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A meta-analysis of anal cancer incidence by risk group: Toward a unified anal cancer risk scale

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Abstract

Certain population groups are known to have higher than average anal cancer risk, namely persons living with HIV (PLHIV), men who have sex with men (MSM), women diagnosed with human papillomavirus (HPV)-related gynecological precancerous lesions or cancer, solid organ transplant recipients (SOTRs) and patients with autoimmune diseases. Our aim was to provide robust and comparable estimates of anal cancer burden across these groups. Summary incidence rates (IRs), as cases per 100 000 person-years (py), were calculated by fixed-effects meta-analysis. IRs were 85 (95% confidence interval [CI] = 82-89) for HIV-positive MSM (n = 7 studies; 2 229 234 py), 32 (95% CI = 30-35) for non-MSM male PLHIV (n = 5; 1626 448 py) and 22 (95% CI = 19-24) for female PLHIV (n = 6; 1 472 123 py), with strong variation by age (eg, from 16.8 < 30 years to 107.5 ≥ 60 years for HIV-positive MSM). IR was 19 (95% CI = 10-36) in HIV-negative MSM (n = 2; 48 135 py). Anal cancer IRs were much higher after diagnosis of vulvar (IR = 48 [95% CI = 38-61]; n = 4; 145 147 py) than cervical (9 [95% CI = 8-12]; n = 4; 779 098 py) or vaginal (IR = 10 [95% CI = 3-30]; n = 4; 32 671) cancer, with equivalent disparity after respective precancerous lesions. IR was 13 (95% CI = 12-15) in SOTRs (n = 5; 1 946 206 py), reaching 24.5 and 49.6 for males and females >10 years after transplant. Anal cancer IRs were 10 (95% CI = 5-19), 6 (95% CI = 3-11) and 3 (95% CI = 2-4) for systemic lupus erythematosus, ulcerative colitis and Crohn's disease, respectively. In conclusion, a unifying anal cancer risk scale, based upon comprehensive meta-analysis, can improve prioritization and standardization in anal cancer prevention/research initiatives, which are in their public health infancy.

KEYWORDS

anal cancer, HIV, incidence, MSM, transplantation

Abbreviations: ASCC, anal squamous cell carcinoma; cART, combination antiretroviral therapy; CI, confidence interval; CIN, cervical intraepithelial neoplasia; DARE, digital anorectal examination; HPV, human papillomavirus; HRA, high-resolution anoscopy; HSILs, high-grade squamous intraepithelial lesions; IR, incidence rate; MSM, men who have sex with men; MSW, men who have sex with women; PLHIV, persons living with HIV; py, person-years; SEER, U.S. Surveillance, Epidemiology, and End Results; SIR, standardised incidence ratio; SLE, systemic lupus erythematosus; SOTRs, solid organ transplant recipients; VAIN, vaginal intraepithelial neoplasia; VIN, vulvar intraepithelial neoplasia.

1 | INTRODUCTION

An estimated 29 000 persons, predominantly women, are diagnosed with anal squamous cell carcinoma (ASCC) every year, for

which human papillomavirus (HPV) infection is considered a necessary cause.[1] HPV vaccination is expected to be the long-term solution to ASCC prevention,[2] but full impact will not be seen for decades. In the meantime, many unvaccinated generations remain at risk and may benefit from early detection or secondary prevention initiatives. Approaches might include detection of early stage anal cancer by digital anorectal examination (DARE),[3] or screening algorithms similar to cervical cancer where a positive anal screening test (eg, cytology) is followed by diagnostic high-resolution anoscopy (HRA) for detection and treatment of anal high-grade squamous intraepithelial lesions (HSILs) to prevent progression to cancer.[4] Although strong evidence and consensus for such secondary prevention approaches are yet to be established, the rarity of anal cancer at a population level (1-2 cases per 100 000 person-years [py]), combined with a current scarcity of relevant medical expertise, means that any initiatives will inevitably need to target groups at highest anal cancer risk.

Important population-level determinants of anal cancer incidence include age (via accumulation of deleterious mutations) and female gender (genital/anal anatomical proximity favoring HPV cross-site transmission).[5] However, anal cancer risk is also heavily driven by sexual behavior,[6] and by immunosuppression,[7] which worsens the carcinogenic outcome of anal HPV infection. Thus, there exist a number of groups at known elevated anal cancer risk. These include men who have sex with men (MSM),[8] persons living with HIV (PLHIV),[9] women with HPV-related gynecological cancer or precancerous lesions,[10] as well as iatrogenically immunosuppressed recipients, most notably solid organ transplant recipients (SOTRs).[11]

Anal cancer risks are often articulated as standardized incidence ratios (SIRs), comparing observed anal cancers with those expected among the general population of similar age, gender and/or time period. SIRs are a useful statistic to contribute to judgments of causal associations, but are not easily comparable with each other, given that they are standardized to general populations with different underlying rates. For example, SIR of vulvar cancer survivors is compared to the expected rate in women of mean age in their 70s, whereas the SIR for HIV-negative MSM is compared to that in men of mean age in their 40/50s. Furthermore, general population rates used for comparisons may already be heavily influenced by high-risk groups (eg, the important contribution of HIV to anal cancer burden among young men in the United States).[12] In order to inform rational provision of anal cancer prevention, it is more relevant to stratify risk according to incidence rates (IRs), an absolute and more easily comparable measure of anal cancer burden.

To this end, we undertook a literature review and meta-analysis of anal cancer incidence in groups at established elevated anal cancer risk. As far as possible, we tried to obtain additional, often unpublished data, stratified by age and/or gender. Our aim was to produce meta-IRs and combine them on a single unifying anal cancer risk scale in order to inform prioritization and standardization in anal cancer prevention/research initiatives.

What's new?

Anal cancer (AC) is quite rare in the general population. However, some groups are known to be at higher risk. In this meta-analysis, the authors identified these groups (e.g., HIV-positive status, other HPV-related cancers, etc.), and were then able to develop an AC-risk scale based on incidence estimates. Because there is currently no consensus regarding standardized screening for AC, this risk scale can help clinicians to prioritize and compare risk profiles for AC research and prevention initiatives. These can then be guided by similar principles of management for populations with similar absolute risk.

2 | METHODS

2.1 | Data sources

We undertook a literature review of studies reporting on anal cancer IR in five major groups considered to be at elevated risk, namely: (a) PLHIV, (b) MSM, (c) women diagnosed with HPV-related precancerous lesions or cancer of cervix, vulva, vagina, (d) SOTRs and (e) patients with autoimmune diseases (systemic lupus erythematosus [SLE], ulcerative colitis and Crohn's disease). MEDLINE was searched using the terms ("anal" OR "anus" OR "anal canal") in combination with ("incidence" OR "IR" OR "SIR" OR "hazard ratio" OR "HR"), any restrictions by calendar period, geographical region or language. Eligible studies were also identified from a number of relevant meta-analyses, including those focusing on MSM,[8] PLHIV,[9] women diagnosed with HPV-related gynecological precancerous lesions or cancer[10,13] or SOTRs.[9,11] Where several publications described the same study population, only the most recent update was included.

From each eligible study, data were extracted on: (a) person-years of follow-up, and (b) observed anal cancers, in order to calculate IR per 100 000 py. Many studies reported IR, or most commonly SIR, without presenting the relevant underlying person-years and observed cases. If possible, the number of person-years was calculated by dividing the number of observed cancers by the reported IR. Otherwise, relevant data were requested from authors (see Acknowledgements section). During the process of contacting authors of two large studies based on US registry linkage in PLHIV,[14] and SOTRs,[15] respectively, it became apparent that updated data sets were available. In this case, we included expanded unpublished data with increased years of follow-up (from 1996 to 2015 for HIV AIDS Cancer Match study[14] and 1987 to 2017 for Transplant Cancer Match study[15]) and additionally stratified according to relevant variables (eg, gender, age and time since transplant).

Given the availability of a previous meta-analysis on HIV-positive MSM published in 2012,[8] and the fact that almost all of the studies included in this previous meta-analysis had been updated and since

republished with more recent follow-up, we decided to restrict estimates for PLHIV only to studies published since 2012.

For women diagnosed with HPV-related gynecological precancerous lesions or cancer, relevant data were additionally extracted from the US Surveillance, Epidemiology, and End Results (SEER) Program database, based on nine registries contributing data from 1975 to 2016 (SEER 9).[16]

For comparison, an approximation of age-specific anal cancer incidence in HIV-negative men and HIV-negative women was also made, by using published age-specific anal cancer for the US general population 2008 to 2014,[17] where population-level HIV prevalence is less than 1%.

Some included studies reported incidence restricted to ASCC only, others for all anal cancer, irrespective of histology. Studies reporting incidence of anorectal cancer only were not included.

2.2 | Statistical analyses

Person-years, observed anal cancers, and anal cancer IR per 100 000 py with corresponding 95% confidence intervals (CIs) are reported for each eligible study. Within each risk group, summary incidence estimates were calculated using fixed-effects meta-analysis. Fixed, rather than random, effects models were chosen in order not to overweight smaller studies, and also to avoid any inconsistencies between overall and age-specific estimates (which were available from a few of the largest studies only). Heterogeneity was measured with the I^2 statistic. Data were expressed visually as forest plots.

Fixed effect summary estimates were translated onto a single unified scale of anal cancer incidence. For certain population groups, additional stratified estimates of crude anal cancer incidence from large studies were also added to the scale, namely by age for PLHIV and for women diagnosed with cervical intraepithelial neoplasia (CIN) grade 3, as well as by gender and time since transplant for SOTRs. We used R software (Version 3.6.2) for all statistical analyses and data representation.

3 | RESULTS

3.1 | Persons living with HIV

Eight studies reported anal cancer IR in PLHIV and are presented stratified by three principal risk groups in Figure 1 (albeit on different scales): (a) MSM, (b) non-MSM males and (c) females.[14,18-24] By far the largest contribution was from the US HIV/AIDS Cancer Match study for which updated estimates were provided since the last publication of these data.[14] Seven studies of MSM living with HIV included a total of 2 229 234 py for which summary anal cancer IR was 85 per 100 000 py (95% CI = 82-89) (Figure 1A). There was significant heterogeneity in IR across studies (I^2 = 93%, P < .01), with five studies reporting IR above 100 per 100 000 py. IRs are also presented from a previous meta-analysis of MSM living with HIV that stratified between the pre-combination antiretroviral therapy (cART) era (IR = 22) and the cART era (IR = 78).[8] However, these data are excluded from summary estimates due to overlap (ie, most studies contributing to the earlier meta-analysis have been expanded and republished).

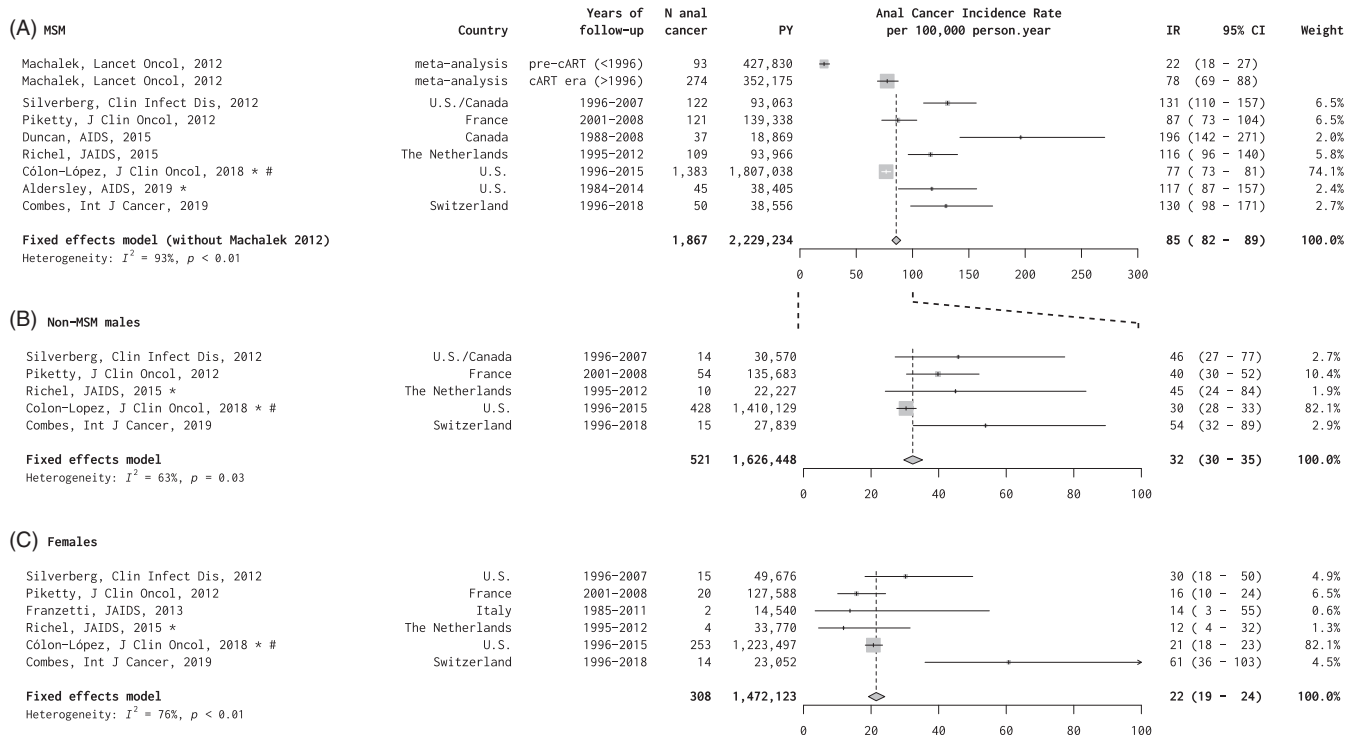

FIGURE 1 A-C, Anal cancer incidence in studies of persons living with HIV, by risk group. *Personal communication. #Updated data set since original publication (see Section 2) CI, confidence interval; IR, incidence rate; MSM, men who have sex with men; PY, person-years

Five studies of non-MSM males living with HIV included a total of 1 626 448 py and summary anal cancer IR was 32 per 100 000 py (95% CI = 30-35), with significant heterogeneity (I^2 = 63%, P = .03) (Figure 1B). Six studies of females living with HIV included a total of 1 472 173 py and summary anal cancer IR was 22 per 100 000 py (95% CI = 19-24), also with significant heterogeneity (I^2 = 76%, P < .01) (Figure 1C). Of note, IRs for non-MSM males and females living with HIV were highest in a study from Switzerland, in which IRs were restricted to persons aged 40 years or older only.

Age-specific anal cancer IRs in PLHIV are shown according to the three risk groups in Table S1, deriving from the updated US HIV/AIDS Cancer Match study, 1996 to 2015. For MSM living with HIV, anal cancer IRs increased from 16.8 per 100 000 py for <30 years up to 107.5 per 100 000 py for ≥60 years. For non-MSM males and females living with HIV, anal cancer IR increased with age from <30 years to ≥45 years, but with no increase between 45 and 59 years and ≥60 years (Table S1).

3.2 | HIV-negative MSM

Only two studies have reported anal cancer IR in HIV-negative MSM, together including 48 135 py.[22,25] Summary anal cancer IR was

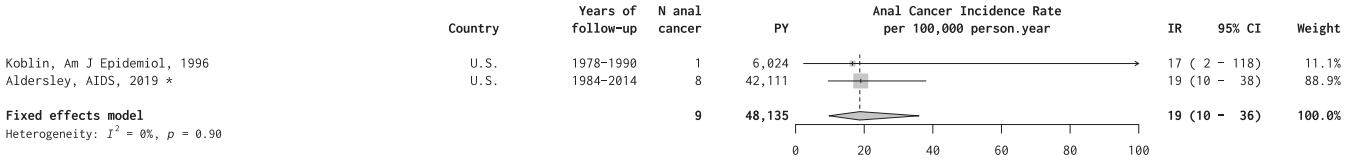

FIGURE 2 Anal cancer incidence in studies of HIV-negative MSM. *Personal communication. CI, confidence interval; IR, incidence rate; MSM, men who have sex with men; PY, person-years

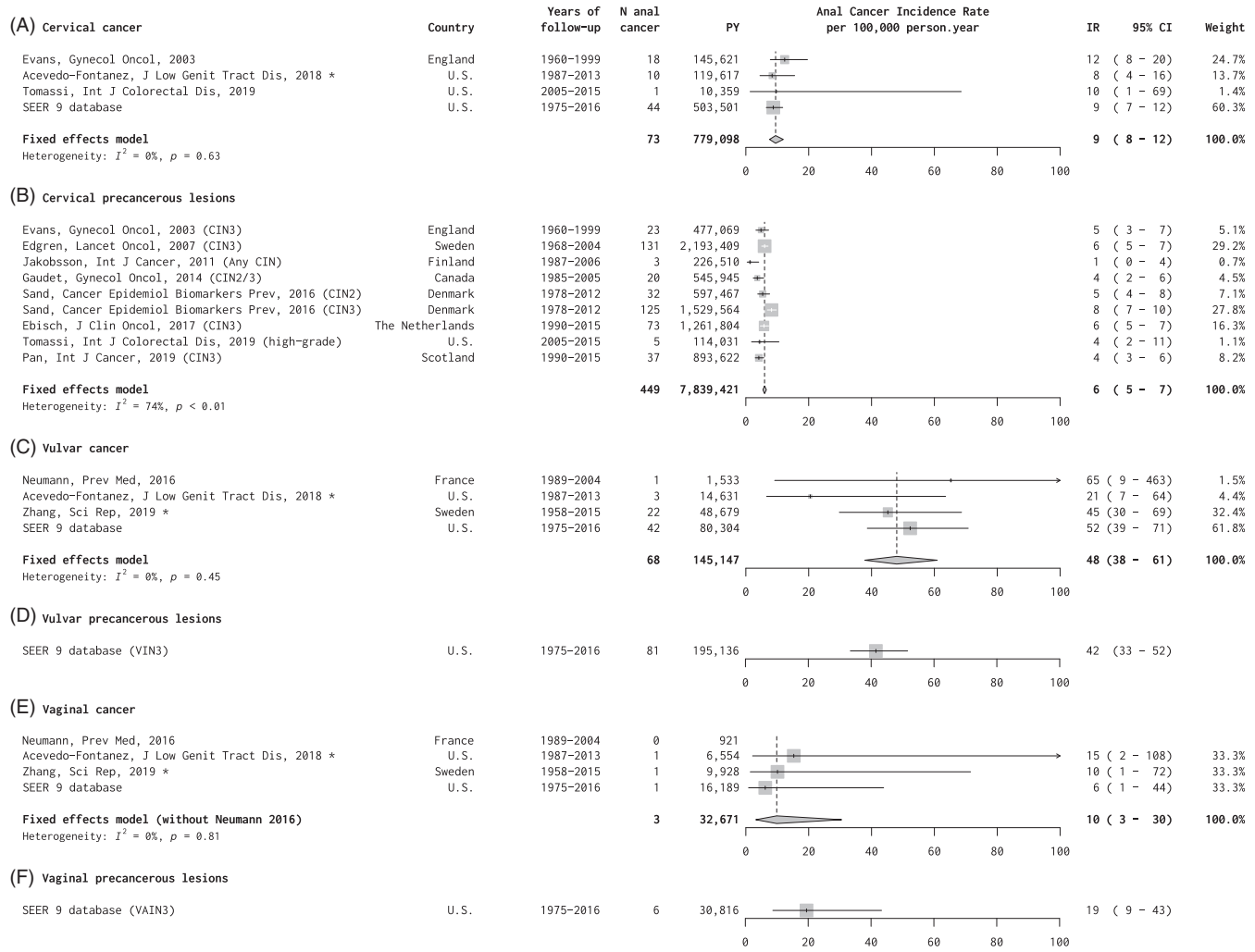

FIGURE 3 A-F, Anal cancer incidence in studies of women with gynecological precancerous lesions or cancer, by site. *Personal communication. CI, confidence interval; CIN, cervical intraepithelial neoplasia; IR, incidence rate; PY, person-years; SEER, US Surveillance, Epidemiology, and End Results Program database; VAIN, vaginal intraepithelial neoplasia; VIN, vulvar intraepithelial neoplasia

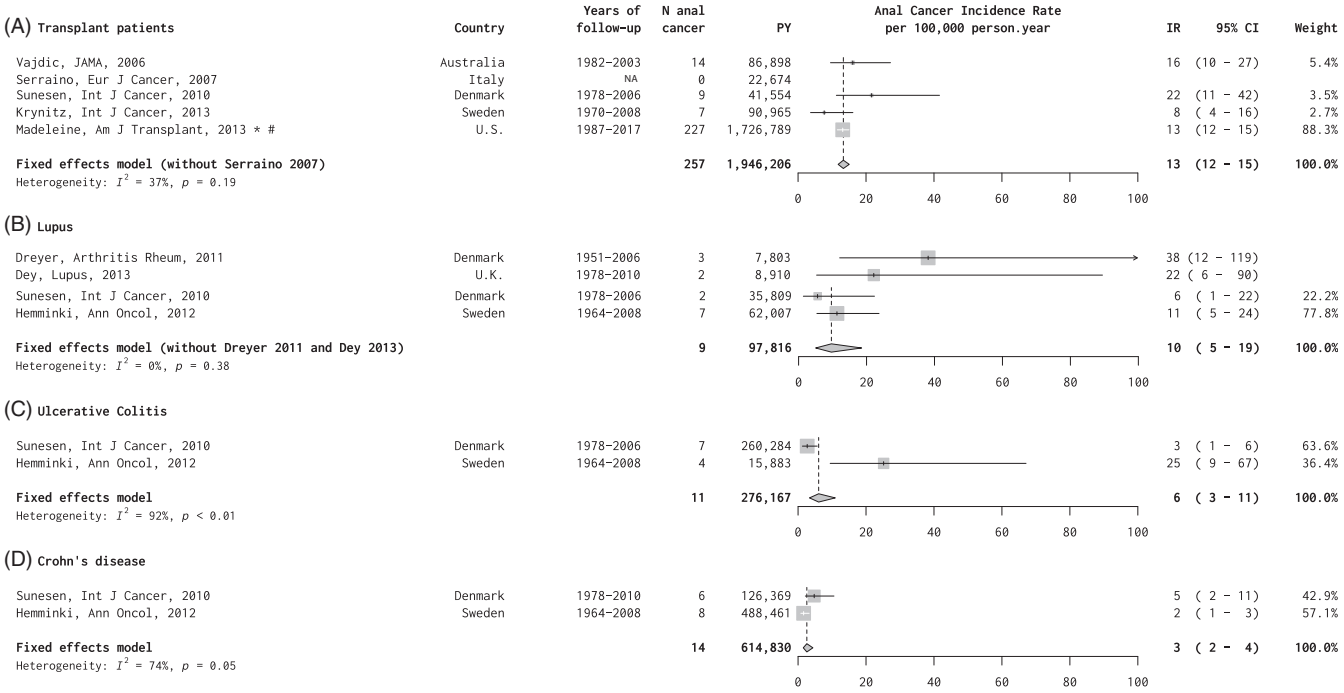

FIGURE 4 Anal cancer incidence in studies of, A, solid organ transplant recipients and, B-D, patients with autoimmune diseases. *Personal communication. #Updated data set since original publication (see Section 2). CI, confidence interval; IR, incidence rate; PY, person years

TABLE 1 Anal cancer incidence in US transplant cancer match study 1987 to 2015, by age, gender and years since transplant

	Males			Females		
	Cases	Person-years	IR per 100 000 person-years (95% CI)	Cases	Person-years	IR per 100 000 person-years (95% CI)
All	99	1 050 327	9.4 (7.7-11.5)	128	676 462	18.9 (15.8-22.5)
Age group (y)						
<30	0	116 804	0.0 (0.0-3.2)	3	97 399	3.1 (0.6-9.0)
30-44	9	194 004	4.6 (2.1-8.8)	19	145 121	13.1 (7.9-20.4)
45-59	42	403 603	10.4 (7.5-14.1)	56	240 592	23.3 (17.6-30.2)
≥60	48	335 916	14.3 (10.5-18.9)	50	193 350	25.9 (19.2-34.1)
Years since transplant						
<5	43	657 746	6.5 (4.7-8.8)	46	412 509	11.2 (8.2-14.9)
5-9	28	278 346	10.1 (6.7-14.5)	42	183 231	22.9 (16.5-31.0)
≥10	28	114 235	24.5 (16.3-35.4)	40	80 722	49.6 (35.4-67.5)

Abbreviations: CI, confidence interval; IR, incidence rate.

19 (95% CI = 10-36) cases per 100 000 py, with no significant heterogeneity (Figure 2).

3.3 | Women diagnosed with HPV-related gynecological (pre)cancers

Four studies provided anal cancer IR for women diagnosed with cervical cancer, including 779 098 py.[16,26-28] The summary anal cancer IR was 9 per 100 000 py (95% CI = 8-12), with no significant heterogeneity (Figure 3A). More than half of the data was provided from SEER 9 database.[16]

Eight studies provided anal cancer IR for women diagnosed with precancerous cervical lesions, including 7 839 421 py, for which summary anal cancer IR was 6 per 100 000 py (95% CI = 5-7) (Figure 3B).[26,28-34] Five of the eight studies, representing 81% of all person-years, included CIN3 only. There was significant heterogeneity (I^2 = 74%, P < .01), with IR for individual studies ranging between 4 and 8 per 100 000 py for studies including CIN2 and/or CIN3, and an IR of 1 in a small study including any CIN (Figure 3B). Two of the largest studies from Sweden and the Netherlands (Ebisch, personal communication) also provided age-stratified IR for women diagnosed with CIN3. After pooling the data from these two studies, anal cancer IR post-CIN3 were

1.3 per 100 000 py for <40 year olds, 8.1 per 100 000 py for 40 to 59 year olds and 15.0 per 100 000 py for ≥60 year olds (Table S2).

Four studies provided anal cancer IR for women diagnosed with vulvar cancer, including 145 147 py.[16,27,35,36] Summary anal cancer IR was 48 per 100 000 py (95% CI = 38-61), with no significant heterogeneity (Figure 3C). More than half of the data on vulvar cancer was provided from SEER 9 database, which also provided the only estimate for precancerous vulvar lesions, being 42 per 100 000 py (95% CI = 33-52) in women diagnosed with vulvar intraepithelial neoplasia (VIN) grade 3 (Figure 3D).

Four studies provided anal cancer IR for women diagnosed with vaginal cancer, including 32 671 py.[16,27,35,36] Summary anal cancer IR was 10 per 100 000 py (95% CI = 3-30), with no significant heterogeneity (Figure 3E). The SEER 9 database provided the only estimate for precancerous vaginal lesions, being 19 cases (95% CI = 9-43) in women diagnosed with vaginal intraepithelial neoplasia (VAIN) grade 3 (Figure 3F).

3.4 | Solid organ transplant recipients

Five eligible studies of SOTRs included a total of 1 946 206 py and summary anal cancer IR was 13 per 100 000 py (95% CI = 12-15), with no significant heterogeneity (Figure 4A).[15,37-40] By far the largest study was the US Transplant Cancer Match study, for which updated estimates were provided since the last publication.[15] Our study also allowed stratification of anal cancer IR by gender, age and years since transplant (Table 1). Anal cancer incidence increased by age of transplant recipients, from 0.0 and 3.1 per 100 000 py in males and females aged <30 years, respectively, up to 14.3 and 25.9 per 100 000 py for those aged ≥60 years. However, years since transplant appeared to identify SOTRs at highest anal cancer risk better than age, with anal cancer IR for ≥10 years after transplant reaching 24.5 and 49.6 per 100 000 py for males and females, respectively (Table 3).

3.5 | Autoimmune diseases

Four eligible studies of patients with SLE included two smaller clinical series including a total of 16 713 py,[41,42] and two larger, more population-based, studies including a total of 97 816 py.[39,43] We estimated summary anal cancer IR for SLE among the population-based studies only, which was 10 per 100 000 py (95% CI = 5-19), lower than in the clinical series (Figure 4B). These two same population-based

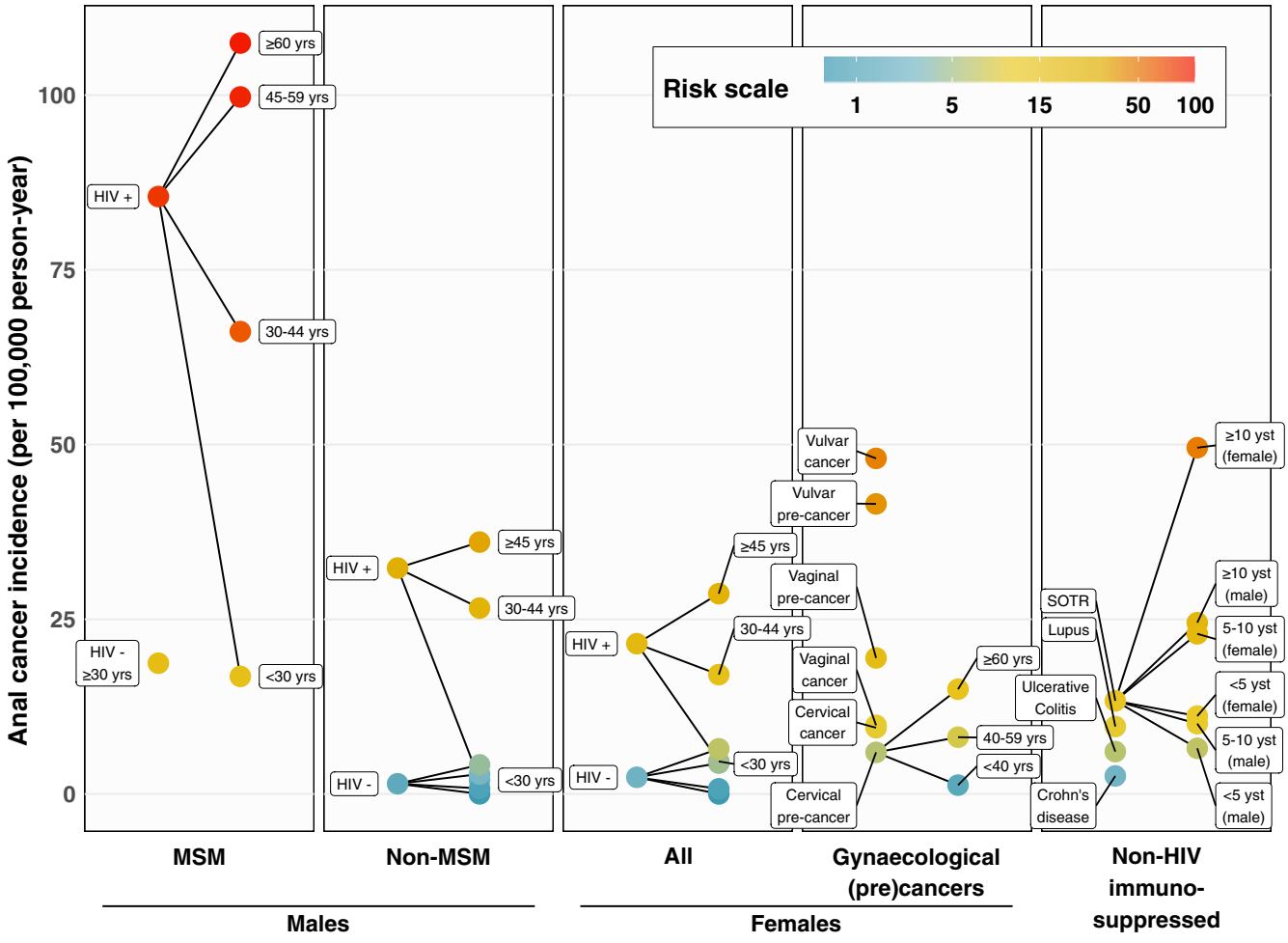

FIGURE 5 Anal cancer risk scale. 95% CIs around the point estimates can be found in the relevant Figures 1-4 and Tables S1 and S2. Estimates for HIV-negative men and men are shown, without labels, for age-groups <30, 30 to 44, 45 to 59, and ≥60 years (see Section 3). CI, confidence interval; MSM, men who have sex with men; MSW, men who have sex with women. yrs, years old; yst, years since transplant

studies also provided anal cancer IR for persons with ulcerative colitis (276 167 py; IR = 6 per 100 000 py [95% CI = 3-11]), and Crohn's disease (614 830 py; IR = 3 per 100 000 py [95% CI = 2-4]) (Figure 4C,D).

3.6 | Unifying anal cancer risk scale

For comparison purposes, all summary anal cancer IR from the above meta-analyses were presented and compared on the same linear scale of anal cancer incidence (cases per 100 000 py) (Figure 5). Figure 5 also includes estimates of age-specific IR from PLHIV subgroups (from Table 1), age-specific IR for women with CIN3 (from Table S1) and gender-specific IR by years from transplant for SOTRs (from Table S2). Last, for reference, Figure 5 also includes age-specific estimates of anal cancer IR in HIV-negative men (0, 1, 3 and 4 per 100 000 py for <30, 30-44, 45-59 and ≥60 years, respectively) and women (0, 1, 4 and 6 per 100 000 py, respectively), based on 2008 to 2014 estimates for the US general population.[17] The aim of Figure 5 is to demonstrate the major differences in anal cancer IR across the selected groups, and how they compare to each other. Although Figure 5 does not reproduce the CI around the plotted summary estimates, nor the significant heterogeneity for certain risk group meta-analyses, these can be found in the forest plots (Figures 1-4).

4 | DISCUSSION

A unifying anal cancer risk scale, based upon meta-analysis of anal cancer incidence, provides a robust representation of the wide spectrum of anal cancer burden existing among populations considered at significantly elevated risk.

It has long been clear that anal cancer risk is highest among MSM living with HIV[8] who have frequent exposure to anal HPV compounded by the worsening of HPV outcome by immunosuppression. Indeed, some guidelines for management of PLHIV already make specific recommendations for secondary prevention of anal cancer[44-46] with a focus on MSM living with HIV. Such a focus is supported by this risk scale, particularly for MSM aged ≥ 45, for whom IR reach 100 per 100 000 py. Even MSM living with HIV aged 30 to 44 years showed anal cancer IR considerably higher than those of any other known risk group.

With respect to other PLHIV, some prevention guidelines make anal screening recommendations for women with a history of cervical lesions (often mirroring recommendations for MSM living with HIV), but most do not focus on other PLHIV.[44-46] As expected, anal cancer incidence in HIV-positive women and men having sex with women (MSW) lay between the incidence among their HIV-negative counterparts and that in HIV-positive MSM, and was heavily age-dependent. Anal cancer risk was also consistently higher in HIV-positive MSW than HIV-positive women, perhaps due to some misclassification of male sexual preference or practices. Of note, although cART is expected to decrease age-specific anal cancer risk,[7] anal cancer IR for PLHIV have actually increased through the pre-cART and cART periods in high income settings,[8,14,47] partly driven by a strong population-level ageing effect, and this is expected to account for the observed heterogeneity in overall IR for studies of PLHIV. This complication is largely overcome by presenting age-specific cancer IR.

Elevated SIR for anal cancer following cervical or vulvo-vaginal cancer are well established.[10] However, the current work highlights some substantial differences between these gynecological cancers. Anal cancer IRs were substantially higher for vulvar (reaching an IR close to 50), than for vaginal and cervical cancer (closer to 10). This may be due to some common susceptibility for HPV-driven vulvar and anal cancer. However, it is not easily attributed to an age effect, given that vaginal cancer has an age-distribution closer to vulvar than to cervical cancer, and that corresponding differences are also seen between VIN3, VAIN3 and CIN3, that have very different age-distributions. Indeed, even anal cancer risk in women with prior CIN3 aged ≥ 60 years fell well below that following VIN or vulvar cancer.

A long established excess risk of anal cancer in SOTRs[9,11] has led to one professional society recently recommending anal cancer screening in this group.[48] However, as shown previously,[15] and further clarified here, considerable risk stratification exists within this population, most notably according to gender and years since transplantation, with IR reaching 50 per 100 000 py in females ≥10 years since transplant. Indeed, years since transplant, that is, time on immunosuppressive drugs, appears to distinguish anal cancer risk better than age per se. Similar risk stratification by duration of immunosuppressive therapy may also exist for patients with autoimmune diseases. However, we did not identify any such stratified data and overall anal cancer IR for patients with SLE, ulcerative colitis and Crohn's disease were lower than that for SOTRs.

The association between receptive anal intercourse and anal cancer in men predates the discovery of HPV16,[49] and is known to exist independently of HIV/AIDS.[6,50] At a population level, HIV-negative MSM represent arguably one of the largest of all the risk groups studied here. Yet it is the group for which anal cancer incidence remains the least well characterized, given that sexual practices and identity are not reported at a population level. Thus, relevant data arise from cohort studies only, most notably the long-standing Multicenter AIDS Cohort Study (MACS), for which the estimated IR for HIV-negative MSM aged ≥ 30 years was 19 per 100 000 py, well below that observed in many other risk groups. However, this estimate is based on only eight observed anal cancers and is expected to conceal important age-specific risk stratification. Indeed, increasing incidence in MACS over time (from five observed anal cancers in an earlier report[47]) may be driven by the aging of study participants (although this does not correspond to a population-wide aging of HIV-negative MSM per se, as is the case of PLHIV). On the other hand, studies such as the MACS may enroll participants at higher than average risk, in which case anal cancer incidence in the wider population of HIV-negative MSM would be even lower. Indeed, there is evidence from meta-analysis of anal HPV16 prevalence that studies of HIV-negative MSM can be biased toward higher risk groups.[51]

A number of limitations of this work are worth highlighting. First, we chose to focus only on major risk stratifiers with robust evidence on anal cancer incidence from population-level research studies which, of note, also tend to be those characteristics that would be pragmatically available for targeted public health programmes. Thus, some more specific associations, such as detailed sexual behaviour (potentially stigmatizing for patients, with no clear evidence of further risk discrimination), degree of HIV-related immunosuppression among PLHIV (a complicated function of duration of immunosuppression as measured by historical CD4 trajectories and cART[7]) and type of organ transplant or type of immunosuppressive therapy (not a major determinant of anal cancer risk[15]) were beyond its scope. Unfortunately, no data on anal cancer incidence in the combinatorial strata of females living with HIV diagnosed with gynecological cancer or precancerous lesions were identified. Neither were any data yet available among women attending HPV-based cervical screening programmes, for which cervical HPV16-positivity has recently been shown to be a strong predictor of anal HPV16 infection,[5] HPV16-positive anal high-grade lesions,[5] and anal intraepithelial neoplasia (AIN) grade 2+.[52] In the future, such data may provide some risk stratification for women without any of the risk factors studied above, who constitute the major part of anal cancer burden at a population-level.

Indeed, the population attributable fraction of anal cancer for any given target group is a function both of risk and population size. The latter is critical to provision of public health interventions that rely on limited capacity and expertise.[53] Some high-risk populations studied here, for example, women with vulvar cancer, are relatively small, whilst others are potentially much larger, for example, HIV-negative MSM. Furthermore, the relative size of these groups may vary by setting: whereas in high-income countries, HIV-negative MSM may be much more numerous than HIV-positive MSW and women, this situation is likely to be reversed in settings with widespread HIV epidemics. Of note, all data in this meta-analysis derive from high-income settings, limited by availability of linkable population-based registries. Indeed, with the exception of HIV-negative MSM, all the groups at elevated risk tend already to be identified and under expert medical care, which could facilitate anal cancer prevention.

Definition of specific risk thresholds at which secondary anal prevention interventions might be recommended is beyond the scope of the current exercise. This requires additional appraisal of benefits vs harm, as well as feasibility (see issue of the size of the target population above), that can vary according to different interventions/algorithms. For example, upon judgment against Wilson and Jungner's 10 classic WHO criteria[53] for assessing the potential for public health screening, the use of DARE for early detection of anal cancer[3] currently appears to meet more of the criteria than does anal cytology and HRA for anal cancer screening.[54] In the meantime, for pragmatic purposes, some broad analogies have been made to risk thresholds in other cancer screening programmes (though even different cancer screening interventions are associated with very different benefit to harm profiles). For example, by extrapolating from colorectal cancer risk among persons recommended to undergo colorectal cancer screening in the United States (ie, those aged ≥50 years), Colón-López et al suggested that a 5-year cumulative incidence of 0.25% (roughly equivalent to an IR of 50 per 100 000 py, ignoring comortality rates) might serve as a lower limit to target groups for anal screening.[14] Another common analogy[54] is with cervical cancer incidence in women aged ≥ 35 years prior to recommendation of Pap smear screening in high-income settings in the 1950s (eg, IR of 30-40 per 100 000 py).

In conclusion, recognizing that there is no current consensus approach for early detection or screening for anal cancer, robust estimates of anal cancer burden can improve prioritization and standardization in anal cancer prevention/research initiatives, which are in their public health infancy. The rarity of anal cancer at a population level, combined with a scarcity of relevant medical expertise and infrastructure, means that any initiatives inevitably need to target groups at highest anal cancer risk. These initiatives may be based on combinations of DARE for early detection of anal cancer or triage tests from anal swabs (eg, cytology, HPV16 infection or some other molecular markers) followed by HRA for detection of anal HSILs. Based on evidence from the anal cancer risk scale, any initiatives can at least be underpinned by a principle of similar management for populations of similar absolute risk.

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CONFLICT OF INTEREST

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DISCLAIMER

Where authors are identified as personnel of the International Agency for Research on Cancer/World Health Organization, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy or views of the International Agency for Research on Cancer/World Health Organization.

DATA AVAILABILITY STATEMENT

The data that support the findings of our study derive from several sources. Publicly available sources are: Cancer incidence in five continents volume XI, (http://ci5.iarc.fr); Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov). For included studies, please refer to cited published references and Acknowledgements section.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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