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Association of Smoking and Flat Adenomas: Results from an Asymptomatic Population Screened with A High Definition Colonoscope

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Abstract

Background—Flat adenomas represent a morphologically distinct class of polyps that may be difficult to detect but little is known regarding risk factors for these lesions. Identification of risk factors for these lesions may aid in colorectal cancer (CRC) screening since patients at risk for these lesions may require special imaging techniques. Smoking, an important risk factor for CRC, may be associated with molecular changes that increase the risk for flat adenomas.

Objective—To examine the association between smoking and flat adenomas.

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This prospective, cross-sectional study was conducted at Stony Brook University, Stony Brook, NY.

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Contribution of each author

Joseph C Anderson, M.D.: study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; statistical analysis; obtained funding; administrative, technical, or material support; study supervision

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Design—Prospective, cross-sectional study.

Setting—University hospital endoscopy center.

Patients—We enrolled asymptomatic patients presenting for CRC screening.

Interventions—We screened patients with high-definition (1080i signal), wide angle (170 Field of View) Olympus 180-series colonoscope. We collected demographics, medication use, family history of CRC, diet history and a smoking history.

Main Outcome Measurements—Polyp morphology which was assessed using the Japanese Research Society Classification (JRSC).

Results—600 patients were enrolled. We observed that smoking was associated with having a flat adenoma of any size (Adjusted Odds Ratio = 2.53; 95% CI, 1.60-4.00), having only flat adenomas that were ≥ 6 mm in diameter Adjusted (OR=3.84; 95% CI, 2.02-7.32) as well as flat advanced adenomas (Adjusted OR=2.81; 95% CI, 1.08-7.30).

Limitations—The study design may not account some confounding variables and provides no information regarding smoking status at the time of initiation of flat adenomas.

Conclusions—Smoking was associated with flat adenomas in our population. Our findings may explain the earlier onset of CRC in smokers as well as the advanced stage that they present with as compared to non-smokers. Smokers may require screening with high definition colonoscopes to detect flat adenomas.

Background

Flat, non-polypoid adenomas were initially described by Muto over 20 years ago¹, and are considered to be more aggressive than their polypoid counterparts. This is supported by many reports in the Japanese literature^{2, 3} with more variation in the Western published reports⁴⁻¹⁰. Yashiro et al provided molecular evidence to suggest that de-novo cancers may arise from these morphologically distinct lesions¹¹. Although screening colonoscopy has been shown to decrease mortality and incidence of colorectal cancer (CRC)¹², there are emerging data suggesting that the magnitude of protection may be higher for the left colon than the right colon¹³; flat lesions may play a role in explaining missed colorectal cancers on the right side of the colon.

Little is known regarding the risk factors for these flat lesions which may account for over half of all adenomas detected with a high definition colonoscope¹⁴. Information regarding risk factors for flat adenomas would aid in screening since patients with important risk factors may require the use of new technologies such as high definition colonoscopy^{14, 15}. In addition, special techniques may be needed for their removal¹⁶⁻¹⁸.

Smoking has been shown to be an important risk factor for colorectal neoplasia in several screening studies^{19, 20} as well as population based studies²¹⁻²⁵. Recent American College of Gastroenterology guidelines state that in addition to age and a family history of CRC, smokers may warrant special consideration such as an earlier age for screening²⁶. Smokers may be at risk for an increased frequency of mutations in the mismatch repair (MMR) enzymes²⁷ associated with micro-satellite instability²⁸. Ogawa et al have observed that micro-satellite instability is higher in non-polypoid cancers than polypoid tumors²⁹. Micro-satellite instability may also be associated with serrated lesions³⁰. In addition, BRAF³¹ and K-ras have been associated with smoking as well as with non-polypoid lesions³²⁻³⁴ and serrated lesions³⁵. Thus smokers may be at higher risk for flat colorectal neoplasia.

The aim of our study was to investigate smoking as a risk factor for flat adenomas in an average-risk population undergoing screening colonoscopy.

Methods

Subjects

Our study was a prospective, cross-sectional examination with a target population of consecutive asymptomatic patients presenting to Stony Brook University Medical Center between November 2006 and October 2007 for screening colonoscopy. The study was approved by our institutional review board and written informed consent was obtained. Patients were excluded if they had gastrointestinal symptoms (hematochezia, change in bowel habits or abdominal pain), a prior colonic neoplasia, prior colon resection, inflammatory bowel disease or prior endoscopy (colonoscopy or sigmoidoscopy) within the past 10 years.

Data, which included demographics, known colorectal cancer risk factors and medications, were entered into a two-page standard form by a nurse who used a structured script for all queries based on validated questionnaires^{36, 37}. A Spanish language questionnaire was used by a Spanish speaking clinician. Heights and weights were obtained by the nurse on the day of endoscopy. Body mass index was calculated by dividing the weight (kilograms) by the square of height (meters). Obesity was defined as a BMI ≥ 30 .

Patients were asked about current or past cigarette use, the number of packs-per-day, the number of years they had smoked, the year of cessation for those who had quit and any changes in their past smoking patterns. As outlined above, this information was ascertained using a standard script³⁷. These figures were used to calculate exposure in pack-years. We defined three smoking categories¹⁹: 1) Non-smokers, 2) Heavy exposure: ≥ 10 pack years and still smoking or quit within the past 10 years, 3) Low exposure: < 10 pack years or those who quit more than 10 years prior. For the main analyses, we compared non-smokers to the heavy exposure group based on our previous studies^{19, 38}. A family history of colorectal and other cancers was recorded and included the relationship to the patient as well as age at diagnosis. Patients were queried about a past history of diabetes and cholecystectomy. Information was collected about medications including past or current use of insulin, statins, aspirin use, NSAIDs/COX2 inhibitors, multivitamins (including Vitamin D), folic acid, hormone replacement therapy and calcium supplementation. Patients reported alcohol (glasses of red/white wine, shots/drinks liquor, cans/bottles beer) consumed per week.

Patients also completed a ten-question dietary survey based on modified questions from the Behavioral Risk Factor Surveillance System State Questionnaire³⁶. The patients were queried about the average number of red meat, fish, chicken, fiber, whole grain products, tomato based food, salad, fruit and vegetable servings per week over the past 5 years. Finally participants were asked about weekly exercise and baseline activity level.

Colonoscopy

One endoscopist using a high-definition (1080i signal), wide angle (170 Field of View) Olympus 180-series colonoscope (Olympus America Inc, Center Valley, PA) performed all colonoscopies with a withdrawal time of at least 8 minutes. All polyps were photo-documented next to a snare catheter for in-vivo measurement, retrieved for histology and morphology was classified according to the Japanese Research Society for Cancer of Colon and Rectum (JRSC) guidelines^{18, 39, 40}. We used a standard method to visualize the polyp for morphologic classification. Specifically, the colon was insufflated so that the polyp was visualized and photo-documented in this setting. Any lesion that was determined to be Ip, Is or Ips was considered polypoid and those that were IIa, IIb or IIc were considered flat or non-polypoid. Advanced neoplasia included large (≥ 1 cm) adenomas (including serrated adenomas), villous adenomas ($>25\%$ villous), high-grade dysplasia or cancer. Polyp size was confirmed by the pathology report⁴¹. Two experienced endoscopists confirmed the

morphology from the photo-documentation for a representative group of adenomas which were randomly selected from our analyzed sample.

Statistical Analysis

We performed statistical analysis using SPSS 17 (Chicago, IL). Descriptive statistics including proportions for categorical data and means for continuous data and standard deviations were calculated. Baseline characteristics were compared between participants classified by smoking status using chi-square or Fisher's Exact tests for categorical data and Mann-Whitney U or t tests for continuous data. We considered results to be significant if the 2-tailed p-value was < 0.05 .

Uni-variate analyses were performed and all risk factors whose association had a p value of less than 0.1 were entered into multivariate logistic regression models. When constructing the models, we did not test for interactions for inclusion of variables in the model. Odds ratios and their 95% confidence intervals were calculated using the regression models with categories of flat adenomas as the outcomes. The final models included those variables that had a p value less than 0.10.

Our main outcome was flat advanced adenomas but we also examined the association with smoking for those who only had flat adenomas ≥ 6 mm and those patients who had any flat adenomas. We present the data in order of increasing size of adenoma. The final multivariable logistic regression analysis was considered the primary definitive result as it determined those variables independently associated with the main outcome of main interest, the finding of flat adenomas, after adjusting for the contributions of the other variables. All other p-values are not corrected for multiple testing, because they were from univariate statistical tests taken as exploratory or they were secondary findings, for descriptive purposes only.

Results

There were 605 patients presenting to the Stony Brook University Medical Center for screening who participated. We excluded one patient with inflammatory bowel disease and four with poor colon preparation. 600 participants (median (Interquartile Range) =56 years (51-61)) (252 males, 348 females) had complete colonoscopy. There were 313 non-smokers, 115 heavy smokers and 172 low exposure smokers. The median number of pack years in the heavy smoking group was 32 (IQR=21-42). Most had smoked more than 20 pack years (79.1%; 91/115). The demographic and lifestyle characteristics as classified by smoking status are shown in Table 1 and Table 2 respectively. We had few patients with a family history of CRC (3.5%). As compared to the non-smokers, the heavy smokers were more likely to describe themselves as Caucasian, regularly use NSAID's, eat more red meat and consume fewer fruits and tomato products. We compared the ages of the different smoking groups using the Mann Whitney U test due to the non-parametric nature of the age distribution of the participants.

We removed 172 patients with low exposure smoking and thus compared the non-smokers (n=313) to the heavy exposure smokers (n=115) for the remainder of the analyses except where noted.

We examined the risk of heavy smoking in patients who had at least one flat adenoma detected, including those who may have had synchronous polypoid lesions. There were 127 patients who had at least one flat adenoma of any size in our analyzed sample of 428 (313 non-smokers and 115 heavy exposure smokers). After uni-variate analyses examining the factors as dichotomous variables, heavy smoking, obesity, age greater than or equal to 56

years, male gender, lack of exercise, not using statins all had an association with any flat adenomas ($p < 0.10$). As shown in Table 3, after multi-variate analysis, heavy smoking, age and male gender were all statistically associated with any flat adenomas of any size.

Another outcome we examined was the risk for having only flat adenomas that were greater than or equal to 6 mm in size. These patients had no polypoid lesions. When we examined the risk for the 44 patients in our analyzed sample (313 non-smokers and 115 heavy) who only had flat adenomas ≥ 6 mm, we observed that smoking, not taking statins regularly and obesity ($\text{BMI} \geq 30$) were significantly associated with this outcome. After multivariate analysis, only smoking and obesity were significantly related (Table 4). Of note, only 7 of these 44 patients (16.0%) had flat lesions distal to the splenic flexure (data not shown).

There were 18 flat advanced adenomas in our analyzed sample; 10 large (> 1 cm in diameter) tubular adenomas, 6 serrated lesions and 2 villous adenomas. There were 4 heavy smokers with serrated adenomas. After univariate analysis, we observed that heavy smoking, BMI, gender and red meat consumption had associations ($p < 0.10$) with having an advanced flat adenoma. After multivariate analysis, heavy smoking was the only variable which was found to be predictive of advanced flat colorectal neoplasia (Table 5).

To explore the question of whether a dose relationship existed between smoking and flat adenomas we divided all of the smokers, which included the 172 low exposure smokers, into 2 groups. These groups were based on our previous work quantifying smoking exposure and advanced colorectal neoplasia³⁸. The two groups were: those smokers with greater than or equal to 30 pack years ($n=87$) and those with less than 30 pack years ($n=200$). When compared to the lower pack year exposure group (< 30 pack years), the higher exposure group (≥ 30 pack years) had an increased risk for having any flat adenoma (Adjusted OR = 2.28; 95% Confidence Interval: 1.32-3.93, $p=0.003$) or having only flat adenomas ≥ 6 mm (Adjusted OR = 3.14; 95% CI: 1.46-6.74, $p=0.003$). There were insufficient numbers of advanced flat adenomas for this analysis.

Finally to further explore the dose relationship we entered the 172 low exposure patients, thus having 3 separate smoking groups, back into the regression analyses with the 313 non-smokers as the reference group and the results were not significantly changed for all outcomes (data not shown).

Discussion

Our study demonstrates that smoking is an important risk factor for flat colorectal adenomas. To our knowledge, our data from an asymptomatic population are the first to demonstrate that smoking has a strong association with these potentially important morphologically distinct lesions. Not only was smoking associated with all flat adenomas but it was also a risk factor for those patients who only had flat adenomas that were larger than 6 mm in diameter. These patients did not have any polypoid adenomas.

Our findings are important since detecting these adenomas may require special high definition colonoscopes⁴². We chose to examine lesions that were greater than or equal to 6 mm because of the clinical relevance of these lesions in issues such as screening with CT Colonography^{43, 44}. We observed that most of these lesions were found proximal to the splenic flexure. Thus if chromo-endoscopy is found to be beneficial in detecting flat adenomas, the entire colon with special attention to the right side will be important in smokers. Using a definition of smoking that has been previously published^{19, 38} we identified a group of smokers with a high amount of tobacco exposure. Our smokers had significant exposure with an average of over 30 pack years and most having smoked more than 20 pack years in total. In addition we observed a dose dependant relationship between

smoking and having any flat adenoma or having only flat adenomas greater than or equal to 6 mm. This is the exposure level that we previously found to be important for advanced neoplasia³⁸ and this is similar to the level which has been determined by recent guidelines to be significant to warrant potential earlier screening for CRC²⁶.

With respect to the histology in the flat adenomas in the heavy smokers, most of the polyps were tubular adenomas. There was a statistically significant association between smoking and advanced flat adenomas but the numbers were small. There were 2 villous adenomas but no cases of high grade dysplasia or adenocarcinoma. Most of the serrated adenomas were in smokers but the numbers were very small. It has been postulated that smokers may be at risk for serrated lesions potentially with BRAF as a molecular link^{31, 35}. More studies will be needed to confirm this hypothesis.

Our findings may explain the observation that smokers often present with CRC at a younger age and at a more advanced stage than non-smokers⁴⁵⁻⁴⁸. If flat polyps are associated with de-novo cancers, the findings of an earlier onset and progression in smokers may be due to their association with flat adenomas.

The strengths of our study included the fact that all of the study participants had thorough examinations of their colon which were performed with a high definition colonoscope by an endoscopist who is experienced with identifying flat lesions. Furthermore we prospectively examined all known risk factors for CRC in our diverse patient population, almost all of whom were at average risk for CRC as defined by family history. In addition all of the patients were asymptomatic and had never been endoscopically screened for CRC.

The limitations of our study include that our findings may be applicable only to populations similar to our relatively young population which had more women than men. These demographics may explain our lower rate of advanced histopathology as compared to a recent Veterans' Affairs study by Soetikno et al⁸. Benya et al demonstrated a similarly low rate of advanced pathology⁴. Finally, although the endoscopist was not blinded to the hypothesis, the results of the patients' questionnaire were not revealed until after the documentation of the procedure. This study has a cross-sectional design the main limitation of which is that it provides no information regarding the exposure (smoking) status at the time of initiation of flat adenomas, the outcome of interest. Confounding may be present regardless of the study design, and consists of a distortion of the association between the main exposure and the outcome, brought about by a failure to control for the effect of a third variable related to both of them.

Although we did not observe an aggressive histology in our flat adenomas, these polyps, especially the larger adenomas, are important precursors to colorectal cancer. Their morphology may make them difficult to detect and thus identifying a risk factor that may increase a patient's predilection for them is clinically important. In summary, we provide the first data that demonstrate that smoking may be significantly associated with flat adenomas, especially those that may be the most clinically relevant.

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Table 1

Demographics by Smoking Classification

	Non-Smokers N=313	Heavy Smokers N=115	Low Exposure Smokers N=172
Age Mean (SD)	56.2(8.2)	55.7(7.0)	59.0(8.1)
Gender (% Male)	114 (36.4%)	53 (46.1%)	85 (49.4%)
BMI (% Obese)	96 (30.7%)	39 (33.9%)	50 (29.1%)
Family History CRC	11 (3.5%)	2 (1.7%)	8 (4.7%)
Pack Years Mean (SD)	0	35.0(18.9)	13.6(10.2)
Education (% HS Graduate)	247 (78.9%)	99 (86.1%)	146 (84.8%)
Ethnicity (% Caucasian)	*159 (50.8%)	76 (66.1%)	121 (70.3%)
Diabetes Mellitus (%)	31 (9.9%)	15 (13.0%)	26 (15.1%)
Regular NSAID use (%)	*48 (15.3%)	30 (26.1%)	37 (21.5%)
Daily ASA use (%)	123 (39.3%)	54 (47.0%)	76 (44.2%)
Statins (%)	96 (30.7%)	32 (27.8%)	49 (28.5%)
Multivitamin (%)	152 (48.6%)	53 (46.1%)	91 (52.9%)
Folic Acid (%)	35 (11.2%)	12 (10.4%)	23 (13.4%)
Calcium use (%)	98 (31.3%)	29 (25.2%)	55 (32.0%)
HRT use (% of females)	32 (16.1%)	14 (22.6%)	18 (20.7%)

p values refer to comparison of Non-smokers and Smokers

*
p<0.01

Table 2

Lifestyle Characteristics by Smoking Classification

	Non-Smokers N=313	Heavy Smokers N=115	Low Exposure Smokers N=172
Fruits (% with ≥ 2 servings/wk)	[†] 221 (70.6%)	56 (48.7%)	112 (65.1%)
Vegetables (% with ≥ 2 servings/wk)	250 (79.9%)	80 (69.5%)	131 (76.2%)
Salad (% with ≥ 2 servings/wk)	180 (57.5%)	59 (51.3%)	101 (58.7%)
Fish (% with ≤ 1 serving/wk)	249 (75.6%)	93 (80.9%)	147 (85.5%)
Dairy (% with < 2 servings/wk)	71 (22.7%)	27 (23.5%)	33 (19.2%)
Chicken (% with ≥ 2 serving/week)	197 (62.9%)	73 (63.5%)	99 (57.6%)
Red Meat (% with ≥ 2 servings/wk)	[†] 88 (28.1%)	52 (45.2%)	54 (31.4%)
WholeGrains(% with <2 servings/wk)	113 (36.1%)	53 (46.1%)	58 (33.7%)
Tomato prods (% with ≤ 1 serving/wk)	[*] 127 (40.6%)	60 (52.2%)	77 (44.8%)
Exercise (% with ≥ 2 hour/wk)	93 (29.7%)	29 (25.2%)	58 (33.7%)

p values refer to Non-smokers vs Smokers

*
p<0.05[†]
p<0.01

Table 3

Risk Factors for Having Any Flat Adenomas

Risk Factor (n)	Cases	Uni-variate Analysis OR (95% CI)	Multivariate Analysis OR (95% CI)
Heavy Smokers (n=115) vs Non-smokers (n=313)	51	2.49 (1.59-3.90)	2.53 (1.60-4.00)
Family History of CRC (n=13) vs Ave Risk	5	1.50 (0.48-4.68)	---
Female (n=261) vs Male Gender	66	0.59 (0.39-0.90)	0.60 (0.39-0.93)
Age $\geq$ 56 years (n=202) vs Age < 56	72	1.72 (1.13-2.62)	1.88 (1.22-2.90)
BMI $\geq$ 30 (n=135) vs BMI < 30	45	1.29 (0.83-2.00)	---

Table 4Risk Factors for Having Only ≥ 6 mm Flat Adenomas

Risk Factor	Cases	Uni-variate Analysis OR (95% CI)	Multivariate Analysis OR (95% CI)
Heavy Smokers (n=115) vs Non-smokers(n=313)	24	3.86 (2.04-7.32)	3.84 (2.02-7.32)
Family History of CRC (n=13) vs Ave Risk	2	1.62 (0.35-7.53)	---
Female (n=261) vs Male Gender	25	0.83 (0.44-1.55)	---
Age ≥ 56 years (n=202) vs Age < 56	24	1.39 (0.74-2.60)	---
BMI ≥ 30 (n=135) vs BMI < 30	21	2.16 (1.15-4.06)	2.14 (1.12-4.09)

Table 5

Risk Factors for Having Advanced Flat Adenomas

Risk Factor	Cases	Uni-variate Analysis OR (95% CI)	Multivariate Analysis OR (95% CI)
Heavy Smokers (n=115) vs Non-smokers (n=313)	9	2.87 (1.11-7.42)	2.81 (1.08-7.30)
Family History of CRC (n=13) vs Ave Risk	1	1.95 (0.24-15.88)	---
Female (n=261) vs Male Gender	14	2.31 (0.75-7.14)	---
Age $\geq$ 56 years (n=202) vs Age < 56	10	1.41 (0.55-3.67)	---
BMI $\geq$ 30 (n=135) vs BMI < 30	9	2.25 (0.87-5.81)	2.20 (0.85-5.70)