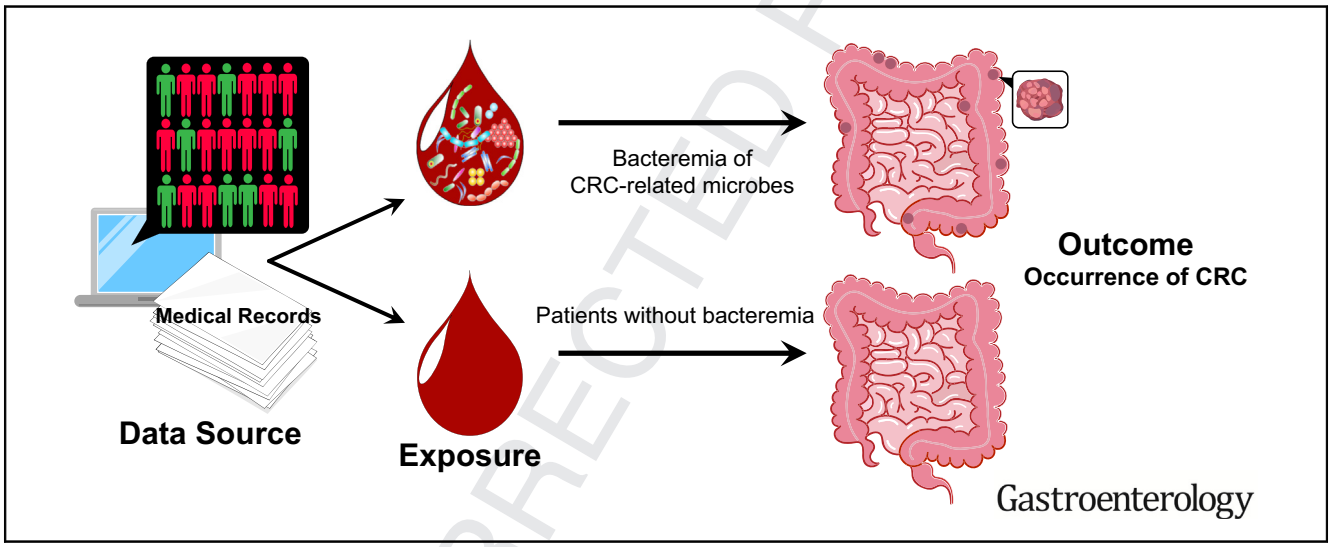
Association Between Bacteremia From Specific Microbes and Subsequent Diagnosis of Colorectal Cancer

Q1 **Thomas N. Y. Kwong**,[1,*] **Xiansong Wang**,[1,2,*] Geicho Nakatsu,[1,2] Tai Cheong Chow,[1] Timothy Tipoe,[1] Rudin Z. W. Dai,[1,2] Kelvin K. K. Tsoi,[3,4] Martin C. S. Wong,[1,3] Gary Tse,[2] Matthew T. V. Chan,[4] Francis K. L. Chan,[1,2] Siew C. Ng,[1,2] Justin C. Y. Wu,[1,2] William K. K. Wu,[1,5] Jun Yu,[1,2] Joseph J. Y. Sung,[1,2] and Sunny H. Wong[1,2]

[1]State Key Laboratory of Digestive Disease, Institute of Digestive Disease, Li Ka Shing Institute of Health Sciences, and CUHK Shenzhen Research Institute, The Chinese University of Hong Kong, Hong Kong; [2]Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong; [3]The Jockey Club School of Public Health and Primary Care, The Chinese University of Hong Kong, Hong Kong; [4]Stanley Ho Big Data Decision Analytics Research Centre, The Chinese University of Hong Kong, Hong Kong; and [5]Department of Anesthesia and Intensive Care, The Chinese University of Hong Kong, Hong Kong



BACKGROUND & AIMS: Colorectal cancer (CRC) development has been associated with increased proportions of *Bacteroides fragilis* and certain *Streptococcus*, *Fusobacterium*, and *Peptostreptococcus* species in the intestinal microbiota. We investigated associations between bacteremia from specific intestinal microbes and occurrence of CRC. **METHODS:** We performed a retrospective study after collecting data on 13,096 adult patients (exposed group) in Hong Kong hospitalized with bacteremia (identified by blood culture test) without a previous diagnosis of cancer from January 1, 2006 through December 31, 2015. We collected data on intestinal microbes previously associated with CRC (genera *Bacteroides*, *Clostridium*, *Filifactor*, *Fusobacterium*, *Gemella*, *Granulicatella*, *Parvimonas*, *Peptostreptococcus*, *Prevotella*, *Solobacterium*, and *Streptococcus*). Clinical information, including patient demographics, comorbid medical conditions, date of bacteremia, and bacterial species identified, were collected. The incidence of biopsy-proved CRC was compared between the exposed and unexposed (patients without bacteremia matched for age, sex, and comorbidities) groups. **RESULTS:** The risk of CRC was increased in patients with bacteremia from *B fragilis* (hazard ratio [HR] = 3.85, 95% CI = 2.62–5.64, $P = 5.5 \times 10^{-12}$) or *Streptococcus gallolyticus* (HR = 5.73, 95% CI = 2.18–15.1, $P = 4.1 \times 10^{-4}$) compared with the unexposed group. In addition, the risk of CRC was increased in patients with bacteremia from *Fusobacterium nucleatum* (HR = 6.89, 95% CI = 1.70–27.9, $P = .007$), *Peptostreptococcus* species (HR = 3.06, 95% CI = 1.47–6.35, $P = .003$), *Clostridium septicum* (HR = 17.1, 95% CI = 1.82–160, $P = .013$), *Clostridium perfringens* (HR = 2.29, 95% CI = 1.16–4.52, $P = .017$), or *Gemella morbillorum* (HR = 15.2, 95% CI = 1.54–150, $P = .020$). We observed no increased risk in patients with bacteremia caused by microbes not previously associated with colorectal neoplasms. **CONCLUSIONS:** In a retrospective analysis of patients hospitalized for bacteremia, we associated later diagnosis of CRC with *B fragilis* and *S gallolyticus* and other intestinal microbes. These bacteria might have entered the bloodstream from intestinal dysbiosis and perturbed barrier function. These findings support a model in which specific members of the intestinal microbiota promote colorectal carcinogenesis. Clinicians should evaluate patients with

bacteremia from these species for neoplastic lesions in the colorectum.

Keywords: Colon Cancer; Marker; Microbiome; Pathogen.

Colorectal cancer (CRC) is the third most common cancer worldwide[1] and poses an enormous burden on the health care system globally. In addition to genetic factors, recent metagenomics studies have suggested a causal relation between microbial dysbiosis and CRC.[2–4] For instance, *Bacteroides fragilis* and certain *Streptococcus*, *Fusobacterium,* and *Peptostreptococcus* species have been shown to be enriched in the CRC microbiota.[5,6] Some of these microbial signatures have been harnessed as biomarkers to improve sensitivity for diagnosing colorectal neoplasia,[7,8] whereas functional studies have shown the mechanistic role of certain bacteria in colorectal carcinogenesis.[9,10] *Fusobacterium nucleatum* and enterotoxigenic *B fragilis* have been shown to exert oncogenic effects through modulating the E-cadherin and β-catenin signaling pathways that subsequently activate downstream proinflammatory responses.[11–13] Similarly, *Streptococcus bovis* has been shown to promote hyper-proliferative and aberrant colonic crypt formation in a murine model through the activation of proinflammatory interleukin (IL)-8 production.[14,15]

Apart from these studies, clinical associations between CRC and septicemia from several bacterial species have been described.[16–19] *Streptococcus bovis* has shown an association, with up to 67% of patients with bacteremia or endocarditis harboring a colorectal tumor.[20] It has been hypothesized that tissue damage at the neoplasm might serve as a site for bacterial entry into the bloodstream. Although remaining elusive, the increased production of IL-23 and IL-17 during colorectal tumorigenesis could contribute to microbial invasion.[21,22] Furthermore, colorectal neoplasms also exhibit barrier dysfunction as indicated by the lack of several barrier proteins, including MUC-2, and tight junction proteins Claudin-4, JAM-A, and JAM-B.[21]

Based on this background, we systematically evaluated the occurrence of CRC diagnosis in patients with bacteremia from microbes enriched in the CRC mucosae using a large territory-wide population cohort. Such work provides insight into the bacterial theory of colorectal carcinogenesis and highlights the relevance of different species. Furthermore, a positive association between these bacteria could be indicative of colorectal tumor development, necessitating a subsequent colonoscopy to look for colorectal neoplasia.

Methods

Study Design

This is a retrospective territory-wide population-based cohort study conducted of adults hospitalized in public hospitals in Hong Kong during a 10-year period from January 1, 2006 to December 31, 2015 (Figure 1).

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Placeholder text • Placeholder text • Placeholder text • Placeholder text • Placeholder text • Placeholder text • Placeholder text • Placeholder text • Placeholder text • Placeholder text •

NEW FINDINGS

Placeholder text • Placeholder text • Placeholder text • Placeholder text • Placeholder text • Placeholder text • Placeholder text • Placeholder text • Placeholder text • Placeholder text •

LIMITATIONS

Placeholder text • Placeholder text • Placeholder text • Placeholder text • Placeholder text • Placeholder text • Placeholder text • Placeholder text • Placeholder text • Placeholder text •

IMPACT

Placeholder text • Placeholder text • Placeholder text • Placeholder text • Placeholder text • Placeholder text • Placeholder text • Placeholder text • Placeholder text • Placeholder text •

Data Source

Study data were retrieved from the electronic medical records of the Clinical Data Analysis and Reporting System (CDARS), which is a computerized database of patient records managed by the Hong Kong Hospital Authority. The database contains clinical information, including patient demographics, disease diagnoses, investigations, procedures, and drug prescription records, in the public hospital system. This public hospital system is composed of 41 hospitals within 7 service clusters that provide more than 90% of all in-patient services in Hong Kong, with more than 1 million discharges and deaths in 2013 through 2014. This electronic database has been used for conducting robust population studies.[23–25] All clinical data were anonymized by the CDARS, with all potential patient identifiers removed upon return of database searches.

Exposure and Primary Outcome

All data of patients with positive blood culture test results from January 1, 2006 to December 31, 2015 were retrieved from the CDARS. Based on our previous metagenomics analyses on gut and mucosal microbiota,[3,6] the exposure of interest was defined by culture-confirmed bacteremia caused by bacteria significantly enriched in the CRC microbiota. This included bacterial species belonging to the 11 genera of *Bacteroides*, *Clostridium*, *Filifactor*, *Fusobacterium*, *Gemella*, *Granulicatella*,

*Authors share co-first authorship.

Abbreviations used in this paper: **CDARS, Clinical Data Analysis and Reporting System; CI, confidence interval; CRC, colorectal cancer; HR, hazard ratio; IL, interleukin.**

0016-5085/$36.00
https://doi.org/10.1053/j.gastro.2018.04.028