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# Different modifiable risk factors for the development of non-advanced adenoma, advanced adenomatous lesion, and sessile serrated lesions, on screening colonoscopy

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**The development of premalignant colorectal polyps is significantly influenced by various lifestyle and modifiable risk factors. In our study, we used a large cohort of 9025 patients, who underwent screening colonoscopies at a university hospital, to assess the risk factors associated with the development of three different colorectal cancer precursor lesions: non-advanced adenomas (NAs), advanced adenomatous lesions (ADLs), and sessile serrated lesions (SSLs). Among the participants, 3641 had NAs, 836 had ADLs, and 533 had SSLs. We identified obesity, current smoking, and appendicular skeletal muscle mass as modifiable lifestyle risk factors that increase the development of NAs and ADLs (all $P < 0.05$). Furthermore, we found a positive correlation between the degree of obesity and an increased risk of developing NAs and ADLs (all $P$ for trend < 0.001), while non-smoking was associated with a decreased risk ($P$ for trend < 0.001 and 0.003, respectively). Smoking was the only modifiable risk factor for developing SSLs (adjusted odds ratio [aOR] 1.58; 95% confidence interval [CI] 1.20–2.07), and the risk was even higher in patients with metabolic syndrome (aOR 1.71; 95% CI 1.05–2.77). Addressing modifiable lifestyle factors such as smoking and obesity could play an important role in reducing the risk of both non-advanced and advanced adenomatous lesions. Smoking cessation is especially important as it is a significant modifiable risk factor for sessile serrated lesions.**

**Keywords** Colorectal neoplasm, Adenoma, Serrated polyp, Life style

Colorectal cancer (CRC) is one of the most common malignancies and a leading cause of cancer-related mortality worldwide[1]. Recent studies on the development of CRC has focused on the conventional adenoma-carcinoma pathway[2]. Nevertheless, accumulating evidence suggests that the serrated pathway is an alternative pathway, accounting for 15–30% of sporadic CRC cases[3].

Conventional adenomas and sessile serrated lesions (SSLs), the two main precursor lesions of these two distinct pathways of CRC, have different genetic and epidemiologic characteristics[4]. Conventional adenomas progress to invasive carcinoma by the accumulation of mutations in genes such as *APC, CNNTB1, KRAS, SMAD4,* and *TP42*. Moreover, these adenomas tend to be more prevalent in the distal colon and rectum[5]. Because of age-related changes in the DNA repair mechanism and other environmental factors, the risk of conventional adenomas increases with age and male sex. Conversely, the serrated pathway involves genetic mutation of *BRAF*, high CpG island methylator phenotype (CIMP), and escape of cellular senescence via methylation of tumor suppressor genes or mismatch repair genes[6]. Additionally, SSLs, unlike conventional adenomas, are less strongly associated with age and sex. Although some studies have reported a lower risk of SSLs in patients < 50 years, the risk did not increase substantially with age[7]. Similarly, the association between SSLs and sex is unclear with the risk of SSLs

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being approximately equal in men and women[4]. These differences in genetic and epidemiologic characteristics suggest that conventional adenomas and SSLs may have distinct risk factors of development and progression.

Additionally, lifestyle and modifiable risk factors play crucial roles in the development and progression of colorectal polyps including adenomas and SSLs. Previous studies have linked smoking, red meat consumption, low-fiber diet, and obesity as risk factors for adenomas[8–11]. Few studies have evaluated the risk factors associated with SSLs; the meta-analysis by Bailie et al., reported that smoking increased the risk of SSLs by more than three times (risk ratio, 3.40; 95% confidence interval [CI] 1.90 – 6.07)[12]. Other studies found that compared to never drinkers, alcohol consumption is associated with the risk of SSLs, with risk ratios from 1.1 to 1.8[13]. However, most previous studies did not clearly differentiate between SSLs and hyperplastic polyps because of the rarity and ambiguity of the definition of SSLs.

Therefore, in this study, we evaluated the modifiable risk factors associated with the development of three different precursor lesions of CRCs: non-advanced adenomas (NAs), advanced adenomatous lesions (ADLs), and SSLs, using a large screening colonoscopy database.

## Results

### Baseline characteristics of the study population

After exclusions, a total of 9025 patients were enrolled in the final analysis (Fig. 1). Table 1 presents the baseline characteristics of the study population. The median age of the enrolled participants was 48 years (interquartile ranges [IQR], 40–57 years), and 59.6% were male (n = 5375). Overall, 3641 (40.3%) participants had NAs, 836 (9.3%) had ADLs, and 533 (5.9%) had SSLs. Among the participants, 37.0% (n = 3338) had obesity (body mass index [BMI] over 25 kg/m$^2$), 34.0% (n = 3064) had central obesity, 25.2% (n = 2277) had metabolic syndrome, and 4.8% (n = 436) had sarcopenia. Nearly half of the participants (47.2%, n = 4257) were current or former smokers: 29.0% were current smokers, and 18.2% were former smokers. Furthermore, 76.2% (n = 6876) of the participants were alcohol drinkers: 70.2% were light drinkers, and 6.0% were heavy drinkers.

### Risk factors associated with the development of non-advanced adenoma, advanced adenomatous lesions and sessile serrated lesions

Multivariable analysis was performed to assess the risk factors associated with the development of precursor lesions in CRC (Fig. 2). For the development of NAs, significant risk factors included older age (aOR 2.360, 95% CI 2.086–2.668, $P = 0.044$), male sex (aOR 1.317, 95% CI 1.098–1.580, $P < 0.001$), hypertension (aOR 1.437, 95% CI 1.216–1.638, $P < 0.001$), obesity (aOR 1.227, 95% CI 1.077–1.398, $P = 0.002$), current smoking (aOR 1.358, 95% CI 1.215–1.517), current alcohol consumption (aOR 1.164, 95% CI 1.038–1.306), and high physical activity (aOR 1.112, 95% CI 1.037–1.250, $P = 0.048$). Additionally, appendicular skeletal muscle mass (ASM) was a significant protective factor against the development of NAs (aOR 0.981; 95% CI 0.963–0.999; $P = 0.044$). In the development of ADLs, older age (aOR 2.987, 95% CI 2.496–3.576, $P < 0.001$), male sex (aOR 1.630, 95% CI 1.193–2.225, $P = 0.003$), hypertension (aOR 1.254, 95% CI 1.075–1.463, $P = 0.004$), obesity (aOR 1.600, 95% CI 1.300–1.969, $P < 0.001$), and current smoking (aOR 1.695, 95% CI 1.396–2.059, $P < 0.001$) were significant risk factors. Furthermore, ASM was a significant protective factor against the development of ADLs (aOR 0.968; 95% CI 0.939–0.998; $P = 0.034$). Current smoking was the only significant risk factor for SSL development (aOR 1.394; 95% CI 1.012–1.764, $P = 0.006$).

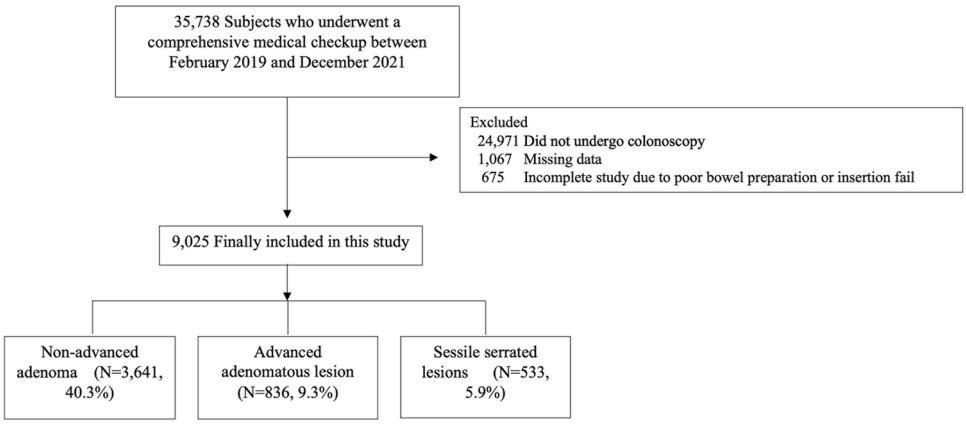



**Figure 1.** Flow diagram for the enrolled study subjects. In total, 9025 patients who underwent a comprehensive medical checkup were selected for statistical analysis after excluding 26,713 participants according to our exclusion criteria. NA was defined as 1 or 2 tubular adenomas < 10 mm in size. ADL was defined as any adenoma > 10 mm, ≥ 3 non-advanced adenomas, any adenoma with villous component, high-grade dysplasia, or invasive colorectal cancer. SSL was defined as one or more SSLs, with or without synchronous NAs.

| Characteristic | Overall patients (n = 9025) | Non-advanced adenomas (n = 3641, 40.3%) | Advanced adenomatous lesions (n = 836, 9.3%) | Sessile serrated lesions (n = 533, 5.9%) |
|---|---|---|---|---|
| Demographic variables | | | | |
| Age (median with IQR) | 48 (40–57) | 53 (44–61) | 57 (49–65) | 49 (41–59) |
| Sex (n, %) | | | | |
| Female | 3650 (40.4) | 1472 (35.6) | 237 (28.3%) | 238 (44.7%) |
| Male | 5375 (59.6) | 2346 (64.4) | 599 (71.7%) | 295 (55.3%) |
| Underlying diseases (n, %) | | | | |
| Diabetes | 551 (6.1) | 314 (8.6%) | 109 (13.0%) | 29 (5.4%) |
| Hypertension | 1371 (15.2) | 783 (21.5%) | 252 (30.1%) | 101 (18.9%) |
| Cerebrovascular disease | 58 (0.6) | 37 (1.0%) | 12 (1.4%) | 2 (0.6%) |
| Heart disease | 144 (1.6) | 78 (2.1%) | 25 (3.0%) | 12 (2.3%) |
| Dyslipidemia | 2351 (26.0) | 1104 (27.8%) | 239 (28.6%) | 150 (28.1%) |
| Modifiable lifestyle factors (n, %) | | | | |
| Obesity (BMI ≥ 25) | 3338 (37.0%) | 1530 (42.0%) | 412 (49.3%) | 211 (39.6%) |
| Central obesity | 3064 (34.0%) | 1362 (37.4%) | 343 (41.0%) | 199 (37.3%) |
| Sarcopenia | 436 (4.8%) | 237 (6.5%) | 78 (40.4%) | 26 (4.9%) |
| Sarcopenic obesity | 317 (3.5%) | 174 (4.8%) | 55 (6.6%) | 20 (3.8%) |
| Smoking status | | | | |
| Never | 4768 (52.8%) | 1847 (50.7%) | 400 (47.8%) | 252 (47.3%) |
| Former | 1639 (18.2%) | 656 (18.0%) | 144 (17.2%) | 93 (17.4%) |
| Current | 2618 (29.0%) | 1138 (31.3%) | 292 (34.9%) | 188 (35.3%) |
| Alcohol drinking status | | | | |
| Never | 2149 (23.8%) | 929 (25.5%) | 226 (27.0%) | 144 (27.0%) |
| Light | 6333 (70.2%) | 2464 (67.7%) | 556 (66.5%) | 355 (66.6%) |
| Heavy | 543 (6.0%) | 248 (6.8%) | 54 (6.5%) | 34 (6.4%) |
| Metabolic syndrome | 2277 (25.2%) | 1083 (29.7%) | 294 (35.2%) | 150 (28.1%) |
| Physical activity | | | | |
| High activity | 33.3% | 1343 (36.9%) | 335 (40.1%) | 184 (34.5%) |
| Moderate activity | 33.3% | 1119 (30.7%) | 244 (29.2%) | 168 (31.5%) |
| Low activity | 33.3% | 1179 (32.4%) | 257 (30.7%) | 181 (34.0%) |
| Laboratory variables (median with IQR) | | | | |
| White blood cell count, $10^3$/L | 5.2 (4.4–6.2) | 5.3 (4.4–6.3) | 5.3 (4.6–6.4) | 5.2 (4.3–6.3) |
| Hemoglobin, g/dL | 14.6 (13.6–15.5) | 14.7 (13.8–15.5) | 14.7 (13.8–15.5) | 14.3 (13.4–15.5) |
| Platelet, $10^9$/L | 245 (213–282) | 242 (210–279) | 239 (205–277) | 246 (214–282) |
| Serum creatinine, mg/dL | 0.84 (0.69–0.97) | 0.85 (0.71–0.98) | 0.85 (0.73–0.99) | 0.83 (0.68–0.96) |
| Total cholesterol, mg/dL | 203 (176–229) | 202 (174–230) | 197 (165–229) | 204 (179–232) |
| Triglyceride, mg/dL | 107 (77–157) | 113 (81–164) | 115 (84–166) | 103 (77–152) |
| HDL cholesterol, mg/dL | 56 (47–66) | 55 (47–64) | 53 (46–63) | 56 (47–66) |
| LDL cholesterol, mg/dL | 125 (104–147) | 125 (102–147) | 121 (96–145) | 127 (108–149) |
| Fasting glucose, mg/dL | 101 (95–110) | 104 (97–113) | 106 (99–118) | 102 (96–111) |
| Hemoglobin A1c | 5.4 (5.2–5.7) | 5.5 (5.3–5.8) | 5.6 (5.3–5.9) | 5.5 (5.2–5.7) |

**Table 1.** Baseline characteristics of the study population. IQR, interquartile range; BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoportein.

## Modifiable risk factors associated with the development of advanced adenomatous lesions and sessile serrated lesions

We evaluated the odds ratio (OR) for modifiable risk factors by adjusting for potential covariates to reveal the impact of precursor lesions on CRC. In the model adjusted for age, sex, underlying diseases, laboratory findings, alcohol, smoking status, physical activity, central obesity, and metabolic syndrome, an increasing degree of obesity was positively associated with increased risk of NA ($P$ for trend < 0.001) and ADLs ($P$ for trend < 0.001), and was more strongly associated with the development of ADLs: the adjusted OR (95% CI) for obese II (BMI ≥ 30) was 1.459 (1.134–1.871) for the development of NA and 1.729 (1.168–2.558) for the development of ADLs. However, obesity was not associated with a risk of developing SSLs (Table 2). In the model adjusted for age, sex, underlying diseases, laboratory findings, obesity, central obesity, physical activity, and metabolic syndrome, smoking status was positively associated with an increased risk of NA, ADLs, and SSLs ($P$ for trend < 0.001, $P$ for trend < 0.001, and $P$ for trend = 0.003, respectively). The risk was highest in current smokers and was attenuated in former smokers for all three precursor lesions of CRC. The association between smoking status and risk was highest for the development of ADLs (aOR for current smoking = 2.070; 95% CI 1.656–2.587), followed by SSLs (aOR

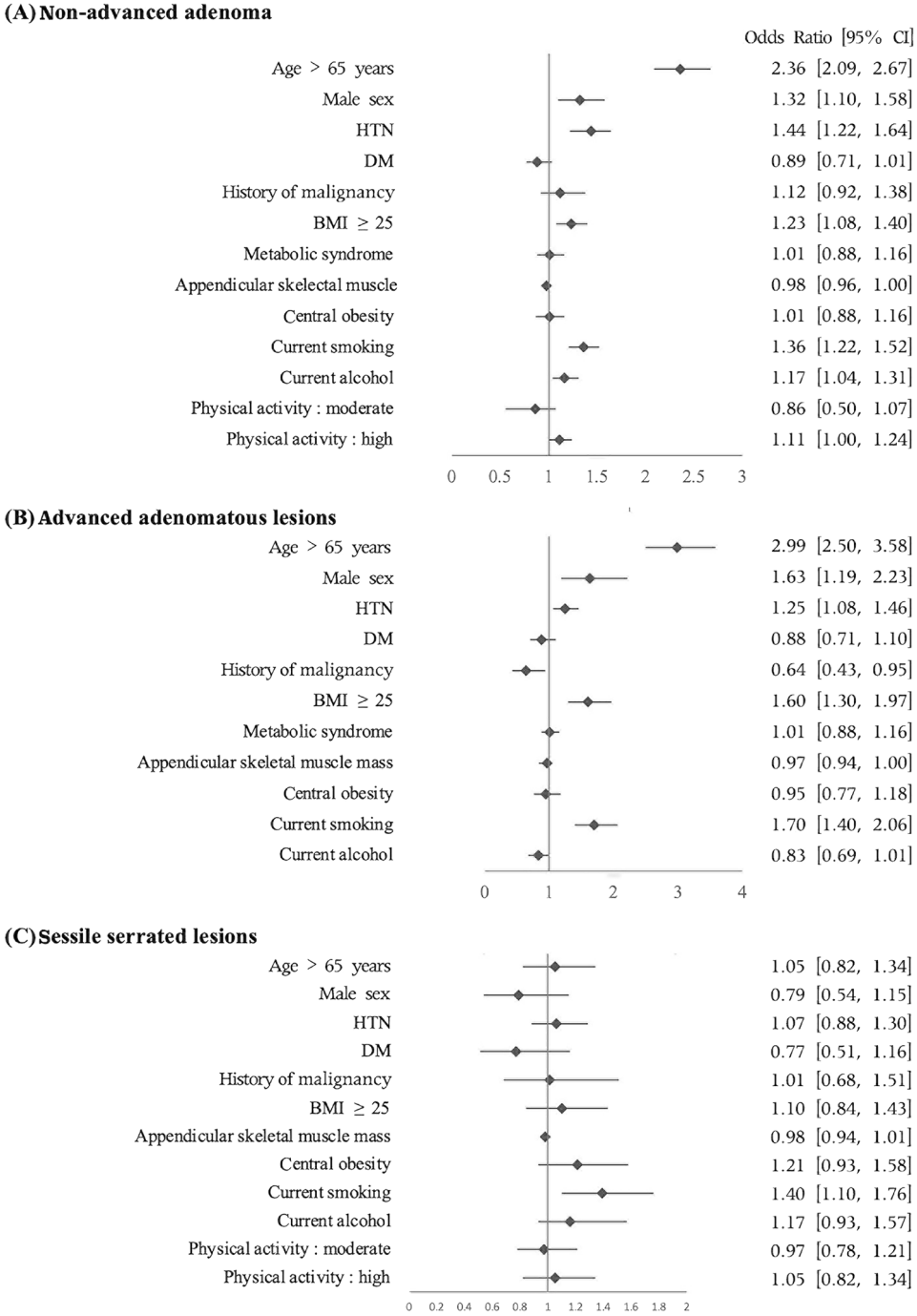



**Figure 2.** Association of risk factors with the development of non-advanced adenomas, advanced adenomatous lesions, and sessile serrated lesions. (**a**) Non-advanced adenomas (**b**) Advanced adenomatous lesions (**c**) Sessile serrated lesions. BMI, body mass index; DM, diabetes mellitus; Hx, history; HTN, hypertension. Odds ratio was adjusted for age, sex, underlying diseases, laboratory findings, alcohol consumption, smoking status, physical activity, obesity, central obesity, and metabolic syndrome.

for current smoking = 1.577; 95% CI 1.202–2.070) (Table 2). There was no increasing trend in the association between alcohol drinking status, ASM, and physical activity, and the development of all precursor lesions of CRC.

Subgroup analysis was performed to identify specific characteristics associated with modifiable risk factors for the development of CRC precursor lesions; the aORs for the development of ADLs were the highest in former and current smokers (3.803 and 5.175, respectively) among those with sarcopenia. Additionally, the aOR for the development of SSLs in current smokers was further increased in participants with metabolic syndrome (aOR 1.706, 95% CI 1.050–2.772) (Table 3).

| | Non-advanced adenoma aOR (95% CI)[a] | Advanced adenomatous lesions aOR (95% CI)[a] | Sessile serrated lesions aOR (95% CI)[a] |
|---|---|---|---|
| Obesity[b] | | | |
| Normal | Reference | Reference | Reference |
| Overweight | 1.201 (1.061–1.359)** | 1.001 (0.805–1.244) | 0.781 (0.601–1.015) |
| Obese I | 1.415 (1.215–1.646)** | 1.572 (1.230–2.010)** | 0.951 (0.688–1.295) |
| Obese II | 1.457 (1.134–1.871)** | 1.729 (1.168–2.558)** | 0.970 (0.589–1.597) |
| *P* for trend | < 0.001 | < 0.001 | 0.272 |
| Appendicular muscle mass | | | |
| Q1 | Reference | Reference | Reference |
| Q2 | 0.952 (0.820–1.107) | 1.102 (0.830–1.462) | 1.029 (0.885–1.365) |
| Q3 | 0.838 (0.675–1.043) | 0.843 (0.581–1.221) | 1.170 (0.760–1.801) |
| Q4 | 0.741 (0.583–0.940)* | 0.848 (0.566–1.272) | 0.831 (0.512–1.348) |
| *P* for trend | 0.038 | 0.118 | 0.103 |
| Smoking status | | | |
| Never | Reference | Reference | Reference |
| Former | 1.258 (1.109–1.428)** | 1.365 (1.098–1.698)** | 1.130 (0.860–1.485) |
| Current | 1.507 (1.320–1.722)** | 2.070 (1.656–2.587)** | 1.577 (1.202–2.070)** |
| *P* for trend | < 0.001 | < 0.001 | 0.003 |
| Alcohol drinking status | | | |
| Never | Reference | Reference | Reference |
| Light | 0.902 (0.806–1.009) | 0.840 (0.696–1.014) | 0.891 (0.715–1.109) |
| Heavy | 0.952 (0.775–1.171) | 0.718 (0.510–1.011) | 1.006 (0.664–1.524) |
| *P* for trend | 0.179 | 0.093 | 0.507 |
| Physical activity | | | |
| Q1 | Reference | Reference | Reference |
| Q2 | 0.862 (0.757–0.982)* | 0.824 (0.650–1.044) | 0.737 (0.554–0.955)* |
| Q3 | 0.969 (0.859–1.093) | 1.027 (0.836–1.261) | 0.947 (0.748–1.200) |
| Q4 | 1.083 (0.957–1.226) | 1.128 (0.922–1.379) | 0.999 ().783–1.274) |
| *P* for trend | 0.008 | 0.059 | 0.096 |

**Table 2.** Association of Modifiable Risk Factors with the development of Non-advanced adenoma, Advanced adenomatous lesions, and Sessile serrated lesions. *$P < 0.05$, **$P < 0.005$. aOR, adjusted odds ratio; CI, confidence interval; Q, quartile. [a]Odds ratio adjusted for age, sex, underlying diseases, laboratory findings, alcohol consumption, smoking status, physical activity, obesity, central obesity, and metabolic syndrome. [b]The obesity was defined according to body mass index (BMI); normal weight (BMI < 23), overweight (23 ≤ BMI < 25), obese I (25 ≤ BMI < 30), and obese II (BMI ≥ 30 mg/k$^2$).

## Discussion

Our study evaluated distinct modifiable risk factors associated with the development of each of the three precursor lesions of CRC: NAs, ADLs, and SSLs. Obesity and current smoking were identified as the two most significant modifiable risk factors, whereas higher ASM emerged as a significant protective factor against the development of NAs and ADLs. Notably, these risk factors exhibited a more robust association with the development of ADLs, indicating a heightened effect on this particular lesion. The association between current smoking and development of ADLs was more significant in patients with sarcopenia. Our study revealed that current smoking was the only modifiable risk factor for the development of SSLs, and this risk was further increased in patients with metabolic syndrome.

In South Korea, individuals can voluntarily undergo medical screening, including colonoscopy, either by paying for it themselves or having it sponsored by their company, independent of the national cancer screening program. Additionally, because Korean colonoscopists are highly specialized professionals who have undergone rigorous qualification examinations, a fact well recognized by the public, and because of the relatively low cost of colonoscopy, it is easily accessible[14]. Therefore, data from these large-scale medical health checkups, including colonoscopies, have been published in previous Korean studies. A study by Kim et al. analyzing screening colonoscopy data from 70,428 individuals showed that men with both metabolic abnormalities and obesity are at an increased risk of ADLs[15] Other studies reported the association between low skeletal muscle mass or visceral obesity and the risk of developing any adenoma or advanced adenomas/cancers[16–18]. However, none of these studies have evaluated the risk according to the subtypes of CRC precursor lesions.

In this study, obesity was one of the most significant modifiable risk factors for the development of precursor lesions of CRC in the conventional adenoma-carcinoma pathway. The degree of obesity was strongly associated with an increased risk: the highest risk was observed in severely obese patients with a BMI ≥ 30 kg/m$^2$. Moreover, the influence of obesity on risk was particularly pronounced for ADLs. Several previous studies have reported

| | Non-advanced adenomas Aor[a] (95% CI) | Advanced adenomatous lesions aOR[a] (95% CI) | Sessile serrated lesions aOR[a] (95% CI) |
|---|---|---|---|
| In subjects with sarcopenia[b] | | | |
| Obesity | | | N/A |
| Normal | Reference | Reference | |
| Overweight | 2.057 (0.818–5.173) | 2.406 (0.638–9.071) | |
| Obese I | 2.422 (0.985–5.956) | 2.073 (0.543–7.918) | |
| Obese II | 4.000 (1.295–12.359)* | 1.096 (0.215–5.593) | |
| *P* for trend | 0.121 | 0.314 | |
| Smoking status | | | |
| Never | Reference | Reference | Reference |
| Former | 1.940 (1.043–3.608)* | 3.803 (1.506–9.603)** | 1.252 (0.360–4.353) |
| Current | 1.949 (1.002–3.791)* | 5.175 (1.915–13.984)** | 1.732 (0.460–6.516) |
| *P* for trend | 0.065 | < 0.004 | 0.710 |
| In subjects with metabolic syndrome[c] | | | |
| Obesity[d] | | | N/A |
| Normal | Reference | Reference | |
| Overweight | 1.390 (0.950–2.034) | 0.939 (0.524–1.1682) | |
| Obese I | 1.872 (1.276–2.749)** | 1.671 (0.945–2.957) | |
| Obese II | 1.735 (1.102–2.730)* | 1.652 (0.834–3.274) | |
| *P* for trend | 0.009 | 0.048 | |
| Smoking status | | | |
| Never | Reference | Reference | Reference |
| Former | 1.120 (0.878–1.430) | 1.249 (0.848–1.840) | 1.061 (0.629–1.789) |
| Current | 1.189 (0.932–1.517) | 1.942 (1.336–2.881)** | 1.706 (1.050–2.772)* |
| *P* for trend | 0.373 | 0.001 | 0.043 |
| In subjects with central obesity[e] | | | |
| Obesity | | | N/A |
| Normal | Reference | Reference | |
| Overweight | 1.179 (0.705–1.973) | 1.306 (0.434–3.931) | |
| Obese I | 1.489 (0.915–2.425) | 2.197 (0.773–6.260) | |
| Obese II | 1.497 (0.888–2.522) | 2.312 (0.786–6.806) | |
| *P* for trend | 0.109 | 0.047 | |
| Smoking status | | | |
| Never | Reference | Reference | Reference |
| Former | 1.258 (1.024–1.545)* | 1.232 (0.880–1.726) | 1.314 (0.864–1.998) |
| Current | 1.354 (1.100–1.668)** | 1.734 (1.240–2.425)** | 1.468 (0.964–2.235) |
| *P* for trend | 0.012 | 0.040 | 0.190 |

**Table 3.** Adjusted risk analysis of development of adenoma in subjects with sarcopenia, metabolic syndrome, and central obesity. *$P < 0.05$, **$P < 0.005$, N/A, not applicable. aOR, adjusted odds ratio; CI, confidence interval. [a]Odds ratio adjusted for age, sex, underlying diseases, laboratory findings, alcohol consumption, smoking status, physical activity, obesity, central obesity, and metabolic syndrome. [b]Sarcopenia was defined as sarcopenia index (SI) < 0.789 in men and < 0.521 in women. The SI was calculated using the following formula: SI = ¼ total appendicular skeletal muscle mass (ASM) (kg)/body mass index (BMI) (kg/m$^2$). [c]Metabolic syndrome was defined as three or more of the following: (1) waist circumference ≥ 90 cm for men and ≥ 80 cm for women; (2) triglyceride (TG) ≥ 200 mg/dL or the use of TG lowering medication; (3) high-density lipoprotein-cholesterol (HDL-C) < 40 mg/dL for men and < 50 mg/dL for women or the use of HDL-C raising medication; (4) Blood pressure ≥ 130/85 mmHg or the use of antihypertensive medication; (5) Fasting glucose ≥ 100 mg/dL or the use of antidiabetic medication. [d]The obesity was defined according to body mass index (BMI); normal weight (BMI < 23), overweight (23 ≤ BMI < 25), obese I (25 ≤ BMI < 30), and obese II (BMI ≥ 30 mg/k$^2$). [e]Central obesity was defined as waist circumference ≥ 90 cm in men and ≥ 85 cm in women.

an association between obesity and the risk of colorectal adenoma, most of which were conducted in Western populations[2,13,19]. In a previous meta-analysis including 36 studies, a 5-unit increase in BMI was reported to be associated with a 19% increased risk of colorectal adenomas, and this risk was similar across races[20]. Few studies have also reported this association in Asian patients. In a recent Chinese population-based study, obesity (BMI ≥ 28 kg/m$^2$) increased the risk of colorectal adenomas by approximately 1.5 fold[21]. Although the mechanism by which obesity increases the risk of adenoma remains unclear, endocrine and inflammatory effect of adipose tissue has been suggested as a possible explanation. Among cytokines, leptin, which is highly expressed in adipose

tissue, triggers the division of colonic epithelial cells through the activation of p42/44 mitogen-activated protein kinase in colorectal cancer cell lines and adiponectin stimulates colorectal carcinogenesis[22]. Proinflammatory cytokines such as tumor necrosis factor, interleukin-6, and macrophage migration inhibitory factor, which are secreted by the immune response in adipose tissue, are thought to have direct tumorigenic effects on colorectal mucosa[23,24]. Significantly obesity, metabolic syndrome, and central obesity exhibited a synergistic impact on the risk of adenoma. Although the reason remains unclear, our results emphasize that the impact is not solely attributable to a single metabolic disease but rather underscores the tumorigenic effect of an unhealthy lifestyle associated with the occurrence of multiple metabolic diseases. Considering that a previous study reported a significant reduction in the risk of metachronous adenoma with a 5% weight loss, high-risk patients with multiple metabolic diseases should be considered for intensive lifestyle intervention and monitoring[25].

In our study, smoking was the sole significant factor for SSL and the lone common risk factor between SSL and adenoma. Few studies have suggested a more pronounced association between smoking and the serrated pathway than between smoking and conventional pathway. Previous studies demonstrated that smoking is a stronger risk factor for SSLs than for adenomas[19,26]. Furthermore, Anderson et al. reported that the risk of synchronous clinically significant serrated polyp and conventional high-risk adenoma was higher in current smokers, when compared to the risk of conventional high-risk adenomas alone[27]. The molecular pathological characteristics of microsatellite instability (MSI), CIMP, and DNA mutations such as *BRAF* and *KRAS* are widely recognized in the context of smoking and CRCs[28]. Given that MSI-high and CIMP-positive status are prominent features in CRC associated with the serrated pathway, the strong link between SSLs is not surprising[29]. In this study, current smoking was found to be a significantly stronger risk factor for SSLs than for conventional adenoma (aOR 1.660, 95% CI 1.264–2.180), although the risk was not as much for ADL. Notably, this risk is particularly prominent in patients with metabolic syndrome. Considering that the detection of SSL is difficult and associated with interval cancer, lifestyle modifications, including smoking cessation, should be considered in high-risk patients with recurrent SSLs.

Third, higher ASM played a significant protective role in the development of both NA and ADLs. Consistent with our findings, a previous large cross-sectional study found that low muscle mass is associated with an increased prevalence of colorectal neoplasia in both men and women, and an increased prevalence of advanced neoplasia in men[16]. Although the mechanisms linking lower ASM and adenoma occurrence remain uncertain, several potential explanations can be suggested. First, low muscle mass is associated with higher levels of inflammation-related serum proteins and cytokines. Fleming et al. reported that patients with low ASM had significantly higher systemic levels of C-reactive protein, interleukin-6, vascular endothelial growth factor, and expression of cell surface receptor CD14[30]. These inflammatory mediators and cell receptors have been shown to promote dysplastic transformation and cancer cell survival. Second, skeletal muscle is the major site of insulin-mediated glucose disposal and myokines synthesis[31]. The low skeletal muscle mass in patients reduced insulin-mediated glucose uptake and, subsequently, induced insulin resistance[18], which has been linked to hyperinsulinemia, higher levels of growth factors such as insulin-like growth factor I, and alterations in nuclear factor kappa B and peroxisome proliferator-activated receptor signaling, which may promote colon neoplasia through their effects on colonocyte kinetics[32]. Considering the protective effect of higher ASM against colonic adenoma, vigorous physical activity, particularly strength training to increase muscle mass, should be considered in high-risk patients with low muscle mass.

This study has several strengths. First, this large-scale study evaluated the association between different modifiable risk factors and the development of colorectal polyps. Second, we standardized the diagnosis of colorectal polyps by uniformly applying current pathology criteria. Third, because this was a cohort study based on screening colonoscopy, the findings can be broadly applied to the general population. Fourth, within the same population group, a risk assessment for each type of colon polyp, such as NAs, ADLs, and SSL, was performed. However, several limitations should be considered when interpreting the results. First, because specific dietary patterns were not studied in detail, the effects of inappropriate diets such as high-fat or low-fiber diets on the risk of polyp development were not investigated. Second, the study questionnaire could not fully capture all aspects of smoking history, including whether the patient was a light smoker or a heavy smoker, owing to the complexity of smoking patterns. Third, there was no information available on medication history, including the use of aspirin, nonsteroidal anti-inflammatory drugs, or statins, which have been shown to reduce the incidence of colorectal cancer.

This large cross-sectional study demonstrated an association between various modifiable risk factors and colorectal polyp development, on screening colonoscopy, and showed that smoking and obesity are strongly linked to an increased risk of developing NA and ADL. Particularly, smoking was the only significant modifiable lifestyle risk factor for SSL. Further prospective, long-term follow-up studies are required to confirm these observations.

## Methods

### Study population

In this cross-sectional cohort study, participants who underwent a comprehensive medical checkup between February 2019 and December 2021 at a tertiary university-affiliated hospital were considered eligible. All individuals voluntarily underwent the medical checkup, either paying for it themselves or having it sponsored by their company. Patients who underwent qualifying colonoscopy, in which the appendiceal orifice was visualized, were enrolled in the study. The exclusion criteria were as follows: (1) participants who did not undergo colonoscopy; (2) insufficient data for the assessment of risk factors including obesity, alcohol consumption, smoking, sarcopenia, and physical activity; and (3) incomplete colonoscopy due to inadequate bowel preparation and insertion failure. Finally, 9025 subjects were selected for statistical analysis (Fig. 1). The study protocol was approved by the

Institutional Review Board of Ewha Seoul Hospital (IRB No. 2023-02-040), and was performed in accordance with the ethical guidelines of the World Medical Association's Declaration of Helsinki.

### Definition of non-advanced adenoma, advanced adenomatous lesion, and sessile serrated lesion

NA was defined as 1 or 2 tubular adenomas < 10 mm in size. ADL was defined as any adenoma > 10 mm, ≥ 3 non-advanced adenomas, any adenoma with villous component, high grade dysplasia, or invasive colorectal cancer. The diagnosis of SSL was confirmed through histological examination, conducted by the pathologists, when there was at least one unequivocal aberrant crypt. Individuals who had one or more SSLs, with or without synchronous NAs, were classified under the SSLs group.

### Definitions of study parameters

A standardized, self-administered questionnaire was used to collect information on demographic characteristics, smoking status, alcohol consumption, preexisting medical conditions, and medication use. Smoking status was categorized as current, former, or never smoked. Alcohol consumption status was categorized as heavy, light, or never drinkers. Heavy alcohol consumption was defined as a daily alcohol intake > 30 g/day for men and > 20 g/day for women. Patients who did not meet these criteria were classified as light drinkers.

The participants were categorized based on BMI according to the Korean Society for the Study of Obesity practice guidelines: underweight (BMI < 18.5 kg/m$^2$), normal weight (18.5 kg/m$^2$ ≤ BMI < 23 kg/m$^2$), overweight (23 kg/m$^2$ ≤ BMI < 25 kg/m$^2$), obese I (25 kg/m$^2$ ≤ BMI < 30 kg/m$^2$), and obese II (BMI ≥ 30 kg/m$^2$) kg/m$^2$.[33] Central obesity was defined as waist circumference ≥ 90 cm for men and ≥ 85 cm for women[34]. Metabolic syndrome was defined as the presence of three or more of the following: (1) waist circumference ≥ 90 cm for men and ≥ 80 cm for women; (2) triglyceride (TG) ≥ 200 mg/dL or the use of TG lowering medication; (3) high-density lipoprotein-cholesterol (HDL-C) < 40 mg/dL for men and < 50 mg/dL for women or the use of HDL-C raising medication; (4) blood pressure ≥ 130/85 mmHg or the use of antihypertensive medication; (5) fasting glucose ≥ 100 mg/dL or the use of antidiabetic medication[35]. Hypertension was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or the use of antihypertensive medication[36]. Diabetes was defined as fasting glucose level ≥ 126 mg/dL or glycated hemoglobin A1C (Hb A1C) ≥ 6.5%, or the use of insulin of oral hypoglycemic agents[37]. Dyslipidemia was defined as one or more of the following: (1) total cholesterol ≥ 240 mg/dL; (2) TG ≥ 200 mg/dL; (3) HDL-C < 40 mg/dL (4) low-density lipoprotein-cholesterol (LDL-C) ≥ 160 mg/ dL; or (5) specific drug treatment[38].

For sarcopenia, ASM was measured using multi-frequency bioelectric impedance analysis (InBody770; InBody Co., Ltd., Seoul, Korea), which showed excellent agreement with dual-energy X-ray absorptiometry and magnetic resonance imaging[39]. The sarcopenia index (SI) was calculated using the following formula: SI = ¼ total ASM (kg)/BMI (kg/m$^2$). Sarcopenia was defined as SI < 0.789 in men and < 0.521 in women, based on a recent recommendation[40]. Sarcopenic obesity is defined as the presence of sarcopenia and BMI ≥ 25 kg/m$^2$[41]. Detailed physical activity assessments were initially obtained through self-reported questionnaires, which were structured identically to those used in the National Health Information Data base of the National Health Insurance Service[42]. On the basis of this survey, weekly physical activity-related energy expenditure (metabolic equivalent task [MET]-min/week) was calculated by summing the product of frequency, intensity, and duration[43].

### Statistical analysis

Baseline characteristics were expressed as frequencies and percentages for categorical variables and as medians and IQR for continuous variables. Student's t-test, $\chi 2$ test, and analysis of variance were used to compare variables. We performed multivariable logistic regression analysis to evaluate risk factors for the development of CRC precursor lesions. In addition, multivariable logistic regression analysis was performed to determine the independent association between modifiable lifestyle factors including obesity, appendicular muscle mass, smoking status, and alcohol drinking status and the risk of NAs, ADLs, and SSLs. This association was examined using models adjusted for potential confounding and mediating variables, including age, sex, underlying diseases, laboratory findings, alcohol consumption, smoking status, physical activity, obesity, central obesity, and metabolic syndrome. The severity of modifiable lifestyle factors was categorized according to the previously described definitions. In subgroup analysis, this analysis was repeatedly performed in individuals with sarcopenia, metabolic syndrome, and central obesity. All the adjusted OR and 95% CIs were calculated using this model. All statistical analyses were performed using SPSS (version 23.0; IBM, Armonk, NY, USA). A *P*-value of < 0.05 was considered statistically significant.

### Ethics declarations and informed consent

The study protocol was approved by the Institutional Review Board of Ewha Seoul Hospital (IRB No. 2023 02 040), and was performed in accordance with the ethical guidelines of the World Medical Association's Declaration of Helsinki. Informed consent was waived from the IRB due to the retrospective design.

### Conference presentation

Presented as a poster presentation at the Korea Digestive Disease Week 2023.

## Data availability

The datasets generated during and / or analysed during the current study are available from the corresponding author on reasonable request.

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## Author contributions

Study concept and design: E.M.S., A.R.C.; Acquisition of data: A.R.C., H.S., H.K., G.K., S.K. Statistical analysis and interpretation of data: E.M.S., A.R.C.; Drafting of the manuscript: E.M.S., A.R.C.; Critical revision of the manuscript for important intellectual content: C.H.T., J.R.B., Y.P.; K.N.S., S.A.J., E.M.S.; Study supervision: E.M.S.

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## Competing interests

The authors declare no competing interests.

## Additional information

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