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Review Article

The Relationship Between *pks*$^+$ Escherichia coli and Colorectal Cancer: A Review

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ABSTRACT

Introduction: According to GLOBOCAN estimates, colorectal cancer (CRC) was the third most common cancer worldwide in 2020, comprising 11% of all cancer diagnoses. Researchers' interest in CRC development has shifted toward the gastrointestinal microbiome, especially the mutagenicity of *pks*$^+$ *E. coli*. Therefore, we aimed to review the current evidence on the relationship between *pks*$^+$ *E. coli* and CRC. Method: We reviewed the literature reporting the association between *pks*$^+$ *E. coli* and CRC, which was obtained from three databases: PubMed, Google Scholar, and the Cochrane Library, published between January 2021 and January 2026. We used the following keywords for our search strategy: pks, Escherichia coli, and colorectal cancer. Result: As stated in the original studies, the contribution of *pks*$^+$ *E. coli* to CRC development was associated with a higher prevalence in the CRC group than in the healthy group. However, these results are inconsistent across the studies.
Conclusion: Given the limited evidence, researchers should conduct larger cohort studies to clarify this relationship and identify other factors contributing to the presence of *pks*$^+$ *E. coli*, particularly across diverse clinical settings. Furthermore, clinical translation, such as the utilization of screening or therapeutic biomarkers, requires prospective validation and standardized detection methods.

1. Introduction

According to GLOBOCAN estimates provided by the International Agency for Research on Cancer (IARC), colorectal cancer (CRC) was the third most common cancer worldwide in 2020, comprising 11% of all cancer diagnoses [1, 2]. In 2022, Asia accounted for 50.2% of global CRC cases, with 966.400 new cases and 462.000 deaths, which reflects the high incidence of the cancer in Asian countries [3]. Mongolia has relatively low CRC incidence and mortality rates compared with countries with high prevalence, such as Japan and China. In Mongolia, the incidence of CRC in the last 5 years (2018–2022) was 7.9 per 100,000 population, and the mortality rate was 4.7 per 100,000 [4].

Scientists have identified multiple risk factors for CRC. As reported in twin and family studies, hereditary factors account for approximately 12% – 35% of CRC cases [5, 6]. Given this relatively low rate, it underscores the importance of other modifiable and non-modifiable risk factors. Alcohol consumption [7], smoking [8], obesity [9], unhealthy dietary patterns [10], a sedentary lifestyle [11], and psychological stress [12] are considered changeable risk factors. On the other hand, unchangeable risk factors consist of age, sex [13], genetic predisposition [14], abdominopelvic radiation exposure [15], family history of colorectal cancer [16], and a personal history of other diseases [17]. The role of the microbiome in the development and progression of CRC is increasingly recognized and appreciated as a modifiable risk factor [18].

Researchers' interest in CRC development has shifted toward the gastrointestinal microbiome, a densely populated ecosystem. This system comprises approximately 10^{13} – 10^{14} microorganisms in the gastrointestinal (GI) tract [19]. This microbial community is predominantly composed of Firmicutes and Bacteroidetes, which together account for about 90% of the total bacterial population [20]. Currently, researchers have identified two types of bacteria linked to colon carcinogenesis: "driver" bacteria, such as Enterococcus faecalis, Escherichia coli, and Bacteroides fragilis [21] and "passenger" bacteria, including Fusobacterium spp. and Streptococcus gallolyticus [22].

The latest meta-analysis on the association between *pks*$^+$ *E. coli* and CRC development suggests that individuals with *pks*$^+$ *E. coli* have a greater risk of developing CRC [23]. However, the role of *pks*$^+$ *E. coli* in cancer initiation, proliferation, and metastasis remains unclear. Moreover, several confounding factors influence both *pks*$^+$ E. coli and CRC development. The individual-specific gut microbiome is an outcome of the complex interplay between host genetics and environmental exposures [24]. As stated in a prospective cohort study, people exposed to a Western diet are more likely to develop CRCs with abundant *pks*$^+$ *E. coli*.

To summarize, substantial evidence indicates that the *pks*$^+$ *E. coli* is associated with the development of CRC. Therefore, developing a well-defined mechanistic model of *pks*$^+$ *E. coli*-mediated CRC

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development can inform CRC screening and characterization of CRC progression as a biomarker, enabling early detection and the development of targeted treatment strategies, such as microbiota modulation and immunomodulatory pathways.

2. Method

This review study included English original articles addressing the relationship between CRC and *pks*$^+$ *E. coli*. Marcianne Elaine Gaab et al. published a meta-analysis study addressing the relationship between *pks*$^+$ *E. coli* and CRC. They included 12 articles published through January 2021 [23]. Therefore, related literature reporting the association between *pks*$^+$ *E. coli* and CRC was obtained from three databases: PubMed, Google Scholar, and the Cochrane Library, published between January 2021 and January 2026. We used the following keywords for our search strategy: pks, Escherichia coli, and colorectal cancer. Duplicate articles, review articles, animal studies, and papers with incomplete information, like conference proceedings and articles without full text, were excluded from the study.

2.1. *E. coli* strains classification

E. coli, a ubiquitous Gram-negative bacillus, inhabits the intestinal flora, especially in the caecum and the colon. Moreover, it can also serve as a pathogen, inducing a broad spectrum of diseases. Recently, *E. coli* has been classified into pathotypes based on their virulence factors and the diseases they predominantly cause in humans [25]. The strain of the pathogenic *E. coli* can be divided into two main groups: the first one is Intestinal Pathogenic Escherichia coli (IPEC), leading to GI infection; the second one is External Pathogenic Escherichia coli (ExPEC), which causes common infections outside of the GI tract [26].

2.2. The *E. coli* infection prevalence and disease manifestations

We reviewed the primary classification of *E. coli* by pathotype, their prevalence, and disease manifestations in **(Table 1)**.

The prevalence of commensal *E. coli* varies by species: it is more than 90% in humans [27, 28] but only 56% in wild mammals, 23% in birds, and 10% in reptiles [29]. The concentration of faces per gram in humans ranges from 10^7 to 10^9 colony-forming units [28]. The prevalence of *E. coli* varies across studies due to differences in study populations, diagnostic methods, and criteria. As stated in a review study that included original studies from 13 developing countries, the average incidence of EPEC among pediatric diarrheal episodes is 5–10% [30]. A retrospective case-control study revealed that children with EPEC infection had frequently experienced diarrhea, vomiting, abdominal pain, and fever, compared to EPEC-negative controls [31].

The review study analyzed data from 21 countries across 10 of the 14 WHO Sub-Regions, representing approximately 30% of the global population. According to the results, the global incidence of EHEC was 2.8 million cases per year, and its annual mortality was 230 deaths [32]. In terms of disease manifestations, bloody or watery diarrhea without fever was common, and it was sometimes associated with abdominal cramping. One of the significant complications of EHEC infection is definitely hemolytic uremic syndrome [25].

The incidence of EIEC varies widely across regions, as reported in numerous studies in Europe, Central and South America, the Middle East, West Africa, and Southeast Asia [33]. Infection with EIEC causes a bacillary dysentery characterized by bloody and mucous diarrhea, abdominal cramps, nausea, and fever [34].

Ibrahim A. Khalil et al. estimated the global incidence of ETEC diarrhea at 220 million cases per year among children under 5 years old [35]. In addition, it is a significant cause of travelers' diarrhea, which is prevalent in regions such as Latin America, Africa, and South Asia [36]. As noted in the observational study, the most prevalent symptom was watery stool among almost all children and adults with ETEC infection. In addition, younger patients experienced frequent vomiting and fever compared to the older patients [37, 38].

The incidence of EAEC infection, which can lead to acute or persistent watery diarrhea, is highest among children living in key endemic regions [39] and immunosuppressed individuals [40]. People with EAEC infection usually present the following symptoms: watery diarrhea and occasionally very mucoid diarrhea, nausea, anorexia, low-grade fever, borborygmi, and tenesmus [41].

Few studies have reported the incidence of DAEC infection, and rates have varied widely, with relatively low values. Among children with diarrhea, DAEC strains were isolated in 18.3% in Brazil and 3.9% in Iran [42, 43]. DAEC infection has been considered a cause of diarrhea, particularly in children older than 24 months [44].

According to the narrative review, UPEC causes 75% of uncomplicated urinary tract infections (UTIs) and 65% of complicated UTIs [45]. Patients diagnosed with UTI caused by UPEC frequently experience dysuria and frequent urination because UPEC strains are more likely to damage the lower urinary tract [46].

The most common pathogens causing sepsis are Staphylococcus aureus and *E. coli*. Among infants with sepsis, *E. coli* is also the most prevalent gram-negative bacterium implicated in neonatal sepsis [47, 48]. In addition, *E. coli* is the most frequently identified pathogen in cases of neonatal meningitis. Specifically, *E. coli* meningitis was 7-fold more common in preterm than term infants [49].

The prevalence of AIEC strains was 28% among patients with inflammatory bowel diseases and 29% among patients with Crohn's disease in a recent meta-analysis [50]. It is well known that *E. coli* significantly contributes to dysbiosis of the local microbiota, thereby aggravating symptoms in inflammatory bowel diseases [51].

2.3. Evidence summary of human studies

Since 2021, a total of 3624 articles related to *pks*$^+$ *E. coli* and CRC have been published in online databases. According to our eligibility criteria, we selected 13 articles for review. The majority of the selected studies employed retrospective cohort and case-control designs. Moreover, these studies usually detected the pks/clb gene cluster in *E. coli* using qPCR in both stool and tissue samples. We summarized the characteristics and results of the included studies in **(Table 2)**.

The prevalence of *pks*$^+$ *E. coli* across selected articles varied by study population and location, ranging from 9.4% to 54.7%. This variation depends on several factors, such as sample size, study population (cancer or healthy subjects), and the detection method of the pks/clb gene cluster in *E. coli*. Thevambiga Iyadorai et al. found significant differences in the presence of *pks*$^+$ *E. coli* isolates from tissue specimens of patients and controls, but not among fecal specimens [52]. It suggests that the detection of the pks/clb gene cluster in *E. coli* may depend on the specimen type. Moreover, the study evaluating the association between the pks/clb gene cluster in *E. coli*, measured in fecal immunochemical test (FIT) samples, and the detection of advanced neoplasia (AN) at colonoscopy included 5020 CRC screening participants. The prevalence of *pks*$^+$ *E. coli* in

FIT samples from individuals with AN (28.6%) and controls (25.9%) was not significantly different. Authors suggest that a one-time *pks*$^{+}$

Table 1: Classification of commensal and pathogenic *E. coli*

Group		Pathotype	Prevalence	Symptoms	Reference
Commensal *E. coli*		Normal flora; widespread in the gut		No symptoms	[27–29]
Pathogenic *E. coli*	IPEC (Intestinal Pathogenic Escherichia coli)	Enteropathogenic *E. coli* (EPEC)	5-10% of pediatric diarrheal episodes in the developing world	Diarrhea, vomiting, fever, and severe abdominal pain	[30, 31]
		Enterohemorrhagic *E. coli* (EHEC)	2.8 million cases per year, globally	Bloody or watery diarrhea without fever, abdominal cramps, dehydration, asthenia, decreased urine output, and hemolytic uremic syndrome	[25]
		Enteroinvasive *E. coli* (EIEC)	Substantial regional heterogeneity	Abdominal cramps, nausea, fever, and bloody and mucus diarrhea	[33, 34]
		Enterotoxigenic *E. coli* (ETEC)	220 million cases annually, with 84.4 million cases reported in children aged < 5 years; most prevalent among travelers	Watery diarrhea, severe dehydration, vomiting, and fever, especially in children	[35–38]
		Enteroaggregative *E. coli* (EAEC)	Children, HIV patients	Watery diarrhea, occasionally very mucoid diarrhea, nausea, anorexia, low-grade fever, borborygmi, and tenesmus	[39–41]
		Diffusely adherent *E. coli* (DAEC)	Higher rates in children in both developing and developed countries	Persistent diarrhea	[42–44]
	ExPEC(Extraintestinal Pathogenic Escherichia coli)	Urophatogenic *E. coli* (UPEC)	75% of uncomplicated UTI cases	Dysuria, frequency, fever	[45, 46]
		Sepsis-associated *E. coli* (SEPEC)	The most prevalent bacteria in sepsis cases	Severe fever, chills, tachycardia, hypotension, and multiple-organ dysfunction syndrome	[47, 48]
		Meningitis-associated *E. coli* (MNEC)	The most frequently identified agent, especially in preterm neonates	Meningitis symptoms	[49]
		Adherent-invasive *E. coli* (AIEC)	$\sim$ 28% among IBD and CD patients	Dysbiosis	[50, 51]

The prevalence information is approximate, depending on the study population, age groups, and method. HIV, Human Immunodeficiency Virus; UTI, Urinary Tract Infection; IBD, Inflammatory Bowel Disease; CD, Crohn's Disease.

Table 2: Summary of studies evaluating the prevalence and clinical significance of *pks*$^+$ *E. coli* in colorectal cancer

Author, year	Study subject	Specimen type and detection method	Prevalence of *pks*$^+$ *E. coli*	Main outcome (relationship between *pks*$^+$ *E. coli* and CRC)
Yen Lin Chu et al., 2025	A total of 358 LS cases, including 386 CRCs, 90 adenomas, and 195 normal subjects.	Tissue sample; qPCR	The prevalence was 13.6%.	*pks*$^+$ *E. coli* was enriched in LS CRCs when compared with sporadic CRCs (OR = 1.60; 95% CI = 1.08–2.35). *pks*$^+$ *E. coli* in the initial CRC was associated with an increased risk of metachronous CRC (HR = 2.32; 95% CI = 1.29–4.17) and metachronous colorectal neoplasia (HR = 1.51; 95% CI = 1.02–2.23).
Toshimitsu Miyasaka et al., 2024	413 patients with CRC	Both tumor and normal tissue; droplet digital PCR	The prevalence was 65.6% (271) in tumor tissues and 62.3% (152) in normal tissues.	High level of *pks*$^+$ *E. coli* in tumor tissue was significantly associated with shallower tumor depth (HR = 5.0, 95% CI = 2.3–11.3) and absence of lymph node metastasis (HR = 3.0, 95% CI = 1.8–5.1). *pks*$^+$ *E. coli*-low and -negative groups were associated with shorter CRC-specific survival (HR = 6.4, 95% CI = 1.7–25.6) and shorter relapse-free survival (HR = 3.1, 95% CI = 1.3–7.3).
Jihoon E. Joo et al., 2024	1697 tumor tissues from 1666 individuals with CRC	Tumor tissue; qPCR	Intratumoral prevalence of *pks*$^+$ *E. coli* was 10.3% (174).	The *APC*: c.835-8 A>G mutation was associated with intratumoral *pks*$^+$ *E. coli* (P = 0.025, OR = 2.20, 95% CI = 1.05–4.25). MMRd status was not associated with *pks*$^+$ *E. coli*.
Willemijn de Klaver et al., 2024	5020 CRC screening patients	Stool sample; qPCR	1322 (26.2%) were *pks*$^+$ *E. coli* positive: 28.6% in AN and 25.9% in controls.	There was no significant difference between the prevalence of *pks*$^+$ *E. coli* in individuals with AN and controls (p = 0.131).
Xiaoming He et al., 2024	100 participants (50 colorectal cancer patients and 50 healthy controls)	Both stool and tissue samples; qPCR	The prevalence was 35%: 46% (23) in the control group and 24% (12) in the CRC group.	A higher proportion of *pks*$^+$ *E. coli* was found in late-onset CRC (17 out of 35) compared to early-onset CRC (3 out of 35; P < 0.05).
Bingjie Chen et al., 2023	366 deep WGS samples: 101 normal samples (74 adjacent and 27 distant normal crypts) and 265 cancer samples.	Both healthy and tumor tissue; WGS	The prevalence was 76.67% in cancer crypts, 70.59% in adjacent normal, and 50% in distant normal from cancer patients, compared to 30% in individuals without cancer.	The *pks*$^+$ signature causes a large proportion of mutations in chromatin modifier genes in MSS cancers. Multiple alterations in cancer driver genes and chromatin modifier genes are consistent with *pks*$^+$-induced short T-dels.
Thevambiga Iyadorai et al., 2023	57 specimens (31 CRC tissue and 26 healthy normal tissue)	Both fecal and tissue samples; PCR	Among 37 fecal specimens, 43.6% had the *pks* gene [61% (13) from CRC and 31.3% (5) from control]. Among 20 tissue samples, 55.0% (11) had *pks*, including 80.0% (8) from CRC patients and 30.0% (3) from healthy controls.	Significant differences in the presence of *pks* among *E. coli* isolates from tissue specimens of patients and controls were observed, but not among those from fecal specimens.
Kota Arima et al., 2022	1175 patients with CRC	Tumor tissue; qPCR	The prevalence was 9.4% (11).	The *pks*$^+$ *E. coli* level was associated with lower disease stage (P = 0.008) but not with tumor location, microsatellite instability, or *BRAF*, *KRAS*, or *PIK3CA* mutations (P > 0.05).
Habiba Tariq et al., 2022	60 patients (35 patients with CRC and 25 relatively healthy patients)	Both tumor and healthy tissue; quadruplex PCR	The prevalence was 18.3% (11 in the CRC group and none in the healthy group).	A significant association between the genotoxin-producing colibactin gene and colorectal cancer was reported (P < 0.002).
Manon Oliero et al., 2022	156 participants: healthy controls (N = 62) and CRC patients (N = 94)	Fecal samples; conventional qualitative PCR	Prevalence of *pks*$^+$ bacteria was 44.2% (69): 42% (26) in healthy controls and 46% (43) in the CRC group.	EOCRC (<50 years) patients were significantly less colonized with *pks*$^+$ *E. coli* than LOCRC patients (P < 0.05).
Motoki Iwasaki et al., 2022	968 screening patients (543 CRC and 425 controls)	Stool sample; qPCR	The prevalence was 31.8% (308): 32.6% (177) in cases and 30.8% (131) in controls.	No significant association was found between *pks*$^+$ *E. coli* and colorectal neoplasia (adjusted OR = 1.04, 95% CI = 0.77–1.41).
Kaixi Liu et al., 2021	139 patients with CRC and 42 healthy individuals	Stool sample; qPCR method	The prevalence was 54.7% (76): 21.4% (9) in control, 67.6% (25) in CAP, and 70.0% (42) in CRC cases.	*pks*$^+$ *E. coli* levels were higher in the CRC group than in either the CAP group or healthy controls. No difference was found among tumor sites. The cut-off value for *pks*$^+$ *E. coli* was 2.25, with a sensitivity of 93.3% and a specificity of 73.3%.
Alfonso Piciocchi et al., 2021	330 adult subjects: 162 healthy tissues, 55 tissues with HP, 79 P/A, and 29 ADC	Both healthy and cancer tissues; qPCR	The prevalence was 38%: 35% (54) in healthy tissue, 42% (22) in HP, 36% (27) in P/A, and 52% (14) in ADC.	There was no significant association between *pks*$^+$ *E. coli* and adenocarcinoma by univariate analysis (OR = 2.01, 95% CI = 0.88–4.64).

ADC, Adenocarcinomas; AN, Advanced Neoplasia; CRC, Colorectal cancer; HP, Hyperplastic Polyps; LS, Lynch Syndrome; MMRd, Mismatch Repair Deficiency; MSS, Microsatellite Stable; P/A, Pre-Cancerous Polyps/Adenomas; qPCR, Quantitative Polymerase Chain Reaction; WGS, Whole Genome Sequencing.

E. coli measurement in stool is not informative of CRC risk in a screening setting [53].

All included studies evaluated the relationship between *pks*$^+$ *E. coli* and CRC incidence, comparing healthy and cancer subjects across cancer types, locations, and disease severity. A total of 9 studies evaluated this relationship, comparing healthy and CRC groups. To compare the presence of *pks*$^+$ *E. coli* between the control and CRC groups, 5 studies reported no significant difference, whereas 4 studies found a significant association between *pks*$^+$ *E. coli* and CRC. Kaixi Liu et al. calculated the accuracy of *pks*$^+$ *E. coli* in predicting CRC and found that the cut-off value was 2.25, with a sensitivity of 93.3% and a specificity of 73.3% [54].

In addition, these studies compared the presence of pks/clb gene cluster in *E. coli* across early- and late-onset cancers, disease stages, and tumor locations. The retrospective cohort study reported that early-onset CRC (EOCRC) patients (<50 years) were significantly less colonized with *pks*$^+$ *E. coli* than late-onset CRC (LOCRC) patients [55]. In another study, the *pks*$^+$ *E. coli* tumors with the APC: c.835-8 A>G mutation were more prevalent in EOCRC than LOCRC (9.5% versus 5.3%), with only the association in EOCRC showing statistical significance. The reason for this association in EOCRC is currently unknown and, if validated, would raise interesting questions about the mechanism in EOCRCs versus LOCRCs [56]. Kota Arima et al. found that the *pks*$^+$ *E. coli* level was associated with lower disease stage but not with tumor location [56]. Moreover, an observational cohort study including 413 patients with CRC found that a high level of *pks*$^+$ *E. coli* in tumor tissue was significantly associated with shallower tumor depth and the absence of lymph node metastasis. Also, they reported that the *pks*$^+$ *E. coli* low and negative groups were associated with shorter CRC-specific survival and shorter relapse-free survival [57].

Two studies evaluated the relationship between *pks*$^+$ *E. coli* and the mutational signature of CRC. The study, including 1697 tumor tissues, found that Mismatch Repair Deficiency (MMRd) status was not associated with the colibactin-associated mutational signature [56]. A total of 366 deep whole-genome sequencing (WGS) analyses showed that a large proportion of mutations in chromatin modifier genes in microsatellite-stable (MSS) cancers are driven by colibactin-associated mutational signature [58].

Yen Lin Chu et al. included 358 Lynch Syndrome (LS) cases and found that *pks*$^+$ *E. coli* in the initial CRC was associated with an increased risk of metachronous CRC and metachronous colorectal neoplasia when compared with CRCs without *pks*$^+$ *E. coli* [59].

Across the selected studies, there were inconsistencies in the results of a significant relationship between *pks*$^+$ *E. coli* and CRC development. Moreover, some studies reported a significant difference in the presence of *pks*$^+$ *E. coli* between early-onset and late-onset cancers, but others did not. The impact of *pks*$^+$ *E. coli* on MSS or MMRd cancers remains unknown. Tissue heterogeneity could influence this relationship. The majority of studies investigated the pks/clb gene cluster in *E. coli* using tissue samples because fecal samples were found to be less accurate. Therefore, researchers should conduct a prospective cohort study using both tissue and fecal samples and provide evidence of its use as a biomarker in screening programs.

2.4. Evidence of the mechanism of how *pks*$^+$ *E. coli* impacts carcinogenesis

2.4.1. Pathogenicity islands and key features of the pks/clb gene cluster in E. coli

HGT-mediated acquisition of large genomic islands, or pathogenicity islands (PAIs), is a key factor in the emergence of several *E. coli* pathotypes. PAIs, a small subgroup of genomic islands, play a significant role in bacterial virulence evolution by compromising virulence-associated factors and facilitating adaptive horizontal gene transfer. It is approximately 54 – 56 kb in size and may vary among different pks-positive strains [24, 60]. The PAI named pks encoded colibactin, a nonribosomal peptide-polyketide secondary metabolite. The colibactin gene cluster within the pks genomic island comprises the clbA-clbS genes, which are responsible for colibactin synthesis [61, 62]. These genes included nonribosomal peptide mega synthases (NRPSs; clbH, clbJ, and clbN), polyketide mega synthases (PKSs; clbC, clbI, and clbO), two hybrid NRPS-PKSs (clbB and clbK), and nine accessory and tailoring enzymes [63].

(Figure 1) was adapted from the original photo with the author's permission. The figure was generated using BioRender Software and published with permission.

Organization of the pks island: pks island encodes the genes required for the synthesis of colibactin. Genes coding for pks (yellow), non-ribosomal peptide synthase genes (blue), hybrid NRPS/PKS (green), and the accessory proteins (red) are shown. They are in connection with the regulator clbR and the integrase (int) (black). As stated in **(Figure 1)**, clbA is a phosphopantetheinyl transferase, clbM is a transporter, and clbP is a peptidase.

The initiation of the biosynthesis of colibactin depends on the activation of pks/NRPS megasynthases (non-ribosomal peptides) by phosphopantetheinyl transferase ClbA. Once the initiation is activated, megasynthases recruit their specific monomers. The ClbN, whose substrate is asparagine, is regarded as the first enzyme involved in the synthesis. The Biosynthesis assembly then proceeds with the successful intervention of the ClbB-ClbC-ClbH-ClbI-ClbJ-ClbK enzymes, which exploit both common substrates, such as malonyl-CoA, alanine, serine, glycine, and cysteine, and uncommon substrates, such as aminocyclopropane-carboxylic acid, to produce the toxin in its pre-colibactin form. Once inactive pre-colibactin is formed, it is exported into the periplasm by ClbM, an efflux pump. The pre-colibactin is hydrolyzed following the insertion of ClbM into the inner membrane. It results in the separation of the cleavage product, or N-myristoyl-D-asparagine, and the active colibactin (ClbP).[63, 65, 66] Among all these genes, researchers have identified that five pks islet genes (ClbG, ClbH, ClbL, ClbM, and ClbS) are mainly activated during tumor development in an inflammation-dependent manner, as shown in a study using bacterial strains and plasmids. It suggests that various colibactin biosynthetic pathways alter the microenvironment during CRC development **(Figure 1)** [67].

2.4.2. The impact of pks$^+$ *E. coli on the mechanism of CRC*

The majority of CRCs are MSS, whereas the minority exhibit microsatellite instability (MSI), accounting for 15% [68]. However, these two types of CRC share many common driver genes and exhibit equivalent numbers of mutations in these genes [69]. MSI colon cancer is considered to have a much higher mutational load because of the lack of a DNA mismatch repair system [70]. It is well established that CpG deamination is the most common mutational process in the human colon, especially in MSS cancers [71]. According to the current evidence, researchers suggest that colibactin causes the formation of DNA cross-links by alkylating adenines [64, 72, 73]. This accumulation of DNA damage encourages the initiation and progression of CRC, leading to the transformation of normal colonic epithelial cells into malignant tumor cells [74].

We briefly integrated the current evidence on the mechanism of CRC induced by the *pks*$^+$ *E. coli* into **(Figure 2)**. There were three crucial phases of CRC development: [74–76].

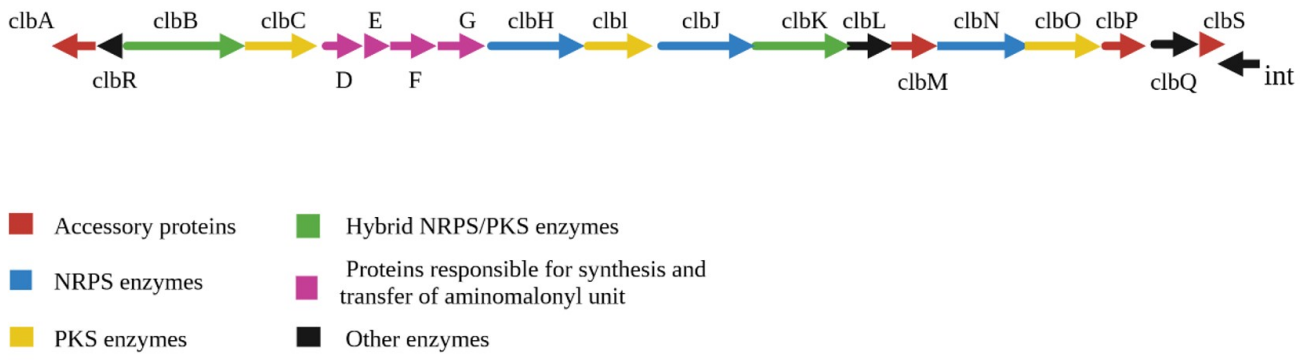


Figure 1: Organization of *pks*$^+$ island (Modified figure based on Nougayrède et al.'s (2006) [64] illustrations)

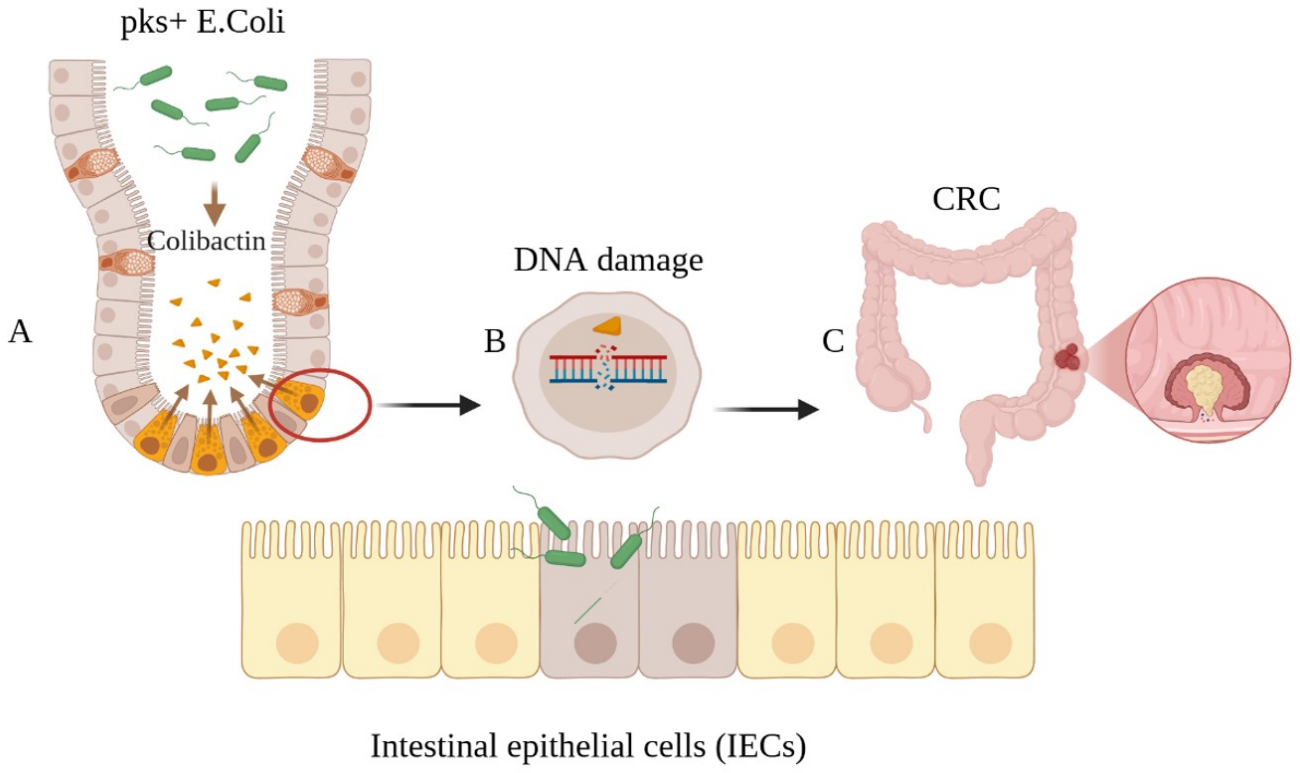


Figure 2: A general illustration of CRC development by induction of *pks*$^+$ Escherichia coli.

A. *pks*$^+$ *E. coli* produces a cyclomodulin called colibactin.

B. The CpG deamination signature is the most prevalent mutational process in human colon cancer and causes C>T mutations at methylated CG sites. Whereas the increasing number of in vivo studies has been determining the colibactin-attributable alterations in colorectal cancer. The WGS study reveals a distinct mutational signature caused by colibactin, as human intestinal organoids are exposed to genotoxic *pks*$^+$ *E. coli* via repeated luminal injections over 5 months. As stated in the study, colibactin promotes DNA alkylation in the intestinal epithelial cells, leading to the formation of interstrand cross-links and DNA double-strand breaks. These crosslinks could be resolved in various ways, including induction of DSBs, Nucleotide Excision Repair, or translation synthesis, which in turn may lead to various mutational outcomes [75, 77].

C. This may result in the development of genomic instability and mutations in the prominent oncogenes and tumor suppressor genes. Over the years, the accumulation of DNA damage may drive both the initiation and progression of CRC, transforming normal colonic epithelial cells into malignant tumor cells **(Figure 2)**. **(Figure 2)** was independently created based on information reviewed in the literature. This figure was also created in BioRender Software, and the publication license was obtained.

It is well supported that *pks*$^+$ *E. coli* cause double-strand DNA breaks and genomic instability in host cells by extensive in vitro and in vivo studies. However, the exact other underlying mechanism

could not be fully established to determine the impact of *pks*$^+$ *E. coli* on colon carcinogenesis, especially metastasis, and its interaction with a specific diet.

3. Discussion

In our study, the exact prevalence of *pks*$^+$ *E. coli* and its significant relationship with CRC are inconsistent across the selected articles. However, the incidence of *pks*$^+$ *E. coli* was higher in cancer tissues than in healthy tissues. This pattern is consistent with other studies. As reported in the literature, the incidence of *pks*$^+$ *E. coli* was lower in healthy cohorts than in case groups: 22% in the USA [78]; 18.5% in Sweden [24, 79]; and 4.35% in Malaysia [52]. Dietary differences could explain this prevalence of evidence of inconsistency. For instance, the western diet has been related to a higher incidence of colorectal cancer containing *pks*$^+$ *E. coli* [29, 80]. In addition, a prospective Japanese study found that energy-adjusted intakes of cruciferous vegetables and vitamin C were significantly associated with a higher prevalence of *pks*$^+$ *E. coli*. Nevertheless, other factors, such as age, sex, and comorbidity, associated with the prevalence of *pks*$^+$ *E. coli* are unknown [81]. To our knowledge, these dietary factors are not considered traditional risk factors for colorectal cancer [82, 83]. But could have a role in the presence of *pks*$^+$ *E. coli*; however, the reported findings are unstable [81]. Furthermore, more research is needed to establish evidence on the factors underlying the prevalence of *pks*$^+$ *E. coli*.

We found that *pks*$^+$ *E. coli* is more enriched in early-onset cancer than late-onset cancer. Marcos Díaz-Gay et al. found that late-onset cases showed enrichment for signatures similar to those observed in age-dependent changes in normal colorectal crypts. In contrast, colibactin-induced signatures were enriched in early-onset cancers. In addition, colibactin was associated with an earlier age of onset, an effect more evident in the distal colon and rectum [84]. Lee-six et al. found that the colibactin-related mutation signature in normal colonic crypts was most prevalent in younger children aged less than 10 years [71]. During the early life stage, our gut microbiome is still evolving, and it is considered a sensitive period to extrinsic influences. Therefore, it could interpret the association between APC: c.835-8 A>G and *pks*$^+$ *E. coli* in EOCRCs [85]. Yen Lin Chu et al. reported that colibactin-producing bacteria are less prevalent in EOCRC than in LOCRC. Therefore, this finding should be further confirmed in larger cohorts and a longitudinal study to determine how early mutagenic exposure of *pks*$^+$ *E. coli* influences later life and induces CRC [59].

4. Limitation

Our review included articles published since 2021, potentially excluding earlier relevant studies. In addition, the prevalence of *E. coli* strains was insufficient to support a worldwide prevalence estimate. It depended on geography, age groups in the population, and detection methods. We could not clearly establish causality regarding the overreach of *pks*$^+$ *E. coli* in cancer due to a limited number of published articles. Therefore, to prove the relationship between *pks*$^+$ *E. coli* and CRC, large prospective studies in more controlled clinical settings are necessary.

5. Conclusion

We evaluated the main characteristics of *pks*$^+$ *E. coli* and its impact on CRC development, and reviewed key features of pathogenic *E. coli* strains. Since the evolution of virulence in *E. coli* strains has been studied, horizontal gene transfer, which is crucial for the spread of the pks genomic island, has been shown to play a key role in this evolution. Therefore, colibactin, encoded by a pks, has been regarded as a key player in carcinogenesis, particularly in CRC. Several studies have proposed a primary underlying mechanism: colibactin promotes DNA alkylation in intestinal epithelial cells, thereby inducing DNA double-strand breaks. However, in human studies, results were inconsistent, and a large cohort study should be conducted to further enrich the current evidence. Furthermore, clinical translation, such as the use of screening or therapeutic biomarkers, requires prospective validation and standardized detection methods.

Conflicts of Interest

The authors declare no conflicts of interest.

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Ethical approval

This review study did not require ethical approval.

Large Language Model

No artificial intelligence tools or large language models were used to generate this manuscript.

Authors' Contributions

BU contributed to project administration, visualization, and conceptualization. CB contributed to methodology and writing-original draft. TS contributed to visualization and writing-original draft. GHD contributed to resources. YT contributed to data curation. TB contributed to writing-review and editing and supervision. GD contributed to visualization and resources. TL contributed to supervision. BB contributed to project administration and conceptualization.

Data Availability

This article is a review of previously published literature and did not generate or analyze any new primary dataset. Therefore, no new data are available. The sources supporting the findings of this review are included in the reference list.

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