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High-Risk Hpv, Precancerous Lesions and Cancer In Anal Condylomas: Systematic Review And Meta-Analysis.

Condylomas as a risk factor for cancer.

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ABSTRACT

INTRODUCTION: anal condylomas are associated with human papillomavirus (HPV) infection and are a risk factor for anal squamous cell carcinoma (SCC).

OBJECTIVE: to conduct a meta-analysis evaluating the prevalence of anal high-risk-HPV, high-grade squamous intraepithelial lesions (HSIL) and SCC in patients with condylomas. The standardised incidence ratio (SIR) and the incidence rate (IR) of anal SCC were also calculated.

METHODS: three electronic databases were searched until April 2020. Meta-analyses were performed using random effects models.

RESULTS: pooled prevalence estimate of HR-HPV in anal condylomas was 40.2% (21.0−63.1) in immunocompromised and 16.4% (10.7−24.3) in non-immunocompromised patients, with an odds ratio (OR) of 3.79 (1.51-9.52, P=0.005) for immunocompromised patients. HR-HPV in condylomas with HSIL was 73.8% (39.1− 92.5) and in non-HSIL cases was 17.7% (9.6−30.2), corresponding to an OR of 12.33 (2.97-51.21, P=0.001) for those with HSIL. The prevalence of HSIL in condylomas was 24.0% (16.4−33.7) in immunocompromised and 11.8% (7.2−18.8) in non-immunocompromised patients, with an OR of 2.51 (1.72-3.65, P<0.001) for immunocompromised patients. The overall prevalence of anal SCC was 0.3% (0.0− 1.7). The SIR of anal SCC was 10.7 (8.5−13.5), 20.1 (14.4−28.2) in men and 7.7 (5.6−10.5) in women. The overall IR of anal SCC was 6.5 per 100 000 persons-year (3.6−11.7), 12.7 (9.1−17.8) in men and 4.7 (1.7−13) in women.

CONCLUSION: patients with a history of anal condylomas have a high risk of anal SCC, especially men. The prevalence of HR-HPV and HSIL in condylomas from immunocompromised patients is high. This information can change patient follow-up and treatment.

KEYWORDS: human papillomavirus, HPV-16, high-grade squamous intraepithelial lesions, anal squamous cell carcinoma, anal condylomas.

INTRODUCTION

Anogenital condylomas are a common human papillomavirus (HPV) infection driven disease, with an annual incidence ranging from 160 to 289 per 100,000 persons (males and females combined), being more common in young adults [1]. Condylomas occur more frequently in the external anogenital areas [2]. HIV-infection is a risk factor for anogenital condylomas [3], and a higher CD4 cell counts and lower HIV RNA were associated with a lower risk of developing anogenital warts [3].

The Lower Anogenital Squamous Terminology Standardization (LAST) [2] defined condylomas as a papillary proliferation with low-grade cytopathic features of HPV infection, normally considered as low-grade squamous intraepithelial lesions (LSIL). It has been reported, that more than 90% of genital warts are associated with HPV 6 and 11 infection [4]. High-risk (HR) HPV can be linked with anal condylomas [4], and they can harbor high-grade squamous intraepithelial lesions (HSIL) [5]. Besides HSIL, they have been associated with more severe lesions, e.g. Buschke-Loewenstein tumors [6] and anal squamous cell carcinoma (SCC) [5].

Anal condylomas are considered a risk factor for anal SCC [5]. Some Societies, e.g. the HIV Medicine Association of the Infectious Diseases Society of America have recommended anal cancer screening in all HIV-patients with a history of anogenital condylomas [7]. However, there is a lack of information on the burden of anal HR-HPV, HSIL and SCC in anal condylomas. Patients with different histological grades of anal squamous intraepithelial lesions have a different follow-up approaches, so this information can be relevant for patient care [8]. Patients with anal HSIL have a higher risk of anal cancer and should have a shorter follow-up interval than patients with low-grade lesions [8].

The aim of this study was to evaluate the prevalence of anal HR-HPV, HSIL and anal SCC in anal condylomas. The standardised incidence ratio (SIR) and the incidence rate (IR) of anal SCC in patients with a history of anal condylomas were also calculated.

MATERIAL AND METHODS

Search strategy and selection criteria

One author searched three electronic databases (PubMed, Web of Science and Embase), after agreement on the search terms. Search was conducted until April 2020. Data were retrieved by two authors independently (AA and CC). In cases of discrepancy, a consensus was reached, and no disagreements required adjudication.

Both MESH terms and text words were used. For anal SCC and anal HSIL in the PubMed search we used the terms “anogenital” OR “anal” OR “anus” AND “neoplasms” OR “cancer” OR “squamous cell carcinoma” OR “carcinoma in situ” OR “precancerous conditions” AND “condylomata acuminata” OR “warts”. For anal HPV “anal” OR “anogenital” AND

“papillomaviridae” OR “papillomavirus” OR “HPV” AND “condylomata acuminata” OR “warts” were used for the database searches.

Reference lists of the retrieved articles and published conference abstracts were also evaluated to identify other relevant studies. Only studies in English and in an adult population were included. Studies with anal and/or perianal warts were both included. Case reports and studies with less than 10 condyloma samples analysed were excluded. Results that included globally the anogenital area, without independent perianal/anal condyloma results could not be included.

For anal HPV only studies involving biopsies or surgical specimens were included. Results from anal swabs were excluded. Only studies detecting anal HPV infection by a PCR-based technique were selected. Studies that used in-situ, Southern blot or dot spot hybridization were excluded. High-risk and low-risk HPV classification of each study was used. Immunocompromised patients were HIV-positive or patients with pharmacology immunosuppression.

Lesions were considered high-grade squamous intraepithelial lesions if the histology showed HSIL, anal intraepithelial neoplasia (AIN) 2 or AIN3, high-grade dysplasia or carcinoma in situ, and needed to be diagnosed by biopsy or surgical excision. The histological classification of each paper was followed. In cases for which p16 was evaluated in AIN2 lesions, only p16-positive AIN2 were considered high-grade lesions, as defined by the LAST [2]. Anal cytology results/diagnosis were not considered for this analysis (only histology). In cases for which there was a first and then a follow-up analysis, only the first result was considered. Results are whenever possible presented by patient (and not by lesion). We did not include studies in which biopsies of suspicious areas were carried out and/or when the selection of condylomas for histological analysis was not done randomly (e.g. by selecting condylomas with known areas of dysplasia). Studies where there was a lack of clarity regarding the histological classification were also not included.

For anal cancer, only cases of SCC were considered. In case there were different papers reporting data/databases from the same country, only the most recent or the larger was included.

Several authors were contacted by email when more information was needed. A first email was sent, and when no reply was given, a second email was sent.

Information on the first author, year and country of publication, population, collection technique, number of patients/samples and the number of lesions was collected for HPV, HSIL and anal SCC prevalence (Table S1, http://links.lww.com/QAD/C183 and S2, http://links.lww.com/QAD/C184). Information on the first author, year and country of publication, data source, number of patients included, number of observed cases and person-years of follow-up was retrieved for anal SCC SIR (Table S3,

http://links.lww.com/QAD/C185) and IR calculation (Table S4, http://links.lww.com/QAD/C186).

Outcomes

The overall prevalence of HR-HPV and HPV-16 in anal condylomas was evaluated, with subgroup analyses conducted according to the histologic type of lesion (LSIL vs. HSIL) and immune status. The prevalence of HSIL and anal SCC in condylomas was also evaluated, with subgroup analysis according to immune status. For anal SCC, a meta-analysis of the SIR and the IR in patients with a history of anal condylomas was conducted, with a subgroup analysis according to gender.

Quality assessment and risk of bias from individual studies

The studies included were observational, the quality assessment was performed using the Newcastle-Ottawa Scale (Table S5, http://links.lww.com/QAD/C188). Studies were considered of high quality if ≥7 points, moderate quality if 5-6 points, and low quality if ≤4 points.

Statistical analysis

Meta-analyses were carried out as previously described by Albuquerque et al [9]. Briefly, for meta-analysis of proportions we used random effects logistic regression [10] with a normally distributed random intercept term on the log-odds scale. A mixed effects Poisson model was used for meta-analysis of SIR, with the observed number of cases specified as the outcome and expected number as an exposure. We used gamma-distributed (multiplicative) random effects, with mean set to 1, to allow for heterogeneity between studies. For meta-analysis of IR, we used the same approach but instead specified person-years of follow-up as the exposure variable for each study. A generalized I^2 statistic was calculated in each analysis as the ratio of between-study variance to the total between-study and within-study variance as previously described [9]. In addition, differences in prevalence and incidence rate outcomes between subgroups (immunocompromised vs non- immunocompromised, HSIL vs no HSIL, men vs women) were formally evaluated using mixed effect logistic and Poisson regression models with random effect terms per study and per subgroup nested within study. These analyses included all studies with subgroup status available (even if only one subgroup were present in any given study). The random effects models used for meta-analysis were fitted using Stata version 15 (StataCorp, College Station, TX), and graphical summaries were constructed using the ggplot2 package in R.

RESULTS

Overall anal HR-HPV and HPV-16 prevalence

The meta-analysis of anal HR-HPV and HPV-16 included eight studies, one each from US [11], Brazil [12], Germany [13], Spain [14], Netherlands [15], Japan [16], Switzerland [17]

and Taiwan [18] with a total of 525 cases (Table S1, http://links.lww.com/QAD/C183, Figure S1, http://links.lww.com/QAD/C179, Figure 1 and Figure S2, http://links.lww.com/QAD/C180). The random-effects pooled overall prevalence of HR-HPV in anal condylomas was 28.6% (95%CI 19.0−40.6), with a heterogeneity of I^2=83.1%. Immunocompromised patients had a prevalence of HR-HPV of 40.2% (21.0−63.1) and non-immunocompromised 16.4% (10.7−24.3), corresponding to an odds ratio (OR) of 3.79 (1.51-9.52, P=0.005) for immunocompromised patients. When analysed by grade, prevalence in HSIL was 73.8% (39.1− 92.5) and in non-HSIL cases was 17.7% (9.6−30.2), corresponding to an OR of 12.33 (2.97-51.21, P=0.001) for those with HSIL.

The overall prevalence of HPV-16 in anal condylomas was 8.3% (5.6−11.9), with a heterogeneity of I^2=29.9%. Immunocompromised patients had a prevalence of HPV-16 of 11.2% (7.0−17.5) and non-immunocompromised 2.8% (0.4−17.3), corresponding to an OR of 4.41 (0.57-34.41, P=0.16) for immunocompromised patients. When analysed by grade, the prevalence in HSIL was 20.9% (6.3−50.9) and in non-HSIL cases was 4.3% (1.6−10.9), corresponding to an OR of 6.58 (1.63-26.64, P=0.008) for those with HSIL.

Anal HSIL and SCC prevalence

For anal HSIL and SCC prevalence 14 studies were included, four from the US [11, 19-21], two from the Netherlands [15, 22], and one each from Australia [23], Spain [24], Brazil [12], France [25], Japan [16], Argentina [26], UK [27] and Sweden [28]. The total number of cases included were 1733 (Table S2, http://links.lww.com/QAD/C184, Figure S3, http://links.lww.com/QAD/C181, Figure 2 and Figure 3).

The random-effects pooled overall prevalence of anal HSIL was 13.8% (9.0−20.6), with a heterogeneity of I^2=83.3%. The data was also analysed by immune status, immunocompromised patients had an HSIL prevalence of 24.0% (16.4−33.7) and non-immunocompromised a prevalence of 11.8% (7.2−18.8), corresponding to an OR of 2.51 (1.72-3.65, P<0.001) for immunocompromised patients.

An analysis of HSIL prevalence in condylomas obtained by excision was also done (excluding those studies where condylomas were collected by biopsy or collection not described), Figure S4, http://links.lww.com/QAD/C182. The overall prevalence of anal HSIL was 17.2% (11.7−24.5), with a heterogeneity of I^2=78.7%, immunocompromised patients had an HSIL prevalence of 22.3% (13.2−35.1) and non-immunocompromised a prevalence of 11.4% (6.3−19.8), corresponding to an OR of 2.53 (1.76-3.64, P<0.001) for immunocompromised patients.

The overall prevalence of anal SCC was 0.3% (0.0− 1.7), with a heterogeneity of I^2=85.9%. Immunocompromised patients had a SCC prevalence of 0.7% (0.1−4.1) and non-immunocompromised a prevalence of 0.1% (0.0− 4.6), corresponding to an OR of 3.33 (0.75-14.4, P=0.11) for immunocompromised patients.

Anal SCC SIR and IR analysis

Three studies were selected, one each from Sweden [29], Denmark [30], and Taiwan [31], with a total of 81 822 patients included (Table S3, http://links.lww.com/QAD/C185 and S4, http://links.lww.com/QAD/C186, Figure S3, http://links.lww.com/QAD/C181, Figure 4 and 5). The overall SIR was 10.7 (8.5−13.5), with a heterogeneity of I^2=0%. When the SIR was analysed by gender, the SIR in men was 20.1 (14.4−28.2) and in women 7.7 (5.6−10.5). The estimated ratio of SIR in men vs. SIR in women was 2.62 (95%CI 1.66 to 4.14, P<0.001).

The SCC IRs were calculated based on observed events and person-years of follow-up. For the study of Blomberg et al [30], exact person-years of follow-up were not provided and so have been approximately calculated using the mean follow-up time reported for men and women. The overall IR of anal SCC was 6.5 per 100 000 persons-year (3.6−11.7), with a heterogeneity of I^2=77.5%. When analysed by gender the IR was 12.7 (9.1−17.8) in men and 4.7 (1.7−13) in women, with an estimated IR ratio of 2.02 (95%CI 1.28 to 3.20, P=0.003).

DISCUSSION

Our study has shown that almost one-third (28.6%) of anal condylomas have detectable HR-HPV, the prevalence being higher in immunocompromised patients (40.2% of anal condylomas). However, even in the non-immunocompromised population the HR-HPV prevalence was 16.4%. When considering lesion grade, the prevalence of HR-HPV in anal HSIL was very high (73.8%), but HR-HPV were also present in the non-HSIL cases, with a prevalence of 17.7 %. Multiple HPV-types can be present in condylomas [4], but initial studies in the cervix, showed than a single HPV-type is associated with an independent cervical intraepithelial lesion, “one virus, one lesion” [32]. Studies in the anus, seem to show the same pattern, in which individual HSIL are caused by a single HPV-type [33].

In the immunocompromised patients with anal condylomas, almost one quarter (24%) had HSIL. Some Societies recommend anal cancer screening in HIV-positive patients with a history of anal condylomas, such as the HIV Medicine Association of the Infectious Diseases Society of America [7], which has recommended screening by anal cytology. Anal cancer screening aims to detect anal precancerous lesions (HSIL) and is normally done by anal cytology, with referral of those with abnormal results to high-resolution anoscopy [34]. However, in patients with anal condylomas, anal cytology might have a low sensitivity to detect HSIL [35], probably due to buried HSIL [8]. The New York State Department of Health AIDS Institute guidelines has suggested that in these patients it is reasonable to consider high-resolution anoscopy even if cytology is benign [8]. A meta-analysis [36] has shown that in the HIV-positives men who sex with men the overall prevalence of anal HSIL (not condylomas) was 29% (22·8–35·4), similar to the calculated prevalence for anal HSIL in condylomas in immunocompromised patients in our meta-analysis. HIV-positive patients might also have other areas of anal/perianal HSIL, not involving condylomas.

The prevalence of anal SCC in anal condylomas in the immunocompromised population was 0.7%. The calculated overall SIR and IR of anal SCC were high, and significantly higher in men than in women. Estimates were consistently high across the studies included, although the limited number available for inclusion does not allow for reliable evaluation of heterogeneity. The anal cancer risk scale described a IR of SCC of 85 (95%CI 82-89) per 100 000 person-years for HIV-positive MSM and 19 (95%CI 10-36) per 100 000 person-years in HIV-negative MSM [37]. Anal sex in men can be associated with this increased risk of anal cancer [29, 30]. Included studies reporting on the SIR did not provided information on sexual behaviour of men, and the proportion of MSM among male population. The study by Blomberg et al [30], with the larger sample size (16,525 men and 33,422 women with a diagnosis of warts) showed that anal cancer risks remained elevated for >10 years following condylomas diagnosis. In men, in two studies [29, 30], the highest SIR following a condylomas diagnosis was found for anal cancer (with several other cancers analysed). The presence of HR-HPV types can predispose to anal cancer [29]. There is a possible higher smoking rate in patients with condylomas [29], given the higher risk of smoking-related cancers in these patients [29, 31].

According to the 2015 Centers for Disease Control guidelines [38], histological analysis of condylomas is suggested when the lesions are atypical, do not respond or worsen during treatment or when the diagnosis is uncertain. In most of the cases, condylomas are treated by ablation or topical therapy and no histological analysis is done. In our meta-analysis, studies included non-suspicious anal condylomas, for which histological analysis has not been recommended. Nonetheless, 24% of the immunocompromised patients had HSIL, and in the low-risk population (of non-immunocompromised) the prevalence was 11.8%. The histological classification can change patient follow-up, it has been recommended that patients with low-grade lesions should be seen in one year time and patients with high-grade lesions in 6 months [8]. HIV-positive patients with a HSIL diagnosis seem to have more recurrences of condylomas [12, 25]. The presence of HSIL in condylomas was also a risk factor for a HSIL relapse [25]. Given the high prevalence of HSIL and the SIR of anal SCC, more studies on the need of an anal cancer screening and the best screening method, in patients with condylomas, are necessary.

The systematic review identified adequate numbers of studies to support several subgroup analyses. When selecting studies for anal HPV and HSIL/cancer analysis only studies involving biopsies or surgical specimens were included. Studies using anal cytology were excluded given the limited representativeness of lesions. For HSIL, by not including studies in which biopsies were targeted to suspicious areas or studies in which the selection of condylomas was not done randomly, we have tried to limit the selection of studies that might over-represent high-grade lesions. For HPV analysis, studies that used in-situ, Southern blot or dot spot hybridization were excluded, because of their limited sensitivity.

This review does, however, have some limitations. There was a significant heterogeneity in the results from studies related to HR-HPV, HSIL and SCC prevalence. This might reflect differences in the population, type of lesions, screening practices and/or the examination

technique. We have performed several subgroup analyses, according to the immune status (for HR-HPV and HSIL), lesion grade (for HR-HPV) and gender (for SCC). For HSIL and SCC prevalence we included both sample collection by biopsy and excision. Biopsy may miss focal lesions and under-represent high-grade lesions or be done in more suspicious areas and over-represent high-grade lesions. Given this, a further subgroup analysis was done excluding studies where collection was carried out by biopsy or the type of collection was not described (higher risk of bias). The overall HSIL prevalence in condylomas obtained by excision was higher (17.2% excision vs. 13.8% excision and/or biopsy), but with very similar results in the immunocompromised and non-immunocompromised analysis. Only Lee et al. study [11] included in the immunocompromised group both HIV-positive and patients on pharmacological immunosuppression, so a subgroup analysis according to this could not be done. Studies reporting on HPV prevalence did not provided HPV vaccinations status, with the exception of Clavero et al. [14] that clearly stated that only non-HPV vaccinated patients were included. Given the fact that most of the studies included adult men, and most countries did not had a gender neutral vaccination program or routinely vaccinated adults, it is very unlikely that HPV vaccinated patients were included in these studies. Studies did not provide the IR, that was calculated for the three studies included. For Blomberg et al [30] we have estimated these values based on the mean follow-up time reported, even if the person-years of follow-up in each group were not given precisely.

CONCLUSIONS

Almost one-third of anal condylomas have HR-HPV, the prevalence being higher in immunocompromised patients and in condylomas with HSIL. Condylomas are normally considered benign/low-grade lesions, but the prevalence of anal HSIL was high, especially in immunocompromised patients, present in almost one quarter of the samples. Patients with condylomas are also a high-risk group for anal SCC, especially men. A histological analysis of atypical condylomas has been recommended, but even non-atypical condylomas can have HSIL and/or cancer, especially those from the immunocompromised population. This information can impact patient care, given that patients with anal LSIL, HSIL and cancer have different follow-up schedules and treatment.

AUTHORS CONTRIBUTION: AA had the article idea, initiated and coordinated the paper, conducted the literature review, wrote the first draft of the manuscript and was responsible for the final decision of submission. CC conducted the literature review, revised the manuscript and provided important intellectual content. OS did the statistical analysis, revised the manuscript and provided important intellectual content.

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FIGURE LEGENDS

Figure 1: Forest plots of high-risk HPV prevalence, with subgroups analysis by immune status and grade of lesion.

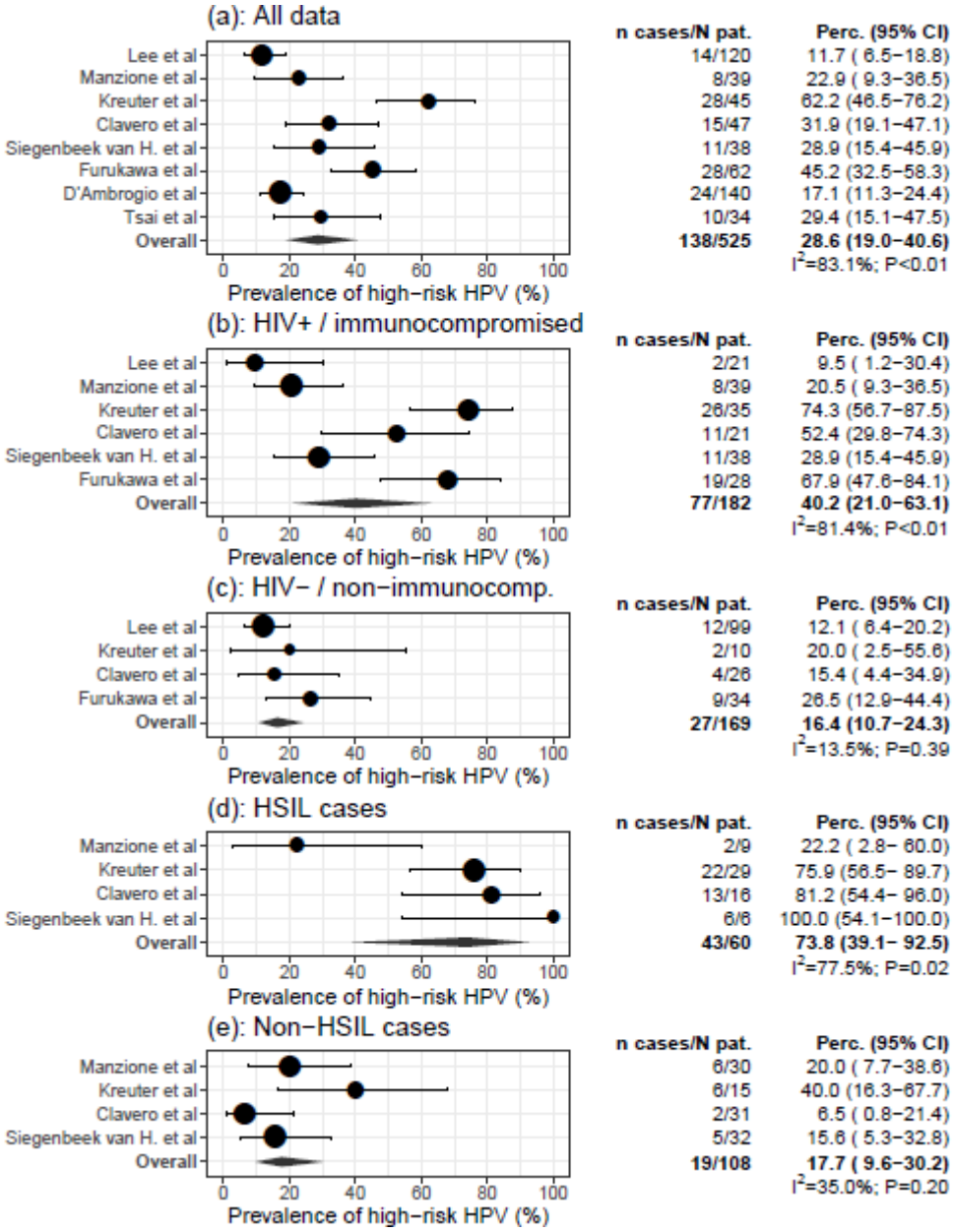

Figure 2: Forest plots of prevalence of HSIL in all condylomas, with subgroup analysis by immune status.

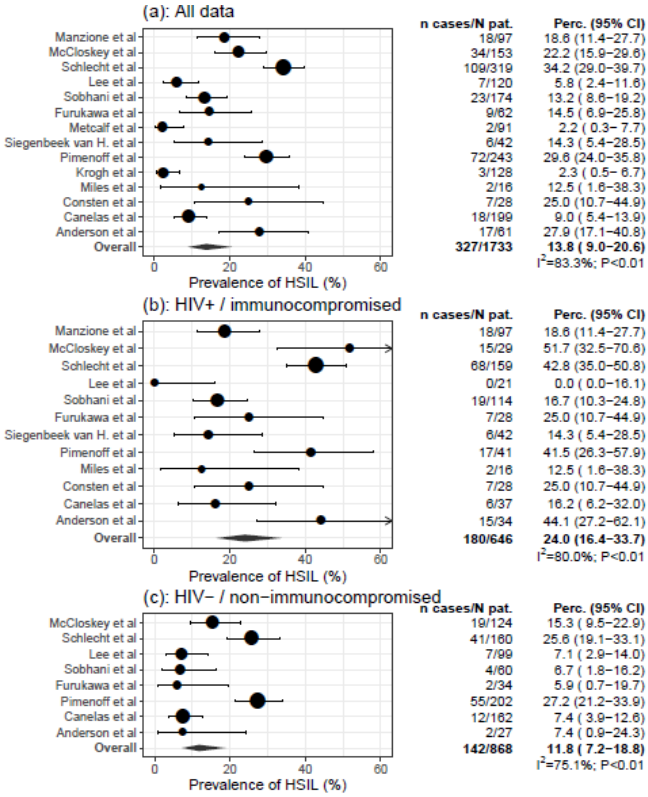

Figure 3: Forest plots of prevalence of SCC in all condylomas, with subgroup analysis by immune status.

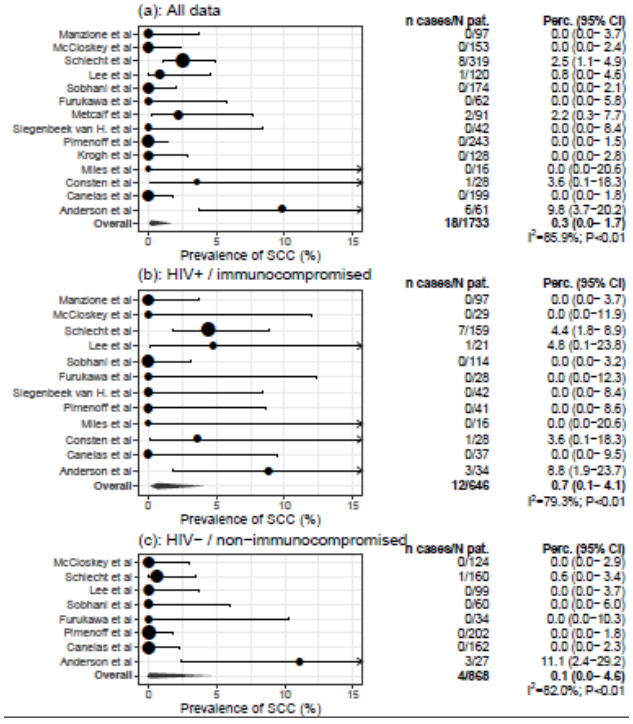

Figure 4: Forest plots of SIR of anal SCC in patients with a history of anal condylomas, with subgroup analysis by gender.

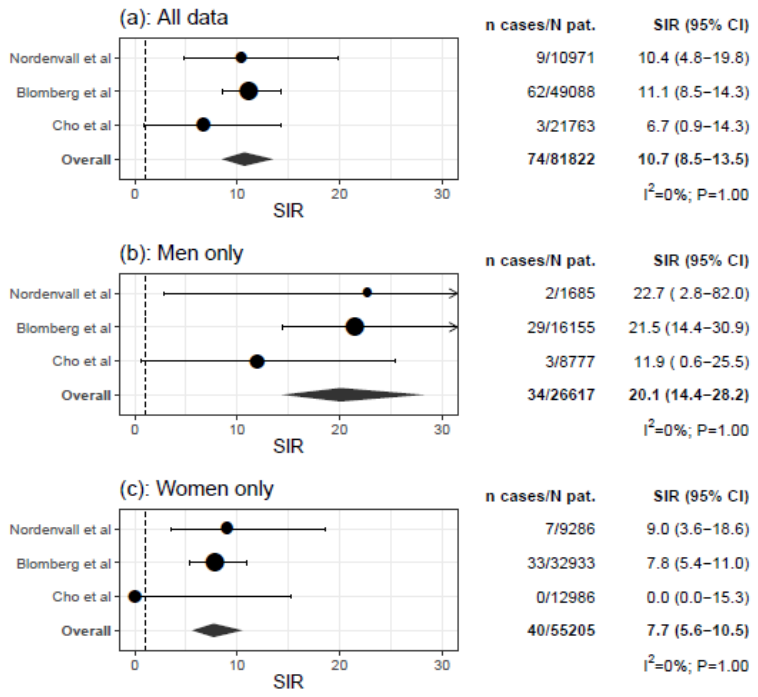
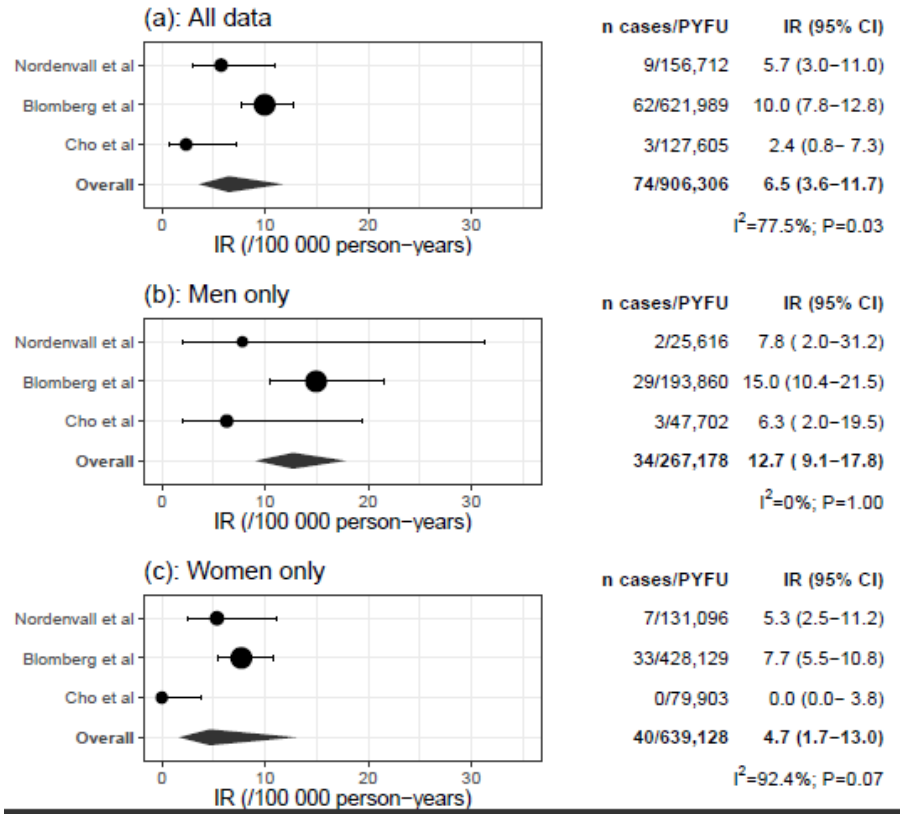
Figure 5: Forest plots of IR of anal SCC in patients with a history of anal condylomas, with subgroup analysis by gender.