



Infective endocarditis and cancer in the elderly

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Abstract Little is known about the magnitude of the association between infective endocarditis and cancer, and about the natural history of cancer patients with concomitant diagnosis of infective endocarditis. We used the SEER-Medicare linked database to identify individuals aged 65 years or more diagnosed with colorectal, lung, breast, or prostate cancer, and without any cancer diagnosis (5 % random Medicare sample from SEER areas) between 1992 and 2009. We identified infective endocarditis from the ICD-9 diagnosis of each admission recorded in the Medpar file and its incidence rate 90 days around cancer diagnosis. We also estimated the overall survival and CRC-specific survival after a concomitant diagnosis of infective endocarditis. The peri-diagnostic incidence of infective endocarditis was 19.8 cases per 100,000 person-months for CRC, 5.7 cases per 100,000 person-months for lung cancer,

1.9 cases per 100,000 person-months for breast cancer, 4.1 cases per 100,000 person-months for prostate cancer and 2.4 cases per 100,000 person-months for individuals without cancer. Two-year overall survival was 46.4 % (95 % CI 39.5, 54.5 %) for stage I–III CRC patients with concomitant endocarditis and 73.1 % (95 % CI 72.9, 73.3 %) for those without it. In this elderly population, the incidence of infective endocarditis around CRC diagnosis was substantially higher than around the diagnosis of lung, breast and prostate cancers. A concomitant diagnosis of infective endocarditis in patients with CRC diagnosis is associated with shorter survival.

Keywords Infective endocarditis · Colorectal cancer · SEER · Medicare

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Introduction

Colorectal, lung, breast, and prostate cancer account for about half of cancers in the United States and in Europe, with more than 800,000 and 1,370,000 new diagnoses per year respectively [1, 2]. The care of these patients is complex and invasive, particularly during the initial year after diagnosis. Concurrent infections may interfere with patient care and lead to worse outcomes. In particular, among patients with colorectal cancer (CRC), *Streptococcus gallolyticus* (formerly named *Streptococcus bovis* biotype I) appears to be associated with an increased risk of infective endocarditis [3].

The association between CRC and endocarditis was first proposed decades ago [4], and is supported by several case series [5] and small case–control studies [6–8]. A meta-analysis of these case–control studies found a strong association (odds ratio 14.5, 95 % confidence interval

5.7–37.6), but it was based on only 16 CRC patients with endocarditis [9] and could not provide information about the incidence of endocarditis around CRC diagnosis. Further, few data exist about the association between endocarditis and the outcomes of CRC patients [10], or between endocarditis and other tumor sites [11].

Here we present the first large-scale prospective study of peridiagnostic incidence of endocarditis among patients with colorectal, breast, lung, and prostate cancer. We also evaluate the association between peridiagnostic endocarditis and the prognosis of patients with CRC.

Methods

Study population

Our study population was extracted from the SEER-Medicare data, a linkage of patient demographic and tumor-specific variables collected by 17 SEER cancer registries across 12 states of the United States with Medicare claim files from the Centers for Medicare and Medicaid Services [12]. SEER data are summarized in the Patient Entitlement and Diagnosis Summary File (PEDSF), which is linked with 100 % of Medicare claims. For the current study we used Medicare claims from the Inpatient, Outpatient, Home Health Agency (HHA), Durable Medical Equipment (DME), Medpar and National Claims History (NCH) files. To identify the date of cancer diagnosis we used the SEER date of diagnosis, which is the month, and year the tumor was first diagnosed, clinically or microscopically, by a recognized medical practitioner [13].

We included patients with histological diagnosis of invasive colorectal adenocarcinoma, lung cancer, breast cancer, or prostate cancer between 1992 and 2009, and who were enrolled in Medicare parts A and B and not in an health maintenance organization during the year before diagnosis. As a control group, we included patients without cancer using a random 5 % sample of Medicare beneficiaries living in areas with SEER registries. We excluded patients with cancers reported by nursing home/hospice, autopsy, or death certificate, and those with an endocarditis diagnosis 12 or more months before cancer diagnosis.

We identified endocarditis from the principal or secondary ICD-9 diagnosis (see codes in table A1) of each admission recorded in the Medpar file [14]. From the PEDSF file, we determined demographic characteristics (age, sex, race, urbanicity), tumor features (TNM stage, grade of differentiation, SEER date of diagnosis) and census tract features (census region, percentage of black population, percentage of residents living below the

poverty level, percentage of residents aged 25 or older with less than 12 years of education, percentage of residents speaking English not well/not at all at age 65+, median income). We summarized comorbidity burden using the Deyo–Charlson–Klabunde comorbidity index [15], derived from the inpatient and outpatient Medicare claims for the period between 12 months to the month before SEER date of diagnosis. We extracted cancer-directed diagnostic tests and therapy (colonoscopy, colectomy, chemotherapy) from the NCH, Outsaf, Medpar and DME files (see codes in table A1) and admissions in the year following cancer diagnosis from the Medpar file. We also extracted the colorectal cancer sentinel sign/symptom (anemia, gastrointestinal bleeding, gastrointestinal symptoms, large bowel obstruction, see codes in table A1) from claims issued during the 3 months previous SEER date of diagnosis. As falsification tests (negative controls for endocarditis), we examined the risk of two other serious infections that are unlikely to be related to either CRC or CRC care, i.e., pyelonephritis and meningitis.

Data analysis

We followed patients from 1 year before cancer diagnosis (random reference date for the non-cancer cohort) until they died, stopped fulfilling the inclusion criteria, or reached the administrative end of follow-up (December 31st, 2010). In our main analyses, we computed the peridiagnostic incidence rate of endocarditis between 90 days before and 90 after cancer diagnosis: number of endocarditis diagnoses divided by number of person-months in that time period. For lung, breast and prostate cancer, we standardized the rate by the age (≤ 70 , 71–75, 76–85, > 85) and sex (for lung cancer only) distribution of CRC patients. We also plotted the monthly incidence rate of endocarditis from -12 to $+24$ months from cancer diagnosis.

We defined overall survival and cancer-related survival as the time from SEER date of diagnosis to death by any cause or cancer respectively. We classified patients as having a concomitant diagnosis of endocarditis if they were diagnosed with endocarditis between 90 days before and 90 days after cancer diagnosis, and as having no concomitant diagnosis of endocarditis otherwise. We constructed Kaplan–Meier curves for survival and cancer-related survival by concomitant endocarditis, and estimated the hazard ratios for endocarditis versus no endocarditis using a Cox model adjusted by sex, age, stage, comorbidity score, structural cardiac condition and presence of an intravascular device. We used a non-parametric bootstrap based on 1000 resamplings to compute 95 % confidence intervals for survival differences at 24 months of follow-up. We used SAS version 9.4 (SAS Institute, Cary, NC) and R [16].

Results

There were 1835 new cases of endocarditis among cancer patients (Fig. 1). For CRC patients, the peri-diagnostic endocarditis incidence rate was 19.8 cases per 100,000 person-months (95 % CI 17.0–22.6). The corresponding rates were much lower for lung, breast, and prostate cancer, and for individuals without cancer (Table 1). In contrast, the incidence of peri-diagnostic pyelonephritis and meningitis did not substantially differ by cancer site and were higher than in patients without cancer (Supplementary Table A2). The endocarditis rate was highest during the month of diagnosis for both CRC (42.1 cases per 100,000 person-months, 95 % CI 32.3, 52.0) and lung cancer (15.6 cases per 100,000 person-months, 95 % CI 10.2, 21.0), but not for breast and prostate cancer (Fig. 2). The use of colonoscopy increases after admission due to an endocarditis (Supplementary Figure A1).

CRC patients with a concomitant diagnosis of endocarditis were more likely to be male, have a structural cardiac condition or intravascular device, have a higher comorbidity score, have presented with anemia as a sentinel symptom, and been diagnosed at earlier stages (Table 2). Among patients diagnosed with potentially

curable CRC (stages I to III), the concomitant diagnosis of endocarditis was associated with a higher postoperative mortality, smaller percentage of patients receiving adjuvant therapy, higher percentage of patients visiting the emergency department, longer lengths of admissions, longer stays in intensive care units, and more clinical evaluations during the first year after CRC diagnosis, compared with not having endocarditis (Table 3).

Two-year overall survival (95 % CI) was 46.4 % (39.5, 54.5) for stage I–III CRC patients with a concomitant diagnosis of endocarditis and 73.1 % (72.9, 73.3) for those without it (risk difference –26.7 %; 95 % CI –33.8, –19.0). These differences were present across the three stages (Table 3; Fig. 3). In contrast, the two-year cancer-specific survival was 84.9 % (79.0, 91.2) for those with a concomitant diagnosis of endocarditis and 85.7 % (85.5, 85.9) for those without it (risk difference –0.7 %; 95 % CI –6.8, 5.3). There were no relevant differences by stage (Table 3; Fig. 3). Compared with no concomitant diagnosis of endocarditis, the hazard ratio for an endocarditis diagnosis was 1.67 (95 % CI 1.42, 1.98) for overall mortality and 1.24 (95 % CI 0.87, 1.77) for cancer-specific mortality during a median follow-up of 34 months (interquartile range, 12–72 months).

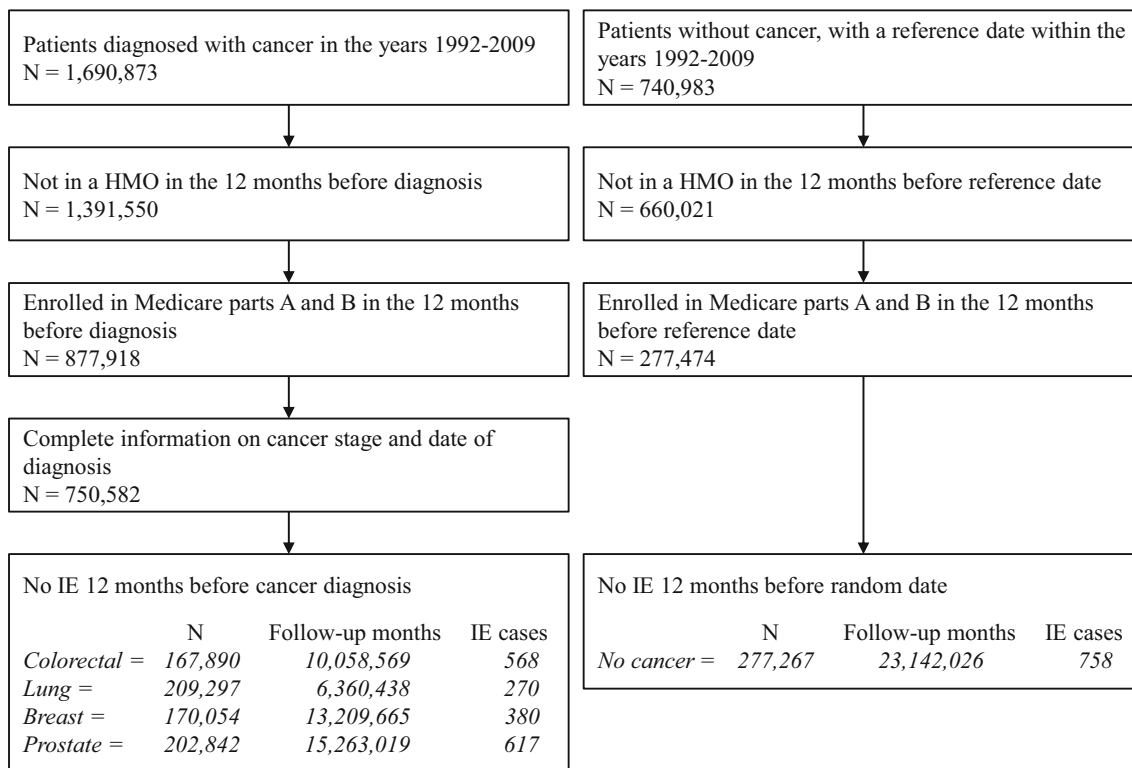


Fig. 1 Flowchart of individuals' selection into the study (HMO health maintenance organization, IE infective endocarditis), SEER-Medicare 1992–2009

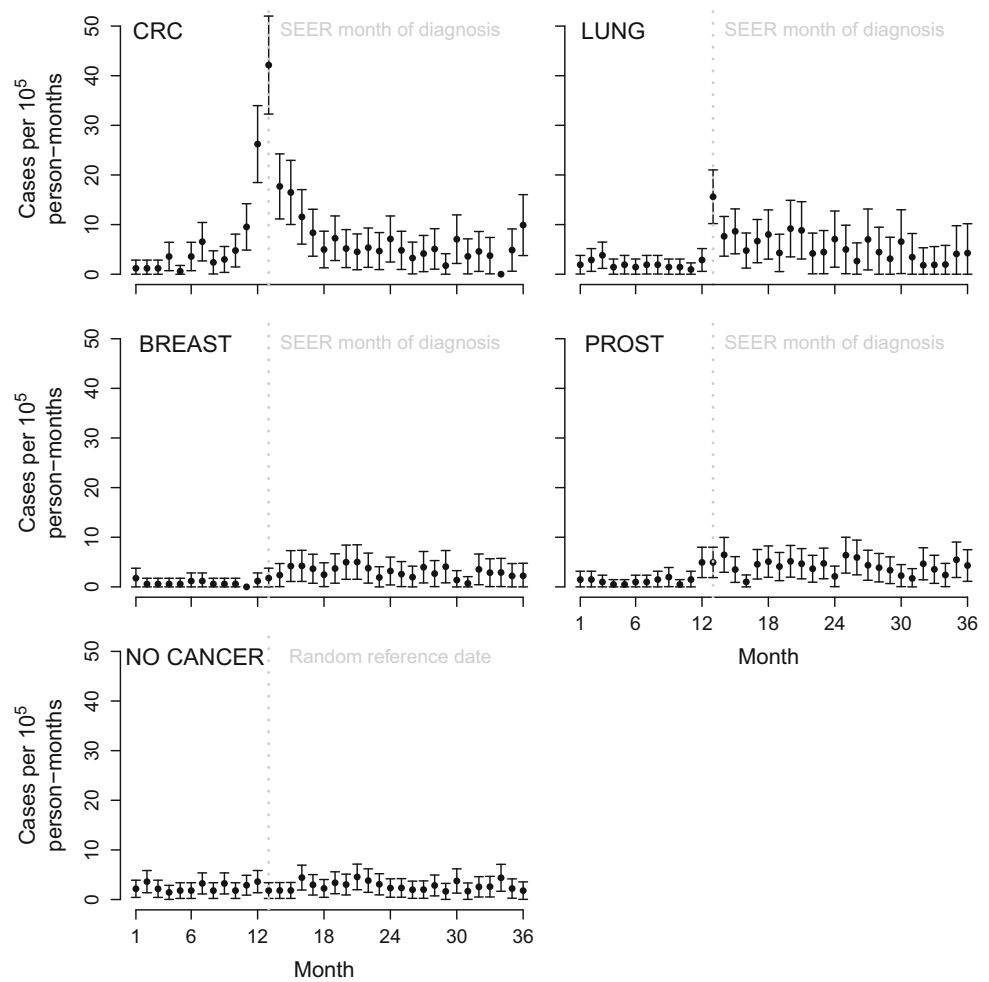
Table 1 Incidence rate of infective endocarditis between 90 days before and 90 days after diagnosis of colorectal, lung, breast, and prostate cancer, SEER-Medicare 1992–2009

Cancer site	Persons	Person-months	Cases	Cases per 100,000 person-months (95 % CI)	
				Unadjusted rate	Standardized rate ^a
Colorectal	167,851	966,072	191	19.8 (17.0–22.6)	19.8 (17.0–22.6)
Lung	209,258	1,163,085	70	6.0 (4.6–7.4)	5.7 (4.2–7.1)
Breast	170,041	1,000,659	17	1.7 (0.9–2.5)	1.9 (1.0–2.8)
Prostate	202,820	1,195,057	44	3.7 (2.6–4.8)	4.1 (2.8–5.4)
Non-cancer ^b	277,207	1,631,021	37	2.3 (1.5–3.0)	2.4 (1.5–3.2)

^a Incidence rate is directly standardized to the age and sex (except for breast and prostate cancer) distribution of CRC patients

^b Incidence rate is calculated using a random index date

Fig. 2 Monthly rates of infective endocarditis around diagnosis of colorectal (CRC), lung, breast and prostate cancer (PROST), and around a random date for individuals without cancer, SEER-Medicare 1992–2009



Discussion

We found that the incidence of endocarditis in the elderly increased fivefold around the diagnosis of CRC compared with the diagnosis of lung, breast, or prostate cancer, or an arbitrary date for individuals without cancer. An increased incidence was not observed for other serious infections.

Our study included over five times more CRC patients with endocarditis than all previous studies combined, and provided the first estimate of endocarditis incidence surrounding the diagnosis of CRC in the elderly: 19.8 cases (95 % CI 17.0–22.6) per 100,000 person-months.

The association between endocarditis and CRC diagnosis can be due to at least four non-mutually exclusive

Table 2 Characteristics of colorectal cancer patients with and without a concomitant diagnosis of infective endocarditis, SEER-Medicare 1992–2009

	No endocarditis (N = 167,699)	Endocarditis (N = 191)
Median age (interquartile range)	77 (71–83)	78 (72–83)
Female (%)	53.3	38.2
Race (%)		
White	86.5	89.5
African American	8.9	*
Asian/Pacific islander	4.2	*
Other/unknown/unspecified	0.5	*
Comorbidity score ^a (%)		
0	52.7	39.3
1	21.3	>17.2
2+	14.9	37.7
Unknown	11.0	<5.8
Structural cardiac condition ^a (%)	10.6	34.6
Intravascular device ^a (%)	3.0	10.5
End stage renal disease ^a (%)	0.8	*
Sentinel symptom ^b (%)		
Anemia	26.4	42.9
Gastrointestinal bleeding	24.1	29.3
Gastrointestinal symptoms	17.7	19.9
Large bowel obstruction	2.4	*
Stage (%)		
I	26.8	38.2
II	31.5	32.5
III	25.0	19.9
IV	16.8	9.4
Grade of differentiation (%)		
Well differentiated	8.9	13.6
Moderately differentiated	63.9	62.3
Poorly differentiated	19.2	17.8
Unknown	8.0	6.3
Location (%)		
Ascending colon	35.3	31.4
Transverse colon	14.5	16.7
Descending colon	27.1	26.7
Rectum	23.1	25.1
Urbanicity (%)		
Big metro (≥ 1 million)	54.0	58.6
Metro (250,000–1 million)	28.4	29.3
Urban (20,000–250,000)	6.2	*
Less urban (2500–20,000)	9.3	*
Rural (rural or <2500)	2.2	*
SEER registry census region (%)		
West	38.2	37.2
Northeast	20.5	34.0
Midwest	19.0	12.0
South	20.7	16.2
Pacific	1.6	*

Table 2 continued

	No endocarditis (N = 167,699)	Endocarditis (N = 191)
Year of CRC diagnosis (%)		
1992–1996	19.0	18.9
1997–2001	26.1	20.4
2002–2006	30.4	30.9
2007–2010	24.5	29.8
Census tract features [median (interquartile range)]		
% did not complete high school	16.7 (10.0–27.1)	15.5 (8.9–24.3)
% below poverty line	8.4 (4.5–15.6)	7.0 (4.0–11.6)
% black race/ethnicity	2.1 (0.6–8.3)	2.1 (0.7–6.7)
% English not well/at all at 65+	1.5 (0–5.4)	2.1 (0–5.9)
Median income (USD)	42,219 (31,906–57,068)	49,131 (35,334–62,316)

* Cells with counts of 11 or lower (≤ 5.8 %) are blinded following SEER-Medicare privacy policy

^a Evaluated the 6th month before colorectal cancer diagnosis

^b Evaluated during the 3 months preceding colorectal cancer diagnosis

^c Missing in 1296 individuals

Table 3 Oncologic management and outcomes in patients diagnosed with stages I–III of colorectal cancer by concomitant diagnosis of infective endocarditis, SEER-Medicare 1992–2009

	No endocarditis (N = 139,600)	Endocarditis (N = 173)
Surgery of primary tumor (%)	79.5	84.4
Postoperative mortality ^a (%)	6.0	12.0
Adjuvant chemotherapy ^b (%)	14.5	^d
Patients visiting the emergency department during 1st year after CRC diagnosis (%)	50.2	79.2
Median (interquartile range) number of visits	2 (1–3)	2 (1–4)
Patients admitted to a hospital during 1st year after CRC diagnosis (%)	90.3	95.4
Median length of total stay ^c (interquartile range)	13 (7–27)	43 (25–73)
Median number of days in intensive care ^d (interquartile range)	0 (0–3)	4 (0–10)
Median number of clinical evaluations during 1st year after CRC diagnosis (interquartile range)	22 (12–36)	43 (26–66)
Number of deaths	89,172	139
Number of cancer-related deaths	32,945	31
Months of follow-up	9,315,640	8,187
2-year overall survival (%)		
Stage I	80.6 (80.2–80.9)	50.6 (38.7–61.4)
Stage II	74.1 (73.7–74.5)	41.4 (29.0–53.4)
Stage III	63.8 (63.4–64.3)	46.9 (30.5–61.8)
2-year CRC-specific survival (%)		
Stage I	93.4 (93.2–93.7)	90.0 (79.0–95.0)
Stage II	87.1 (86.8–87.4)	80.9 (66.0–89.8)
Stage III	75.5 (75.1–75.9)	80.1 (60.0–90.8)

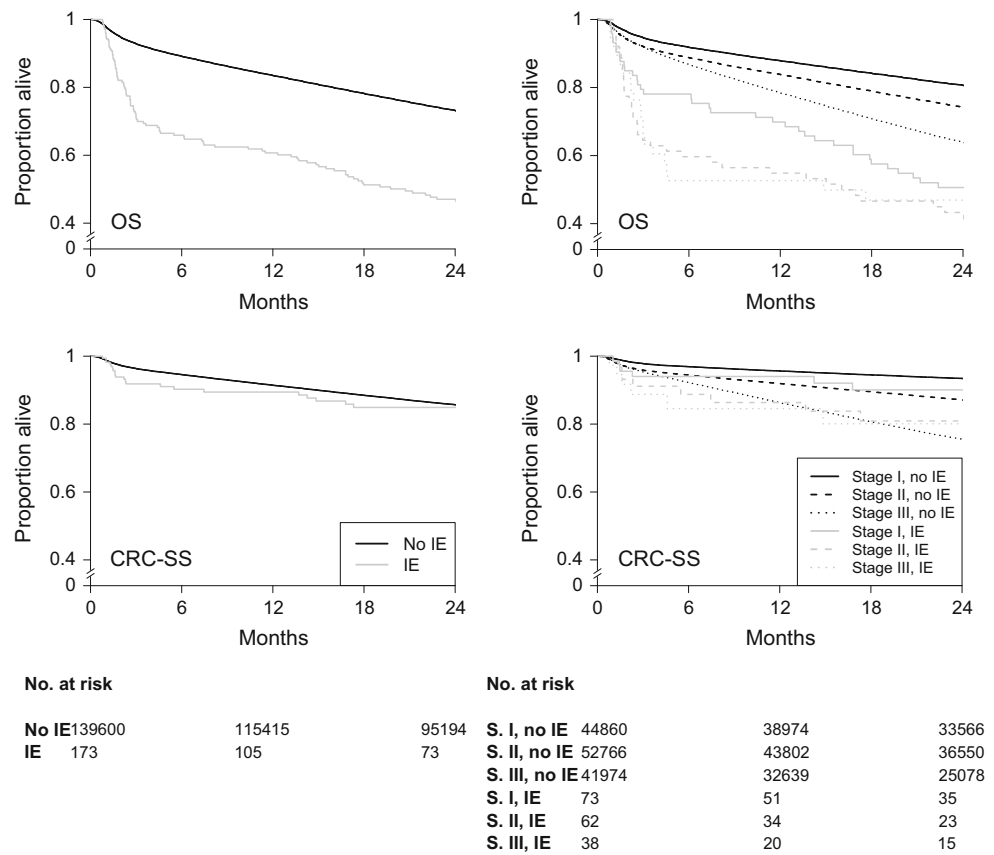
^a Postoperative mortality defined as death in the 30 days following surgery

^b Stages II and III (N = 94,840)

^c Sum of days that year through all admissions

^d Cells with counts of 11 or lower (≤ 6.4 %) are blinded following SEER-Medicare privacy policy

Fig. 3 Overall survival (OS) and colorectal cancer-specific survival (CRC-SS) stratified by infective endocarditis, and by infective endocarditis and stage, SEER-Medicare 1992–2009



reasons, which are summarized in Fig. 4. First, undiagnosed CRC (or pre-neoplastic lesions like adenomas) could cause endocarditis, perhaps by allowing the translocation of bacteria [17] (Fig. 4a). Second, patients diagnosed with endocarditis often receive a subsequent colonoscopy as part of the diagnostic work-up (Supplementary Figure A1), which could lead to a higher rate of CRC detection (Fig. 4b). Third, a common causative factor could independently lead to CRC diagnosis and endocarditis (Fig. 4c). For example, colonoscopy could cause both an increased rate of CRC diagnosis and of endocarditis by disrupting the bowel mucosal barrier and thus facilitate the seeding of bacteria in the bloodstream. The colonoscopy can be performed for screening purposes as shown in Fig. 4c or as a result of CRC symptoms (i.e. Figure 4c with an arrow from CRC to colonoscopy). Similarly, the observed small increase in endocarditis incidence in the month of lung cancer diagnosis supports the hypothesis that localized trauma associated with diagnostic procedures (in this case bronchoscopy) might increase the risk of endocarditis. Finally, the association between CRC and endocarditis could be due to common etiologic factors such as immunosuppression, smoking, and alcohol (Fig. 4d).

Regardless of the reason why endocarditis and CRC diagnosis are associated, CRC patients with concomitant

endocarditis had a 25 % increase in two-year mortality, but no changes in CRC-specific mortality. This increased mortality risk suggests that clinicians need to be vigilant for endocarditis in CRC patients, particularly during the peri-diagnostic period. Future studies on the risks and benefits of anti-microbial prophylaxis also could be warranted. Not only did endocarditis increase the risk of non-cancer specific death, but it also was associated with changes in cancer treatment. Because decisions on oncologic therapies depend on the predicted survival of patients, our findings will help inform clinical decisions in elderly patients, an increasing fraction of the oncologic patients [18, 19] who are under-represented in clinical research [20]. Our results suggest that the increase in mortality associated to endocarditis is not through worse oncological outcomes.

Our study has several limitations. While the quality of the diagnosis of cancer in SEER-Medicare is high, no formal validation of endocarditis diagnoses in Medicare claims has been done. However, endocarditis represents a serious infection for which patients are unlikely to avoid care, and an expensive condition for which care is likely to be well documented in claims data. Further, ICD-9 codes have been found to be accurate surrogates of bacterial infections in other administrative datasets [21] and have

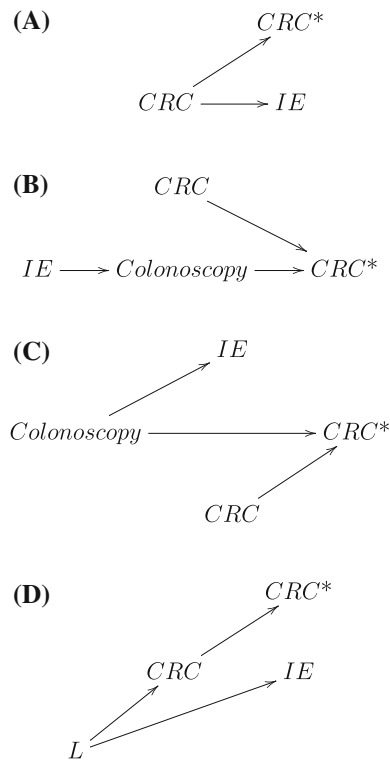


Fig. 4 Causal diagrams [27] for several explanations for the association between colorectal cancer diagnosis and infective endocarditis (*CRC* presence of colorectal cancer or precursor lesions, *CRC** diagnosis of colorectal cancer, *IE* infective endocarditis, *L* common causes of CRC and IE)

been used as the basis of several studies on endocarditis [14, 22, 23]. Classifying patients as having a concomitant diagnosis of endocarditis if they were diagnosed with endocarditis between 90 days before and 90 days after cancer diagnosis might introduce a selection bias because patients that do not survive for at least 90 days after the date of cancer diagnosis are less likely to be classified in the endocarditis group. However, only 7 % patients died during this period and sensitivity analyses using 60 or 120 days instead of 90 days yielded equivalent results (Supplementary Table A3). Our large database study lacked bacteriological data, but the pathogen most frequently associated with endocarditis among CRC patients is *Streptococcus gallolyticus* subsp. *gallolyticus* (formerly *Streptococcus bovis* I) [3], possibly because of its ability to translocate through the bowel wall when its permeability is increased by cancer [24], its immune-evasion properties [25], and its affinity to the collagen type I in damaged heart valves [26].

In summary, our study provides a precise estimate of the association between CRC and endocarditis as well as of the association between endocarditis and the survival of older adults with CRC. These findings help inform clinical

decisions for cancer patients, including the diagnostic workup of patients with CRC and fever of unknown origin, as well as cost-effectiveness assessments of clinical pathways for CRC care.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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