

Appendix Table 1. Read codes for case identification

Medcode	Read code	Cancer type	Colon	Rectum	Proximal colon	Distal colon
1220	B13.00	Malignant neoplasm of colon	Yes			
9088	B130.00	Malignant neoplasm of hepatic flexure of colon	Yes		Yes	
6935	B131.00	Malignant neoplasm of transverse colon	Yes		Yes	
10864	B132.00	Malignant neoplasm of descending colon	Yes			Yes
2815	B133.00	Malignant neoplasm of sigmoid colon	Yes			Yes
3811	B134.00	Malignant neoplasm of caecum	Yes		Yes	
22163	B134.11	Carcinoma of caecum	Yes		Yes	
18632	B135.00	Malignant neoplasm of appendix	Yes		Yes	
10946	B136.00	Malignant neoplasm of ascending colon	Yes		Yes	
18619	B137.00	Malignant neoplasm of splenic flexure of colon	Yes			Yes
93478	B138.00	Malignant neoplasm, overlapping lesion of colon	Yes			
48231	B13y.00	Malignant neoplasm of other specified sites of colon	Yes			
28163	B13z.00	Malignant neoplasm of colon NOS	Yes			
9118	B13z.11	Colonic cancer	Yes			
35357	B14.00	Malignant neoplasm of rectum, rectosigmoid junction and anus		Yes		
27855	B140.00	Malignant neoplasm of rectosigmoid junction		Yes		
1800	B141.00	Malignant neoplasm of rectum		Yes		
7219	B141.11	Carcinoma of rectum		Yes		
5901	B141.12	Rectal carcinoma		Yes		
55659	B14y.00	Malig neop other site rectum, rectosigmoid junction and anus		Yes		
50974	B14z.00	Malignant neoplasm rectum,rectosigmoid junction and anus NOS		Yes		
24048	B180200	Malignant neoplasm of retrocaecal tissue	Yes		Yes	
30165	B18y200	Malignant neoplasm of mesorectum		Yes		
11009	B1z..00	Malig neop oth/ill-defined sites digestive tract/peritoneum	Yes			
17559	B1z0.00	Malignant neoplasm of intestinal tract, part unspecified	Yes			
11628	B1z0.12	Cancer of bowel	Yes			

Appendix Table 2. Oral antibiotic class, substance name and therapeutic effects

Class	Drug substance name	Primary clinical therapeutic use	Other antimicrobial activity *
Penicillins^a	Amoxicillin	Anti-anaerobic/aerobic	N/A
	Ampicillin	Anti-anaerobic/aerobic	N/A
	Bacampicillin	Anti-anaerobic/aerobic	N/A
	Carfecillin	Anti-aerobic	Anti-anaerobic
	Cloxacillin	Anti-aerobic	Anti-anaerobic
	Flucloxacillin	Anti-aerobic	Anti-anaerobic
	Phenoxymethylpenicillin	Anti-anaerobic/aerobic	N/A
	Pivampicillin	Anti-anaerobic/aerobic	N/A
	Pivampicillin/Pivmecillinam	Anti-anaerobic/aerobic	N/A
Talampicillin	Anti-anaerobic/aerobic	N/A	
Tetracyclines^a	Tetracycline	Anti-anaerobic	Anti-aerobic
	Chlortetracycline	Anti-anaerobic	Anti-aerobic
	Clomocycline	Anti-anaerobic	Anti-aerobic
	Doxycycline	Anti-anaerobic	Anti-aerobic
	Lymecycline	Anti-anaerobic	Anti-aerobic
	Minocycline	Anti-anaerobic	Anti-aerobic
	Oxytetracycline	Anti-anaerobic	Anti-aerobic
Cephalosporins^a	Cefaclor	Anti-aerobic	Anti-anaerobic
	Cefadroxil	Anti-aerobic	Anti-anaerobic
	Cefalexin	Anti-aerobic	Anti-anaerobic
	Cefixime	Anti-aerobic	Anti-anaerobic
	Cefpodoxime	Anti-aerobic	Anti-anaerobic
	Cefprozil	Anti-aerobic	Anti-anaerobic
	Cefradine	Anti-aerobic	Anti-anaerobic
	Ceftibuten	Anti-aerobic	Anti-anaerobic
	Cefuroxime	Anti-aerobic	Anti-anaerobic
Macrolides^a	Azithromycin	Anti-aerobic	Anti-anaerobic
	Clarithromycin	Anti-aerobic	Anti-anaerobic
	Erythromycin	Anti-aerobic	Anti-anaerobic
Quinolones (include nalidixic acid)^b	Cinoxacin	Anti-aerobic	Anti-anaerobic
	Ciprofloxacin	Anti-aerobic	Anti-anaerobic
	Enrofloxacin	Anti-aerobic	Anti-anaerobic
	Levofloxacin	Anti-aerobic	Anti-anaerobic
	Moxifloxacin	Anti-anaerobic	Anti-aerobic
	Nalidixic Acid	Anti-aerobic	Anti-anaerobic
	Norfloxacin	Anti-aerobic	Anti-anaerobic
	Ofloxacin	Anti-aerobic	Anti-anaerobic
	Temafloxacin	Anti-aerobic	Anti-anaerobic
Sulpha and trimethoprim^b	Sulfadiazine	Anti-aerobic	N/A
	Sulfamethoxazole/Trimethoprim	Anti-aerobic	N/A
	Sulfametopyrazine	Anti-aerobic	N/A
	Trimethoprim	Anti-aerobic	N/A
Others	Chloramphenicol ^a	Anti-anaerobic	Anti-aerobic
	Clindamycin ^a	Anti-anaerobic/aerobic	N/A
	Fosfomycin ^b	Anti-aerobic	N/A
	Linezolid ^b	Anti-aerobic	Anti-anaerobic
	Nitrofurantoin ^b	Anti-aerobic	N/A

	Tinidazole ^b	Anti-anaerobic	N/A
	Vancomycin ^a	Anti-anaerobic	Anti-aerobic
	Metronidazole ^b	Anti-anaerobic	N/A

N/A: not applicable, *potential off-target antimicrobial activity

a. Broad spectrum, b. narrow spectrum

Appendix Table 3. Sensitivity analysis of antibiotics based on therapeutic effects on anaerobes/aerobes

		S1	S2	S3	S4	S5	S6
Penicillins	Amoxicillin	Anti-anaerobic	Anti-anaerobic	Anti-anaerobic	Anti-aerobic ^a	Anti-anaerobic	Anti-aerobic ^a
	Ampicillin	Anti-anaerobic	Anti-anaerobic	Anti-anaerobic	Anti-aerobic ^a	Anti-anaerobic	Excluded ^d
	Bacampicillin	Anti-anaerobic	Anti-anaerobic	Anti-anaerobic	Anti-anaerobic	Anti-anaerobic	Excluded ^d
	Carfecillin	Anti-anaerobic	Anti-anaerobic	Anti-anaerobic	Anti-anaerobic	Anti-anaerobic	Excluded ^d
	Flucloxacillin	Anti-aerobic ^a	Anti-aerobic	Anti-aerobic	Anti-aerobic	Anti-aerobic	Excluded ^d
	Phenoxymethylpenicillin	Anti-anaerobic	Anti-anaerobic	Anti-anaerobic	Anti-anaerobic	Anti-anaerobic	Excluded ^d
	Pivampicillin	Anti-anaerobic	Anti-anaerobic	Anti-anaerobic	Anti-anaerobic	Anti-anaerobic	Excluded ^d
	Pivampicillin/Pivmecillinam	Anti-anaerobic	Anti-anaerobic	Anti-anaerobic	Anti-anaerobic	Anti-anaerobic	Excluded ^d
	Talampicillin	Anti-anaerobic	Anti-anaerobic	Anti-anaerobic	Anti-anaerobic	Anti-anaerobic	Excluded ^d
Tetracyclines	Tetracycline	Anti-anaerobic	Anti-anaerobic	Anti-anaerobic	Anti-anaerobic	Anti-anaerobic	Excluded ^d
	Chlortetracycline	Anti-anaerobic	Anti-anaerobic	Anti-anaerobic	Anti-anaerobic	Anti-anaerobic	Excluded ^d
	Clomocycline	Anti-anaerobic	Anti-anaerobic	Anti-anaerobic	Anti-anaerobic	Anti-anaerobic	Excluded ^d
	Doxycycline	Anti-anaerobic	Anti-anaerobic	Anti-anaerobic	Anti-anaerobic	Anti-anaerobic	Excluded ^d
	Lymecycline	Anti-anaerobic	Anti-anaerobic	Anti-anaerobic	Anti-anaerobic	Anti-anaerobic	Excluded ^d
	Minocycline	Anti-anaerobic	Anti-anaerobic	Anti-anaerobic	Anti-anaerobic	Anti-anaerobic	Excluded ^d
	Oxytetracycline	Anti-anaerobic	Anti-anaerobic	Anti-anaerobic	Anti-anaerobic	Anti-anaerobic	Excluded ^d
Cephalosporins	Cefaclor	Anti-aerobic ^a	Anti-aerobic	Anti-anaerobic ^a	Anti-aerobic	Excluded ^a	Excluded ^d
	Cefadroxil	Anti-aerobic ^a	Anti-aerobic	Anti-anaerobic ^a	Anti-aerobic	Excluded ^a	Excluded ^d
	Cefalexin	Anti-aerobic ^a	Anti-aerobic	Anti-anaerobic ^a	Anti-aerobic	Excluded ^a	Excluded ^d
	Cefixime	Anti-aerobic ^a	Anti-aerobic	Anti-anaerobic ^a	Anti-aerobic	Excluded ^a	Excluded ^d
	Cefpodoxime	Anti-aerobic ^a	Anti-aerobic	Anti-anaerobic ^a	Anti-aerobic	Excluded ^a	Excluded ^d
	Cefprozil	Anti-aerobic ^a	Anti-aerobic	Anti-anaerobic ^a	Anti-aerobic	Excluded ^a	Excluded ^d
	Cefradine	Anti-aerobic ^a	Anti-aerobic	Anti-anaerobic ^a	Anti-aerobic	Excluded ^a	Excluded ^d
	Ceftibuten	Anti-aerobic ^a	Anti-aerobic	Anti-anaerobic ^a	Anti-aerobic	Excluded ^a	Excluded ^d
Cefuroxime	Anti-aerobic ^a	Anti-aerobic	Anti-anaerobic ^a	Anti-aerobic	Excluded ^a	Excluded ^d	
Macrolides	Metronidazole	Anti-anaerobic	Anti-anaerobic	Anti-anaerobic	Anti-anaerobic	Anti-anaerobic	Excluded ^d
Quinolones	Cinoxacin	Anti-aerobic	Anti-aerobic	Anti-aerobic	Anti-aerobic	Anti-aerobic	Excluded ^d
	Ciprofloxacin	Anti-aerobic	Anti-aerobic	Anti-aerobic	Anti-aerobic	Anti-aerobic	Excluded ^d
	Enoxacin	Anti-aerobic	Anti-aerobic	Anti-aerobic	Anti-aerobic	Anti-aerobic	Excluded ^d
	Levofloxacin	Anti-aerobic	Anti-aerobic	Anti-aerobic	Anti-aerobic	Anti-aerobic	Excluded ^d
	Moxifloxacin	Anti-anaerobic	Anti-anaerobic	Anti-anaerobic	Anti-anaerobic	Anti-anaerobic	Excluded ^d
	Nalidixic Acid	Anti-aerobic	Anti-aerobic	Anti-aerobic	Anti-aerobic	Anti-aerobic	Excluded ^d
	Norfloxacin	Anti-aerobic	Anti-aerobic	Anti-aerobic	Anti-aerobic	Anti-aerobic	Excluded ^d
	Ofloxacin	Anti-aerobic	Anti-aerobic	Anti-aerobic	Anti-aerobic	Anti-aerobic	Excluded ^d
	Temafloxacin	Anti-aerobic	Anti-aerobic	Anti-aerobic	Anti-aerobic	Anti-aerobic	Excluded ^d
Sulpha and trimethoprim	Sulfadiazine	Anti-aerobic	Anti-aerobic	Anti-aerobic	Anti-aerobic	Anti-aerobic	Excluded ^d
	Sulfamethoxazole/Trimethoprim	Anti-aerobic	Anti-aerobic	Anti-aerobic	Anti-aerobic	Anti-aerobic	Excluded ^d
	Sulfametypyrazine	Anti-aerobic	Anti-aerobic	Anti-aerobic	Anti-aerobic	Anti-aerobic	Excluded ^d
	Trimethoprim	Anti-aerobic	Anti-aerobic	Anti-aerobic	Anti-aerobic	Anti-aerobic	Excluded ^d

Others	Chloramphenicol	Anti-anaerobic	Anti-anaerobic	Anti-anaerobic	Anti-anaerobic	Anti-anaerobic	Excluded ^a
	Nitrofurantoin	Anti-aerobic	Anti-aerobic	Anti-aerobic	Anti-aerobic	Anti-aerobic	Excluded ^a
	Tinidazole	Anti-anaerobic	Anti-anaerobic	Anti-anaerobic	Anti-anaerobic	Anti-anaerobic	Excluded ^a
	Vancomycin	Anti-anaerobic	Excluded ^a	Anti-anaerobic	Anti-anaerobic	Anti-anaerobic	Excluded ^a

S: Sensitivity analysis

a. Key changes in each category

Appendix Table 4. Characteristics of cases with proximal and distal colon cancers and corresponding controls

	Proximal colon		Distal colon	
	Cases	Controls	Cases	Controls
N	3036	14236	2443	11526
Duration of follow-up (years), Median (IQR)	8.6 (5.2-15.9)	8.5 (5.2-12.8)	8.9 (5.5-13.2)	8.9 (5.4-13.1)
Age (years), Median (IQR)	74 (66, 81)	74 (65, 80)	71 (63, 78)	70 (63, 78)
Sex				
Male	1411 (46.5)	6548 (46.0)	1420 (58.1)	6648 (57.7)
Female	1625 (53.5)	7688 (54.0)	1023 (41.9)	4878 (42.3)
BMI category^a				
Normal	843 (27.8)	4422 (31.1)	668 (27.3)	3568 (31.0)
Overweight	1094 (36.0)	4751 (33.4)	907 (37.1)	4107 (35.6)
Obese	617 (20.3)	2476 (17.4)	546 (22.3)	2064 (17.9)
Missing	482 (15.9)	2587 (18.2)	322 (13.2)	1787 (15.5)
Smoking status^b				
Never smoker	1330 (43.8)	6290 (44.2)	1033 (42.3)	4695 (40.7)
Current smoker (trivial-light)	107 (3.5)	497 (3.5)	89 (3.6)	447 (3.9)
Current smoker (moderate)	147 (4.8)	744 (5.2)	105 (4.3)	654 (5.7)
Current smoker (heavy)	161 (5.3)	680 (4.8)	130 (5.3)	644 (5.6)
Current smoker (amount unknown)	213 (7.0)	907 (6.4)	143 (5.9)	746 (6.5)
Ex-smoker	827 (27.2)	3768 (26.5)	807 (33.0)	3463 (30.0)
Missing	251 (8.3)	1350 (9.5)	136 (5.6)	877 (7.6)
Alcohol use^c				
Non-drinker	319 (10.5)	1543 (10.8)	161 (6.6)	1006 (8.7)
Current drinker (trivial-light)	853 (28.1)	3973 (27.9)	791 (32.4)	3598 (31.2)
Current drinker (moderate)	314 (10.3)	1205 (8.5)	304 (12.4)	1296 (11.2)
Current drinker (heavy)	40 (1.3)	166 (1.2)	65 (2.7)	205 (1.8)
Current drinker (amount unknown)	957 (31.5)	4433 (31.1)	721 (29.5)	3349 (29.1)
Ex-drinker	59 (1.9)	270 (1.9)	58 (2.4)	212 (1.8)
Missing	494 (16.3)	2646 (18.6)	343 (14.0)	1860 (16.1)
Diabetes history	310 (10.2)	1181 (8.3)	245 (10.0)	929 (8.1)
Chronic NSAID use^d	219 (7.2)	1403 (9.9)	181 (7.4)	1042 (9.0)
Chronic Aspirin use^d	619 (20.4)	3028 (21.3)	470 (19.2)	2374 (20.6)

Data are n (%) unless otherwise stated

a. Normal: 18.5 – 24.9, Overweight: 25.0 – 29.9, Obese: 30.0 and above

b. Trivial, light, moderate, or heavy current smoking were assigned when either the general practitioner had recorded a Read code with one of these terms, or when the units per day were recorded as 0-1 (trivial), 1-9 (light), 10-19 (moderate), 20+ (heavy).

c. Trivial, light, moderate, or heavy current drinking were assigned when either the general practitioner had recorded a Read code with one of these terms, or when the units per day were recorded as 0-1 (trivial), 1-2 (light), 3-6 (moderate), 7+ (heavy).

d. Cumulative days prescribed for 365 days and above

Appendix Table 5. Use of antibiotics in cases with proximal and distal colon cancers and corresponding controls

	Proximal colon			Distal colon		
	Cases	Controls	P value	Cases	Controls	P value
N	3036	14236	-	2443	11526	-
Any antibiotic use	2211 (72.8%)	9995 (70.2%)	0.004	1740 (71.2%)	8069 (70.0%)	0.23
Anti-anaerobic/aerobic effects						
Anti-anaerobic activity	2103 (69.3%)	9522 (66.9%)	0.011	1681 (68.8%)	7734 (67.1%)	0.10
Anti-aerobic activity	905 (29.8%)	4146 (29.1%)	0.45	601 (24.6%)	2973 (25.8%)	0.22
Class						
Cephalosporins	601 (26.9%)	2653 (26.3%)	0.56	423 (24.0%)	1981 (24.3%)	0.79
Macrolides	684 (30.6%)	3147 (31.2%)	0.59	543 (30.8%)	2593 (31.8%)	0.42
Penicillins	1828 (81.8%)	8166 (80.9%)	0.36	1461 (82.9%)	6663 (81.7%)	0.24
Quinolones	365 (16.3%)	1569 (15.5%)	0.36	221 (12.5%)	1122 (13.8%)	0.17
Sulpha and trimethoprim	724 (32.4%)	3329 (33.0%)	0.58	466 (26.4%)	2328 (28.6%)	0.074
Tetracyclines	462 (20.7%)	2108 (20.9%)	0.81	370 (21.0%)	1688 (20.7%)	0.78
Others	290 (13.0%)	1278 (12.7%)	0.69	200 (11.4%)	969 (11.9%)	0.53

Appendix Table 6. Use of antibiotics and colorectal cancer risk, excluding prevalent cases within 1 year of registration

Colon			Rectum		
Antibiotic use	N (cases)/N (controls)	OR(95% CI)	N (cases)/N (controls)	N (cases)/N (controls)	OR(95% CI)
0 day	5662/28622	Ref	0 day	3040/14414	Ref
1-15 days	5197/24624	1.08 (1.03-1.13)	1-15 days	2571/11909	1.02 (0.96-1.08)
16-30 days	2849/12889	1.14 (1.08-1.20)	16-30 days	1292/6031	0.99 (0.92-1.07)
31-60 days	2817/12608	1.15 (1.09-1.21)	31-60 days	1212/5568	1.01 (0.93-1.09)
>60 days	3201/14132	1.16 (1.1-1.23)	>60 days	1139/6101	0.85 (0.78-0.93)

Appendix Table 7. Use of antibiotics and colorectal cancer risk, including transverse colon as distal colon

Proximal colon			Distal colon		
Antibiotic use	N (cases)/N (controls)	OR(95% CI)	N (cases)/N (controls)	N (cases)/N (controls)	OR(95% CI)
0 day	762/3918	Ref	0 day	766/3780	Ref
1-15 days	736/3384	1.14 (1.01-1.28)	1-15 days	707/3321	1.05 (0.94-1.18)
16-30 days	388/1813	1.14 (0.99-1.32)	16-30 days	403/1702	1.17 (1.01-1.35)
31-60 days	454/1794	1.35 (1.17-1.56)	31-60 days	376/1815	1.02 (0.88-1.19)
>60 days	454/1794	1.11 (0.96-1.28)	>60 days	376/1815	1.05 (0.90-1.22)

Appendix Table 8. Use of antibiotics and colorectal cancer risk, excluding lifestyle data before the start of research standard follow-up

Colon			Rectum		
Antibiotic use	N (cases)/N (controls)	OR(95% CI)	N (cases)/N (controls)	N (cases)/N (controls)	OR(95% CI)
0 day	5662/28746	Ref	0 day	3040/14469	Ref
1-15 days	5197/24624	1.09 (1.04-1.13)	1-15 days	2571/11909	1.02 (0.96-1.08)
16-30 days	2849/12889	1.15 (1.09-1.21)	16-30 days	1292/6031	1.00 (0.93-1.08)
31-60 days	2817/12608	1.16 (1.10-1.23)	31-60 days	1212/5568	1.02 (0.94-1.10)
>60 days	3201/14132	1.18 (1.12-1.24)	>60 days	1139/6101	0.86 (0.79-0.94)

Appendix Table 9. Use of antibiotics and colorectal cancer risk, extended antibiotic exposure assignment to include only antibiotic prescriptions more than 3 years prior to CRC diagnosis

Colon			Rectum		
Antibiotic use	N (cases)/N (controls)	OR(95% CI)	N (cases)/N (controls)	N (cases)/N (controls)	OR(95% CI)
0 day	8344/40831	Ref	0 day	4286/20363	Ref
1-15 days	4614/21923	1.05 (1.00-1.09)	1-15 days	2277/10394	1.03 (0.96-1.09)
16-30 days	2327/10577	1.10 (1.04-1.16)	16-30 days	1028/4810	0.99 (0.91-1.07)
31-60 days	2196/9594	1.14 (1.07-1.21)	31-60 days	866/4285	0.92 (0.84-1.01)
>60 days	2245/10074	1.11 (1.05-1.18)	>60 days	797/4226	0.86 (0.78-0.94)

Appendix Table10. Summaries of literature on antibiotics-cancer association

Author/study	Year	Population	Study design	N (cases)	Exposure	Outcome	Adjusted covariates	Odds ratio/Relative Risk
Kilkinen et al ¹	2008	Finland	Case control study	7513 colon cancer, 5126 rectal cancer	Number of prescriptions in categories	Various cancer risk, including CRC	Age, sex	6 or more prescriptions vs 0-1 prescription: colon, 1.15 [1.04–1.26]; rectum, 1.03 [0.90–1.17])
Wang et al ²	2014	Taiwan	Nested case-control study	3593 incident colon cancer, 1979 rectal cancer	Use of antibiotics in binary term	CRC risk	Socioeconomic status, comorbidities and any use of other medications, including aspirin, NSAIDs, systemic corticosteroids, statins and fibrates, oral hypoglycemic agents, insulins and antihypertensive drugs	Use of any anti-anaerobic antibiotics: Colon, 2.31 [2.12–2.52]; Rectum, 1.69 [1.50-1.90]
Boursi et al ³	2015	United Kingdom	Nested case-control study	20990 CRC	Number of prescriptions in categories	CRC risk	BMI, smoking history, alcohol consumption, presumed previous CRC screening colonoscopies, medical co-morbidities including diabetes mellitus, and medications (aspirin and NSAIDs)	Penicillin >10 courses vs no use: 1.20 [1.11–1.31]
Cao et al ⁴	2017	United States, Nurses	Case control study	1195 colorectal adenoma	Days in categories	Adenoma risk	Age, sex, history of CRC, diabetes history, use of menopausal hormone therapy, BMI, height, regular aspirin use, current use of colonoscopy, vitamin, physical activity, smoking, alcohol intake, total calories, folate intake, calcium intake, and red and processed meat intake	Any antibiotic use for ≥2 months vs no use between age 20 and 39: 1.36 [1.03-1.79]; between age 40 and 59: 1.69 [1.24-2.31]
Dik et al ⁵	2015	Netherlands	Nested case-control study	4029 CRC	Number of prescriptions in categories; grouped by anaerobic and aerobic agents and by classes	CRC risk	Age, sex, diabetes history, PPI use, acetylsalicylic acids use, NSAIDs use, lipid-lowering agents, estrogens and immunosuppressive drugs	Any antibiotic use ≥ 8 prescriptions vs. no use: 1.26 [1.11–1.44]; Anti-anaerobic agents:1.45 [1.07–1.97]; Anti-aerobic agents:1.25 [1.10–1.43]

CRC: colorectal cancer; PPI: Proton Pump Inhibitors; NSAIDs: nonsteroidal anti-inflammatory drugs; BMI:Body mass index ; TMP-SMX: Trimethoprim/sulfamethoxazole

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