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# Risk of Colorectal Cancer and Associated Mortality in HIV: A Systematic Review and Meta-Analysis

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**Background:** As people with HIV live longer, the numbers of colorectal cancer cases are expected to increase. We sought to compare the colorectal cancer incidence and cause-specific mortality among people living with and without HIV.

**Design:** Systematic review and meta-analysis.

**Methods:** We searched 5 electronic databases up to June 28, 2016, for primary studies reporting standardized incidence ratios (SIRs), standardized mortality ratios (SMRs)/hazard ratios or data sufficient for estimating these summary measures. We performed a random effects pooled analysis to estimate SIR and SMR of colorectal cancer in HIV.

**Results:** Of 8110 articles, we included 27 studies from North America (n = 18), Europe (n = 7), the Pacific region (n = 4), and South America (n = 1). Overall, 1660 cases of colorectal cancer and colon cancer (excluding rectal cancer) occurred among 1,696,070 persons with HIV. In pooled analysis, we found no summary risk of malignancy among those with HIV relative to an uninfected population (SIR 1.00; 95% confidence interval 0.82 to 1.22; $I^2$ = 89.2%). Colorectal cancer–specific mortality was higher among people with HIV but did not reach statistical significance (SMR 2.09; 95% confidence interval: 1.00 to 4.40; $I^2$ = 85.0%).

**Conclusions:** Rates of colorectal cancer are similar between people with and without HIV. Existing screening guidelines are likely adequate for people with HIV.

**Key Words:** colorectal neoplasms/epidemiology, HIV infections/complications, meta-analysis, incidence

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## INTRODUCTION

People with HIV are at higher risk of cancer than HIV-negative individuals.[1–3] Although rates of classic AIDS-defining malignancies have declined since the introduction of combination antiretroviral therapy (cART),[4–6] the incidence of infection-related malignancies such as anal cancer, liver cancer, and Hodgkin's lymphoma have increased over the same period and occur at rates that are markedly higher than those of the general population.[1,3,7] The postulated mechanism for the heightened risk of malignancy, particularly of infection-related disease, reflects a causal complement comprising risk factors such as smoking, oncogenic pathogen coinfection, and HIV-related immunosuppression.[1,8] A central role for immunosuppression is supported by results of a recent meta-analysis documenting a higher incidence of infection-related cancers in both people with HIV and organ transplant recipients relative to the general population.[2] Although this same meta-analysis did not find a higher risk of non-infection–associated epithelial cancers [eg, breast and colorectal cancers (CRC)] among people with HIV, the incidence of these malignancies may increase in this population by virtue of the age-related risk for these cancers and the prolonged life expectancy of people with HIV.[9]

CRC is the third leading cause of cancer-related death in North America, with an estimated 49,190 expected to die from the disease in 2016.[10] Early detection and treatment of CRC is associated with improved prognosis and facilitated by period

screening using endoscopic visualization or fecal occult blood testing.[11] Current guidelines recommend that screening for CRC be initiated at the age of 50 among people at average risk of disease, with earlier and more frequent screening advocated for individuals at higher risk of CRC, such as those with inflammatory bowel disease or first degree relatives with a history of this illness.[11] Although people with HIV are generally considered at average risk of CRC, there are inconsistent reports on the epidemiology of CRC in this population with respect to disease risk. Specifically, the standardized incidence ratio (SIR) for CRC in persons with HIV relative to the general population has ranged from 0.45 to 2.3 across studies.[4,12–20] Furthermore, the prevalence of adenomatous polyps, known precursors of malignancy, among people with HIV, exceeds the prevalence of the general population (range 1.0%–34.3%) in most, but not all, studies.[21–25]

Previous meta-analyses reported SIR and 95% confidence intervals (CIs) of CRC in persons with HIV of 0.97 (0.78 to 1.19) up to March 2007[2] and 1.1 (0.69 to 1.7) up to March 2009.[3] However, several new studies have been published since the last review was undertaken, and no reviews have examined CRC-related mortality among people with HIV.[7,9,26–29] Accordingly, we aimed to systematically identify observational studies, assess study quality, and estimate pooled SIRs of CRC among people with HIV, compared with a referent population of persons not living with HIV. Our secondary aims were to summarize evidence for differences between persons with and without HIV with respect to site and stage at diagnosis, treatment modalities and all-cause and CRC-specific mortality. These data are critical to identify whether people with HIV are at higher risk of CRC than the general population and to inform screening guidelines for these patients.

## METHODS

### Search Strategy and Inclusion Criteria

Our study protocol is described elsewhere (modifications in Supplemental Digital Content, Table 1, http://links.lww.com/QAI/B20).[30] Briefly, we searched 5 databases (Ovid MEDLINE, Ovid EMBASE, Cumulative Index of Nursing and Allied Health Literature, Scopus, and Web of Science) for potentially relevant studies published in English up to June 28, 2016 (Supplemental Digital Content, Table 2, http://links.lww.com/QAI/B20 for MEDLINE search strategy). The MEDLINE search strategy was adapted for the other databases searched. Iterative secondary reference searching of included publications was conducted to identify other potentially relevant studies. The primary outcome of the systematic review is the SIR of CRC among people with HIV relative to HIV-negative individuals. A study was eligible for initial inclusion if it (1) provided a comparison of the incidence of CRC (including colon or colorectal) in adults (≥18 years) with HIV and a referent population of HIV-negative individuals; (2) used an observational study design; and (3) reported SIR and 95% CI: or sufficient information to estimate both (total number of adults with HIV, duration of follow-up, observed number of cases of CRC, or colon cancer during follow-up), and corresponding data for the HIV-negative comparator population. Secondary outcomes included site (proximal versus distal colon, colon versus rectum) and stage of diagnosis, treatment modalities and outcomes, including standardized mortality ratio (SMR) [or equivalents, including hazard ratio (HR)] of all-cause or CRC-specific mortality among those with HIV relative to a referent HIV uninfected population (Supplemental Digital Content, Table 3, http://links.lww.com/QAI/B20). References were managed in RefWorks-COS (Proquest LLC, Cambridge Information Group, Bethesda, MD). After deduplication, 3 authors (T.J.O., J. D.N., and T.A.) independently screened titles and abstracts using DistillerSR (Evidence Partners, Ottawa, Canada), with a fourth reviewer (A.-M.T.) consulted when necessary.

When 2 or more publications reported the same endpoint from one institution, cohort, or study, each article was reviewed to consider potential for pooling outcomes based on reported data. Specifically, we considered whether individual publications from the study overlapped in the source populations giving rise to cases of CRC and referent controls and the period of time during which the study was conducted. When 2 or more publications were identified that were deemed sufficiently alike based on these characteristics, we included only the study with the longest duration of follow-up in the meta-analysis and provided a qualitative description of the remaining studies.

### Data Extraction and Quality Assessment

Full-text articles were retrieved, and 3 authors (T.J.O., T.A., and J.D.N.) independently abstracted study data using standardized forms. Studies were further excluded if they provided insufficient data to estimate outcomes of interest. Data extracted included publication details, study design and methods, study sample/participant characteristics, and reported outcome measure(s), including variables used to standardize SIR/SMR estimates (Supplemental Digital Content, Table 4, http://links.lww.com/QAI/B20). For 10% of the included studies, data were double extracted to check for accuracy. Differences in publication inclusion and data abstraction were resolved through consensus.

Two reviewers assessed the quality of included studies using the Newcastle–Ottawa Scale. This scale awards a maximum of 9 stars to each study: 4 stars for the adequate selection of study groups, 2 stars for comparability of study groups on the basis of the design and analysis, and 3 stars for the adequate ascertainment of the outcome. Stars were awarded based on a predefined list of criteria outlined in the scale. We defined studies that scored 7 of 9 as high quality.[31,32] Disagreement in study eligibility, data extraction, and quality assessment were resolved by consensus between reviewers. This process involved both reviewers together returning to the original abstract and/or manuscript to review study eligibility according to the protocol and reabstract the relevant data. Finally, 2 team members (T.J.O. and T.A.) reviewed all data to ensure accuracy before analysis.

### Statistical Analysis

We report the SIR and 95% CI of CRC among persons with HIV relative to rates in persons not infected with HIV. If

point estimates and spread or variability were not directly reported, we estimated unadjusted SIR and 95% CI using reported observed and expected cases. We assessed derived ratios of CRC and colon cancers independently and in a summary effect using the method by DerSimonian and Laird[33] and assumptions of a random effects model weighted by the inverse of the variances, with ascertainment of individual study influence on summary estimates.

We used the $I^2$ statistic to estimate the percentage of variability between studies caused by between-study heterogeneity.[34] We defined substantial heterogeneity as $I^2 > 60\%$. We reasoned that sources of heterogeneity could be related to temporal changes in the epidemiology of cancer among people with HIV, country of publication, sources of cases and controls (eg, population-based registries versus clinical cohorts), and patient characteristics such as sex. Accordingly, a priori defined subgroup meta-analyses were conducted to explore potential sources of heterogeneity based on available reported data, including sex, study location (United States vs. others), and whether the study reported data from the period before or after (1996 and onward) the introduction of cART. For outcomes with at least 10 individual studies, publication bias was assessed by constructing a funnel plot,[35] by the Egger regression asymmetry test, and by the Begg[36] adjusted rank correlation test. Individual study influence was assessed by removal-and-replacement of individual studies and assessment of change in summary estimates. Statistical analyses were performed in RevMan5 (The Cochrane Collaboration, London, United Kingdom). A 2-sided $P$ value $<0.05$ was regarded as statistically significant. Reporting was done in accordance with PRISMA Guidelines[37] (Supplemental Digital Content, Table 5, http://links.lww.com/QAI/B20). We did not contact corresponding authors for additional study details if not reported in the full-text article.

## RESULTS

### Characteristics of Included Studies

The literature search identified 10,691 citations (Fig. 1). After excluding duplicates and reviewing titles and abstracts, 64 articles were retrieved for full-text evaluation. Thirty-seven studies subsequently excluded because they did provide point estimates or data for estimating SIRs or they did not report on CRC. Our review, therefore, yielded 27 retrospective cohort studies representing 23 unique populations included in meta-analyses (Table 1).[1,6,13,15,19,20,38–56] Studies were included in Table 1 but not included in the meta-analysis because of overlapping populations and/or study periods are listed in the Supplemental Digital Content.

With the exception of 3 studies reporting mortality outcomes,[48,49,53] we could not summarize other secondary data outcomes, including site and stage of diagnosis and treatment, because of lack of reporting. Included articles reported data from the United States (n = 17),[17–19,38–51] 3 from Italy,[15,52,53] 2 each from Australia[6,13] and Taiwan,[55,56] and single articles reporting data from Canada,[50] Brazil,[51] the United Kingdom,[20] France,[52] Germany,[54] and Denmark.[1] Four articles[38,39,43,55] included in the review were excluded

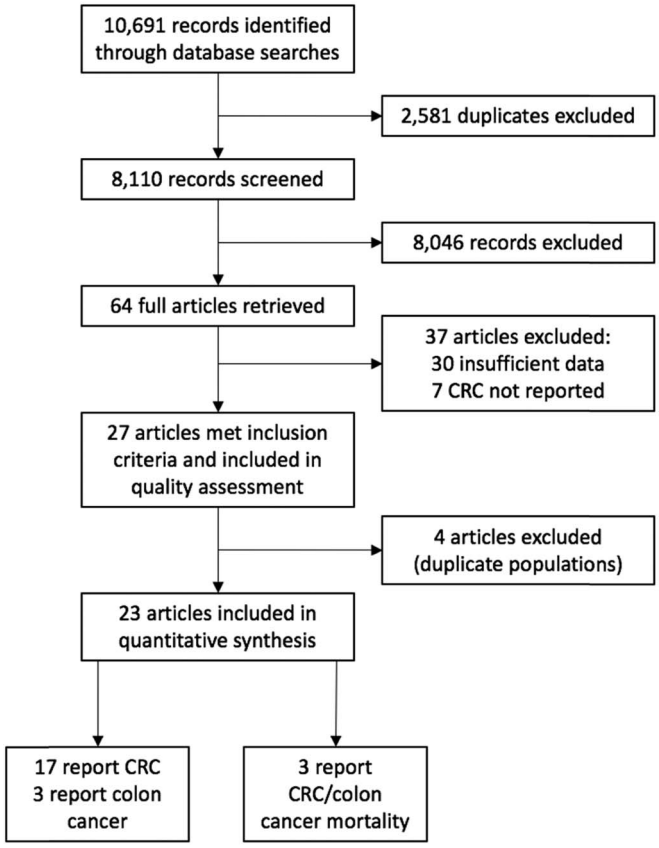


**FIGURE 1.** Flow chart detailing the search for and selection of studies.

from quantitative synthesis because of overlapping reports from the same study population (Supplemental Digital Content, Table 6, http://links.lww.com/QAI/B20). Most (89%) samples were registry based; only 3 were hospital based.[1,19,54] Of the 22 studies that reported sex distribution, the overall median percentage of men was 74.9% [interquartile range (IQR): 63.4%–85.3%]. Eighteen studies reported age in the observed population, with the median being 43.0 years (IQR: 39.6–47.1). Race/ethnicity was reported by 14 studies where the median of mean or median Caucasian race was 53.4% (IQR: 49.1%–58.7%). Fewer than 10% of included studies reported CD4 cell count, viral load, or percentage on cART at baseline or at time of CRC diagnosis.

Applying the Newcastle–Ottawa Scale criteria, we assessed the quality of the body of literature included in the systematic review as high (score ≥8) (Table 2).

### Incident Risk of CRC Diagnosis

A minimum of 7,359,993 person-years of follow-up was reported (person-time not reported in 7 studies), with 1,550,017 participants, among whom 1643 cases of CRC were diagnosed. Studies of incident colon cancer (excluding cancer of the rectum) represented a minimum of 611,654 person-years of follow-up (person-time not reported in one study) and 146,053 participants, with 78 cases of colon cancer

**TABLE 1.** Characteristics of Studies Identified From Systematic Review of CRC Incidence and Associated Mortality in Those HIV+ Compared With an Uninfected Population (Sorted by Country and Year of Publication)

| Study | Country | HIV+ Source Population | HIV− Source Population |
|---|---|---|---|
| Long et al, 1999[19] | USA | Single HIV clinic cohort, patients in care | Tumor registry (same hospital as HIV clinic) |
| Cooksley et al[41] | USA | County-level HIV registry | County-level cancer registry (same county as HIV registry) |
| Gallagher et al[42] | USA | State-level HIV registry | State-level cancer registry (same state as HIV registry) |
| Engels et al[17] | USA | Multisite HIV/AIDS Cancer Match (HACM) study | State cancer registry databases |
| Patel et al[18] | USA | Multisite Adult and Adolescent Spectrum of HIV Disease and HIV Outpatient Study (HOPS) programs | Surveillance, Epidemiology, and End Results (SEER) program |
| Simard et al[38],* | USA | HACM Study | Multisite cancer registry (same as HIV+) |
| Silverberg et al[39],* | USA | Multisite, single provider (Kaiser Permanente) | Cancer registry (same hospital network as HIV+) |
| Keller et al, 2010[40] | USA | Multisite clinic-based Medicaid providers | Multisite clinic-based Medicaid providers (same as HIV+) |
| Shiels et al[43],* | USA | Multisite HIV/AIDS Cancer Match Study | Multisite cancer registry (same as HIV+) |
| Park et al[44] | USA | Veterans Aging Cohort Study (VACS) | VACS |
| Robbins et al[45] | USA | HACM Study | Multisite cancer registry (same as HIV+) |
| Robbins et al[46] | USA | HACM Study | SEER program |
| Shiels et al[47] | USA | HACM Study | Multisite Transplant Cancer Match study |
| Coghill et al[48] | USA | HACM Study | Multisite cancer registry (same as HIV+) |
| Marcus et al[49] | USA | Multisite, single provider (Kaiser Permanente) | Cancer registry (same hospital network as HIV+) |
| Silverberg et al[50] | USA/Canada | Multisite HIV cohort (North American Cohort Collaboration on Research and Design, NA-ACCORD) | 5 contributing cohorts reporting data from HIV- demographically similar to NA-ACCORD participants |
| Castilho et al[51] | USA/Brazil | Multisite HIV cohort of patients in care | National cancer registry (Brazil) and SEER program (USA) |
| Grulich et al[13] | Australia | Australian National multisite HIV/AIDS registry | National multisite cancer registry |
| van Leeuwen et al, 2009[7] | Australia | Australian National multisite HIV/AIDS registry | Australian National Cancer Statistics Clearing House (NCSCH) |
| Newnham et al[20] | United Kingdom | Multisite HIV registry | Multisite cancer registry (same as HIV+) |
| Serraino et al[52] | Italy/France | Multisite HIV registries (Italian HIV Seroconversion Study, Italy; Dossier Médical Informatique-2, France) | National cancer registries |
| Dal Maso et al, 2009[15] | Italy | National Italian AIDS Registry | Multisite Italian cancer registries |
| Zuchetto et al[53] | Italy | National Italian AIDS Registry | National Register of Causes of Death |
| Vogel et al[54] | Germany | Single HIV clinic cohort | Regional (Saarland) Cancer Registry, same catchment area as HIV cohort |
| Chen et al[55],* | Taiwan | National Health Insurance Research Database | National Health Insurance Research Database |
| Chen et al[56] | Taiwan | Longitudinal Health Insurance Database (National Health Insurance Research Database) | Longitudinal Health Insurance Database (National Health Insurance Research Database) |
| Helleberg et al[1] | Denmark | Multisite HIV cohort of patients in care | National cancer registry |

| Study | Period of Follow-up | Reported Person-years | Observed Cancer (n) | Variables Used to Standardize SIR/SMR |
|---|---|---|---|---|
| Long et al, 1999[19] | 1996–2005 | 19,491 | CRC (2) | Age, sex, race/ethnicity, calendar year |
| Cooksley et al[41] | 1985–1994 | Not reported | Colon (11) | Age, sex |
| Gallagher et al[42] | 1981–1994 | 567,254 | Colon (5) | Age, sex |
| Engels et al[17] | 1991–2002 | 186,157 | CRC (28) | Age, sex, race/ethnicity, calendar year, registry site |
| Patel et al[18] | 1992–2003 | 157,819 | CRC (24) | Age, sex, race/ethnicity |
| Simard et al[38],* | 1980–2004 | 396,445 | CRC (227) | Age, sex, race/ethnicity, calendar year, registry site |
| Silverberg et al[39],* | 1996–2008 | 90,961 | CRC (35) | Age, sex, race/ethnicity, calendar period, hospital location |
| Keller et al, 2010[40] | 2006 | 55,424 | CRC (94) | Age, sex, Race/ethnicity, comorbidity index, duration of follow-up |
| Shiels et al[43],* | 1996–2007 | Not reported | Colon (61) | Age |
| Park et al[44] | 1996–2008 | Not reported | CRC (124) | Age, sex, race/ethnicity, calendar period |
| Robbins et al[45] | 1996–2010 | 275,975 | CRC (404) | Age, sex, race/ethnicity, calendar period |
| Robbins et al[46] | 2003–2010 | 859,522 | CRC (360) | Age, sex, race/ethnicity, calendar period |
| Shiels et al[47] | 1980–2010 | 4,471,704 | CRC (472) | Age, sex, race/ethnicity, calendar year, registry site |
| Coghill et al[48] | 1996–2010 | Not reported | CRC (130†) | Age, sex, race/ethnicity, calendar year, cancer stage |

**TABLE 1.** (*Continued*) Characteristics of Studies Identified From Systematic Review of CRC Incidence and Associated Mortality in Those HIV+ Compared With an Uninfected Population (Sorted by Country and Year of Publication)

| Study | Period of Follow-up | Reported Person-years | Observed Cancer (n) | Variables Used to Standardize SIR/SMR |
|---|---|---|---|---|
| Marcus et al[49] | 1996–2011 | Not reported | CRC (53†) | Age, sex, race/ethnicity, cancer stage |
| Silverberg et al[50] | 1996–2009 | 475,660 | CRC (35) | Age, sex, race/ethnicity, cohort site |
| Castilho et al[51] | 1998–2010 | 12,334 | CRC (7) | Age, sex |
| Grulich et al[13] | 1980–1999 | Not reported | CRC (7) | Age, sex, year, location (state) |
| van Leeuwen et al, 2009[7] | 1982–2004 | 135,179 | CRC (17) | Age, sex |
| Newnham et al[20] | 1985–2001 | 189,756 (158,658 men; 31,098 women) | CRC (28) | Age, sex |
| Serraino et al[52] | 1985–2005 | 44,400 | Colon (1) | Age, sex |
| Dal Maso et al, 2009[15] | 1986–2004 | 101,669 | CRC (23) | Age, sex, HIV risk factors, time of cancer diagnosis relative to AIDS diagnosis |
| Zuchetto et al[53] | 2006–2011 | Not reported | CRC (10†) | Age, sex |
| Vogel et al[54] | 1996–2009 | 8772 | CRC (3) | Age, sex |
| Chen et al[55],* | 1998–2009 | 66,634 (59,613.34, men; 7,021, women) | CRC (110) | Age, sex |
| Chen et al[56] | 2000–2011 | Not reported | CRC (11) | Age, sex, calendar year |
| Helleberg et al[1] | 1995–2011 | 18,670 | CRC (4) | Age, sex, HIV risk factors, duration on cART, year of study inclusion |

*Excluded from meta-analysis of incidence of SRC because of overlap with other publications.
†Total reported deaths due to CRC, not number of cases occurring in registry.
AIDS, acquired immune deficiency syndrome; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency syndrome.

diagnosed. All studies included in quantitative synthesis adjusted for age and sex, at a minimum.

Results from random effects meta-analysis demonstrated no summary effect risk of CRC and colon cancers among people with HIV relative to an uninfected population (SIR 1.00; 95% CI: 0.82 to 1.22) (Fig. 2). We observed substantial and significant heterogeneity in the magnitude of the effect across included studies ($I^2 = 89.2\%$, $P < 0.00001$). In analyses that pooled results from publications reporting CRC cancer and colon cancer separately, we observed no summary effect risk specific to CRC (SIR 1.04; 95% CI: 0.85 to 1.27), whereas a lower risk of colon cancer was observed among people with HIV relative to an uninfected comparator population (SIR 0.63; 95% CI: 0.52 to 0.75) (Supplemental Digital Content, Figure 1, http://links.lww.com/QAI/B20). In sensitivity analyses, no significant changes were observed by individual removal of publications (range of summary point estimate SIRs 0.92–1.23) or exclusion of the study contributing the largest number of CRC cases[47] (SIR 0.97; 95% CI: 0.90 to 1.04) ($I^2 = 91\%$, $P < 0.00001$). Furthermore, no significant changes were observed in SIR after individual removal of either one of two publications drawing CRC cases from the same population (SIRs 1.00 and 0.97).[46,47] By contrast, exclusion of the study contributing the largest number of cases to the colon cancer–only analysis suggested no association between HIV and this outcome (SIR 0.77; 95% CI: 0.50 to 1.20).[43]

In subgroup analysis, results were consistent for studies conducted in the United States (SIR 0.95; 95% CI: 0.66 to 1.38) and elsewhere (SIR 1.0; 95% CI: 0.32 to 3.14), as well as for studies identifying CRC cases from hospitals (SIR 1.10; 95% CI: 0.63 to 1.92) and registries (SIR 0.97; 95% CI: 0.78 to 1.21). In addition, the summary estimate was similar among 5 studies reporting data exclusively before cART (1995 and earlier)[6,15,18,41,46] (SIR 1.48; 95% CI: 0.79 to 2.43) and 12 studies of data from 1996 and onward[6,15,18,19,40,44–46,50,51,54,56] (SIR 1.18; 95% CI: 0.80 to 2.16). By contrast, pooled results from 3 studies reporting 21 cases for women found a higher rate of CRC among women with HIV[20,41,56] (SIR 3.53; 95% CI: 1.57 to 7.96) (Supplemental Digital Content, Figure 2, http://links.lww.com/QAI/B20). No such change was observed in the 4 studies independently reporting men[20,41,54,56] (SIR 1.41; 95% CI: 0.31 to 6.37) (Supplemental Digital Content, Figure 3, http://links.lww.com/QAI/B20). Significant heterogeneity was observed in all subgroup analyses (range $I^2$ = 88–92%, $P < 0.0001$).

Asymmetry was observed in the funnel plot of studies of CRC/colon SIR, a finding which may reflect the inclusion of a small number of heterogeneous studies with null effects, (Supplemental Digital Content, Figure 4, http://links.lww.com/QAI/B20). There was no evidence of publication bias using the Begg test ($P = 0.78$) or Egger test ($P = 0.28$), although these tests are insensitive when small numbers of studies are included.[57] A post hoc trim-and-fill method[58] was also applied to assess the effect of publication bias, with no effective change in summary SIR point estimates from 0.96 to 1.12 with the addition of 4 hypothetical studies.

## Risk of CRC Mortality

Three studies reported a total of 194 CRC-attributed deaths. All studies adjusted for age and sex, at a minimum. Although the random effects meta-analysis demonstrated summary risk of death due to CRC among those with HIV relative to an uninfected population, there was inadequate precision to reject the null hypothesis of no difference (SMR 2.09; 95% CI: 1.00 to 4.40) (Fig. 3). Substantial and significant heterogeneity in the magnitude of the effect across included studies was detected ($I^2 = 85.0\%$, $P = 0.001$). Bias

**TABLE 2.** Quality Assessment (Newcastle-Ottawa Scale) Results From Studies Identified From Systematic Review of CRC Incidence and Associated Mortality in Those HIV+ Compared With an Uninfected Population

| | Selection | | | | Comparability | Outcome | | | Overall |
|---|---|---|---|---|---|---|---|---|---|
| **Study** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **Score*** |
| Long et al, 2008[19] | * | * | * | * | ** | * | * | — | 8 |
| Engels et al[17] | * | * | * | * | ** | * | — | * | 8 |
| Patel et al[18] | * | * | * | * | ** | * | * | — | 8 |
| Simard et al[38] | * | * | * | * | ** | * | — | — | 7 |
| Silverberg et al[39] | * | * | * | * | ** | * | * | — | 8 |
| Keller et al, 2014[40] | * | * | * | * | ** | * | — | — | 7 |
| Cooksley et al[41] | * | * | * | * | ** | * | * | — | 8 |
| Gallagher et al[42] | * | * | * | * | ** | * | * | — | 8 |
| Shiels et al, 2010[43] | * | * | * | * | ** | * | * | — | 8 |
| Park et al[44] | * | * | * | * | ** | * | * | — | 7 |
| Robbins et al[45] | * | * | * | * | ** | * | * | — | 7 |
| Robbins et al[46] | * | * | * | * | ** | * | * | — | 7 |
| Shiels et al[47] | * | * | * | * | ** | * | * | — | 7 |
| Coghill et al[48] | * | * | * | * | ** | * | * | — | 7 |
| Marcus et al[49] | * | * | * | * | ** | * | * | — | 8 |
| Silverberg et al[50] | * | * | * | * | ** | * | * | — | 7 |
| Castilho et al[51] | * | * | * | * | ** | * | * | — | 7 |
| Grulich et al[13] | * | * | * | — | ** | * | * | — | 7 |
| van Leeuwen et al, 2009[7] | * | * | * | * | ** | * | * | — | 7 |
| Newnham et al[20] | * | * | * | * | ** | * | * | — | 8 |
| Serraino et al[52] | * | — | * | * | * | * | * | — | 6 |
| Dal Maso et al, 2009[15] | * | * | * | * | ** | * | * | — | 8 |
| Zuchetto et al[53] | * | * | * | * | ** | * | * | — | 7 |
| Vogel et al[54] | * | * | * | * | ** | * | * | — | 8 |
| Chen et al[55] | * | * | * | * | ** | * | * | — | 8 |
| Chen et al[56] | * | * | * | * | ** | * | * | — | 7 |
| Helleberg et al[1] | * | * | * | * | ** | * | * | — | 8 |

Newcastle–Ottawa scale[30] for cohort studies includes criteria to evaluate the following: (A) selection: (1) representativeness of the exposed cohort; (2) selection of nonexposed cohort; (3) ascertainment of exposure; and (4) demonstration that outcome of interest was not present at start of study. (B) Comparability: (5) comparability of cohorts on the basis of the design of analysis. (C) Outcome: (6) assessment of outcome; (7) was follow-up long enough for outcomes to occur; and (8) adequacy of follow-up of cohorts. One star allocated for demonstration of criteria present, except comparability which can have a maximum of 2 stars for different categories of exposure. No stars (—) reflect item unreported.

*Newcastle–Ottawa Scale range 0–9 (where higher scores indicate higher quality of reporting).

was not assessed because of the small number of included studies.

## DISCUSSION

We performed a comprehensive systematic review of the literature and meta-analysis to assess the risk of CRC among people with HIV relative to an uninfected population. Relative to the most recently published meta-analysis, we included 12 additional studies reporting SIRs for CRC and 3 studies reporting mortality.[3] Overall, 27 retrospective cohort studies were considered relevant, with the body of literature judged to be of high quality. From 23 studies included in meta-analysis, our results support the hypothesis that the incidence of CRC is similar between persons with HIV and a referent population. Although the risk of CRC mortality was also similar between people with and without HIV, few studies reported on this outcome, and further research is required to confirm this finding. Results were consistent for studies conducted in the United States and elsewhere, as well as before and after the introduction of cART.

Our results corroborate those of previously published meta-analyses, finding a similar incidence of CRC among people with HIV relative to the general population.[2,3] The finding that HIV does not impart an increased risk of CRC is somewhat unexpected in light of studies demonstrating a higher prevalence of adenomatous polyps in people with HIV relative to uninfected individuals.[21–25] The mechanism through which HIV increases the risk of polyps is not completely understood and likely multifactorial. Although some studies have found that antiretroviral therapy, detectable viral load, and CD4 cell count influence the development of polyps, these results have not been consistently observed.[21–23] A nearly 2-fold increase in the risk of polyps has been associated with smoking, which is more prevalent in people with HIV relative to HIV-negative individuals.[1] Furthermore, HIV and its treatments have been associated with elevations in insulin and proinflammatory cytokines, as well as reduced levels of adiponectin, all of which may promote neoplastic growths of the colonic mucosa.[60–65] Finally, HIV may activate β-catenin signaling pathway, a process associated with the initiation of intestinal neoplasia.[66] Because the adenomatous polyp-CRC pathway is thought to give rise to a large proportion of CRCs, a correspondingly higher rate of CRC in people with HIV would be expected. This discrepancy may occur because endoscopic investigations are frequently used for diagnostic and screening purposes in people with HIV, given the high prevalence of gastrointestinal symptoms and human papillomavirus-associated anorectal disease in this population.[67–71] In one study examining CRC screening in predominantly male patients with HIV, only 3.8% of colonoscopies were undertaken for routine screening, with the remainder being performed for diagnostic reasons.[70] A separate study found that men with HIV were more likely to undergo colonoscopy or sigmoidoscopy than HIV-negative men.[72] The use of endoscopic investigations in people with HIV may permit early identification and removal of adenomatous polyps before malignant transformation occurs, thereby mitigating any excess risk of CRC associated with a higher prevalence of these growths. This assertion may also explain in part the lower risk of colon cancer observed among people with HIV after meta-analysis, although this finding should be interpreted cautiously because it was influenced strongly by data from one large study.[43]

Our finding of an increased risk of CRC in women warrants cautious interpretation because it is based on few cases identified from 3 studies with significant and substantial heterogeneity. More specifically, this finding was driven by studies in the United States (SIR 4.0, 95% CI: 1.1 to 10.2) and Taiwan (SIR 5.8; 95% 3.2 to 9.7) with samples of persons with HIV who were overwhelmingly (>90%) men.[41,56]

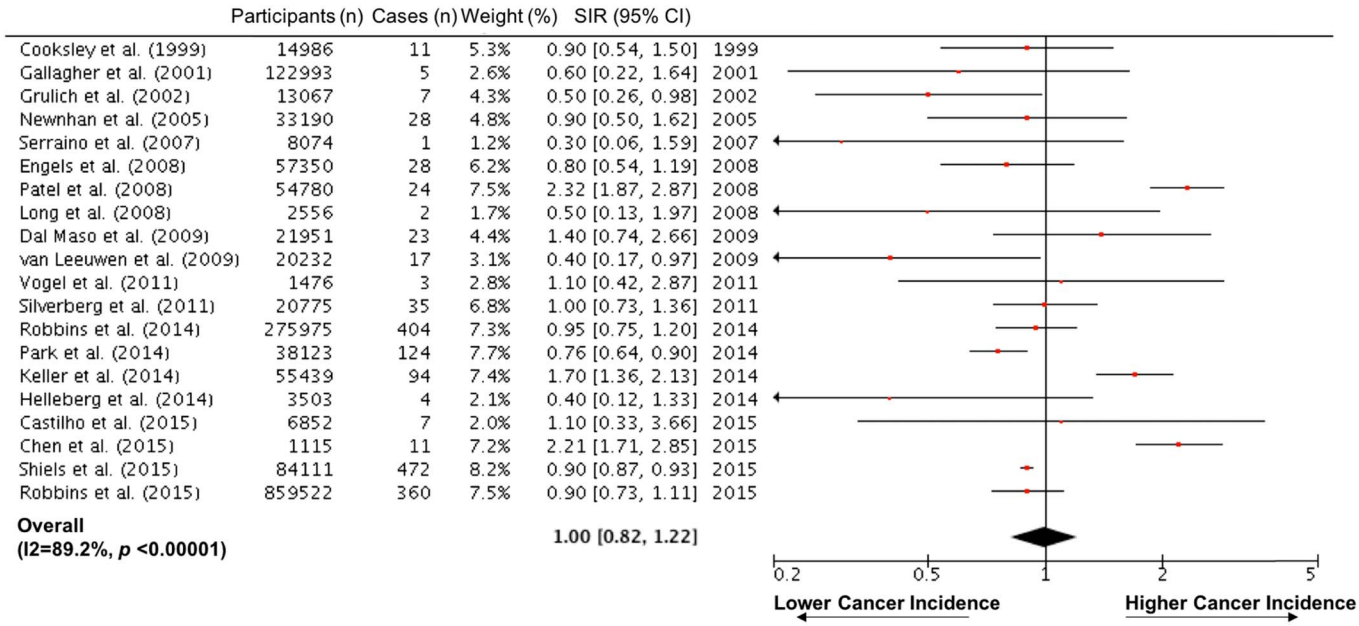


**FIGURE 2.** Results from random effect meta-analysis of SIR and 95% CIs of incident CRC among those with HIV+ compared with an uninfected population.

Given our lack of precision around point estimates for women, further research is required to confirm whether women with HIV are a high risk population for CRC, and to uncover the biologic, social, or health system explanations for such a disparity.

We also observed a 2-fold higher rate of CRC-related mortality in people with HIV relative to uninfected individuals, although this finding should be considered preliminary, given it is based on 3 studies and does not meet conventional criteria for statistical significance. Furthermore, it is possible that our literature search may have missed studies related to this outcome because it was developed primarily for identifying studies comparing the incidence of CRC in people with and without HIV. This finding is, however, consistent with research demonstrating an increased risk of cancer-specific mortality[53] among people with HIV relative to the general population and is further supported by evidence demonstrating that people with HIV and CRC are less likely to receive cancer treatment than uninfected people with CRC.[73] In addition, small studies have found that patients with HIV have more advanced stage disease at presentation relative to uninfected individuals, which may also contribute to a higher risk of disease-attributable death.[74,75]

Strengths of this study include the large sample size, geographic and temporal diversity of the contributing cohorts, and evaluation of CRC risk separately for men and women with HIV. However, several limitations merit emphasis. Most notably, data regarding important risk factors for CRC, including race/ethnicity, smoking, alcohol consumption, and body mass index, were not consistently reported in studies. We were, therefore, unable to adjust for these variables or examine whether differences existed between different groups. Similarly, we were unable to assess the impact of stage of CRC, treatment modalities, and nonmortality outcomes attributed to the incident cancer diagnosis. In addition, the pooled SIR estimate should be interpreted cautiously because individual study SIRs were derived from populations which differed in age and sex composition, as well as genetic predisposition to CRC. Moreover, the review synthesized results from study-level data only. Consequently, although we are able to draw inferences about the incidence of CRC among persons with HIV overall, we are unable to make definitive conclusions regarding individual risk of CRC among those with HIV. Estimates for those included studies who compared to a general, uninfected population may also be inferior to internal comparisons, biasing the effect of HIV

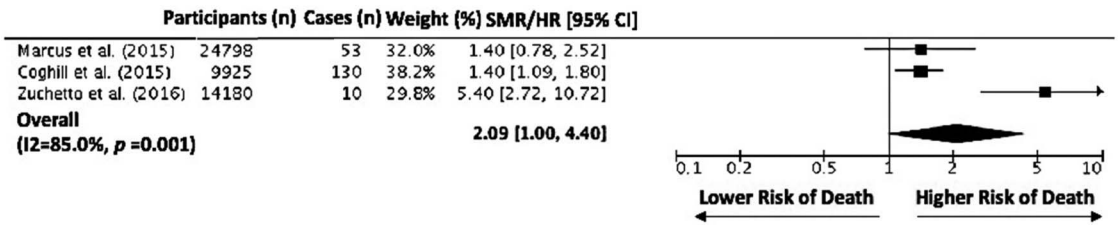


**FIGURE 3.** Results from random effect meta-analysis of SMR and 95% CIs of incident CRC among those with HIV+ compared with an uninfected population.

status on CRC risk. General limitations of all systematic reviews are applicable in that, despite comprehensive searching, our strategy may have failed to identify eligible studies. Last, we did not contact study authors for additional data of potentially relevant studies, thus leading to potential exclusion.

Our systematic review and meta-analysis contributes to the emerging body of literature regarding non-AIDS–defining cancers among the aging cohort of people with HIV. Our findings suggest that CRC screening guidelines developed for the general population are likely adequate for people with HIV, with risks and benefits of each modality being considered in light of individual risk for disease and underlying health. Further evaluation to explore whether people with HIV are at higher risk of CRC-related death and whether the incidence of CRC varies within the population of persons with HIV is warranted to inform clinical care and indicate where targeted interventions to promote screening are required.

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