RESEARCH LETTER

Using a Population Database to Assess Lifestyle Factors in Serrated Polyposis Syndrome and Sporadic Sessile Serrated Lesions

Serrated polyposis syndrome (SPS) presents with multiple serrated colon polyps and has an increased risk for the development of colorectal cancer (CRC).[1] Similar to SPS, individuals with sporadic sessile serrated lesions (SSLs) also have an elevated risk of CRC.[1] Lifestyle risk factors of SPS or sporadic SSL have not been well studied in large population database. Prior data suggest certain modifiers such as tobacco usage as a risk factor in the development of SPS and sporadic SSL.[2] Aspirin has been suggested to reduce the risk of SSLs.[3,4] To examine lifestyle factors that may contribute to the risk of SPS or SSL development, we investigated these factors in a retrospective cohort of 59 SPS and 753 SSL patients in Utah for a statewide healthcare system linked to a population database containing decades of demographic and medical records linked to extensive genealogy records, the Utah Population Database (UPDB).

Patients who met World Health Organization criteria for SPS (n = 59) were obtained from hereditary cancer registries of the Huntsman Cancer Institute at the University of Utah between 2001 and 2017. Patients identified as having SSL (n = 753) and age- and gender-matched (2:1) controls with normal colonoscopy reports (n = 1622) were selected from University of Utah Health patient data from 2000 to 2012 linked to the UPDB as described previously (1). Lifestyle diagnosis histories of obesity (body mass index [BMI] ≥30), tobacco, alcohol, cannabis, and aspirin use prior to earliest patient enrollment (SPS) or endoscopy date (SSL) were obtained from International Classification of Diseases (ICD) 9 and ICD10 codes in University of Utah Health and statewide diagnoses records (1996–2022) linked to the UPDB, as listed in Table A2. Lifestyle factors and risk of SPS or SSL compared with normal controls were estimated from multivariable conditional logistic regression models accounting for sex and age with covariate adjustment for tobacco, alcohol, and cannabis use disorders and aspirin use. Risk of SPS was further adjusted for family history (FH) of CRC, while the risk of SSL was stratified by the absence or presence of CRC FH in the first-, second-, and third-degree relatives of study subjects.

Patient characteristics and their lifestyle factors are described in Table A1. Over 90% of patients self-reported as white. SPS patients were younger than SSL and had higher tobacco usage. SPS, SSL, and normal colonoscopy patients did not differ by sex. Personal history of CRC and FH of CRC and gastrointestinal malignancies were higher in patients with SPS.

Tobacco use conferred a modest increased risk of SPS development; however, significance was not reached (relative risk [RR]: 1.87; 95% confidence interval [CI]: 0.86–4.09) (Table). Tobacco use increased the risk of sporadic SSL, both in those who had a FH of CRC (n = 165, RR 2.63, 95% 1.50–4.60) or without a CRC FH (n = 588, RR 2.10, 95% CI 1.61–2.73). Aspirin use was not associated with the risk of SSL in subjects with FH of CRC (RR 0.77 95% CI 0.31–1.90) but interestingly showed a statistically significant increased risk in those without CRC FH (RR 1.86, 95% CI 1.07–3.25). Neither obesity nor cannabis use increased the risk of SPS or SSL; alcohol use did not increase the risk of SSL and was excluded from the SPS model due to sample size. All risk variables were analyzed to compare SSL with first-degree relatives vs SSL with more distant relatives with CRC and no significant differences were observed.

Our study showed using tobacco increased the risk of sporadic SSL by greater than twofold irrespective of the FH of CRC and may modestly increase the risk of SPS. Tobacco has shown an increased risk of development of SSL in prior studies although these studies did not differentiate SSL individuals with and without FH of CRC and demonstrate tobacco as an independent risk factor of development of SSL.[3] These findings may suggest environmental factors may act independently of genetic factors to drive SSL development.

Prior studies have shown an association of high BMI and alcohol that was not found in our study.[2,5] Our study cohort was comprised of mostly healthy individuals (normal BMI, no/low alcohol usage) and may not be ideal for assessment of these variables. Cannabis and its association with SPS and SSL, has not previously been studied to our knowledge, however our cohort had only a small number of diagnosed cannabis users and we did not observe an association.

Aspirin did not show a protective effect in individuals with SSL and our study suggests it may increase the risk of SSL occurrence. It should be noted that our SSL cohort had only 3% of individuals with a history of aspirin intake. Aspirin may also represent a surrogate of an underlying inflammatory process (for which aspirin was being used) rather than an independent factor. This association is contrary to some prior studies that have shown a protective effect of aspirin.[3,4,6,7] One prior study showed no benefit of aspirin in *BRAF*-mutated CRC suggesting aspirin to have unlikely major effect on serrated pathway cancers.[8] Another recent study showed no long-term benefit from aspirin in the prevention of advanced serrated lesions.[9] Some of the prior studies that demonstrated benefit included aspirin within nonsteroidal anti-inflammatory drugs for analysis (except study by Bouwens[6] and Wallace et al[3]) that makes it difficult to assess the role of aspirin individually with SSL. It is relevant to note that Wallace et al included hyperplastic polyps in their study and Bouwens et al studied no aspirin usage as opposed to daily aspirin intake and its

Table. Risk Variables Analyzed in SPS, SSL (With/Without Family History of CRC)

	SPS (n = 59)			SSL with FH CRC (n = 165)			SSL without FH CRC (n = 588)		
Characteristic	OR	95% CI	*P* value	OR	95% CI	*P* value	OR	95% CI	*P* value
Obese (BMI ≥ 30)	1.09	0.49, 2.41	.83	1.51	0.94, 2.42	.085	1.10	0.85, 1.42	.47
Tobacco use disorders	1.87	0.86, 4.09	.12	2.63	1.50, 4.60	**<.001**	2.10	1.61, 2.73	**<.001**
Aspirin use	0.32	0.04, 2.81	.30	0.77	0.31, 1.90	.57	1.86	1.07, 3.25	**.029**
Cannabis use disorders	0.55	0.07, 4.13	.56	1.01	0.25, 4.11	.99	0.66	0.34, 1.29	.23
Family history of colorectal cancer	1.94	0.90, 4.18	.090						
Alcohol use disorders				0.87	0.24, 3.16	.83	1.09	0.51, 2.32	.83

The bold values states that the comparison was statistically significant (basically a difference in findings were noted).
OR, odds ratio.

association with SSL. One prior study has shown a decreased risk of SPS from nonsteroidal anti-inflammatory drugs.[7] We found only one recent study that evaluated the use of aspirin in the development of CRC in SPS and did not show an association.[7]

The biggest strength of our study is the ability to use a population and statewide database and risk stratify based on detailed multigenerational FH of cancer. Limitations include the use of ICD9/10 codes to determine information on covariates. For tobacco use disorders, ICD codes have been shown to effectively identify smoking status.[10] We could not quantify the amount of tobacco usage. Individuals with alcohol abuse disorders may be captured in the medical records as compared to moderate users. Similarly, ICD codes for long-term aspirin use may not adequately capture over-the-counter purchases, duration of exposure, or dosage.

In conclusion, tobacco avoidance may protect against the occurrence of SSL. Further studies to assess aspirin exposure through text searches of electronic medical records or patient questionnaires are warranted. In addition, mechanistic studies are needed to understand the role of aspirin in SPS and sporadic SSL.

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Supplementary Materials

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Abbreviations used in this paper: **BMI, body mass index; CRC, colorectal cancer; FH, family history; RR, relative risk; SPS, serrated polyposis syndrome; SSL, sessile serrated lesion; UPDB, Utah Population Database**

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Conflicts of Interest:
The authors disclose no conflicts.

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Ethical Statement:
This study was approved by the institutional review board at the University of Utah.

Data Transparency Statement:
Data for this study were attained from the UPDB. UPDB data are available to other researchers through controlled access. Access is governed and approved by the Resource for Genetic and Epidemiologic Research (RGE) committee at the University of Utah, which includes representatives of the data providers whose data are included in UPDB. RGE approval must be linked to an Institutional Review Board (IRB) protocol which may be held external to the University of Utah.

Reporting Guidelines:
STROBE. Cells in tables with counts <11 are suppressed in accordance with Utah DHHS guidelines.