MAJOR ARTICLE

Clinical Importance of *Streptococcus gallolyticus* Infection Among Colorectal Cancer Patients: Systematic Review and Meta-analysis

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Background. *Streptococcus bovis* has long been associated with colorectal cancer (CRC). However, not all genospecies are as closely related to CRC. With this systematic review, we aim to increase the awareness of the association between *S. bovis* biotype I (*Streptococcus gallolyticus*) and CRC and urge for uniform molecular microbiological classification.

Methods. In January 2011, the PubMed database was searched for all studies that investigated the association between *S. bovis*, infective endocarditis (IE), and CRC. A total of 191 studies were screened for eligibility and yielded 52 case reports and 31 case series, of which 11 were used for meta-analysis on the association between *S. bovis* biotype, IE, and adenomas/carcinomas (CRC).

Results. Among the *S. bovis*–infected patients who underwent colonic evaluation, the median percentage of patients who had concomitant adenomas/carcinomas was 60% (interquartile range, 22%), which largely exceeds the disease rate reported in the general asymptomatic population. Meta-analysis showed that patients with *S. bovis* biotype I infection had a strongly increased risk of having CRC (pooled odds ratio [OR], 7.26; 95% confidence interval [CI], 3.94–13.36) and IE (pooled OR, 16.61; 95% CI, 8.85–31.16), compared with *S. bovis* biotype II–infected patients. Notably, CRC occurred more often among patients with *S. bovis* IE than among patients with *S. bovis* infection at other sites (pooled OR, 3.72; 95% CI, 2.03–6.81).

Conclusions. Our meta-analysis clearly indicates that *S. bovis* should no longer be regarded as a single species in clinical practice, because *S. gallolyticus* (*S. bovis* biotype I) infection, in particular, has an unambiguous association with CRC.

The association between streptococcal endocarditis and colorectal cancer (CRC) was first reported in 1951 by McCoy and Mason [1]. In the 1970s, this association was rediscovered by Hoppes and Lerner, who reported that among 14 *Streptococcus bovis* endocarditis cases, 9 (64%) had concomitant gastrointestinal disease [2]. This was supported by the finding that the fecal carriage rate was approximately 5 times higher in patients with CRC than in healthy control subjects [3]. Of importance, several of these patients with villous adenoma or carcinoma had no clinical signs or symptoms referable to gastrointestinal cancer [3]. Consequently, cancer was solely discovered on the basis of *S. bovis* infection in these patients.

Since the publication of these remarkable associations, a vast amount of case studies on *S. bovis* infection with underlying occult CRC have been published. However, restrictions of the phenotypic microbiological typing techniques used in many of these studies [4] has hampered distinction between the 3 known *S. bovis* biotypes I, II/1, and II/2. In an attempt to modernize and harmonize molecular classification of *S. bovis* subspecies, Schlegel et al [5] proposed in 2003 to rename

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these biotypes into *Streptococcus gallolyticus* subsp *gallolyticus*, *Streptococcus infantarius* subsp *infantarius* (II/1), *S. infantarius* subsp *coli* (II/1), and *S. gallolyticus* subsp *pasteurianus* (II/2), based on molecular characteristics (Table 1) [6–8]. The latter nomenclature has been embraced by some but not by the majority of studies that have appeared in literature since then. This lack of uniform microbiological classification in scientific literature has led to an underestimation of the relationship between *S. bovis* and CRC, because not all genospecies seem to be as closely related to colonic malignancies. With this systematic review, we aim to increase the awareness of the specific association between *S. gallolyticus* subsp *gallolyticus* (biotype I) and CRC. Furthermore, we urge for proper classification of *S. bovis*–related strains to increase the understanding of disease pathology, which could have major implications for the early detection of CRC and patients' health.

METHODS

Data Sources and Study Selection

In January 2011, a total of 4 independent searches of PubMed (www.ncbi.nlm.nih.gov/pubmed) were performed using the following search terms: "*Streptococcus bovis* AND colorectal cancer (MeSH terms)," "*Streptococcus gallolyticus* AND colorectal cancer (MeSH terms)," "*Streptococcus infantarius* AND colorectal cancer (MeSH terms)," "*Streptococcus pasteurianus* AND colorectal cancer (MeSH terms)," "*Streptococcus bovis* and malignancy," and "endocarditis AND colorectal cancer (MeSH terms)." After elimination of duplicates, this yielded a total of 191 records. Studies that reported infection with *S. bovis* or one of its subspecies were selected for individual evaluation. Case series from the period during 1970–2010 with a clear description of CRC rates among *S. bovis*–infected patients aged >20 years were selected for further evaluation. All narrative literature reviews, studies that were not published in the English language, and studies comprising in vitro research were excluded. Thus, a total of 52 case reports and 31 case series were included in this review. Of the 31 case series, 11 provided detailed information (see below) suitable for inclusion in the meta-analysis (Supplementary Figure 1; online only).

Data Extraction

The 52 case reports were screened for the following information: type of infection, *S. bovis* biotypes involved, stage of premalignant and malignant lesions, and underlying diseases other than CRC. The 31 case series were screened to extract the following information: number of patients, mean age of patients, number of gastrointestinal evaluations, number of infective endocarditis (IE) cases, biotypes reported, number of adenomas and carcinomas, and presence of other infections or gastrointestinal disorders. Adenomas include neoplastic polyps (adenomatous polyps, villous adenomas, tubular adenomas, and adenomas) but exclude nonneoplastic polyps (Supplementary Table 1; online only). Because most articles did not use the genotypic designation of the *S. bovis/Streptococcus equinus* complex (Table 1) [5], we used the former phenotypic designation and assumed that species that were characterized as *S. bovis* biotype I belonged to the genospecies *S. gallolyticus* subsp *gallolyticus*. The synonyms for the different genotypes (Table 1) were used throughout this review, and the *S. bovis* biotype II strains were grouped together, because 6 studies did not specify the number of species belonging to biotype II/1 and II/2. When no further classification was reported, the general term "*S. bovis*" was used. From these data, the CRC occurrence among all patients with *S. bovis* infection and among colonic evaluated subjects was calculated. Unless stated otherwise, the term "CRC" relates both to carcinomas and to adenomas. CRC occurrence was subcategorized by *S. bovis* biotype when possible. The median prevalence with corresponding interquartile range (IQR; defined as Q3–Q1) was calculated for a combined overview of the case series. The methods used to determine the rate of CRC, the *S. bovis* biotype involved, and the presence of IE are presented in Figure 1.

Table 1. Nomenclature of the Principal Human Species of the *Streptococcus bovis/Streptococcus equinus* Complex

New name	Former phenotypic designation	Synonym
Streptococcus gallolyticus subsp *gallolyticus*	*S. bovis* biotype I	*S. gallolyticus*
Streptococcus infantarius subsp *infantarius*	*S. bovis* biotype II/1	*S. infantarius*
S. infantarius subsp *coli*	*S. bovis* biotype II/1	*Streptococcus lutiensis*
S. gallolyticus subsp *pasteurianus*	*S. bovis* biotype II/2	*Streptococcus pasteurianus*

Abbreviation: subsp, subspecies.

Meta-analysis

For quantitative meta-analysis, 11 of the 31 case series were selected that discriminated between *S. bovis* biotypes or between IE and other infection sites. The aim of this meta-analysis was to assess the risk of CRC or IE among *S. bovis* biotypes. Furthermore, the risk of CRC among *S. bovis* IE or infections at other sites was assessed. Data were extracted independently by 2 reviewers, and discrepancies in data extraction were resolved by repeated manuscript review to reach consensus. We reported only patients who underwent gastrointestinal evaluation when possible. We calculated odds ratios (ORs) with 95% confidence intervals (CIs) for all studies with sufficient data on the previously specified associations. Pooled ORs were calculated as the weighted mean of the ORs for the associations of interest. Weights were assigned according to the inverse of the variance.

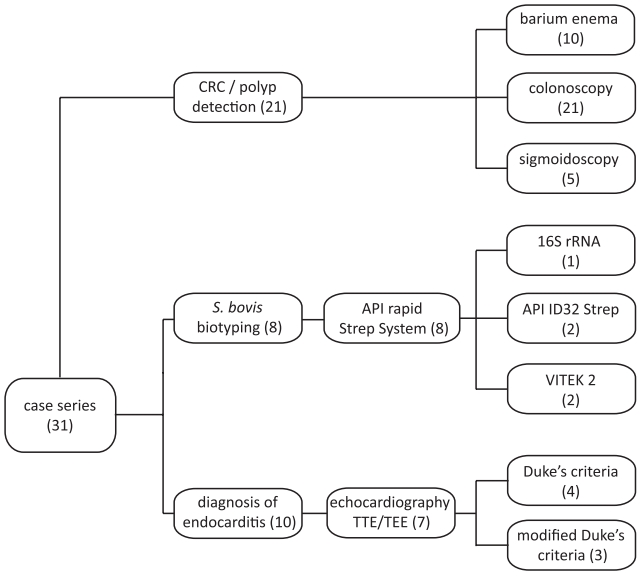

Figure 1. Flow diagram of methods used to assess biotype, infective endocarditis (IE), colorectal cancer (CRC). This flow-diagram shows the methods used for the determination of *S. bovis* biotypes, diagnosis of IE, and assessment of colonic disease in 31 case series. The number of studies that used the indicated method is shown in brackets. In 21 of these case series, colonic evaluations were performed. Abbreviations: TEE, transesophageal echocardiography; TTE, transthoracic echocardiography.

Heterogeneity was tested using χ^2 tests and was quantified using the I^2 statistic [9]. Because all values of the I^2 statistic were $<50\%$, fixed-effects models were used. Statistical analyses were performed using RevMan software version 5.0.25 for Windows (The Nordic Cochrane Centre, The Cochrane Collaboration).

RESULTS

Case Reports and Case Series

A total of 52 case reports from the period 1951–2010 were reviewed (Supplementary Table 2; online only). Evaluation of these case reports showed that *S. bovis* IE might be associated with CRC. However, evaluation of case reports may introduce selection bias, which could lead to an overestimation of the observed association. Therefore, 31 case series were investigated to examine the relationship between *S. bovis* biotypes, IE, and CRC in an evidence-based manner. Of the 31 included case series, 24 retrospectively and 7 prospectively included *S. bovis*–infected patients [2, 8, 10–38]. The age of patients was reported in 29 studies and ranged from 48 to 74 years, with a mean age of 64 years. From these data, the proportion of *S. bovis*–infected patients who had concomitant CRC (both adenomas and carcinomas) was calculated (Table 2). The median prevalence of CRC among *S. bovis*–infected patients was 39% (IQR, 24%) (Figure 2). However, not all persons underwent colonic evaluation, and therefore, lesions could have easily been missed, resulting in underestimation of the actual prevalence of CRC among *S. bovis*–infected patients. When only the colonic-evaluated patients were taken into account, the median prevalence of CRC among *S. bovis*–infected patients markedly increased to 60% (IQR, 22%). In 20 of these case series, a distinction was made between adenomas and carcinomas. Strikingly, the median prevalence of carcinomas was 18% (IQR, 13%), whereas that of adenomas was 43% (IQR, 22%). This could suggest that *S. bovis* infection is predominantly associated with premalignant colonic lesions. Unfortunately, only the study by Hoen et al [20] investigated the proportion of CRC in an age-matched control population. They reported adenomas and carcinomas in 27% of healthy control subjects, compared with 56% of *S. bovis*–infected patients (Table 2). The general population aged 60–70 years had a rate of 0.3% for carcinomas and 10%–25% for adenomas (Figure 2) [39–43]. Together, these data make it presumable that *S. bovis*–infected individuals have increased rates of both adenomas and carcinomas.

Biotypes and Colorectal Cancer

A total of 12 case series provided detailed information on *S. bovis* biotypes. Of these studies, 3 provided the number of *S. bovis* biotype I and II infections but did not report the number of CRC cases stratified by biotype [28, 36, 38]. Another 3 studies comprised almost exclusively *S. bovis* biotype I–infected patients, with reported prevalence of CRC of 33%, 52%, and 59% (Table 2) [26, 29, 34]. The remaining 6 studies were included in the meta-analyses [8, 18, 31, 32, 35, 37] and showed that patients with a *S. bovis* biotype I infection had a statistically significantly increased risk of CRC, compared with *S. bovis* biotype II–infected individuals (pooled OR, 7.26; 95% CI, 3.94–13.36) (Figure 3). However, it should be noted that the inconsistent naming of *S. bovis* because of characterization through phenotypic and genotypic methods could have biased the results of this analysis. Nonetheless, from these studies, it is evident that infection with *S. bovis* biotype I, currently known as *S. gallolyticus*, is strongly associated with CRC (prevalence range, 33%–71%) that markedly exceeds the normal prevalence of CRC (10%–25%) in the general population.

Biotypes and Infective Endocarditis

It has previously been reported that *S. bovis* biotype I infection is more often associated with IE than is *S. bovis* biotype II infection [44]. To investigate this further, 7 case series that stratified the number of IE cases by biotype were selected for statistical analysis [8, 18, 31, 32, 36–38]. This analysis showed that 43%–100% of the *S. bovis* biotype I–infected patients presented with IE, whereas IE was markedly less common (8%–29%) among *S. bovis* biotype II–infected patients (pooled

Table 2. Case Series on *Streptococcus bovis* and Colorectal Cancer

Reference	First author (year)	Mean age, year	Total no. and biotype	No. with CE	No. with IE	No. with adenomas	No. with carcinomas	CRC/total, %	CRC/CE, %	Adenomas/CE, %	Carcinomas/CE, %
[2]	Hoppes (1974)	61	14			2		14			
[10]	Murray (1978)	61	36		26	2	2	11			
[11]	Levy (1978)	74	3	2	3		2	67	100		
[12]	Klein (1979)	70	29	15	13	4	8	41	73	27	53
[13]	Wilson (1981)	59	21		21	4	1	24			
[14]	Reynolds (1983)	72	19	10	14	4	2	32	50	40	10
[15]	Beeching (1985)	66	12	9	10	5	3	67	89	56	33
[16]	Leport (1987)	NR	34	23	34	9	6	44	65	39	26
[17]	Pigrau (1988)	48	16		5		1	6			
[18]	Ruoff (1989)	67	38	12	19		15	39			
			I (17)	*12*	*16*		*12*	*71*	*100*		
			II/1 (12)		*1*		*1*	*8*			
			II/2 (9)		*2*		*2*	*22*			
[19]	Zarkin (1990)	57	92	43	26	9	7	17	37	21	16
[20]	Hoen[a] (1994)	61	32	32		15	3	56	56	47	9
			64	64		15	2	27	27	23	3
[21]	Ballet (1995)	61	53	43	53	16	9	47	58	37	21
[22]	Kupferwasser (1998)	67	22	21	22	4	2	27	29	19	10
[23]	Gonzalez-Quintela (2001)	61	20	13	10	3	3	30	46	23	23
[24]	Duval (2001)	62	20	16	20	8	3	55	69	50	19
[25]	Pergola (2001)	64	40	40	40		4	10	10		10
[26]	Herrero (2002)	65	14	9	14	1	2	21	33	11	22
			I (11)	*9*							
			II/2 (1)								
[27]	Gonzalez-Juanatey (2003)	63	20	13	20	7	1	40	62	54	8
[28]	Lee (2003)	61	37		4[b]		4	11			
			I (2)								
			II/1 (3)								
			II/2 (32)								
[29]	Tripodi (2004)	59	30	28	30[c]	13	1	47	50	46	4
			I (28)	*27*	*28*	*13*	*1*	*47*	*52*		
			II (2)	*1*	*2*		*0*				
[30]	Gold (2004)	74	41	17	12	13	3	39	94	76	18
[31]	Jean (2004)	61	60	19	15		11[d]	18	47		
			I (10)		*8*		*5*	*50*			
			II (37)		*4*		*6*	*16*			
[32]	Corredoira (2005)	67	64		34		27	44			
			I (42)		*31*		*24*	*57*			
			II (22)		*3*		*3*	*14*			
[33]	Alazmi (2006)	56	38	10	7	3	3	16	60	30	30
[34]	Giannitsioti (2007)	63	142[e,f]	92	142	55	5	42	65	60	5
			I (71)	*46*		*24*	*3*	*38*	*59*	*52*	*7*
			II/1 (5)								
			II/2 (3)								

Table 2 continued.

Reference	First author (year)	Mean age, year	Total no. and biotype	No. with CE	No. with IE	No. with adenomas	No. with carcinomas	CRC/total, %	CRC/CE, %	Adenomas/CE, %	Carcinomas/CE, %
[35]	Corredoira (2008a)	NR	133[e]				54	41			
			I (90)				*51*	*57*			
			II/1 (28)				*3*	*11*			
			II/2 (15)								
[36]	Corredoira (2008b)	66	107[g]	71	55	25	4	39	59	49	10
			I (69)		*52*						
			II (38)		*3*						
[8]	Beck (2008)	70	46[e]	15	13	8	3	24	73	53	20
			I (21)		*9*	*5*	*2*	*33*			
			II/1 (14)[h]		*4*	*3*	*1*	*29*			
			II/2 (11)								
[37]	Vaska (2009)	68	20	14	8	5	5	50	71	36	36
			I (10)	*9*	*6*	*2*	*5*	*70*	*78*	*22*	*56*
			II (10)	*5*	*2*	*3*		*30*	*60*	*60*	
[38]	Fernández-Ruiz (2010)	71	59	33	16	15	6	36	64	45	18
			I (12)								
			II (10)								

Numbers in italics represent the cases that have been specified according to biotype I, II/1 and II/2 (see Table 1 for synonyms).

Abbreviations: CE, colonic evaluation; CI, confidence interval; CRC, colorectal cancer (defined as adenomas, comprising adenomatous polyps, villous adenoma, and advanced adenoma, and carcinomas); IE, infective endocarditi; NR, not reported.

[a] 32 cases and 64 controls; risk ratio for developing endocarditis was 3.6 (95% CI, 1.4–9.4) for tumors; 3.4 (95% CI, 1.2–9.2) for adenomas, and 5.7 (95% CI, .9–48.5) for adenocarcinomas.

[b] Includes cases of cholangitis.

[c] Seventeen of 30 patients had concomitant liver disease; 4 patients had both liver disease and colonic neoplasia.

[d] Two patients had CRC prior to *Streptococcus bovis* infection (without colonoscopy).

[e] Subspecies defined in nomenclature by Schlegel et al (see Table 1).

[f] Includes 63 unspecified biotypes.

[g] Endocarditis cases.

[h] *Infantarius* subspecies *coli*.

OR, 16.61; 95% CI, 8.85–31.16) (Figure 3). This finding strongly suggests that *S. bovis* biotype I is a more potent causative agent for IE than is *S. bovis* biotype II.

Infective Endocarditis in Relation to Colorectal Cancer

Because *S. bovis* biotype I, in particular, is strongly associated with both CRC and IE, it can be envisaged that CRC occurs more often among *S. bovis* endocarditis cases than among cases of *S. bovis* infection at other locations. Therefore, 6 case series that stratified the number of CRC cases by infection site were included in this analysis [10, 19, 23, 36–38]. As indicated in Figure 3, the percentage of CRC among patients with IE ranged from 12% to 93%, whereas this was lower among patients with *S. bovis* infection at other locations (10%–50%), yielding a pooled OR of 3.72 (95% CI, 2.03–6.81). Omitting the study of Corredoira et al [36], which contributed almost half of the CRC cases, did not alter the pooled OR substantially (pooled OR, 3.49; 95% CI, 1.22–9.95). This finding confirms that *S. bovis* IE is more likely to relate to an underlying occult colon malignancy than is *S. bovis* infection at other sites. Taken together, these data make it tempting to speculate that *S. bovis* biotype I/*S. gallolyticus*, which is highly associated with both CRC and IE, contains specific virulence factors that links its potency to establish IE with colonic lesions.

DISCUSSION

Summary of Evidence

To our knowledge, this is the first meta-analysis on *S. bovis* infection that evaluated the relationship between different subtypes of this bacterium, infection sites, and adenomatous and carcinomatous colonic lesions. These analyses clearly showed that adenomas or carcinomas (CRC) were significantly more prevalent among patients with *S. bovis* biotype I infection than among patients who were diagnosed with a *S. bovis*

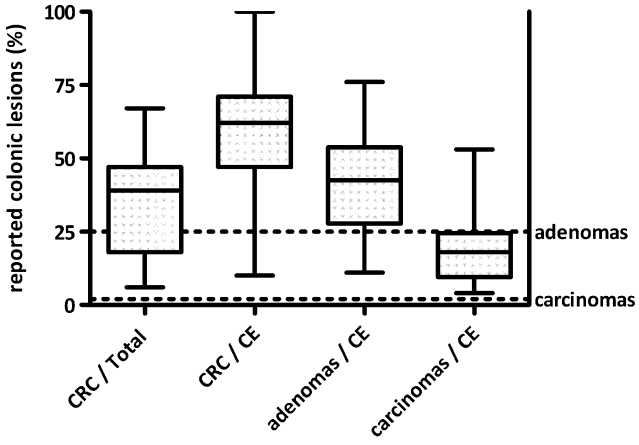

Figure 2. Box-whisker plots of case series. Graphical representation of the occurrence of colorectal cancer (CRC; in %) among all 31 case series (CRC/total) and among a selection of 21 case series that reported the number of gastrointestinal (GI) evaluations (CRC/CE). The combined cases of the latter 21 case series were further subdivided into adenomas (adenomas/CE) and carcinomas (carcinomas/CE). Box-whisker plots show the lowest, first quartile, median, third quartile, and highest values of the percentages reported in Table 2. Dotted lines represent the respective 25% and 0.3% incidences for adenomas and carcinomas in the asymptomatic age-matched population. Abbreviation: CE, colonic evaluation.

biotype II infection. In fact, the incidence of CRC among *S. bovis* biotype II–infected patients may not even exceed that in the general asymptomatic population [39–43]. These different associations may have accounted for the wide prevalence range of CRC that has been reported over the years (Figure 2). Of importance, because most studies did not discriminate *S. bovis* biotypes, the association of *S. bovis* biotype I and CRC has systematically been underestimated. With our current meta-analysis, we emphasize that *S. bovis* biotype I is a sign of occult CRC. Conspicuously, both *S. bovis* IE and CRC are more frequently diagnosed in the older population [44–47]. In this respect, it is important to know that *S. bovis* biotype I has been recently renamed *S. gallolyticus*. We and others have shown that collagen I/IV binding is one of the distinguished features of *S. gallolyticus* strains [48–50]. Superior binding to collagen I on heart valves could be responsible for the increased occurrence of *S. gallolyticus* IE, compared with that caused by other *S. bovis* biotypes. Intriguingly, polyps and early colorectal tumors are surrounded by a continuous and increased expression of collagen IV, which is distinct from healthy tissues [51–53]. Thus, *S. gallolyticus* strains may also have a competitive advantage to colonize collagen-rich premalignant or malignant sites in the intestine. Together, this could explain why *S. gallolyticus* (*S. bovis* biotype I) is strongly associated with both IE and CRC. Recently, *S. gallolyticus* DNA was detected in 49% of CRC tissue samples, whereas only 8% of healthy colonic samples were found to be positive [54], which correlates with increased fecal carriage of *S. bovis* in patients with CRC [3, 55]. Previous research showed that the antibody response against *S. gallolyticus* antigens was significantly increased in patients with early stages of CRC, compared with asymptomatic control subjects [56, 57]. Moreover, *S. bovis* has been cultured from blood samples from asymptomatic individuals with occult CRC [58, 59]. Together, these findings show that these infection can occur at the subclinical level, which accentuates the potency of *S. gallolyticus* as a diagnostic tool for CRC.

Limitations

During the course of this meta-analysis, some difficulties emerged during data extraction and evaluation that could have introduced bias. The first and most important limitation that could have led to information bias was the inconsistent naming of *S. bovis* subspecies among studies. Evolving insights and microbiological techniques have extended the knowledge on its genotypic and phenotypic characteristics [5]. However, this new nomenclature has only slowly been adopted by clinicians and is still not consistently used throughout studies and case reports. Second, for various reasons, not all included patients were screened by colonoscopy, leading to underestimation of the association between *S. bovis* and CRC. Conversely, some studies did not specify whether polyps were adenomas or belonged to nonneoplastic polyps, which could have overestimated the association. Furthermore, most studies included cases based on retrospective chart evaluation, which may have introduced selection bias. For example, if only patients who already were suspected of having gastrointestinal disease were screened, the observed association would have been overestimated. Finally, the diagnosis of IE according to (modified) Duke's criteria is a subjective procedure that is based on the opinion of the individual physician and could therefore differ substantially among hospitals. This could have introduced detection bias across studies [60, 61].

CONCLUSIONS AND RECOMMENDATIONS

The most important conclusion of this meta-analysis is that *S. bovis* biotypes should no longer be regarded as a single species, because *S. gallolyticus* (*S. bovis* biotype I), in particular, has an unambiguous association with CRC. In this respect, we would like to increase the awareness of the new nomenclature of different *S. bovis* subspecies among physicians [62, 63] and recommend that clinical microbiologists, researchers, and physicians use the classification as proposed by Schlegel et al [5], both in clinical practice and in scientific publications (Table 1). To implement such a classification regime implies that, in all cases, molecular genetic techniques should be used for the determination of *S. bovis* group bacteria. Second, we stimulate researchers to conduct properly designed case-control studies,

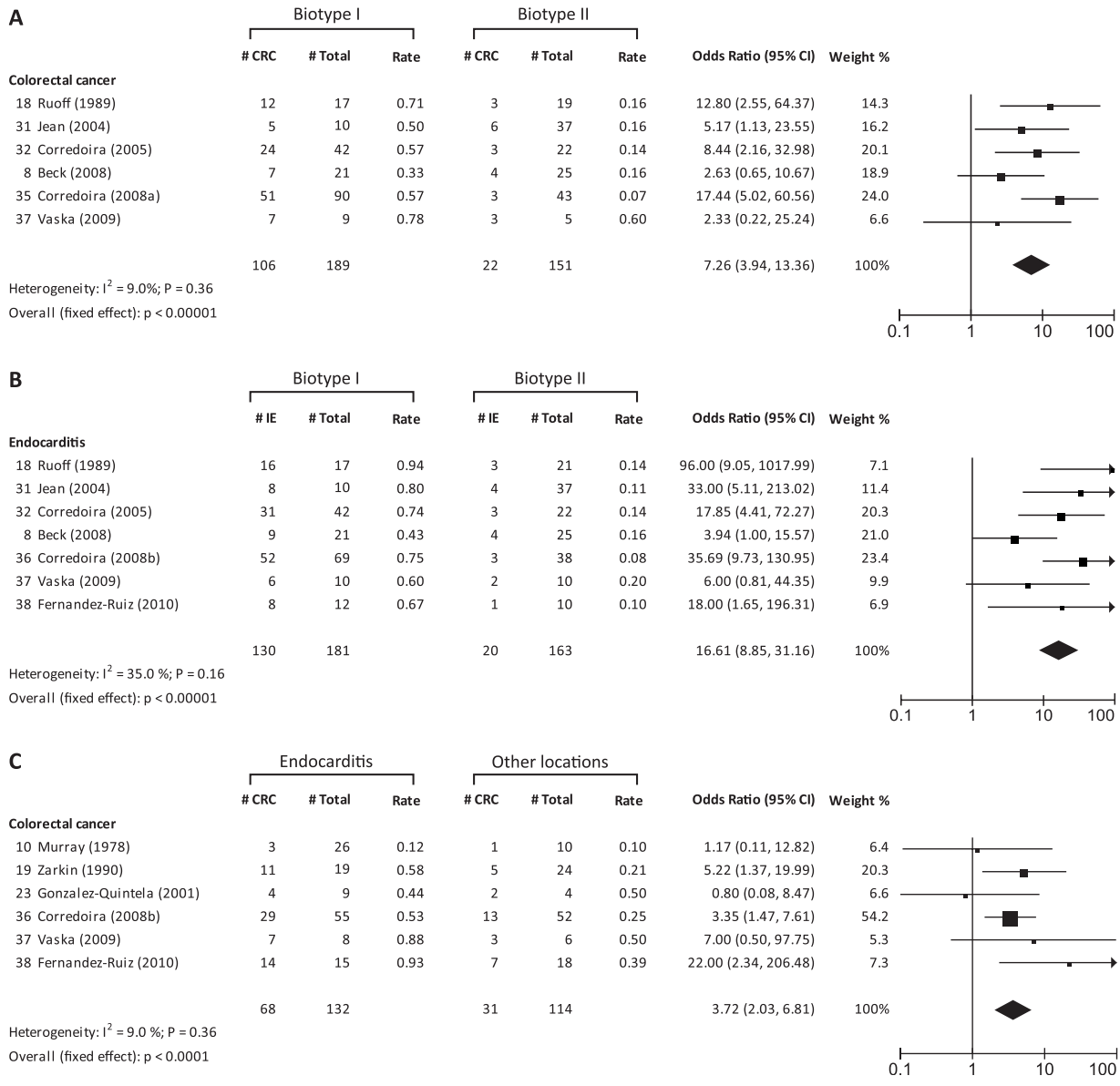

Figure 3. Forest plots on the relationship between biotype, infective endocarditis (IE), and colorectal cancer (CRC). Forest plots were generated to provide a more detailed view on the relationship between *Streptococcus bovis* biotype, IE, and CRC. Pooled odds ratios (ORs) were calculated as the weighted mean of the ORs for the associations of interest. The occurrence of (*A*) CRC and (*B*) IE among *S. bovis* biotype I–infected patients, compared with that among *S. bovis* biotype II–infected patients, and (*C*) CRC among patients with *S. bovis* IE, compared with patients with *S. bovis* infection at other sites, is shown.

including colonoscopic evaluation of all included participants, to further unravel the association between *S. gallolyticus* infection and different stages of CRC. Finally, we encourage research that aims at the elucidation of those virulence features (eg, collagen-binding properties) that are responsible for the specific association between *S. gallolyticus* IE and CRC. We believe that microbiological classification tools based on such features will allow further improvement of the guidelines to screen for underlying occult malignancy in case of bacterial infection. Furthermore, this may provide tools for the early detection of subclinical infections that are associated with CRC in a larger part of the population. The annual incidence of this disease is approximately 1 million cases in Western societies. Unfortunately, approximately 40% of the cases are detected during an advanced stage, resulting in a sharp decline in prognosis. Therefore, the early detection of CRC is one of the great challenges in the battle against this disease. Ultimately, *S. gallolyticus*–related diagnostic tools may aid CRC screening programs and, thereby, contribute to a decrease in the morbidity and mortality associated with this disease.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://www.oxfordjournals.org/our_journals/cid/).

Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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Potential conflicts of interest. All authors: No reported conflicts.

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