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A review: the role of *Streptococcus bovis* in colorectal cancer

Abstract

Cancer, ranking second among the most commonly encountered diseases worldwide, is exhibiting an increasing incidence over time. Among cancer types, lung cancer, breast cancer, and prostate cancer hold the top three positions. Following these, digestive system cancers are the most frequently observed. The rising cancer-related mortality rates and potential difficulties during treatment exacerbate the fears and concerns of cancer patients. Throughout history, cancer has been attempted to be explained through theories such as lymphatic, humoral, blastoma, trauma, chronic irritation, and parasitic hypotheses. In contemporary times, a wealth of information exists concerning the roles of viruses and bacteria in cancer development. Among bacteria, the sole member acknowledged as a human carcinogen by the International Agency for Research on Cancer (IARC) is Helicobacter pylori. While there is no conclusive evidence regarding Streptococcus bovis's capacity to induce cancer, substantial suspicions surround this matter. This review delves into the relationship between the *Streptococcus bovis* group of bacteria, which is associated with cancer but not listed by the IARC, and colorectal cancer.

Keywords: streptococcus bovis, colorectal cancer, carcinogens

Volume 5 Issue 3 - 2023

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Received: September 10, 2023 | **Published:** September 22, 2023

Introduction

Throughout the history of medicine, the disease most extensively researched has been cancer. References to cancer and its fatal consequences are found in Babylonian cuneiform tablets, ancient Indian manuscripts, and Egyptian papyri, including the Ebers Papyrus (15th century BC).[1] Today, it stands as a significant issue for all countries worldwide. The projection by the International Agency for Research on Cancer (IARC), a branch of the World Health Organization, for the year 2030 is that cancer will be the leading cause of death.[2] Among the most commonly encountered cancer types globally, lung cancer, breast cancer, and prostate cancer hold the top three positions. Following these, digestive system cancers are the most prevalent. The increasing cancer-related mortality rates and potential difficulties during treatment amplify the fears and concerns of cancer patients.[3] Between the years 1628 and 1694, the first scientific study on cancer was conducted by Marcello Malpighi. In the past, cancer was explained through theories such as humoral, lymphatic, blastoma, chronic irritation, trauma, and parasitic hypotheses.[4] In 1903, Borrel proposed the idea that cancer could have a viral origin. In 1909, Ellerman and Bank demonstrated that leukemia is contagious among chickens, and in 1956, Dr. Stanley indicated that cancer viruses are present in every individual, and some factors trigger their activation. In 1974, Dr. Mak and Dr. Hawatson from the Ontario Cancer Institute in Canada discovered a virus that causes leukemia in humans.[5]

In recent years, studies have identified associations with viruses, protozoa, helminths, and certain bacteria in various cancer types. Up to this point, particularly in digestive system cancers, certain bacteria (such as *Helicobacter bilis*, *Helicobacter hepaticus*, *Campylobacter jejuni*, *Clostridium* spp., *Bacteroides* sp., *Salmonella typhi)*, along with *Streptococcus spp*. bacteria, have been observed to actively contribute to colorectal cancer (CRC).[5–8]

Characteristic features of cancer cells include continuous division without dependence on any factor, resistance to growth-inhibitory signals, lack of response to apoptosis, maintenance of telomere sequences allowing unlimited replication, and the ability to migrate to other regions and generate disease.[9] Globally, lung and prostate cancers alternately hold the first two places in the deadly ranking. CRC stands as the third most commonly occurring cancer type. Approximately 600,000 individuals worldwide die from colon cancer annually, accounting for around 8% of total cancer deaths worldwide. CRC primarily affects elderly adults; less than 20% of CRCs are found in individuals under 50 years old. However, there is a rapid increase in CRC among the young population, raising questions about lifestyle risk factors and even infectious etiology.[10] The American Cancer Society found a yearly increase in CRC incidence of 2.9% in women and 3.5% in men worldwide from 1992 to 2005. In contrast, there is a 20% decrease in CRC incidence in populations over 50 years old. Overall, an individual's lifetime risk of CRC is approximately 5%.[11]

CRC includes adenocarcinomas, adenosquamous carcinomas, spindle cell carcinomas, squamous cell carcinomas, mucinous carcinomas, signet ring cell carcinomas, and undifferentiated carcinomas, each having distinct clinical characteristics and requiring slightly different treatment approaches.[12] CRC formation generally evolves from a pre-existing polyp, progressing through stages of adenoma-dysplasia-carcinoma (Figure 1) and attains a lethal size within a span of 5 to 10 years.[13] This timeline underscores CRC as one of the most preventable cancers through early detection. Particularly, the removal of high-risk polyps before malignant transformation significantly diminishes the risk of cancer.[12,14]

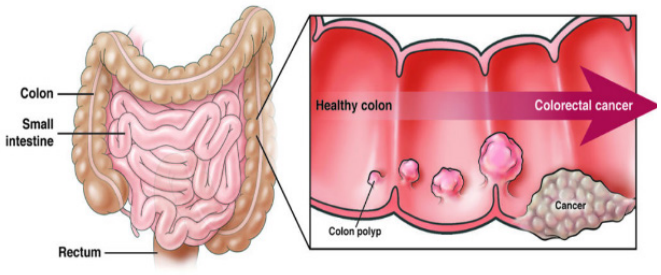

Figure 1 The CRC formation.[15]

Materials and methods

Streptococci

More than 100 species have been identified within the Streptococcus genus to date. Especially with the advancement of next-generation sequencing technologies, this number is likely to increase further. In the past 5 years alone, over 10 new species have been discovered, primarily from the oral cavity and gastrointestinal system of mammals. *Streptococci* have the potential to cause invasive infections, many of which hold significant public health importance. They can be found as part of the normal flora in the body and can also exist as saprophytes in food items like milk and dairy products.[16]

Streptococci constitute a diverse group of microorganisms. They are generally characterized as gram-positive cocci, often appearing in chains or pairs. Unlike staphylococci, *streptococci* yield negative results in catalase reactions. Many of these microorganisms are facultative anaerobes, meaning they can thrive in both oxygen-rich and oxygen-poor environments. The medically significant *streptococci* are typically non-motile and lack spores, while some species are enveloped by structures such as capsules composed of polysaccharides or hyaluronic acid. These attributes make them amenable to cultivation in nutrient-enriched media, such as those containing blood or serum. In solid culture media, most of these microorganisms form disk-like colonies with diameters of 1-2 mm.[17]

Streptococcus species

Group A Streptococcus; Streptococcus pyogenes

Streptococcus bacteria are among the most common microorganisms causing diseases in humans. When grown on blood agar, they typically form small, grayish colonies with a wide zone of complete hemolysis (beta hemolysis) surrounding them. Among the cellular components of these bacteria, commonly encountered ones include lipoteichoic acid, M protein, capsular polysaccharide, streptokinase, streptolysin, nucleases, hyaluronidase, and erythrogenic toxins. Additionally, *streptococci* can produce various enzymes, including proteinases, phosphatases, esterases, amylases, N-acetyl glucosamine amidase, neuraminidase, lipoproteinases, ribonucleases, diphosphopyridine nucleotidase, and esterases.[18]

Infections caused by Group A Streptococcus can lead to various diseases such as erysipelas, sepsis, endocarditis, puerperal sepsis, toxic shock-like syndrome, skin and subcutaneous tissue infections, streptococcal pharyngitis, scarlet fever, acute rheumatic fever, and acute glomerulonephritis.[19]

Group B Streptococcus; Streptococcus agalactiae

B group streptococci, known as Streptococcus agalactiae, generally exhibit characteristics typical of the Streptococcus family. When cultured on blood agar, they form larger, purplish colonies compared to A group *streptococci* and often have a narrow hemolysis zone around them. However, 5% to 15% of them may not exhibit hemolysis. B group *streptococci* are commonly found in the genital and intestinal flora of humans, particularly in pregnant individuals, nursery personnel, and newborns, without causing disease.[20]

Infections caused by these bacteria can include sepsis, pneumonia, osteomyelitis, arthritis, and meningitis in newborns. In adults, they can lead to conditions such as endometritis, endocarditis, pyelonephritis, pneumonia, cellulitis, septic arthritis, and meningitis. B group *streptococci* present in the vaginal flora of women can also be found in 50% of their partners' urethra, potentially causing urethritis.[21]

Group C *Streptococci*

Group C *Streptococci* consist of species like S. equisimilis, S. zooepidemicus, beta-hemolytic S. equi, and S. dysgalactiae, which can also be alpha-hemolytic or non-hemolytic. These bacteria can be responsible for diseases such as pharyngitis, tonsillitis, sepsis, pneumonia, meningitis, osteomyelitis, arthritis, and endocarditis.[22]

Group D *Streptococci*

Their microscopic appearance can be in pairs or short chains of diplococci. Enterococcus faecalis, Enterococcus faecium, and Streptococcus durans are microorganisms that are resistant to penicillin and exhibit alpha, beta, or gamma hemolysis characteristics. *Streptococcus bovis* and Streptococcus equinus, on the other hand, are non-enterococcal Group D streptococci.[23]

Group D *streptococci* and enterococci are often part of the normal flora in the intestines, mouths, and sometimes the skin of both humans and some animals. Under suitable conditions, they can cause various diseases in humans, including endocarditis, urinary tract infections, abscesses, and cholecystitis.[24]

Viridans Streptococci

Viridans group *streptococci* make up 30% to 60% of the normal oral flora in humans. These bacteria can be found on the surfaces of teeth, in the spaces between gums and teeth, in root canals, on the palate, tongue, and the mucous membranes of the pharynx. To cause infections, they need to leave their natural habitat and encounter reduced host resistance. They exhibit alpha hemolysis when grown on blood agar.[25]

Viridans *streptococci* can be isolated as the causative agents of dental root infections, subacute bacterial endocarditis, chronic lung infections, genital and urinary infections, cholangitis, peritonitis, and various abscesses.[18,25]

Other streptococcus species

Aerococcus

These bacteria have a size of 1.0-2.0 micrometers and form tetrads. They are gram-positive and microaerophilic, being catalase-negative. When grown on blood agar, they exhibit green hemolysis. Aerococcus is generally considered a saprophytic bacterium and has been isolated from certain cases of endocarditis and hospital environments.[18]

Gemella

Gemella bacteria, on the other hand, appear as diplococci or single cocci with flat, opposing faces. They are gram-positive and form colonies on blood agar that resemble small beta-hemolytic streptococcal colonies. This genus includes only one species, Gemella haemolysans.[18]

Peptococcus

Peptococcus bacteria are gram-positive cocci that appear singly, in pairs, tetrads, or clusters with a size ranging from 0.3 to 1.3 micrometers. Their colonies on blood agar are small (0.5 mm in diameter), round, shiny, and non-hemolytic, with a black color. Peptococcus niger can be part of the normal flora in the vaginal area and the umbilical region.[18]

Peptostreptococcus

Peptostreptococcus bacteria, forming irregular clusters or chains of cocci, are gram-positive anaerobic cocci. Isolating Peptococcus

Citation: Şahin T, Kiliç O, Acar AG, et al. A review: the role of *Streptococcus bovis* in colorectal cancer. *Art Human Open Acc J.* 2023;5(3):165–173.
DOI: 10.15406/ahoaj.2023.05.00203

and *Peptostreptococcus* species can be challenging. Particularly, the presence of gram-positive cocci in direct stained preparations of clinical specimens without growth in aerobic cultures, but with suspected gram-positive cocci in anaerobic cultures, indicates the presence of these bacteria.[26]

Peptostreptococcus species can be isolated from various sources, including the female genital tract in both normal and pathological conditions, blood in cases of puerperal sepsis, the normal respiratory and intestinal flora of humans and some animals, some pyogenic infections, septic war wounds, and appendicitis.[27]

Classification of species within the *streptococcus* genus

Species within the Streptococcus genus are classified based on various factors. These factors encompass serological characteristics of the cell wall, the presence of capsular antigens, colony morphology, types of hemolysis exhibited on blood agar, biochemical reactions, and sensitivity to physical/chemical agents.[28]

Streptococcus bovis

These bacteria, referred to as S. bovis, are categorized as Streptococcus gallolyticus (formerly *S. bovis* biotype I), Streptococcus infantarius (*S. bovis* biotype II.1), and Streptococcus pasteurianus (*S. bovis* biotype II.2). These bacteria typically form small non-hemolytic or alpha-hemolytic colonies, and they cannot grow in a 6.5% salt solution. They yield negative results in the catalase test, test positively for leucine aminopeptidase, and test negatively for PYR (pyrrolidonyl arylamidase). Gram-positive cocci in pairs or short chains define their morphology.[29]

These species can be found as normal components of the intestinal flora in about 2-12% of healthy adults. However, they are also prevalent in individuals with gastrointestinal cancer. *S. bovis* group bacteria express the Lancefield Group D antigen and exhibit phenotypic characteristics reminiscent of enterococci.[30] The exact pathogenesis mechanism of *S. bovis* is not fully understood, and thus, the virulence factors associated with these infections are not completely elucidated. The following are some factors that contribute to the survival and growth of this organism within the host:[31–33]

1. **Surface proteins:** *Streptococcus bovis* possesses a series of genes encoding microbial surface components recognizing adhesive matrix molecules (MSCRAMM) that can recognize adhesive proteins and other components of the extracellular matrix of host cells. These molecules remain in the organism's cell wall and are specific to certain cells within the host. The genomic sequences of *S. bovis* support the presence of three pilus gene clusters known as pil1, pil2, and pil3. Pil1 has been identified as the initial virulence factor and is responsible for biofilm formation even without collagen binding ability. It plays a crucial role in the initial attachment and colonization stages of infective endocarditis. Additionally, the colonization of the intestinal tract by *S. bovis* has been found to depend on the Pil3 pilus, which aids in bacterial attachment by binding to colonic mucus and fibrinogen in humans.
2. **Biofilm formation:** Specific *S. bovis* strains can create biofilms that can lead to nosocomial (hospital-acquired) infections around medical devices such as catheters. The formation of biofilms serves as a barrier not only against antimicrobial agents but also against immune cells, offering protection to the bacteria. This biofilm formation process is supported by the presence of fibrinogen-binding adhesins and other enzymes.
3. **Soluble cell wall antigens:** In cases of colorectal cancer caused by S. bovis, soluble cell wall antigens have been identified as playing a significant role in triggering inflammation and carcinogenic processes. These proteins or antigens induce the activity of interleukin-8 (IL-8) in different cell types within the body. IL-8 is known to induce the overexpression of cyclooxygenase-2 (Cox-2), leading to increased prostaglandin levels in Caro-2 cells. This, in turn, results in elevated production of oxygen radicals and nitric oxide in the intestinal mucosa cells, causing mutagenesis that further supports the induction of cancer.

Many Streptococcus species do not thrive well in traditional growth media like Nutrient Agar, necessitating the use of specialized media containing specific carbohydrates and nutrients. Blood agar and Chocolate agar are commonly used for diagnosing S. bovis, with observation of hemolysis patterns being essential. For more selective isolation, specialized media like Brain Heart Infusion Agar and Trypticase Soy Agar/Broth with defibrinated sheep blood can be utilized (Figure 2).[34]

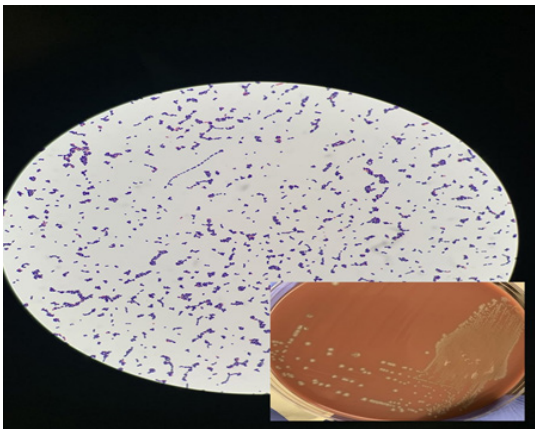

Figure 2 Microscopic images of *Streptococcus bovis* on blood agar.[35]

Pathogenesis of *Streptococcus* bovis

While *Streptococcus bovis* is considered a commensal in the gastrointestinal system of animals, it can also lead to various forms of infection. The complete mechanism of infection and the pathogenesis of the disease are not fully understood. However, it is believed that biofilm formation plays a critical role in the organism's growth and survival. Different virulence factors expressed by this organism assist in the pathogenesis process.[36,37]

Colonization

i. The organism can enter the host's body through various routes, such as oral ingestion of different food sources.

ii. Subsequently, bacteria reach the gastrointestinal region and adhere to the epithelial cells of the mucosal layer.

iii. Attachment is initiated through "Microbial Surface Components Recognizing Adhesive Matrix Molecules" (MSCRAMM) and other adhesive proteins.

iv. The initial attachment process is followed by the binding of pil1 protein, which can attach to collagen and further support colonization.

v. These steps of attachment and colonization are vital for the organism's ability to reproduce, multiply, and establish itself within the body.

Invasion

i. Following colonization, bacteria begin to penetrate deeper tissues and can cause infections in various parts of the body by entering the bloodstream.

ii. Mucosal damage allows bacteria to enter the bloodstream and cause infective endocarditis.

iii. Bacteria can bind to factors like thrombin, thrombocytes, and fibrin, inducing blood clotting and contributing to the organism's protection.

iv. Proteins like Pil1 and Pil3 interact with intrinsic clotting pathways, influencing significant events during endocarditis.

v. Soluble cell wall proteins produced by the organism can enhance inflammation and trigger cancer processes.

vi. These chemical reactions can induce mutagenesis in mucosal cells, promoting the development of cancer.

Clinical symptoms of streptococcus bovis

Previously, *S. bovis* was commonly considered a low-grade pathogen associated with bacteremia and endocarditis. In addition to infective endocarditis, the possibility of *S. bovis* infections has been suggested in various areas such as osteomyelitis, discitis, and neck abscesses outside the colon. Depending on the geographical location of patients, other types of infections such as colorectal adenoma, cholecystitis, cholangitis, and biliary tract diseases have also been linked to *S. bovis*.[38,39]

Infective Endocarditis

i. The organism can induce blood clotting by binding to fibrinogen-binding proteins and collagen, leading to infective endocarditis.

ii. Patients may experience symptoms like chills, fever, and chest pain.

iii. Infective endocarditis has been closely associated with both bacteremia and colon cancer.

Malignancies

i. S. bovis bacteremia has been associated with malignancy in approximately 29% of patients with tumor lesions in areas such as the colon, gallbladder, lungs, or others.

ii. Chronic inflammation and the production of carcinogenic metabolites can lead to lesions in the colorectal region, providing a foundation for the development of malignancies.

Result

S. bovis and colorectal cancer

S. bovis is a largely commensal species found in the intestines of animals, and it serves as a benign type that helps prevent the colonization of different pathogenic microorganisms. However, in individuals with suppressed immunity, it possesses various structures and proteins that support the colonization and invasion of host tissue surfaces. These structures not only aid the organism in entering the body and initiating invasion but also protect the organism from the host immune system.[40]

The *S. bovis* group bacteria have long been associated with colorectal cancer (Table 1). Meta-analyses conducted have revealed that patients infected with *S. bovis* biotype I have a significantly higher risk of developing colorectal cancer compared to those infected with biotype II. This analysis demonstrates that *S. bovis* is not just a bacterium, but it plays a role in the formation and progression of CRC and certain diseases. However, research has not yet determined whether *S. bovis* is a causative agent of colorectal cancer or if it aids in the growth and proliferation of pre-existing cancer within the lumen of the colon. Nonetheless, there is a clear established link between this group and colon adenomas/carcinomas based on studies conducted to date.[41,42]

Table 1 Results of the *S. bovis* bacterial group in patients with CRC

Disease type	Patient number	Methods	Results	Reference
CRC	63	Facklam method	% 58 positive	43
CRC	12	İmmunocapture mass spectrometry assay	% 91 positive	44
CRC	64	Colonoscopy, Elisa and in situ hybridization experiment	% 18-62 positive	45
CRC	82	Elisa	% 60 positive	46
Rat - colon cells	-	Elisa	Increase in IL-8 production	47
Rat - colon cells	-	Elisa, Western blot, Cell culture	Induction of IL-8, PGE2 and COX-2 expression, promotion of neoplastic lesions	48
Colorectal lesıons	41	PCR	% 8 positive	49
CRC	29	PCR	% 7 positive	50
CRC	12	Tube dilution technique	% 42 positive	51
Colorectal lesıons	34	Colonoscopy	% 9 positive	52
Colorectal and duodenal cancer	16	-	% 6 positive	53
Colorectal neoplasia.	14	Antibiotic susceptibility test	% 29 positive	54
CRC	21	Insulation	% 5 positive	55
CRC and Colorectal neoplasia.	25	Serological methods	% 8 positive (CRC) % 28 positive (Colorectal neoplasia)	56
CRC and Colorectal neoplasia.	92	Serological methods	% 17 positive (CRC) % 24 positive (Colorectal neoplasia)	57

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Table 1 Continued...

Disease type	Patient number	Methods	Results	Reference
CRC	32	Serological methods	% 9 positive	58
CRC	53	Colonoscopy and serological methods	% 4 positive	59
CRC	20	Microbiological methods	% 15 positive	60
CRC	20	Microbiological methods, Fisher's exact probability test and Mann-Whitney U test	% 15 positive	61
CRC	40	Colonoscopy and serological methods	% 10 positive	62
CRC	12	PCR	% 17 positive	63
Colorectal neoplasia.	20	Colonoscopy and serological methods	% 77 positive	64
CRC	37	Microbiological methods	% 11 positive	65
CRC	199	Microbiological methods	% 46,7 positive	66
CRC	17	Microbiological methods and Fisher's exact probability test	% 17 positive	67
Colorectal lesions	19	Agar dilution method	% 47 positive	68
CRC	46	Microbiological methods	% 13 positive	69
CRC	20	Microbiological methods	% 45 positive	70
CRC	59	Microbiological methods	% 18 positive	71
CRC	1	Microbiological methods	% 100 positive	72
CRC	1	Microbiological methods	% 100 positive	73
CRC	2	Microbiological methods	% 100 positive	74
CRC	2	Microbiological methods	% 100 positive	75
CRC	1	Microbiological methods	% 100 positive	76
CRC and Colorectal neoplasia.	3	Microbiological methods	% 100 positive	77
CRC	4	Colonoscopy, barium enema and proctoscopic examination	% 25 positive	78
CRC	6	Sigmoidoscopy, colonoscopy, barium enema	% 83,3 positive	79
CRC	1	Microbiological methods	% 100 positive	80
CRC	1	Colonofiberoscopy	% 100 positive	81
CRC	1	Microbiological methods	% 100 positive	82
Colorectal lesions	1	Microbiological methods	% 100 positive	83
CRC	1	Microbiological methods	% 100 positive	84
Colorectal neoplasia.	1	Microbiological methods	% 100 positive	85
CRC	1	Microbiological methods	% 100 positive	86
CRC	1	Microbiological methods	% 100 positive	87
CRC	3	Microbiological methods	% 100 positive	88
Colorectal neoplasia.	1	Colonoscopy and microbiological methods	% 100 positive	89
CRC	1	Colonoscopy and microbiological methods	% 100 positive	90
CRC	1	Colonoscopy, biopsy and microscopic examination	% 100 positive	91
CRC	1	Colonoscopy and microbiological methods	% 100 positive	92
CRC	1	Colonoscopy and microbiological methods	% 100 positive	93
CRC	20	Retrospective research in hospital records	% 67 positive	94
CRC	1	Microbiological methods	% 100 positive	95
CRC	2	Clinical findings, standard radiographs and laboratory tests	% 100 positive	96
CRC	15	Colonoscopy and microbiological methods	% 20 positive	97
CRC	1	Colonoscopy, biopsy and microbiological methods	% 100 positive	98
Colorectal neoplasia.	18	Colonoscopy and biopsy	% 100 positive	99
CRC	1	Computed tomography and microbiological methods	% 100 positive	100
CRC	1	Colonoscopy and microbiological methods	% 100 positive	101

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Table 1 Continued...

Disease type	Patient number	Methods	Results	Reference
CRC and Colorectal neoplasia.	25	PCR, colonoscopy and microbiological methods	% 65 positive	102
Rat - colon cells	-	PCR	Increase in IL-6, Scyb1, Ptgs2, IL-1b, TNF and Ccl2 levels	103
CRC	48	Colonoscopy and microbiological methods	% 64,6 positive	104
CRC	20	Colonoscopy, biopsy and microbiological methods	% 35 positive	105
CRC	1	Positron emission tomography and microbiological methods	% 100 positive	106
CRC	1	Colonoscopy and microbiological methods	% 100 positive	107
CRC	35	Microbiological methods, PCR and Elisa	% 37,1 positive	108
CRC	30	Colonoscopy and microbiological methods	% 47 positive	109

Streptococcus bovis is a part of the normal intestinal flora in humans and animals, but it is also responsible for infectious diseases (10-15% of all bacterial endocarditis cases). Various cases of bacteremia and metastatic abscesses involving the spleen, liver, soft tissues, bone, meninges, and endocardium have been reported to be associated with S. bovis, particularly related to colonic diseases, digestive system disorders, and specifically colonic neoplasms or chronic liver diseases.[110]

Endocarditis and/or bacteremia caused by *Streptococcus bovis* serve as early indicators of possible colorectal cancer presence. While further studies are needed to determine the exact pathophysiology, clinicians should be aware of this association. Rigorous investigation for colon cancer is advised in all patients presenting with *S. bovis* endocarditis/bacteremia; such patients may also present with liver disease or, rarely, extracolonic malignancies.[111]

Conclusion

In conclusion, there is strong epidemiological evidence that *S. bovis* can contribute to colorectal cancer. Moreover, its frequent detection in the majority of CRC cases, its greater and/or higher concentration in malignant tissues compared to corresponding healthy tissues, its localization in tissue at every stage of cancer development, and its support of cancer progression indicate that it should be included in the list of infectious agents by the IARC.[112]

Furthermore, cases of infective endocarditis related to the bovis group have shown an increase in recent years.[113] Considering this information, any patient with bovis group bacteremia should undergo echocardiography and colonoscopy, and biliary tract imaging should also be considered. In light of the above data, we believe that clinical trials should be included to explore effective antibiotics against bovis group bacteria in patients with CRC, before resorting to heavy treatments like chemotherapy.

Acknowledgments

None.

Conflicts of interest

The authors declare that there is no conflict of interest.

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Citation: Şahin T, Kiliç O, Acar AG, et al. A review: the role of *Streptococcus bovis* in colorectal cancer. *Art Human Open Acc J*. 2023;5(3):165–173.
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