



Association between antibiotic usage and colorectal cancer development: a territory-wide study

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Introduction

Recent studies suggested that antibiotics may modulate colorectal cancer (CRC) risk due to gut dysbiosis. We aimed to investigate the effects of different antibiotics on CRC development in older subjects.

Methodology

This was a retrospective cohort study based on a territory-wide healthcare database (CDARS) in Hong Kong. All patients aged ≥60y who had undergone index diagnostic or screening colonoscopy with no CRC diagnosed between 2005 and 2013 were recruited. Exclusion criteria included inflammatory bowel disease, prior colectomy, prior CRC and CRC detected within 6m of index colonoscopy.

Table 1. Characteristics of antibiotic users and non-users

	All (n=97,162)	Antibiotic users (n=58,704)	Antibiotic non-users (n=38,458)
Age at index colonoscopy (years)	71.4 (65.1 – 77.8)	72.7 (66.1 – 78.9)	69.5 (64.0 – 75.8)
Male sex (n, %)	50841 (52.3%)	30625 (52.2%)	20216 (52.6%)
History of colonic polyps (n, %)	29663 (30.5%)	19666 (27.2%)	9997 (26.0%)
Polypectomy at index colonoscopy (n, %)	16087 (16.6%)	10027 (17.1%)	6060 (15.8%)
Smoking (n, %)	3637 (3.7%)	3332 (5.7%)	305 (0.8%)
Alcohol (n, %)	495 (0.5%)	389 (0.7%)	106 (0.3%)
DM (n, %)	11442 (11.8%)	10533 (17.9%)	909 (9.1%)
Hypertension (n, %)	23512 (24.2%)	17468 (29.8%)	6044 (15.7%)
Dyslipidemia (n, %)	7290 (7.5%)	5112 (8.7%)	2178 (5.7%)
AF (n, %)	5029 (5.2%)	4098 (7.0%)	931 (2.4%)
IHD (n, %)	11141 (11.5%)	8394 (14.3%)	2747 (7.1%)
CHF (n, %)	5737 (5.9%)	5045 (8.6%)	692 (1.8%)
Stroke (n, %)	6541 (6.7%)	5066 (8.6%)	1475 (3.8%)
CRF (n, %)	2986 (3.1%)	2664 (4.5%)	322 (0.8%)
Cirrhosis (n, %)	696 (0.7%)	593 (1.0%)	103 (0.3%)
Dementia (n, %)	1225 (1.3%)	1084 (1.8%)	141 (0.4%)
Parkinsonism (n, %)	726 (0.7%)	585 (1.0%)	141 (0.4%)
Aspirin (n, %)	22004 (22.6%)	15864 (27.0%)	6140 (16.0%)
NSAIDs (n, %)	8000 (8.2%)	5649 (9.6%)	2351 (6.1%)
COX-2 inhibitors (n,%)	108 (0.1%)	71 (0.1%)	37 (0.1%)
Statins (n,%)	17651 (18.2%)	11629 (19.8%)	6022 (15.7%)
Annual center endoscopy volume	2892 (2045 – 3316)	2892 (2054 – 3316)	2887 (2033 – 3291)
Annual center polypectomy rate*	24.6% (21.7% - 28.2%)	24.6% (21.7% - 28.0%)	24.7% (21.6% - 28.4%)

Table 3. Association between nature of antibiotics and CRC according to cancer subsite

	No. of patients and events	aHR	95% CI	P-value
Rectum (n=96,737, event=601)				
Anti-anaerobic vs anti-aerobic activity				
Nonuse	n=38,322; event=287	Ref	-	-
Anti-anaerobic	n=50,381; event=271	0.64	0.53 – 0.76	< 0.001
Anti-aerobic	n=8,034; event=43	0.68	0.49 – 0.93	0.017
Broad vs narrow spectrum activity				
Nonuse	n=38,322; event=287	Ref	-	-
Broad-spectrum	n=54,872; event=294	0.63	0.53 – 0.75	< 0.001
Narrow-spectrum	n=3,543; event=20	0.77	0.49 – 1.22	0.277
Oral vs intravenous antibiotics				
Nonuse	n=38,322; event=287	Ref	-	-
Oral	n=34,690; event=178	0.65	0.54 – 0.78	< 0.001
Intravenous	n=3,481; event=23	0.77	0.50 – 1.18	0.237
Oral + intravenous	n=20,244; event=113	0.60	0.47 – 0.76	< 0.001
Proximal colon (n=96,307, event=171)				
Anti-anaerobic vs anti-aerobic activity				
Nonuse	n=38,080; event=45	Ref	-	-
Anti-anaerobic	n=50,222; event=112	1.69	1.18 – 2.41	0.004
Anti-aerobic	n=8,005; event=14	1.33	0.73 – 2.43	0.354
Broad vs narrow spectrum activity				
Nonuse	n=38,080; event=45	Ref	-	-
Broad-spectrum	n=54,695; event=117	1.60	1.13 – 2.29	0.009
Narrow-spectrum	n=3,532; event=9	2.08	1.02 – 4.27	0.045
Oral vs intravenous antibiotics				
Nonuse	n=38,080; event=45	Ref	-	-
Oral	n=34,580; event=68	1.53	1.05 – 2.24	0.028
Intravenous	n=3,470; event=12	2.61	1.37 – 4.97	0.004
Oral + intravenous	n=20,177; event=46	1.65	1.07 – 2.56	0.024
Distal colon (n=96,390, event=254)				
Anti-anaerobic vs anti-aerobic activity				
Nonuse	n=38,126; event=91	Ref	-	-
Anti-anaerobic	n=50,252; event=142	0.99	0.75 – 1.31	0.944
Anti-aerobic	n=8,012; event=21	1.02	0.63 – 1.64	0.944
Broad vs narrow spectrum activity				
Nonuse	n=38,126; event=91	Ref	-	-
Broad-spectrum	n=54,737; event=159	1.03	0.78 – 1.35	0.852
Narrow-spectrum	n=3,527; event=4	0.49	0.18 – 1.33	0.163
Oral vs intravenous antibiotics				
Nonuse	n=38,126; event=91	Ref	-	-
Oral	N=34,597; event=85	0.94	0.70 – 1.27	0.706
Intravenous	N=3,466; event=8	0.85	0.41 – 1.76	0.664
Oral + intravenous	N=20,201; event=70	1.12	0.80 – 1.58	0.513

Table 4. Association between CRC and duration of antibiotic use

	No. of patients and events	aHR*	95% CI	p-value
Rectum (n=96,737, event=601)				
Nonuse	n=38,372; event=287	Ref	-	-
< 2 weeks	n=21,587; event=127	0.73	0.59 – 0.91	0.004
≥ 2 weeks	n=36,828; event=187	0.58	0.48 – 0.71	< 0.001
Proximal colon (n=96,307, event=171)				
Nonuse	n=38,080; event=45	Ref	-	-
< 2 weeks	n=21,509; event=49	1.73	1.15 – 2.60	0.008
≥ 2 weeks	n=36,718; event=77	1.57	1.07 – 2.30	0.021
Distal colon (n=96,390, event=254)				
Nonuse	n=38,126; event=91	Ref	-	-
< 2 weeks	n=21,512; event=52	0.92	0.65 – 1.30	0.634
≥ 2 weeks	n=36,752; event=111	1.04	0.78 – 1.40	0.786

Table 2. Association between antibiotics and CRC after index colonoscopy negative for CRC

	Number of patients and events	aHR*	95% CI	p-value
Rectum (n=96,737, event=601)				
Nonuse	n=38,372; event=287	Ref	-	-
Any antibiotic use	n=58,480; event=314	0.64	0.54 – 0.76	< 0.001
Proximal colon (n=96,307, event=171)				
Nonuse	n=38,080; event=45	Ref	-	-
Any antibiotic use	n=58,227; event=126	1.63	1.15 – 2.32	0.006
Distal colon (n=96,390, event=254)				
Nonuse	n=38,126; event=91	Ref	-	-
Any antibiotic use	n=58,264; event=163	0.99	0.76 – 1.30	0.965

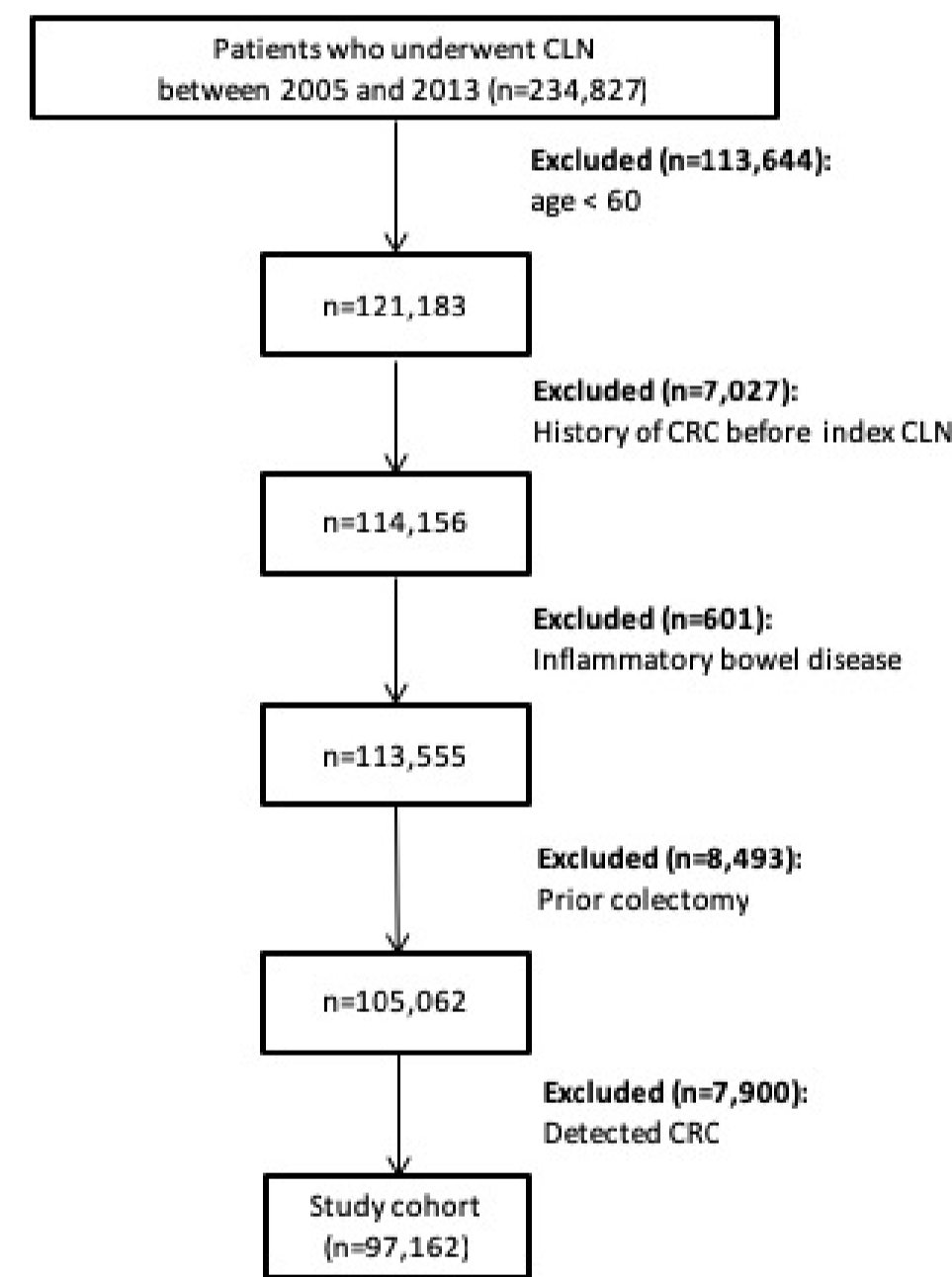


Figure. Patient selection flow diagram

Primary outcome: CRC that developed >6m after index colonoscopy

Observation: CRC diagnosis, death or end of study (31 December 2017)

Exposure: any antibiotic use up to 5y before index colonoscopy

(11 classes of antibiotics – penicillins, cephalosporins, macrolides, carbapenems, quinolones, tetracyclines, aminoglycosides, nitroimidazoles, glycopeptides, sulpha/trimethoprim, and others (clindamycin, nitrofurantoin, linezolid, rifampicin, rifaximin, and daptomycin).)

Covariates: refer to **Table 1**

Statistical analysis: Multivariable Cox proportional hazards

→ adjusted hazard ratio (aHR) of CRC with antibiotics

Stratified analysis:

- **Proximal colon** [from cecum to transverse colon] vs **distal colon** [from splenic flexure to sigmoid colon] vs **rectum**
- **Duration** (nonuse, < 2weeks, ≥ 2 weeks)
- **Nature of antibiotics** (anti-anaerobic vs anti-aerobic, broad vs narrow spectrum, and oral vs intravenous)

Results

- 97,162 (male: 50,841 [52.3%]); median age at index colonoscopy: 71.4 years (IQR:65.1–77.8) (**Table 1**)
- Median duration of antibiotic use: 15 days (IQR:7–31)
- Pre-colonoscopy antibiotics were associated with lower rectal cancer risk (aHR:0.64;95% CI:0.54–0.76) but higher proximal colon cancer risk (aHR:1.62;95%CI:1.14–2.30); while there was no significant association between antibiotics and distal colon cancer (aHR:0.99;95% CI:0.76–1.30) (**Table 2**)
- Differential effects of antibiotics on CRC according to their (1) anti-anaerobic vs anti-aerobic activity, (2) broad-spectrum vs narrow spectrum activity, and (3) oral vs intravenous vs both route (**Table 3**)
- The aHR of rectal cancer with antibiotic use <2 weeks and ≥2 weeks was 0.73 (95% CI:0.59–0.91) and 0.58 (95% CI:0.48–0.71), respectively; as for proximal colon cancer, aHRs was 1.73 (95% CI:1.15–2.60) and 1.57 (95% CI:1.07–2.30) for antibiotic use <2 weeks and ≥2 weeks, respectively (**Table 4**)

Conclusion

- Antibiotics were associated with reduced cancer risk in rectum but increased risk in proximal colon
- This phenomenon varied with respect to antibiotic class and spectrum
- Further studies are needed to discern the interaction of antibiotics and topical gut microbiota on CRC development