Gynecologic cancer in HIV-positive women: a systematic review and meta-analysis

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BACKGROUND: While there is a significant body of literature on cervical cancer in HIV-positive women, little is known about other gynecologic cancers in this population.

OBJECTIVE: The objective of this systematic review and meta-analysis is to describe the incidence, presentation, treatment, and outcomes for HIV-positive women with non—acquired immunodeficiency syndrome—defining gynecologic cancers.

STUDY DESIGN: We searched MEDLINE, EMBASE, ClinicalTrials.gov, and the Cochrane Central Register of Controlled Trials for English-language studies published from 2000 to May 1, 2017. Studies containing 1 or more HIV-positive women with endometrial, ovarian, or vulvovaginal cancer and reporting incidence, treatment regimen, or survival were included. Two authors independently reviewed abstracts and full-text articles for inclusion and assessed study quality (details of the review protocol were registered as PROSPERO-CRD42017064525). Pooled estimates of incidence were calculated using random-effects models. Pooled estimates of cancer presentation and outcomes were averaged from case studies.

RESULTS: Of 5744 abstracts screened, we identified 70 articles on 58 studies on 292,202 women with HIV and 528 women with HIV and gynecologic cancer for inclusion. Most articles (53%) focused on incidence, and only 3, 4, and 20 articles focused on treatment and outcomes of endometrial, ovarian, and vulvovaginal cancers, respectively. The standardized incidence ratios for endometrial, ovarian, and vulvovaginal cancers were 4.38 (95% confidence interval 0.26—8.49) for endometrial cancer, 3.21 (95% confidence interval 2.29—4.13) for ovarian cancer, and 21.93 (95% confidence interval 13.50—30.35) for vulvovaginal cancer. Fifty-seven percent of women were diagnosed at an early stage, and all received cancer treatment.

CONCLUSION: In women with HIV, the incidence of ovarian and vulvovaginal cancer were higher than the general population, while incidence of endometrial cancer was similar. However, there was a paucity of data on treatment and outcomes for non—acquired immunodeficiency syndrome—defining gynecologic cancers. Given the increased incidence of gynecologic cancer, specific research on this population is essential to improve treatment and outcomes for HIV-positive women.

Key words: acquired immunodeficiency syndrome, AIDS, cancer, HIV, human immunodeficiency virus, human papillomavirus

Introduction

Women account for 25% of the population living with human immunodeficiency virus (HIV) in the United States and more than 50% of the population with HIV worldwide.[1,2] With the advent of highly active antiretroviral therapy (HAART), the life expectancy of women with HIV has increased dramatically.[3] This increase in life expectancy may lead to a greater burden of both acquired immunodeficiency syndrome (AIDS)-defining cancers, including cervical cancer, Kaposi sarcoma, and non-Hodgkin lymphoma, and non-AIDS-defining cancers, both of which are more common with increasing age. Individuals with HIV are more likely to develop a wide variety of cancers than the general population, especially cancers related to the human papillomavirus (HPV).[4–6] However, little is known about the incidence of gynecologic cancers other than cervical cancer worldwide, and specifically, whether the rate of endometrial, ovarian, and vulvar cancers differs from the general population.

Moreover, when women with HIV develop cancer, they experience disparities in care compared to women without HIV.[7,8] The reasons for this are likely multifactorial and may include a disproportionate prevalence of HIV in women of lower economic status, oncologists' comfort in treating women with HIV, and barriers to accessing health care.[9] Although there is a significant body of literature focused on the treatment and outcomes of cervical cancer in women with HIV, studies focusing on treatment outcomes, including potential disparities, in non-AIDS-defining gynecologic cancers are understudied.

Thus, the objectives of this systematic review and meta-analysis are (1) to assess the incidence of endometrial, ovarian, and vulvovaginal cancers in women with HIV compared to the general population; (2) to examine cancer presentation and oncologic treatments received by HIV-positive women with endometrial, ovarian, vulvar, or vaginal cancer; and (3) to characterize gynecologic cancer outcomes among women with HIV.

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Received Aug. 17, 2018; revised Jan. 17, 2019; accepted Feb. 7, 2019.

The authors report no potential conflicts of interest. This work was self-funded by the study authors.

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0002-9378/$36.00 • https://doi.org/10.1016/j.ajog.2019.02.022

AJOG at a Glance

Why was this study conducted?

While there is a significant body of literature on cervical cancer in HIV-positive women, little is known about other gynecologic cancers in this population.

Key findings

Our meta-analysis and systematic review of 57 studies found a higher incidence of vulvovaginal cancer and of ovarian cancer in women with HIV compared to women without HIV. Few studies looked at cancer outcomes.

What does this add to what is known?

There was a paucity of data on treatment and outcomes for non–acquired immunodeficiency syndrome–defining gynecologic cancers. Given the higher incidence of gynecologic cancer—and anticipated increase with longer life expectancy post-highly active antiretroviral therapy—among women with HIV, specific research on this population is essential to improve cancer treatment and outcomes for HIV-positive women.

Materials and Methods

Sources

We searched MEDLINE, EMBASE, ClinicalTrials.gov, and the Cochrane Central Register of Controlled Trials from January 1, 2000 to May 1, 2017. Electronic searches were supplemented by reviewing reference lists of included studies and prior systematic reviews, hand-searching the journal *Gynecologic Oncology*, and contacting authors of included studies for any additional published or unpublished studies meeting review inclusion criteria. If the search identified a meeting abstract, we searched MEDLINE for whether there was a related full-text article by the same authors. We developed search terms based on input from a reference librarian and prior systematic reviews on HIV or gynecologic cancer (Appendix: Supplemental Table 1).[10,11] We limited the search to English language articles.

Details of the review protocol were registered on PROSPERO, an international database of prospectively registered systematic reviews, and can be accessed at http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42017064525. As a meta-analysis of existing data, our review was exempt from institutional review.

Study selection

Studies were included if they met the following criteria: (1) included 1 or more women diagnosed with HIV and International Federation of Gynecology and Obstetrics (FIGO) stage 1 or higher endometrial, ovarian, vulvar, or vaginal cancer; (2) examined the incidence or oncologic treatment of HIV-positive women with endometrial, ovarian, vulvar, or vaginal cancer; and (3) reported outcomes measures including, but not limited to, standardized incidence ratio, incidence rate, stage at diagnosis, treatment regimen, overall survival, progression-free survival, or adverse events. We included all ages, histologic types of tumor, and stages of HIV/AIDS. We included all study designs other than reviews or editorials. To avoid overlapping patient data in publications reporting on the same cohort of

FIGURE 1
Flow diagram of study selection

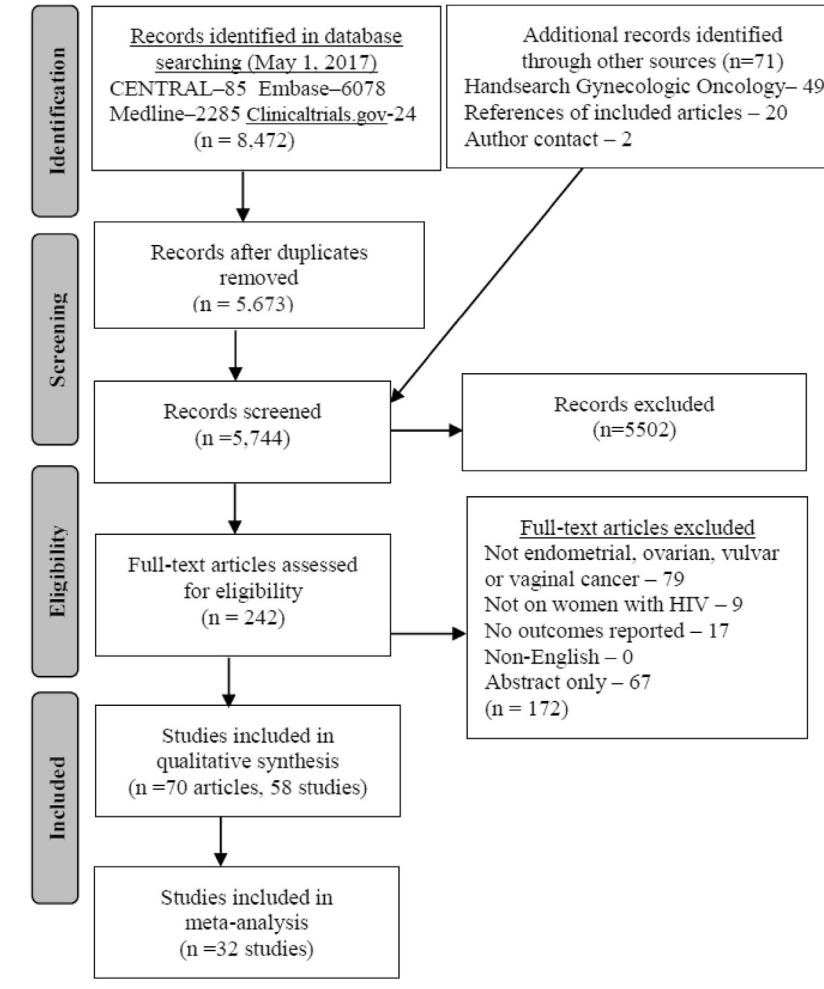

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TABLE 1
Characteristics and cancer incidence in included studies

Author, year	Country	Study method	Time period	Number of women with HIV	Number of gynecologic cancer cases
Akarolo-Anthony 2014[23]	Nigeria	Retrospective cohort	2009–2012	10,580	2
Alalade 2009[43]	Wales (United Kingdom)	Case report	2008	1	1
Albu 2000[44]	USA	Case series	1993–1998	96	8
Belotte 2012[45]	USA	Case report	2012	1	1
Bogani 2017[46]	Italy	Retrospective cohort	1998–2008	4	2
Bradbury 2016[47]	Spain	Retrospective cohort	1994–2011	37	2
Brown 2005[48]	USA	Case series	1999–2002	3	3
Calabresi 2013[49]	Italy	Retrospective cohort	1999–2009	1430	3
Castilho 2015[50]	Brazil, USA	Retrospective cohort	1998–2010	1916	3
Chen 2014[26]	Taiwan	Prospective cohort	1998–2009	1491	9
Clemente 2017[51]	Italy	Case report	2010–2016	1	1
Dal Maso 2009[24,28]	Italy	Prospective cohort	1986–2005	4891	7
Dedes 2008[33]	Switzerland	Case series	1992–2007	31	2
Dhir 2008[29]	India	Prospective cohort	2001–2005	85	6
Dryden-Peterson 2015[20]	Botswana	Retrospective cohort	2003–2008	NR	135
Elit 2005[52]	Canada	Case report	2002–2004	1	1
Engels 2006[21]	USA	Prospective cohort	1980–2002	71564 (AIDS only)	15
Engels 2008[4]	USA	Prospective cohort	1991–2002	19,785	12
Fordyce 2000[31]	USA	Retrospective cohort	1981–1994	15146 (AIDS only)	4
Franceschi 2010[53,54]	Switzerland	Prospective cohort	1985–2003	2045	2
Franzetti 2013[22]	Italy	Prospective cohort	1985–2011	1542	8
Gallagher 2001[55]	USA	Prospective cohort	1981–1994	1,288 (AIDS only)	11
Giaquinto 2000[56]	Italy	Case report	1996–2000	1	1
Godbole 2016[57]	India	Retrospective cohort	1996–2008	11710	11
Goedert 2006[15,16,18,27,32,58,59]	USA	Prospective cohort	1980–2002	85,268	73
Grulich 2002[60]	Australia	Retrospective cohort	1995–1998	1151	1
Helleberg 2014[61]	Denmark	Prospective cohort	1995–2011	1574	1
Herida 2003[62]	France	Prospective cohort	1992–1999	19,597	6
Knox 2000[63]	USA	Case report	.	1	1
Kurnit 2015[17]	USA	Retrospective cohort	2010–2014	232	6
Lanjewar 2015[64]	India	Case report	.	1	1
Lee 2000[65]	USA	Case report	.	1	1
Majeed 2006[66]	South Africa	Case report	.	1	1
Massad 2012[30,67–69]	USA	Prospective cohort	1994–2008	2791	5
Mayor 2016[70]	USA	Prospective cohort	1992–2009	1218	7
Mbulaiteye 2006[19]	Uganda	Retrospective cohort	1988–2002	8423	9
Moodley 2000[71]	South Africa	Case report	1990–2000	1	1
Moodley 2003[72]	South Africa	Case report	.	1	1

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TABLE 1
Characteristics and cancer incidence in included studies *(continued)*

Author, year	Country	Study method	Time period	Number of women with HIV	Number of gynecologic cancer cases
Moodley 2004[73]	South Africa	Case report	.	1	1
Newnham 2005[74]	United Kingdom	Prospective cohort	1985–2001	7110	2
Nguessan 2013[75]	Ivory Coast	Case report	.	1	1
Patel 2008[5]	USA	Prospective cohort	1992–2003	.	17
Phelps 2001[35]	USA	Prospective cohort	1993–2000	871	1
Raffetti 2015[76]	Italy	Retrospective cohort	1986–2012	4152	5
Ramirez-Marrero 2010[77]	USA	Prospective cohort	1987–2003	6830	7
Rao 2015[78]	India	Case report	.	1	1
Riera 2013[36]	Belgium	Case report	.	1	1
Sachdeva 2016[79]	India	Retrospective cohort	2009–2013	NR	1
Salters 2016[12]	Canada	Retrospective cohort	1994–2008	2211	3
Sekowski 2008[80]	South Africa	Case report	.	5	5
Sengayi 2016[81]	South Africa	Retrospective cohort	2004–2010	4450	11
Silverberg 2009[6]	USA	Retrospective cohort	1996–2007	1926	22
Simbiri 2014[37]	Botswana	Case series	.	13	13
Sitas 2000[14]	South Africa	Case-control	1995–1999	NR	28
Strehl 2012[82]	Germany	Case report	2009	1	1
Tanaka 2018[25,39]	Brazil	Retrospective cohort	1997–2012	NR (AIDS only)	43
Vogel 2011[83]	Germany	Prospective cohort	1996–2009	280	1
Yanik 2016[13]	USA	Case-control	2004–2011	NR	NR
Zucchetto 2016[38]	Italy	Retrospective cohort	2006–2011	1070	4

N = 70 articles on 58 studies.

AIDS, acquired immunodeficiency syndrome; *N/A*, not applicable; *NR*, not reported.

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women, we included the articles with the largest sample size.

Duplicate articles (same title and authors) were removed using Mendeley (Elsevier, Inc., Philadelphia, PA). Two reviewers screened titles and abstracts for initial assessment for inclusion using Covidence (Veritas Health Innovation Ltd., Melbourne, Victoria, Australia). Two reviewers then reviewed full-text articles for final inclusion/exclusion. Agreement between the reviewers was assessed using a kappa statistic, and disagreements were resolved by consensus.

Data extraction and risk-of-bias assessment

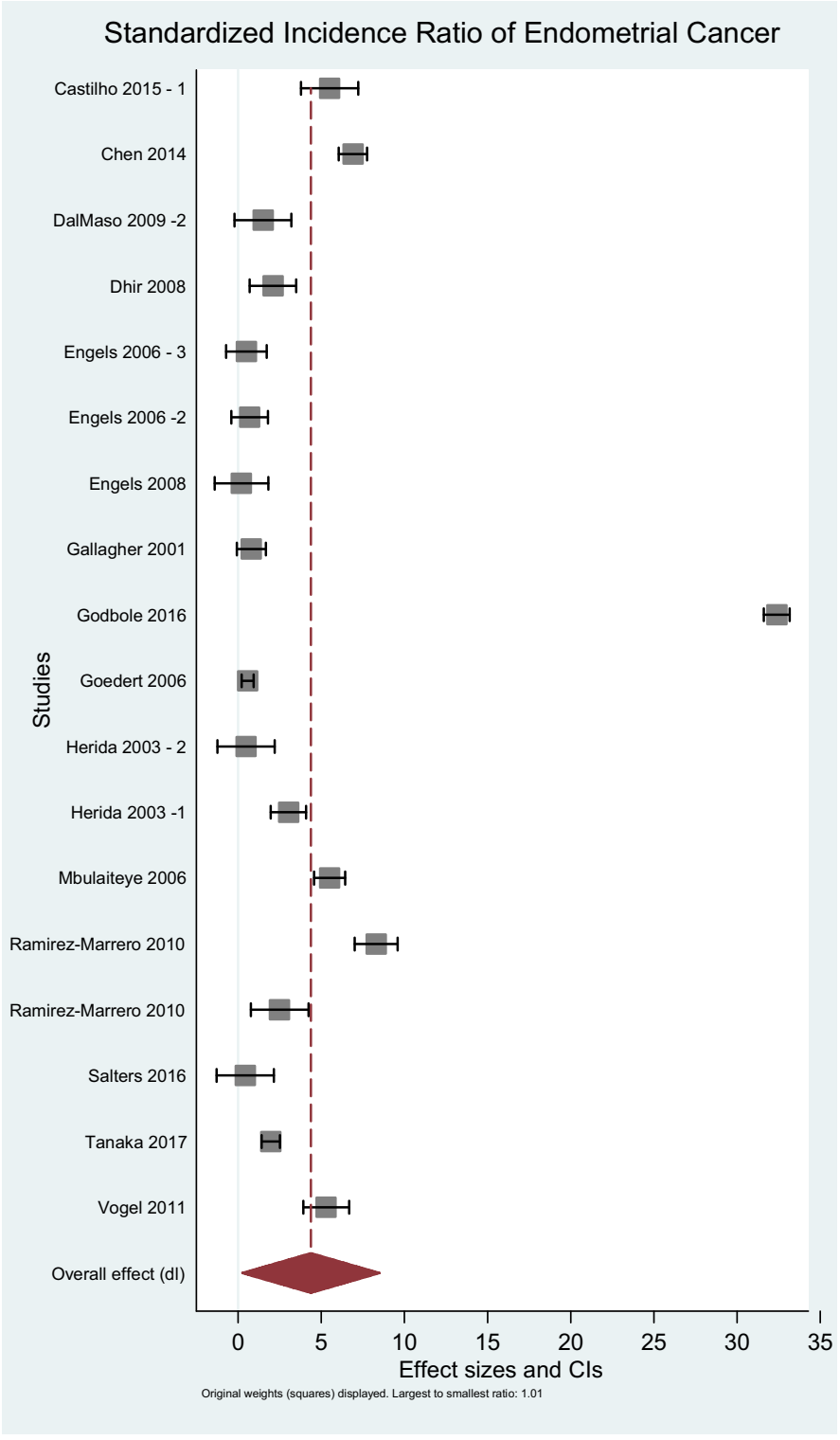
Data were extracted by 2 reviewers independently using a standardized form. Extracted data included author, year of publication, journal, study location, study design, study population, incidence rate or rate ratio, patient age, stage of cancer, CD4 count and HAART treatment at diagnosis (when available), oncologic treatment received, available outcome date, adverse events, and items for assessment for risk of bias. Differences in data extraction were resolved by review of the original articles.

Two independent reviewers assessed quality and the risk of bias in included studies using a standardized quality assessment tool from the National Heart, Lung, and Blood Institute. The maximum score for a cohort study was 14, and the maximum score for a case-control study was 9. We included studies at all levels of quality/risk of bias in data synthesis.

Analysis

Results are presented in a narrative synthesis for each type of gynecologic cancer. For incidence, we performed aggregate data DerSimonian-Laird random-effects meta-analysis using Stata 11.0 (StataCorp, College Station, TX) when 3 or more cohort studies reported standardized incidence ratios or incidence rate. For age-standardized incidence rates where standard error was not reported, we estimated study-specific standard error using the following formula: standard error = ln(upper 95% confidence interval of study) − ln (standardized incidence ratio of study)/1.96,

FIGURE 2
Standardized incidence ratio of endometrial cancer



CI, confidence interval.

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where ln represents the natural logarithm.[10] We used stratified bivariate meta-analyses and meta-regression to explore heterogeneity in incidence for each gynecologic cancer by AIDS status, pre-HAART (pre-1996), use of a cancer registry, and prospective study design.[10,11] We assessed heterogeneity between the studies included in meta-analysis using the I^2 statistic and visual inspection of funnel plots.

For presentation and treatment data, we calculated the mean age and CD4 count at diagnosis for each type of gynecologic cancer. We also calculated the proportion of women presenting at early stage of cancer and of women on HAART treatment at diagnosis by cancer type. For survival, we report the percent surviving at 5 years postdiagnosis by cancer type when there were case reports of multiple HIV-positive women with the specific gynecologic cancer.

Results

Of 5744 abstracts screened, we identified 70 articles on 58 studies (Figure 1). These articles included 292,202 women with HIV and 528 women with HIV and gynecologic cancers other than cervical cancer. The kappa statistic for interrater reliability was 0.88 (95% confidence interval [CI] 0.83–0.94). Twenty studies were conducted in North America, 18 in Europe, 12 in Africa, 7 in Asia, 1 in South America, and 1 in North and South America (Table 1). The majority of studies were prospective cohorts from HIV cancer registries and of moderate quality (Appendix: Supplemental Table 2). There were 23 articles on endometrial cancer in HIV-positive women, 29 on ovarian cancer, and 33 articles on vulvovaginal cancer. The majority of studies (31, 53%) for each of these cancers focused on incidence rather than treatment or cancer-related outcomes. There were 4, 6, and 21 articles focusing on presentation, treatment, and outcomes of endometrial, ovarian, and vulvovaginal cancers, respectively.

Incidence of gynecologic cancers in women with HIV

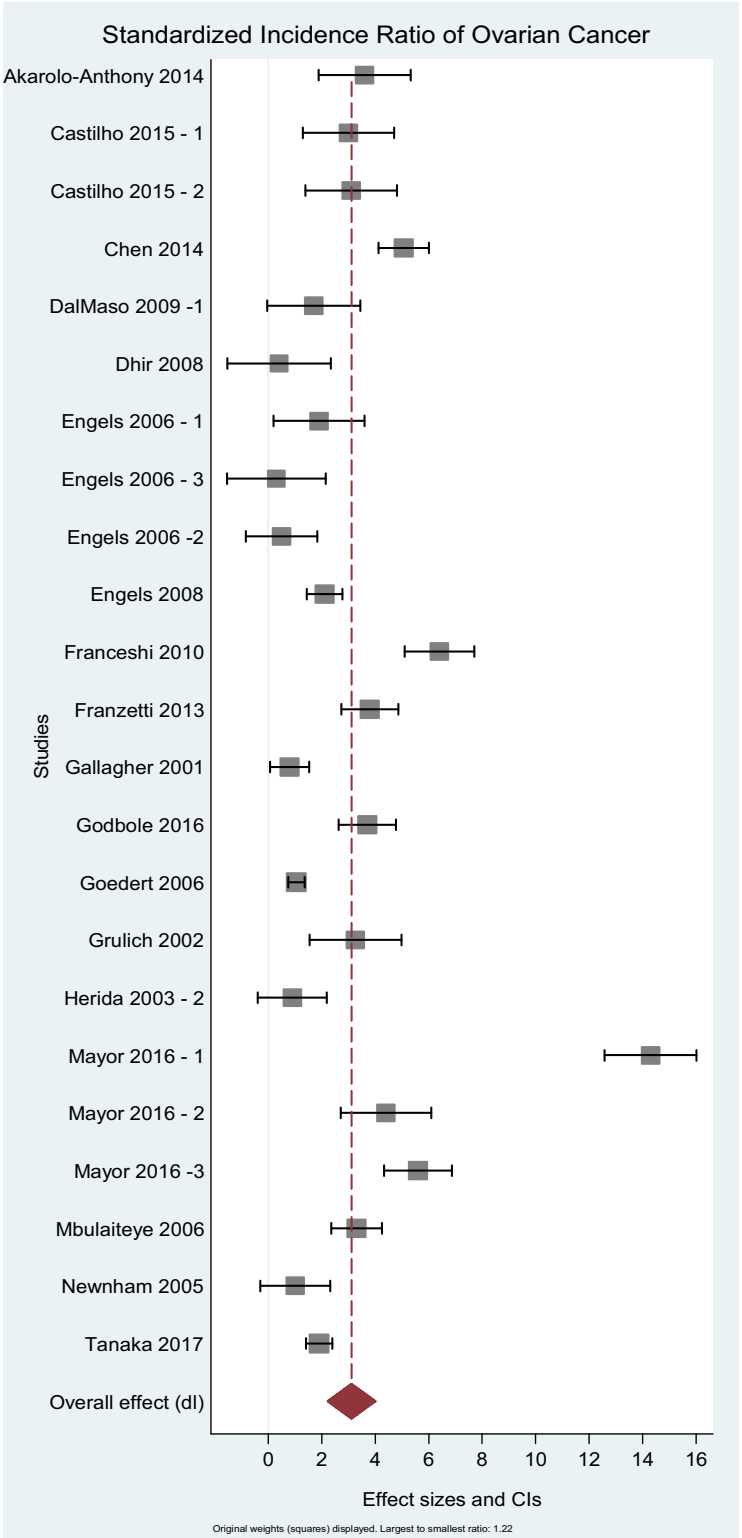
For endometrial cancer, 22 cohort studies reported on the incidence in

HIV-positive women. The standardized incidence ratio for endometrial cancer in HIV-positive women compared to noninfected women was 4.38 (95% CI 0.26–8.49, 18 studies). The incidence of endometrial cancer in HIV-positive women was 50 cases per 100,000 person-years (95% CI 30–80) (11 studies) (Figure 2). Three studies reported a similar standardized incidence ratio of endometrial cancer to the general population,[12–14] and 3 studies reported a lower incidence rate or reduced risk among women with HIV.[15–17] Two studies reported that the incidence of endometrial cancer increased over the past 20 years in women with HIV,[18,19] while one study found no change in age-standardized incidence over time.[20]

For ovarian cancer, 25 cohort studies reported on the incidence in HIV-positive women. The standardized incidence ratio was 3.11 (95% CI 2.22–4.00, 23 studies) with an incidence rate of 70 per 100,000 person-years (95% CI 40–100, 10 studies) (Figure 3). The standardized incidence ratio for ovarian cancer was similar in HIV-positive women compared to the general population in 7 studies,[4,15,19,21–24] while 2 studies reported an increase in standardized incidence ratio.[25,26] One study reported a nonsignificant increase over time in incidence of ovarian cancer among women with HIV.[18]

For vulvar and vaginal cancers, 19 cohort studies reported on the incidence in HIV-positive women. The standardized incidence ratio was 21.93 (95% CI 13.50–30.35, 13 studies) with an incidence of 1000 per 100,000 person-years (95% CI 1000–2000, 12 studies) (Figure 4). For vaginal cancers only, the standardized incidence ratio was 23.45 (95% CI 9.63–37.26, 6 studies) with an incidence of 70 per 100,000 person-years (95% CI 20–110, 6 studies). Compared to the general population, the standardized incidence ratio for vulvar or vaginal cancers was increased in HIV-positive women in 9 studies[5,6,21,22,25,27–30] and not different in 4 studies.[4,12,21,31] Two studies reported an increased incidence of vulvovaginal cancer over the past 20 years[18,22], while 3 studies reported no difference.[24,27,32] The risk of vulvar or

FIGURE 3
Standardized incidence ratio of ovarian cancer



CI, confidence interval.

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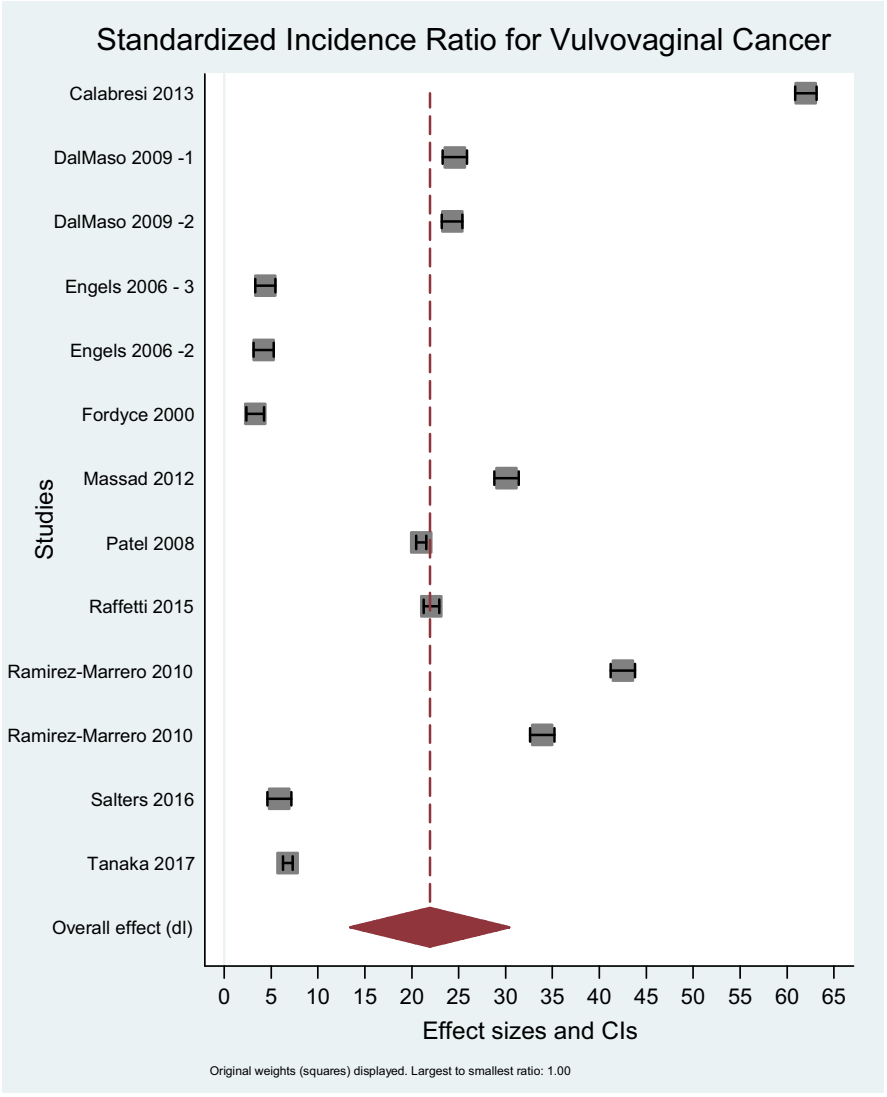
FIGURE 4
Standardized incidence ratio of vulvovaginal cancer



CI, confidence interval.

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vagina cancer increased significantly after an AIDS diagnosis and continued to increase over time after AIDS diagnosis in 1 cancer registry cohort study (*P*-for-trend $< .001$).[32] The rate of progression from vulvar intraepithelial neoplasia to vulvar cancer was 8.3% in 2 years of follow-up in 1 cohort study and was higher in women with HIV in another cohort (29/1000 persons-year [95% CI: 9.4—67.6] compared to 3.7/1000 person-year [95% CI: 0.09—21]).[33,34]

In univariate meta-regressions, post-HAART time period, use of a cancer registry, and prospective study design were not associated with any significant differences in incidence of endometrial, ovarian, vulvar, or vaginal cancers. AIDS status was associated with a lower standardized incidence ratio of ovarian cancer ($P = .03$) (Appendix: Supplemental Table 3).

Presentation and treatment of gynecologic cancers in women with HIV

Fifty-seven percent of women with HIV and gynecologic cancer were diagnosed at an early stage (stages I—II), and 43% were on HAART at cancer diagnosis.

There were 3 studies identified that focused on the presentation and treatment of endometrial cancer in HIV-positive women: 1 cohort study and 2 case reports. A large cohort study in the United States found no significant difference in stage at presentation or tumor grade in HIV-positive and HIV-negative women with endometrial cancer.[16] HIV-positive women with endometrial cancer developed endometrial cancer at a mean age of 46 years (range 38—53 years, 2 studies). In the 2 case reports, both were diagnosed with stage I endometrial adenocarcinoma and treated with primary surgery (Table 2).[35,36]

There were 6 studies that focused on presentation and treatment of ovarian cancer in HIV-positive women: 2 cohort studies and 4 case reports. Women with HIV were diagnosed with ovarian cancer at a median age of 33 years (range 16—57 years). Among women in whom stage was reported, 2 were diagnosed at an early stage (IA) and 1 at a late stage (IIIC). Two studies reported minimal adverse effects from chemotherapy in women with HIV and ovarian cancer (Table 3).

Twenty studies focused on the presentation and treatment of vulvar cancer in HIV-positive women: 10 cohort studies and 10 case reports. Vulvar cancer was diagnosed at a younger age in women with HIV compared to women without HIV.[37] Women with HIV were diagnosed with vulvovaginal cancer at a mean age of 38 years (range 12—50 years) (Table 4). Around half of women with HIV (54%) were diagnosed at an early stage of vulvovaginal cancer and treated with wide local excision. Four studies reported adverse effects of treatment, ranging from recurrent herpes infection to severe radiation skin toxicity necessitating cessation of treatment.

Cancer-related outcomes in women with HIV and gynecologic cancers

There were 22 studies, of which 20 were case reports, that focused on outcomes of endometrial, ovarian, and vulvovaginal cancers in HIV-positive women. One cohort study reported a higher standardized mortality rate in endometrial

cancer among women with HIV compared to those without HIV (52.5, 95% CI 14.3−134.5).[38] In the 4 case studies reporting survival in women with HIV and ovarian cancer, survival appeared similar to that in women without HIV. One cohort study reported no difference in hazard ratios of death at 1 or 5 years after ovarian or vulvovaginal cancer diagnosis in women with AIDS compared to the general population; hazard ratios at 5 years were 1.23 (95% CI 0.19−7.88) and 1.94 (95% CI 0.50-7.51) for ovarian and vulvovaginal cancers, respectively. Sixty-seven percent of women with ovarian cancer were alive 5 years after cancer diagnosis.[39] In the 14 studies reporting on survival in vulvovaginal cancer, survival ranged from 1 month to more than 8 years related to stage at vulvar or vaginal cancer diagnosis. In the largest cohort study, 78% of women with AIDS were alive 5 years after vulvovaginal cancer diagnosis.[39]

Comment

In this systematic review of 58 studies, including 292,202 women with HIV and 528 women with HIV and gynecologic cancer, we found a paucity of data on presentation, treatment, and outcomes of women with HIV and non-AIDS-defining gynecologic cancers, particularly for endometrial and ovarian cancers. Most of the published studies in this arena focus on the incidence of gynecologic cancers. Our meta-analysis shows that women with HIV developed endometrial cancer at a similar rate to the general population, women with HIV were slightly more likely to develop ovarian cancer, and women with HIV are substantially more likely to develop vulvovaginal cancer than women without HIV.

In vulvovaginal cancers, we notably found a risk for women with HIV more than double the incidence reported in the 2 earlier meta-analyses.[10,11] The majority of the studies reporting these high incidence rates were conducted in the post-HAART era, suggesting that as the lifespan of women with HIV increases, the burden of such HPV-related cancers may also increase.[5] We also found a slight increase in risk of ovarian

TABLE 2
Women with HIV and endometrial cancer: characteristics and outcomes of included case studies

Author	Year	Country	Number of patients	Histology	Age at cancer diagnosis (mean years)	HAART at diagnosis	CD4 count at diagnosis	Stage	Treatment	Adverse treatment effects	Recurrence	Progression-free survival	Overall survival
Phelps	2001	USA	1	Endometrial adenocarcinoma	38	No	574	Stage IB	Surgery	NR	NR	43+ months	43+ months
Riera	2013	Belgium	1	Endometrial adenocarcinoma	53	Yes	594	Stage IB	Total abdominal hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymphadenectomy → chemotherapy, palliative radiotherapy with tamoxifen	NR	Yes	7 months	19 months

HAART, highly active antiretroviral therapy; *NR*, not reported.

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TABLE 3
Women with HIV and ovarian cancer: characteristics and outcomes of included case studies

Author	Year	Country	Number of patients	Histology	Age at cancer diagnosis (mean years)	HAART treatment at presentation	CD4 count at presentation	Stage	Treatment	Adverse treatment effects	Recurrence	Progression-free survival	Overall survival
Knox	2000	USA	1	Poorly differentiated mixed adenocarcinoma	39	Yes	684	IIIC	Explorative laparotomy, total abdominal hysterectomy, bilateral salpingo-oophorectomy, optimal cytoreduction, 6 cycles carboplatin and paclitaxel	Grade 3 neutropenia and leukopenia, grade 2 anemia	NR	NR	NR
Sachdeva	2016	India	1	Ovarian cancer	57	Yes	NR	NR	Chemotherapy	NR	NR	45+ months	45+ months
Moodley	2000	South Africa	1	Epithelial ovarian cancer	31	No	311	NR	Cytoreduction, chemotherapy and radiation > palliative radiation	NR	Yes	9 years	9+ years
Moodley	2003	South Africa	1	Endodermal sinus tumor	16	No	903	IA	Right salpingo-oophorectomy, chemotherapy	None	No	1+ year	1+ year
Moodley	2004	South Africa	1	Ovarian granulosa cell tumor	23	No	455	IA	Right salpingo-oophorectomy	NR	NR	14+ months	14+ months
Tanaka	2018	Brazil	6	NR	NR	NR	NR	NR	NR	NR	NR	NR	66.7% survival 5 years after cancer diagnosis

HAART, highly active antiretroviral therapy; *NR*, not reported.

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TABLE 4
Women with HIV and vulvovaginal cancer: characteristics and outcomes of included case studies

Author	Year	Country	Number of patients	Histology	Age at cancer diagnosis (mean years)	HAART treatment at diagnosis	CD4 count at diagnosis (mean)	Stage	Treatment	Adverse treatment effects	Recurrence	Progression-free survival	Overall survival
Akarolo-Anthony	2014	Nigeria	1	SCC	39	Yes	80	IA	Imiquimod	None	NR	NR	6+ months
Belotte	2012	USA	1	SCC	NR	No	700	IIIA	Chemoradiation	NR	No	24+ months	24+ months
Brown	2005	USA	3	SCC	37	NR	493	IA (1), 1B (1), IVA (1)	1A: WLE > posterior radical vulvectomy 1B: Radical vulvectomy, lymphadenectomy IVA: TAH-RSO, radical vulvectomy > chemoradiation > posterior exenteration	Grade 3 cutaneous toxicity led to stopping radiation	Yes, in stage IA @ 6 months All cases had VIN postsurgery	6 months to 4 years	1–4+ years
Clemente	2017	Italy	1	SCC	50	No	300s	IIIB	Chemoradiation	NR	VIN, anal carcinoma	48 months	60+ months
Dedes	2008	Switzerland	2	SCC	37	Yes (50%)	NR	IA (2)	WLE	NR	NR	NR	NR
Elit	2005	Canada	1	SCC	33	No	300	IIIA	Radiation > laparotomy (aborted exenteration)	Sepsis	Yes	1 month	9 months
Frisch (Goedert 2006)	2000	USA	13	SCC	33	NR	NR	NR	NR	NR	NR	NR	NR
Giaquinto	2000	Italy	1	SCC	12	Yes	300	II	Hemivulvectomy, clitoral ambulation, bilateral inguinal lymphadenectomy -> laser vaporization, topical interferon-beta	NR	NR	3+ years	3+ years
Lanjewar	2015	India	1	SCC	32	Yes	61	NR	WLE	NR	NR	NR	NR

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(continued)

TABLE 4
Women with HIV and vulvovaginal cancer: characteristics and outcomes of included case studies *(continued)*

Author	Year	Country	Number of patients	Histology	Age at cancer diagnosis (mean years)	HAART treatment at diagnosis	CD4 count at diagnosis (mean)	Stage	Treatment	Adverse treatment effects	Recurrence	Progression-free survival	Overall survival
Lee	2000	USA	1	SCC	44	NR	339	IVA	Repair of vesicovaginal fistula (at presentation), lymphadenectomy, cervical conization, chemoradiation	Disease progression	N/A	3+ months	3+ months
Majeed	2006	South Africa	1	SCC	24	NR	218	IVA	Radiation	CD4 declined to 68	NR	6+ months	6+ months
Massad	2011	USA	2	SCC	NR	NR	NR	IB	WLE	NR	Yes (1 at 6 years post-WLE)	NR	14+ years, 8+ years
Massad	2012	USA	2	SCC	NR	NR	NR	II	Radiotherapy (1), WLE + radiotherapy (1)	Disease progression (1)	No	NR	10 months; 7+ years
Nguessan	2013	Ivory Coast	1	SCC	25	NR	NR	III	Chemotherapy, partial vulvectomy, lymphadenectomy	NR	No	6+ months	6+ months
Rao	2015	India	1	SCC	29	No	216	IA	Radical vulvectomy	NR	No	9+ months	9+ months
Sekowski	2008	South Africa	5	SCC	29	No	257	III (1), IV (4)	Radiotherapy (IV), Chemo-radiation (III)	NR	No	NR	1 month to 3+ years
Simbiri	2014	Botswana	13	SCC	38	Yes (38%), no (62%)	431	NR	NR	NR	NR	NR	NR
Strehl	2012	Germany	1	SCC	44	Yes	403	IA	Radical vulvectomy > imiquimod	Recurrent hypertrophic herpes simplex	Yes	5 months	2+ years
Tanaka	2018	Brazil	9	NR	NR	NR	NR	NR	NR	NR	NR	NR	77.8% survival 5 years after cancer diagnosis

HAART, highly active antiretroviral therapy; *N/A*, not applicable; *NR*, not reported; *SCC*, squamous cell carcinoma; *TAH-RSO*, total abdominal hysterectomy with right salpingo-oophorectomy; *VIN*, vulvar intra-epithelial neoplasia; *WLE*, wide local excision.

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cancer in women with HIV, which was not seen in previous studies. This may reflect differences in risk factors (for example, differences in rates of smoking) or in tumor biology with immunosuppression.[40,41]

Few studies looked at presentation, treatment, and outcomes in HIV-positive women with endometrial or ovarian cancers. This may reflect that, until recently, women with HIV did not live long enough to experience the burden of these cancers. Moreover, most clinical trials of gynecologic cancer treatment exclude women with HIV. The paucity of data in this area highlights the need for further investigation to help guide and inform treatment for these patients, especially as the age-related burden of these cancers will increase in years to come. The future burden of these cancers may be particularly great in non-Western settings where the prevalence of HIV is greater and cancer treatment resources are more limited. The cohort studies included in our study followed hundreds of women with gynecologic cancer, and follow-up on cancer outcomes among their study participants could be one way to investigate this area.

For vulvovaginal cancer, there were slightly more studies focusing on the presentation, treatment, and outcomes in HIV-positive women. These studies suggest that approximately half of women were diagnosed with early-stage disease. A minority of patients were on HAART at cancer diagnosis, increasing their likelihood of developing HPV-related cancers. This is consistent with prior studies on non-AIDS-defining cancers, showing that individuals with HIV, especially those with a low CD4 count, are more likely to present at a late or unknown stage than individuals without HIV.[7] While studies of other cancers in individuals with HIV suggest that they are less likely to receive cancer treatment than those without HIV, all the women in our review received some form of treatment for their cancer.[7,42] Future studies should examine barriers to non-AIDS-defining cancer treatment in women with HIV, and the impact of HIV status on cancer recurrence and survival in women with gynecologic cancer.

Strengths and limitations

Our systematic review and meta-analysis has limitations, including those inherent to this study design. We limited our search to English-language studies published after 2000. Although this could lead to possible exclusion of earlier studies, the 2 prior systematic reviews on incidence of non-AIDS-defining cancers did not identify any studies on gynecologic cancer pre-2000.[10,11] We did not have the patient data necessary to analyze the impact of smoking, CD4 count, or receipt of HAART treatment on cancer incidence in women with HIV. Individual cohort studies used different methods for age-standardization of incidence rates, and several studies adjust incidence rates for additional variables, such as time period and race. While there was this and other heterogeneity between the studies, we analyzed for variables likely to contribute to study heterogeneity in our meta-regression. We found no significant evidence of publication bias in funnel plots (data available on request). For treatment and outcome data, our findings are limited by the fact that many articles (21) on these outcomes were case series or case reports. These articles—and their small numbers of patients—may not reflect the diversity of experience of gynecologic cancer among women with HIV. These studies frequently lacked patient-specific information, including histology, body mass index, and medical comorbidities, and we were unable to assess adherence of gynecologic cancer treatment to clinical guidelines, such as those of the National Comprehensive Cancer Network.

Conclusion and implications

As women with HIV live longer, the burden of gynecologic cancers in this population will grow. Our meta-analysis shows that women with HIV face the same risk of endometrial cancer, a slightly higher risk of ovarian cancer, and a substantially higher risk of vulvar and vaginal cancers than women in the general population. However, data on presentation, treatment, and cancer-related outcomes are limited for women with HIV, particularly for endometrial and ovarian cancers. Further investigation to inform best practices in this population is critical in order to guide optimal treatment for HIV-positive women with gynecologic cancers. ■

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SUPPLEMENTAL TABLE 1

Search terms

MEDLINE	EMBASE	Cochrane Library
1. ("HIV Infections"[MeSH] OR "HIV"[MeSH] OR hiv [tw] OR hiv-1*[tw] OR hiv-2*[tw] OR hiv1[tw] OR hiv2[tw] OR hiv infect*[tw] OR human immunodeficiency virus[tw] OR human immunedeficiency virus[tw] OR human immuno-deficiency virus[tw] OR human immune-deficiency virus[tw] OR ((human immun*) AND (deficiency virus[tw])) OR "acquired immunodeficiency syndrome"[tw] OR "acquired immunedeficiency syndrome"[tw] OR "acquired immuno-deficiency syndrome"[tw] OR "acquired immune-deficiency syndrome"[tw] OR ((acquired immun*) AND (deficiency syndrome[tw])) OR "sexually transmitted diseases, viral" [MESH:NoExp])	1. 'HIV'/exp OR 'human immunodeficiency virus infection'/exp OR 'human immunodeficiency virus 1'/exp OR 'human immunodeficiency virus 1 infection'/exp OR 'human immunodeficiency virus 2'/exp OR 'human immunodeficiency virus 2 infection'/exp OR 'human immunodeficiency virus infected patient'/exp OR 'acquired immune deficiency syndrome'/exp OR 'human immunodeficiency virus' OR 'human immunedeficiency virus' OR 'human immuno-deficiency virus' OR 'human immune-deficiency virus' OR ((human immun*) AND (deficiency virus)) OR 'acquired immunodeficiency syndrome' OR 'acquired immunedeficiency syndrome' OR 'acquired immuno-deficiency syndrome' OR acquired immune-deficiency syndrome' OR ((acquired immun*) AND (deficiency syndrome)) OR 'sexually transmitted diseases, viral'/	1. 'HIV' OR 'hiv1' OR 'hiv-1' OR 'hiv2' OR 'hiv-2' OR 'human immunodeficiency virus' OR 'human immunedeficiency virus' OR 'human immuno-deficiency virus' OR 'human immune-deficiency virus' OR ((human immun*) AND ('deficiency virus')) OR 'acquired immunodeficiency syndrome' OR 'acquired immunedeficiency syndrome' OR 'acquired immuno-deficiency syndrome' OR 'acquired immune-deficiency syndrome' OR ((acquired immun*) AND ('deficiency syndrome'))
2. ((endometri* OR uterus OR uterine OR "corpus uteri") AND (neoplasm* OR cancer OR cancers or carcinoma* OR malignanc* OR tumor OR tumors)) OR "Endometrial Neoplasms"[Mesh] OR "Uterine Neoplasms" [Mesh] OR "Endometrial Stromal Tumors"[Mesh]	2. 'endometrium cancer'/exp OR 'uterus cancer'/exp OR (endometr* OR uterus OR uterine OR 'corpus uteri') AND (neoplas* OR cancer* OR carcinom* OR adenocarcinoma* OR malignan* OR tumor* OR tumour* OR "tumour" OR "tumours")	2. ((endometri* OR uterus OR uterine OR "corpus uteri") AND (neoplasm* OR cancer OR cancers or carcinoma* OR malignanc* OR tumor OR tumors))
3. "Ovarian Neoplasms"[Mesh] OR ((adnexa* OR fallopian OR ovaria* OR ovary OR ovaries OR ovary) AND (neoplas* OR cancer* OR carcinom* OR adenocarcinoma* OR malignan* OR tumor* OR tumour* OR tumors OR tumour OR tumours))	3. (adnexa* OR fallopian OR ovari* OR ovary) AND (neoplas* OR cancer* OR carcinom* OR adenocarcinoma* OR malignan* OR tumor* OR tumour* (neoplas* OR cancer* OR carcinom* OR adenocarcinoma* OR malignan* OR tumor* OR tumour* OR "tumour" OR "tumours") OR 'ovary cancer'/exp OR 'ovary carcinoma'/exp	3. (adnexa* OR fallopian OR ovari* OR ovary) AND (neoplas* OR cancer* OR carcinom* OR adenocarcinoma* OR malignan* OR tumor* OR tumour* OR "tumour" OR "tumours")
4. ((vagina* OR vulva* or clitoris or clitoral) AND (neoplas* OR cancer* OR carcinom* OR adenocarcinoma* OR malignan* OR tumor* OR tumour* OR tumors OR tumours OR adenosquamous OR growth*)) OR "Vulvar Neoplasms"[Mesh] OR "Vaginal neoplasms"[Mesh]	4. 'vulva tumor'/exp OR 'vulva carcinoma'/exp OR 'vaginal tumor'/exp OR 'vaginal carcinoma'/exp OR (vagina* OR vulva* OR clitoris OR clitoral) AND (neoplas* OR cancer* OR carcinom* OR adenocarcinoma* OR malignan* OR tumor* OR tumour* OR adenosquamous OR growth*)	4. ((vagina* OR vulva* OR clitoris OR clitoral) AND (neoplas* OR cancer* OR carcinom* OR adenocarcinoma* OR malignan* OR tumor* OR tumour* OR adenosquamous OR growth*))
5. 1 AND (2 OR 3 OR 4)	5. 1 AND (2 OR 3 OR 4)	5. 1 AND (2 OR 3 OR 4)

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SUPPLEMENTAL TABLE 2

Assessment of risk of bias of included studies (n = 59 studies)

Author Year	1. Was the research question or objective in this paper clearly stated?	2. Was the study population clearly specified and defined?	3. Was the participation rate of eligible persons at least 50%?	4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	5. Were a sample size justification, power description, or variance and effect estimates provided?	6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (eg, categories of exposure, or exposure measured as continuous variable)?	9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	10. Was the exposure(s) assessed more than once over time?	11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	12. Were the outcome assessors blinded to the exposure status of participants?	13. Was loss to follow-up after baseline 20% or less?	14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	Total
Cohort studies															
Akarolo-Anthony 2014	1	0	0	1	0	0	1	0	1	0	1	0	1	0	6
Bogani 2017	1	1	1	1	1	0	1	1	1	1	1	0	1	1	12
Bradbury 2016	1	0	1	1	0	0	1	1	1	1	1	0	1	0	9
Calabresi 2013	1	1	1	1	1	0	1	1	1	1	1	0	1	1	12
Castilho 2015	1	0	1	1	0	0	0	1	0	1	0	0	0	1	6
Chen 2014	1	1	1	1	1	1	1	1	1	1	1	0	1	1	13
Dal Maso 2009	1	1	1	1	1	1	1	1	1	1	1	0	1	1	13
Dhir 2008	1	1	0	1	1	1	1	0	1	1	1	0	1	0	10
Dryden-Peterson 2015	1	1	0	1	1	0	1	1	1	1	1	0	1	0	10
Engels 2006	1	1	1	1	1	1	1	1	1	1	1	0	1	1	13
Engels 2008	1	1	1	1	1	1	1	1	1	1	1	0	1	1	13
Fordyce 2000	1	1	1	1	1	0	1	1	1	1	1	0	1	0	11
Franceschi 2010	1	1	1	0	1	1	1	1	1	1	1	0	1	1	12
Franzetti 2013	1	1	1	1	1	1	1	1	1	1	1	0	1	0	12
Gallagher 2001	1	1	1	1	1	1	1	1	1	1	1	0	1	1	13
Godbole 2016	1	1	1	1	1	0	1	1	1	1	1	0	1	0	11
Goedert 2006	1	1	1	1	1	1	1	1	1	1	1	0	1	1	13
Grulich 2002	1	1	1	1	1	0	1	1	1	1	1	0	1	0	11
Helleberg 2014	1	1	1	1	1	1	1	1	1	1	1	0	1	1	13
Herida 2003	1	1	1	1	1	1	1	1	1	1	1	0	1	1	13
Kurnit 2015	1	1	1	1	1	0	1	0	1	0	1	0	1	0	9
Massad 2012	1	1	1	1	1	1	1	1	1	1	1	0	1	1	13

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(continued)

SUPPLEMENTAL TABLE 2

Assessment of risk of bias of included studies (n = 59 studies) *(continued)*

Author Year	1. Was the research question or objective in this paper clearly stated?	2. Was the study population clearly specified and defined?	3. Was the participation rate of eligible persons at least 50%?	4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	5. Were a sample size justification, power description, or variance and effect estimates provided?	6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (eg, categories of exposure, or exposure measured as continuous variable)?	9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	10. Was the exposure(s) assessed more than once over time?	11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	12. Were the outcome assessors blinded to the exposure status of participants?	13. Was loss to follow-up after baseline 20% or less?	14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	Total
Mayor 2016	1	1	1	1	1	1	1	1	1	1	1	0	1	1	13
Mbulaiteye 2006	1	1	1	1	1	0	1	1	1	1	1	0	1	1	12
Newnham 2005	1	1	1	1	1	1	1	1	1	1	1	0	1	0	12
Patel 2008	1	1	1	1	1	1	1	1	1	1	1	0	1	1	13
Phelps 2001	1	1	1	1	0	1	1	1	1	1	1	0	1	0	11
Raffetti 2015	1	1	1	1	1	0	1	1	1	1	1	0	1	1	12
Ramirez-Marrero 2010	1	1	1	1	1	1	1	1	1	1	1	0	1	1	13
Sachdeva 2016	1	1	1	1	0	0	0	0	1	1	1	0	1	0	8
Salters 2016	1	1	1	1	1	0	1	1	1	1	1	0	1	0	11
Sengayi 2016	1	1	1	1	1	0	1	1	1	1	1	0	1	0	11
Silverberg 2009	1	1	1	1	1	0	1	1	1	1	1	0	1	0	11
Tanaka 2018	1	1	1	1	1	0	1	0	1	1	1	0	1	0	10
Vogel 2011	1	1	1	1	1	1	1	1	1	1	1	0	1	1	13
Zucchetto 2016	1	1	1	1	1	0	1	0	1	1	1	0	1	1	11

Case reports

	1. Was the study question or objective clearly stated?	2. Was the study population clearly and fully described, including a case definition?	3. Were the cases consecutive?	4. Were the subjects comparable?	5. Was the intervention clearly described?	6. Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants?	7. Was the length of follow-up adequate?	8. Were the statistical methods well described?	9. Were the results well described?	Total
Alalade 2009	1	1	0	0	1	1	0	0	1	5
Albu 2000	0	1	1	1	1	1	1	0	1	7

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(continued)

SUPPLEMENTAL TABLE 2

Assessment of risk of bias of included studies (n = 59 studies) *(continued)*

	1. Was the study question or objective clearly stated?	2. Was the study population clearly and fully described, including a case definition?	3. Were the cases consecutive?	4. Were the subjects comparable?	5. Was the intervention clearly described?	6. Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants?	7. Was the length of follow-up adequate?	8. Were the statistical methods well described?	9. Were the results well described?	Total
Belotte 2012	1	1	0	0	1	1	1	0	1	6
Brown 2005	1	1	1	1	1	1	1	0	1	8
Clemente 2017	1	1	0	0	1	1	1	0	1	6
Dedes 2008	1	1	1	1	1	1	1	1	1	9
Elit 2005	1	1	0	0	1	1	1	0	1	6
Giaquinto 2000	1	1	0	0	1	1	1	0	1	6
Knox 2000	1	1	0	0	1	1	0	0	1	5
Lanjewar 2015	1	1	0	0	1	1	0	0	1	5
Lee 2000	1	1	0	0	1	1	1	0	1	6
Majeeed 2006	1	1	0	0	1	1	0	0	1	5
Moodley 2000	1	1	0	0	1	1	0	0	1	5
Moodley 2003	1	1	0	0	1	1	0	0	1	5
Moodley 2004	1	1	0	0	1	1	0	0	1	5
Rao 2015	1	1	0	0	1	1	0	0	1	5
Riera 2013	1	1	0	0	1	1	1	0	1	6
Sekowski 2008	0	0	1	1	1	1	0	0	1	5
Simbiri 2014	1	1	1	1	0	1	0	0	1	6
Sitas 2000	1	1	1	1	1	1	1	1	1	9
Strehl 2012	1	1	0	0	1	1	0	0	1	5
Yanik 2016	1	0	1	1	1	1	1	1	1	8

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SUPPLEMENTAL TABLE 3

Univariate meta-regression of gynecologic cancer incidence and study characteristics

	Endometrial cancer SIR		Ovarian cancer SIR		Vulvar and vaginal cancer SIR	
	95% CI	*P* value	95% CI	*P* value	95% CI	*P* value
AIDS						
Yes	2.09 (0.36–3.83)	.34	1.02 (0.75–1.28)	.03	19.60 (8.04–31.16)	.63
No	5.84 (-1.87 to 13.54)		4.08 (2.80–5.37)		24.64 (11.19–38.09)	
Post-HAART						
Yes	2.83 (0.92–4.74)	.40	2.87 (1.52–4.21)	.47	26.10 (5.05–47.15	.33
No	1.50 (0.05–2.94)		4.25 (0.51–7.99)		10.70 (-1.66 to 23.06)	
Use of Cancer Registry						
Yes	4.65 (-0.07 to 9.37)	.34	3.35 (2.33–4.36)	.55	No nonregistry studies	N/A
No	3.00 (0.55–5.46)		2.24 (0.72–3.76)			
Prospective study design						
Yes	2.69 (1.03–4.35)	.18	3.44 (1.93–4.94)	.66	23.12 (14.87–31.37)	.77
No	7.77 (-3.53 to 19.07)		2.78 (1.93–3.63)		20.01 (1.88–38.14)	

AIDS, acquired immunodeficiency syndrome; *CI*, confidence interval; *HAART*, highly active antiretroviral therapy; *N/A*, not applicable; *SIR*, standardized incidence rate.

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