Association between *Streptococcus galloyticus* and colorectal cancer in Mansoura University hospitals

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**ABSTRACT**

*Streptococcus galloyticus* (*S. galloyticus*) bacteria are associated with colorectal cancer and adenoma. About 25–80% of patients with *S. bovis* bacteremia have concomitant colorectal tumors. This case control study aimed to detect the prevalence of *S. galloyticus* in colorectal cancer tissues of patients attending Gastrointestinal Surgery Center (GISC) for colonoscopy, determine the correlation with the endoscopic finding and identify risk factors for acquisition of *S. galloyticus*. Case samples were colorectal cancer tissue, obtained from 48 colorectal cancer patients who performed colonoscopy before administration of chemotherapy, control samples were normal colonic tissue taken from 48 persons who performed colonoscopy for any reason other than colorectal cancer. For isolation and identification of *S. galloyticus*, the samples were processed, seeded on bile esculin agar, suspected colonies were identified with Gram staining, catalase, and pyrrolidonyl arylamidase test. Age was significantly older in cases compared to controls. Both gender and residence did not significantly differ between the study groups. Occupational contact with animals was significantly higher in cases compared to control. The prevalence of *S. galloyticus* in colorectal cancer tissues was 35.4%. *S. galloyticus* on the surface was positive in 64.6% of cases, versus only 18.8% of controls. On univariate analysis, diarrhea was a significant risk factor for having surface *S. galloyticus*. No significant risk factors for colonizing *S. galloyticus* in tissue were identified. The early detection of *S. galloyticus* in cases of colorectal adenomas might be of high value in screening high risk groups for colorectal cancer.

**Introduction**

The human gastrointestinal tract is colonized by over 10^{14} bacteria, approximately 10-fold of the total number of cells in the human body [1]. Disruptions to the microbiome have been associated with severe pathologies of the host, including metabolic disease, cancer and inflammatory bowel disease [2,3]. The composition of the gut microbiota is determined and influenced by a number of endogenous and exogenous factors, such as geographic origin, age, genetics, diet, and the use of prebiotics and antibiotics [4,5]. Accumulating evidence suggests that gut bacteria play critical roles in maintaining human health in many aspects. For example, gut bacteria prevent the growth of pathogenic bacteria, regulate the gut development, maintain epithelial integrity by regulating tight junction permeability [6,7]. Colorectal cancer (CRC) is the third most common diagnosis and second deadliest malignancy for both sexes combined. CRC has...
both strong environmental associations and genetic risk factors. The incidence of new cases and mortality has been steadily declining for the past years, except for younger adults (younger than 50 years), possibly related to an increase in cancer screening and better therapy modalities [8]. *Streptococcus gallolyticus* (*S. gallolyticus*), previously known as *Streptococcus bovis*, have been associated clinically with malignancy of the colon and rectum. The relationship between *S. bovis* and CRC was recognized in the 1950s and many case reports and retrospective studies on this association have been published since then. *S. gallolyticus* is an opportunistic pathogen that normally resides asymptomatically in the human intestinal tract [9]. According to Dr. Parkin’s estimate, 17.8% of the worldwide cancer incidence is attributable to infectious agents, resulting in approximately 1.9 million cases per year [10]. These include a variety of infectious agent [9,11]. Several mechanisms have been proposed, including direct effects on host cell proliferation and communication pathways, impairment of host immune system, induction of genomic instability and chronic inflammation [12]. Chronic inflammation often accompanies increased host cell turnover, which increases the probability of mutagenic events, and enhanced formation of reactive oxygen and nitrogen species that damage DNA and induce genomic instability [13,14]. It was found that 25 to 80% of patients with *S. gallolyticus* bacteremia and 18 to 62% of patients with *S. gallolyticus* endocarditis have underlying colorectal tumors [15]. *S. gallolyticus* was found to be mildly associated with some benign lesions (diverticulosis, inflammatory bowel disease, cecal volvulus, perirectal abscess hemorrhoids, and benign polyps), while it was strongly associated with most malignant diseases (cancer and neoplastic polyps) of the colon [16,17]. Therefore we set out this study to determine the prevalence of *S. gallolyticus* in colorectal cancer tissues of patients attending Gastrointestinal Surgery Center (GISC) for colonoscopy, determine the correlation with the endoscopic finding and identify risk factors for acquisition of *S. gallolyticus*.

**Patients and methods**

**Patients**

This case-control study included a total of 48 colorectal cancer patients who attended GISC, Faculty of Medicine, Mansoura University and performed colonoscopy before administration of chemotherapy, starting from October 2018 to December 2019. Control samples were obtained from normal colonic mucosa of 48 patients who performed colonoscopy for any reason other than colorectal cancer. Patients with age younger than 18 years, antibiotic use in the previous month and poor or inadequate preparation for colonoscopy were excluded from the study. The following data were collected from the included subjects, demographic data (age, gender, occupation and residence), clinical data (diarrhea, rectal bleeding, tenesmus, crampy abdominal pain, anorexia, nausea, vomiting, or fever).

**Specimen collection**

All included participants in the study were subjected to colonoscopy and biopsy for histopathological and microbiological examination. **Case group**, samples were obtained from colonic tissue lesion. **Control Group**, samples were obtained from normal colonic mucosa.

**Microbiological methods (Processing of colorectal samples)**

Samples from cases and control groups were collected in 1 ml phosphate buffer saline (PBS) in screw capped tubes and were sent to the Microbiology Diagnostic and Infection Control
Unit (MDICU), Medical Microbiology and Immunology Department, Mansoura Faculty of Medicine.

**Isolation of S. gallolyticus**

The isolation of *S. gallolyticus* was done according to the following protocol for preparation of colorectal tissue sample [18]. For detection of surface bacteria, colorectal samples were rinsed thoroughly by shaking for 3 minutes in 1 ml of PBS for the recovery of mucosal attached bacteria then PBS was centrifuged at 3000 x g for 5 minutes at 15°C [19]. The pellet was suspended in 0.5 ml of brain heart infusion broth and an antibiotic disc impregnated with ertapenem was added in order to delay growth of Gram-negative rods. Samples were incubated for 18 h at 37°C, then 5 µl of the samples were seeded on bile esculin agar and were incubated for a period of 18 h at 37°C in 5% CO₂ atmosphere [20].

**Identification of S. gallolyticus**

*S. gallolyticus* was identified by colony morphology; black-colored colonies caused by esculin hydrolysis as illustrated in Figure 1, Gram stained films and biochemical reactions including catalase and pyrrolidonyl arylamidase (Becton, Dickinson and company, USA).

**Ethical consideration**

All the data were collected after approval of institutional research board (IRB) of Medical Faculty of Mansoura University (Code number: MS.19.05.648). Informed written consent was taken from all study participants.

*Figure 1.* The black colored colonies of *Streptococcus gallolyticus* on bile esculin agar.
Statistical analysis

For statistical analysis, difference between continuous variables, summarized as mean ± SD (standard deviation) for parametric data mean. The two groups were compared with student t-test. Differences between frequencies were analyzed using a χ2 test. A P < 0.05 was set to indicate statistical significance.

Results

Patients’ characteristics

Forty-eight cases and 48 controls who underwent colonoscopy in GISC, Faculty of Medicine, Mansoura University were enrolled in the study. The mean age of the included subjects was 55.98 and 46.83 years for cases and controls, respectively. Age was significantly older in cases compared to controls. As regard gender, females represented 50 and 45.8% of the included subjects in both groups, respectively. Also, most of the included subjects were from rural areas (72.9 and 70.8% in both groups, respectively). Both gender and residence did not significantly differ between the study groups. Occupational contact with animals was significantly higher in cases compared to control (43.8% and 31.2%, respectively). Nevertheless, handling raw meat and raw milk products did not significantly differ between the two groups (Table 1). The incidence of rectal bleeding, weight loss, and crampy abdominal pain showed a significant increase in cases compared to controls; however, the incidence of diarrhea and anorexia was significantly increased in controls. There was no significant difference between cases and controls regarding the prevalence of tenesmus, nausea, vomiting, and fever (Table 2).

| Table 1. Analysis of demographic and dietary data in the two study groups. |
|--------------------------------|-----------------|-----------------|-----------------|
| Data                          | Cases (N = 48)  | Control (N = 48) | Test of significance |
| Age (years)                   | 55.98 ± 11.53   | 46.83 ± 15.17    | t = 3.325         |
| Gender                        | Male            | Female           | χ² = 0.167       |
|                              | 24              | 26               | P = 0.683        |
|                               | 50%             | 54.2%            |                 |
| Residence                     | Urban           | Rural            | χ² = 1.811       |
|                              | 13              | 35               | P = 0.204        |
|                               | 27.1%           | 72.9%            |                 |
| Occupational contact with animals |                |                  | χ² = 13.503      |
|                              | 21              | 21               | P < 0.001*       |
|                               | 43.8%           | 70.8%            |                 |
| Consumption of raw meat       | 0               | 0                | NA              |
| Handling raw meat             | 23              | 24               | χ² = 0.042       |
|                              | 47.9%           | 50%              | P = 0.838        |
| Drinking raw milk or raw milk products | 40          | 39               | χ² = 0.071       |
|                              | 83.3%           | 81.2%            | P = 0.789        |

N, number; t, student t test; χ², chi-square; P, predictive value; NA, not available; * , Statistically significant.

Prevalence of S. galolyticus

S. galolyticus on the surface was positive in 64.6% of cases, versus only 18.8% of controls (p < 0.001). On analysis of S. galolyticus in tissue, 17 cases showed positivity (35.4%) compared to 3 controls (6.2%) (P < 0.001).

Correlation with endoscopic and histopathological finding

Endoscopic examination revealed the presence of rectal mass in 33.3% of cases, sigmoid mass (14.6%), and cecal mass (12.5%). As regard controls, 15 subjects (31.25%) had normal colonoscopy examination, whereas internal piles were the commonest finding in that group (43.8%). Other findings in cases are summarized in Table 3. On analysis of histopathological examination findings, all cases were positive either for carcinoma or adenoma with dysplasia. On the other hand, intact colonic examination was the commonest finding in controls (77.1%), followed by nonspecific colitis (10.4%), ulcerative colitis.
Table 2. Analysis of clinical data in the two study groups.

| Clinical data       | Cases (N = 48) | Control (N = 48) | Test of significance |
|---------------------|---------------|------------------|----------------------|
| Diarrhea            | 6 (12.5%)     | 22 (45.8%)       | χ² = 12.908          |
| Rectal bleeding     | 40 (83.3%)    | 23 (47.9%)       | χ² = 13.345          |
| Tenesmus            | 16 (33.3%)    | 16 (33.3%)       | χ² = 0.001*          |
| Crampy abdominal pain | 46 (95.8%) | 39 (81.2%)       | χ² = 5.031           |
| Anorexia            | 1 (2.1%)      | 6 (12.5%)        | χ² = 2.852           |
| Nausea              | 2 (4.2%)      | 6 (12.5%)        | χ² = 2.182           |
| Vomiting            | 2 (4.2%)      | 4 (8.3%)         | χ² = 0.711           |
| Fever               | 8 (16.7%)     | 6 (12.5%)        | χ² = 0.334           |
| Weight loss         | 29 (60.4%)    | 15 (31.2%)       | χ² = 8.224           |

N, number; χ², chi-square; P, predictive value; NA, not available; * Statistically significant.

Table 3. Analysis of results of colonoscopy in the two study groups.

| Results of colonoscopy       | Cases (N = 48) | Control (N = 48) | P value |
|------------------------------|---------------|------------------|---------|
| Cecal mass                   | 6 (12.5%)     | 0 (0%)           | 0.086   |
| Colonic mass                 | 3 (6.25%)     | 0 (0%)           | 0.341   |
| Colonic polyps               | 1 (2.1%)      | 2 (4.2%)         | 0.587   |
| Colonic ulcerations          | 0 (0%)        | 1 (2.1%)         | 0.564   |
| Colonic unhealthy mucosa     | 1 (2.1%)      | 0 (0%)           | 0.564   |
| Diverticulus                 | 0 (0%)        | 2 (4.2%)         | 0.385   |
| Free colon and rectum        | 0 (0%)        | 15 (31.2%)       | <0.001* |
| Hepatic flexure mass         | 2 (4.2%)      | 0 (0%)           | 0.385   |
| Inflamed mucosa              | 0 (0%)        | 5 (10.4%)        | 0.123   |
| Internal piles               | 0 (0%)        | 21 (43.8%)       | 0.001*  |
| Left colon mass              | 4 (8.3%)      | 0 (0%)           | 0.256   |
| Left colon mass/ transverse colon mass | 1 (2.1%) | 0 (0%) | 0.564 |
| Rectal mass                  | 16 (33.3%)    | 0 (0%)           | 0.029*  |
| Rectal mass/ colonic mass    | 1 (2.1%)      | 0 (0%)           | 0.564   |
| Rectal ulcers                | 0 (0%)        | 1 (2.1%)         | 0.564   |
| Recto-sigmoidal mass         | 3 (6.25%)     | 0 (0%)           | 0.341   |
| Sigmoid mass                 | 7 (14.6%)     | 0 (0%)           | 0.078   |
| Splenic flexure mass         | 2 (4.2%)      | 0 (0%)           | 0.3585  |
| Transverse colon Mass        | 1 (2.1%)      | 0 (0%)           | 0.564   |

N, number; P, predictive value; * Statistically significant.

(6.2%), and juvenile polyposis (4.2%) (Table 4). In correlation of presence of S. galloyticus inside tissues of colorectal cancer and endoscopic findings it was mostly associated with rectal cancer (41.2%) (Table 5).

Risk factors for acquisition of S. galloyticus

As shown in Table 6, by univariate analysis, diarrhea was a significant risk factor for having surface S. galloyticus (p = 0.032). No significant risk factors for colonizing S. galloyticus in tissue were identified in the current study (Table 7).

Discussion

This case control study was conducted at GISC aiming to find the association between surface and tissue S. galloyticus and colorectal cancer. In this study a total of 48 cases diagnosed with colorectal cancer in addition to 48 controls were included. The mean age of the included cases was 55.98 years, which was significantly older compared to controls (mean = 46.83 – p = 0.001). Another study reported that the mean age of the included cases was 51 years [8], which is near to the age reported in this study. But in contrast another study by Kassem et al, the mean age of the included cases was 40.42 years (range, 17–72) [21]. In this study, gender distribution did not significantly differ between the two groups (p = 0.693). In the cases group equal number of males and females were included. This is in line with Kearney and his associates who found that both male and female genders constituted 50% of cases in the colorectal cancer group [22]. Conversely, another Egyptian study had reported much higher prevalence for female gender, as they constituted 63.2% of cancer colon cases [21]. Although this study results showed that occupational contact with animals was significantly higher in cases compared to controls (43.8 vs. 31.2% respectively), the existing literature, to the best of our knowledge, is poor as regard handling of this relationship. Perhaps, this exposure could increase the chance of S. galloyticus
Table 4. Analysis of results of pathological specimen examination in the two study groups.

| Results of pathological examination                  | Cases (N = 48) | Control (N = 48) | P value |
|------------------------------------------------------|----------------|-----------------|---------|
| Adenocarcinoma of low grade malignancy               | 1 (2.1%)       | 0 (0%)          | 0.564   |
| Chronic nonspecific colitis                          | 0 (0%)         | 5 (10.4%)       | 0.123   |
| Grade 2 adenocarcinoma                               | 18 (37.5%)     | 0 (0%)          | < 0.001*|
| Grade 2 adenocarcinoma signet ring                   | 1 (2.1%)       | 0 (0%)          | 0.564   |
| Intact                                               | 0 (0%)         | 37 (77.1%)      | < 0.001*|
| Juvenile polyposis                                   | 0 (0%)         | 2 (4.2%)        | 0.385   |
| Moderate differentiated adenocarcinoma               | 20 (41.7%)     | 0 (0%)          | < 0.001*|
| Mucoid adenocarcinoma                               | 1 (2.1%)       | 0 (0%)          | 0.123   |
| Signet ring cell carcinoma                          | 1 (2.1%)       | 0 (0%)          | 0.123   |
| Tubular adenocarcinoma with low grade dysfunction    | 4 (8.3%)       | 0 (0%)          | 0.341   |
| Ulcerative colitis                                   | 0 (0%)         | 3 (6.2%)        | 0.256   |
| Villo tubular adenoma with grade 2 dysplasia         | 2 (4.2%)       | 0 (0%)          | 0.385   |

N, number; P, predictive value; *, Statistically significant; B, Regression coefficient.

Table 5. Correlation between presence of *S. gallolyticus* in tissues of colorectal cancer and endoscopic findings.

| Colonoscopic findings                                 | CRC cases N = 48 | Presence of *S. gallolyticus* inside tissue samples N = 17 (%) |
|------------------------------------------------------|------------------|-----------------------------------------------------------------|
| Cecal mass                                           | 6                | 2 (11.8)                                                        |
| Colonic polyps                                       | 1                | 1 (5.8)                                                         |
| Left colonic mass                                    | 4                | 1 (5.8)                                                         |
| Rectal mass                                          | 16               | 7 (41.2)                                                        |
| Recto sigmoid mass                                   | 3                | 2 (11.8)                                                        |
| Sigmoid mass                                         | 7                | 3 (17.7)                                                        |
| Splenic flexure mass                                 | 2                | 1 (5.9)                                                         |

CRC, colorectal cancer.

Table 6. Univariate analysis of risk factors for positive *S. gallolyticus* on the surface.

| Variables                                           | Univariate analysis |
|-----------------------------------------------------|---------------------|
| Age                                                 | 0.794               |
| Gender                                              | 0.999               |
| Residence                                           | 0.352               |
| Private or occupational contact with animals        | 0.760               |
| Consumption of raw meat                             | 0.999               |
| Handling raw meat                                   | 0.863               |
| Drinking raw milk or raw milk products              | 0.830               |
| Diarrhea                                            | <0.001*             |
| Rectal bleeding                                     | 0.658               |
| Tenesmus                                            | 0.128               |
| Crampy abdominal pain                               | 0.999               |
| Anorexia                                            | 0.998               |
| Nausea                                              | 0.998               |
| Vomiting                                            | 0.578               |
| Fever                                               | 0.280               |
| Weight loss                                         | 0.794               |

95% CI, 95% Confidence interval; P, predictive value; *, Statistically significant; B, Regression coefficient.

colonization which are commensals of the gastrointestinal tracts in animals [23], and that led eventually to the incidence of colorectal cancer. In this study, old age was a significant risk factor for colorectal cancer on multivariate analysis (p = 0.027). Age is a major risk factor for sporadic CRC. Large bowel cancer is uncommon before the age of 40; the incidence begins to increase significantly between the ages of 40 and 50, and age-specific incidence rates increase in each
Table 7. Univariate analysis of risk factors for positive S. galloyticus in tissues.

| Variables                                | Univariate analysis |
|------------------------------------------|---------------------|
| Age                                      | 0.819               |
| Gender                                   | 0.942               |
| Residence                                | 0.324               |
| Private or occupational contact with animals | 0.429             |
| Consumption of raw meat                  | 0.690               |
| Handling raw meat                        | 0.483               |
| Drinking raw milk or raw milk products   | 0.970               |
| Diarrhea                                 | 0.130               |
| Rectal bleeding                          | 0.719               |
| Tenesmus                                 | 0.505               |
| Crampy abdominal pain                    | 10.000              |
| Anorexia                                 | 10.000              |
| Nausea                                   | 0.999               |
| Vomiting                                 | 0.269               |
| Fever                                    | 0.368               |
| Weight loss                              | 0.819               |

succeeding decade thereafter [24]. More recent data from the United States Surveillance, Epidemiology, and End Results (SEER) database and other Western cancer registries suggest that CRC incidence is increasing in the under age 50 group while it is decreasing in older groups [25,26]. On multivariate analysis of the risk factors for cancer colon in our study, the presence of rectal bleeding, and weight loss were significant predictors of having rectal cancer. Both of blood in stool and unintended weight loss are documented red flag signs that should raise suspicion of malignant lesion in cases previously diagnosed with irritable colon [27]. The presence of diarrhea was protective against having cancer colon on multivariate analysis in our study. Colorectal cancer leads to a significant alternation in bowel habits, mainly in the form of constipation. If diarrhea is present, it is often of the spurious not the true type [28]. This also supports our findings. When it comes to the detection of S. galloyticus in the current study, it was detected on the surface of 64.4 and 18.8% of cases and controls respectively (p < 0.001). In addition, it was detected in the tissue of 35.4 and 6.2% of cases and controls respectively (p < 0.001). This denotes the higher prevalence of S. galloyticus colonization in colon cancer cases. The association of S. galloyticus with colorectal cancer has been described through the incidence of S. galloyticus bacteremia and/or endocarditis [29]. Similarly, Abdulamir et al. reported that S. galloyticus were found to be remarkably isolated in tumorous and non-tumorous tissues of colorectal cancer with bacteremia, 20.5% and 17.3%, and colorectal cancer without bacteremia, 12.8% and 11.5%, respectively while only 2% of control tissues revealed the same organism (p < 0.05). Nevertheless, such contrast was not found in mucosal isolation [30]. Moreover, Paritsky and his colleagues reported that cases who expressed positivity for the presence of S. galloyticus in their colon had significantly higher incidence of colonic polyps (22.4 vs. 5.2% in negative cases – p = 0.0003), and malignant colonic tumors (34.7 vs. 0% in negative cases – p < 0.0001) [31]. Our findings also confirmed the previous data that correlated the association of S. galloyticus with colorectal cancer [32]. However, Burns et al. did not get the same findings; they found that the incidence of galloyticus carriage in all colons with polyps was intermediate between normal colons and colons with carcinoma; however, the difference did not achieve statistical significance [33]. As cancer colon usually follows the adenoma carcinoma sequence, the incrimination of S. galloyticus bacteria in colonic adenoma makes it a contributing factor in cancer colon pathogenesis [34]. In the current study, univariate analysis showed that diarrhea was a significant risk factor for having surface S. galloyticus. Whereas no significant predictors for colonizing S. galloyticus in tissues (p < 0.05). Dumke and his associates
reported that closer contacts with animals and the usage of animals’ waste as significant risk factors for the detection of *S. galloyticus* in human feces [35]. Our study has some limitations; first, it is a single center study, and the included sample size was relatively small. Besides, the presence of *streptococcus* bacteremia should have been assessed as well.

**Conclusion**

Our study showed higher prevalence of *S. galloyticus* colonization in colon cancer cases, therefore early detection of *S. galloyticus* in cases of colorectal adenomas might be of high value in screening high-risk groups for colorectal cancer.

**Availability of data and material**

It is further warranted that the article is original that it is not under consideration by another journal at this time, and that neither the text nor the data reported have been published previously.

**Authors’ contributions**

Each undersigned author warrants that he or she has participated sufficiently in the work described to justify authorship as defined by the International Committee of Medical Journal Editors.

**Consent for publication**

The undersigned authors transfer all copyright ownership of the manuscript entitled [Association between Streptococcus galloyticus and Colorectal Cancer in Mansoura University hospital] to the *Egyptian Journal of Basic and Applied (EJBAS)*, in the event the work is published.

**Ethics approval and consent to participate**

All the data were collected after approval of institutional research board (IRB) of Medical Faculty of Mansoura University (Code number: MS.19.05.648). Informed written consent was taken from all study participants.

**Disclosure statement**

No potential conflict of interest was reported by the author(s).

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