Observational Study

Medicine®

OPEN

The risk of colorectal neoplasm in ex- and never-smokers according to urinary cotinine level

Seung Jae Roh, MD[a], Bun Kim, MD, PhD[a,*], Ju Yeon Oh, MD[b], Kyung Su Han, MD, PhD[a], Byung Chang Kim, MD[a], Chang Won Hong, MD, PhD[a], Dae Kyung Sohn, MD, PhD[a]

Abstract

To investigate the relationship between urinary cotinine and colorectal neoplasm (CRN).

The participants in the health screening cohort of the National Cancer Center who underwent screening colonoscopy between June 2007 and December 2009 were included. A total of 8121 subjects who underwent urinary cotinine measurement within 14 days from the index colonoscopy were included. Cotinine positivity was defined as having a urinary cotinine level ≥50 ng/mL. Follow-up colonoscopy data were collected by reviewing the patients' medical records.

Patients were classified according to their urinary cotinine level and self-reported smoking status, and the number of patients with cotinine positivity was 1960 (24.1%). There was no significant difference in the cumulative CRN and advanced CRN (ACRN) risks according to the self-reported smoking status. However, cotinine positivity at the time of index colonoscopy was an independent risk factor for CRN (hazard ratio [HR]= 1.23, $P = .006$) in follow-up colonoscopy. Moreover, in never- and ex-smokers, cotinine positivity was an independent risk factor for CRN (HR = 1.95, $P = .019$; HR = 2.12, $P = .003$, respectively) and ACRN (HR = 8.89, $P < .001$; HR = 5.03, $P = .003$) during follow-up colonoscopy. The cumulative incidence of CRN and ACRN was higher in the cotinine-positive never- and ex-smokers than in the cotinine-negative never- and ex-smokers ($P < .001$ and $P = .008$, respectively).

CRN or ACRN is more likely to occur at follow-up colonoscopy in the urinary cotinine-positive never- and ex-smokers than in the urinary cotinine-negative group. Therefore, urinary cotinine measurements may provide useful information on never- or ex-smokers undergoing screening colonoscopy.

Abbreviations: ACRN = advanced colorectal neoplasm, AHR = adjusted hazard ratio, BMI = body mass index, CRC = colorectal cancer, CRN = colorectal neoplasm, HR = hazard ratio.

Keywords: colonoscopy, colorectal neoplasm, smoking, urinary cotinine

1. Introduction

Many previous studies have reported that smoking increases the incidence of adenomatous polyps and colorectal cancers (CRC).[1,2] Moreover, several studies have reported that smoking is a risk factor for colorectal neoplasms (CRNs).[1,3,4] However, most of the studies conducted in the past have been based on self-reported smoking history. It is possible that this may not reflect accurate information about smoking. Owing to the social demands for smoking cessation, respondents may answer inaccurately, may not reflect passive smoking and individual differences in cigarette smoking metabolism, and may have

Editor: Saurabh Chawla.

This study was approved by the Institutional Review Board (IRB) of the National Cancer Center (NCCNCS-07-071).

This study was supported by a grant from the National Cancer Center, Korea (NCC-1810060 and NCC-1910212).

All participants provided consent prior to the study.

The authors affirm that human research participants provided informed consent for publication of the images provided as Figures. The participants have consented to the submission of the study to the journal. The participants signed informed consent forms regarding the publishing of their data.

The code cannot be provided because the statistical analysis was performed using the SPSS program; however, the saved SPSS file can be provided upon reasonable request.

The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

[a] *Center for Colorectal Cancer,* [b] *Department of Internal Medicine, Research Institute and Hospital, National Cancer Center, Goyang, Korea.*

[*] *Correspondence: Bun Kim, Center for Colorectal Cancer, Research Institute and Hospital, National Cancer Center, 323, Ilsan-ro, Ilsandong-gu, Goyang-si, Gyeonggi-do, 10408, Korea (e-mail: kimbun@ncc.re.kr).*

How to cite this article: Roh SJ, Kim B, Oh JY, Han KS, Kim BC, Hong CW, Sohn DK. The risk of colorectal neoplasm in ex- and never-smokers according to urinary cotinine level. Medicine 2021;100:22(e25842).

Received: 17 March 2020 / Received in final form: 11 March 2021 / Accepted: 17 April 2021

http://dx.doi.org/10.1097/MD.0000000000025842

limitations in controlling various confounding factors of cigarette exposure.[5]

Cigarette smoking causes many physiological changes and there are several metabolic intermediates of tobacco. Several biomarkers, such as plasma, saliva, and urinary cotinine, expired air carbon monoxide (CO), and plasma thiocyanate are known to facilitate the measurement of tobacco metabolites, which provide relatively accurate estimates of the diversity and exposure to carcinogens.[6,7] Among these, urinary cotinine is a metabolite of nicotine, which is measured at a higher level than plasma or saliva cotinine, reflecting the actual smoking status relatively accurately, thus facilitating the measurement and increasing the time period for measuring biomarkers.[6] Plasma thiocyanate has the disadvantage of poor specificity for detecting light smoking,[6] and exhaled CO is not measured in smokeless tobacco or electronic cigarette exhalent.[7] Therefore, urinary cotinine level is known as an objective and quantitative indicator related to smoking. Nevertheless, only a few studies have investigated the association between cotinine and the risk of CRN to date.

Therefore, the aim of this study was to evaluate the level of urinary cotinine in smoking status and to determine the association between CRN and advanced CRN (ACRN) in screening colonoscopy.

2. Materials and methods

2.1. Study design and population

Consecutive patients who participated in the voluntary health screening program of the National Cancer Center, Korea, between April 2007 and December 2009 were considered. Participants who underwent colonoscopy during screening were enrolled in the "Colorectal Polyp Registry at the National Cancer Center of Korea." Among the 16,330 participants enrolled in the Colorectal Polyp Registry, 5364 participants who did not provide informed consent in the questionnaire, 848 participants who underwent colonoscopy for diagnostic purposes, and 40 participants who had previously undergone colorectal cancer were excluded. In addition, 1,954 participants who did not undergo measurement of cotinine levels and 3 participants with duration of more than 2 weeks between colonoscopy and urinary cotinine measurements were excluded. Finally, 8121 participants were included in the analysis, and all participants provided consent prior to the study (Fig. 1). Clinicopathological factors, including age, sex, medical history, family history, colonoscopy findings, laboratory results, and histologic features, were obtained from the medical records or from a questionnaire. This study was approved by the Institutional Review Board (IRB) of the National Cancer Center (NCCNCS-07-071).

2.2. Measurements and definitions

Data such as smoking status, sex, age, drink status, medical history, family history, body weight, and height were obtained through a self-administered questionnaire. CRC family history was defined as the presence of CRC within at least one degree. Obesity was defined as body mass index $\geq 25\,kg/m^2$ according to the cutoff value for Asians.[8] Patients who quit smoking for more than 1 year and those who did not smoke were referred to as

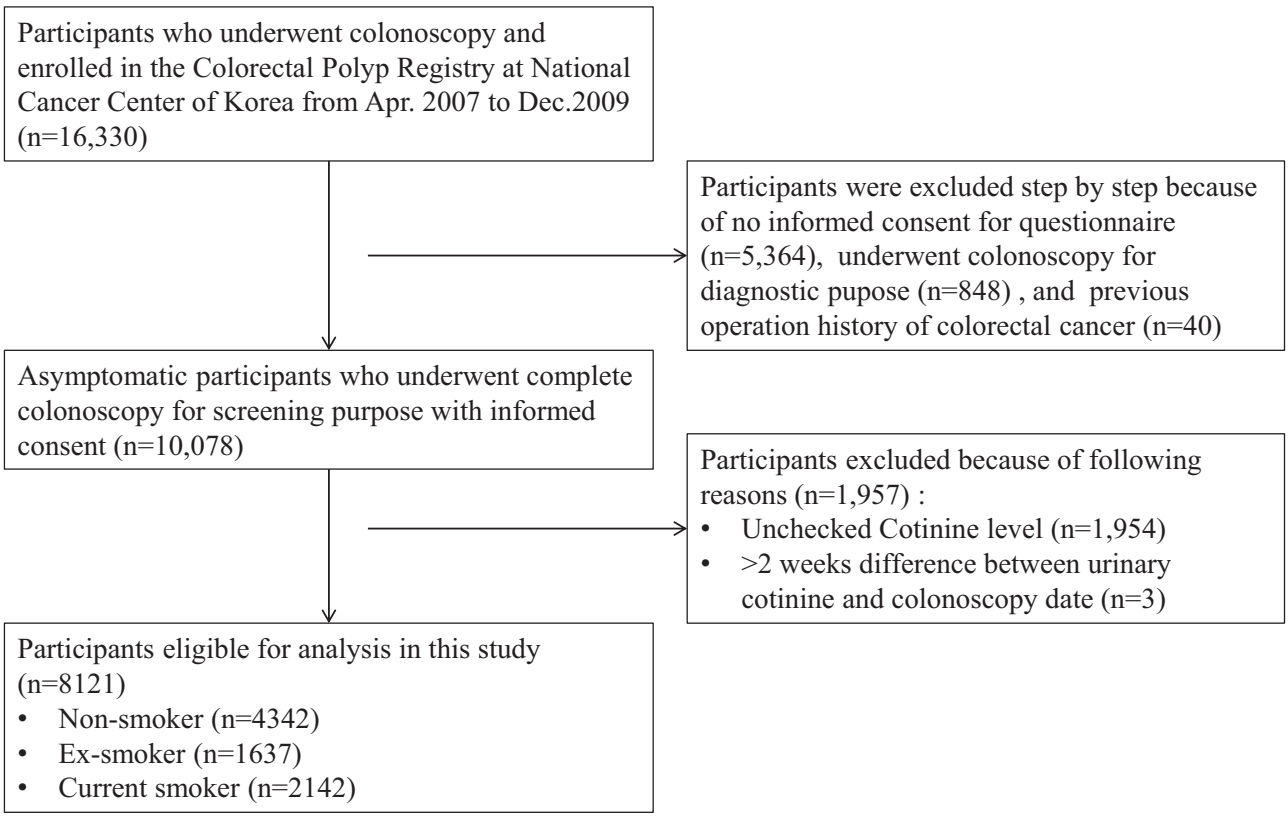

Figure 1. Inclusion and exclusion criteria of the study.

ex- and never-smokers. All current smokers and ex-smokers had smoked more than 10 packs.

Only cotinine measured within 14 days of colonoscopy was considered significant. For testing fresh urine specimens, a total of 5.0 mL of urine was obtained, and urine cotinine levels were measured by homogeneous enzyme immunoassay within a few hours. A homogenous enzyme immunoassay system was used for analysis (DRI Cotinine Assay; Microgenics Corp, Fremont, CA). Smokers confirmed as having urinary cotinine were defined as participants with urinary cotinine levels ≥50 ng/mL.[6] We categorized cotinine positive smokers into 3 groups according to the tertile distribution of urinary cotinine levels (50 to 499 ng/mL, 500 to 999 ng/mL, and ≥1000 ng/mL) to examine the dose-response relationship between urinary cotinine and the cumulative risk of CRN. We classified "participants who answered that they had never smoked but had cotinine levels ≥50 ng/mL" as "hidden smokers." All selected participants were examined using video colonoscopy (Olympus CF-H260 or CF-Q260, Olympus Optical Co., Ltd, Tokyo, Japan) by board-certified endoscopists. All colonoscopists involved in this study had previously performed more than 1,000 colonoscopy procedures per year for more than 5 years. The participants received either 4-L doses of a polyethylene glycol solution (Colyte F powder, Taejoon Pharm, Seoul, Korea) or two 45-mL doses of sodium phosphate (C. B. Fleet Co., Inc., Lynchburg, Virginia) before the index colonoscopy and Coolprep (Taejoon Pharmaceuticals, Seoul, Korea) before follow-up colonoscopy. Suspicious neoplastic lesions were removed via biopsy, snare polypectomy, or endoscopic mucosal resection. Colorectal neoplasia was removed by endoscopic resection or surgery, as determined by the colonoscopist. Biopsy or removed specimens were examined by experienced pathologists who were unaware of the patients' clinical findings.

CRN was defined as a cancer or any adenoma, whereas ACRN was defined as a cancer or advanced adenoma. Advanced adenoma was defined as the presence of one of the following features: >10-mm diameter, tubulovillous or villous structure, and high-grade dysplasia.[9]

2.3. Statistical analysis

The data were stratified according to the smoking status (never-, ex-, current) as recorded in the self-reported questionnaire and smoking status (cotinine negative, cotinine positive) according to their urinary cotinine level. Baseline characteristics were compared by chi-square and one-way analysis for self-reported smoking status and urinary cotinine levels. Comparison of smoking status and CRN or ACRN measured by colonoscopy performed at the time of cotinine measurement was analyzed by logistic regression analysis. The differences in CRN and ACRN at follow-up colonoscopy between groups were determined using log-rank test. Self-reported smoking status or cotinine levels were further compared by subdividing daily smoking, pack-year, and urinary cotinine levels. To compare the risk of CRN or ACRN at follow-up colonoscopy, age, sex, colon polyp history, obesity, and current alcohol drinking status were corrected by log-rank analysis and analyzed using the Cox proportional hazards regression model. The smoking status determined by the first measured urinary cotinine level and the cotinine status measured at follow-up was classified into four categories to analyze the risk of CRN and ACRN using the Cox proportional hazards regression model. All P values were three tailed, and $P < .05$ was considered statistically significant.

3. Results

3.1. Baseline patient characteristics of the study population

In our study, a total of 8121 patients whose cotinine were measured were analyzed. There were 4342 never-smokers, 1637 ex-smokers, and 2142 current smokers classified according to their self-reported smoking status. According to the urinary cotinine level, 6161 individuals were cotinine negative and 1960 people were cotinine positive. Sex, age, alcohol drinking status, CRC family history, colon polyp history, body mass index (BMI), adenoma at the time of cotinine measurement, CRN, adenoma observed at follow-up colonoscopy, CRN, and interval between the first and last follow-up endoscopy were compared. The self-reported smoking status and smoking status by urinary cotinine level showed significant differences in sex, age, current drinking, colorectal polyp history, and BMI (Table 1).

Smoking history by self-report and smoking status by urinary cotinine level were compared (Table 2). In the self-report, there were 88 cotinine-positive never-smokers, accounting for 2% of all never-smokers. Although they quit smoking for more than 1 year, 4.0% were still positive for cotinine. In the self-reported current smokers, there were 336 (5.5%) cotinine-negative individuals.

3.2. Risk of CRN according to cotinine status

Cumulative risks for CRN and ACRN over time were also compared (Table 3). There was no significant difference in the cumulative CRN and ACRN risks according to the self-reported smoking status, and the daily amount was significantly higher in the cumulative risk of CRN than in the never-smoker group (adjusted hazard ratio [AHR] 1.37, $P < .001$). In the pack-year, the cumulative CRN risk was significantly higher in the individuals with more than 10 pack-years than in the never-smokers (AHR 1.32, $P = .002$). The urinary cotinine-positive group had a significantly higher risk of cumulative CRN (AHR 1.23, $P = .006$), but no significant difference in ACRN (AHR 1.56, $P = .078$). The cumulative CRN risk was significantly different between the 50-499 (AHR 1.28 P value = .024) and 500–999 (AHR 1.34, P value = .005) groups and the cotinine-negative group, but not in the 1000-or-more groups. The cumulative ACRN risk was not significantly different among the urinary cotinine-negative groups subdivided according to their cotinine levels. When we grouped the individuals according to their self-reported smoking status and urinary cotinine level, there was no significant difference in cumulative CRN or ACRN risk according to the urinary cotinine levels in current smokers. However, in the never- or ex-smokers, the urinary cotinine-positive group had significantly increased cumulative risk of CRN and ACRN.

The correlation between smoking cessation and cotinine level in ex-smokers is as follows. Of the total 1637 ex-smokers, 1,398 (85.4%) responded with data for the duration of smoking cessation. The average duration of smoking cessation for these 1,398 people was 10.8 ± 9.0 (range, 1–65) years. There were a total of 830 (59.4%) and 568 (42.2%) ex-smokers with an average duration of smoking cessation < 10 years and ≥10 years, respectively. In ex-smokers with an average duration of smoking cessation < 10 years and ≥10 years, the average urine cotinine levels were 18.2 ± 114.3 ng/mL and 4.8 ± 51.6 ng/mL, respectively, which was significantly different (P value = .003). Forty

Table 1

Baseline characteristics and demographics of enrolled patients.

Characteristics	Value n = 8,121 (%)	Never-smoker n = 4342 (%)	Ex-smoker n = 1637 (%)	Current smoker n = 2,142 (%)	*P* value	Cotinine negative n = 6,161 (%)	Cotinine positive* n = 1,960 (%)	*P* value
Sex, Male	4279 (52.7)	826 (19.0)	1532 (93.6)	1921 (89.7)	<.001	2572 (41.7)	1707 (87.1)	<.001
Age, median yr (mean ± SD)	48.2 ± 9.8	48.5 ± 10.0	50.5 ± 9.5	45.8 ± 9.0	<.001	48.9 ± 10.0	45.9 ± 9.1	<.001
Current drinker	4965 (61.1)	1899 (43.7)	1279 (78.1)	1787 (83.4)	<.001	3399 (55.2)	1566 (79.9)	<.001
Family history of CRC	364 (4.5)	186 (4.3)	76 (4.6)	102 (4.8)	.466	268 (4.3)	96 (4.9)	.307
History of colorectal polyps	210 (2.6)	78 (1.8)	62 (3.8)	70 (3.3)	<.001	146 (2.4)	64 (3.3)	.030
BMI (kg/m^2) (mean ± SD)	23.6 ± 3.1	23.0 ± 3.0	24.4 ± 2.8	24.1 ± 3.1	<.001	23.4 ± 3.0	24.1 ± 3.1	<.001
Obesity (BMI ≥25 kg/m^2)	2437 (30.0)	1003 (23.1)	657 (40.1)	777 (36.3)	<.001	1733 (28.1)	704 (35.9)	<.001
Urinary cotinine, [mean ± SD, (value range)]	197.0 ± 439.4 (0∼2657)	10.7 ± 93.8 (0∼2329)	17.9 ± 115.8 (0∼2040)	711.5 ± 586.9 (0∼2657)	<.001	0.41 ± 3.9 (0∼49)	814.9 ± 544.8 (51∼2657)	<.001
Any Adenoma	2259 (27.8)	904 (20.8)	631 (38.5)	724 (33.8)	<.001	1573 (25.5)	686 (35.0)	<.001
Low grade	2251 (27.7)	899 (20.7)	629 (38.4)	723 (33.8)	<.001	1566 (25.4)	685 (34.9)	<.001
High grade	52 (0.6)	19 (0.4)	16 (1.0)	17 (0.8)	.012	40 (0.6)	12 (0.6)	.858
TVA or VA	88 (1.1)	32 (0.7)	34 (2.1)	22 (1.0)	<.001	66 (1.1)	22 (1.1)	.849
Size ≥ 10mm	280 (3.4)	108 (2.5)	66 (4.0)	106 (4.9)	<.001	189 (3.1)	91 (4.6)	.001
≥3 Adenoma	378 (4.7)	110 (2.5)	127 (7.8)	141 (6.6)	<.001	244 (4.0)	134 (6.8)	<.001
Serrated adenoma	121 (1.5)	46 (1.1)	24 (1.5)	51 (2.4)	<.001	72 (1.2)	49 (2.5)	<.001
Advanced adenoma of index colonoscopy	261 (3.2)	93 (2.1)	70 (4.3)	98 (4.6)	<.001	174 (2.8)	87 (4.4)	<.001
Advanced colorectal neoplasm of index colonoscopy	275 (3.4)	101 (2.3)	73 (4.5)	101 (4.7)	<.001	184 (3.0)	91 (4.6)	<.001
Colorectal cancer of index colonoscopy	16 (0.2)	8 (0.2)	4 (0.2)	4 (0.2)	.674	11 (0.2)	5 (0.3)	.506
Any adenoma of follow up colonoscopy	960 (11.8)	392 (9.0)	257 (15.7)	311 (14.5)	<.001	659 (10.7)	301 (15.4)	<.001
Colorectal neoplasm of follow up colonoscopy	965 (11.9)	395 (9.1)	259 (15.8)	311 (14.5)	<.001	663 (10.8)	302 (15.4)	<.001
Advanced adenoma of follow up colonoscopy	78 (1.0)	31 (0.7)	24 (1.5)	23 (1.1)	.006	50 (0.8)	28 (1.4)	.015
Advanced colorectal neoplasm of follow up colonoscopy	82 (1.0)	33 (0.8)	25 (1.5)	24 (1.1)	.007	53 (0.9)	29 (1.5)	.017
Colorectal cancer of follow up colonoscopy	5 (0.1)	2 (0.0)	2 (0.1)	1 (0.0)	.346	4 (0.1)	1 (0.0)	.829
Interval between index and last follow-up colonoscopy (mo)	22.2 ± 37.2	21.3 ± 36.8	26.3 ± 39.2	20.9 ± 36.0	<.001	22.5 ± 37.4	21.4 ± 36.4	.276

BMI = body mass index, CRC = colorectal cancer, SD = standard deviation, TVA = tubulovillous adenoma, VA = villous adenoma.
* Cotinine positive was defined as an individual having a urinary cotinine level ≥50 ng/mL.

(4.8%) and eight (1.4%) ex-smokers with an average duration of smoking cessation < 10 years and ≥10 years, respectively, were positive for urine cotinine (≥50 ng/mL), which was significantly different (*P* value = .001). The incidence of CRN was 134 (16.1%) and 92 (16.2%) in ex-smokers with an average duration of smoking cessation < 10 years and ≥10 years, respectively, which was not significantly different (*P* value = .979); whereas the incidence of ACRN was 6 (0.7%) and 11 (1.9%), respectively, which was significantly different (*P* value = .042).

3.3. Risk of CRN according to changes in cotinine status

After the first measurement of urinary cotinine status, 2556 patients were followed up. They were divided into four groups according to the positive difference in urinary cotinine status (Table 4). The cumulative risk of CRN and ACRN was higher in the positive-to-negative converted group than in the urinary cotinine continuing negative group. In the continuing positive group, the risk of metachronous CRN was 1.36 times higher (*P* = .001), but there was no significant difference in ACRN (AHR 1.48, *P* = .214). When comparing only the positive-to-negative converted group and the continuing positive group, the hazard ratio of CRN did not show a significant difference between the two groups (AHR 0.91, *P* = .572). The hazard ratio of ACRN also showed no significant difference between the two groups (AHR 0.64, *P* = .328).

Table 2

Cotinine status and self-reported smoking status at the time of index colonoscopy.

	Urinary cotinine negative n = 6161	Urinary cotinine positive n = 1960
Self-reported Never-smokers n = 4342 (%)	4,254 (98.0)	88 (2.0)
Self-reported ex-smokers n = 1637 (%)	1571 (96.0)	66 (4.0)
Self-reported current smokers n = 2142 (%)	336 (5.5)	1,806 (92.1)

3.4. Cumulative incidence of CRN and ACRN

The cumulative incidence of CRN and ACRN was compared according to the cotinine status (Fig. 2). The average duration to identifying CRN from measuring the first urine cotinine level was 54.0 (range, 8–131) months; it was 54.6 (range, 11–131) months in the cotinine-negative group, and 52.6 (range, 8–125) months in the cotinine-positive group, which was not significantly different (*P* value = .224). In addition, the average duration to identifying ACRN from measuring the first urine cotinine level was 62.8 (range, 12–127) months, 66.9 (range, 12–127) months in the cotinine-negative group, and 55.2 (range, 12–126) months in the cotinine-positive group, which was not significantly different (*P* value = .195). Cumulative incidence of CRN was significantly higher in the cotinine-positive group than in the

Table 3

Multivariate analysis of the factors associated with colorectal neoplasm or advanced colorectal neoplasm in follow-up colonoscopy.

	CRN		ACRN	
	Adjusted HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value
Self-reported smoking status				
Never-smoker	1 (reference)	1 (reference)		
Ex-smoker	1.06 (0.86 –1.29)	.591	1.02 (0.53–1.99)	.948
Current smoker	1.13 (0.93–1.37)	.224	0.97 (0.50–1.89)	.930
Daily amount of cigarette smoking				
≤10 cigarette	1.03 (0.83–1.28)	.768	0.75 (0.34–1.67)	.487
>10 cigarette	1.37 (1.15–1.64)	<.001	1.36 (0.75–2.44)	.310
Pack-years				
≤10 pack-years	1.08 (0.87–1.35)	.504	0.81 (0.35–1.84)	.606
>10 pack years	1.32 (1.11–1.57)	.002	1.19 (0.67–2.11)	.556
Urinary cotinine-verified status				
Cotinine-negative	1 (reference)	1 (reference)		
Cotinine-positive	1.23 (1.06–1.43)	.006	1.56 (0.95–2.56)	.078
Urinary cotinine level (ng/mL)				
<50	1 (reference)	1 (reference)		
50–499	1.28 (1.03–1.59)	.024	1.67 (0.83–3.35)	.153
500–999	1.34 (1.09–1.65)	.005	1.50 (0.74–3.01)	.262
≥1000	1.06 (0.84–1.34)	.601	1.52 (0.72–3.21)	.267
Self-reported smoking and urinary cotinine level				
Never-smokers & Cotinine negative	1 (reference)	1 (reference)		
Never-smokers & Cotinine positive	1.95 (1.12–3.41)	.019	8.89 (3.08–25.68)	<.001
Ex-smokers & Cotinine negative	1 (reference)	1 (reference)		
Ex-smokers & Cotinine positive	2.12 (1.29–3.47)	.003	5.03 (1.73–14.67)	.003
Current smokers & cotinine negative	1 (reference)	1 (reference)		
Current smokers & cotinine positive	1.25 (0.89–1.76)	.190	1.19 (0.35–4.02)	.776

Values were adjusted for age, sex, colon polyp history, obesity, current drinker.
ACRN = advanced colorectal neoplasm, CRN = colorectal neoplasm, HR = hazard ratio.

cotinine-negative group ($P < .001$), and ACRN was also significantly higher in the cotinine-positive group ($P = .008$). When the individuals were classified according to their cotinine status and self-reported smoking status (Fig. 3), the cumulative incidence of CRN and ACRN was significantly higher in the cotinine-positive never- and ex-smokers ($P = .004, < .001$). However, there was no significant difference in the cumulative incidence between CRN and ACRN in the cotinine-positive and cotinine-negative current smokers ($P = .166$ and $.698$).

4. Discussion

This study investigated the association between urinary cotinine and CRN according to the smoking status of screened asymptomatic patients. The self-reported smoking status in our study did not show a significant difference with respect to the cumulative risk of CRN or ACRN, but there was a significant increase in the cumulative risk of CRN in patients smoking a half pack of cigarettes (>10 cigarettes) daily and those smoking for > 10 years. However, the cumulative risk of CRN was significantly increased in urinary cotinine-positive patients than in urinary cotinine-negative patients. For those who answered current smokers in the self-reported questionnaire, the cumulative risk of CRN or ACRN did not increase according to the difference in urinary cotinine level. However, never- and ex-smokers showed a significant increase in the risk of cumulative occurrence in both urinary cotinine-positive CRN and ACRN. When urinary cotinine was followed up, the risk of CRN accumulation was significantly higher in the cotinine-positive group than in the cotinine-negative group, even if the cotinine status was changed from positive to negative.

In our study, the proportion of never-smokers by self-report was 2.58% (n = 154/5979) of the cotinine-positive hidden smokers. These hidden smokers may be those who provided

Table 4

Multivariable analysis of the relationship between changes in cotinine status and colorectal neoplasm or advanced colorectal neoplasm.

		CRN		ACRN	
	n	Adjusted HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value
Change in urinary cotinine status					
Negative → Negative	1869	1 (reference)		1 (reference)	
Negative → Positive	66	1.01 (0.64–1.60)	.973	0.71 (0.10–5.21)	.733
Positive → Negative	118	1.46 (1.09–1.96)	.012	2.47 (1.07–5.69)	.033
Positive → Positive	503	1.36 (1.14–1.63)	.001	1.48 (0.80–2.74)	.214

Values were adjusted for age, sex, colon polyp history, obesity, current drinker.
ACRN = advanced colorectal neoplasm, CRN = colorectal neoplasm, HR = hazard ratio.

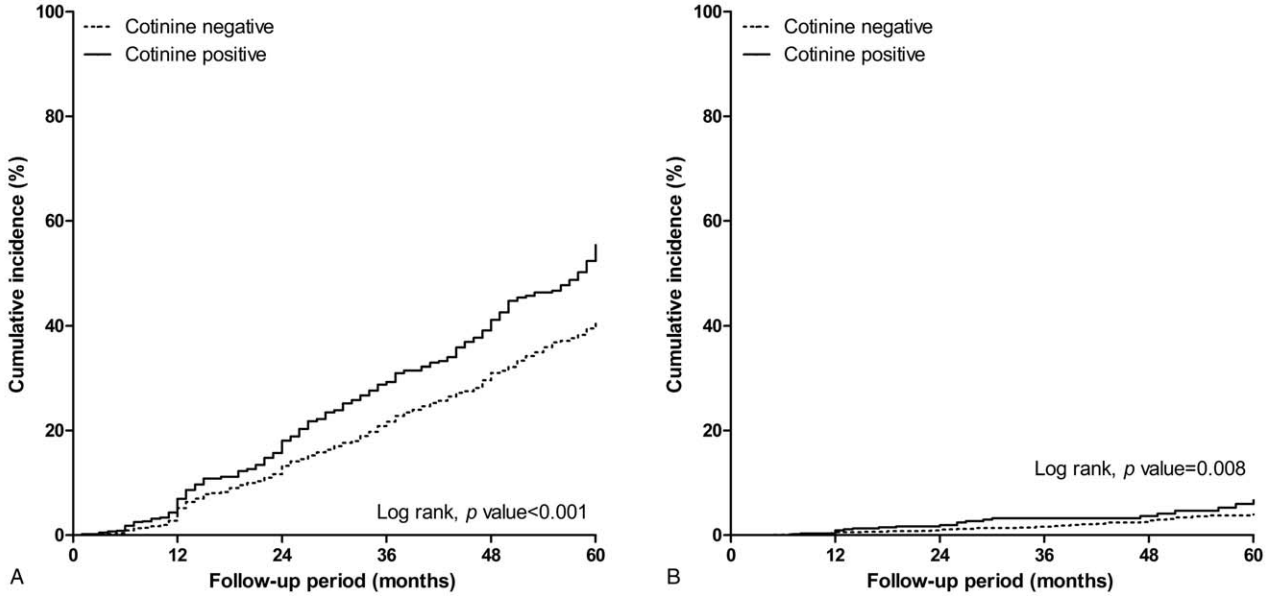

Figure 2. Cumulative incidence of colorectal neoplasm and advanced colorectal neoplasm according to cotinine status. A, Cumulative incidence of colorectal neoplasm. B, Cumulative incidence of advanced colorectal neoplasm.

an incorrect answer in the questionnaire or those who have been exposed to passive smoking. Some studies have reported that even never-smokers have increased cotinine levels when exposed to passive smoking. [10–12] In the large-scale meta-analysis studied by Botteri et al, the relative risk of adenoma of the former smokers was 1.47 times higher than that of the never-smokers, and that of the ever smokers was 1.82 times higher.[2] Colorectal cancer showed no significant difference in current smokers, but it was 1.17 times higher in former smokers and 1.18 times higher in never smokers.[4] Moreover, these studies all used self-reported smoking status. Kim et al[5] reported that when the individuals were subcategorized according to urinary cotinine and self-report smoking status, the risk of CRN or ACRN was significantly higher in cotinine-positive never- and ex-smokers, but, there was no significant difference in the risk of CRN or ACRN between the cotinine-positive and cotinine-negative current smokers. These results suggest that urinary cotinine is more associated with the risk of CRN than self-report smoking status.

In the present study, 88 patients (2.0%) who were never-smokers by self-report were cotinine positive, whereas 66 patients (4.0%) who were ex-smokers by self-report were cotinine positive. Moreover, there were 336 (5.5%) current smokers by self-report who were cotinine negative. The meta-analysis comparing the self-report with the biochemical measurements of tobacco showed that the self-report was mostly accurate, but there is a lack of formalized methods and questionnaires for validation, and the classification of exposure does not match in every study.[13] Self-reporting is a subjective assessment that is associated with misclassification bias due to recall error and lack of knowledge,[14] and it is difficult to quantify the absorption of the smoking substances.[15] In contrast, the biomarkers associated with tobacco exposure, such as urinary cotinine, can more accurately reflect the exposure or smoking status. Cotinine is a metabolite of nicotine and a biomarker that is widely used apart from the self-reporting tool.[7] Cotinine is relatively less affected by diet or pollution exposure and has a longer half-life than nicotine (nicotine: 2–3 hours, cotinine: 15–19 hours); thus, nicotine levels fluctuate throughout the day, but cotinine levels remain constant throughout the day.[7,16] In addition, since cotinine is involved in all causes and metabolic processes of tobacco exposure, it may provide objective evidence that controls the various confounding factors of tobacco exposure.[17] It may also reflect individual differences in the degree of nicotine metabolism to cotinine and the rate of cotinine clearance.[18] However, since cotinine levels can change with physiologic differences (pregnancy, disease state), race, colorectal time-genetic differences, and environmental factors (hormones, drug interactions), the differences can vary in each person.[7] Therefore, to address the shortcomings of cotinine measurement, the analysis was performed by combining the self-reported data and the data based on the urinary cotinine expression. Moreover, follow-up cotinine measurement was performed to correct false negative or positive cases.

The interesting results in our study were that the smokers who never stopped smoking had a 1.95 times cumulative risk of CRN, whereas the ex-smokers had a 2.12 times cumulative risk of CRN. The cumulative risk of ACRN was 8.89 and 5.03, respectively. This suggests that the effects of smoking on CRN can be reversible. When the cumulative risk rate for CRN was investigated through the follow-up of urinary cotinine, the cumulative risk of CRN and ACRN was 1.46 times and 2.47 times higher in the positive-to-negative converted group than in the continuing negative group. When comparing only the positive group with respect to the initial cotinine level, there was no significant difference in the hazard ratio of ACRN or CRN, irrespective of whether the follow-up cotinine level was negatively converted. This suggests that the possibility of CRN development within a few years is significantly increased even when cotinine levels are reduced. We believe that the ineffectiveness of this cotinine negative conversion was because of the long time required for the impact of smoking cessation to take effect. Even in a previous study, it took approximately 20 years for the prevalence of lung cancer to increase after cigarette consumption increased, and this is called the "time lag effect.[19]" Therefore, a longer period of study will be required to determine the effects of cotinine

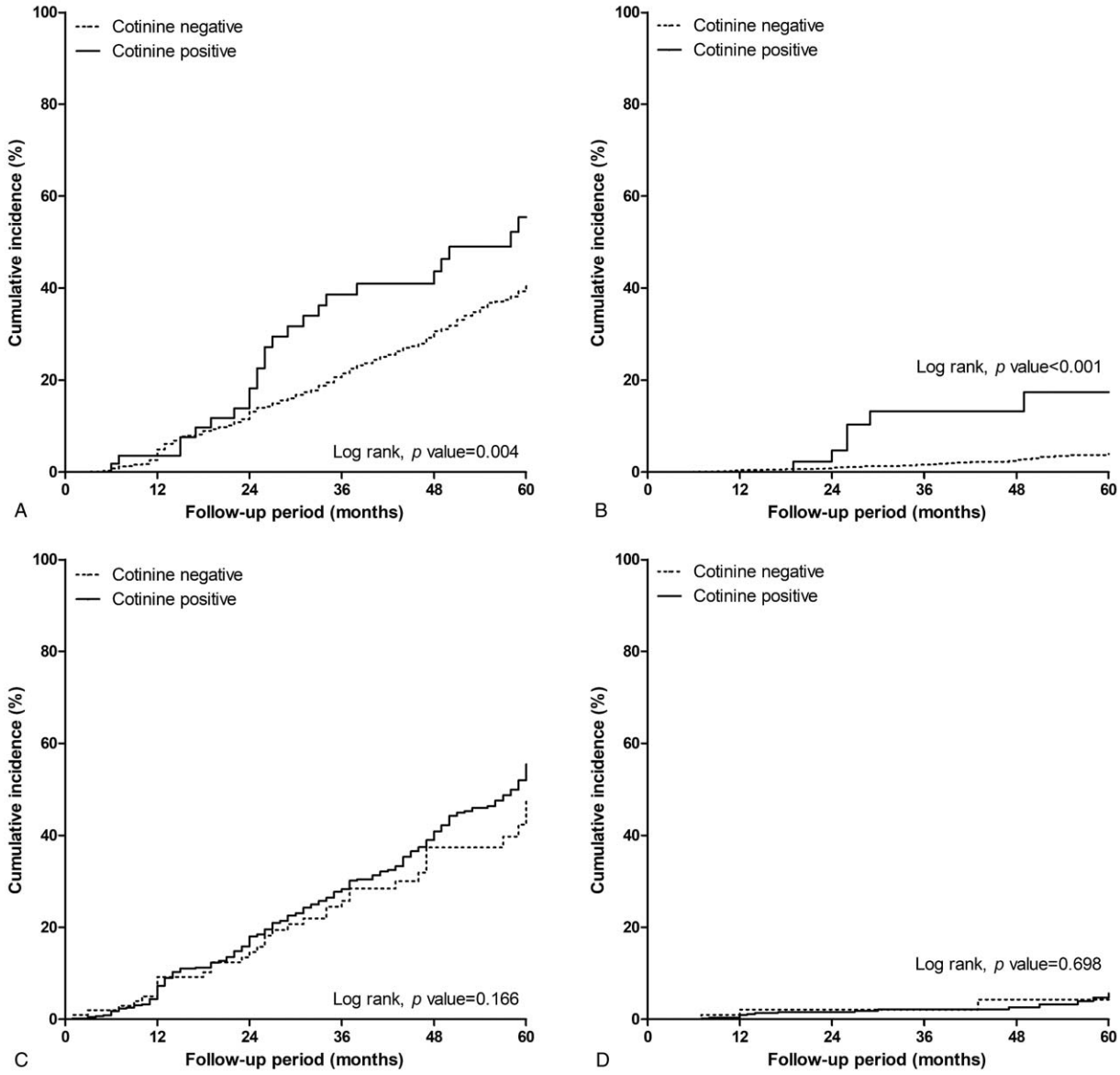

Figure 3. Cumulative incidence of colorectal neoplasm (CRN) and advanced colorectal neoplasm (ACRN) according to self-reported and cotinine status. A, CRN (never- and ex-smokers). B, ACRN (never- and ex-smokers). C, CRN (current smokers). D, ACRN (current smokers).

negative conversion in colorectal neoplasms. Jung et al[20] reported that when cotinine was observed in the polypectomy group during index colonoscopy, the risk of CRN was increased in the continuing positive or negative-to-positive converted group compared to the continuing negative group, which differed from the results of our study. This study was limited to patients who underwent polypectomy at the time of index colonoscopy, and as a screening for employees covered by the Korean Industrial Safety and Health Law, the participants were younger. Therefore, these differences may lead to differences in the results of the study; thus, more investigations will be needed.

When analyzing the duration of smoking cessation and development of CRN or ACRN, there was a significant difference in the incidence of ACRN, even though there was no significant difference in the incidence of CRN. These results imply that the duration of smoking cessation could affect the development of colorectal neoplasms. Nevertheless, this study was limited in accurately demonstrating the effects of smoking cessation periods because the follow-up period was not long enough. In addition, this study focused on the correlation between urinary cotinine level and development of colorectal neoplasms. Therefore, we expect that smoking cessation periods and development of colorectal neoplasms would be explored in future research.

There are some limitations to our study. First, those who voluntarily participated in the colonoscopy examinations may have more health concerns and better lifestyle, or economic statuses compared to the general population, which may have introduced a selection bias. Second, among the risk factors of CRN previously reported in the meta-analysis by Peng et al[3] medication history (non-steroidal anti-inflammatory drugs, aspirin), history of hypertension or diabetes mellitus, and eating habits (eating red meat or vegetables) could not be reflected.

However, the research included all risk assessments for factors such as age, sex, family history, BMI, and smoking status. Third, recall bias may occur because not only smoking status but also information about past history such as drinking status, colorectal polyp, or family history is self-reported. Fourth, the interval between index colonoscopy and last follow-up colonoscopy is relatively short (mean, 22 months), because patients tended to undergo screening slightly earlier than recommended. This may not further reflect the risk of developing additional CRNs or ACRNs. However, despite this short interval, the risk of CRN increased significantly with time. Fifth, the concentration of cotinine according to smoking may vary according to race, but this study was only performed on the South Korean population. Finally, follow-up was not performed on all included participants, and follow-up urinary cotinine was measured in only 31% of the participants (2556/8121).

Despite these limitations, our data provide an objective link to smoking status and the cumulative risk of CRN. Our findings indicate that urinary cotinine status is more related to CRN risk than self-report smoking status. Moreover, in the never- or ex-smokers by self-report who were cotinine-positive, the cumulative risk of CRN and ACRN increased. Moreover, cotinine positive-to-negative converted group showed an increased risk of CRN than the continuing negative group. Therefore, this study suggests that urinary cotinine measurement could provide helpful information of never- or ex-smokers undergoing screening colonoscopy.

Author contributions

B Kim was involved in formulating the study concept and design, acquisition of the data, analysis and interpretation of the data, drafting of the manuscript, and overall supervision. SJ Roh was involved in the acquisition, analysis, and interpretation of the data. JY Oh was involved in the acquisition of the data. KS Han, BC Kim, CW Hong, and DK Sohn were involved in data interpretation and improvement.

Conceptualization: Bun Kim.
Data curation: Seung Jae Roh, Ju Yeon Oh.
Formal analysis: Seung Jae Roh.
Funding acquisition: Bun Kim.
Investigation: Bun Kim.
Methodology: Bun Kim.
Project administration: Bun Kim, Kyung Su Han, Byung Chang Kim, Chang Won Hong, Dae Kyung Sohn.
Resources: Bun Kim.
Software: Seung Jae Roh.
Supervision: Bun Kim, Kyung Su Han, Byung Chang Kim, Chang Won Hong, Dae Kyung Sohn.
Writing – original draft: Seung Jae Roh.
Writing – review & editing: Bun Kim.

References

[1] Tsoi KK, Pau CY, Wu WK, et al. Cigarette smoking and the risk of colorectal cancer: a meta-analysis of prospective cohort studies. Clin Gastroenterol Hepatol 2009;7:682–8.
[2] Botteri E, Iodice S, Raimondi S, et al. Cigarette smoking and adenomatous polyps: a meta-analysis. Gastroenterology 2008;134:388–95.
[3] Peng L, Weigl K, Boakye D, et al. Risk scores for predicting advanced colorectal neoplasia in the average-risk population: a systematic review and meta-analysis. Am J Gastroenterol 2018;113:1788–800.
[4] Botteri E, Iodice S, Bagnardi V, et al. Smoking and colorectal cancer: a meta-analysis. JAMA 2008;300:2765–78.
[5] Kim NH, Jung YS, Yang HJ, et al. Association between cotinine-verified smoking status and risk of colorectal neoplasia. J Clin Gastroenterol 2019;53:e107–12.
[6] SRNT Subcommittee on Biochemical Verification . Biochemical verification of tobacco use and cessation. Nicotine Tob Res 2002;4:149–59.
[7] Benowitz NL, Bernert JT, Foulds J, et al. Biochemical Verification of Tobacco Use and Abstinence: 2019 Update. Nicotine Tob Res 2019.
[8] Wen CP, David Cheng TY, Tsai SP, et al. Are Asians at greater mortality risks for being overweight than Caucasians? Redefining obesity for Asians. Public Health Nutr 2009;12:497–506.
[9] Lieberman DA, Rex DK, Winawer SJ, et al. Guidelines for colonoscopy surveillance after screening and polypectomy: a consensus update by the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology 2012;143:844–57.
[10] Lee PN. Relation of urinary cotinine concentrations to cigarette smoking and to exposure to other people's smoke. Thorax 1991;46:274.
[11] Ogden MW, Morgan WT, Heavner DL, et al. National incidence of smoking and misclassification among the U.S. married female population. J Clin Epidemiol 1997;50:253–63.
[12] Baltar VT, Xun WW, Chuang SC, et al. Smoking, secondhand smoke, and cotinine levels in a subset of EPIC cohort. Cancer Epidemiol Biomarkers Prev 2011;20:869–75.
[13] Florescu A, Ferrence R, Einarson T, et al. Methods for quantification of exposure to cigarette smoking and environmental tobacco smoke: focus on developmental toxicology. Ther Drug Monit 2009;31:14–30.
[14] Chen R, Tavendale R, Tunstall-Pedoe H. Measurement of passive smoking in adults: self-reported questionnaire or serum cotinine? J Cancer Epidemiol Prev 2002;7:85–95.
[15] Rebagliato M. Validation of self reported smoking. J Epidemiol Community Health 2002;56:163–4.
[16] Connor Gorber S, Schofield-Hurwitz S, Hardt J, et al. The accuracy of self-reported smoking: a systematic review of the relationship between self-reported and cotinine-assessed smoking status. Nicotine Tob Res 2009;11:12–24.
[17] Cross AJ, Boca S, Freedman ND, et al. Metabolites of tobacco smoking and colorectal cancer risk. Carcinogenesis 2014;35:1516–22.
[18] Benowitz NL, Jacob P3rd. Metabolism of nicotine to cotinine studied by a dual stable isotope method. Clin Pharmacol Ther 1994;56:483–93.
[19] Loeb LA, Ernster VL, Warner KE, et al. Smoking and lung cancer: an overview. Cancer Res 1984;44(12 Pt 1):5940–58.
[20] Jung YS, Kim NH, Lee MY, et al. Effect of cotinine-verified change in smoking status on risk of metachronous colorectal neoplasia after polypectomy. Clin Gastroenterol Hepatol 2019;18:163–70.