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EDITORIAL

Women with cervical cancer precursor lesions: a high-risk group for human papillomavirus (HPV)-related oropharyngeal cancer?

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Human papillomavirus (HPV) is the most common sexually transmitted infection globally with more than 80% of sexually active individuals acquiring the infection during their life [1]. Virtually all cervical cancers and a subset of vaginal, vulvar, anal and penile cancers are caused by oncogenic HPV infections [2]. Furthermore, it is now firmly established that HPV can also cause a subset of head and neck cancers, especially oropharyngeal squamous cell carcinomas (OPSCCs). Patients with HPV-positive OPSCC are generally younger, have less exposure to tobacco and alcohol, and have a more favourable prognosis than HPV-negative OPSCC patients [3,4]. The incidence of HPV-related OPSCC has increased in recent years in Denmark [5] and other developed countries [6]. HPV-positive OPSCCs now account for approximately 58–65% of all OPSCC cases in Denmark [5] and other Nordic countries [7,8]. Furthermore, in several countries, the annual number of HPV-positive OPSCCs is expected to surpass the number of cervical cancer cases before 2020 [5,6]. Therefore, a detailed understanding of the epidemiology and natural history of HPV-related OPSCC is becoming increasingly important.

One important issue to address is the potential interplay between HPV infection and HPV-related diseases at anogenital and oropharyngeal sites. For example, do women diagnosed with cervical cancer precursor lesions subsequently have an elevated risk of developing HPV-related OPSCC? Answering this question is essential from a natural history perspective to improve our understanding of the potential similarities and differences between HPV-related pathogenesis at anogenital and oropharyngeal sites. Clinically, such knowledge may be important to guide follow-up and management of women treated for high-grade cervical intraepithelial neoplasia (CIN).

Nationwide, prospective studies from Denmark [9] and Holland [10] found a 2–5-fold increased risk of OPSCC in women with CIN3 compared to women without previous CIN3. Similar trends were seen in registry studies from Sweden [11], Canada [12] and England [13]. However, these registry-based studies were unable to distinguish between HPV-positive and HPV-negative OPSCC. In a recent Dutch retrospective clinical study, women with HPV-positive OPSCC were more likely than women with HPV-negative OPSCC to have had an abnormal Pap smear registered before the OPSCC diagnosis [14]. The mechanisms behind these findings are not fully understood. However, women with previous high-grade CIN or HPV-related genital warts [15] may have an immune dysregulation which impairs their ability to clear HPV, thus increasing the risk of viral persistence and subsequent HPV-related OPSCC. In addition, women with previous high-grade CIN may have a behavioural pattern increasing their risk of both cervical and oropharyngeal HPV-related disease, e.g., multiple vaginal and oral sexual partners or smoking [3].

In this issue of *Acta Oncologica*, Christensen et al. report the results of an interesting Danish study aiming to further elucidate the potential association between cervical abnormalities and subsequent HPV-related OPSCC [16]. The authors included all female OPSCC patients in Eastern Denmark during 2000–2014 (n = 417) and determined the HPV and p16 status of the tumours. By linkage with nationwide registries, the authors compared the history of severe cervical abnormalities (defined as CIN2, high-grade squamous intraepithelial lesions or worse) in women with HPV-positive *versus* HPV-negative OPSCC. They found that women with HPV-positive OPSCC tended to be slightly more likely than those with HPV-negative OPSCC to have a history of severe cervical abnormalities when adjusting for age and smoking (odds ratio = 1.35). However, the result was not statistically significant (p=.4), and in addition, the estimate was not adjusted for cervical cancer screening history. The authors conclude that no association could be established based on their data.

Given the prior evidence and potential mechanisms described above it may be surprising that Christensen et al. did not find a statistically significantly increased risk of prior high-grade CIN in women with HPV-positive OPSCC, compared with their HPV-negative counterparts. It is possible that the study, in spite of the relatively large sample, was underpowered to demonstrate the expected association. The seeming discrepancy between this study and previous findings underlines the need for further investigations into the interplay between HPV infection and HPV-related disease at the cervix and oropharynx. Specifically, population-based studies are needed to investigate determinants of cervical and oral HPV co-infection and differences in risk factors for viral persistence at each site. Furthermore, immunologic

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studies are required to further elucidate the differences and similarities of immune responses to anogenital and oral HPV infection.

For both epidemiologic and immunologic studies, taking into account the potential confounding or modifying effect of smoking behaviour is of crucial importance. Smoking is a well-known risk factor for both cervical cancer and OPSCC [3]. The data of Christensen et al. [16] indicate that the association between HPV status in OPSCC and history of cervical abnormalities may be more pronounced in smokers than in non-smokers. However, the statistical power was limited, and larger studies are needed to further disentangle the impact of smoking on risk of OPSCC in women with previous high-grade CIN.

In summary, some studies suggest that women with a history of cervical premalignancies are at increased risk of OPSCC [9,10] and also non-cervical anogenital cancers [10,12,13,17]. From a clinical perspective, women with high-grade CIN may, therefore, be a relevant target group for interventions to prevent subsequent HPV-related disease. However, we currently have no effective screening methods for HPV-related OPSCC, because no precursor lesions have been identified [3]. Furthermore, screening using oral HPV testing is challenging due to the low lifetime risk of OPSCC in individuals with oral HPV infection [18]. There is increasing evidence that HPV vaccination can prevent oral HPV infection [19,20], thus underlining the potential for primary prevention. However, given the long lag time from HPV infection to development of cancer, it will likely take several decades before we see the effect of current vaccination programmes on the OPSCC incidence. Therefore, further studies are warranted of potential opportunities for preventing HPV-related OPSCC in order to curb the steadily increasing incidence rates of this disease.

Disclosure statement

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