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

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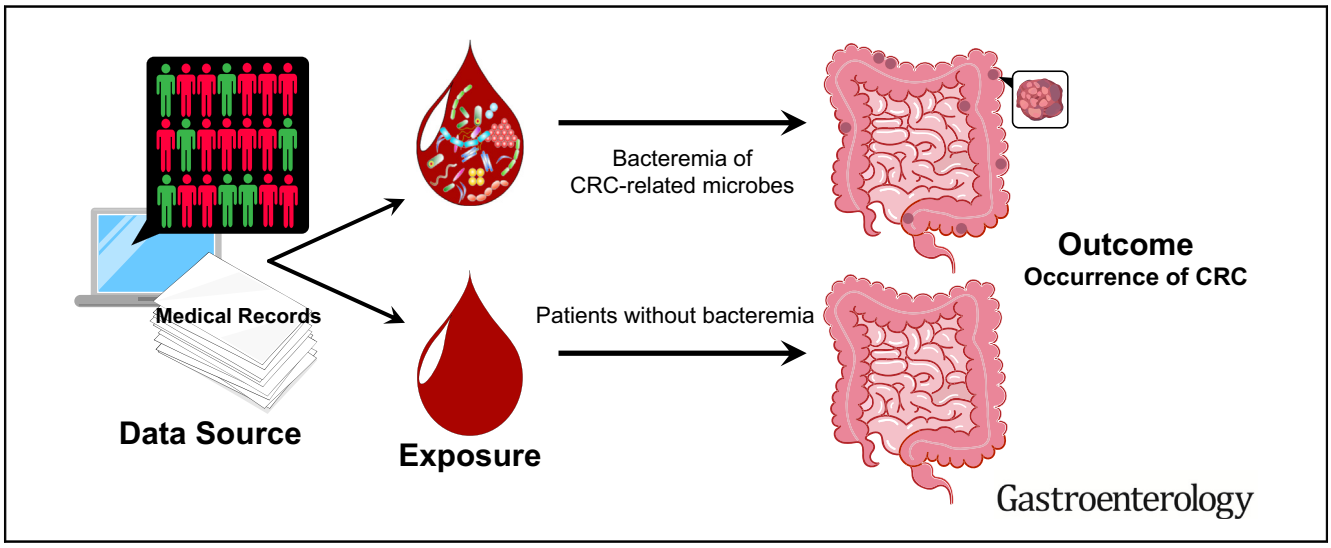


**BACKGROUND & AIMS:** Colorectal cancer (CRC) development has been associated with increased proportions of *Bacteroides fragilis* and certain *Streptococcus*, *Fusobacterium*, and *Peptostreptococcus* species in the intestinal microbiota. We investigated associations between bacteremia from specific 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.

CLINICAL AT

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 $\beta$-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.

**WHAT YOU NEED TO KNOW**

BACKGROUND AND CONTEXT

Colorectal cancer (CRC) is associated with intestinal dysbiosis. However, the relationship between CRC and septicemia from enriched members of the CRC microbiota is unknown.

NEW FINDINGS

The authors observed significant associations between CRC and bloodstream infections caused by *Streptococcus gallolyticus*, *Bacteroides fragilis*, *Fusobacterium nucleatum*, *Peptostreptococcus species* and some other bacteria.

LIMITATIONS

The authors defined bacteremia by positive bacterial culture. Sub-clinical bacteremia may be missed.

IMPACT

Bacteremia from these CRC-associated species may warrant colorectal workup to look for neoplastic lesions.

# 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).

## 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*, *Parvimonas*, *Peptostreptococcus*, *Prevotella*, *Solobacterium*, and

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

**Most current article**


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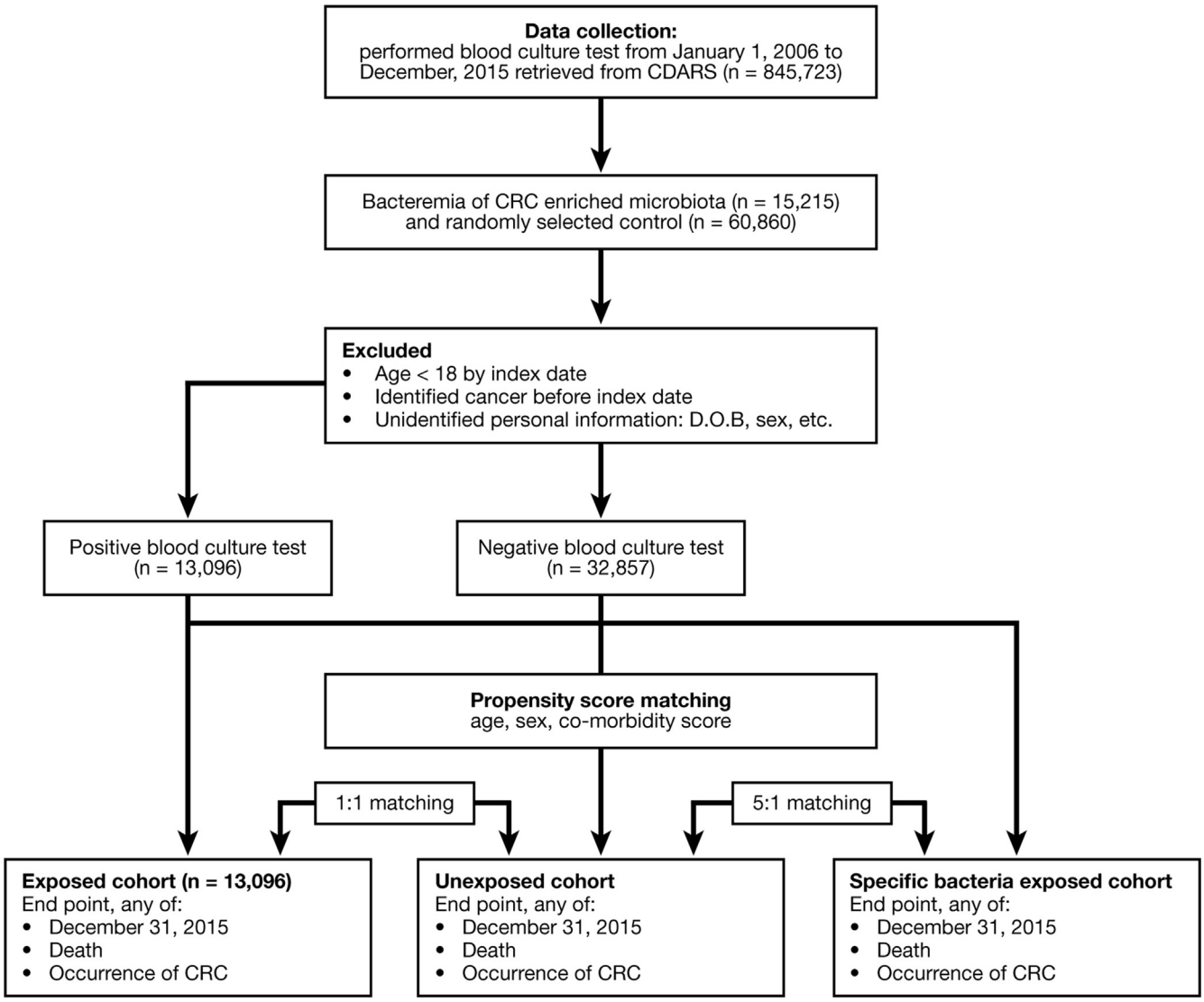


**Figure 1.** Flowchart of study design. D.O.B., date of birth.

*Streptococcus*. Relevant clinical information, including patient demographics, comorbid medical conditions, date of bacteremia diagnosis, and bacterial species, were recorded. The primary outcome of interest was defined by the subsequent diagnosis of CRC. The biopsy-proved diagnosis dates were recorded.

## Bacterial Nomenclature

The associations of CRC with bacteria were analyzed at the genus and species levels. The most recent nomenclature for *Streptococcus* species was adapted. The *Streptococcus milleri* group included *S anginosus*, *S constellatus*, and *S intermedius*.[26] The *S bovis* group included *S gallolyticus*, *S infantarius*, *S lutetiensis*, and related subspecies.[27]

## Statistical Analysis

Data of age-, sex-, and comorbidity-matched controls from the same period were retrieved for comparison (Figure 1). The index start date was defined as the date of first positive blood culture test results for cases and the date of first negative blood culture test results for controls. All patients at least 18 years old by the index date were included. Limited by the large amount of data retrieved, baseline comorbidities between subjects with and without bacteremia were matched at a ratio of 1 to 1. When categorizing by bacteremia-causing bacteria, the case subjects were matched to control subjects at a ratio of 1 to 5 (Figure 1). Patients with a previously identified cancer before the index date were excluded. The exposure of interest was bacteremia and the primary outcome was the occurrence of CRC after the index date. The comorbidity score of each subject was calculated by patients' *International Statistical Classification of Diseases and Related Health Problems, Ninth Revision* code of selected disease diagnose code by the R package ("icd"), and these diseases are listed in Supplementary Table 1. Patients were matched with the control cohort by propensity score, which included age without categorization, sex, and comorbidity score, to control potential confounders. Using the R package "MatchIt," we used nearest neighbor matching with the 1:5 ratio for selecting a matched group for specific bacteria. Using the Kaplan-Meier estimator, the cumulative incidence, hazard ratio (HR), and 95% confidence interval (CI) of biopsy-proved CRC were

calculated to study the association between the bacterium and CRC. The HR of each bacterium was calculated by the Cox proportional hazards regression model adjusting for covariates. Bacteria uncommonly causing bacteremia with no more than 12 cases, including *Filifactor* and *Solobacterium* genera, were not analyzed because a meaningful statistical comparison was not possible.

To identify the duration of which the CRC diagnosis was increased after the incident bacteremia, we calculated the inflection points for all significantly associated bacteria that had a CRC case number higher than 5 to achieve a statistically significant comparison. This represented the time point after which the increased risk of CRC diagnosis was normalized and became comparable with the unexposed group. The average slope between the point of event and the end of the survival curve was calculated from 1 to 48 months, and the inflection point was defined as the number of days after the incident bacteremia at which the average slopes of the exposed and unexposed cohorts intercepted or came in closest proximity. We also retrieved tumor stage and location and tested for associations with bacteremia using the Fisher exact test.

### Ethical Statement

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Joint Clinical Research Ethics Committee of the Chinese University of Hong Kong and the Hospital Authority New Territory East Cluster. All clinical data were anonymized by the CDARS, with all potential patient identifiers removed upon return of database searches.

## Results

### Patient Characteristics

We identified 845,723 patients receiving a blood culture test from January 1, 2006 to December 31, 2015. A total of 15,215 patients with bacteremia with bacteria from the selected genera were retrieved, along with 60,860 randomly selected patients without bacteremia. After excluding patients younger than 18 years and those with a pre-existing diagnosis of cancer, patients were matched by propensity score and 13,096 patients with bacteremia of defined bacterial genera (exposed cohort) and 32,857 matched patients without bacteremia (unexposed cohort) were included for analysis (Figure 1).

### Increased Diagnosis of CRC in Patients With Bacteremia

This study evaluated the subsequent CRC diagnosis in patients with bacteremia from CRC-associated microbiota. The subjects exposed to bacteremia of CRC-related microbiota were matched to unexposed subjects at a ratio of 1 to 1. The mean age was 70.2 ± 38.4 years for the exposed cohort and 70.3 ± 38.3 years for the unexposed cohort, with slightly more women in the 2 groups (Table 1). The mean comorbidity scores were comparable between the 2 groups (Table 1). Overall, we observed a larger proportion of patients in the exposed cohort receiving a subsequent diagnosis of CRC than patients in the unexposed cohort (1.69% vs 1.16%; HR = 1.72, 95% CI = 1.40–2.12, $P = 2.6 \times 10^{-7}$).

**Table 1.** Characteristics of Patients Included in This Study

| Characteristics | Exposed cohort (n = 13,096) | Unexposed cohort (n = 13,096) |
|---|---|---|
| Demographics | | |
| Age (*y*), mean (SD) | 70.2 (38.4) | 70.3 (38.3) |
| Women, n (%) | 7,186 (54.9) | 7,225 (55.2) |
| Patients with subsequent diagnosis of CRC, n (%) | 221 (1.69) | 152 (1.16) |
| Baseline comorbidities, n (%) | | |
| Comorbidity score | 0.826 | 0.816 |
| Myocardial infarction | 517 (3.95) | 546 (4.17) |
| Cerebrovascular disease | 2,389 (18.2) | 2,177 (16.6) |
| Chronic pulmonary disease | 1,060 (8.09) | 1,360 (10.4) |
| Congestive heart failure | 1,584 (12.1) | 1,585 (12.1) |
| Dementia | 771 (5.89) | 661 (5.05) |
| Diabetes mellitus | 2,356 (18.0) | 2,107 (16.1) |
| Moderate or severe liver disease | 296 (2.26) | 115 (0.88) |
| Peripheral vascular disease | 313 (2.39) | 192 (1.47) |
| Renal disease | 1,000 (7.64) | 1,049 (8.01) |

SD, standard deviation.

For analyses of specific bacteria, we observed a strong association with *Bacteroides* species (HR = 3.71, 95% CI = 2.73–5.03, $P < 1.0 \times 10^{-16}$) and the *S bovis* group (HR = 3.87, 95% CI = 2.34–6.42, $P = 1.52 \times 10^{-7}$; Table 2 and Supplementary Figure 1). Significant associations also were observed for other enriched bacteria, including *Clostridium* species (HR = 4.38, 95% CI = 2.80–6.85, $P = 9.0 \times 10^{-11}$), *Peptostreptococcus* species (HR = 3.06, 95% CI = 1.47–6.35, $P = .003$), *Fusobacterium* species (HR = 3.79, 95% CI = 1.40–10.3, $P = .009$), *Prevotella* species (HR = 5.21, 95% CI = 1.27–21.4, $P = .022$) and *Granulicatella* species (HR = 7.23, 95% CI = 1.01–51.9, $P = .049$; Table 2 and Supplementary Figure 1).

### Significant Associations With Specific Bacterial Groups or Species

The nomenclature of the *S bovis* group was recently renamed, and currently the group is composed of *S gallolyticus*, *S infantarius*, *S lutetiensis*, and several related subspecies.[27] It has been shown that the majority of *S bovis* bacteremia associated with CRC is caused by *S gallolyticus* subspecies *gallolyticus*, but not with other subspecies (Supplementary Table 2).[27] Therefore, their species associations were examined further. Consistent with previous reports, a significant association between CRC and bacteremia with *S gallolyticus* subspecies *gallolyticus* was observed (HR = 5.73, 95% CI = 2.18–15.1, $P = 4.1 \times 10^{-4}$), whereas no significant differences were observed for other species within the *S bovis* group (Table 3, Supplementary Figure 2 and Supplementary Table 2). A strong association also was observed for *B fragilis* (HR = 3.85, 95% CI = 2.62–5.64, $P = 5.5 \times 10^{-12}$; Table 3 and Supplementary Figure 2).

Our analyses were extended to other bacteria at the species level and significant associations were observed between CRC and bacteremia with *F nucleatum* (HR = 6.89,

**Table 2.** Statistical Analysis of Cancer Diagnosis in Patients With Bacteremia Caused by CRC-Related Bacteria at Genus or Bacterial Group Level

| Bacteria | Exposed cohort, n | CRC cases, n (%) | Unexposed cohort, n | CRC cases, n (%) | HR (95% CI) | *P* value[a] | Adjusted HR (95% CI) | Adjusted *P* value[a] |
|---|---|---|---|---|---|---|---|---|
| *Bacteroides* species | 2,074 | 65 (3.13) | 10,370 | 117 (1.13) | 3.62 (2.67–4.91) | $1.1 \times 10^{-16}$ | 3.71 (2.73–5.03) | $<1.0 \times 10^{-16}$ |
| *Clostridium* species | 875 | 31 (3.54) | 4,375 | 53 (1.21) | 4.36 (2.79–6.81) | $9.5 \times 10^{-11}$ | 4.38 (2.80–6.85) | $9.0 \times 10^{-11}$ |
| *Streptococcus bovis* group | 662 | 25 (3.78) | 3,310 | 39 (1.18) | 3.79 (2.29–6.27) | $2.0 \times 10^{-7}$ | 3.87 (2.34–6.42) | $1.5 \times 10^{-7}$ |
| *Peptostreptococcus* species | 501 | 11 (2.20) | 2,505 | 22 (0.88) | 2.82 (1.37–5.81) | .005 | 3.06 (1.47–6.35) | .003 |
| *Fusobacterium* species | 352 | 6 (1.70) | 1,760 | 11 (0.63) | 3.80 (1.40–10.3) | .009 | 3.79 (1.40–10.3) | .009 |
| *Prevotella* species | 181 | 4 (2.21) | 905 | 4 (0.44) | 5.99 (1.50–24.0) | .011 | 5.21 (1.27–21.4) | .022 |
| *Granulicatella* species | 69 | 2 (2.90) | 345 | 2 (0.58) | 7.40 (1.03–52.9) | .046 | 7.23 (1.01–51.9) | .049 |
| *Gemella* species | 110 | 4 (3.64) | 550 | 6 (1.09) | 3.38 (0.95–12.0) | .060 | 3.42 (0.96–12.2) | .058 |
| *Streptococcus milleri* group | 1,557 | 25 (1.61) | 7,785 | 99 (1.27) | 1.44 (0.93–2.23) | .103 | 1.48 (0.95–2.29) | .083 |
| *Parvimonas* species | 46 | 0 (0) | 230 | 1 (0.44) | ND | ND | ND | ND |

ND, not determined.
[a]*P* value was determined by Wald test.

95% CI = 1.70–27.9, $P = .007$) and *Clostridium septicum* (HR = 17.1, 95% CI = 1.82–160, $P = .013$; Table 3 and Supplementary Figure 2). Furthermore, other bacterial species enriched in CRC microbiota, including *Clostridium perfringens* (HR = 2.29, 95% CI = 1.16–4.52, $P = .017$) and *Gemella morbillorum* (HR = 15.2, 95% CI = 1.54–150, $P = .020$), were significantly associated with CRC (Table 3 and Supplementary Figure 2).[3,6] All these associations remained significant after adjustments to various confounding conditions by the fit proportional hazards regression model (Table 3 and Supplementary Table 1).

## Lack of Association With Non–CRC-Related Microbiota and Other Diseases

To confirm the specificity of association between CRC microbiota and subsequent cancer diagnosis, we evaluated occurrence of CRC in patients with bacteremia caused by bacteria with no known association with colorectal neoplasia. We observed no significant association between any of these bacteria and the outcome of CRC diagnosis (Supplementary Table 3).

To further corroborate our findings, we tested for associations between CRC-related microbiota and other diseases, including non-CRC cancers and nonmalignant gastrointestinal diseases. These included 3 cancers of the stomach, breast, and nasopharynx and 3 gastrointestinal diseases, including functional digestive disorders, inflammatory bowel diseases, and colonic diverticula. Apart from the few bacterial genera commonly implicating diverticulitis as a complication of colonic diverticulosis, we observed no significant associations between CRC-related microbiota and other diseases (Supplementary Tables 4–6).

## Infection Points, Tumor Stage, and Location

We investigated the inflection point for each bacterial genus to identify the time point after which the increased risk of CRC diagnosis normalized. Most bacteria showed inflection points within 1 year of the bacteremia diagnosis, including *C perfringens* (100 days), *Peptostreptococcus* species (121 days), and *Fusobacterium* species (127 days); most patients were diagnosed with CRC within 6 months after the incident bacteremia (Supplementary Table 7). The inflection

**Table 3.** Statistical Analysis of Cancer Diagnosis in Patients With Bacteremia Caused by CRC-related Bacteria

| Bacteria | Exposed cohort, n | CRC cases, n (%) | Unexposed cohort, n | CRC cases, n (%) | HR (95% CI) | *P* value[a] | Adjusted HR (95% CI) | Adjusted *P* value[a] |
|---|---|---|---|---|---|---|---|---|
| *Bacteroides fragilis* | 1,338 | 42 (3.14) | 6,690 | 73 (1.09) | 3.72 (2.54–5.45) | $1.4 \times 10^{-11}$ | 3.85 (2.62–5.64) | $5.5 \times 10^{-12}$ |
| *Streptococcus gallolyticus* | 203 | 8 (3.94) | 1,015 | 10 (0.99) | 5.38 (2.09–13.8) | $4.8 \times 10^{-4}$ | 5.73 (2.18–15.1) | $4.1 \times 10^{-4}$ |
| *Fusobacterium nucleatum* | 79 | 4 (5.06) | 395 | 4 (1.01) | 6.91 (1.72–27.8) | .006 | 6.89 (1.70–27.9) | .007 |
| *Clostridium septicum* | 13 | 4 (30.8) | 65 | 1 (1.54) | 23.2 (2.58–208) | .005 | 17.1 (1.82–160) | .013 |
| *Clostridium perfringens* | 522 | 11 (2.11) | 2,610 | 35 (1.34) | 2.27 (1.15–4.48) | .018 | 2.29 (1.16–4.52) | .017 |
| *Gemella morbillorum* | 38 | 3 (7.89) | 190 | 1 (0.53) | 16.9 (1.76–163) | .014 | 15.2 (1.54–150) | .020 |

NOTE: Bacterial species with significant associations are shown.
[a]*P* value was determined by Wald test.

points for *Streptococcus* species generally occurred late, at 1 year after the incident bacteremia (Supplementary Table 7). Incident bacteremia from *S bovis* was associated with diagnosis of early-staged CRC ($P = .004$; Supplementary Table 7).

We examined the association between the etiology of bacteremia and its tumor location, from which certain bacteria might preferentially originate. We did not observe any significant difference (Supplementary Table 7).



## Discussion

Recent studies have associated dysbiosis of the gut microbiota with several gastrointestinal diseases including CRC,[2–4] whereas subsequent functional studies have pinpointed specific bacterial species playing a mechanistic role in carcinogenesis.[5,9,10,12] Interestingly, of the highly enriched bacteria in the CRC microbiota, many also can cause bacteremia. In this study, we investigated the relation between bacteremia from CRC microbiota and subsequent onset of cancer. To our knowledge, this is the first large-scale study to systemically explore this relation using a large territory-wide population database cohort.

This study provides support to the bacterial theory of colorectal carcinogenesis, especially for the 3 well-studied bacteria, namely *S gallolyticus*, *B fragilis*, and *F nucleatum*. Moreover, we identified novel candidate species that might play a role in CRC development, such as *C perfringens* and *G morbillorum*, which were enriched in the CRC microbiota.[3,6] Because many of these bacteria are common colonic symbionts that reside in the large intestine, their presence in the bloodstream suggests an abnormal entry from dysbiotic mucosae, possibly through neoplastic tissues. Consistent with this hypothesis, *S gallolyticus* and *F nucleatum* have been found to preferably colonize and reside in neoplastic lesions.[28,29] Furthermore, it is established that chronic inflammation plays a major role in CRC development. The antigens of *S gallolyticus* can stimulate the production of various inflammatory cytokines such as tumor necrosis factor-$\alpha$, IL-1$\beta$, IL-6, and IL-8.[15,28] These inflammatory cytokines also can promote vasodilatation, enhancing capillary permeability at the site of the neoplasm and possibly serving as a portal of entry into the bloodstream.[30] Similarly, *F nucleatum* also can generate proinflammatory microenvironment by recruiting myeloid-derived immune cells to promote tumor development.[13] The increased permeability of blood vessels at the inflamed microenvironment might have facilitated this bacterium to enter the blood circulation, thus causing bacteremia. The impaired epithelial barrier at neoplastic lesions could be a universal mechanism for various CRC-enriched microbes to gain access to the circulatory system during the early stage of colorectal tumorigenesis.

We calculated the inflection points of the curves to estimate the duration of which the likelihood of CRC diagnosis would be increased after the incident bacteremia, because this could illuminate the underlying microbiology. Hypothetically, bacteria involved in early carcinogenesis could translocate to the mucosal vasculature to cause bacteremia through an adenoma. This might raise the likelihood of CRC diagnosis for a long period after the incident bacteremia, because it takes years for an adenoma to turn into a carcinoma. In contrast, bacteria involved late in the adenoma-to-carcinoma cascade might cause bacteremia with a sizable tumor; as such, most CRC cases would be diagnosed shortly after the incident bacteremia. Consistent with the late-occurring inflection points, there have been studies reporting associations between *S bovis* and premalignant colorectal neoplasia,[31,32] suggesting its possible early role in colorectal carcinogenesis. This is compatible with the stage analysis showing an association between *S bovis* bacteremia and early-staged CRC diagnosis. Conversely, the early-occurring inflection points for *Fusobacterium* and *Peptostreptococcus* species might imply a change in cancer microenvironment in CRC, because these 2 bacterial genera have been shown to form a co-occurrence network in the CRC metacommunity.[3,6] Nevertheless, further functional studies are needed to support the etiologic relations between these bacteria and CRC.

A major strength of this study is the relatively large sample and availability of accurate clinical data. Because bacteremia and biopsy-proved cancer were well-defined and objectively coded events, the data source is highly reliable. The robustness of data also is supported by the significant associations of *B fragilis* and *S bovis*, with a similar magnitude compared with those reported in previous studies.[16,19] The availability of other clinical data, including patient demographics and comorbid conditions, allowed us to perform matching and adjustment to minimize confounding effects. A substantial number of cases shares confounding conditions such as diabetes mellitus. To adjust for these confounders, comorbidity matching for each bacterium was carried out with a relatively large control cohort (1:5 ratio) to minimize this error.

It is noteworthy that despite intravenous antibiotics treatment, the episodes of bacteremia were still associated with development of CRC. This could imply ongoing carcinogenesis despite bacterial clearance from the blood. This might be possible given the multifactorial etiologies of colorectal carcinogenesis or recolonization of the procarcinogenic bacteria after the antibiotic regimen. Previous studies have suggested that certain bacterial species, such as *F nucleatum*, preferably colonize the proximal colon compared with the distal colon, which could lead to increased tumor development in this region.[33] However, we did not observe a significant difference between bacterial etiology and tumor location in our cohort.

One limitation of this study is the possibility of subclinical bacteremia causing biases in the statistical estimates. In this study, bacteremia was defined by positive bacterial culture result, rather than more sensitive molecular techniques such as polymerase chain reaction or sequencing. Nevertheless, this should be sufficient because bacteriology remains the current standard in detecting viable bacteria in the blood. Furthermore, this potential bias should have been neutralized by its effects in the groups with and without CRC.

Because colorectal screening is not routinely done in patients with bacteremia in Hong Kong, the identification of novel bacterial species in these patients with significant impact on subsequent CRC diagnosis might necessitate a change in clinical management. As the large HRs indicate, bacteremia from some CRC-associated bacteria predates a diagnosis of CRC with high specificity and therefore should alert clinicians to consider colonoscopy to look for neoplastic lesions for early detection of colorectal neoplasia, which could advance the disease diagnosis and lower mortality.[34] These data emphasize the need to carefully examine the bowel in patients presenting with these unusual bacteremia cases without an alternative septic source.

## Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2018.04.028.

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Authors disclose no conflicts.

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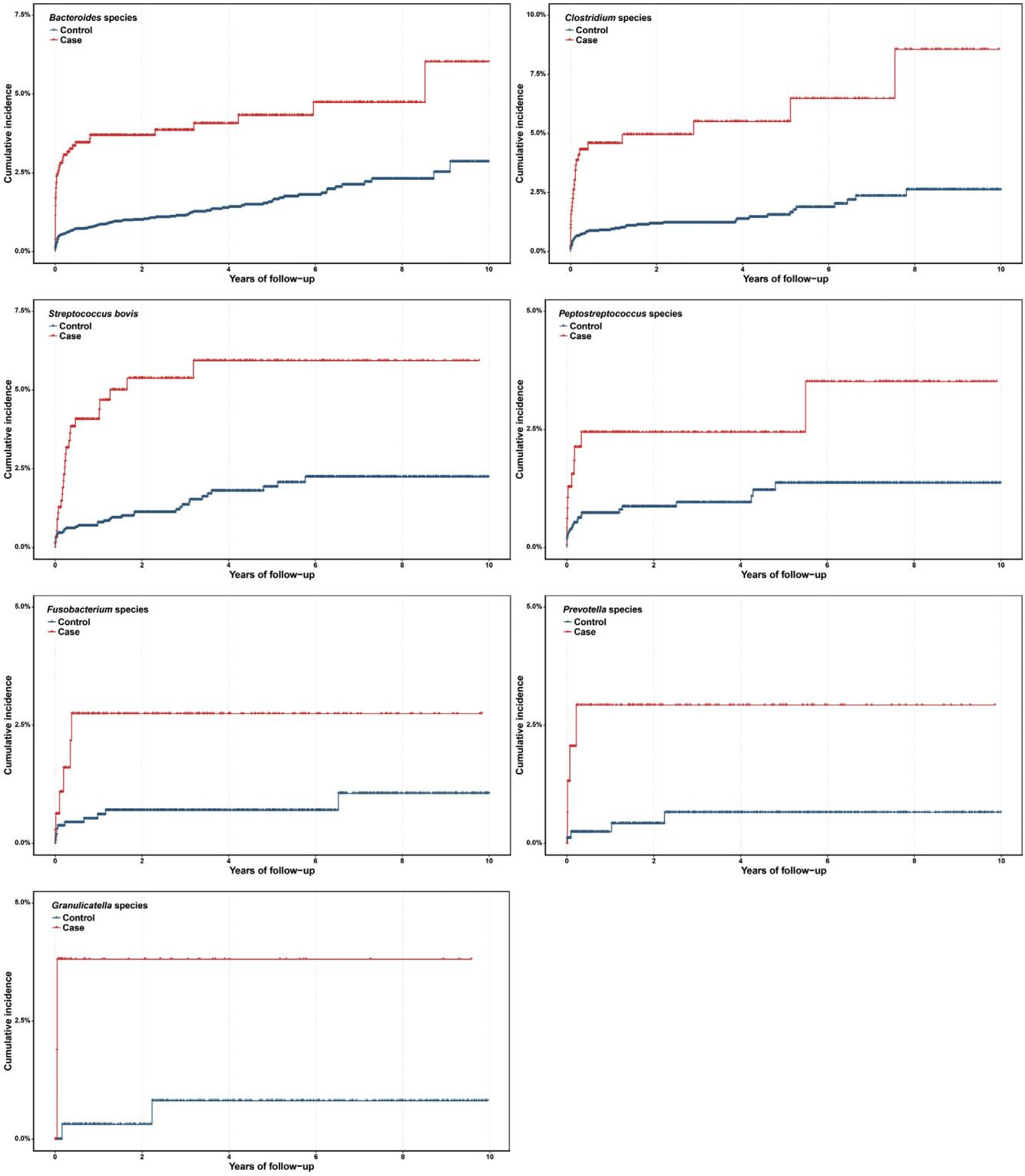
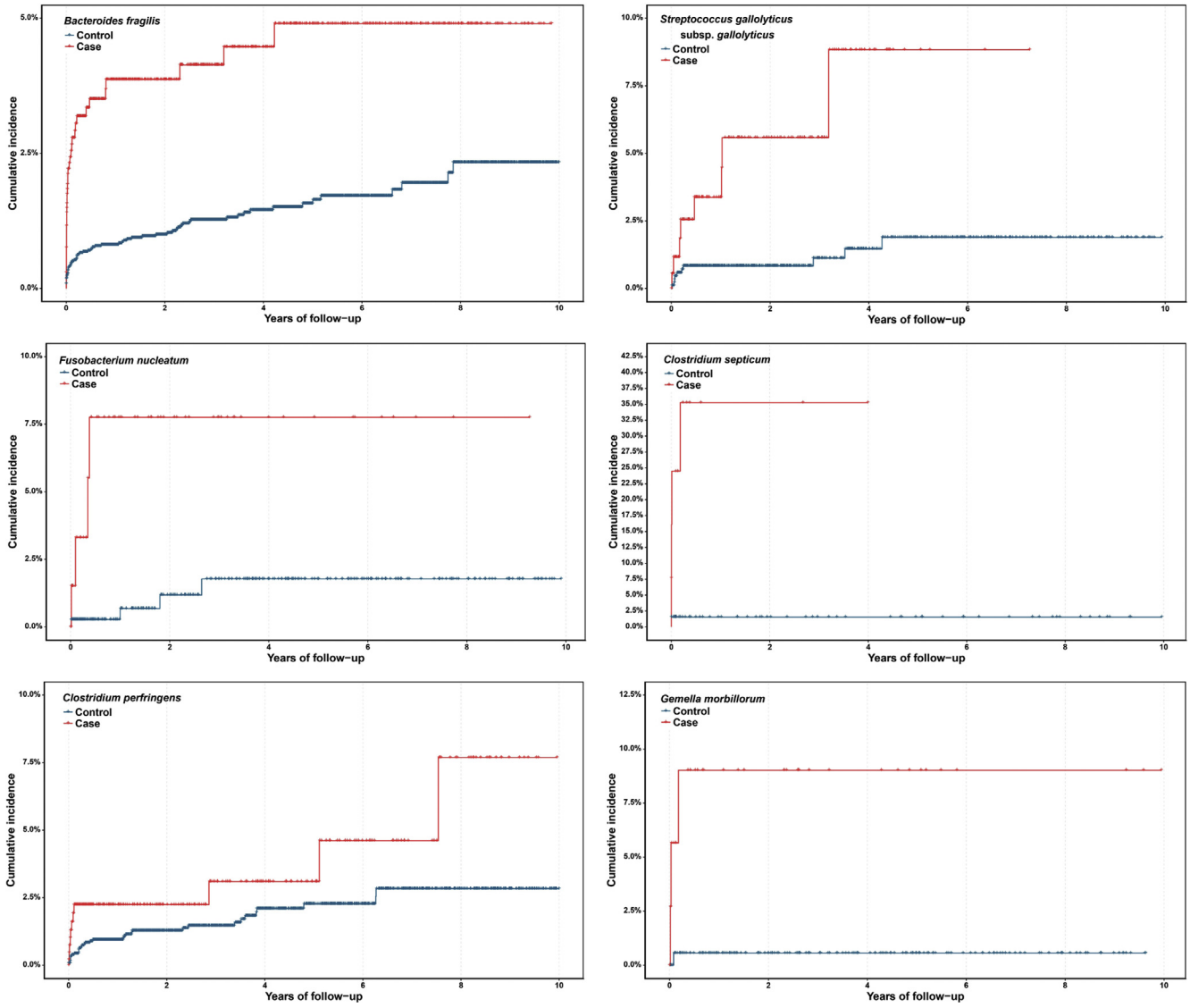



**Supplementary Figure 1.** Rate of subsequent cancer diagnosis in patients with bacteremia caused by CRC-enriched bacteria at the genus level.




**Supplementary Figure 2.** Rate of subsequent cancer diagnosis in patients with bacteremia caused by CRC-enriched bacteria at the species level.

**Supplementary Table 1.** ICD-9 Diagnostic Codes for Comorbidity Score Calculation Used in This Study

| ICD-9 code | Description |
|---|---|
| 410, 412 | myocardial infarction |
| 430-438 | cerebrovascular disease |
| 490-496, 500-505, 506.4 | chronic pulmonary disease |
| 428 | congestive heart failure |
| 290 | dementia |
| 250 | diabetes mellitus |
| 572.2-572.8 | moderate or severe liver disease |
| 433.9, 441, 785.4, V43.4 | peripheral vascular disease |
| 582, 583, 585, 586 | renal disease |

ICD-9, *International Statistical Classification of Diseases and Related Health Problems, Ninth Revision*.

**Supplementary Table 2.** Statistical Analysis of Cancer Diagnosis in Patients With Bacteremia Caused by CRC-Related Bacteria at Species Level

| Bacteria | HR (95% CI) | *P* value[a] | Adjusted HR (95% CI) | Adjusted *P* value[a] |
|---|---|---|---|---|
| *Streptococcus intermedius* | 5.96 (0.83–42.6) | .075 | 6.49 (0.910–46.2) | .062 |
| *Streptococcus agalactiae* | 0.45 (0.20–1.05) | .064 | 0.460 (0.200–1.06) | .070 |
| *Peptostreptococcus micros* | 3.55 (0.59–21.3) | .165 | 5.44 (0.770–38.7) | .090 |
| *Streptococcus oralis* | 3.35 (0.61–18.3) | .163 | 3.82 (0.630–23.2) | .146 |
| *Streptococcus pneumoniae* | 0.610 (0.31–1.21) | .157 | 0.610 (0.310–1.22) | .164 |
| *Clostridium innocuum* | 5.20 (0.43–62.9) | .195 | 5.13 (0.430–60.7) | .195 |
| *Fusobacterium mortiferum* | 2.82 (0.27–29.2) | .385 | 2.47 (0.210–29.8) | .474 |
| *Bacteroides caccae* | 3.40 (0.31–37.8) | .319 | 2.33 (0.180–30.5) | .519 |
| *Peptostreptococcus asaccharolyticus* | 2.10 (0.21–20.5) | .524 | 2.04 (0.210–19.8) | .538 |
| *Streptococcus dysgalactiae* subspecies *dysgalactiae* | 1.66 (0.17–15.9) | .662 | 1.82 (0.190–17.9) | .606 |
| *Streptococcus dysgalactiae* subspecies *equisimilis* | 1.16 (0.54–2.50) | .694 | 1.18 (0.550–2.52) | .676 |
| *Streptococcus sanguinis* | 1.32 (0.28–6.21) | .726 | 1.39 (0.280–6.87) | .688 |
| *Streptococcus mitis* | 1.15 (0.33–3.94) | .828 | 1.23 (0.360–4.27) | .740 |
| *Streptococcus pyogenes* | 1.11 (0.38–3.21) | .853 | 1.19 (0.410–3.48) | .749 |
| *Streptococcus constellatus* | 1.09 (0.51–2.33) | .818 | 1.12 (0.530–2.39) | .762 |
| *Streptococcus gordonii* | 0.98 (0.11–8.40) | .986 | 1.01 (0.110–8.83) | .995 |
| *Bacteroides vulgatus* | $4.4 \times 10^9$ (0.00–∞) | .999 | $5.5 \times 10^{11}$ (0.00–∞) | 1.000 |

NOTE: Bacterial species with no significant association are shown.
[a]*P* value was determined by Wald test.

**Supplementary Table 3.** Statistical Analysis of Cancer Diagnosis in Patients With Bacteremia Caused by non–CRC-Related Bacteria

| Bacteria | Exposed cohort, n | CRC cases, n (%) | Unexposed cohort, n | CRC cases, n (%) | HR (95% CI) | *P* value[a] | Adjusted HR (95% CI) | Adjusted *P* value[a] |
|---|---|---|---|---|---|---|---|---|
| *Diphtheroids* species | 1,299 | 12 (0.92) | 2,598 | 31 (1.19) | 0.94 (0.48–1.84) | .864 | 1.03 (0.53–2.03) | .924 |
| *Aeromonas* species | 949 | 8 (0.84) | 1,898 | 20 (1.05) | 0.99 (0.43–2.24) | .972 | 0.95 (0.41–2.19) | .903 |
| *Morganella* species | 760 | 2 (0.26) | 1,520 | 17 (1.12) | 0.32 (0.07–1.41) | .134 | 0.34 (0.08–1.50) | .154 |
| *Serratia* species | 689 | 7 (1.02) | 1,378 | 17 (1.23) | 1.06 (0.44–2.57) | .893 | 1.12 (0.46–2.73) | .800 |
| *Micrococcus* species | 570 | 3 (0.53) | 1,140 | 17 (1.49) | 0.39 (0.11–1.32) | .128 | 0.43 (0.12–1.47) | .177 |

[a]*P* value was determined by Wald test.

**Supplementary Table 4.** Statistical Analysis of Non-CRC Cancer Diagnoses in Patients With Bacteremia Caused by CRC-Related Bacteria

| Bacteria | Exposed cohort, n | Cases, n (%) | Unexposed cohort, n | Cases, n (%) | HR (95% CI) | *P* value[a] | Adjusted HR (95% CI) | Adjusted *P* value[a] |
|---|---|---|---|---|---|---|---|---|
| Stomach cancer | | | | | | | | |
| *Bacteroides* species | 2,074 | 4 (0.19) | 10,370 | 31 (0.3) | 0.88 (0.31–2.49) | .803 | 0.85 (0.30–2.41) | .755 |
| *Clostridium* species | 875 | 3 (0.34) | 4,375 | 13 (0.3) | 1.80 (0.51–6.34) | .362 | 1.79 (0.51–6.30) | .367 |
| *Peptostreptococcus* species | 501 | 3 (0.6) | 2,505 | 9 (0.36) | 1.97 (0.53–7.27) | .311 | 2.24 (0.58–8.59) | .241 |
| *Fusobacterium* species | 352 | 0 (0) | 1,760 | 7 (0.4) | ND | ND | ND | ND |
| *Prevotella* species | 181 | 1 (0.55) | 905 | 1 (0.11) | 6.06 (0.38–97.2) | .204 | 5.30 (0.33–85.5) | .240 |
| *Gemella* species | 110 | 0 (0) | 550 | 0 (0) | ND | ND | ND | ND |
| *Granulicatella* species | 69 | 0 (0) | 345 | 0 (0) | ND | ND | ND | ND |
| *Parvimonas* species | 46 | 0 (0) | 230 | 1 (0.43) | ND | ND | ND | ND |
| *Streptococcus milleri* group | 1,557 | 7 (0.45) | 7,785 | 26 (0.33) | 1.58 (0.68–3.64) | .285 | 1.56 (0.67–3.62) | .300 |
| *Streptococcus bovis* group | 662 | 5 (0.76) | 3,310 | 12 (0.36) | 2.63 (0.92–7.47) | .070 | 2.65 (0.91–7.66) | .072 |
| *Bacteroides fragilis* | 1,324 | 2 (0.15) | 4,874 | 12 (0.25) | 0.94 (0.21–4.25) | .934 | 1.08 (0.24–4.98) | .919 |
| *Clostridium perfringens* | 510 | 2 (0.39) | 1,929 | 5 (0.26) | 2.02 (0.39–10.5) | .400 | 2.57 (0.47–14.1) | .277 |
| *Streptococcus gallolyticus* | 203 | 1 (0.49) | 778 | 2 (0.26) | 2.43 (0.22–26.9) | .469 | 2.97 (0.25–29.6) | .627 |
| *Fusobacterium nucleatum* | 77 | 0 (0) | 277 | 1 (0.36) | ND | ND | ND | ND |
| *Gemella morbillorum* | 37 | 0 (0) | 134 | 1 (0.75) | ND | ND | ND | ND |
| *Clostridium septicum* | 13 | 0 (0) | 46 | 0 (0) | ND | ND | ND | ND |
| Breast cancer | | | | | | | | |
| *Bacteroides* species | 2,074 | 5 (0.24) | 10,370 | 22 (0.21) | 1.62 (0.61–4.30) | .329 | 1.78 (0.67–4.74) | .250 |
| *Clostridium* species | 875 | 1 (0.11) | 4,375 | 4 (0.09) | 2.32 (0.26–20.7) | .452 | 2.68 (0.29–24.6) | .382 |
| *Peptostreptococcus* species | 501 | 1 (0.2) | 2,505 | 2 (0.08) | 2.80 (0.25–31.0) | .4 | 2.76 (0.25–30.5) | .408 |
| *Fusobacterium* species | 352 | 0 (0) | 1,760 | 4 (0.23) | ND | ND | ND | ND |
| *Prevotella* species | 181 | 0 (0) | 905 | 0 (0) | ND | ND | ND | ND |
| *Gemella* species | 110 | 2 (1.82) | 550 | 1 (0.18) | 9.77 (0.88–108.2) | .063 | 7.43 (0.63–87.6) | .111 |
| *Granulicatella* species | 69 | 0 (0) | 345 | 0 (0) | ND | ND | ND | ND |
| *Parvimonas* species | 46 | 0 (0) | 230 | 1 (0.43) | ND | ND | ND | ND |
| *Streptococcus milleri* group | 1,557 | 5 (0.32) | 7,785 | 24 (0.31) | 1.27 (0.48–3.32) | .631 | 1.30 (0.49–3.42) | .597 |
| *Streptococcus bovis* group | 662 | 2 (0.3) | 3,310 | 8 (0.24) | 1.62 (0.34–7.66) | .539 | 1.38 (0.29–6.59) | .690 |
| *Bacteroides fragilis* | 1,324 | 3 (0.23) | 4,874 | 6 (0.12) | 2.55 (0.63–10.3) | .187 | 3.76 (0.82–17.2) | .088 |
| *Clostridium perfringens* | 510 | 0 (0) | 1,929 | 1 (0.05) | ND | ND | ND | ND |
| *Streptococcus gallolyticus* | 203 | 0 (0) | 778 | 1 (0.13) | ND | ND | ND | ND |
| *Fusobacterium nucleatum* | 77 | 0 (0) | 277 | 1 (0.36) | ND | ND | ND | ND |
| *Gemella morbillorum* | 37 | 0 (0) | 134 | 0 (0) | ND | ND | ND | ND |
| *Clostridium septicum* | 13 | 0 (0) | 46 | 0 (0) | ND | ND | ND | ND |
| Nasopharyngeal cancer | | | | | | | | |
| *Bacteroides* species | 2,074 | 3 (0.14) | 10,370 | 8 (0.08) | 2.83 (0.75–10.7) | .126 | 2.39 (0.63–9.07) | .202 |
| *Clostridium* species | 875 | 1 (0.11) | 4,375 | 1 (0.02) | 9.49 (0.59–151.7) | .112 | 7.85 (0.49–126.1) | .146 |
| *Peptostreptococcus* species | 501 | 0 (0) | 2,505 | 1 (0.04) | ND | ND | ND | ND |
| *Fusobacterium* species | 352 | 0 (0) | 1,760 | 2 (0.11) | ND | ND | ND | ND |
| *Prevotella* species | 181 | 0 (0) | 905 | 0 (0) | ND | ND | ND | ND |
| *Gemella* species | 110 | 1 (0.91) | 550 | 1 (0.18) | 5.37 (0.34–85.8) | .235 | 5.57 (0.35–89.2) | .225 |
| *Granulicatella* species | 69 | 0 (0) | 345 | 0 (0) | ND | ND | ND | ND |
| *Parvimonas* species | 46 | 0 (0) | 230 | 0 (0) | ND | ND | ND | ND |
| *Streptococcus milleri* group | 1,557 | 1 (0.06) | 7,785 | 7 (0.09) | 0.87 (0.11–7.10) | .898 | 0.84 (0.10–6.88) | .873 |
| *Streptococcus bovis* group | 662 | 0 (0) | 3,310 | 0 (0) | ND | ND | ND | ND |
| *Bacteroides fragilis* | 1,324 | 0 (0) | 4,874 | 2 (0.04) | ND | ND | ND | ND |
| *Clostridium perfringens* | 510 | 1 (0.2) | 1,929 | 2 (0.1) | 2.87 (0.26–31.7) | .389 | 2.78 (0.24–31.9) | .411 |
| *Streptococcus gallolyticus* | 203 | 0 (0) | 778 | 0 (0) | ND | ND | ND | ND |
| *Fusobacterium nucleatum* | 77 | 0 (0) | 277 | 0 (0) | ND | ND | ND | ND |
| *Gemella morbillorum* | 37 | 0 (0) | 134 | 0 (0) | ND | ND | ND | ND |
| *Clostridium septicum* | 13 | 0 (0) | 46 | 0 (0) | ND | ND | ND | ND |

ND, not determined.
[a]*P* value was determined by Wald test.

**Supplementary Table 5.** ICD-9 Diagnostic Codes Used for Statistical Analysis of Nonmalignant Gastrointestinal Diseases

| ICD-9 code | Description |
|---|---|
| 564 | functional digestive disorders, not elsewhere classified |
| 555, 556 | regional enteritis (including Crohn disease), ulcerative colitis |
| 562.1 | diverticula of colon (including diverticulosis and diverticulitis, with or without hemorrhage) |

ICD-9, *International Statistical Classification of Diseases and Related Health Problems, Ninth Revision*.

**Supplementary Table 6.** Statistical Analysis of Nonmalignant Gastrointestinal Disease Diagnoses in Patients With Bacteremia Caused by CRC-Related Bacteria

| Bacteria | Exposed cohort, n | Cases, n (%) | Unexposed cohort, n | Cases, n (%) | HR (95% CI) | *P* value[a] | Adjusted HR (95% CI) | Adjusted *P* value[a] |
|---|---|---|---|---|---|---|---|---|
| Functional digestive disorders | | | | | | | | |
| *Bacteroides* species | 1,909 | 56 (2.93) | 7,636 | 288 (3.77) | 1.12 (0.84–1.49) | .452 | 1.18 (0.88–1.58) | .268 |
| *Clostridium* species | 821 | 14 (1.71) | 3,284 | 139 (4.23) | 0.71 (0.41–1.24) | .232 | 0.72 (0.41–1.25) | .244 |
| *Peptostreptococcus* species | 473 | 10 (2.11) | 1,892 | 84 (4.44) | 0.56 (0.29–1.08) | .082 | 0.60 (0.31–1.17) | .132 |
| *Fusobacterium* species | 324 | 8 (2.47) | 1,296 | 48 (3.7) | 1.04 (0.49–2.21) | .915 | 1.18 (0.55–2.52) | .667 |
| *Prevotella* species | 167 | 8 (4.79) | 668 | 20 (2.99) | 2.22 (0.97–5.06) | .058 | 2.07 (0.89–4.82) | .091 |
| *Gemella* species | 106 | 5 (4.72) | 424 | 10 (2.36) | 2.14 (0.73–6.26) | .165 | 2.08 (0.68–6.36) | .201 |
| *Granulicatella* species | 68 | 0 (0) | 272 | 11 (4.04) | ND | ND | ND | ND |
| *Parvimonas* species | 41 | 0 (0) | 164 | 11 (6.71) | ND | ND | ND | ND |
| *Streptococcus milleri* group | 1,477 | 46 (3.11) | 5,908 | 214 (3.62) | 1.04 (0.76–1.43) | .803 | 1.05 (0.76–1.45) | .751 |
| *Streptococcus bovis* group | 615 | 22 (3.58) | 2,460 | 87 (3.54) | 1.26 (0.79–2.02) | .329 | 1.26 (0.79–2.02) | .338 |
| *Bacteroides fragilis* | 1,214 | 33 (2.72) | 4,584 | 186 (4.06) | 0.93 (0.64–1.35) | .715 | 1.21 (0.83–1.76) | .327 |
| *Clostridium perfringens* | 476 | 6 (1.26) | 1,817 | 79 (4.35) | 0.40 (0.18–0.93) | .033 | 0.45 (0.20–1.04) | .062 |
| *Streptococcus gallolyticus* | 182 | 5 (2.75) | 728 | 21 (2.88) | 1.57 (0.58–4.24) | .376 | 1.59 (0.58–4.38) | .369 |
| *Fusobacterium nucleatum* | 68 | 0 (0) | 262 | 18 (6.87) | ND | ND | ND | ND |
| *Gemella morbillorum* | 35 | 3 (8.57) | 130 | 8 (6.15) | 1.92 (0.50–7.30) | .340 | 3.80 (0.83–17.45) | .087 |
| *Clostridium septicum* | 12 | 0 (0) | 44 | 3 (6.82) | ND | ND | ND | ND |
| Inflammatory bowel diseases | | | | | | | | |
| *Bacteroides* species | 2,069 | 2 (0.1) | 8,276 | 6 (0.07) | 1.83 (0.37–9.08) | .461 | 1.77 (0.35–8.82) | .488 |
| *Clostridium* species | 875 | 0 (0) | 3,500 | 0 (0) | ND | ND | ND | ND |
| *Peptostreptococcus* species | 500 | 0 (0) | 2,000 | 2 (0.1) | ND | ND | ND | ND |
| *Fusobacterium* species | 351 | 0 (0) | 1,404 | 0 (0) | ND | ND | ND | ND |
| *Prevotella* species | 181 | 0 (0) | 724 | 1 (0.14) | ND | ND | ND | ND |
| *Gemella* species | 110 | 0 (0) | 440 | 0 (0) | ND | ND | ND | ND |
| *Granulicatella* species | 69 | 0 (0) | 276 | 0 (0) | ND | ND | ND | ND |
| *Parvimonas* species | 46 | 0 (0) | 184 | 0 (0) | ND | ND | ND | ND |
| *Streptococcus milleri* group | 1,557 | 0 (0) | 6,228 | 5 (0.08) | ND | ND | ND | ND |
| *Streptococcus bovis* group | 662 | 0 (0) | 2,648 | 1 (0.04) | ND | ND | ND | ND |
| *Bacteroides fragilis* | 1,321 | 1 (0.08) | 4,871 | 1 (0.02) | 5.49 (0.34–87.7) | .229 | 4.56 (0.27–76.1) | .290 |
| *Clostridium perfringens* | 510 | 0 (0) | 1,924 | 0 (0) | ND | ND | ND | ND |
| *Streptococcus gallolyticus* | 203 | 0 (0) | 778 | 0 (0) | ND | ND | ND | ND |
| *Fusobacterium nucleatum* | 77 | 0 (0) | 277 | 0 (0) | ND | ND | ND | ND |
| *Gemella morbillorum* | 37 | 0 (0) | 134 | 0 (0) | ND | ND | ND | ND |
| *Clostridium septicum* | 13 | 0 (0) | 46 | 0 (0) | ND | ND | ND | ND |
| Diverticula disease | | | | | | | | |
| *Bacteroides* species | 2,026 | 64 (3.16) | 8,104 | 116 (1.43) | 3.08 (2.27–4.19) | 5.55E-13 | 3.21 (2.36–4.37) | 1.27E-13 |
| *Clostridium* species | 863 | 12 (1.39) | 3,452 | 45 (1.3) | 1.76 (0.93–3.34) | .083 | 1.85 (0.98–3.52) | .006 |
| *Peptostreptococcus* species | 492 | 8 (1.63) | 1,968 | 24 (1.22) | 1.55 (0.70–3.46) | .280 | 1.59 (0.70–3.61) | .270 |
| *Fusobacterium* species | 347 | 10 (2.88) | 1,388 | 16 (1.15) | 3.67 (1.66–8.12) | .001 | 4.16 (1.85–9.35) | .001 |
| *Prevotella* species | 180 | 4 (2.22) | 720 | 15 (2.08) | 1.33 (0.44–4.02) | .610 | 1.43 (0.46–4.42) | .538 |
| *Gemella* species | 109 | 0 (0) | 436 | 6 (1.38) | ND | ND | ND | ND |
| *Granulicatella* species | 69 | 0 (0) | 276 | 5 (1.81) | ND | ND | ND | ND |
| *Parvimonas* species | 45 | 0 (0) | 180 | 4 (2.22) | ND | ND | ND | ND |
| *Streptococcus milleri* group | 1,531 | 26 (1.7) | 6,124 | 93 (1.52) | 1.33 (0.86–2.06) | .198 | 1.34 (0.86–2.07) | .195 |
| *Streptococcus bovis* group | 646 | 24 (3.72) | 2,584 | 53 (2.05) | 2.18 (1.34–3.53) | .002 | 2.07 (1.27–3.37) | .003 |
| *Bacteroides fragilis* | 1,295 | 43 (3.32) | 4,798 | 69 (1.44) | 3.11 (2.12–4.56) | 5.86E-09 | 3.44 (2.33–5.09) | 6.11E-10 |
| *Clostridium perfringens* | 504 | 11 (2.18) | 1,898 | 25 (1.32) | 2.35 (1.16–4.79) | .018 | 2.41 (1.18–4.95) | .016 |
| *Streptococcus gallolyticus* | 197 | 4 (2.03) | 762 | 10 (1.31) | 2.02 (0.62–6.57) | .245 | 1.94 (0.56–6.71) | .296 |
| *Fusobacterium nucleatum* | 75 | 1 (1.33) | 266 | 1 (0.38) | 5.54 (0.33–94.0) | .236 | 35.7 (0.30–4,176.3) | .141 |
| *Gemella morbillorum* | 37 | 0 (0) | 132 | 1 (0.76) | ND | ND | ND | ND |
| *Clostridium septicum* | 12 | 0 (0) | 45 | 2 (4.44) | ND | ND | ND | ND |

ND, not determined.
[a]*P* value was determined by Wald test.

**Supplementary Table 7.** Descriptive Analyses of Infection Point, Tumor Location, and Stage for CRC-related bacterial genera

| Bacteria | CRC cases, n | Infection point (*d*) | Tumor location (distal) | Tumor location (proximal) | *P* value[a] (location) | Stage (stage 1 or 2) | Stage (stage 3 or 4) | *P* value[a] (stage) |
|---|---|---|---|---|---|---|---|---|
| *Bacteroides* species | 65 | 294 | 42 | 23 | .654 | 20 | 45 | .450 |
| *Clostridium* species | 31 | 438 | 16 | 15 | .428 | 9 | 22 | .542 |
| *Peptostreptococcus* species | 11 | 121 | 7 | 4 | 1 | 3 | 8 | .749 |
| *Fusobacterium* species | 6 | 127 | 4 | 2 | 1 | 3 | 3 | .67 |
| *Prevotella* species | 4 | ND | 2 | 2 | .649 | 1 | 3 | 1 |
| *Gemella* species | 4 | ND | 3 | 1 | 1 | 2 | 2 | .624 |
| *Granulicatella* species | 2 | ND | 1 | 1 | 1 | 1 | 2 | 1 |
| *Parvimonas* species | 0 | ND | 0 | 0 | 1 | 0 | 0 | 1 |
| *Streptococcus milleri* group | 25 | 1,384 | 17 | 8 | .519 | 7 | 18 | .506 |
| *Streptococcus bovis* group | 25 | 374 | 13 | 12 | .518 | 17 | 8 | .004 |

ND, not determined.
[a]*P* value was determined by Fisher exact test.