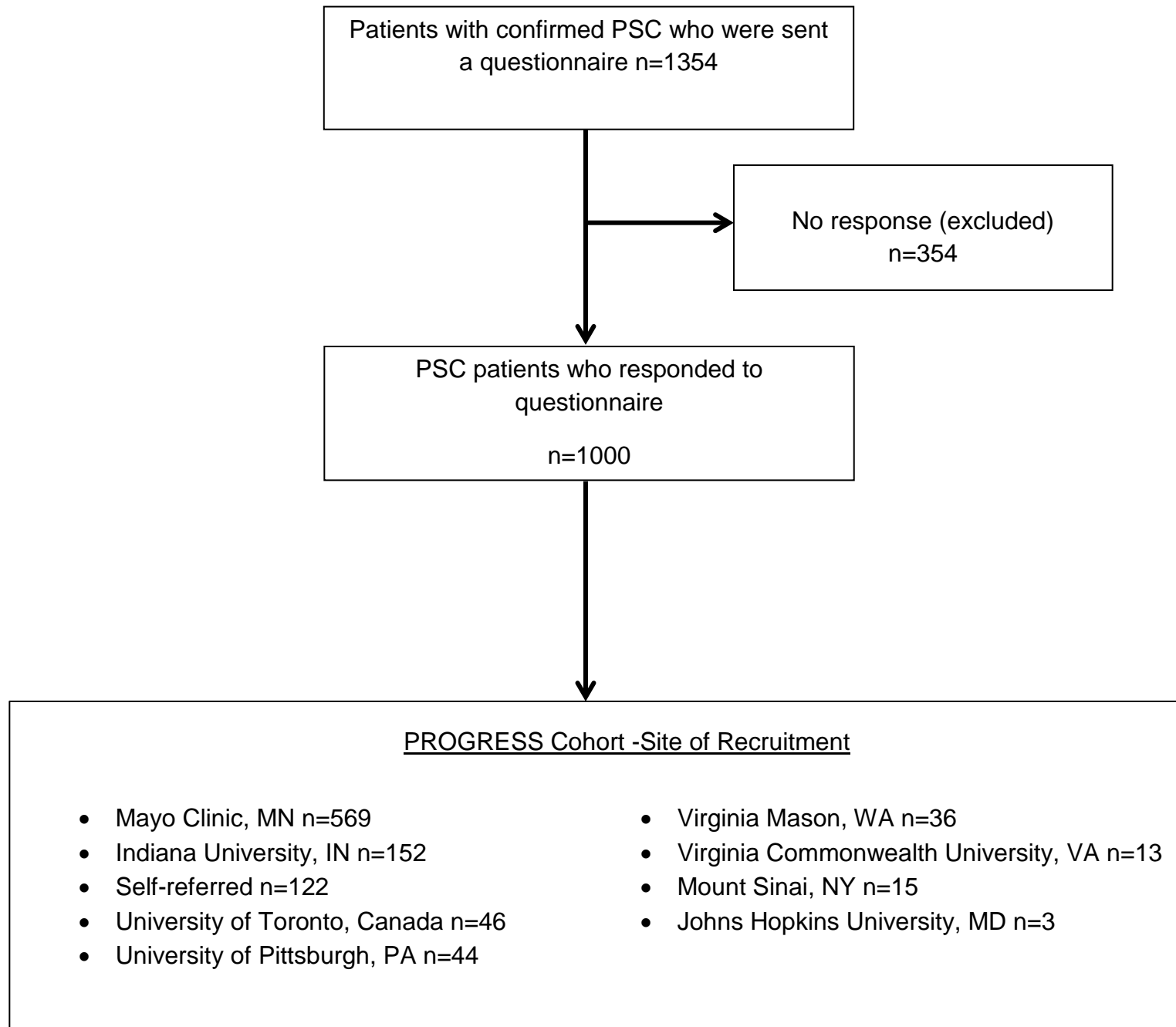


Supplementary Figure 1. Site of Case Recruitment



Abbreviations: PSC (primary sclerosing cholangitis); PROGRESS: PSC Resource of Genetic Risk, Environment and Synergy Studies).

Supplementary Table 1. Comorbidities, Chewing Tobacco & Second Hand Smoke Exposure Reported Among Cases and Controls<sup>1</sup>

	<b>Controls (n=663)</b>	<b>Cases (PSC) (n=1000)</b>	<b>P-value</b>
<b>Lupus</b>	0%	0%	-
<b>Scleroderma</b>	0%	0%	-
<b>Multiple Sclerosis</b>	0%	0%	-
<b>Polymyositis</b>	0%	0%	-
<b>Vitiligo</b>	1%	0%	0.10
<b>Sarcoidosis</b>	0%	0%	-
<b>Rheumatoid Arthritis</b>	2%	3%	0.58
<b>Sjogrens Syndrome</b>	0%	1%	0.67
<b>Raynaud's disease</b>	3%	2%	0.50
<b>Chewing Tobacco Use (ever)</b>	7%	5%	0.59
<b>Age Started Chewing Tobacco</b>	20.0 (14.0-17.0)	19.5 (18.0-25.0)	0.53
<b>Average Use of Chewing Tobacco</b>			0.29
Once a Month or Less	25%	2%	
Several Times Per Month	21%	16%	

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Several Times Per Week	15%	24%	
Daily	39%	58%	
<b>Ever Lived with a Smoker</b>	63%	58%	0.78
<b>Hours Per Day Exposed to Smoke in House</b>	4.0 (2.0-8.0)	4.0 (2.0-8.0)	0.34
<b>Yrs Lived with a Smoker</b>			0.78
Less than 1 yr	1%	2%	
1-5 yrs	12%	9%	
6-10 yrs	12%	9%	
More than 11 yrs	75%	77%	
<b>Ever Worked with a Smoker</b>	53%	48%	0.34
<b>Hours per Day Exposed to Smoke at Work</b>	4.0 (1.0-8.0)	4.0 (1.0-8.0)	0.64
<b>Yrs Worked with a Smoker</b>			0.46
Less than 1 yr	3%	7%	
1-5 yrs	37%	35%	

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6-10 yrs	22%	21%
More than 11 yrs	38%	37%

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<sup>1</sup> Control values are age- and gender-adjusted to the distribution of the cases. Therefore, the number of subjects is not reported. The P-value is derived from the logistic regression model adjusting for age and gender.

Abbreviations: PSC (primary sclerosing cholangitis); yrs (years).

Supplementary Table 2. Sensitivity Analysis Excluding those Younger than 21 years<sup>1</sup>

	<b>OR (95% CI), P-value</b> <b>PSC-IBD vs. Controls</b>	<b>OR (95% CI), P-value</b> <b>PSC-woIBD vs. Controls</b>
<b>Smoked Cigarettes (ever)</b>	0.5 (0.4-0.7) p<.001	0.9 (0.7-1.3) p=0.55
<b>Currently Smoke Cigarettes</b>	0.5 (0.1-1.0) p=0.06	1.3 (0.5-3.1) p=0.56
<b>Pack Yrs</b>	0.8 (0.7-0.96) p=0.01	1.0 (0.8-1.1) p=0.61
<b>Appendix Removal</b>	1.7 (1.3-2.3) p<.001	1.1 (0.8-1.6) p=0.51
<b>Tonsillectomy</b>	0.8 (0.6-1.1) p=0.14	1.0 (0.7, 1.4) p=0.92
<b>Tonsillectomy as Child (0-19 Years)</b>	0.9 (0.7-1.2) p=0.70	1.1 (0.8-1.6) p=0.53
<b>Recurring UTIs</b>	1.6 (1.1-2.3) p=0.03	1.9 (1.2-3.) p<0.01
<b>Frequency of Recurring UTI</b>	1.2 (0.8-1.7) p=0.47	1.1 (0.7-1.8) p=0.73
<b>Hormone Based Contraceptive Use (ever)</b>	0.7 (0.5-1.1) p=0.10	0.9 (0.5-1.6) p=0.74
<b>HRT use (ever)</b>	0.6 (0.4-0.8) p<0.01	0.5 (0.3-0.8) p<0.01
<b>Freq Steak or Burger (fastfood or panfried)</b>	1.3 (1.1-1.6) p<0.01	1.1 (0.9-1.4) p=0.41

	<b>OR (95% CI), P-value PSC-IBD vs. Controls</b>	<b>OR (95% CI), P-value PSC-woIBD vs. Controls</b>
<b>Freq Steak/Burger (grilled)</b>	0.9 (0.8-0.96) p<0.01	0.9 (0.8-0.98) p=0.02
<b>Steak or Burgers (how well done)</b>	1.3 (1.2-1.5) p<.001	1.2 (1.1-1.4) p<0.01
<b>Freq Chicken (fastfood or panfried)</b>	1.2 (1.0-1.6) p=0.06	1.4 (1.01-1.8) p=0.04
<b>Freq Chicken (grilled)</b>	0.8 (0.8-0.9) p<.001	0.9 (0.8-1.3) p=0.11
<b>Freq Grilled/Barbequed Meat (C-S-B)</b>	0.8 (0.7- 0.9) p<.001	0.8(0.7-0.97) p=0.02
<b>Freq Fastfood/Panfried (C-S-B)</b>	1.4(1.1-1.8) p<0.01	1.3(1.0-1.8) p=0.09
<b>Eat Fish (yes/no)</b>	0.4 (0.2-0.6) p<.001	0.5 (0.3-0.9) p=0.02
<b>Freq Fish (any method)</b>	0.4 (0.3-0.6) p<.001	0.7(0.4-1.2) p=0.26
<b>Freq Vegetables</b>	0.9 (0.8-0.9) p<.001	0.9 (0.9-0.99) p=0.04
<b>Freq Fruit</b>	0.9 (0.8-0.9) p<.001	1.0 (0.9-1.0) p=0.52
<b>Freq Milk</b>	1.0 (0.9-1.0) p=0.07	0.9 (0.9- 0.97) p<0.01

<sup>1</sup>Control values are age- and gender-adjusted to the distribution of the cases. Therefore, the number of subjects is not reported. The P-value is derived from the logistic regression model adjusting for age and gender.

Controls n=652; PSC-IBD n=693; PSC-wolBD n=251

Abbreviations: IBD (inflammatory bowel disease); PSC (primary sclerosing cholangitis); PSC-IBD (PSC with IBD); PSC-wolBD (PSC without IBD); odds ratio (OR); CI (confidence interval); hormone replacement therapy (HRT); years (yrs); urinary tract infections (UTI's);freq (frequency); C-S-B (chicken-steak-burger).

Supplementary Table 3. Sensitivity Analysis Excluding Self-Reported Diagnosis of Primary Sclerosing Cholangitis<sup>1</sup>

	<b>OR (95% CI), P-value</b> <b>PSC-IBD vs. Controls</b>	<b>OR (95% CI), P-value</b> <b>PSC-woIBD vs. Controls</b>
<b>Smoked Cigarettes (ever)</b>	0.5 (0.4-0.7) p<.001	0.9 (0.7-1.3) p=0.55
<b>Currently Smoke Cigarettes</b>	0.5 (0.1-1.0) p=0.06	1.3 (0.5-3.1) p=0.56
<b>Pack Yrs</b>	0.8 (0.7-0.96) p=0.01	1.0 (0.8-1.1) p=0.61
<b>Appendix Removal</b>	1.7 (1.3-2.3) p<.001	1.1 (0.8-1.6) p=0.51
<b>Tonsillectomy</b>	0.8 (0.6-1.1) p=0.14	1.0 (0.7, 1.4) p=0.92
<b>Tonsillectomy as Child (0-19 Years)</b>	0.9 (0.7-1.2) p=0.70	1.1 (0.8-1.6) p=0.53
<b>Recurring UTIs</b>	1.6 (1.1-2.3) p=0.03	1.9 (1.2-3.) p<0.01
<b>Frequency of Recurring UTI</b>	1.2 (0.8-1.7) p=0.47	1.1 (0.7-1.8) p=0.73
<b>Hormone Based Contraceptive Use (ever)</b>	0.7 (0.5-1.1) p=0.10	0.9 (0.5-1.6) p=0.74
<b>HRT use (ever)</b>	0.6 (0.4-0.8) p<0.01	0.5 (0.3-0.8) p<0.01



	<b>OR (95% CI), P-value</b> <b>PSC-IBD vs. Controls</b>	<b>OR (95% CI), P-value</b> <b>PSC-woIBD vs. Controls</b>
<b>Freq Steak or Burger (fastfood or panfried)</b>	1.3 (1.1-1.6) p<0.01	1.1 (0.9-1.4) p=0.41
<b>Freq Steak/Burger (grilled)</b>	0.9 (0.8-0.96) p<0.01	0.9 (0.8-0.98) p=0.02
<b>Steak or Burgers (how well done)</b>	1.3 (1.2-1.5) p<.001	1.2 (1.1-1.4) p<0.01
<b>Freq Chicken (fastfood or panfried)</b>	1.2 (1.0-1.6) p=0.06	1.4 (1.01-1.8) p=0.04
<b>Freq Chicken (grilled)</b>	0.8 (0.8-0.9) p<.001	0.9 (0.8-1.3) p=0.11
<b>Freq Grilled/Barbequed Meat (C-S-B)</b>	0.8 (0.7- 0.9) p<.001	0.8(0.7-0.97) p=0.02
<b>Freq Fastfood/Panfried (C-S-B)</b>	1.4(1.1-1.8) p<0.01	1.3(1.0-1.8) p=0.09
<b>Eat Fish (yes/no)</b>	0.4 (0.2-0.6) p<.001	0.5 (0.3-0.9) p=0.02
<b>Freq Fish (any method)</b>	0.4 (0.3-0.6) p<.001	0.7(0.4-1.2) p=0.26
<b>Freq Vegetables</b>	0.9 (0.8-0.9) p<.001	0.9 (0.9-0.99) p=0.04
<b>Freq Fruit</b>	0.9 (0.8-0.9) p<.001	1.0 (0.9-1.0) p=0.52

	<b>OR (95% CI), P-value</b> <b>PSC-IBD vs. Controls</b>	<b>OR (95% CI), P-value</b> <b>PSC-woIBD vs. Controls</b>
<b>Freq Milk</b>	1.0 (0.9-1.0) p=0.07	0.9 (0.9- 0.97) p<0.01

<sup>1</sup>Control values are age- and gender-adjusted to the distribution of the cases. Therefore, the number of subjects is not reported. The P-value is derived from the logistic regression model adjusting for age and gender.

Controls n=652; PSC-IBD n=693; PSC-woIBD n=251

Abbreviations: IBD (inflammatory bowel disease); PSC (primary sclerosing cholangitis); PSC-IBD (PSC with IBD); PSC-woIBD (PSC without IBD); odds ratio (OR); CI (confidence interval); hormone replacement therapy (HRT); years (yrs); urinary tract infections (UTI's);freq (frequency); C-S-B (chicken-steak-burger) .

Supplementary Table 4. Sensitivity Analysis Excluding Patients with Liver Transplant at Time of Questionnaire<sup>1</sup>

	<b>OR (95% CI), P value</b> <b>PSC-IBD vs. Controls</b>	<b>OR (95% CI), P value</b> <b>PSC-wolBD vs. Controls</b>
<b>Smoked Cigarettes (ever)</b>	0.5 (0.4-0.7) p<.001	1.0 (0.7-1.4) p=0.87
<b>Currently Smoke Cigarettes</b>	0.4 (0.1-1.3) p=0.12	1.6 (0.7- 4.0) p=0.27
<b>Pack Yrs</b>	0.9 (0.7-1.0) p=0.15	1.0 (0.8-1.1) p=0.64
<b>Appendix Removal</b>	1.7 (1.3- 2.3) p<.001	1.0 (0.7-1.6) p=0.78
<b>Tonsillectomy</b>	0.8 (0.6-1.0) p=0.055	0.9 (0.7-1.3) p=0.75
<b>Tonsillectomy as Child (0-19 Years)</b>	0.9 (0.7-1.2) p=0.35	1.0 (0.7-1.5) p=0.93
<b>Recurring UTIs</b>	1.6 (1.02-2.4) p=0.04	1.8 (1.1-3.1) p=0.02
<b>Frequency of Recurring UTIs</b>	1.2 (0.8-1.8) p=0.42	1.0 (0.6-1.7) p=0.89
<b>Hormone Based Contraceptive Use (ever)</b>	0.8 (0.5-1.2) p=0.24	0.9 (0.5-1.5) p=0.67
<b>HRT use (ever)</b>	0.4 (0.3- 0.7) p<.001	0.5 (0.3-0.8) p<0.01
<b>Freq Steak/Burgers (fastfood/panfried)</b>	1.2 (1.1-1.5) p=0.04	1.1 (0.9-1.5) p=0.37

	<b>OR (95% CI), P value</b> <b>PSC-IBD vs. Controls</b>	<b>OR (95% CI), P value</b> <b>PSC-w/oIBD vs. Controls</b>
<b>Freq Steak/Burgers (grilled)</b>	0.9 (0.8-0.96) p<0.01	0.9 (0.8-0.98) p=0.02
<b>Steak/Burger (how well done)</b>	1.3 (1.1-1.5) p<.001	1.3 (1.1-1.5) p<0.01
<b>Freq Chicken (fastfood/panfried)</b>	1.2 (0.9-1.5) p=0.15	1.3 (1.01-1.8) p<0.01
<b>Freq Chicken (grilled)</b>	0.8 (0.7-0.9) p<.001	0.9 (0.8-1.1) p=0.33
<b>Freq Grilled/Barbequed Meat (C-S-B)</b>	0.8 (0.7-0.9) p<.001	0.9 (0.7-0.99) p=0.049
<b>Freq Fastfood/Panfried (C-S-B)</b>	1.3 (1.0-1.7) p=0.04	1.3 (1.0-1.9) p=0.08
<b>Eat Fish (yes/no)</b>	0.4 (0.2-0.6) p<.001	0.5 (0.8-0.9) p=0.02
<b>Freq Fish</b>	0.5 (0.3-0.8) p<0.01	0.8 (0.5-1.4) p=0.46
<b>Freq Vegetables</b>	0.9 (0.8-0.95) p<.001	0.9 (0.8-0.98) p=0.02
<b>Freq Fruit</b>	0.9 (0.9-1.0) p=0.051	1.0 (0.9-1.1) p=0.95
<b>Freq Milk</b>	1.0 (0.9-1.0) p=0.08	0.9 (0.8-0.97) p<0.01

<sup>1</sup>Control values are age- and gender-adjusted to the distribution of the cases. Therefore, the number of subjects is not reported. The P-value is derived from the logistic regression model adjusting for age and gender.

Controls n=654; PSC-IBD n=565; PSC-wolBD n=205

Abbreviations: IBD (inflammatory bowel disease); PSC (primary sclerosing cholangitis); PSC-IBD (PSC with IBD); PSC-wolBD (PSC without IBD); odds ratio (OR); CI (confidence interval); hormone replacement therapy (HRT); years (yrs); urinary tract infections (UTI's);freq (frequency); C-S-B (chicken-steak-burger).

Supplementary Table 5. Sensitivity Analysis Excluding Patients When Self-Reported Inflammatory Bowel Disease Status Could Not Be Corroborated By Medical Record Review <sup>1</sup>

	<b>OR (95% CI), P value</b> <b>PSC-IBD vs. Controls</b>	<b>OR (95% CI), P value</b> <b>PSC-w/oIBD vs. Controls</b>
<b>Smoked Cigarettes (ever)</b>	0.5 (0.4-0.7) p<.001	0.9 (0.6-1.2) p=0.45
<b>Currently Smoke Cigarettes</b>	0.5 (0.2-1.2) p=0.13	1.4 (0.6- 3.5) p=0.42
<b>Pack Yrs</b>	0.8 (0.6-0.9) p<0.01	1.0 (0.8-1.2) p=0.82
<b>Appendix Removal</b>	2.0 (1.5- 2.6) p<.001	1.2 (0.8-1.7) p=0.45
<b>Tonsillectomy</b>	0.9 (0.7-1.1) p=0.27	1.0 (0.7-1.4) p=0.97
<b>Tonsillectomy as Child (0-19 Years)</b>	1.0 (0.7-1.3) p=0.91	1.1 (0.8-1.6) p=0.48
<b>Recurring UTIs</b>	1.7 (1.1-2.5) p=0.01	1.8 (1.1-3.0) p=0.02
<b>Frequency of Recurring UTIs</b>	1.1 (0.7-1.6) p=0.71	1.0 (0.6-1.7) p=0.90
<b>Hormone Based Contraceptive Use (ever)</b>	0.7 (0.4-1.0) p=0.05	0.9 (0.5-1.5) p=0.67
<b>HRT use (ever)</b>	0.6 (0.4- 0.9) p=0.02	0.4 (0.3-0.7) p<0.01

	<b>OR (95% CI), P value</b> <b>PSC-IBD vs. Controls</b>	<b>OR (95% CI), P value</b> <b>PSC-w/oIBD vs. Controls</b>
<b>Freq Steak/Burgers (fastfood/panfried)</b>	1.3 (1.1-1.6) p<0.01	1.1 (0.9-1.5) p=0.39
<b>Freq Steak/Burgers (grilled)</b>	0.9 (0.8-0.96) p<0.01	0.9 (0.8-0.99) p=0.03
<b>Steak/Burger (how well done)</b>	1.4 (1.3-1.6) p<.001	1.3 (1.1-1.4) p<0.01
<b>Freq Chicken (fastfood/panfried)</b>	1.3 (1.0-1.6) p=0.03	1.3 (1.0-1.7) p=0.07
<b>Freq Chicken (grilled)</b>	0.8 (0.7-0.9) p<.001	0.9 (0.8-1.1) p=0.21
<b>Freq Grilled/Barbequed Meat (C-S-B)</b>	0.8 (0.7-0.9) p<.001	0.9 (0.7-0.99) p=0.04
<b>Freq Fastfood/Panfried (C-S-B)</b>	1.5 (1.1-1.9) p<0.03	1.3 (0.9-1.8) p=0.12
<b>Eat Fish (yes/no)</b>	0.4 (0.3-0.6) p<.001	0.5 (0.3-0.8) p=0.01
<b>Freq Fish</b>	0.4 (0.3-0.6) p<0.01	0.6 (0.4-1.1) p=0.10
<b>Freq Vegetables</b>	0.9 (0.8-0.9) p<.001	0.9 (0.9-1.01) p=0.08
<b>Freq Fruit</b>	0.9 (0.8-0.9) p<0.001	1.0 (0.9-1.1) p=0.79

	<b>OR (95% CI), P value</b> <b>PSC-IBD vs. Controls</b>	<b>OR (95% CI), P value</b> <b>PSC-woIBD vs. Controls</b>
<b>Freq Milk</b>	0.9 (0.9-1.0) p=0.05	0.9 (0.9-0.98) p=0.01

<sup>1</sup>Control values are age- and gender-adjusted to the distribution of the cases. Therefore, the number of subjects is not reported. The P-value is derived from the logistic regression model adjusting for age and gender.

Controls n=654; PSC-IBD n=635; PSC-woIBD n=218

Abbreviations: IBD (inflammatory bowel disease); PSC (primary sclerosing cholangitis); PSC-IBD (PSC with IBD); PSC-woIBD (PSC without IBD); odds ratio (OR); CI (confidence interval); hormone replacement therapy (HRT); years (yrs); urinary tract infections (UTI's);freq (frequency); C-S-B (chicken-steak-burger).



Supplementary Table 6. Sensitivity Analysis Including Only Those Cases with Confirmed Ulcerative Colitis Diagnosis <sup>1</sup>

	<b>OR (95% CI), P value</b> <b>PSC-UC vs. Controls</b>
<b>Smoked Cigarettes (ever)</b>	0.5 (0.4-0.7) p<0.01
<b>Currently Smoke Cigarettes</b>	0.3 (0.1-1.2) p=0.09
<b>Pack Yrs</b>	0.7 (0.5-0.8) p<0.01
<b>Appendix Removal</b>	2.0 (1.4-2.7) p<0.01
<b>Tonsillectomy</b>	0.9 (0.7-1.2) p=0.52
<b>Tonsillectomy as Child (0-19 Years)</b>	1.1 (0.8-1.5) p=0.63
<b>Recurring UTIs</b>	1.8 (1.1-2.8) p=0.01
<b>Frequency of Recurring UTIs</b>	0.9 (0.6-1.5) p=0.72
<b>Hormone Based Contraceptive Use (ever)</b>	0.7 (0.4-1.1) p=0.13
<b>HRT use (ever)</b>	0.6 (0.4-0.9) p=0.02
<b>Freq Steak/Burgers (fastfood/panfried)</b>	1.4 (1.1-1.7) p<0.01

	<b>OR (95% CI), P value</b> <b>PSC-UC vs. Controls</b>
<b>Freq Steak/Burgers (grilled)</b>	0.9 (0.8-0.97) p=0.01
<b>Steak/Burger (how well done)</b>	1.4 (1.3-1.7) p<0.01
<b>Freq Chicken (fastfood/panfried)</b>	1.4 (1.1-1.8) p<0.01
<b>Freq Chicken (grilled)</b>	0.8 (0.7-0.9) p<0.01
<b>Freq Grilled/Barbequed Meat (C-S-B)</b>	0.8 (0.7-0.9) p<0.01
<b>Freq Fastfood/Panfried (C-S-B)</b>	1.6 (1.2-2.1) p<0.001
<b>Eat Fish (yes/no)</b>	0.5 (0.3-0.8) p<0.01
<b>Freq Fish</b>	0.5 (0.3-0.8) p<0.01
<b>Freq Vegetables</b>	0.9 (0.8-0.9) p<0.01
<b>Freq Fruit</b>	0.9 (0.8-0.9) p<0.01
<b>Freq Milk</b>	1.0 (0.9-1.0) p=0.33

<sup>1</sup>Control values are age- and gender-adjusted to the distribution of the cases. Therefore, the number of subjects is not reported. The P-value is derived from the logistic regression model adjusting for age and gender.

Controls n=654; PSC-UC n=517

Abbreviations: UC (ulcerative colitis); PSC (primary sclerosing cholangitis); PSC-UC (PSC with ulcerative colitis); odds ratio (OR); CI (confidence interval); hormone replacement therapy (HRT); years (yrs); urinary tract infections (UTI's);freq (frequency); C-S-B (chicken-steak-burger).