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Anal high-risk human papillomavirus infection, squamous intraepithelial lesions and anal cancer in patients with inflammatory bowel disease: a systematic review and meta-analysis.

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Abstract

Background: Ulcerative colitis (UC) and Crohn's disease (CD) can be associated with severe comorbidities, namely opportunistic infections and malignancies. We present the first systematic review and meta-analysis evaluating the burden of anal human papillomavirus disease in patients with UC and CD.

Methods: PubMed, Web of Science and Scopus were searched until November 2022. Meta-analyses were performed using random effects models. The protocol was recorded at PROSPERO register with the number CRD42022356728.

Results: Six studies including 78 711 patients with UC with a total follow-up of 518 969 person-years described the anal cancer incidence rate. For anal cancer incidence rate in CD, six studies were selected including 56 845 patients with a total follow-up of 671 899 person-years. The incidence of anal cancer was 10.2 (95%CI 4.3−23.7) per 100 000 person-years in UC and 7.7 (3.5−17.1) per 100 000 person-years in CD. A subgroup analysis of anal cancer in perianal CD including 7 105 patients was calculated with incidence of 19.6 (12.2−31.6) per 100 000 person-years (three studies included). Few studies described prevalence of anal cytological abnormalities (four studies including 349 patients), and high-risk human papillomavirus (three studies including 210 patients), with high heterogeneity. Prevalence of cytological abnormalities or high-risk human papillomavirus was not associated with pharmacological immunosuppression in the studies included.

Conclusion: The incidence of anal cancer is higher in UC than in CD, with the exception of perianal CD. There is limited and heterogenous data on anal high-risk human papillomavirus infection and squamous intraepithelial lesions prevalence in this population.

KEYWORDS: ulcerative colitis; Crohn's disease; anal cancer.

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Introduction

The global burden of inflammatory bowel diseases (IBD) has been substantially increasing in many countries.[1] Crohn´s disease (CD) and ulcerative colitis (UC) are associated with an increased risk of complications, namely opportunistic infections[2] and malignancies.[3] An increased risk of cervical high-risk human papillomavirus (HPV) infection, cervical precancerous lesions and cervical cancer has been described in patients with IBD.[4-6] Anal squamous cell carcinoma (SCC) is the most common type of anal cancer comprising around 80% of the cases.[7] Anal cancer is the most serious complication of anal HPV infection and more than 90% of anal SCC cases are associated with HPV, with high-risk HPV16 being the most common type.[8-10]

In the last two decades there has been an increase of anal cancer incidence in men and women.[11] There were 30 416 cases of anal SCC estimated globally in 2020.[12] Anal cancer has an annual incidence rate of 1.9 per 100 000 person-years according to the Surveillance, Epidemiology, and End Results Program.[13] However, there are several groups where the incidence rate is much higher, namely people living with HIV, solid organ transplant recipients or women with a history of vulvar cancer or precancer.[14] Immunosuppressed patients are a particularly high-risk group, the incidence rate of anal cancer in men who have sex with men (MSM) living with HIV is 85 per 100 000 person-years, 40 times higher than in the general population.[14] The global incidence rate in solid organ transplant recipients is 13 per 100 000 person-years, being even higher in females with more than 10 years of transplantation at 49.6 per 100 000 person-years.[14]

High-grade squamous intraepithelial lesion (HSIL) or anal intraepithelial lesions (AIN) grade 2 and 3 are anal precancerous lesions.[15] Several Societies have recommended anal cancer screening in the highest risk group of patients living with HIV that are MSM.[16] This screening is based on anal cytology and referral of those with cytological abnormalities, namely atypical squamous cells of undetermined significance (ASC-US) or a higher grade, to high resolution anoscopy.[16] In this technique, the anal canal and perianal area are visualised under magnification after acetic acid staining aiming to detect anal HSIL [17,18] that can then be treated to minimise the risk of anal cancer.[19] Recent

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results from the ANCHOR study have shown that by treating anal HSIL the progression rate for anal cancer is significantly reduced.[19]

Patients with IBD may be at an increased risk of anal HPV infection and associated complications, namely anal precancerous lesions and anal cancer. We have conducted a first systematic review and meta-analysis to evaluate the burden of anal HPV disease in this population.

Methods

Search strategy and selection criteria

The study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) recommendations.[20] The protocol was recorded at PROSPERO register with the registration number CRD42022356728.

Three electronic databases: PubMed, Web of Science and Scopus were searched for articles published from inception until November 2022. Data were selected and retrieved by two authors independently (AA and CC) and in cases of disagreement a consensus was reached.

We have also included conference abstracts and reference lists of the retrieved articles in the search, and only considered studies in English. Case reports and case series were excluded. Anorectal cancers and anal transitional zone cancers were not considered. Authors were contacted by email when more information was needed.

For anal cancer and anal HSIL we used the terms “anal” OR “anus” AND “neoplasms” OR “squamous cell carcinoma” AND “Inflammatory Bowel Diseases” OR “Ulcerative colitis” OR “Crohn Disease”. For anal HPV “anal” OR “anus” AND “papillomaviridae” OR “papillomavirus” OR “HPV” AND “Inflammatory Bowel Diseases” OR “Ulcerative colitis” OR “Crohn Disease” were used. For anal cytology the term used were: “anal” OR “anus” AND “cytology” AND “Inflammatory Bowel Diseases” OR “Ulcerative colitis” OR “Crohn Disease”.

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The results were presented according to the type of disease, UC and CD. For anal HPV we included studies that search for anal HPV infection in the anal canal, and presented the results by high-risk HPV and HPV16. For anal cytology liquid and non-liquid cytology were considered and the results presented according to the Bethesda terminology:[21] negative for intraepithelial lesions or malignancy (NILM), atypical squamous cells of undetermined significance (ASC-US), low-grade squamous intraepithelial lesions (LSIL), atypical squamous cells cannot exclude high-grade (ASC-H), HSIL or SCC. For anal HSIL, we only included studies where the diagnosis was done by biopsies collected during a high-resolution anoscopy. For anal cancer, where different papers reported data/databases from the same country, only the most recent or with the larger number of patients was included to avoid population overlap.

Information on the first author, year and country of publication, data source, number of patients included, number of cases observed (Table S1), person-years of follow-up and incidence rate was retrieved for anal cancer. Information on the first author, year and country of publication, population, type of testing, number of patients/samples and the number of lesions/abnormal samples/infected patients was collected for anal high-risk HPV and HPV16 (Table S2) and cytology and HSIL (Table S3).

Outcomes

The incidence rate of anal cancer in patients with UC and CD was calculated, with a subgroup analysis for perianal CD. Analysis was also conducted for incidence of anal SCC where data on this specific histological diagnosis was available. Anal high-risk HPV, anal HPV16, abnormal anal cytology and the prevalence of HSIL on histology were also analyzed.

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Quality assessment and risk of bias from individual studies

The quality assessment was performed using the Newcastle–Ottawa Scale and studies were considered of high quality if at least 7 points, moderate quality if 5–6 points, and low quality if 4 points or less (Table S4).

Statistical analysis

Meta-analyses were carried out as previously described by Albuquerque et al.[22] A mixed effects Poisson model was used for meta-analysis of incidence rate, with the observed number of cases specified as the outcome and person-years of follow-up as the exposure variable for each study. We used gamma-distributed (multiplicative) random effects, with mean set to 1, to allow for heterogeneity between studies. Meta-analysis of prevalence for HPV and abnormal anal cytology is not presented because of high heterogeneity in the methodology and patient populations of studies identified.

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.[22] The random effects models used for meta-analysis were fitted using Stata version 17 (StataCorp, College Station, Texas, USA), and graphical summaries were constructed using the ggplot2 package in R (R Foundation, Vienna, Austria).

Results

Anal cancer

For the meta-analysis of the incidence rate of anal cancer in patients with UC, six studies [23-28] (Table S1, Figure S1) with 78 711 patients and a total follow-up of 518 969 person-years were included. The incidence of anal cancer was 10.2 (95% CI 4.3−23.7) per 100 000 person-years in UC (Figure 1). Heterogeneity between studies was I^2=66.6%.

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We also analyzed those studies where histological type of anal cancer was specified. Analysis of the incidence of anal SCC in patients with UC was also calculated including three studies[23,27,29] with 52 016 patients, with an incidence rate of 12.65 (95% CI 3.85 to 41.57) per 100 000 person-years (Table S1, Figure 2). Heterogeneity between studies was I^2=75.9%.

The meta-analysis of the incidence rate of anal cancer in patients with CD included six studies[23, 24, 26-29] (Table S1, Figure S1) with 56 845 patients and a total follow-up of 671 899 person-years. The incidence of anal cancer in CD was 7.7 (95% CI 3.5−17.1) per 100 000 person-years (Figure 1), I^2 was 73.3%.

A subgroup analysis of anal cancer in perianal CD showed an incidence rate of 19.6 (95%CI 12.2−31.6) per 100 000 person-years, with three studies included,[27,30,31] involving 7105 of patients with perianal CD (Table S1, Figure 3). There was no heterogeneity between studies (I^2 was 0%).

Analysis of the incidence rate of anal SCC in patients with CD included three studies[23, 27, 29] with 52 717 patients and the incidence was 3.18 (95%CI 1.3 to 7.77) per 100 000 person-years (Table S1, Figure 2), I^2 was 45.69%.

Anal High-risk HPV and HPV16

Three studies[32-34] described the prevalence of high-risk anal HPV and HPV16 in patients with IBD (Table S2, Figure S2). One study was a cohort study[32] and two were case-control studies.[33,34] In total, 210 patients with IBD were included: 164 with CD, 43 with UC and 3 with IBD-U.

The study by Cranston et al[32] included 46 patients with IBD (50% of them immunosuppressed) and the prevalence of anal high-risk HPV and HPV16 was 84.8% and 65%, respectively. There was no statistical difference between the prevalence of high-risk HPV and HPV16 in immunosuppressed (corticosteroids or immunomodulators) and non-immunosuppressed patients.

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The study by Vuitton et al[33] included 101 patients with IBD (83% of them immunosuppressed) and the prevalence of anal high-risk HPV and HPV16 was 25.7% and 10.9%, respectively. The prevalence of anal high-risk HPV and HPV16 infection in UC patients did not differ from that in non-IBD patients. For CD, patients had anal high-risk HPV and HPV16 infection significantly more often than the rest of the population, but there was no difference between immunosuppressed and non-immunosuppressed patients regarding high-risk HPV and HPV16.

The study by Guzela et al[34] included 63 patients with CD (49% of them immunosuppressed), with a prevalence of high-risk HPV of 17.5% and HPV 16 of 7.9%. There was no statistical difference between the prevalence of high-risk HPV and HPV 16 in patients with CD immunosuppressed (corticosteroids, immunomodulators and/or biologics) and non-immunosuppressed, and also between CD patients and the healthy control group.

Anal cytology/histology

Four studies were included[32, 34, 35, 36] with a total of 349 patients with IBD: 245 with CD, 88 with UC and 16 with IBD-U (Table S3, Figure S3). Two studies were case-control studies[34, 35] and two cohort studies. [32, 35]

Only one study[32] provided clear data on high-resolution anoscopy and histology (Table S3). In this study, all patients included were submitted to high-resolution anoscopy and four had anal HSIL (9% prevalence).

Cranston et al[32] included 46 patients with IBD (50% of them immunosuppressed) and the prevalence of a cytology with ASC-US or higher was 45.7%. There was no healthy control group for comparison with patients with IBD, the prevalence of abnormal anal cytology was not increased by IBD-specific immunosuppression.

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Guzela et al[34] included 63 patients with CD (only 59 patients with adequate samples), 49% of them were immunosuppressed, and the prevalence of a cytology with ASC-US or higher was 72.9%. The prevalence of cytological abnormalities did not differ between patients with IBD and healthy controls, and also by the use of immunosuppressive therapy.

Shah et al[35] included 194 patients with IBD (52% were immunosuppressed), and the prevalence of a cytology with ASC-US or higher was 8.8%. They have compared the prevalence of anal cytological abnormalities in immunosuppressed patients with IBD with both non-immunosuppressed patients with IBD and healthy controls and found no difference.

The study by Savio et al[36] included 50 patients (88% of them immunosuppressed), with a prevalence of ASC-US or higher of 4%.

Of the 349 patients included, only one patient with UC had a high-grade cytology, namely an ASC-H result.[32]

Discussion

This systematic review and meta-analysis was the first to summarize all data for the burden of anal HPV disease, including anal high-risk HPV infection, with analysis for the most common oncogenic type of HPV (HPV16), and anal squamous intraepithelial lesions, detected by cytology and high-resolution anoscopy/histology. There were two previous meta-analyses that have described incidence and risk of anal cancer in patients with UC and CD,[14, 37] we have included more studies and described the results also considering perianal CD.

HPV infection is the most common sexually transmitted infection in sexually active adults, more than 80% of women and men acquire HPV by age 45 years.[38] This infection is normally cleared with time and it is the persistence of a high-risk infection that can be deleterious.[39] Several risk factors for

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anal HPV infection have been described, namely immunosuppression,[14] current smoking,[40, 41] receptive anal sex[42, 43] and multiple sexual partners.[42, 43]

Data from the Surveillance, Epidemiology, and End Results showed that anal cancer had an annual incidence rate of 1.9 per 100 000 person-years, in the general population.[13] In our meta-analysis, the incidence of anal cancer in patients with UC was more than five times higher to what has been described in the general population. Our results also shown that the incidence is higher in patients with UC than in CD. In many cases, studies did not provide the histological type of cancer, but around 80% of anal cancers cases are anal SCC[7] that comprises the majority of the burden of these cancers. In cases where studies provided data specifically for anal SCC we have also performed an analysis for the incidence rate of anal SCC in UC and CD, that was in agreement with the previous results, and confirmed a higher rate in patients with UC than in CD. The incidence of anal SCC in UC was 12.65 (95% CI 3.85 to 41.57) and in CD 3.18 (95%CI 1.3 to 7.77) per 100 000 person-years. A previous systematic review published on 2013 on anal SCC in patients with IBD suggested that the incidence was higher in CD than in UC, and that there was no increased risk in patients with UC.[44] This information had already been contradicted in another meta-analysis[14] and confirmed by our study. The exception seems to be patients with perianal CD that have the highest incidence rate at 19.6 (95%CI 12.2−31.6) per 100 000 person-years, with consistent results between the studies included.

By presenting cancer data by incidence rate, we can better compare rates with the general population and also with other high-risk groups for anal SCC. The described incidence rates of anal SCC are far below what is reported for MSM living with HIV at 85 per 100 000 person-years.[14] However, when considering solid organ transplant recipients, the incidence rate of anal SCC in patients with UC is similar, with a global incidence of 13 per 100 000 person-years[14] and seem even higher for patients with perianal CD.

When considering anal cancer screening, most of the recommendations favor anal cytology as the first screening method, as it is simple, less expensive and less invasive than other options.[45] In this procedure a cytology brush is inserted in the anal canal blindly and then removed with rotation for 20-

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30 seconds.[45] Patients with any abnormal result should be referred for high-resolution anoscopy for lesion detection.[16] There is a poor correlation between the cytological and the histological grades,[46] but in more than 90% of the cases a high-grade cytology also reflects the presence of histological HSIL.[47] For anal cytology, studies had a heterogeneous prevalence, but only one patient with IBD had an anal cytology that was highly suggestive of high-grade lesions, namely a case of ASC-H, a very low prevalence. There are no data on the follow-up of all abnormal cytological results, as none of the studies provided this information.[34-36] In the study by Cranston et al[32] all patients included were submitted to high-resolution anoscopy, not just the ones with abnormal cytology, and four patients had anal HSIL on histology. There is no data on the sensitivity of anal cytology compared with histology in this population and the best screening method, if any to consider.

Previous studies in women with UC and CD have shown a higher risk of cervical low-grade and high-grade dysplasia and the association with the IBD immunosuppressive therapy.[5, 6, 48] The ECCO guidelines on opportunistic infections have recommended that immunosuppressed female IBD patients should undergo annual cervical cancer screening.[2] However, in our systematic review for anal high-risk HPV, HPV16 infection and abnormal anal cytology prevalence, in the studies included, there was no statistical difference in patients with IBD with or without immunosuppressive therapy.[32-35] The number of studies and patients is small when comparing anal vs. cervical HPV, and there is a high heterogeneity between studies. However, this could also suggest a different pathophysiological mechanism between HPV disease in the anus vs. cervix of patients with IBD. Further analyses examining the effect of immunosuppression in patients with IBD on anal cancer risk are required.

Previous studies[40, 49] have shown that patients with benign inflammatory anal lesions (anal fissures, fistulas, and perianal abscesses) had an increased risk for anal SCC that was associated with chronic inflammation of the anal mucosa. Mucosal ulcerations can also increase the rates of pathogen transmission as it has been shown for sexually transmitted infections.[50] Inflammation has long been described as a risk factor for several types of gastrointestinal cancer, e.g. the link between ulcerative colitis and colorectal cancer.[49] Patients with UC and perianal CD, who seem to have the highest risk

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of anal cancer in the IBD cohort, are a distinctive population from women with cervical HPV infection, people living with HIV and solid transplant recipients, as they have inflammation in the rectum and in the anal mucosa as part of their disease. This can also explain the lowest risk in the CD cohort, that with the exception of perianal CD, significantly fewer patients with CD will have rectal or anal inflammation. Perianal CD can also pose several difficulties in early anal cancer diagnosis. Maintaining a high index suspicion is necessary in these patients.[51]

One of the major strengths of our paper was the exclusion of studies that presented the results for anorectal cancers globally and not only for anal cancer. We only included data from each country once, and when different studies reported the same country databases only the most recent or with the larger number of patients was included to avoid duplicated results. Results were presented by disease type whenever data was available and separate analyses were done for anal SCC and perianal CD. However, our study has some limitations. The studies did not provide information on immunosuppressive therapy as a risk factor for anal cancer that allowed a subgroup analysis. A study on HPV-related cancers after solid organ transplantation using a large US database, showed that maintenance therapy with azathioprine increased the risk of anal cancer in this population.[52] Information on smoking as a risk factor was also not available. Current smoking has been consistently described as risk factor for anal cancer[40, 41, 42] and it was suggested that might have an effect at late stages of disease progression.[41] Given the heterogenous results provided by the four studies included for cytology, varying the prevalence of cytological abnormalities from 4 to 72.9%, no meta-analysis was presented (calculated I^2 was 93.7%). These heterogenous results do not seem to be associated with immunosuppression in the different cohorts, that was similar for most studies. The study with the lower prevalence of cytological abnormalities of 4%[36] was the one with a higher percentage of patients immunosuppressed (88%). The same pattern was seen for anal high-risk HPV with high heterogeneity in the results (I^2 was 94.7%), with a prevalence of anal high-risk HPV varying from 17.5 to 84.8% and no meta-analysis of the results was done.

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An effect of HPV vaccine was unlikely in the present study, as the first vaccine was approved in 2006 and anal cancer has a median age at onset of 62 years.[53] The last European Crohn's and Colitis Organization guidelines on opportunistic infection recommended gender neutral HPV vaccination on young adults with IBD.[2] HPV vaccines can be safely administered to immunocompromised IBD patients as an inactive vaccine.[2] It seems to have a good immunogenicity and safety profile in this population.[54]

Conclusions

This systematic review and meta-analysis was the first to described the entire spectrum of anal HPV disease in patients with IBD. For anal cancer, we have included more studies than previous meta-analyses, and presented the results also considering perianal CD disease.

Patients with IBD seem to have a higher incidence of anal cancer than described in the general population. The global incidence of anal cancer is higher in patients with UC than in CD, with the exception of perianal CD.

There are limited data on anal high-risk HPV infection and squamous intraepithelial lesions prevalence in patients with IBD, especially considering the scarce data on anal HSIL prevalence detected by high-resolution anoscopy. Cytological abnormalities or high-risk HPV was not associated with pharmacological immunosuppression in the studies included.

Patients with UC and perianal CD have inflammation in the rectum and/or anus as part of their disease and given this, are substantially different from other high-risk groups for anal cancer, e.g. people living with HIV and transplant recipients that have immunosuppression as their major risk factor.

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Figures Legends:

Figure 1: Forest plots of incidence rates of anal cancer in patients with UC and CD

Figure 2: Forest plots of incidence rates of anal squamous cell carcinoma in UC and CD

Figure 3: Forest plots of incidence rates of anal cancer in perianal CD

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Figure 1

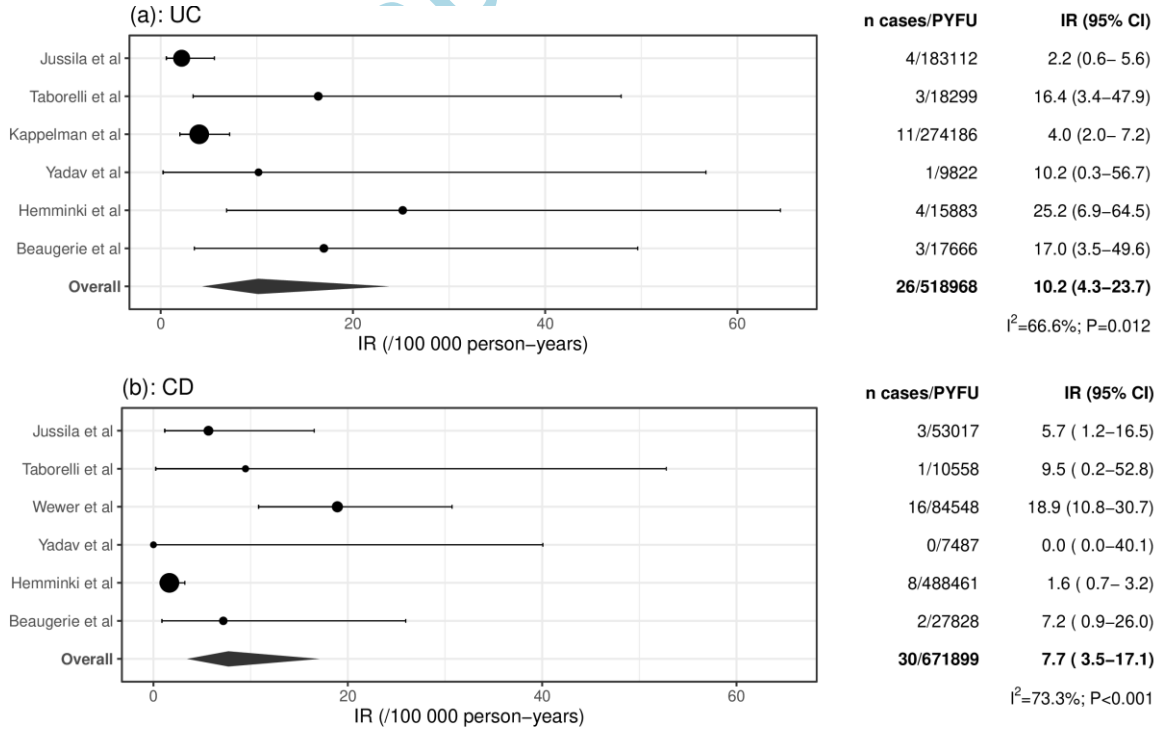

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Figure 2

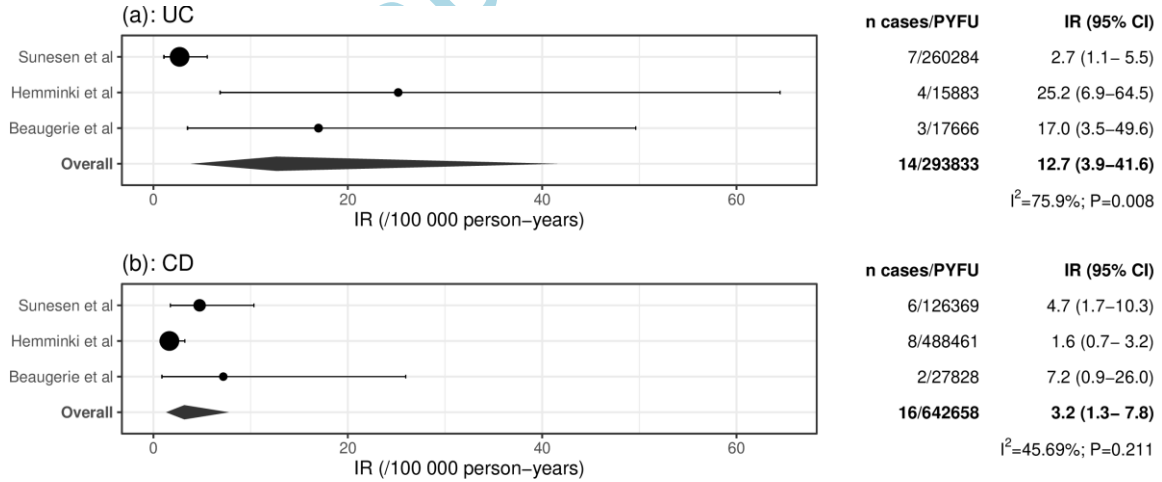

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Figure 3