Risk of colorectal cancer due to *Streptococcus galloyticus*: a systematic review

Edre Mohammad Aidid, DrPH1, Mohd Shaiful Ehsan Shalihin, MMED FAM MED2, Azmi Md Nor, MMED Surgery3, Hairul Aini Hamzah, PhD4, Nurul Fatihah Ab Hamid, MBBS5, Nur Arfa Nadhirah Saipol Bahri, MBBS5, Nuha Dini Ab Ghani, MBBS5

1Department of Community Medicine, Kulliyyah of Medicine, International Islamic University, Kuala Lumpur, Malaysia, 2Department of Family Medicine, Kulliyyah of Medicine, International Islamic University, Kuala Lumpur, Malaysia, 3Department of Surgery, Kulliyyah of Medicine, International Islamic University, Kuala Lumpur, Malaysia, 4Department of Basic Medical Science, Kulliyyah of Medicine, International Islamic University, Kuala Lumpur, Malaysia, 5Kulliyyah of Medicine, International Islamic University, Kuala Lumpur, Malaysia

**ABSTRACT**

Introduction: World Health Organization (2019) has declared colorectal cancer (CRC) as the second most common cancer in females and third in males, where the incidence seems to rise year by year. One of the very few potential pathogens specifically associated with malignant colonic diseases is *Streptococcus galloyticus* (Sg). Sg is a part of the intestinal flora which formerly known as biotype I of *Streptococcus bovis*, belongs to Group D streptococci. Owing to only a few researches done in determining evidence to support Sg as a determinant of CRC, a systematic review is constructed.

Materials and Methods: Full-text articles on case-control and cohort studies published from 1st January 2010 to 1st October 2020 were searched using Google Scholar, PubMed and JSTOR. People of all age groups and Sg bacteraemia or colonisation were the type of participant and exposure used for the search strategy, respectively. Data collection was done by three reviewers and checked by two reviewers for discrepancies. All the papers were critically appraised using the STROBE statement. Qualitative synthesis was done by descriptive comparison, distribution of Sg according to stage comparison, method used for Sg detection comparison and risk of bias comparison.

Result: Seven out of 11 articles that fulfil the eligibility criteria were selected. Four papers have low overall risk of bias due to low confounding or selection bias. Sg is found to be a risk factor for CRC from three papers studied, whereas the other four papers did not include the strength of association. Only two papers studied the association between the distribution of Sg and stages of CRC, where the results were contradictory from each other, making it to be inconclusive. The most common method used for Sg detection is a culturing technique, followed by molecular and biochemical techniques.

Conclusion: There is insufficient evidence to prove the association between Sg bacteraemia as the risk factor for CRC as well as the association between the Sg distribution and stages of CRC. Culturing technique is the most common method used for the detection of bacteria, but it requires subsequent investigations to confirm the presence of Sg. Thus, it is recommended that more studies need to be done using strong statistical analysis to control for most of the confounders with comprehensive explanation and use of more methods in the detection of Sg.

**KEYWORDS:**

*Streptococcus galloyticus*, colorectal cancer, case–control studies, cohort studies, systematic review

**INTRODUCTION**

World Health Organization 2019 reported CRC as the second most common cancer in females and third in males. In 2018, 861,000 deaths and 1.8 million new cases were notified. The number of new cases is expected to be more than 2.2 million cases which account for 60% increase and 1.1 million deaths by 2030. Among the well-established risk factors are unhealthy nutrition, smoking, ageing, polyps, gene and gastrointestinal infection. One of the very few potential pathogens specifically associated with malignant colonic diseases is Sg.

Sg which is formerly known as biotype I of *Streptococcus bovis*, belongs to Group D streptococci, a broad group of genetically diverse bacteria known as *S. bovis/S. equinus complex* (SBSEC). In 2.5 to 15 percent of people, Sg is a part of the intestinal flora. Various studies have shown that cytokine-based effects of long-lasting bacterial inflammation were the main element of transformative changes in the colorectal mucosa. From several epidemiological studies, it was found that the association of Sg and CRC ranges from 47% to 85%. These variations were almost certainly due to different methods being used for Sg detection or possibly due to differences in selected populations.

Currently, there are a lot of tools used for the detection of Sg but the most common method is still not well established. The same goes with the association of Sg and CRC, where there was only few research made. Hence, a systematic review is done.

**MATERIALS AND METHODS**

The primary objective of this systematic review is to identify evidence to support Sg bacteraemia or colonisation as a risk...
factor for colorectal cancer (CRC). Secondary objectives would be to determine the most common method used to detect Sg bacteraemia or colonisation and to know there is any association between Sg load and CRC stages.

Criteria for considering studies for this review:

- Types of studies: Case–control or cohort study designs.
- Types of participants: People of all age groups.
- Types of exposures: *Streptococcus gallolyticus* or *Streptococcus bovis*.

**Search methods for identification of studies (including PRISMA flowchart)**

Case–control and cohort studies published from 1st January 2010 to 1st October 2020 were searched using PubMed, J-Store and Google Scholar. A total of 37 full-text articles were selected. Three elements of the search strategy were developed using the Boolean term ‘AND’ or ‘OR’:

1. Exposure subject heading: (*Streptococcus gallolyticus* OR *Streptococcus bovis*) AND
2. Disease subject heading: ((Colorectal Cancer OR Neoplasm OR Malignancy)) AND
3. Study design subject heading: ((Case-control OR Cohort))

The search strategy resulted in a total of seven studies that were included in this review. The PRISMA flow diagram for the search strategy is summarised in Figure 1.

**Data Collection and Analysis**

Data collection was done by three reviewers and checked by two reviewers, consisting of medical doctor from the Department of Community Medicine and medical students, Kulliyyah of Medicine, International Islamic University Malaysia. All the papers were critically appraised using the STROBE statement.

Qualitative synthesis was done by descriptive comparison, distribution of Sg according to stage comparison, method used for Sg detection comparison and risk of bias comparison. Meta-analysis was not done due to difficulty in obtaining some of the estimates which were not reported in the articles.

**RESULT**

**Descriptive Result**

Table 1 depicts the descriptive study of the seven articles selected for the review.

**Risk of Bias in Included Studies**

The overall risk of bias is based on the author’s judgement and discussion with other reviewers for this systematic review as listed in Table II below.

**Distribution of Streptococcus gallolyticus according to stages of CRC**

Table III shows the distribution of Sg according to stages of CRC in two selected articles.

**Most common method of Sg detection in Sg bacteraemia and colonisation**

Table IV portrays the comparison of methods and tools used to detect Sg infection in bacteraemia and colonisation.

**DISCUSSION**

**Descriptive Studies**

In the current review, we found seven studies that determining the association between Sg with colorectal cancer. The main findings and level of evidence are demonstrated in Tables I and II, respectively. Out of these seven studies, Tsai et al., 2016 and Kwong et al., 2018 has taken other alternative way to Sg infection as a risk factor in colorectal cancer patients by conducting retrospective cohort studies.\(^{7,4}\)

There was a wide range in number of participants involved in each study. Boltin et al., 2015, Al Sharara et al., 2013 and Kwong et al., 2018 use good cases to control ratio which is more than 4, hence selection bias can be controlled.\(^{8,10}\) Moreover, the study population in previous studies involved multiple countries, covering each continent which means the association of Sg and colorectal cancer is an established risk factor for the world population and not constricted to certain population only.

Al Sharara et al., 2013 significantly demonstrated those with Sg bacteraemia will have 21.6 times high risk to develop colorectal carcinoma compared to those who not being infected.\(^{11}\) This is supported by Corredoira-Sánchez et al., 2012 and Kwong et al., 2018 which depict 5.1 and 3.87 times more risk, respectively.\(^{8,10}\) Boltin et al., 2015 and Tabl et al., 2019 also found a correlation between Sg bacteraemia with colorectal cancer; however, the strength of association is not being divulged by the author.\(^{8}\)

In addition, Rezasoltani et al., 2018 in their paper, they found out there is an association between Sg with colorectal polyp that is showing medium to high dysplasia grade.\(^{11}\) This finding can be another clue to support the association, taken into account that 90% of cases with benign condition of colorectal polyp is the precursor for developing colorectal cancer.\(^{11}\) Tsai et al., 2016 on the other hand, revealed those who were diagnosed with colorectal cancer with Sg bacteraemia has 12.37 times the risk of getting comorbid malignancy.\(^{7}\)

**Risk of Bias**

There were four studies with low risk of bias. Theoretically, the observation of a case–control study is retrospective. However, all of the case–control studies observed both CRC and Sg simultaneously. One study may have the lowest selection bias as the eligibility criteria were clearly mentioned compared to other studies in which the selection criteria for both cases and controls include antibiotic or probiotic utilisation, symptoms of fever and diarrhoea, history of lower...
<table>
<thead>
<tr>
<th>Author</th>
<th>Study Design</th>
<th>Sample Size</th>
<th>Population</th>
<th>Period (Year)</th>
<th>Exposure</th>
<th>Outcome</th>
<th>Odd ratio/relative risk (confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boltin et al., 2015</td>
<td>Case–control</td>
<td>15 cases, 103 controls</td>
<td>Patients presenting for colonoscopy Clalit Health Services, Israel</td>
<td>Between January 1998 and December 31, 2014</td>
<td>Streptococcus bovis</td>
<td>Colorectal neoplasia</td>
<td>-</td>
</tr>
<tr>
<td>Corredoira- Sánchez et al., 2012</td>
<td>Case–control</td>
<td>98 cases, 196 controls</td>
<td>From a single center (more information is not provided)</td>
<td>Between 1988 and May 30, 2011</td>
<td>Streptococcus galolyticus subsp. galolyticus</td>
<td>Colorectal neoplasia</td>
<td>5.1 (3.0–8.6) [&lt;0.05]</td>
</tr>
<tr>
<td>Al Sharara et al., 2013</td>
<td>Case–control</td>
<td>10 cases, 200 controls</td>
<td>From database of Microbiological Laboratory at American University of Beirut Medical Center</td>
<td>Between January 1996 and October 2010</td>
<td>Streptococcus bovis</td>
<td>Colorectal neoplasia</td>
<td>21.6 (5.4–86.1) [&lt;0.05]</td>
</tr>
<tr>
<td>Tabl et al., 2019</td>
<td>Case–control</td>
<td>35 cases, 20 controls</td>
<td>Patient attending the Departments of General Surgery and Hepatology, University Hospitals</td>
<td>Between October 2016 and August 2018</td>
<td>Streptococcus galolyticus</td>
<td>Colorectal cancer</td>
<td>-</td>
</tr>
<tr>
<td>Rezasoltani et al., 2018</td>
<td>Case–control</td>
<td>87 cases, 31 controls</td>
<td>Patients attending Department of Surgery Taleghani Hospital, Tehran- Iran</td>
<td>Between January 1, 2015 and December 31, 2017</td>
<td>S. bovis/ galolyticus</td>
<td>Colorectal polyp with medium to high dysplasia grade</td>
<td>-</td>
</tr>
<tr>
<td>Tsai et al., 2016</td>
<td>Retrospective cohort</td>
<td>34 cases, 15 controls</td>
<td>From database records of Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan</td>
<td>Between January 2004 and January 2014</td>
<td>Streptococcus bovis with colorectal cancer</td>
<td>Other malignancy</td>
<td>12.376 (2.207-69.402) [&lt;0.05]</td>
</tr>
<tr>
<td>Kwong et al., 2018</td>
<td>Retrospective Cohort</td>
<td>662 cases, 3310 controls</td>
<td>Public hospitals in Hong Kong</td>
<td>Between January 1, 2006 and December 31, 2015</td>
<td>Streptococcus bovis</td>
<td>Colorectal cancer</td>
<td>3.87 (2.34-6.42) [&lt;0.05]</td>
</tr>
</tbody>
</table>
### Table II: Risk of bias in reviewed studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Selection bias</th>
<th>Exposure assessment bias</th>
<th>Confounder</th>
<th>Other bias</th>
<th>Overall risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boltin et al., 2015</td>
<td>Low</td>
<td>Low</td>
<td>High as strategies to control the confounding factors were not stated</td>
<td>None is identified</td>
<td>Low</td>
</tr>
<tr>
<td>Corredoira-Sánchez et al., 2012</td>
<td>Low due to lack of description on source population and eligibility criteria for cases and controls.</td>
<td>Low</td>
<td>None is identified</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>Al Sharara et al., 2013</td>
<td>High because controls were not representative of source population of cases and lack of description on eligibility criteria.</td>
<td>Low</td>
<td>None is identified</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>Tabl et al., 2019</td>
<td>Low</td>
<td>Low</td>
<td>None is identified</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>Rezasoltani et al., 2018</td>
<td>Low</td>
<td>Low</td>
<td>None is identified</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>Tsai et al., 2016</td>
<td>Low</td>
<td>Low</td>
<td>None is identified</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>Kwong et al., 2018</td>
<td>Low</td>
<td>Low</td>
<td>None is identified</td>
<td>Low</td>
<td></td>
</tr>
</tbody>
</table>

### Table III: Distribution of Streptococcus gallolyticus according to stages of CRC

<table>
<thead>
<tr>
<th>Author</th>
<th>Method of Streptococcus gallolyticus detection</th>
<th>Distribution of Streptococcus gallolyticus according to stages</th>
<th>P-value / CI</th>
</tr>
</thead>
</table>
| Tabl et al., 2019 | 1. Bacteriological isolation  2. Molecular detection | Sg negative  
n = 22  
Stage 1: 40.9%  
Stage 2: 18.2%  
Stage 3: 27.3%  
Stage 4: 13.6%  
Sg positive  
n = 13  
Stage 1: 7.7%  
Stage 2: 30.8%  
Stage 3: 46.2%  
Stage 4: 15.4% | >0.05 |
| Kwong et al., 2018 | 1. Culture | Sg negative with CRC  
n = 39  
Sg positive with CRC  
n = 25  
Stage 1 or 2: 68%  
Stage 3 or 4: 32% | <0.05 |
GI surgery and pregnancy or lactation. These factors were relevant to prevent an altered microenvironment of the large intestine that may lead to bias in Sg measurement.

According to Eshaghi et al., both culture and molecular methods were recommended to obtain a faster result or when there is a possibility of sample infection and late-growing microorganisms. Thus, it is agreed that Sg assessment needs at least two methods of measurement or investigations to avoid bias. For the purpose of discussion, techniques to grow the organism, such as culture, will not be considered as a method of measurement. Four out of seven studies have low exposure assessment bias as they have two methods of Sg measurement and similarly assessed for both case and controls.

Table IV: Methods used for detection of Streptococcus galloolyticus in Streptococcus galloolyticus bacteraemia and colonisation

<table>
<thead>
<tr>
<th>Author</th>
<th>Source of samples</th>
<th>Molecular technique</th>
<th>Culture</th>
<th>Microscopy</th>
<th>Biochemistry</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boltin et al., 2015</td>
<td>Stool, colonic fluid, or colonic tissue</td>
<td>Blood</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Correidoira-Sánchez et al., 2012</td>
<td>Blood</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Al Sharara et al., 2013</td>
<td>Blood</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tabl et al., 2019</td>
<td>Blood</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rezasoltani et al., 2018</td>
<td>Fecal material</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tsai et al., 2016</td>
<td>Blood</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kwong et al., 2018</td>
<td>Blood</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>4</td>
<td>6</td>
<td>2</td>
</tr>
</tbody>
</table>

Confounder is defined as a variable that has an association with the outcome, associated with the exposure and not a factor in the causal pathway of the disease. Adjustment of confounder is essential to prevent false measurement of association between exposure of interest and outcome. For the purpose of discussion, confounders are considered as well-
known risk factors for colorectal cancer. Most of the studies
control the confounders by matching the age and gender of
controls to the cases.2,4,10,11 This is fitting to the study as it is
found that male gender has 1.5 times higher risk to develop
CRC while old age is a well-known risk factor for CRC.16

**Distribution of Sg According to Stages**

Sg is well-known for its relation to colorectal cancer, and this
connection should be thoroughly studied in order to reduce
the burden of CRC.11 In this current review, the percentage of
CRC cases according to its stages is looked upon and
compared with the distribution of Sg. Recent research by
Kwong et al., 2018 showed 68% of CRC patients with positive
Sg infection have Stage 1 or 2 CRC compared to only 32% for
stages 3 or 4 with the significant association.11 This is in line
with another paper by Abdulamir et al., 2009 which also
stated that early-stage adenomas have more incidence with
the presence of Sg than later-stage carcinomas.11 The
association between the presence of Sg and these early stages
of CRC is vital and might aid in detecting disease sooner, thus
preventing further deterioration of diseases. In addition, most
patients with colorectal cancer in Malaysia have been
diagnosed at a late stage, and if compared with other
developed Asian countries, Malaysia has a lower 5-year
relative survival by stage.11 Hence, by knowing these
predominant stages of CRC in relation to the distribution of
Sg, precautionary measures can be taken appropriately to
ensure early detection of disease which can be done with
various available methods and tools for Sg identification.

**Most Common Method of Sg Detection in Sg bacteraemia
and Colonisation**

There is wide variation in the association of Sg and CRC
across different studies. The discrepancies and variations in
association of Sg and CRC across different studies may result
from different genetic background, geographical differences
as well as different methods for Sg detection or specimens
used.11 To our knowledge, currently, there are no validated
tools to diagnose Sg infection. This could be a reason why
there are differences in choices of methods and preparation to
detect Sg. From the current review, it is found that six out of
seven studies use culturing techniques in detecting Sg.
However, it is important to note that most of the culture
methods were used to grow the bacteria for use in subsequent
investigations such as biochemical tests and microscopy. It is
found that positive Sg detection almost certainly needs
enrichment media.11 From the bacterial culture, most of the
isolates were tested biochemically to identify Sg. A recent
study that compares culture and molecular methods in the
detection of Sg concluded that both of the methods are
currently deemed inadequate or standard, thus both
investigations done simultaneously are recommended for the
identification of Sg.11 From this review, it is advocated for
future researchers to provide a comprehensive description of
Sg detection for further references and more studies done on
the tool sensitivity and specificity in the detection of Sg.

**CONCLUSION AND RECOMMENDATION**

The authors conclude that there was insufficient evidence to
prove the association between Sg bacteraemia or colonisation
as the risk factor for CRC. Only three out of seven papers that
are being studied showed a significant association between
these two variables. Plus, the other three papers did not
include the strength of association in their study. Hence, they
are inconclusive. On the other hand, the association between
Sg load and colorectal cancer stages is significantly proved by
one study. However, the finding is uncertain considering the
high risk of bias. Culturing technique is the most common
method used to detect *Streptococcus gallolyticus* bacteraemia
or colonisation. Even so, it still requires further investigations
to confirm the presence of *Streptococcus gallolyticus*. However,
results from this review should be interpreted with caution
due to the small number of studies obtained from this
systematic review and the possibility of publication bias.

Patients that are found to be infected with Sg in any
pathology are recommended to do colonoscopy or faecal
occult blood test for CRC screening. More studies need to be
done to determine the association between the distribution of
Sg and stages of CRC. A comprehensive explanation of Sg
detection and two or more methods of detection is
recommended for further studies. Further research is
warranted using strong statistical analysis to control for most
of the confounders as well as to do research for different
target populations and meta-analysis of high-quality
randomised controlled trials.

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