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Global prevalence of *Fusobacterium nucleatum* and *Bacteroides fragilis* in patients with colorectal cancer: an overview of case reports/case series and meta-analysis of prevalence studies

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Abstract

Background Colorectal cancer (CRC) is the second deadliest carcinoma across the globe and has been known as a multi-factor induced-disease. Emerging research have demonstrated that bacterial colonization may contribute to the initiation and promotion of the CRC. The presence of *Fusobacterium nucleatum* (*F. nucleatum*) and *Bacteroides fragilis* (*B. fragilis*) in the gut is associated with the development of CRC. In this study, the prevalence of *F. nucleatum* and *B. fragilis* among CRC patients has been assessed worldwide through a systematic review and meta-analysis.

Methods The extensive search was performed using "*Fusobacterium nucleatum*", "*Bacteroides fragilis*", "Colorectal cancer" and all relevant keywords. Then, a systematic paper screening was done following a comprehensive search in Embase, Web of Science, and PubMed databases while the time range was limited between the years 2000 and 2024. Afterwards, statistical analysis was performed utilizing the comprehensive meta-analysis (CMA) software (version 2.0, Biostat, USA).

Results According to the meta-analysis of prevalence studies, the prevalence of *F. nucleatum* among 19 countries and *B. fragilis* among 10 countries were indicated to be 38.9% (95% CI 33.7–44.3%) and 42.5% (95% CI 34.4–51.1%), respectively, among the CRC patients. It was then revealed that Asia had the highest prevalence of *F. nucleatum* while most of the *B. fragilis* isolates in CRC cases were reported in European countries. Moreover, the data suggested that the most common comorbidity observed among the CRC cases was diabetes.

Conclusion Our results emphasized the high prevalence of *F. nucleatum* and *B. fragilis* in CRC patients. Based on this meta-analysis review, regulating the gut microbiota in CRC patients seemed to be a promising approach to improving the efficacy of CRC therapy.

Keywords Colorectal cancer, *Fusobacterium nucleatum*, *Bacteroides fragilis*, Meta-analysis

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Introduction

Colorectal cancer (CRC) is characterized by the uncontrolled growth of epithelial cells in the colon or rectum [1]. Globally, CRC as the second most deadly cancer [2]. Its incidence is increasing in Asia, America, and Europe, whereas lower rates are reported in countries such as India and regions of Africa [3, 4]. Epidemiological studies suggest that CRC development and progression are influenced by genetic, epigenetic and environmental factors [5]. Key environmental risk factors include a low-fiber diet, sedentary lifestyle, obesity, smoking, and high alcohol consumption [6, 7]. Recent research highlights the significant role of intestinal microbiota in colorectal carcinogenesis, emphasizing its significant role as a major component of environmental factors [8, 9]. CRC patients exhibit a significant increase in *Bacteroides fragilis* (*B. fragilis*), *Fusobacterium nucleatum* (*F. nucleatum*), Enterococcaceae, Peptostreptococus, *Enterococus faecalis*, *Escherichia coli*, and a decrease in Faecalibacterium, Blautia, Clostridium, Bifidobacterium and Roseburia [10]. These changes might produce enrichment in pro-inflammatory opportunistic pathogens and a decrease in butyrate-producing bacteria, which may contribute to inducing inflammation and stimulating carcinogenic processes, including the activation of oncogene signaling pathways, angiogenesis, and proliferation [11]. Recent evidence has shown *F. nucleatum*, which is the microflora of the human oral cavity, is linked to CRC [12]. *F. nucleatum* adhesin FadA and Fap2 bind to epithelial and endothelial cells, modulating signaling pathways and inducing inflammatory cytokines [5, 13]. Furthermore, it has been reported that the induction of inflammatory cytokines like interleukin 6 (IL-6), IL-17, and tumor necrosis factor α (TNFα) in the peritumor mucosa leads to angiogenesis, tumor cell metastasis, and subsequently CRC progression [14]. *B. fragilis* expressing the toxin (BFT) enhances tumorigenesis and disrupts cytoskeletal structure (15). BFT is a zinc-dependent metalloprotease toxin that disrupts cell junctions of E-cadherin and β-catenin, leading to increased intestinal permeability and inflammation [16]. BFT exerts its neoplastic effects by causing DNA damage and accumulating mutations, leading to cell proliferation and transcription of genes involved in tumor progression (c-myc) [15, 17]. It is worth to mention that Christian Gethings et al., [18] demonstrated there is a strong correlation between the existence of *F. nucleatum* in colorectal tumor tissues and worse survival rates among CRC patients. These findings suggest the *F. nucleatum* as a potential biomarker of CRC while having a passive prognostic role and increase the probability of this bacterium playing an important role in CRC progression.

The present research aimed to study the prevalence of *F. nucleatum* and *B. fragilis* among CRC patients based on case reports/case series and prevalence studies all over the world.

Methods

Literature search

A systematic search was performed to identify the prevalence of *F. nucleatum* and *B. fragilis* in CRC patients. The search included the keywords "*Fusobacterium nucleatum*" OR "*F. nucleatum*" OR "*Bacteroides fragilis*" OR "*B. fragilis*" AND "Colorectal cancer" OR "CRC" OR "Colon cancer" OR "Rectal cancer" across three principal electronic databases: Medline (via PubMed), Embase, and Web of Science, for the period from 2000 to 2024.

Studies were included if they reported the prevalence or incidence of *F. nucleatum* and/or *B. fragilis* among CRC cases. Exclusion criteria comprised non-human studies, reviews, editorials and studies not providing specific prevalence data. Two independent reviewers screened the titles and abstracts of the identified articles, followed by full-text screening. Discrepancies were resolved through discussion by a third reviewer. Additionally, the bibliographies of identified articles were reviewed for additional relevant studies. This review was performed and documented in compliance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [19]. A PRISMA flow diagram was used to illustrate the study selection process, and a PRISMA checklist was completed.

Inclusion and exclusion criteria

All of the original papers published in English investigating the prevalence of *F. nucleatum* and/or *B. fragilis* in CRC patients were selected for further analysis, while articles not reporting aforementioned information were excluded. Duplicated studies, conferences abstract, reviews, letter to editors, non-clinical studies, and articles without full-text availability were identified and removed using reference management software and manual verification,

Data extraction and definitions

The variables extracted from eligible studies were the following: The author's last name, year of publication, country/continents, number of CRC cases, number of cases having *F. nucleatum* and/or *B. fragilis*, CRC mean age, and isolation source. The data was then extracted from the selected studies by two independent authors (PAE and MPE) using a standardized extraction form. Afterwards, the jointly reconciled data and disagreements were discussed and resolved between the authors through involvement of a third reviewer (FS). Thereafter, two independent researchers recorded the data to avoid bias.

Quality assessment

A meticulous quality check was carried out by two researchers (PAE and MPE), independently, based on the checklist provided by JBI (Joanna Briggs Institute) and subsequently, high-quality studies were chosen for the final analysis [20].

Meta-analysis

Comprehensive meta-analysis (CMA) software (version 2.0, Biostat, USA) was used to perform all the statistical analyses. Statistical heterogeneity was assessed for each analysis through the I2 statistic. If the I2 is greater than 75%, it indicates more heterogeneity, and if it is less than 75%, it indicates less heterogeneity. After observing statistical heterogeneity among studies, the data was analyzed utilizing a random-effect model. Also, p-value < 0.5 considered as publication bias in our study. Eventually, Begg's test was conducted to statistically evaluate the publication bias Additionally, Egger's test was performed to corroborate the findings of Begg's test. These statistical methods ensured a robust and reliable meta-analysis by addressing heterogeneity and potential biases.

Results

Search results

The paper-selection procedure is represented in Fig. 1. Initially, A total of 3315 papers were identified by the three electronic databases. After eliminating duplicates (n = 1572), 1743 articles remained for title and abstract screening. Thereafter, 401 met the inclusion criteria and were retained for full-text review, amongst 330 studies were excluded. The excluded papers were categorized as studies published in languages other than English, non-original studies, conference abstracts, reviews, articles

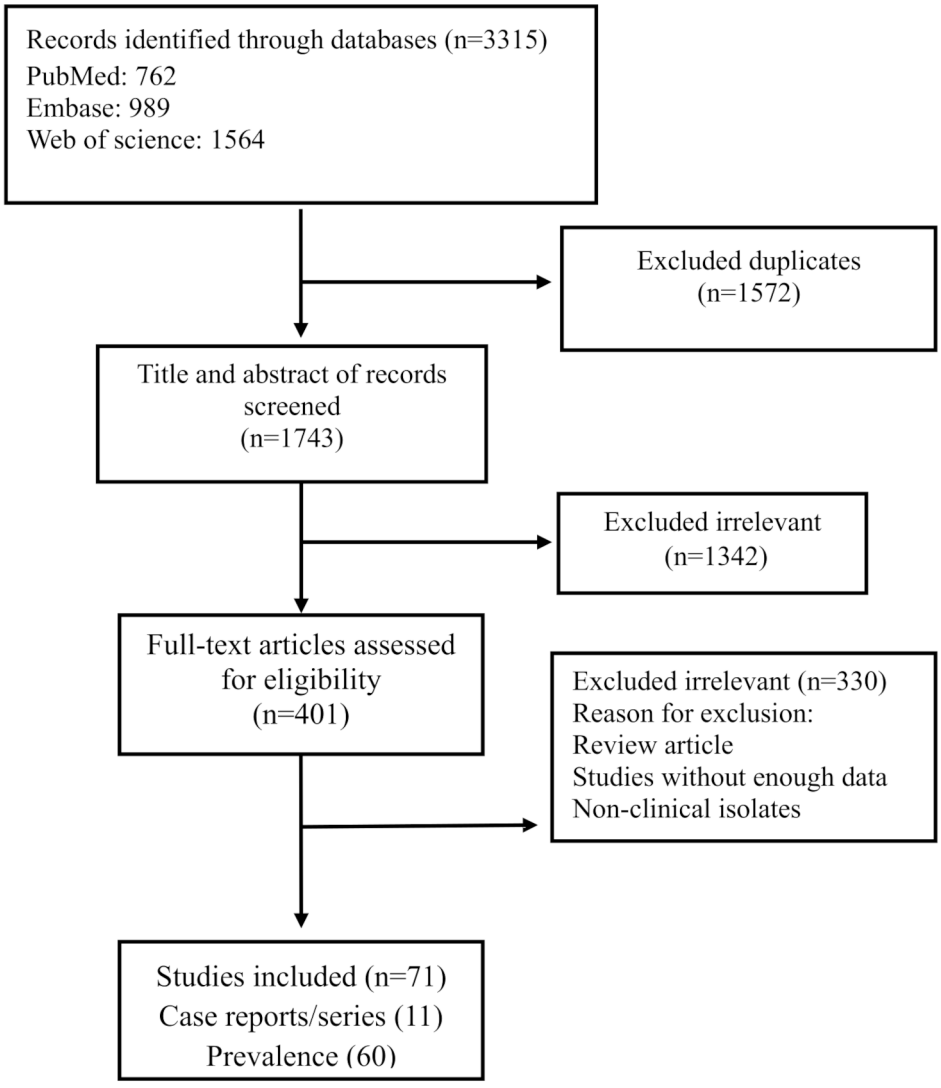

Fig. 1 Flow chart of study selection for inclusion in the systematic review

without full text, studies without appropriate data, and data on other bacteria or other types of cancer. A total of 71 studies were finally eligible for inclusion in the present systematic review and meta-analysis. Among these, 60 articles (40 on *F. nucleatum* and 20 on *B. fragilis*) were prevalence studies (Tables 1 and 2), and 11 articles (4 on *F. nucleatum* and 7 on *B. fragilis*) were case reports or case series (Table 3).

The prevalence of *F. nucleatum* among patients with CRC based on prevalence studies

A meta-analysis of prevalence studies indicated that the prevalence of *F. nucleatum* among CRC cases was reported in 19 countries (Sweden, Italy, Australia, Brazil, Canada, China, Denmark, France, Germany, Iran, Iraq, Ireland, Japan, Korea, Malaysia, New Zealand, Spain, Turkey, USA) with an overall prevalence of 38.9% (95% confidence interval (CI) 33.7–44.3, I2: 90.2%) among

Table 1 Characteristics of included *F. nucleatum* prevalence studies

First author	Published time	Country	Number of CRC patients	number of F. nucleatum in CRC patients	Male	Female	CRC Mean age
Nardelli [35]	2021	Italy	20	10	20	20	69.4
Mima [36]	2020	Japan	256	140	152	104	NR
Chen [37]	2017	China	98	61	58	40	58.7
Komiya [38]	2019	Japan	14	8	NR	NR	NR
Lo [39]	2022	China	116	54	68	48	68
Datorre [12]	2021	Brazil	139	54	74	65	60.65
Xie [40]	2022	China	184	37	101	83	53.8
Feng [41]	2019	China	15	10	7	8	41.3
Kashani [42]	2020	Iran	35	24	NR	NR	NR
Mo [43]	2021	China	108	63	94	68	58
Choi [44]	2021	Korea	51	12	NR	NR	64.83
Amitay [31]	2017	Germany	44	20	NR	NR	NR
Liu1 [45]	2020	China	51	7	nr	NR	NR
Li [46]	2021	China	70	26	57	43	44
Bi [47]	2021	China	158	81	NR	NR	> 18
Carvalho [48]	2019	Brazil	152	35	81	71	60.63 ± 13.7
Yamamoto [49]	2021	Japan	200	44	125	75	69
Rye [50]	2022	Australia	42	18	25	17	68
Janati [51]	2022	Canada	22	1	28	15	63.9
Bostanshirin [52]	2023	Iran	40	28	24	16	60
Bostanghadiri [5]	2023	Iran	100	44	59	41	56.39
Khodaverdi [53]	2021	Iran	40	27	41	39	56.37
Nielsen [54]	2019	Denmark	99	29	44	55	71 ± 10.1
Narii [55]	2023	Japan	499	147	NR		60.9
Liu2 [56]	2021	China	51	25	63	39	64
Amini [3]	2022	Iran	47	29	45	38	60.44
Aitchison [57]	2022	New Zealand	57	27	50	100	57
Shariati [11]	2021	Iran	30	7	20	10	57
Lee [58]	2021	Korea	112	44	66	46	65
Perichon [2]	2022	France	81	12	66	40	64.1
Madhloom [59]	2020	Iraq	42	15	NR	NR	NR
Eisele [60]	2021	Germany	105	44	63	42	63.5
Perez [61]	2024	Spain	93	14	64	59	65
Pang [62]	2023	Malaysia	83	48	37	46	50
Kurt [63]	2021	Turkey	22	15	39	39	65.8
Gao [64]	2021	China	71	12	80	82	61.58
Benej [65]	2023	USA	595	141	NR	NR	NR
Genua [66]	2023	Ireland	192	45	156	136	61
Dregelies [67]	2023	Germany	177	40	98	79	60
Serrano [68]	2023	Sweden	10	6	3	7	70.8

NR: Not Reported

Table 2 Characteristics of included *B. fragilis* prevalence studies

First author	Published time	Country	Number of CRC patients	number of B. fragilis in CRC patients	Male	Female	CRC Mean age
Rye [50]	2022	Australia	42	10	25	17	68
Oliero [69]	2022	Canada	94	30	85	71	67
Png [70]	2021	China	12	8	21	16	25.8
Shao [71]	2021	China	23	5	NR	NR	NR
Gao [64]	2021	China	71	10	80	82	61.58
Zhou [72]	2023	China	92	69	62	30	64.6
Nielsen [54]	2019	Denmark	99	36	44	55	71 ± 10.1
Kvich [73]	2023	Denmark	37	19	49	31	28
Perichon [2]	2022	France	81	25	66	40	64.1
Messaritakis [74]	2020	Greece	397	220	246	151	65
Haghi [75]	2019	Iran	60	35	30	30	53
Jasemi [76]	2020	Iran	31	11	33	29	59.03
Zamani [77]	2020	Iran	68	32	36	32	NR
Shariati [11]	2021	Iran	30	20	20	10	57
Khodaverdi [53]	2021	Iran	40	18	41	39	56.37
Nardelli [35]	2021	Italy	20	11	20	20	69.4
Kim [78]	2023	Korea	99	53	50	49	61
Lee [79]	2015	Korea	143	27	117	26	58.3 ± 10.4
Li [80]	2021	Korea	130	30	177	100	63.5
Osman [81]	2021	Malaysia	18	13	23	13	64.88

NR: Not Reported

Table 3 Characteristics of case reports/case series studies

First author	Published time	Country	Number of CRC patients	number of F. nucleatum in CRC patients	number of B.fragilis in CRC patients	Male	Female	CRC Mean age
Lechuz [82]	2000	Spain	1	NR	1	1	NR	68
Levy [83]	2007	USA	1	NR	1	NR	NR	NR
Pisanu [84]	2007	Italy	1	NR	1	NR	1	54
Lieuw-a-Fa [85]	2008	Netherlands	1	NR	1	1	NR	60
Mannaerts [86]	2009	Netherlands	1	1	NR	1	NR	68
Gamboa [87]	2010	USA	1	NR	1	1	NR	67
Kalapila [88]	2013	USA	1	NR	1(MDR)	1	NR	70–79
Yen [89]	2016	Taiwan	1	NR	1	1	NR	69
Shigefuku [90]	2017	Japan	1	1	NR	1	NR	78
Braczynski [91]	2017	Germany	1	1	NR	NR	1	71
Thomas [92]	2020	Ireland	3	2	NR	1	1	74.5

NR: Not Reported

4321 CRC patients (Fig. 2-A). The number of males were higher than females (Table 1). The forest plots are shown in Fig. 3 and all the required data for the meta-analysis are summarized in Fig. 2. According to our analysis, neither the Begg's adjusted rank tests nor the Egger's regression asymmetry test is significant (Fig. 4). The highest prevalence of *F. nucleatum* in CRC cases was in Asia (43.4%), Europe (32.8%), and America (25.9%), respectively (supplementary Figure S1). As shown in Table 1, the most CRC + *F. nucleatum* in Asia belonged to China (376/993, 37.8%), Japan (339/993, 34.1%), and Iran (159/993, 16%), respectively. The highest CRC + *F. nucleatum* rate was observed in Germany (104/235, 44.2%), Ireland (45/235, 19.1%), Denmark (29/235, 12.3%). Among American countries, USA (141/231, 61%) and Brazil (89/231, 38.5%) had the highest number of CRC + *F. nucleatum* reports. There were no reports from Africa. Only two studies were conducted in Oceania, which was not included in this subgroup analysis. Except for patients whose mean age was not reported (in 7 studies), the patients' mean age was 60.6 years.

The prevalence of *B. fragilis* among patients with CRC based on prevalence studies

The estimated rate of *B. fragilis* in 1587 patients with CRC in 10 Countries (Australia, Canada, China, Denmark, France, Greece, Iran, Italy, Korea, and Malaysia) was 42.5% [95% CI 34.4– 51.1, I2: 89.1%] (Fig. 2-B), where

A

Model	Number Studies	Point estimate	Lower limit	Upper limit	Z-value	P-value	Q-value	df (Q)	P-value	I-squared	Tau Squared
		Effect size and 95% interval			Test of null (2-Tail)		Heterogeneity				Tau-square
Fixed	40	0.360	0.345	0.375	-17.121	0.000	398.205	39	0.000	90.206	0.430
Random effects	40	0.389	0.337	0.443	-3.952	0.000					

B

Model	Number Studies	Point estimate	Lower limit	Upper limit	Z-value	P-value	Q-value	df (Q)	P-value	I-squared	Tau Squared
		Effect size and 95% interval			Test of null (2-Tail)		Heterogeneity				Tau-square
Fixed	20	0.442	0.416	0.468	-4.303	0.000	175.228	19	0.000	89.157	0.519
Random effects	20	0.425	0.344	0.511	-1.706	0.088					

Fig. 2 Summary of the meta-analysis on the prevalence studies of *F. nucleatum* (**A**) and *B. fragilis* (**B**) among patients with CRC worldwide

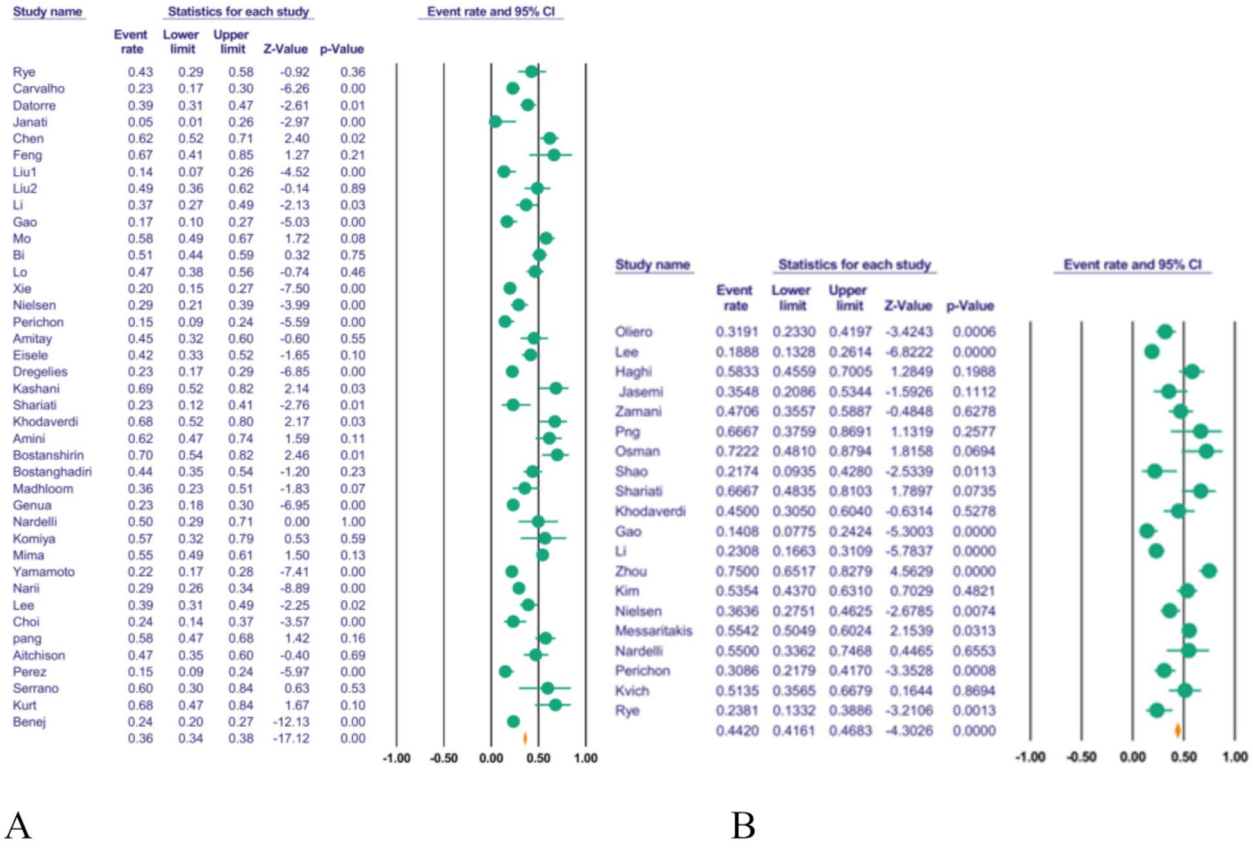

Fig. 3 Forest plot of the meta-analysis on the prevalence of *F. nucleatum* (**A**) and *B. fragilis* (**B**) among patients with CRC (Random effects model)

males had higher numbers than females. The forest plot and funnel plot are presented in Figs. 3 and 4. The highest prevalence of *B. fragilis* in confirmed CRC cases was in Europe (45%) and Asia (44.2%) (Supplementary Figure S2). The highest presence of CRC + *B. fragilis* in Europe belonged to Greece (220/311, 70.7%) and Denmark (55/311, 17.6%). Among Asian countries, Iran (116/331, 35%), Korea (110/331, 33.2%), and China (92/331, 27.7%) had the highest prevalence of CRC + *B. fragilis*. There were no reports from Africa. Only one study was conducted in Oceania and America which was not included in this subgroup analysis. Except for patients whose mean age was not reported (in 2 studies), the patients' mean age was 58 years.

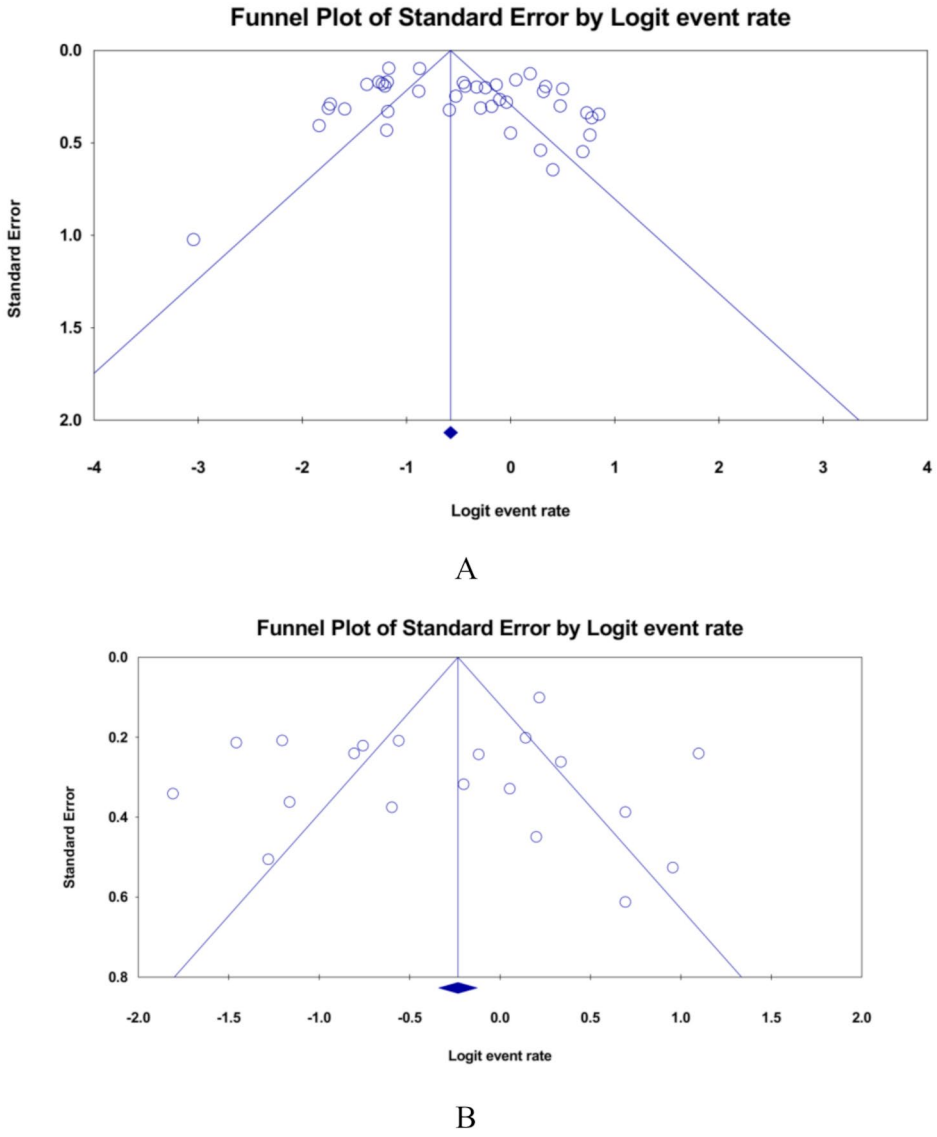

Fig. 4 Funnel plot of the meta-analysis on the prevalence of *F. nucleatum* (**A**) and *B. fragilis* (**B**) among patients with CRC (*P*-value for Egger's test (*F. nucleatum* = 0.07 and *B. fragilis* = 0.2) and Begg's test (*F. nucleatum* = 0.1 and *B. fragilis* = 0.2) provides a comprehensive assessment of publication bias in this meta-analysis)

The prevalence of underlying disease and isolation source among patients with CRC based on prevalence studies

According to the results, diabetes (1.3%) and hypertension (0.8%) were the most common comorbidities among CRC patients. As shown in Table 4, within the included studies, isolation source in CRC patients for identifying *F. nucleatum* and *B. fragilis* were biopsy (36.7%), stool (28.6%), formalin-fixed, paraffin-embedded (FFPE) (21.9%), respectively. Moreover, these bacteria were mainly identified by quantitative polymerase chain reaction (qPCR) and PCR respectively (Fig. 5).

The prevalence of *F. nucleatum* and/or *B. fragilis* among patients with CRC based on case reports/case series

The *F. nucleatum* and/or *B. fragilis* was investigated among CRC patients, following a systematic search through the mentioned electronic databases. Table 3 provides a list of characteristics belonging to selected case reports/case series studies. The cases were mostly observed in the USA (3 cases) then Ireland (2 cases). Among the patients whose genders were specified, 8 patients with CRC + *F. nucleatum* and/or *B. fragilis* were males, whereas 3 were females. After the evaluation of the results of the analyzed papers it was revealed that out of 13 patients with CRC + *F. nucleatum* and/or *B. fragilis*, 5 patients (38.4%) showed coinfections. Moreover, three

Table 4 Characteristics of type of underlying disease and clinical source of the included studies

	Variables	No. of studies	No. of patients	No. of patients /Total (%)
Type of underlying disease	Diabetes	3	82	82/5908 (1.3%)
	Hypertension	1	51	51/5908 (0.8%)
	Chronic obstructive pulmonary disease	1	3	3/5908 (0.05%)
	Atrial fibrillation	1	4	4/5908 (0.06)
	Chronic liver disease	1	10	10/5908 (0.1)
Type of isolation source	biopsy	30	2167	2167/5908 (36.7)
	stool	13	1693	1693/5908 (28.6)
	FFPE	13	1294	1294/5908 (21.9)

FFPE: formalin-fixed, paraffin-embedded

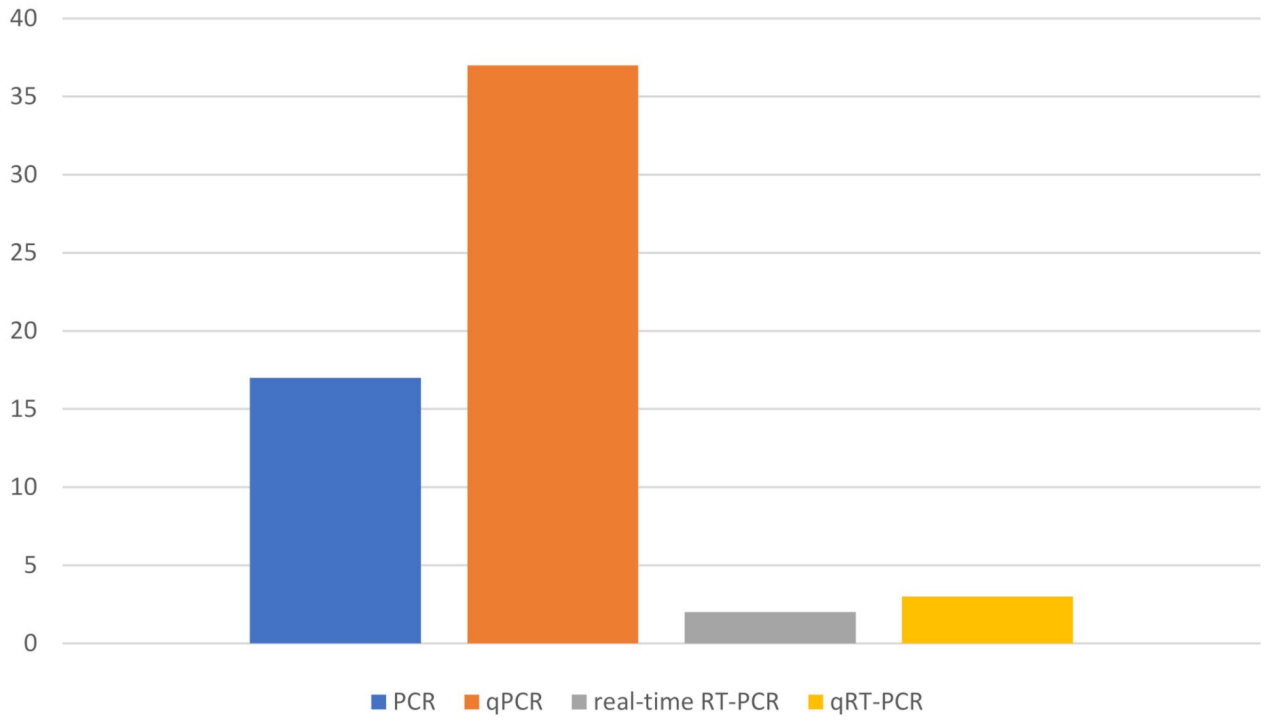

Fig. 5 Molecular detection of *F. nucleatum* and *B. fragilis* in CRC patients

patients had other diseases (fournier gangrene, diabetes, and prostatic hyperplasia). Culture and CT-scan were the most commonly used diagnostic methods, according to our investigations (Table 3).

Discussion

CRC is a multifaceted global health issue influenced by complex interactions between host genetics, environmental factors, and the intestinal microbiota [21]. To the best of our knowledge, this review is the first study assessing the prevalence of *F. nucleatum* and/or *B. fragilis* in CRC patients worldwide.

Meta-analysis of the prevalence studies showed that in 4321 CRC patients, the prevalence of *F. nucleatum* was 38.9% across the globe. Notably, the existence of *F. nucleatum* in CRC tissues can be considered a worse prognosis [22]. According to the meta-analysis conducted in this study, the highest prevalence of CRC + *F. nucleatum* was detected in Asia. It is also worth to note that the Asia-Pacific region contributes the biggest burden of CRC cases and CRC-associated deaths (51.8% and 52.4%, respectively) in the world [23], with China having the highest rate among Asian countries. This increase in prevalence may be linked to the fast economic growth in this country as there is a correlation between the incidence of CRC and economic transition from a low to high Human Development Index (HDI), a combined index of per capita income, life expectancy and education [24]. In agreement with our findings, Janati et al., [25] in a meta-analysis review reported a similar prevalence of *F. nucleatum* in CRC, although the number of their reviewed studies was lower than our research (only 12). Since women have about 20% fewer colorectal adenomas and CRCs, gender is an issue in CRC screening; however,

they have more right-sided lesions. Right-sided lesions have been reported to be more difficult to identify with tests for faecal blood due to their poor blood creation in faeces [26]. Similarly, in this study, the number of males in CRC + *F. nucleatum* and CRC + *B. fragilis* cases were 1.2 and 1.4 times higher in comparison to females. Elderlies have a higher risk factor for complications as older patients usually suffer from underlying diseases and are vulnerable [27]. The mean age of CRC patients among *F. nucleatum* group were 60.6 years. In a systematic review and meta-analysis study conducted by Arhin et al., in 2022 [28],, the overall annual age standardized incidence rates of CRC in Africa was 5.25 and were slightly higher in males with the mean age 53 and 58 for men and women, respectively. The slightly higher incidence of CRC in younger individuals compared to our results could attribute to limited geographic area.

Meta-analysis of the prevalence studies showed that in 1587 CRC patients, the prevalence of *B. fragilis* was 42.5% worldwide. Our analysis yielded the highest prevalence rates in European countries, especially in Greece. According to an epidemiological study conducted in Greece reviewing anaerobic infections, it has been revealed that patients with *B. fragilis* were more frequent among those with recent surgery; it was also reported that the total mortality was 10.9% and was associated with bacteremia or malignancy [29]. Our data analysis highlighted those individuals with a mean age 58 years had experienced higher CRC incidence rates. Notably, incidence rates were higher (1.4 times) in men compared to women.

From our meta-analysis findings, *F. nucleatum* and *B. fragilis* were mainly identified through biopsy (in 30 reports), stool (in 18 reports), FFPE (in 8 reports), respectively. There are a variety of different diagnostic methods for CRC detection, which can basically be divided into non-invasive and more invasive methods, including stool or blood tests, and imaging or endoscopy procedures, respectively [30]. Nonetheless, scientists have demonstrated that stool specimens are unable to display the full mucosal bacterial composition in CRC patients. In this regard, Gevers et al. conducted research on microbiome diversity; it was then revealed that microbiome diversity such as Fusobacterium spp. was only detectable through tissue specimens compared to stool samples collected during diagnostic procedures [31]. However, one of the most dependable sources of archival materials for molecular research are fresh frozen tissue samples. Although, in certain centers, the possibility of sample collection may be restricted. On the other hand, a wide range of tissue types are collected regularly as FFPE tissue samples, which can be stored at room temperature and are easily accessible, making them an appropriate starting material for retrospective analyses testing considerable numbers of samples concurrently. In spite of the availability advantage, this conserved tissue type is only applicable in gene expression-based studies due to the subcellular impacts of the fixation procedure, resulting in degraded RNA [32]. Also, according to data from our meta-analysis study, among 5908 CRC patients in both groups, 82 individuals (1.38%) had diabetes. Several studies have suggested diabetes as a risk factor for CRC and it also has been reported that the use of exogenous insulin had a correlation with increased risk of CRC [33, 34].

To better explain the results, limitations of this meta-analysis were also considered. First, in most studies the genes responsible for encoding enterotoxin isotype (*bft-1*, *bft-2*, and *bft-3*) were not observed in *B. fragilis*-positive samples, therefore, we could not compare the possible effects of various genes involved in CRC among patients. Second, since most of the studies did not report the exact stage of the tumor and survival rate, it was impossible to find a relationship between the survival rate and the stage of the cancer in the current study. Third, the high heterogeneity observed in this meta-analysis is believed to be associated with the inclusion of outlying studies with data that contradict with others. Generally, it is thoughtless to eliminate studies based on their results while carrying out a meta-analysis as it could cause bias. Fourth, in various studies, the prevalence of *F. nucleatum* and *B. fragilis* in the control group was not investigated, making us unable to compare the control group and CRC patients in terms of these bacteria's prevalence. The last limitation was that none of the included studies considered the potential confounding effect of risk factors including (fiber-rich) diet as well as chemo-resistance to CRC. Since environmental factors in particular dietary habits are crucial determinants for the gut microbial composition and function, and can contribute to CRC risk, it is necessary to conduct a comprehensive study on this subject. Moreover, conducting research on other bacteria species and their possible role in CRC pathogenesis will be helpful to have a complete profile of the patients with CRC compared to the control group.

Conclusion

In conclusion, this meta-analysis found a high prevalence of *F. nucleatum* and *B. fragilis* among CRC patients worldwide from 2000 to 2024. However, it is crucial to acknowledge the limited representation of studies from Oceania, and the absence of research conducted in Africa, addressing this gap through various studies on these continents is recommended to gain a more comprehensive understanding of the prevalence of these bacteria in CRC patients globally. Furthermore, our analysis underscores gender differences in CRC patients, with males exhibiting higher prevalence rates of *F. nucleatum* and *B. fragilis* infections compared to females.

This highlighted the importance of considering gender-specific factors in CRC research and clinical practice. In-depth studies of the gut microbiota hold promise for developing novel approaches to CRC diagnostic and treatment. By elucidating the role of *F. nucleatum* and *B. fragilis* in CRC pathogenesis, researchers can potentially identify new biomarkers for earlier detection and novel therapeutic targets. Such advancements may ultimately improve outcomes for CRC patients worldwide. In conclusion, this meta-analysis sheds light on the global prevalence of *F. nucleatum* and *B. fragilis* in CRC patients and underscores the need for further research to enhance our understanding of these bacteria's role in CRC and inform innovative strategies for prevention and management.

Abbreviations

B. fragilis	*Bacteroides fragilis*
CMA	Comprehensive meta-analysis
CRC	Colorectal cancer
F. nucleatum	*Fusobacterium nucleatum*
FFPE	Paraffin-embedded FFPE
IL-6	Interleukin 6
JBI	Joanna Briggs Institute
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
qPCR	Quantitative polymerase chain reaction
TNFα	Tumor necrosis factorα

Supplementary Information

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Supplementary Material 1

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Author contributions
MD and FS designed the study. FS performed the search strategy. FS, PAE, and MPE conducted the data extraction. FS, PAE, and AD wrote the manuscript. MD and FS carried out the statistical analysis. MD and FS separately evaluated inclusion and exclusion criteria. MD, MG, and MS did critical editing and revising of the text. MD and FS were responsible for the accuracy and integrity of the manuscript. All authors read and approved the final manuscript.

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Data availability
All data supporting the findings of this study are available within the paper and its Supplementary Information.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
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Competing interests
The authors declare no competing interests.

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