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BURDEN OF ANAL SQUAMOUS CELL CARCINOMA, SQUAMOUS INTRAEPITHELIAL LESIONS AND HPV16 INFECTION IN SOLID ORGAN TRANSPLANT RECIPIENTS: A SYSTEMATIC REVIEW AND META-ANALYSIS.

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ABBREVIATIONS

AIN: anal intraepithelial neoplasia

ASC-H: atypical squamous cells that cannot be excluded as high-grade

ASC-US: atypical squamous cells of undetermined significance

ASIL: anal squamous intraepithelial lesions

HPV: human papillomavirus

HRA: high-resolution anoscopy

HSIL: high-grade squamous intraepithelial lesions

IR: incidence rate

LAST: lower anogenital squamous terminology

LSIL: low-grade squamous intraepithelial lesions

MSM: men who have sex with men

PRISMA: preferred reporting items for systematic reviews and meta-analyses

SCC: squamous cell carcinoma

SIR: standardised incidence ratio

SOTR: solid organ transplant recipients

ABSTRACT

The number of solid organ transplant recipients (SOTR), and their life expectancy, is increasing, with higher risk for long-term complications from immunosuppression. We carried out a systematic review describing the burden of anal squamous cell carcinoma (SCC), and its surrogates, in SOTR. We conducted mixed effect model-based meta-analyses evaluating incidence of anal SCC [standardised incidence ratio (SIR) versus general population, and absolute incidence rate (IR)], prevalence of anal squamous abnormalities and human papillomavirus (HPV) 16.

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Generalised I^2 statistics were calculated, quantifying heterogeneity. Anal SCC incidence in SOTR was elevated versus the general population (pooled SIR = 6.8, 95% CI 4.3-10.9; six studies including 241,106 SOTR; I^2=82.3%), with an absolute IR of 12.3 (95% CI 10.4-14.7) per 100,000 person-years (five studies including 1,079,489 person-years; I^2=0%). Prevalence of abnormal anal cytology was 12.9% (95% CI 9.2-17.7%; six studies including 328 SOTR; I^2=17.4%). For histology, the pooled prevalence estimate of anal squamous intraepithelial lesions was 22.4% (95% CI 17.3-28.5%; three studies including 214 SOTR; I^2=0%), with 4.7% (95% CI 2.5-8.5%; I^2=0%) high-grade squamous intraepithelial lesions. Pooled anal HPV16 prevalence was 3.6% (95% CI 1.6-7.8%; four studies including 254 SOTR; I^2=17.6%). There was substantial and consistent evidence of elevated anal SCC incidence in SOTR.

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INTRODUCTION

Anal human papillomavirus (HPV) infection, especially HPV16, is an important etiologic factor of anal precancerous lesions and anal squamous cell carcinoma (SCC).[1,2] These anal HPV complications have been shown to occur at increased rates in specific groups, such as HIV-positive patients,[3] men who have sex with men (MSM),[3] women with a previous history of genital neoplasia[4,5] and solid organ transplant recipients (SOTR).[6] Much of the literature has been focused on HIV-positive MSM as a high-risk group, and it is relatively sparse regarding other groups.

Most countries have seen a substantial increase in anal SCC in recent years,[7] and the number of cases is expected to grow over the coming decades.[8,9] The number of SOTR is also rising: according to the United Kingdom National Health Service Organ Donation and Transplantation Activity Report 2017/18, kidney, liver, and lung or heart–lung transplants increased by 7%, 8% and 20% respectively from April 2017 to March 2018 compared with the previous year.[10] Transplant recipients are living longer on immunosuppressive therapy and therefore are exposed to an increased risk of infections and cancer.[11] A longer time since transplant (over five years) has been found to be associated with a higher incidence of *in situ* and invasive anal cancers.[6]

SOTR seem to have an increased risk of anal HPV infection, anal precancerous lesions and anal SCC.[6,12,13] Given this, the American Society of Transplantation Infectious Diseases Community of Practice guidelines,[14] recommended yearly anal cancer screening using anal cytology, and referral of those with squamous cytological abnormalities to high-resolution anoscopy (HRA). However, the prevalence of these surrogate markers for anal SCC is largely unknown, and studies have reported different results.

This systematic review and meta-analysis aimed to evaluate the incidence of anal SCC, the prevalence of anal HPV16 infection and anal squamous intraepithelial lesions in SOTR.

MATERIAL AND METHODS

Search strategy, selection criteria and outcome

The study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) recommendations.[15] The PRISMA checklist is provided as supplementary information S1. The protocol for the review was not recorded in a prospective registry.

Two authors (AA and GC) searched two electronic databases (PubMed and Scopus) for articles published from January 1990 until 14th February 2020. For anal SCC we used the terms “anus

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neoplasms" OR "anal neoplasms" OR "anal cancer" AND "transplantation" OR "transplant" OR "recipients" OR "transplanted". For anal HPV, the terms "anal" AND "papillomaviridae" OR "papillomavirus" OR "HPV" AND "transplantation" OR "transplant" OR "recipients" OR "transplanted" were used for the database searches. For anal cytology the terms "anal cytology" AND "transplantation" OR "transplant" OR "recipients" OR "transplanted" were selected. For the anal intraepithelial neoplasia (AIN) or anal squamous intraepithelial lesions (ASIL) search, the terms "anus neoplasms" OR "anal neoplasms" AND "transplantation" OR "transplant" OR "recipients" OR "transplanted" were used. Reference lists of the retrieved articles were also evaluated to identify other relevant studies. In cases of discrepancy, a consensus was reached, and no disagreements required adjudication. Only studies in English were included. Conference reports (abstracts) were also included. Case reports, book chapters, studies involving only paediatric cohorts, describing pre-transplant malignancies, with an evaluation prior to the start of immunosuppression, or involving HIV-positive SOTR only, were excluded.

The outcomes analysed were: 1) standardised incidence ratio (SIR) and incidence rate (IR) of anal SCC; 2) prevalence of anal HPV16 infection; 3) prevalence of anal squamous cytology abnormalities (≥ atypical squamous cells of undetermined significance [ASC-US]) and cytological high-grade squamous intraepithelial lesion (HSIL); 4) prevalence of ASIL and histological anal HSIL diagnosed by HRA.

For anal SCC, only studies with a description of the IR or SIR in SOTR were selected. Studies describing anogenital cancer SIR, without providing isolated anal SCC data could not be included. In these selected studies, the description of the IR or data for calculation of the IR were also recorded when described. When several studies described the same national cohort and used the same national database for information, only one was included, normally the one with a larger samples size (more information on National database study selection is provided in Supplementary information S2). The authors of one study[13] were contacted by email and asked to provide information on IR for anal SCC, but this data was not available up to the submission. The authors of a conference paper were contacted by email and ask to provide information on HPV16, that was included.[16]

The studies reporting anal HPV16 prevalence were included if they reported anal HPV16 detection in cytology/swab samples and used PCR-based techniques. Studies evaluating HPV16 in anal biopsies or not reporting HPV16 prevalence were excluded.

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The Bethesda terminology[17] was used to classify anal cytology as negative, ASC-US, low-grade squamous intraepithelial lesion (LSIL), atypical squamous cells that cannot be excluded as high-grade (ASC-H), or HSIL. ASC-US was considered the threshold for abnormal squamous anal cytology. Unsatisfactory cytology samples were excluded from the final analysis.

For the analysis of anal squamous intraepithelial lesions (ASIL), only studies using HRA for diagnosis were included. Studies evaluating the prevalence of AIN/ASIL in which only a positive anal cytology was used to select patients for HRA were excluded. For lesion classification, the Lower Anogenital Squamous Terminology (LAST) classification was used and the results presented as LSIL and HSIL.[18] LSIL included lesions classified as LSIL, AIN1, condylomas or signs of HPV infection.[18] HSIL included lesions classified as HSIL, AIN2 or AIN3, which are considered anal SCC precancerous lesions.[18]

Information on the first author, year and country of publication, type of transplant cohort, the data source (for anal SCC), contribution of each study (anal HPV16, cytology, histology, anal SCC SIR and/or IR), and whether each was a case-control study are presented in Table 1.

Statistical analysis

For meta-analysis of proportions, we used random effects logistic regression.[19] To account for heterogeneity, we included a normally distributed random intercept term on the log-odds scale.

For any individual study of anal SCC incidence, the estimate of SIR is calculated by dividing the observed number of cases (O_i) by the expected number of cases (E_i) for an age-matched sample from the background population. Given the SIR estimate and O_i for a given study, we can recover: $E_i = O_i/\widehat{SIR}_i$. The expected number of cases is usually treated as fixed and known for any given population, so we did not account for uncertainty in estimates of these values. For any single study, the number of observed cases can therefore be treated as following a Poisson distribution with expectation $E_i \times SIR_i$, where SIR_i is the parameter to be estimated and exact confidence intervals can be derived from the Poisson distribution.

We accounted for the data structure of individual study results by using a mixed effects Poisson model for meta-analysis of SIR estimates, specifying the observed number of cases as the outcome (allowing studies with zero events to be included) and expected number as an exposure. We used gamma-distributed (multiplicative) random effects, with mean set to one, to allow for heterogeneity between studies. This approach is similar to the 'random baseline' model described by Cai et al.[20] For meta-analysis of IR, we used the same approach but instead specified person-

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years of follow-up as the exposure variable for each study. When anal SCC SIR and IR were reported for different organ transplant groups within a single cohort, these were treated as separate results within the meta-analysis. Neither subgroup analyses nor meta-regression were carried out due to the small number of studies for each outcome and the limited availability of data on potential stratification factors.

A generalised I^2 statistic was calculated in each analysis as the ratio of between-study variance to the total between-study and within-study variance. The former quantity was obtained directly from the mixed effects analysis, while the latter was calculated as the average within-study estimate variance based on a normal approximation on the log scale for Poisson models and logit scale for logistic models weighted by number of patients minus one; studies with zero events were dropped from estimation of within-study variance in each case. The random effects models used for meta-analysis were fitted using Stata version 15 (StataCorp, College Station, TX, USA), and graphical summaries were constructed using the ggplot2 package in R.

RESULTS

Anal squamous cell carcinoma

Six studies, with a total of 241,106 transplant recipients, reported on anal cancer SIR and were included (Figure 1a and 2a, Table S3). A study each was included from the USA,[6] the UK,[13] Sweden,[21] Denmark,[22] Australia[23] and Italy/France.[24] The pooled estimate of SIR for anal SCC in SOTR was 6.8 (95% CI 4.3–10.9) (Figure 2a). The heterogeneity in the individual estimates of SIR was I^2=82.3%.

Of these six studies, five reported data for the IR analysis,[6,21,22,23,24] with a total of 1,079,489 person-years follow-up. The pooled model estimate of the overall IR was 12.3 (95% CI 10.4–14.7) per 100,000 person-years (Figure 2b). Heterogeneity between studies was I^2=0%.

Anal HPV16

Prevalence of HPV16 genotyping from anal cytology/swabs was reported in four studies, on a total of 254 samples (Figure 1b and 3a, Table S4). Studies were conducted in the UK,[25] Poland,[26] Australia[16] and Brazil.[27] Three studies were in a kidney,[25,27] and one in a liver transplant cohort.[26] None of the studies included a healthy control group. The pooled estimate of the prevalence of HPV16 was 3.6% (95% CI 1.6–7.8%) (Figure 3a). Heterogeneity between studies was I^2=17.6%.

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Anal cytology

Six studies, and a total of 328 satisfactory samples were included in final analyses (Figure 1c and 3b, Table S5). Two studies were conducted in the USA[28,29] and one each in the UK,[25] Portugal,[30] Australia[16] and Brazil[27] all using liquid-based cytology. Four studies were in a kidney transplant cohort,[25,27,28] one was in a liver transplant cohort,[30] and one in a mixed cohort of kidney, pancreas and liver transplants.[29] Of note, all studies had unsatisfactory sample rates lower than 15%, except the study by Khan et al.[29] with an unsatisfactory sample rate of 19% (data not shown).

The pooled estimate for the prevalence of 'abnormal' squamous result on anal cytology was 12.9% (95% CI 9.2–17.7%) (Figure 3b). The level of heterogeneity was I^2=17.4%. Only one study compared the prevalence of anal squamous cytological abnormalities (≥ASCUS) in the transplanted cohort (17%) with that in a healthy control group (2%), identifying a statistically significant increase (p=0.005).[30]

The pooled estimate for the prevalence of anal HSIL on cytology was 2.4% (95% CI 1.2–4.8%) with a heterogeneity of I^2=0% (Figure 3c).

Anal squamous intraepithelial lesions (histology)

For the meta-analysis, three studies fulfilled the study criteria and were included (Figure 1d, Table S6). A total of 214 transplant recipients underwent HRA. Studies were conducted in the UK,[12] USA[28] and Brazil.[31] All studies were in kidney transplant recipients. Of note, two studies performed biopsies of abnormal areas and non-abnormal areas[12,31] and one from abnormal areas only.[28]

The pooled estimate of the prevalence of ASIL on HRA was 22.4% (95% CI 17.3–28.5%) (Figure 3d). The estimated heterogeneity was I^2=0%. Only one study[12] compared the prevalence between transplanted (24%) and healthy controls (0.7%) ($p<0.05$). The pooled estimate of the prevalence of anal HSIL was 4.7% (95% CI 2.5–8.5%) with a heterogeneity I^2=0% between studies (Figure 3e).

DISCUSSION

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The incidence of anal SCC has been increasing in recent years, and will continue to grow in the next two decades.[8, 9] The benefits of HPV vaccination programs are not expected to manifest for a number of years, and better prevention strategies and more information on other high-risk groups besides HIV-positive MSM are needed. Our study shows that there is a fair amount of studies using large National databases reporting anal SCC incidence in SOTR to date.

A previous meta-analysis published in 2007[32] compared the cancer incidence in HIV-positive patients and SOTR. For anal cancer, HIV-positive patients had an SIR of 28.75 (95% CI 21.6–38.3), and transplant patients an SIR of 4.85 (95% CI 1.36–17.3), with only two studies included in the latter analysis. Our meta-analysis included six studies for SIR calculation and reported a higher SIR of 6.8 (95% CI 4.3–10.9). According to the SEER, the annual incidence of anal cancer in the general population, between 1975 and 2016, was 1.9 per 100,000 person-years.[33] The calculated IR of anal SCC in our meta-analysis was 12.3 per 100,000 person-years, significantly higher than that expected in the general population, and with no apparent heterogeneity between studies. This estimated IR allows comparison of anal cancer incidence not only with the general population (e.g. SIR), but with other populations of established clinically relevant anal cancer risk. HIV-positive patients and transplant recipients seem to share the same risk factor of immunodeficiency for cancers driven by infections, but the risk seems much higher for HIV-positive patients.[32] In a previous meta-analysis by Machalek et al.[3] published in 2012, evaluating the burden of anal HPV disease in HIV-positive MSM, the reported IR for anal SCC was 45.9 per 100,000 person-years. In HIV-positive patients the presence of other co-risk factors, namely receptive anal intercourse, larger number of lifetime sexual partners and higher smoking rate, might contribute to this higher risk.[22,28] In kidney transplant recipients, the risk of anal cancer is increased only after transplantation, and not during end-stage kidney disease before renal replacement therapy and during dialysis, which suggests that immunosuppression is responsible for the increased risk.[23] The risk of anal SCC in transplant recipients seems to be associated to gender and transplant duration. In the study by Madeleine et al,[6] there was an increase risk in females by comparison with males, and was also higher for patients with more than five years of transplantation.

HIV-negative MSM are also considered a high-risk group for anal SCC, and there are a much larger number of studies in the literature evaluating anal HPV16[3,34] and ASIL prevalence[3] in this population than we have found for SOTR. Interestingly in the same meta-analysis by Machaek et al.,[3] the reported IR of anal SCC for HIV-negative MSM was only 5.1 per 100,000 person-years,

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based on only two studies included, i.e. less than half of the pooled incidence we report for SOTR. Of note, population-based studies on anal SCC incidence in HIV-negative MSM are more difficult to conduct given that sexual preference data is not collected in most (if not all) population-based registers. Many countries do, however, have accurate transplant registries that can be linked to cancer registries.

Data on anal HPV16, squamous cytological and histological abnormalities in SOTR are still limited. Nevertheless, the data that we did find were very consistent, with low heterogeneity between studies. HPV16 is by far the most carcinogenic HPV type in the anus, and therefore a useful surrogate for anal cancer risk.[2] Our study showed a 3.6% prevalence of anal HPV16 infection. Excluding HPV16 studies based on anal biopsies reduced the potential for bias. For anal squamous cytology abnormalities, the pooled estimate for prevalence in SOTR was 12.9%. A rate of less than 5% of unsatisfactory samples on anal cytology in high-risk groups (e.g. HIV-positive MSM) and less than 15% in lower-risk groups (e.g. HIV-negative women) has been recommended.[35] All studies that were included had unsatisfactory sample rates lower than 15% except one.[29] When considering histological ASIL only studies using HRA were included. HRA is the gold standard for AIN/ASIL detection, and when this technique is not used lesions are frequently missed.[36] HRA was performed in all patients reducing the possibility of underestimating the true prevalence of HSIL. This can occur due to patients with normal anal cytology not being submitted to HRA. The pooled prevalence estimate of AIN was 22.4%, with a 4.7% prevalence of anal HSIL.

With respect to prevention measures, the American Society of Transplantation Infectious Diseases Community of Practice guidelines advocated for yearly anal cytology in SOTR and referral of those with abnormalities to HRA.[14] The recommendation for yearly screening in SOTR[14] is based largely on the fact that recommendations for screening HIV-positive patients have suggested this timing.[37] Currently, insufficient infrastructure and trained clinicians exist to take on a routine screening programme.[38] HRA is an invasive technique with a long learning curve,[39] and very few trained providers. There are several unanswered questions relating to anal cancer screening in SOTR. Some of the variables that need consideration in future studies include the method of screening, the timing of the introduction of screening, the screening frequency and the risk pattern of the immunosuppressive drugs in use. Azathioprine seem to pose an increased risk for invasive anal cancer, and corticosteroids for in situ anal cancer.[6] The role of anal HPV16 testing needs to be further evaluated in this setting, and case-control studies comparing prevalence

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HPV16 with a healthy control population are needed. There is also a lack of published data from randomised control trials showing that screening and the treatment of anal HSIL can prevent anal SCC.

This study has several limitations. A large proportion of the data gathered are from kidney transplant recipients, being the most commonly transplanted organ, and so generalisation of our results to other types of SOTR is more limited. Study heterogeneity was substantial for anal SCC SIR, possibly driven by differences in the background population IRs used for standardisation within each study. The pooled SIR estimate should therefore not be over-interpreted, although it does provide clear evidence of significant excess over background rates. No meta-regression and subgroup analysis was conducted. In the meta-analysis of anal SCC incidence, the only potentially useful stratification could have been for type of organ transplanted. However, there was no heterogeneity in the studies included, and the biggest study (by far) by Madeleine et al.,[6] did not stratify by organ. There was little heterogeneity and we were not showing meta-associations, but rather descriptive proportions and rates, for which there is less pressure to show positive results (and as such bias is less likely to exist). Lastly, there were only two studies comparing the prevalence of squamous cytological abnormalities[30] and histological ASIL,[12] respectively, between SOTR and healthy controls, and so they could not be meta-analysed. However, both showed a statistically significant excess of anal lesions in SOTR compared to the control group, which is somewhat consistent with the more robust finding of the significantly increased SIR seen for anal SCC.

The number of SOTR is increasing, as well as their life expectancy while on immunosuppressive drugs. This poses an increased risk of the development of complications associated with this medication, such as carcinogenic infections. Anal HPV16 infection and viral persistence have been associated with the development of anal precancerous lesions and anal SCC. There are several studies reporting data on anal SCC incidence using large national databases, and our meta-analysis confirmed an increased risk in SOTR. Data are limited for prevalence of anal HPV16, squamous cytological and histological abnormalities, but highly consistent between studies.

DISCLOSURE:

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FIGURE LEGENDS:

Figure 1a-d: Flowcharts for the study selection involving anal squamous cell carcinoma, anal HPV16, anal cytology abnormalities and anal squamous intraepithelial lesions.

Figure 2: Forest plots of a) the standardised incidence ratio (SIR) and b) the incidence rate (IR) for anal squamous cell carcinoma in solid organ transplant recipients in individual studies (●) with summary estimates from our meta-analysis (◆). Plots of individual study estimates are scaled in relation to the number of patients in (a) and person-years of follow-up (PYFU) in (b), and error bars show 95% CIs (as reported in study). The dashed vertical line in (a) shows an SIR of 1.

Figure 3: Forest plot of prevalence of a) detection of HPV16, b) abnormal anal cytology, c) anal cytology HSIL, d) AIN/ASIL on HRA among solid organ transplant recipients in individual studies and e) histological anal HSIL (●) with summary estimates from our meta-analysis (◆). Plots of individual study estimates are scaled in relation to the number of patients included, and error bars show 95% CIs (calculated using binomial distribution).

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SUPPORTING INFORMATION

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

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Table 1: Summary of the 15 studies included

Reference	Year	Country	Cohort	Data source	HPV16 cytology/swabs	Anal cytology	AIN/ASIL all patients with HRA	Anal SCC	
								SIR	IR
Patel et al.[25]	2010	UK	Kidney transplant ≥ 18 years-old	-	X	X	-	-	
Grat et al.[26]	2014	Poland	Liver transplant < 3 weeks		X		-	-	
Eleuterio Jr et al.[27]	2019	Brazil	Kidney transplant women ≥18 years-old		X	X	-	-	
Albuquerque et al.[30]	2017	Portugal	Liver transplant ≥2 years ≥18 years-old		-	X (C)	-	-	
Khan et al.[29]	2019	USA	Liver, pancreas and kidney ≥1 year		-	X	-	-	
Rosales et al.[16]	2018	Australia	Kidney transplant over 18 years-old		X	X	-	-	
Olgivie et al.[28]	2008	USA	Kidney transplant ≥6 months		-	X	X		
Ogunbiyi et al[12]	1994	UK	Kidney transplant ≥6 months ≥15 years-old		-		X (C)		
Tramujas da Costa e Silva et al.[31]	2008	Brazil	Kidney transplant		-	-	X	-	
Vadjic et al.[23]	2006	Australia	Kidney transplant	Australia and New Zealand Dialysis and Transplant Registry and the Australian National Cancer Statistics Clearing House	-	-	-	X	X
Serraino et al.[24]	2007	Italy/France	Kidney, heart, lung and liver transplant	Italian and French cancer registries, Italian transplant recipients	-	-	-	X	X
Collett et al.[13]	2010	UK	Kidney, heart, lung and liver transplant	UK Transplant Registry, Cancer registries in England, Wales and Scotland	-	-	-	X	-
Sunesen et al.[22]	2010	Denmark	Solid organ transplant (type of organ not described)	Danish Cancer Registry, Danish National Patient Registry, Danish Registry of Causes of Death	-	-	-	X	X
Krynitz et al.[21]	2012	Sweden	Kidney, liver, heart and/or lung transplant	Swedish National Patient Register and Swedish Cancer Register	-	-	-	X	X
Madeleine et al.[6]	2013	USA	Kidney, heart, lung, liver, pancreas and	USA organ transplant registry and 15	-	-	-		

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			combined	USA state and local cancer registries				X	X

AIN: anal intraepithelial neoplasia, ASIL: anal squamous intraepithelial lesions, HPV: human papillomavirus, HRA: high-resolution anoscopy, IR: incidence rates, SCC: squamous cell carcinoma, SIR: standardised incidence ratio

(C): presence of a healthy control group

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Figure 1a: Study selection for anal squamous cell carcinoma.

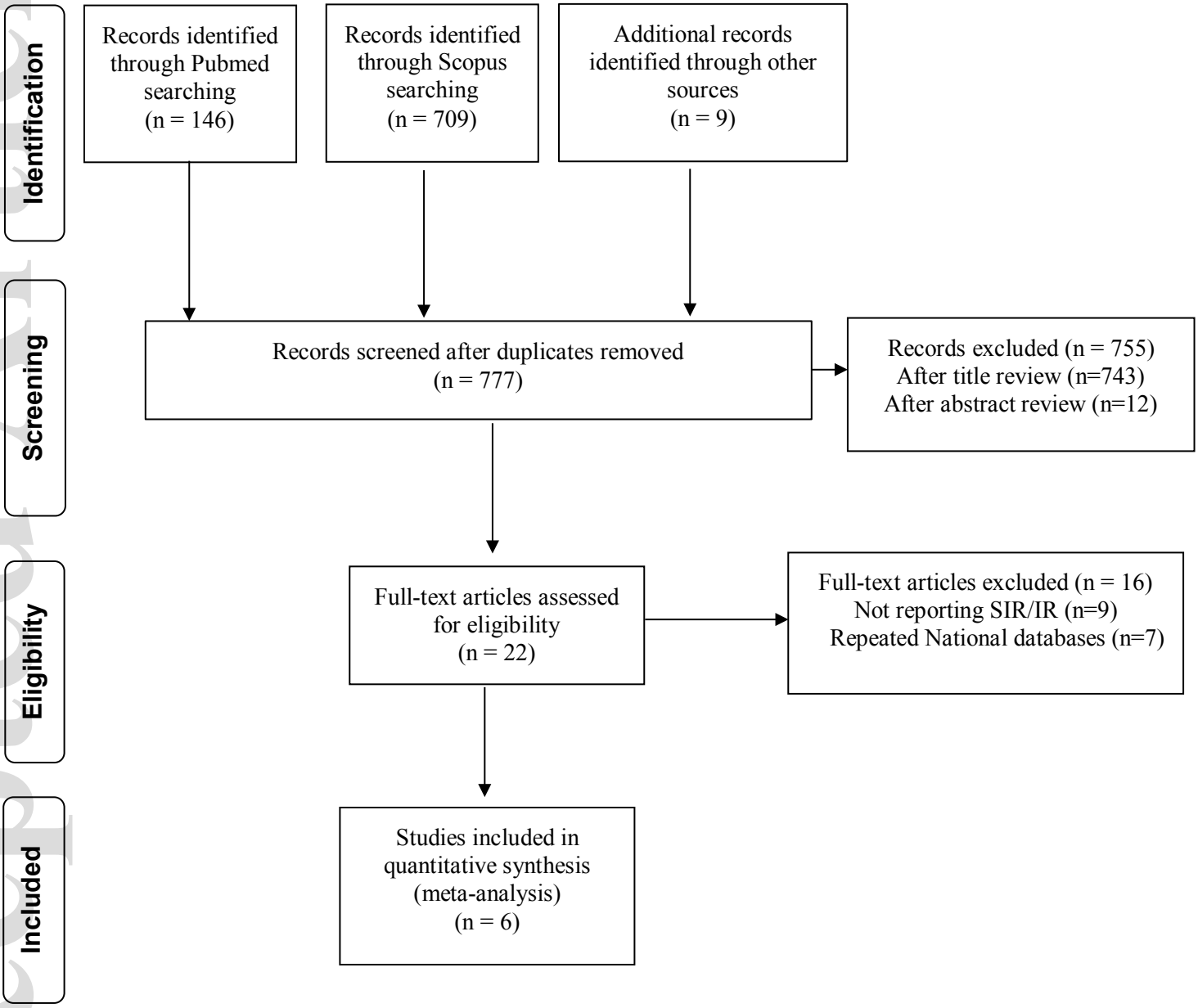

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Figure 1b: Study selection for human papillomavirus 16.

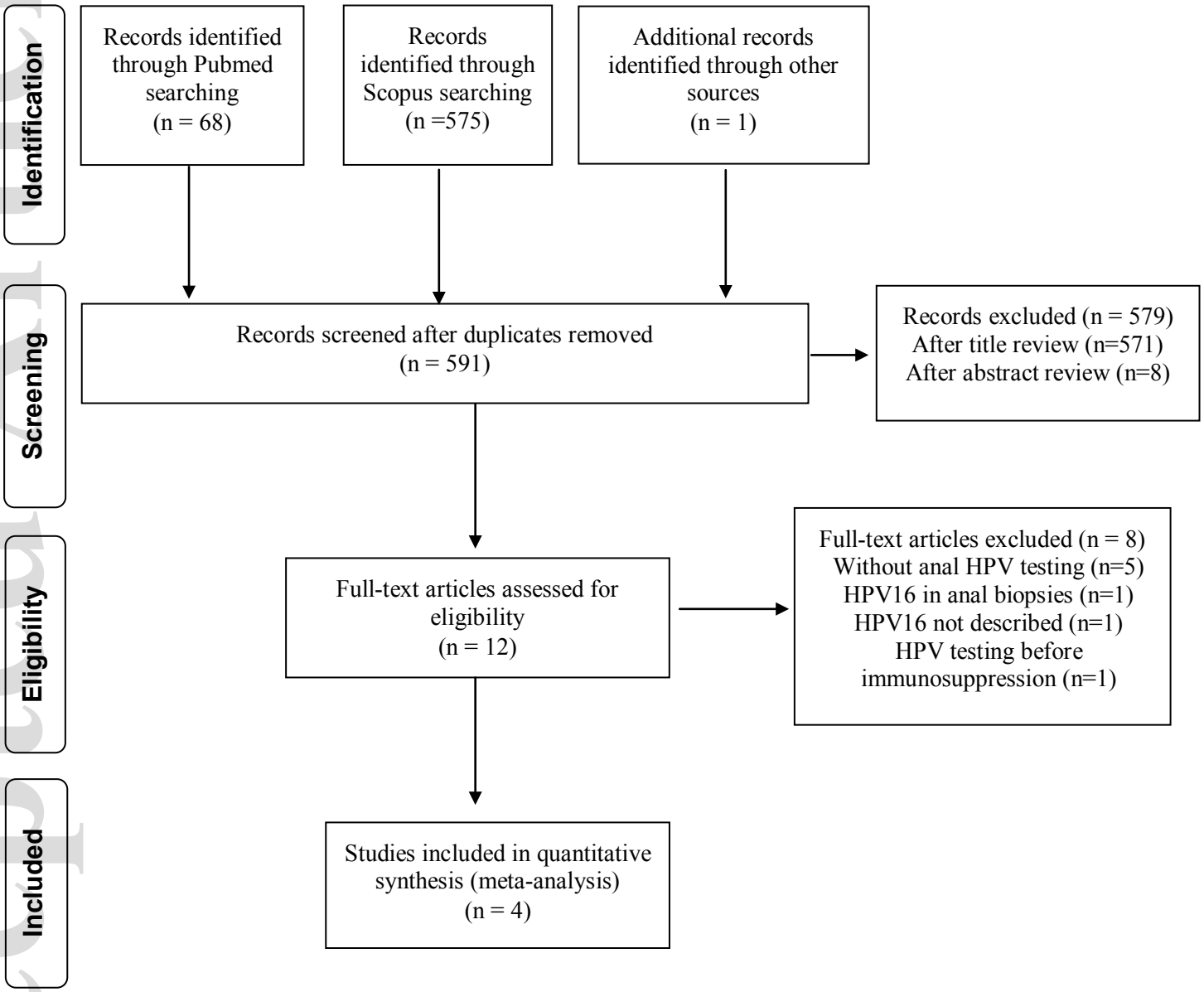

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Figure 1c: Study selection for anal cytology abnormalities.

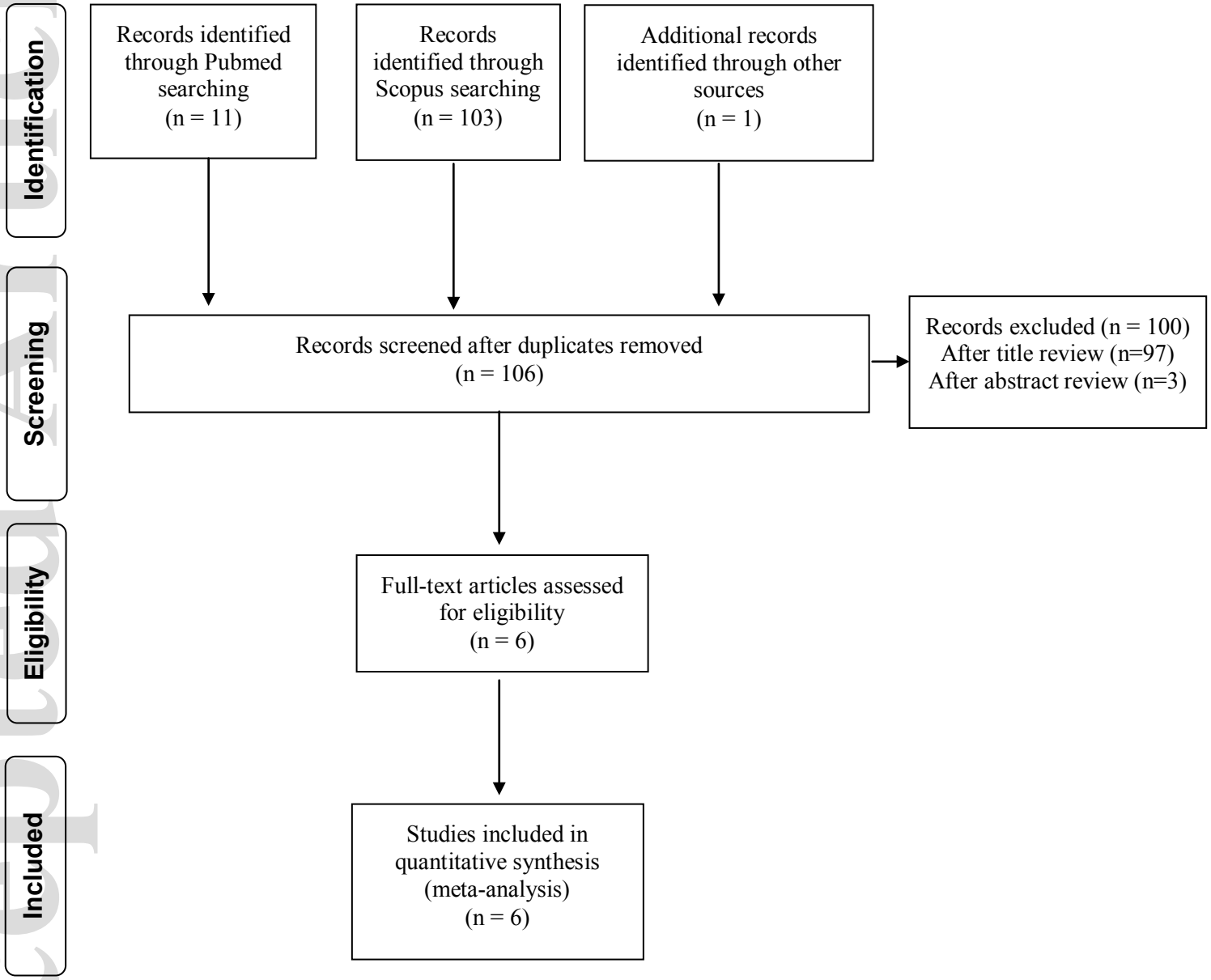

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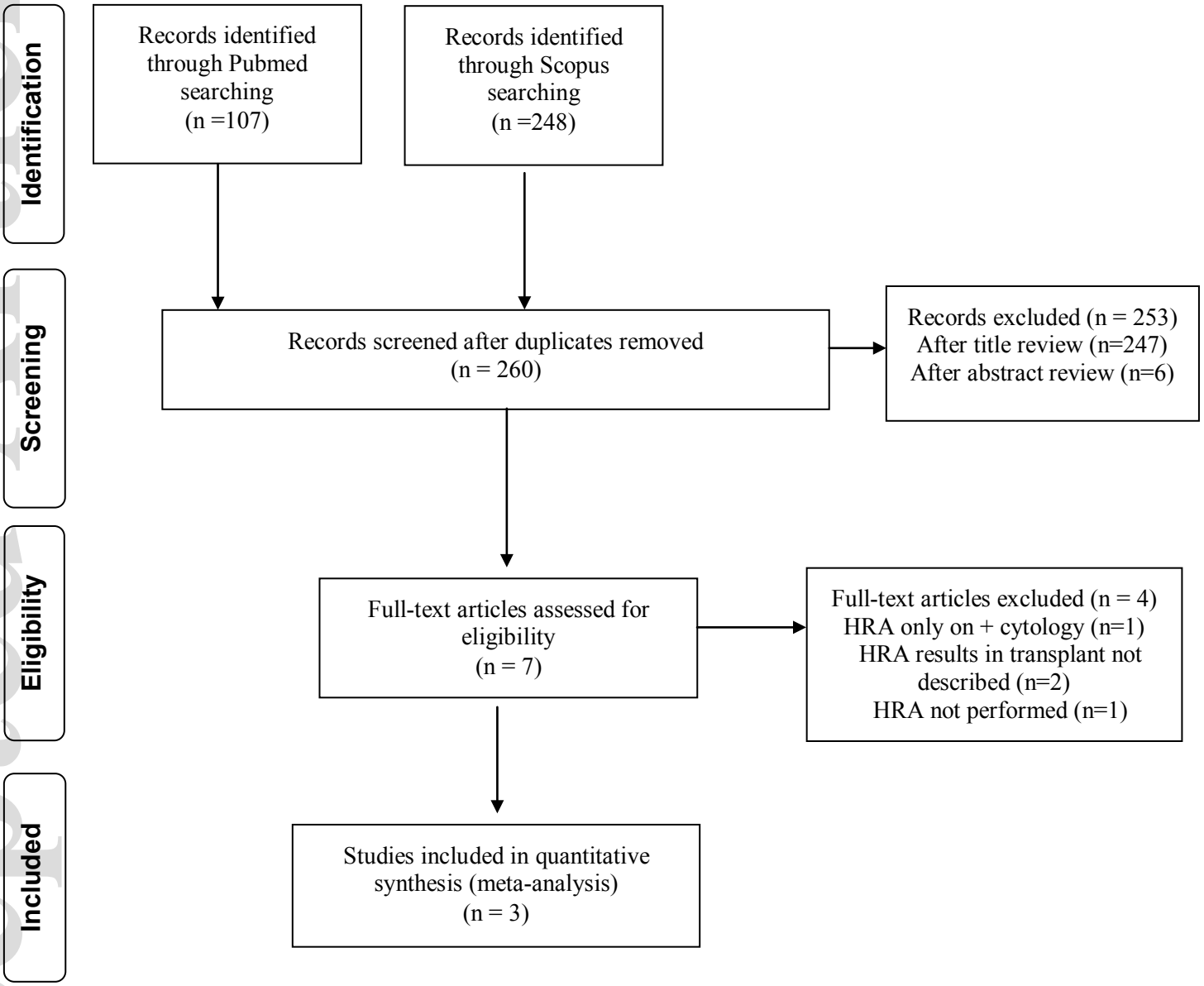
Figure 1d: Study selection for anal squamous intraepithelial lesions.



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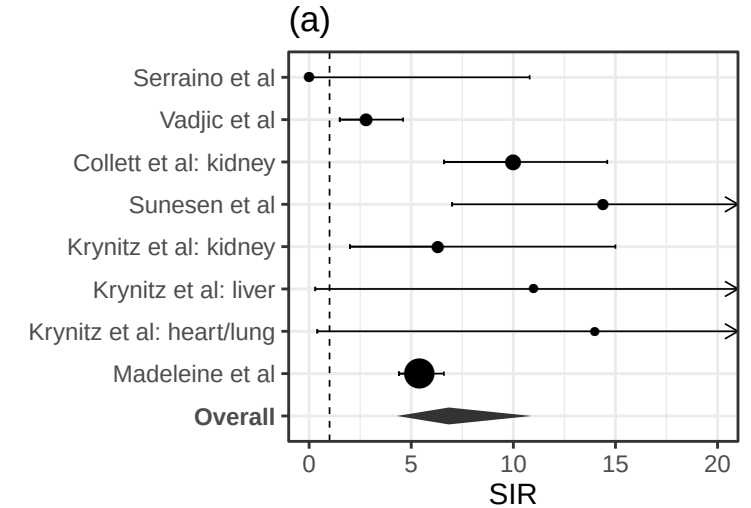
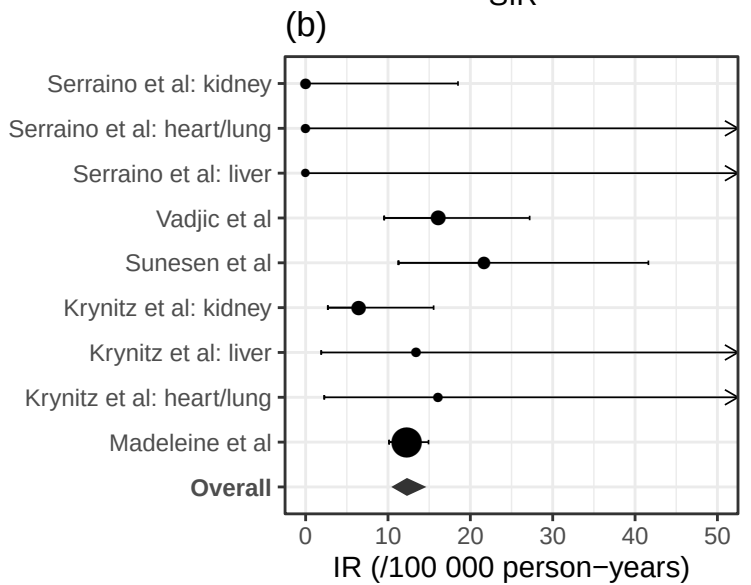
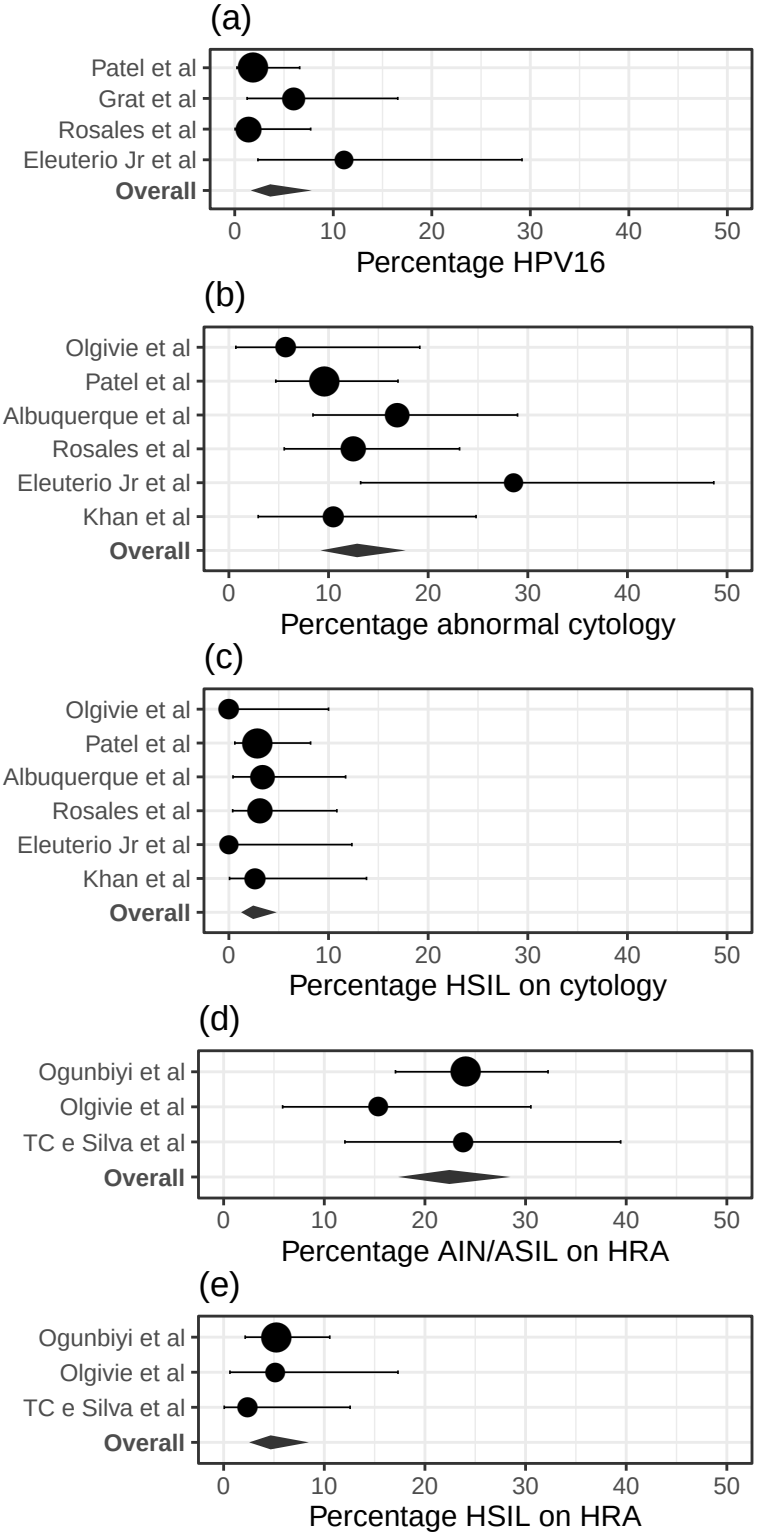


	n cases/N pat.	SIR (95% CI)
Serraino et al	0/2875	0.0 (0.0−10.8)
Vadjic et al	14/10180	2.8 (1.5− 4.6)
Collett et al: kidney	27/25104	10.0 (6.6−14.6)
Sunesen et al	9/5113	14.4 (7.0−26.4)
Krynitz et al: kidney	5/7952	6.3 (2.0−15.0)
Krynitz et al: liver	1/1221	11.0 (0.3−62.0)
Krynitz et al: heart/lung	1/1012	14.0 (0.4−77.0)
Madeleine et al	103/187649	5.4 (4.4− 6.6)
Overall	**160/241106**	**6.8 (4.3−10.9)**
		I^2=82.3%; P=0.001



	n cases/PYFU	IR (95% CI)
Serraino et al: kidney	0/16196	0.0 (0.0− 18.5)
Serraino et al: heart/lung	0/4970	0.0 (0.0− 60.4)
Serraino et al: liver	0/1508	0.0 (0.0−198.9)
Vadjic et al	14/86898	16.1 (9.5− 27.2)
Sunesen et al	9/41554	21.7 (11.3− 41.6)
Krynitz et al: kidney	5/77288	6.5 (2.7− 15.5)
Krynitz et al: liver	1/7450	13.4 (1.9− 95.3)
Krynitz et al: heart/lung	1/6227	16.1 (2.3−114.0)
Madeleine et al	103/837398	12.3 (10.1− 14.9)
Overall	**133/1079489**	**12.3 (10.4− 14.7)**
		I^2=0%; P=1.00



	n cases/N pat.	Perc. (95% CI)
	2/107	1.9 (0.2− 6.6)
	3/50	6.0 (1.3−16.5)
	1/70	1.4 (0.0− 7.7)
	3/27	11.1 (2.4−29.2)
	9/254	**3.6 (1.6− 7.8)**
		I^2=17.6%; P=0.32

	n cases/N pat.	Perc. (95% CI)
	2/35	5.7 (0.7−19.2)
	10/104	9.6 (4.7−17.0)
	10/59	16.9 (8.4−29.0)
	8/64	12.5 (5.6−23.2)
	8/28	28.6 (13.2−48.7)
	4/38	10.5 (2.9−24.8)
	42/328	**12.9 (9.2−17.7)**
		I^2=17.4%; P=0.35

	n cases/N pat.	Perc. (95% CI)
	0/35	0.0 (0.0−10.0)
	3/104	2.9 (0.6− 8.2)
	2/59	3.4 (0.4−11.7)
	2/64	3.1 (0.4−10.8)
	0/28	0.0 (0.0−12.3)
	1/38	2.6 (0.1−13.8)
	8/328	**2.4 (1.2− 4.8)**
		I^2=0%; P=1.00

	n cases/N pat.	Perc. (95% CI)
	32/133	24.1 (17.1−32.2)
	6/39	15.4 (5.9−30.5)
	10/42	23.8 (12.1−39.5)
	48/214	**22.4 (17.3−28.5)**
		I^2=0%; P=1.00

	n cases/N pat.	Perc. (95% CI)
	7/133	5.3 (2.1−10.5)
	2/39	5.1 (0.6−17.3)
	1/42	2.4 (0.1−12.6)
	10/214	**4.7 (2.5− 8.5)**
		I^2=0%; P=1.00