 8,929 (5.13%)  | 1,770 (6.99%)  | 379 (8.09%)  |            |
| Regular exercise | 600,422 (50.41%) | 84,996 (48.79%)| 12,272 (48.5%)| 2,470 (52.7%)| <0.0001    |
| Low income*      | 299,661 (25.16%) | 45,141 (25.91%)| 6,542 (25.85%)| 1,131 (24.16%)| <0.0001    |
| Comorbidity      |                  |                |               |              |            |
| HTN              | 543,490 (45.63%) | 85,819 (49.27%)| 13,183 (52.1%)| 2,447 (52.26%)| <0.0001    |
| DM               | 184,798 (15.52%) | 29,805 (17.11%)| 4,731 (18.7%) | 919 (19.63%) | <0.0001    |
| Dyslipidemia     | 396,604 (33.3%)  | 59,287 (34.04%)| 8,600 (33.99%)| 1,652 (35.28%)| <0.0001    |
| Metabolic syndrome | 530,083 (44.51%) 81,807 (46.96%) | 12,354 (48.82%) | 2,284 (48.78%) | <0.0001    |

Data are expressed as mean ± standard deviation, median (25–75%), or \(n\) (%). BMI, body mass index; BP, blood pressure; DM, diabetes mellitus; FIT, fecal immunochemistry test; HDL, high-density lipoprotein; HTN, hypertension; LDL, low-density lipoprotein. * Household income <30% of the median.
results and psoriasis than those with IBD (aHR 1.345 vs. 0.831) (data not shown).

**Subgroup Analysis**

We evaluated the relative risk of psoriasis according to age, sex, BMI, and comorbidities (Table 3). The association of one or more positive FIT results with the risk of psoriasis was nonsignificantly greater in middle-aged subjects (50–64 years), females, those with a BMI <25 kg/m², subjects with DM, and those without dyslipidemia. The association of FIT positivity with the incidence of psoriasis was significantly greater in subjects without HTN (aHR 1.602, 95% CI 1.31–1.958) than in those with HTN (aHR 1.115, 95% CI 0.894–1.391, p for interaction = 0.0318).

An analysis stratified by age, sex, and presence or absence of DM, HTN, or dyslipidemia was conducted. Higher aHRs for developing Alzheimer’s disease were ob-

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**Table 2. Association between FIT results and incidence of psoriasis**

| Group           | Patients, n | Events, n | Duration, person-years | Incidence rate per 1,000 person-years | HR (95% CI) model 1<sup>a</sup> | HR (95% CI) model 2<sup>b</sup> | HR (95% CI) model 3<sup>c</sup> |
|-----------------|-------------|-----------|------------------------|---------------------------------------|-------------------------------|-------------------------------|-------------------------------|
| Negative FIT    | 1,190,967   | 29,669    | 7,889,814.85           | 3.76                                  | 1 (reference)                 | 1 (reference)                 | 1 (reference)                 |
| Positive FIT    | 204,180     | 5,598     | 1,351,025.35           | 4.14                                  | 1.101 (1.07–1.133)            | 1.054 (1.024–1.085)           | 1.047 (1.018–1.078)           |
| Positive FITs, n|             |           |                        |                                       |                               |                               |                               |
| 1               | 174,194     | 4,662     | 1,153,479.27           | 4.042                                 | 1.074 (1.042–1.108)           | 1.034 (1.003–1.067)           | 1.029 (0.997–1.061)           |
| 2               | 25,304      | 761       | 166,356.77             | 4.575                                 | 1.216 (1.132–1.307)           | 1.13 (1.051–1.214)            | 1.118 (1.04–1.201)            |
| 3               | 4,682       | 175       | 31,189.32              | 5.611                                 | 1.495 (1.289–1.734)           | 1.353 (1.166–1.569)           | 1.342 (1.157–1.557)           |

BMI, body mass index; CI, confidence interval; DM, diabetes mellitus; FIT, fecal immunochemistry test; HR, hazard ratio; HTN, hypertension. <sup>a</sup> Model 1: unadjusted. <sup>b</sup> Model 2: adjusted by age and sex. <sup>c</sup> Model 3: adjusted by age, sex, BMI, smoking, alcohol consumption, regular exercise, HTN, DM, and dyslipidemia.

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**Fig. 1.** Cumulative incidence of psoriasis by the number of positive FIT results. The incidence of psoriasis was significantly increased in patients with positive FIT results, and this tendency was more pronounced with higher FIT numbers. FIT, fecal immunochemistry test.
**Table 3.** Subgroup analysis of the incidence of psoriasis according to age, sex, BMI, HTN, DM, and dyslipidemia

|                          | Number of positive FIT results | Events, n | Incidence rate per 1,000 person-years | HR (95% CI) model 3 | p for interaction |
|--------------------------|--------------------------------|-----------|---------------------------------------|---------------------|------------------|
| **Age**                  |                                |           |                                       |                     |                  |
| <65 years                | 0                              | 17,149    | 3.41662                               | 1 (reference)       |                  |
|                          | 1                              | 2,507     | 3.60393                               | 1.017 (0.975–1.061) |                  |
|                          | 2                              | 390       | 4.00284                               | 1.088 (0.984–1.203) |                  |
|                          | 3                              | 111       | 5.84254                               | 1.539 (1.277–1.855) |                  |
| ≥65 years                | 0                              | 12,520    | 4.36157                               | 1 (reference)       | 0.1022           |
|                          | 1                              | 2,155     | 4.70679                               | 1.042 (0.996–1.091) |                  |
|                          | 2                              | 371       | 5.38259                               | 1.155 (1.041–1.28)  |                  |
|                          | 3                              | 64        | 5.24989                               | 1.093 (0.853–1.397) |                  |
| **Sex**                  |                                |           |                                       |                     |                  |
| Male                     | 0                              | 16,211    | 4.71749                               | 1 (reference)       | 0.08             |
|                          | 1                              | 2,810     | 4.81197                               | 1.004 (0.965–1.045) |                  |
|                          | 2                              | 536       | 5.48626                               | 1.14 (1.046–1.243)  |                  |
|                          | 3                              | 122       | 5.85629                               | 1.229 (1.028–1.469) |                  |
| Female                   | 0                              | 13,458    | 3.02193                               | 1 (reference)       | 0.6488           |
|                          | 1                              | 1,852     | 3.25186                               | 1.065 (1.014–1.118) |                  |
|                          | 2                              | 225       | 3.27711                               | 1.063 (0.932–1.213) |                  |
|                          | 3                              | 53        | 5.1173                                | 1.666 (1.272–2.182) |                  |
| **Obesity**              |                                |           |                                       |                     |                  |
| No                       | 0                              | 18,672    | 3.69035                               | 1 (reference)       |                  |
|                          | 1                              | 2,848     | 3.94871                               | 1.022 (0.982–1.063) |                  |
|                          | 2                              | 445       | 4.3822                                | 1.087 (0.989–1.194) |                  |
|                          | 3                              | 106       | 5.77232                               | 1.396 (1.154–1.69)  |                  |
| Yes                      | 0                              | 10,997    | 3.88568                               | 1 (reference)       | 0.0318           |
|                          | 1                              | 1,814     | 4.19683                               | 1.039 (0.989–1.092) |                  |
|                          | 2                              | 316       | 4.87582                               | 1.164 (1.041–1.302) |                  |
|                          | 3                              | 69        | 5.37978                               | 1.257 (0.992–1.592) |                  |
| **HTN**                  |                                |           |                                       |                     |                  |
| No                       | 0                              | 15,521    | 3.60629                               | 1 (reference)       |                  |
|                          | 1                              | 2,229     | 3.7883                                | 1.012 (0.968–1.058) |                  |
|                          | 2                              | 445       | 4.3822                                | 1.087 (0.989–1.194) |                  |
|                          | 3                              | 96        | 6.415                                 | 1.602 (1.31–1.958)  |                  |
| Yes                      | 0                              | 14,148    | 3.9454                                | 1 (reference)       | 0.7773           |
|                          | 1                              | 2,433     | 4.30551                               | 1.044 (1.01–1.09)   |                  |
|                          | 2                              | 431       | 5.00597                               | 1.171 (1.064–1.289) |                  |
|                          | 3                              | 79        | 4.86922                               | 1.115 (0.894–1.391) |                  |
| **DM**                   |                                |           |                                       |                     |                  |
| No                       | 0                              | 24,535    | 3.66865                               | 1 (reference)       |                  |
|                          | 1                              | 3,765     | 3.92131                               | 1.025 (0.99–1.061)  |                  |
|                          | 2                              | 603       | 4.43939                               | 1.115 (1.028–1.209) |                  |
|                          | 3                              | 134       | 5.31579                               | 1.301 (1.098–1.541) |                  |
| Yes                      | 0                              | 5,134     | 4.27096                               | 1 (reference)       | 0.1638           |
|                          | 1                              | 897       | 4.63947                               | 1.045 (0.973–1.122) |                  |
|                          | 2                              | 158       | 5.1757                                | 1.13 (0.964–1.324)  |                  |
|                          | 3                              | 41        | 6.85456                               | 1.49 (1.096–2.027)  |                  |
| **Dyslipidemia**         |                                |           |                                       |                     |                  |
| No                       | 0                              | 19,536    | 3.70354                               | 1 (reference)       |                  |
|                          | 1                              | 2,975     | 3.90443                               | 1.011 (0.973–1.051) |                  |
|                          | 2                              | 484       | 4.40696                               | 1.101 (1.006–1.205) |                  |
|                          | 3                              | 120       | 5.96559                               | 1.457 (1.217–1.744) |                  |
| Yes                      | 0                              | 10,133    | 3.87516                               | 1 (reference)       |                  |
|                          | 1                              | 1,687     | 4.3088                                | 1.06 (1.006–1.116)  |                  |
|                          | 2                              | 277       | 4.90001                               | 1.148 (1.019–1.294) |                  |
|                          | 3                              | 55        | 4.96661                               | 1.131 (0.868–1.475) |                  |

Model 3: adjusted by age, sex, BMI, smoking, alcohol consumption, regular exercise, DM, HTN, and dyslipidemia. The variables used in each subgroup analysis are excluded. BMI, body mass index; CI, confidence interval; DM, diabetes mellitus; FIT, fecal immunochemistry test; HR, hazard ratio; HTN, hypertension. 1 BMI >25 kg/m² according to the Asia-Pacific BMI criteria [35].
served among males, among those without DM or HTN, and in those with dyslipidemia; there were no significant differences in analyses comparing incidence rates between sexes, DM, or dyslipidemia status (Table 3). However, there was a significantly higher incidence of Alzheimer’s disease in individuals without HTN (HR 1.13 vs. 1.07, \( p = 0.0021 \)). Of note, younger patients (40–64 years) with psoriasis had a significantly higher incidence of Alzheimer’s disease than older patients (≥65 years) (HR 1.30, 95% CI 1.23–1.39 vs. HR 1.08, 95% CI 1.06–1.11, \( p \) for interaction < 0.0001).

However, the relative risk of psoriasis in those with increased FIT number was higher in people without HTN (\( p \) for interaction < 0.05) compared with people with HTN.

**Discussion**

In this large, nationwide, population-based study we found a significantly increased risk of newly diagnosed psoriasis among subjects with positive FIT results compared to those with negative FIT results. Furthermore, the risk of psoriasis significantly increased in proportion to the number of positive FIT results. The incidence of psoriasis was unaffected by age, sex, and comorbidities, but the association was stronger in individuals without than in those with HTN (aHR 1.60 vs. 1.12).

FITs are used for population-based CRC screening, and positive FIT results are associated with a higher risk of CRC or its precursor lesion, adenoma, and CRC mortality [8, 18]. Recent cohort studies from Taiwan and Scotland reported that positive FIT results were related to an increased all-cause mortality rate, even if CRC was excluded [8, 19]. In addition, the level of glycated Hb was significantly higher in patients with a positive FIT result [20], and positive FIT results were associated with cardiovascular diseases (ischemic stroke and myocardial infarction), suggesting a link with systemic inflammation. In this study, positive FIT results were associated with psoriasis, a chronic inflammatory skin disease, suggesting a relationship between skin disorders and gut health. Moreover, epidemiologic studies have shown that psoriasis is associated with dyslipidemia, obesity, HTN, DM, and metabolic syndrome [10, 12, 21, 22], risk factors for FIT positivity. Notably, after adjusting for these confounding factors, positive FIT results were associated with a proportionally increased risk of psoriasis.

Although the mechanism underlying the association between FIT results and the risk of psoriasis is unclear, there are several possibilities. First, a chronic inflammatory environment may link positive FIT results and psoriasis. The FIT can detect inflammatory conditions manifesting as mucosal ulceration and occult blood loss, and in a meta-analysis it was predictive of mucosal healing in patients with ulcerative colitis [23, 24]. A colonic inflammatory status and the consequent disruption of the intestinal epithelial barrier, i.e., “leaky gut,” may lead to occult blood in feces, resulting in bacterial translocation and release of cytokines into the systemic circulation [8, 25]. Elevated levels of pro-inflammatory cytokines including tumor necrosis factor alpha, interleukin 1β, and interleukin 6 may stimulate T cell proliferation and activation, triggering the development of inflammatory and immune-mediated psoriatic skin lesions [26].

A second proposed mechanism underlying the link between FIT positivity and psoriasis is the gut microbiota. Gut dysbiosis is reportedly associated with the development of psoriasis [27, 28]. Myers et al. [28] found that the composition of the intestinal microbiome in patients with psoriasis was distinct from that of control subjects. The gut-skin axis is implicated in the link between skin diseases and the gut microbiome via inflammatory mediators, metabolites, and the intestinal barrier [29]. Intestinal dysbiosis could lead to psoriasis by promoting an aberrant inflammatory response in genetically predisposed individuals.

It is also possible that microvascular impairment is linked to the association between FIT positivity and psoriasis. Vascular endothelial growth factor is a mediator of pathological angiogenesis and is upregulated in psoriasis [30]. The psoriatic microvasculature is characterized by tortuous and leaky blood vessels, which facilitate leukocyte migration into inflamed skin [26]. In patients with psoriasis, cutaneous angiogenesis may be a marker of systemic vascular pathology, which could lead to a positive FIT result. It is interesting that the association between positive FIT results and psoriasis was significantly stronger in individuals without HTN. Psoriasis increases the risk of cardiovascular diseases, including HTN and coronary artery calcification [31, 32]. A population-based cohort study of South Koreans showed that HTN was independently associated with a greater prevalence of psoriasis [22]. However, elevated blood pressure, a component of metabolic syndrome, was reportedly negatively associated with psoriasis development [12]. Because of its high comorbidity burden [33], it is important to identify risk factors for psoriasis; also, further study of the effect of HTN on the risk of psoriasis is required. In this study, repetitive positive FIT results significantly in-
fluenced the risk of psoriasis even in the absence of risk factors.

To our knowledge, this is the first study of the association between FIT positivity and psoriasis in a representative South Korean population. However, this study had several limitations. First, we could not obtain colonscopic outcomes for individuals with positive FIT results and other fecal inflammatory markers, especially fecal calprotectin due to limited data from the NHIS. Though sensitivity analyses with subjects without CRC revealed robust results, further studies are needed to clarify the impact of FITs in psoriasis development based on the risk of CRC and its precursor lesions. In addition, fecal calprotectin, which is a well-known marker of mucosal inflammation and predicts mucosal status in patients with IBD [23], could not be adjusted for to better estimate the psoriasis risk. However, risk of psoriasis showed similar association in sensitivity analyses according to the IBD diagnosis. Second, we could not evaluate the association between FIT positivity and the severity of psoriasis because the NHIS database provides the results of only serum tests performed at medical checkups. Third, no information was available on the use of medications – such as aspirin, nonsteroidal anti-inflammatory drugs, and iron supplementation – that could lead to false-positive FIT results. In addition, the use of antihypertensive or antidiabetic medications, which are potential confounders, could not be assessed. For instance, calcium channel blockers increase the risk of psoriasis [22], and thiazolidinedione exerts a beneficial effect on psoriasis [34]. Finally, because of the retrospective, observational nature of the study, the causality of the relationship between FIT results and psoriasis could not be determined.

In conclusion, a positive FIT result was predictive of an increased risk of psoriasis. Therefore, individuals with a positive FIT result are at risk of not only colorectal neoplasia but also of chronic inflammatory skin diseases. Further study is needed to evaluate the causality of that relationship. Overall, our findings suggest the importance of FITs in dermatology as well as for CRC screening.

Key Message
The risk of psoriasis was significantly increased in patients with positive FIT results compared to the FIT-negative population.

Statement of Ethics
The study was based on a national database, the South Korean NHIS, and a written informed consent statement was not required. The study was approved by the Institutional Review Board of Seoul National University Hospital (IRB number: E-1906-008-1036).

Conflict of Interest Statement
The authors have no conflicts of interest.

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Author Contributions
H.J. Lee and K. Han were involved in the study concept and design, acquisition of data, analysis and interpretation of data, and drafting of the manuscript. H. Soh, S.-J. Koh, J.P. Im, H.E. Park, and J.S. Kim were involved in the interpretation of data, drafting of the manuscript, and critical revision of the manuscript for important intellectual content. M. Kim was involved in the study concept and design, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, and study supervision.

Data Availability Statement
The data that support the findings of this study are available from the corresponding author upon reasonable request.

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