Cancer Epidemiology 58 (2019) 12–16

Contents lists available at ScienceDirect

Cancer Epidemiology

journal homepage: www.elsevier.com/locate/canep

Association of anal symptoms with anal high grade squamous intraepithelial lesions (HSIL) among men who have sex with men: Baseline data from the study of the prevention of anal cancer (SPANC)

S.L. Goddard[a,b,*], D.J. Templeton[a,c,d], K. Petoumenos[a], F. Jin[a], R.J. Hillman[e], C. Law[e], J.M. Roberts[f], C.K. Fairley[g,l], S.M. Garland[h,i,j,k], A.E. Grulich[a], I.M. Poynten[a], on behalf of the Study for the Prevention of Anal Cancer (SPANC) Research Team

[a] The Kirby Institute, Wallace Wurth Building, UNSW Sydney, Randwick, New South Wales 2031, Australia
[b] Sydney Sexual Health Centre, Nightingale Wing, Sydney Hospital, Macquarie Street, Sydney, New South Wales 2000, Australia
[c] Sexual Health Service, Sydney Local Health District, 16 Marsden Street, Camperdown, Sydney, New South Wales 2050, Australia
[d] Sydney Medical School, The University of Sydney, Sydney, New South Wales 2006, Australia
[e] St Vincent's Hospital, 390 Victoria Street, Darlinghurst, Sydney, New South Wales 2010, Australia
[f] Douglass Hanly Moir Pathology, 14 Giffnock Avenue, Macquarie Park, Sydney, New South Wales 2113, Australia
[g] Melbourne Sexual Health Centre, 580 Swanston Street, Carlton, Victoria 3053, Australia
[h] Department of Microbiology and Infectious Diseases, Royal Women's Hospital, 20 Flemington Road, Parkville, Victoria 3052, Australia
[i] Department of Microbiology, Royal Children's Hospital, 50 Flemington Road, Parkville, Victoria 3052, Australia
[j] Infection Immunity, Murdoch Children's Research Institute, Flemington Road, Parkville, Victoria 3052, Australia
[k] Department of Obstetrics and Gynaecology, University of Melbourne, Grattan Street, Parkville, New South Wales 3052, Australia
[l] Central Clinical School, Faculty of Medicine, Nursing and Health Sciences, Monash University, 99 Commercial Road, Melbourne, Victoria 3004, Australia

ARTICLE INFO

Keywords:
Anogenital conditions
Anogenital cancer
HPV
Homosexuality

ABSTRACT

Background: The association between anal high-grade squamous intraepithelial lesion (HSIL) and anal symptoms has not been systematically investigated.
Methods: The Study of Prevention of Anal Cancer is a prospective cohort study of men who have sex with men (MSM) ≥ 35 years old in Sydney, Australia. Self-reported symptoms were collected. Anal cytology and high-resolution anoscopy were undertaken. Using baseline visit data, men negative for squamous intra-epithelial lesion (SIL) were compared with men diagnosed with composite-HSIL (cytology and/or histology). Logistic regression analyses were performed to assess the association of symptoms with HSIL.
Results: Among 414 MSM included (composite-HSIL (n = 231); negative for SIL (n = 183)), 306 (73.9%) reported symptom(s) within the last 6 months. There was no association between any symptom and composite-HSIL. A significant association between anal lump and a larger burden of HSIL (at least 2 intra-anal octants) (anal lump within last month: p = 0.014; anal lump within last 6 months: p = 0.010) became non-significant after adjusting for HIV-status and recent anal warts (anal lump within last month: p = 0.057; anal lump within last 6 months: p = 0.182).
Conclusions: Among MSM age 35 years and older, most anal symptoms are not a useful marker of anal HSIL.

1. Introduction

Human papillomavirus (HPV) is the most common sexually transmitted infection (STI) worldwide [1]. Chronic infection of the anal canal with high-risk HPV types can lead to high-grade squamous intraepithelial lesions (HSIL), which may progress to anal squamous cell carcinoma (SCC) [2,3]. The incidence of anal SCC has been increasing worldwide for several decades [4], which has led to calls for programs to detect anal HSIL and early stage SCC among high-risk groups, such as men who have sex with men (MSM). Anal SCC may

* Corresponding author at: The Kirby Institute, Wallace Wurth Building, UNSW Sydney, Randwick, New South Wales 2031, Australia.
E-mail addresses: sgoddard@kirby.unsw.edu.au (S.L. Goddard), david.templeton@health.nsw.gov.au (D.J. Templeton), kpetoumenos@kirby.unsw.edu.au (K. Petoumenos), jjin@kirby.unsw.edu.au (F. Jin), richard.hillman@unsw.edu.au (R.J. Hillman), Carmella.law@svha.org.au (C. Law), jroberts@dhm.com.au (J.M. Roberts), cfairley@mshc.org.au (C.K. Fairley), Suzanne.garland@thewomens.org.au (S.M. Garland), agrulich@kirby.unsw.edu.au (A.E. Grulich), mpoynten@kirby.unsw.edu.au (I.M. Poynten).

https://doi.org/10.1016/j.canep.2018.10.009
Received 31 July 2018; Received in revised form 18 October 2018; Accepted 21 October 2018
Available online 12 November 2018

present with anal symptoms [5]. Whether anal HSIL is associated with symptoms, has not, to our knowledge, been systematically investigated.

The Study of Prevention of Anal Cancer (SPANC) is a prospective cohort study of HPV infections and related anal lesions among older MSM in Sydney, Australia [6]. In this analysis, we aimed to evaluate whether recent anal symptoms were associated with anal HSIL among MSM attending their baseline SPANC visit.

2. Material and methods

2.1. Study population

The methodology of SPANC has previously been published [6]. Briefly, men aged 35 years and over who reported sex with another man in their lifetime were recruited from gay community social events/organisations (and by participant referral), between September 2010 and August 2015. Men who reported previous high-resolution anoscopy (HRA) and/or anal cancer, were excluded. Self-reported anal symptoms did not affect study eligibility. SPANC participants attended a baseline visit, followed by study visits at 6 months, 12 months, 24 months and 36 months. Due to the possibility that previous study visits (and in particular previous diagnoses of anal abnormalities) may effect participant reporting of recent symptoms, only data from the baseline visit were included in the analysis.

Participants completed a computer assisted self-interview (ACASI QDS, Bethesda, MD), including questions regarding sexual behaviours, history of anal warts and anal symptoms (itch, bleeding, pain with defaecation, lump, tear, 'sores', discharge and 'feeling that something was left after a bowel movement' (defined as tenesmus from this point forwards)). Participants were asked whether they had experienced each symptom within the last six months, and if so, when the symptom had last been present (today, last week, last month, over a month ago). Anal swabs were collected for cytology and HPV detection/genotyping and HRA with biopsy of any suspected squamous intra-epithelial lesion (SIL) was performed. The anal canal was divided in to eight "octants" and anoscopists recorded the location of any intra-anal abnormality and/or biopsy by octant, on a standardised data collection tool. Anal cytology was reported according to the Bethesda System [7] and anal biopsies were reviewed in accordance with the Lower Anogenital Squamous Terminology Project [2,6]. Cytology-histology "composite" endpoints (highest disease grade) were used [8]. For this analysis, "composite-negative" men (i.e. negative on cytology and histology, or negative on cytology and no suspected HPV-associated lesions observed), were compared with men diagnosed with "composite-HSIL" (HSIL on cytology and/or histology). To minimise the effect of any association between symptoms and other grades of SIL, men diagnosed with "composite-low-grade squamous intraepithelial lesion (LSIL)", "composite-atypical squamous cells of undetermined significance (ASCUS)", "composite-atypical squamous cells unable to exclude HSIL (ASC-H)" or anal SCC, were excluded.

2.2. Statistical analysis

Each symptom was dichotomised as "present" or "absent", and a composite outcome of "any anal symptom" in the last month, and last six months was defined. Pearson's Chi-squared test was used to compare the number of symptoms (none, 1–2, 3–4, ≥5) reported by men who were composite-negative with men diagnosed with composite-HSIL. Logistic regression analyses were performed to evaluate the association of each anal symptom with the outcome composite-HSIL, adjusted for HIV-positivity, number of lifetime receptive anal intercourse partners (RAI) and age (HIV-positive status and higher number of lifetime RAI partners have previously been identified as predictors of HSIL within the SPANC cohort [9]). We also assessed the association between intra-anal burden of HSIL and each anal symptom. Intra-anal burden of HSIL was defined according to the number of octants of biopsy-proven HSIL and was defined as negative, HSIL 1 octant, HSIL ≥ 2 octants. Participants with HSIL diagnosed by cytology-only were excluded. Logistic regression analyses were performed to evaluate the association of larger intra-anal burden of HSIL, with each anal symptom as the outcome. Data analyses were performed using STATA version 14 (Stata Corporation, College Station, TX, US).

3. Results

Among 617 SPANC participants, 1 participant was excluded as unable to tolerate HRA. Of the remaining 616 participants, 414 were diagnosed with either composite-HSIL (n = 231, 37.5%) or as composite-negative (n = 183, 29.7%) at the baseline visit, and were included in this analysis. Men who were diagnosed with composite-LSIL, composite-ASCUS, composite-ASC-H or anal SCC were excluded (n = 202). The median age was 49 years (IQR 43–56) and 36.5% (n = 151) were HIV-positive. The vast majority (n = 387, 93.5%) of participants included in this analysis identified as "gay" or "homosexual", 16 (3.9%) identified as "bisexual", 2 (0.5%) identified as "heterosexual" and 9 (2.2%) identified as "queer" or "other". Of the 393 (94.9%) men who completed a baseline question on HPV vaccination status, very few (n = 8, 2.0%) reported receiving prior vaccination.

The prevalence of self-reported anal symptoms among men diagnosed with composite-HSIL and men who were composite-negative are outlined in Table 1. More than half reported at least one anal symptom within the last month (230, 55.6%) and three-quarters reported at least one symptom within the last six months (306, 73.9%). There was no significant difference in the number of symptoms reported by men diagnosed with composite-HSIL compared with men who were composite-negative (last month: χ^2 =0.4492, p = 0.930; last six months: χ^2 = 3.7490, p = 0.290).

In univariate analyses, none of the anal symptoms were significantly associated with the outcome composite-HSIL. There remained no association between any anal symptom and composite-HSIL after adjustment for HIV-status, lifetime number of RAI partners and age (Table 1).

Of 231 men diagnosed with composite-HSIL, 36 (15.6%) were cytology-only diagnoses, 124 (53.7%) had HSIL diagnosed at one anal octant and 71 (30.7%) had HSIL diagnosed at 2 or more intra-anal octants. Compared with composite-negative men, men who had at least two octant-HSIL were significantly more likely to report recent anal lump (anal lump within last month: OR 3.65, 95% CI 1.30–10.22, p = 0.014; anal lump within last six months: OR 2.49, 95% CI 1.24–4.98, p = 0.010). For men who had single octant HSIL there was no significant difference in the odds of self-reported recent anal lump (anal lump within last month: OR 1.28, 95% CI 0.42–3.90, p = 0.666; anal lump within last six months: OR 0.93, 95% CI 0.46–1.90, p = 0.845) compared to composite-negative men. There was no significant association between any other anal symptom and larger burden of HSIL.

Of the 406 participants who answered a baseline question on history of anal warts, 29 (7.1%) reported a history of anal warts within the last 12 months. Anal lump was also strongly associated with self-reported anal warts in the last year (anal lump last month: OR 3.93 95% CI 1.35–11.42, p = 0.012; anal lump last 6 months: OR 6.15 95% CI 2.77–13.64 p < 0.001). The association between anal lump and HSIL diagnosed at 2 or more intra-anal octants was no longer significant when adjusting for HIV status and history of self-reported warts in the last year (anal lump last month: aOR 2.94, 95% CI 0.97–8.90, p = 0.057; anal lump last 6 months: aOR 1.68, 95% CI 0.78–3.61, p = 0.182).

4. Discussion

Anal symptoms were commonly reported by SPANC participants at their baseline visit. Anal lump was associated with a larger intra-anal

Table 1
Association of self-reported anal symptoms and composite-HSIL among SPANC participants.

	Composite Negative n = 183 n (%)	Composite HSIL n = 231 n (%)	Univariate analysis		Adjusted analysis (adjusted for age, HIV status, number of lifetime receptive anal intercourse partners)[a]	
			OR (95% CI)	p-value	aOR (95% CI)	p-value
Self-reported anal symptom reported within last month[b]						
Any anal symptom	104 (56.8)	126 (54.6)	0.91 (0.62-1.35)	0.642	0.81 (0.53-1.24)	0.336
Discharge	6 (3.3)	10 (4.3)	1.33 (0.48-3.74)	0.583	1.07 (0.36-3.20)	0.897
Itch	38 (20.8)	49 (21.2)	1.03 (0.64-1.65)	0.912	0.96 (0.57-1.60)	0.871
Sore(s)[a]	6 (3.3)	12 (5.2)	1.63 (0.60-4.43)	0.337	1.36 (0.48-3.83)	0.560
Lump	7 (3.8)	18 (7.8)	2.12 (0.87-5.20)	0.099	2.05 (0.80-5.23)	0.135
Pain defecating	23 (12.6)	29 (12.6)	1.00 (0.56-1.79)	0.997	0.84 (0.44-1.58)	0.581
Bleeding	35 (19.1)	42 (18.2)	0.94 (0.57-1.55)	0.806	0.84 (0.49-1.43)	0.517
Tearing	10 (5.5)	12 (5.2)	0.95 (0.40-2.25)	0.903	0.70 (0.29-1.72)	0.436
Tenesmus	63 (34.4)	69 (29.9)	0.81 (0.54-1.23)	0.324	0.70 (0.45-1.11)	0.130
Self-reported anal symptom within last 6 months						
Any anal symptom	135 (73.8)	171 (74.0)	1.01 (0.65-1.58)	0.953	0.89 (0.55-1.43)	0.619
Discharge	7 (3.8)	15 (6.5)	1.75 (0.70-4.38)	0.235	1.41 (0.54-3.72)	0.485
Itch	58 (31.7)	79 (34.2)	1.12 (0.74-1.69)	0.591	0.95 (0.60-1.49)	0.809
Sore(s)[a]	16 (8.7)	26 (11.4)	1.34 (0.70-2.59)	0.377	1.07 (0.54-2.14)	0.848
Lump	22 (12.0)	36 (15.6)	1.35 (0.76-2.39)	0.301	1.33 (0.71-2.48)	0.370
Defecating	36 (19.7)	51 (22.1)	1.16 (0.72-1.87)	0.551	1.03 (0.61-1.74)	0.914
Bleeding	63 (34.4)	85 (36.8)	1.11 (0.74-1.66)	0.617	0.95 (0.61-1.47)	0.812
Tearing[a]	23 (12.6)	36 (15.6)	1.28 (0.73-2.24)	0.396	1.25 (0.68-2.32)	0.469
Tenesmus	74 (40.4)	92 (39.8)	0.97 (0.66-1.45)	0.900	0.88 (0.57-1.35)	0.561

[a] Data missing: anal sore in last month (n = 2) and last six months (n = 3); anal tear in last 6 months (n = 1). Adjusted analyses missing a further 11 participants due to missing number of lifetime receptive intercourse partners.

[b] Column percentages. Reference category for univariate analysis was symptom not present.

burden of HSIL, which may be partly explained by the recent presence of anal warts, but there was no association between any other anal symptom and HSIL.

A previous Australian study of HIV-negative and HIV-positive MSM found half of the participants reported “any anal symptom” within the last year [10], but anal symptoms in the SPANC cohort were even more common. Men who were concerned about anal symptoms may have been more likely to participate in a study about anal cancer prevention, but nonetheless, our data suggests that anal symptoms are very common among MSM.

There was no significant association between recent anal symptoms and HSIL. To our knowledge, this is the first study to systematically investigate the association of anal symptoms and HSIL. An American cohort study of MSM found an association between anal discharge and the presence of any grade of anal SIL among HIV-positive men, but did not consider HSIL alone [11]. An Australian cross-sectional study investigated predictors of HSIL among HIV-negative and HIV-positive GBM and found no association between “any anal symptom” in the last year and histologically-confirmed HSIL. However, only men with abnormal cytology underwent subsequent HRA, and only 21 men were diagnosed with HSIL [12].

There was a significant association in univariate analysis between recent anal lump and larger burden of HSIL. Whereas anal HSIL is most frequently flat in appearance, LSIL (which includes anal warts) is more likely to have a raised contour [13]. In this analysis, anal lump was strongly associated with a history of self-reported anal warts and the univariate association of anal lump with a larger burden of intra-anal HSIL was no longer significant when adjusting for recent self-reported warts and HIV status. This suggests that the association of anal lump with larger HSIL burden was due, at least in part, to co-existing anal warts and HSIL. A high proportion of co-existent anal HSIL has been previously reported among men referred for excision of anal condyloma [14]. The common pathway of sexual acquisition of HPV for both anal warts and HSIL makes it plausible that men diagnosed with HSIL would also be more likely to have been diagnosed with recent anal warts.

Anal bleeding was common in this cohort of MSM, but there was no association with HSIL. Among women, post-coital vaginal bleeding (PCB) can be a symptom of cervical cancer and can be an indication for colposcopy [15]. However, PCB is common within the general population and is most often secondary to benign causes [15]. A high prevalence of HSIL has been found among women referred to colposcopy with PCB [15,16], although this study is likely to be influenced by selection bias. In a cross-sectional study of more than 2 million cervical cytology tests in Brazil [17], women age 30 years and older were more likely to have cervical HSIL detected where there was a documented history of genital bleeding. However, more than 99% of cervical HSIL was detected among women without reported genital bleeding [17].

In a retrospective case series, 95% of people reported anal symptoms prior to diagnosis of anal SCC [5], and the prevalence of anal bleeding (43%) was four-fold higher than the prevalence of PCB in cervical cancer [5,15]. However, anal symptoms seem to be highly prevalent among MSM and therefore an association between anal symptoms and HSIL may be difficult to detect, even if it were to exist.

This study is limited by the lack of symptom detail, including the symptom duration. Also, the small absolute numbers of some symptoms impacted on the ability to detect small associations. The differing time frame for reporting of anal symptoms and anal warts (within the last 6 months and last 12 months, respectively) limits interpretation of the association between anal lump and anal warts. Also, misclassification of participant HSIL diagnoses is possible, although this would have been minimised by the use of composite- diagnoses (i.e. including cytology only). The strength of this study lies in the use of systematically collected, prospective symptom data, in addition to the use of cytology and histological data. The use of baseline data is also a strength, since knowledge of the presence of anal HSIL could influence the reporting of anal symptoms.

In summary, we found a high prevalence of anal symptoms in this cohort of older MSM. There was no significant association between composite-HSIL and any self-reported symptom in either the last month, or last 6 months. An association between recent anal lump and a larger burden of intra-anal HSIL may be explained by recent anal warts. These findings suggest that most anal symptoms are not a clinically useful marker for the presence of anal HSIL among older MSM. However further consideration should be given to the potential utility of anal lump and anal warts as a predictor of HSIL.

Ethics

Ethics approval for the conduct of the SPANC study was obtained from the St Vincent’s Hospital Ethics Committee (HREC/09/SVH/168).

Funding

The SPANC study was supported by the National Health and Medical Research Council [grant number 568971]; the Cancer Council New South Wales [grant number 13-11]. Cytologic testing materials were provided by Hologic Pty Ltd. The Kirby Institute is affiliated with the Faculty of Medicine, University of New South Wales, and funded by the Australian Government of Health and Ageing.

Competing interests

AEG has received honoraria and research funding from CSL Biotherapies, honoraria and travel funding from Merck. CKF has received honoraria, travel funding and research funding from CSL and Merck, and owns shares in CSL Biotherapies. SMG has received advisory board fees and grant support from CSL and GlaxoSmithKline, and lecture fees from Merck, GlaxoSmithKline and Sanofi Pasteur; in addition, has received funding through her institution to conduct clinical HPV vaccine studies for MSD and GlaxoSmithKline and is a member of the Merck Global Advisory Board as well as the Merck Scientific Advisory Committee for HPV. RJH has received support from CSL Biotherapies and MSD. All other authors declare that they have no conflicts of interest.

Authors’ contributions

SLG (PhD student) contributed to the study design, performed the data analysis and drafted the manuscript. AEG, DJT and IMP conceived of the study, participated in its design, analysis and interpretation of data, and helped draft and review the manuscript. KP assisted with statistical analysis and reviewed the manuscript. FJ assisted with data analysis and reviewed the manuscript. All other authors reviewed and contributed to the manuscript.

Acknowledgments

The authors thank all the participants. In addition to the co-authors of this manuscript, the SPANC study team includes Annabelle Farnsworth, Clare Biro, Adele Richards, Julia Thurloe, Deborah Ekman, Ross McDonald, Marjorie Adams, Sepehr Tabrizi, Alyssa Cornall, Samuel Phillips, Monica Molano Luque, Simon Comben, Kirsten McCaffery, Kirsten Howard, Patrick Kelly, Daniel Seeds, Andrew Carr, Lance Feeney, Russ Gluyas, Garrett Prestage, Matthew Law, Brian Acraman, Patrick McGrath, Robert Mellor, Piero Pezzopane, Rick Varma, Julian Langton-Lockton and Winnie Tong.

References

[1] D.M. Parkin, F. Bray, Chapter 2: the burden of HPV-related cancers, Vaccine 24 (Suppl. 3) (2006) S3/11-25.
[2] T.M. Darragh, T.J. Colgan, J.T. Cox, D.S. Heller, M.R. Henry, R.D. Luff, et al., The

lower anogenital squamous terminology standardization project for HPV-Associated lesions: background and consensus recommendations from the college of American pathologists and the American society for colposcopy and cervical pathology, J. Low. Genit. Tract Dis. 16 (3) (2012) 205–242.
[3] A. Kreuter, A. Potthoff, N.H. Brockmeyer, T. Gambichler, J. Swoboda, M. Stucker, et al., Anal carcinoma in human immunodeficiency virus-positive men: results of a prospective study from Germany, Br. J. Dermatol. 162 (6) (2010) 1269–1277.
[4] F. Islami, J. Ferlay, J. Lortet-Tieulent, F. Bray, A. Jemal, International trends in anal cancer incidence rates, Int. J. Epidemiol. 46 (3) (2017) 924–938.
[5] T.R. Read, K.L. Huson, J.L. Millar, A. Haydon, I.W. Porter, A.E. Grulich, et al., Size of anal squamous cell carcinomas at diagnosis: a retrospective case series, Int. J. STD AIDS 24 (11) (2013) 879–882.
[6] D.A. Machalek, A.E. Grulich, R.J. Hillman, F. Jin, D.J. Templeton, S.N. Tabrizi, et al., The Study of the Prevention of Anal Cancer (SPANC): design and methods of a three-year prospective cohort study, BMC Public Health 13 (2013) 946.
[7] D. Solomon, D. Davey, R. Kurman, A. Moriarty, D. O'Connor, M. Prey, et al., The 2001 Bethesda System: terminology for reporting results of cervical cytology, JAMA 287 (16) (2002) 2114–2119.
[8] D.A. Machalek, I.M. Poynten, F. Jin, R.J. Hillman, D.J. Templeton, C. Law, et al., A composite cytology-histology endpoint allows a more accurate estimate of anal high-grade squamous intraepithelial lesion prevalence, Cancer Epidemiol. Biomarkers Prev. 25 (7) (2016) 1134–1143.
[9] D. Machalek, Prevalence and risk factors associated with high-grade anal squamous intraepithelial lesions (HSIL)-AIN2 and HSIL-AIN3 in homosexual men, Papillomavirus Res. 2 (2016) 97–105.
[10] C.M. Vajdic, M.T. van Leeuwen, F. Jin, G. Prestage, G. Medley, R.J. Hillman, et al., Anal human papillomavirus genotype diversity and co-infection in a community-based sample of homosexual men, Sex. Transm. Infect. 85 (5) (2009) 330–335.
[11] J.M. Palefsky, E.A. Holly, M.L. Ralston, S.P. Arthur, N. Jay, J.M. Berry, et al., Anal squamous intraepithelial lesions in HIV-positive and HIV-negative homosexual and bisexual men: prevalence and risk factors, J. Acquir. Immune Defic. Syndr. Hum. Retrovirol. 17 (4) (1998) 320–326.
[12] R.J. Hillman, M.T. van Leeuwen, C.M. Vajdic, L. McHugh, G.P. Prestage, L.P. Botes, et al., Prevalence and predictors of high-grade anal intraepithelial neoplasia in a community-based sample of homosexual men, Sex. Health 9 (6) (2012) 574–579.
[13] N. Jay, J.M. Berry, C. Miaskowski, M. Cohen, E. Holly, T.M. Darragh, et al., Colposcopic characteristics and Lugol's staining differentiate anal high-grade and low-grade squamous intraepithelial lesions during high resolution anoscopy, Papillomavirus Res. 1 (2015) 101–108.
[14] H.P. Schlecht, D.K. Fugelso, R.K. Murphy, K.T. Wagner, J.P. Doweiko, J. Proper, et al., Frequency of occult high-grade squamous intraepithelial neoplasia and invasive cancer within anal condylomata in men who have sex with men, Clin. Infect. Dis. 51 (1) (2010) 107–110.
[15] M. Shapley, J. Jordan, P.R. Croft, A systematic review of postcoital bleeding and risk of cervical cancer, Br. J. Gen. Pract. 56 (527) (2006) 453–460.
[16] A.N. Rosenthal, T. Panoskaltsis, T. Smith, W.P. Soutter, The frequency of significant pathology in women attending a general gynaecological service for postcoital bleeding, BJOG 108 (1) (2001) 103–106.
[17] J.C. Xavier-Junior, D.B. Vale, L.C. Zeferino, R.M. Dufloth, Association between concurrent genital bleeding and cervical cancer: a cross-sectional study, Acta Obstet. Gynecol. Scand. 94 (9) (2015) 949–953.