

IS SCREENING FOR ANAL SQUAMOUS INTRAEPITHELIAL LESIONS IN WOMEN WITH GENITAL HUMAN PAPILLOMAVIRUS INTRAEPITHELIAL LESIONS NECESSARY?

HÁ NECESSIDADE DE RASTREIO PARA LESÃO INTRAEPITELIAL ANAL EM MULHERES COM LESÕES INTRAEPITELIAIS GENITAIS POR PAPILOMAVÍRUS HUMANO?

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ABSTRACT

Introduction: There seems to be a fairly close relationship between genital and anal lesions associated with human papillomavirus (HPV) and with the pathogenesis of malignancies in such sites. **Objective:** This review seeks to analyze published papers that suggest the necessity for anal intraepithelial lesions screening in women with HPV genital intraepithelial lesions. **Methods:** A systematic review of original research published between 2001 and 2014 was performed in the databases PubMed, HighWire, Cochrane Library and Google Scholar. The keywords for the search were: “screening” or “early detection of cancer” and “anus” or “anus diseases” or “neoplasms anus” and “woman” or “women” and “HPV” or “DNA probes, HPV”. **Results:** 1,203 articles were selected in the first search. After the reviewers applied exclusion and inclusion criteria and analyzed the papers, 15 were selected to compose this review. Most of them showed higher rates of anal intraepithelial lesions in women with genital intraepithelial lesions than in regular women. We also found a correlation between genital neoplasms and anal infection by oncogenic HPV types and the role of the virus in the pathogenesis of anal cancer. **Conclusion:** Screening for anal lesions in women with HPV genital lesions should be indicated, and further studies are required to determine the best methods.

Keywords: early detection of cancer; anus; neoplasm; women; papillomavirus infections.

RESUMO

Introdução: Parece haver uma relação bastante estreita entre lesões genitais e anais associadas ao papilomavírus humano (HPV), bem como sua relação com a patogênese de neoplasias nesses sítios. **Objetivo:** Avaliar a existência de dados publicados que sugiram a necessidade de rastreamento para lesão intraepitelia anal entre mulheres com lesões genitais associadas ao HPV. **Métodos:** Foi realizada uma revisão sistemática de pesquisas originais publicadas entre 2001 e 2014 nos bancos de dados: PubMed, HighWire, Biblioteca Cochrane e Google Acadêmico. As palavras-chave para busca foram: “rastreamento” ou “detecção precoce de câncer” e “anus” ou “anus diseases” ou “anus neoplasms” e “woman” ou “women” e “HPV” ou “DNA probes, HPV”. **Resultados:** A busca inicial retornou 1.203 artigos. Após a aplicação dos critérios de exclusão e inclusão e da análise dos revisores, restaram 15 trabalhos, que foram empregados para compor a presente revisão. Grande parte dos estudos apontou que mulheres com lesões genitais pelo HPV apresentavam maior risco de lesões anais, em comparação com mulheres normais. Verificou-se também a relação entre neoplasia genital e infecção anal por tipos oncogênicos do HPV e o papel do vírus no desenvolvimento de câncer anal. **Conclusão:** O rastreamento de lesões anais em mulheres com lesões genitais por HPV deve ser indicado. O método mais adequado para tal ainda deve ser mais bem estudado.

Palavras-chave: detecção precoce de câncer; ânus; neoplasmas; mulheres; infecções por papilomavírus.

INTRODUCTION

Infection by human papillomavirus (HPV) is related to the pathogenesis of numerous types of cancer, including cervical, anal, vulvar, penis and even head and neck cancer. The closest relation is found with cervical cancer, where research indicates 99.7% of cases associated with HPV infection⁽¹⁾, followed by anal cancer with a 90% rate of correlation. Although this is a rare neoplasm (incidence of 1:100,000), the number of cases has grown in the last years among both women and men⁽¹⁾.

Screening programs have been used aimed at early detection of cervical lesions, whose incidence is of 500,000 new cases per year worldwide. However, anal cancer — with 30,000 new cases per years — has not been screened routinely⁽²⁾. For some risk groups, especially men with human immunodeficiency virus (HIV) and who have sex with other men, current protocols cover annual anal cytology screening⁽²⁾. On the other hand, there is no program for women, even those who present HPV lesions in the lower genitourinary tract.

Comparative studies on anal and cervical cytology sampling have shown that HPV infection in one of these sites increases the risk of lesions in the adjacent region. This may indicate that a cervical lesion could be a source for anal infection⁽³⁾. Another hypothesis raised is that the anal mucosa could function as a vat for the virus⁽⁴⁾. Therefore, there seems to be a close relation between genital and anal lesions, as well as with the pathogenesis of neoplasms in these sites^(3,4). Although this association is well

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known, there is no consensus about the use of a method that can identify anal intraepithelial lesions in women presenting genital intraepithelial lesions.

OBJECTIVE

To look for data suggesting the need for screening of anal intraepithelial lesions among women presenting genital lesions related to HPV.

METHODS

In order to perform the systematic review, we carried out a search on medical literature databases between January 2001 and January 2014. The websites chosen were PubMed, HighWire, Cochrane Library and Google Scholar. Keywords used were “screening” or “early cancer detection” and “anus” or “anus disease” or “anus neoplasms” and “woman” or “women” and “HPV” or “DNA probes, HPV”.

Studies carried out only with men, with immunocompromised patients and those on subjects other than intra-anal lesions were excluded from the review; papers published over than 12 years earlier, review articles and case reports were not selected either. Finally, only studies written in English, Portuguese and Spanish were picked.

Three reviewers participated in the article selection, in compliance with recommendations by the Brazilian Medical Society (AMB)⁽⁵⁾. At first, studies were chosen based on their headings. Then, the abstracts were analyzed in order to restrict the selection to papers that were really on the theme proposed and that met the inclusion criteria. Papers approved were then included in the research. If the reviewers disagreed on any of the studies, this would be assessed by a fourth one to define if it would be excluded or included. Finally, the articles selected composed the sample of our work.

RESULTS

The search on databases returned 1,203 results, but after the application of inclusion criteria, 125 articles were selected in the first phase. Then, the qualitative analysis excluded 110 more articles, totaling 15 studies included (**Figure 1**) and (**Table 1**).

In a case-control study by Dailing *et al.*⁽³⁾, HPV was identified by polymerase chain reaction (PCR), among 187 women diagnosed with anal cancer, in 89% of them (149 women), and HPV type 16 was found in 74% of cases⁽³⁾.

Blomberg *et al.*⁽⁴⁾, in a cohort study carried out in 1978-2008 with 32,933 Danish women presenting genital warts, found that the presence of these lesions is strongly related to the emergence of anal, vulvar, vaginal, cervical, penis, and even head and neck cancers. Relative risk estimates for anal and vulvar cancer were higher between the first and fourth years of follow-up after genital warts diagnosis and, although the risk decreases over the years, it remained significantly increased for more than 10 years. In a cross-sectional study conducted with 102 women presenting high-grade neoplasm or cancer in the lower genitourinary tract who were submitted to anal cytology and HPV search by PCR, Park *et al.*⁽⁶⁾ reported that women with genital neoplasms were at higher risk of anal infection

by oncogenic HPV types, regardless of the site of the neoplasia (cervical, vaginal, vulvar or more than one site).

Valari *et al.*⁽²⁾ conducted a study with 235 women with suspicion or confirmation of HPV-related pathologies in cervical, vaginal or vulvar regions, where HPV, high-risk HPV and (messenger ribonucleic acid) mRNA were researched in anal and cervical material, with positive results in 45%, 31% and 8%, respectively, for anus and 56%, 39% and 25%, respectively, for vagina; positive results for mRNA was significantly lower for the anal compared to the cervical region. Absolute or partial agreement between HPV types in both sites was 74%. According to these authors, presence of genetic material in the cervix was a risk factor for its presence in the anal regions, and in HPV tests, having had more than three sexual partners was also a risk factor.

In a prospective study conducted with 185 women from 5 different places in the USA, using anal and cervical cytology (liquid-base cytology, ThinPrep™) with HPV DNA detection by PCR in both sites, Hessol *et al.*⁽⁷⁾ found 9% of abnormal anal cytology and histology, being atypical (2%), condylomas (2%), anal intraepithelial neoplasm (AIN-I) (3%) and AIN-3 (1%), and 19% of abnormal cervical cytology and histology, being atypical (11%), condylomas (3%), cervical intraepithelial neoplasms (CIN-I) (3%), CIN-II (1%) and CIN-III (1%).

Regarding HPV infection in different spots, 50% of the women had anal infection and 15% had cervical infection, and in 8% of the cases both sites were infected. As to the type of HPV in anal infection, 12% had only oncogenic types and 33% had only non-oncogenic types, as both types were found in 5% of the sample. In cervical infection, 6% had only oncogenic types and 7% only non-oncogenic types, with both types being identified in 2% of the women. In this group, the proportion of women reporting practice of anal sex was 46%.

Palefsky *et al.*⁽⁸⁾ conducted a cohort study with 68 women with risk factors for HIV infection to investigate the presence of HPV in the anus by PCR and hybrid capture, and PCR detected HPV in 24 (42%) of the 57 women in the sample. HPV was detected by hybrid

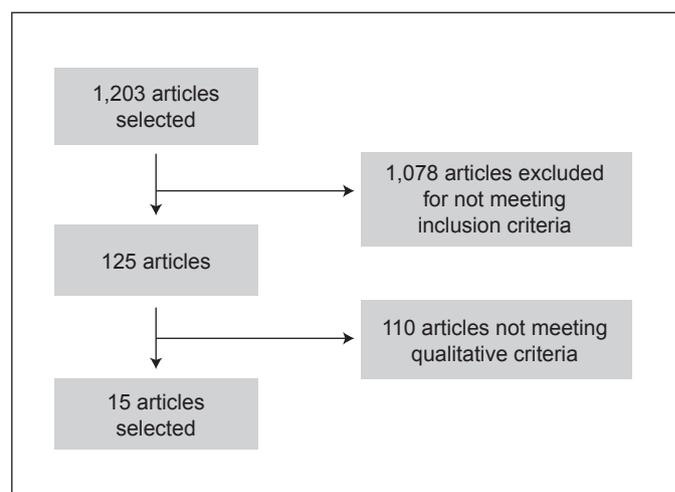


Figure 1 – Selection of studies.

Table 1 – Studies analyzed in the systematic review on the need for screening for anal intraepithelial lesions in women presenting genital intraepithelial lesions caused by human papillomavirus.

Study	Year of publication	Study design	Women (n)	Method of analysis	Results
Blomberg <i>et al.</i>	2012	Retrospective cohort study	32,933	Statistical analysis	Presence of genital warts increases the risk of cervical and anal cancer.
Crawford <i>et al.</i>	2011	Cross-sectional study	100	Anal histology Oropharyngeal histology	HPV detected in anal samples of 100% of women presenting low-degree GSIL and 82.7% of those with high-degree GSIL.
Hessol <i>et al.</i>	2011	Prospective cohort study	185	Anal cytology Cervical cytology PCR	
Jacyntho <i>et al.</i>	2011	Cross-sectional study	260	Perianoscopy Vulvoscopy Colposcopy High-resolution anoscopy	Incidence of ASIL in women with GSIL was significantly higher than among non-affected women.
Nielsen <i>et al.</i>	2011	Retrospective cohort study	1,434 (anal cancer) 388 (anal intraepithelial neoplasia)	Statistical analysis	Incidence of anal cancer doubled in Denmark because of the increase in HPV neoplasm.
Valari <i>et al.</i>	2011	Cross-sectional study	235	Cytology PCR Flow cytometry Statistical analysis	Cervical HPV infection is the leading predictor factor for anal affection.
Calore <i>et al.</i>	2010	Cross-sectional study	49	Cervical cytology Anal cytology	Patients with cervical HSIL are at higher risk of presenting abnormal anal cytology results.
Goodman <i>et al.</i>	2010	Prospective cohort study	897	PCR	The chance of women with cervical HPV lesion presenting anal lesions with the same etiology is higher than among normal women and vice-versa.
Giraldo <i>et al.</i>	2009	Cross-sectional study	260	Anoscopy	Women with GSIL have ASIL more frequently than normal patients.
Park <i>et al.</i>	2009	Cross-sectional study	102	Anal cytology PCR	Women with genital neoplasm are at higher risk of anal involvement by high-risk HPV types.
Véo <i>et al.</i>	2008	Cross-sectional study	80	Genital hybrid capture Anal hybrid capture	Incidence of HPV in the anal region of women presenting cervical lesions was higher than in women of the control group.
Edgren <i>et al.</i>	2007	Retrospective cohort study	3,747,698	Statistical analysis	The risk of anal cancer is 4.68 times higher among women with CIN-III compared to normal women.
Hernandez <i>et al.</i>	2005	Prospective cohort study	1,363	PCR	Women with cervical HPV are 3.3 times more likely to present anal involvement compared to normal women.
Dailing <i>et al.</i>	2004	Case-control study	187	PCR	89% of anal tumors in women were positive for HPV.
Palefsky <i>et al.</i>	2001	Prospective cohort study	68	PCR Hybrid capture	Patients at risk for HIV infection presented high rates of HPV infection.

HPV: human papillomavirus; GSIL: genital squamous intraepithelial lesions; PCR: polymerase chain reaction; ASIL: anal squamous intraepithelial lesions; HSIL: high-grade cervical intraepithelial lesions; CIN: intraepithelial cervical neoplasia; HIV: human immunodeficiency virus.

capture in 20 (30%) out of 67 samples. The same group of authors reported that, among patients submitted to anal and cervical HPV detection, 43% had anal infection and 24% had cervical infection. Hessol *et al.*⁽⁷⁾ found that 50% of their sample had anal infection and 15% had cervical involvement, while Valari *et al.*⁽²⁾ reported high positivity rates (45%) for HPV DNA at anal smears, similarly to cervical smears (56%).

Calore *et al.*⁽⁹⁾ assessed 49 women with abnormal cervical cytology and reported that among women with low-grade squamous intraepithelial lesions (SIL), 50% also had abnormal anal cytology, while 61.5% of those with high-grade SIL had abnormal anal results. These findings would suggest that patients with cervical high-grade SIL are more prone to presenting abnormal anal cytology.

A cohort study⁽¹⁰⁾ with 897 Hawaiian women carried out in 1998-2008 aimed to compare the risk of infection in the cervix or secondary infection in the anus to a previous adjacent infection. The authors reported that the risk of women with cervical HPV infection developing anal infection is higher among women without precedent infections. In turn, a cross-sectional study with 260 Brazilian women (184 with GSIL and 76 without it)⁽¹¹⁾ showed that history of more than 4 anal sexual relations per year and presence of genital herpes were risk factors for the emergence of ASIL. The study also showed that the prevalence of ASIL in women with GSIL was significantly higher than in women without the lesions (17.4% against 2.6%). Finally, women with GSIL in 3 or more sites (cervix, vagina, vulva or perianal region) have 13.1 times higher risk of ASIL compared to control group.

Another cross-sectional study with 100 women presenting cervical lesions, where histology sampling of the anal and oropharyngeal regions were collected, HPV was detected in anal cells of 100% of low-grade genital lesions and in 82.7% of high-grade genital lesions⁽¹⁾.

In a cross-sectional study using anoscopy in 260 patients of the Brazilian public health service, where 184 has genital squamous intraepithelial lesions (GSIL) and 76 were normal (control group), Giraldo *et al.*⁽¹²⁾ showed that low and high-grade anal lesions (ASIL) were more common in patients with GSIL. Besides that, they found out that women with high-grade GSIL had 5.2 times more ASIL than those without genital lesions, and women with low-grade GSIL had 7.66 times more ASIL than those of the control group.

In accordance with these findings, Véo *et al.*⁽¹³⁾ used hybrid capture to search for low and high-risk HPV in the anal and genital regions of 80 women and found out that, in a group of women with CIN-II or III in the genital region, incidence of HPV in the anus was 35%, against 10% in control group. Furthermore, high-risk HPV was detected in 22.5% of the women in study group against 5% in control group. In a cohort study starting in 1999, in Hawaii, with 1,363 women who had anal and cervical samplings submitted to PCR for HPV detection, Hernandez *et al.*⁽¹⁴⁾ showed that women with cervical infection had a 3.3 times higher risk of presenting anal infection compared to healthy women.

Edgren *et al.*⁽¹⁵⁾, in a cohort study with 3,747,698 Swedish women aging 18–50 years, found out that the risk for anal cancer emergence was 4.68 times higher, on average, among women presenting CIN-III lesions compared to those with no lesion.

Finally, a study performed in Denmark in 1998-2008 by Nielsen *et al.*⁽¹⁶⁾ considered important features regarding intra-anal neoplasms. The incidence of HPV-related cancer has increased, being more common among 60 years-old, that's why there is a benefit in the use of preventive methods, including HPV vaccine.

CONCLUSION

Research show that the risk of HPV anal lesions in women with HPV cervical lesions is high^(1,2,4,5,8-12,14). Genital infection by HPV is the main predictor for anal infection, and a significant correlation has been found between the types of HPV identified in anal lesions and those found in cervical lesions⁽²⁾.

Considering these associations between anal and cervical infections, as well as an apparent cause-effect relation, ASIL screening in women with GSIL should be mandatory. Screening indication seems to be a Public Health issue, once it would probably mean prevention of intra-anal neoplasms, which are more frequent each year.

The most appropriate and cost-effective method for screening nowadays is an important matter of questioning. Further studies comparing data regarding different techniques are needed to establish the best one.

Conflict of interests

The authors report no conflict of interests.

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