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Review

Is there an increased risk of cancer among spouses of patients with an HPV-related cancer: A systematic review

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ABSTRACT

Background: High-risk human papillomaviruses (HR-HPV) are the cause of most ano-genital cancers and a fast growing subset of oropharyngeal cancer. As these malignancies occur as a result of an HPV- infection transmitted through intimate contact, many patients with HPV- induced cancer and their partners are concerned about HPV-transmission and the potential partners' cancer risk. Few studies have addressed this issue and whether the HPV-related cancer risk of partners of patients with HPV-related cancers is comparable to or greater than that of the general population.
Methods: We performed a systematic review of the published literature addressing this issue. Out of 1055 references screened, 53 articles were found eligible for inclusion.
Results: Regarding the issue of coincidence of HPV-induced oropharyngeal and/or anogenital cancers in couples, 13 case-reports or case-series were reported and 9 larger studies based on population-registries. Four of these registry studies showed an increased risk of cervical cancer in the partner while four did not. Among the four positive studies, odds ratios for the development of HPV-related cancer among spouses were between 2.6 and 6.7. One study showed an increased risk of tongue or tonsil cancer among husbands of women with cervical dysplasia or cancer. Overall the absolute risk increase in all these studies was small, on the order of 1–3%, although potentially underestimated. Indeed, all these studies have assessed partner's cancer risk at only one anatomical site whereas HPV- related malignancies can affect different locations.
Conclusion: This systematic review suggests a small trend of increase risk in HPV-associated cancers among spouses of patients with HPV-related cancer.

Introduction

High-risk human papillomaviruses (HR-HPV) are the cause of most anogenital cancers and a rising proportion of head and neck squamous cell carcinoma located in the oropharynx (chiefly the tonsils and base of tongue/lingual tonsil) [1,2]. HPV-related cancers account for 60 to 80% of oropharyngeal cancers (OPC) in North America and Northern Europe and could become, in the near future, the predominant type of head and neck malignancies in several western countries [3,4]. Oral and genital HR-HPV infections are both transmitted by mucosal contact and potentially through mucosal secretions most commonly attributed to sexual behaviors [5,6]. Nationally representative surveys of the US population have reported that the overall point prevalence of oral and genital HPV infection was respectively 7% and 42% [7,8], and that the lifetime prevalence is around 80%. These rates vary according to several parameters including age, sex, immune status (immuno-compromise vs. immuno-competent) and sexual behavior [7,8]. Individuals with a high lifetime number of sexual partners have a significantly increased risk of HPV infection [7,8] and related diseases including cancers. However other categories of the population could also be at risk such as the current and past partners of patients with HPV-induced cancer or dysplasia. While spouses may be at increased risk to develop an HPV-related malignancy, HPV-driven carcinogenesis is a long and complex process that involves multiple factors including immunity. Actual HPV infection has likely been previously cleared in most patients with an HPV-related cancer [9]. Any observed increased risk in spouses of HPV cancer patients may simply reflect shared HPV exposures from

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many years (perhaps decades prior) to the cancer diagnosis in the patients. Only a minority of infections will persist chronically and will potentially lead to intra-epithelial neoplasia and ultimately to invasive cancer [9]. Therefore, it is possible that the risk incurred by spouses of patients with HPV-related cancer does not exceed that of the general population.

Many patients and their partners express concerns about the risk of HPV transmission to the partner and the associated risk for developing a HPV-related cancer. But providing relevant answers is challenging as the literature on this topic is scarce and has never been compiled to provide a comprehensive overview of the associated risks. The aim of this article is to perform a systematic review of the literature, to discuss the implications for patient counseling and to provide some directions for future research. We will first present articles evaluating concurrent cases of HPV-induced anal and genital cancers in couples, then those evaluating concurrent cases of HPV-induced oropharyngeal cancers in partners of patient with oropharyngeal or cervical cancer, and finally the prevalence and concordance of HPV infection in sexual partner of patient with HPV-related cancer.

Methods

The National Institutes of Health "PubMed" search engine and Cochrane database were searched for relevant citations published from January 1984 to April 2016, using the following keywords : "Human papillomavirus" AND "wife (ves) or husband(s) or partner(s) or spouse(s) or couple(s) or consort(s)" AND " Cancer(s) or neoplasm(s)" AND "cervical/cervix or penis/penile or oral/oropharynx/oropharyngeal or anal or vaginal or vulvar " limiting to English publications in humans. Using these terms, we identified 1055 references. After an initial screening of titles and abstracts for relevance to the topic in consideration, 63 studies were identified that appeared to evaluate the risk of HPV infection or related cancer in sexual partners of patients with HPV-related pre cancer or cancer. Studies assessing the risk of HPV infection in partners of patients with HPV infection but without associated cancerous or precancerous lesions and those focusing on immunosuppressed populations were excluded. Using these criteria, 37 manuscripts were identified; 16 additional articles (published from 1933 to 1979) were identified from the bibliographical references of these selected manuscripts. A total number of 53 manuscripts were finally reviewed on the basis of originality and relevance to the broad scope of this review.

This work was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The quality of the studies was evaluated using the key criteria for observational studies developed by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group [10]. However there is no current validated scale to rate such studies, and as all of them are retrospective studies based on registries, the risk of bias is high for all of them and the limitations are discussed individually.

The results are grouped according to the topic investigated and presented and discussed qualitatively. No quantitative analysis could be performed due to the variety of methods used in many studies.

Concurrent cases of HPV-induced genital cancers in couples

The earliest report describing cases of HPV-driven cancers in husbands and wives dates back to the 1930s. At that time, Giordano [11] reported a case of carcinoma of the penis occurring in a man whose wife had died from cervical cancer. Although this report was anecdotal, it raised awareness on the fact that male and female genital malignancies may share a common etiology that could be sexually transmitted from one partner to the other. Subsequently, similar cases [12–18] had been repeatedly described (Table 1) and generated hypotheses for future studies.

In a Japanese study, Kurihara and Asano [19] were the first to report that the rates of cervical and penile cancers were geographically correlated. This was subsequently confirmed in other countries [20–22] and led some to wonder if these findings were consistent with reports suggesting that genital cancers aggregate in spouses. Martinez [23] was the first to address specifically this issue in a robust manner (Table 2). Using a case-control study within the Central Cancer Registry of Puerto Rico, he identified the wives of 889 men diagnosed with penile squamous cell carcinoma, between 1950 and 1968, and as a control group the wives of 889 men with upper aero-digestive tract cancer matched by age and year of diagnosis. The upper aero-digestive tract was chosen as a control group because cancers occurring within this anatomical site predominate among lower socio-economic groups, as was the case with penile cancers. Martinez found that the spouses of the penile carcinoma group developed 8 cases of cervical cancer compared to none among the control wives, and an expected number of 1.2 cases in the general Costa-Rican population.

A decade later, Graham et al. [24] identified the wives or ex-wives of 227 males with cancer of the penis in the New York State Cancer Registry from upstate New York from 1960 to 1964. By comparing the observed and expected numbers of cancer cases at

Table 1
Case reports describing cases of HPV-driven cancers in husbands and wives.

Authors	Year	Anatomical site	No. of couple	Matching strains
Giordano [11]	1933	Penis & cervix	1	NP
Bervis et al. [12]	1950	Penis & cervix	1	NP
Goldberg et al. [13]	1979	Penis & cervix	1	NP
Cartwright et al. [14]	1980	Penis & cervix	2	NP
Mac Gregor et al. [15]	1980	Penis & cervix	2	NP
Sinha et al. [16]	1982	Penis & cervix	1	NP
Cocks et al. [17]	1989	Penis & cervix	1	NP
Uemaetomari [69]	2007	Tonsil & tonsil	1	+
Haddad et al. [35]	2008	Tonsil & tonsil	1	+
Andrews et al. [34]	2009	Tonsil & tonsil	2	+
Huang et al. [36]	2010	Nasopharynx & cervix	2	NP
Mitamura et al. [70]	2015	Penis & Vulve	1	+
Brobst TD[71]	2016	Tonsil & tonsil	1	+[a]

NP: not performed.
From 1933 until today, several case reports have described concurrent cases of HPV-related carcinomas in couples. The most recent works have shown that the same HR-HPV strains were involved in husband and wife.
[a] In the study of Brobst et al. [70], husband and wife were infected with an almost identical HPV16 strain (homology >97% within the compared DNA sequence). The author suggested that both partners were infected by the same virus. Although, one can not completely exclude that each partner carried the infection before their relationship.

Table 2
Risk of cancer among spouses of a patient with penile cancers or cervical dysplasia/carcinoma (population based studies).

Reference (country/year)	Disease considered	Cases description	Control description	Rate among cases	Rate among controls	Risk difference
Martinez[a] (Puerto-Rico/1969)	Cervix cancer	Wives of men with penile cancer (n = 889)	Wives of males with other malignancies (n = 889)	8	0 (expected: 1.2)	RR = 6.7
Kessler (USA/1977)	Cervix cancer or CIS	Other wives of males previously married with a woman with cervical cancer (n = 1087)	Matched women of the same age and married in the same churches (n = 659)	29 (2.7%)	7 (1.1%)	OR = 2.55 [1.1–5.9]*, p < 0.05
Graham[b] (USA/1979)	Cervix cancer	Wives of men with penile cancer (n = 227)	Upstate New York population (expected rates)	6	Expected: 1.85	RR = 3.24, p < 0.01
Smith[c] (England/1980)	Death from cervix cancer	Wives of men with penile cancer (n = 711)	England and Wales population (expected rates)	11	Expected: 3.9	RR = 2.84, p = 0.002
Hellberg[d] (Sweden/1989)	Cervix cancer	Wives of men with penile cancer (n = 968)	Participants from the Swedish Population Registry (n = 968)	8	7 (expected:5.5)	OR = 1.14 [0.41–3.2]*
Maiche[e] (Finland/1990)	Cervix cancer	Wives of men with penile cancer (n = 224)	Finland population (expected rates)	2	Expected: 1.88	RR = 1.05 [0.13–3.8]
Iversen[f] (Norway/1997)	Cervix cancer	Wives of men with penile cancer (n = 423)	Matched wives of men without penile cancer (n = 444)	5	3	OR = 1.75 [0.42–7.37]
Hemminki (Sweden/2000)	Tongue and tonsil cancer	Husbands of women first diagnosed with in-situ or invasive cervical cancer	Swedish population (expected rates)	Tongue: 20 Tonsil: 10	Expected Tongue: 8.28 Tonsil:3.68	RR: Tongue: 2.42 [1.47–3.74] Tonsil: 2.72 [1.29–5.01]
De Bruijn[g] (Netherlands/2013)	(pre)malignant cervical lesions	Wives of men with penile cancer (n = 139)	General Dutch population estimates	Abnormal PAP: 10 (5.1%)	Abnormal PAP, expected rate 3.3%	NP

Abbreviations: NP, not provided; OR, Odds ratio; PAP, Papanicolaou test smear; RR, risk ratio.
* Indicates that OR or RR and their confidence intervals have been computed based on the article findings but were not provided in the article.
[a] 889 penile cancer cases were registered in the cancer registry of Puerto-Rico from 1950 to 1960. The number of wives that were identified and their follow up period was not provided.
[b] 227 penile cancer cases were registered in cancer registry from Upstate New-York from 1960 to 64. 202 wives (89%) were identified and studied from 1951 to 75.
[c] 1022 death certificates mentioning cancer of the penis in men, born before 1915, were identified from 1964 to 1973. 195 were excluded (single men or no record of marital status). 711 wives (86%) were identified and studied from 1939 to 74.
[d] 1064 penile cancer cases were registered in national Swedish cancer registry from 1958 to 80. 968 wives (91%) were identified and studied from 1958 to 80.
[e] 275 penile cancer cases were registered in the finnish cancer registry from 1955 to 1977. 240 wives (87%) were identified and studied from 1953 to 1980.
[f] 671 penile cancer cases were registered in the Norway cancer registry from 1960 to 92. 423 wives (74%) were identified and studied from 1960 to 92.
[g] 418 penile cancer cases treated in the Netherlands from 2004 to 10. 177 were excluded. 139 wives (57%) were identified. The follow up period was not provided.

various anatomic sites, between 1951 and 1975, they found that the number of women with cancer of the cervix was significantly larger than the numbers expected (6 vs. 1.8, $p < 0.01$) whereas the number of other cancer types did not exceed expectation. The following year, Smith et al. [25] reached the same conclusion after performing a similar study in 711 women who were married in 1939 to men who died with cancer of the penis between 1964 and 1973 in England and Wales. They noted 11 deaths related to cervical carcinoma although 3.9 were expected ($p = 0.002$).

Kessler et al. [26] attempted to determine if the risk of developing a cervical cancer was significantly increased among women married to men who at some other time in their lives were married to another woman who developed a cervical cancer. From a cohort of 4186 patients diagnosed with a cervical cancer or a carcinoma in situ between 1950 and 1969, the authors identified 1087 other women who were previously or subsequently married to the same men. A control group composed of a random sample of 659 women similar in age, race and marital status was selected from wedding registries. Cervical cancer or carcinoma in situ was detected in 29 (2.7%) cases and in only 7 (1.1%) controls, which was statistically significant ($p < 0.05$). This study demonstrated the existence of "marital clusters" of cervical cancer in which 2 women married to the same men have both developed cervical malignancies. Interestingly, none of these men had a penile cancer. Although these findings seem to strengthen the previously described studies, the tendency of certain men to marry women with a greater risk to develop cervical cancer cannot be ruled out. Indeed, cervical neoplasia is frequently associated with certain social and behavioral characteristics, which could influence particular men to repeatedly choose such women for their marital or sexual partners.

Contrary to the above studies, 4 more recent studies [27–30] from Northern Europe did not support the assumption that wives of men with penile cancer incur an increased risk of cervical cancer. Hellberg et al. [27] have compared the occurrence of cervical cancer in 968 wives of men with penile cancer with a matched control group. From 1958 to 1980, they found 8 cases of cervical cancer among the cases and 7 in the controls. Maiche et al. [28] studied 240 wives of men affected with penile cancer from 1953 to 1980. They observed 2 cases of cervical cancer whereas the expected number was 1.9. Iversen et al. [29] compared the medical files of 423 wives of 671 men diagnosed with penile cancer, between 1960 and 1992, with those of a control group composed of 444 wives of healthy men. They found 15 HPV-related lesions in the cases (precancerous and cancerous) as compared with 10 in the controls (odds ratio: 1.6 (95% CI: 0.7–3.6). They concluded that the risk of pre-invasive and invasive cervical carcinoma was increased in partners but not significantly. Finally, De Bruijn et al. [30] have reported on 139 wives of penile cancer patients from the Dutch cervical cancer screening program and found 1 woman with cervical cancer and 2 other cases with high grade dysplasia (CIN 3), which was not different from the prevalence in the general population.

What lessons can be drawn from these studies? The earliest studies [23–26] showed clearly that partners of patients have an increased risk of genital malignancy whereas the most recent ones [27–30] suggest that this risk is comparable to that of the general

population. It is tempting to consider that the recent studies [27–30] are more accurate and therefore closer to the truth. Actually, important limitations may have led to underestimate the rate of cervical cancer among spouses of men with penile cancer. Firstly, all these studies are retrospective. Secondly, a significant fraction of spouses of men with penile cancer were not identified (9–43%), particularly in 2 of the 4 studies [28,30] that concluded that the risk was not increased (see caption of Table 2). Thirdly, study duration was sometimes too short and consequently women who developed a cervical cancer prior or after the study period would have been missed. For instance, in the study of Iversen et al. [29] men with penile cancer were diagnosed from 1955 to 1977 whereas the cases of cervical cancer were recorded between 1953 and 1980. Similarly, de Bruyn et al. [30] identified men diagnosed with penile cancer from 2004 to 2010 and the study was published in 2013, suggesting that the recording of cervical precancerous lesions ended in 2010 or shortly after. Additionally, none of these studies was able to control for condom use and it is possible that the rate of condom use was different in studies showing or not an association. While not fully protective the use of condom could have confounded the exposure rates of the partners in the studies. Finally, it is important to highlight that the cancer of the penis, which was used by all these studies to identify the cases, is caused by HR-HPV in only approximately 40–50% of the cases [31], leading to a dilution of the potential relationship between the male's penile cancer and his spouse's cervical cancer.

Concurrent cases of HPV-induced oropharyngeal cancers in partners of patient with oropharyngeal or cervical cancer

As the etiological role of HR-HPV in oropharyngeal cancers has only been recently discovered [32], very few studies have addressed the issue of cancer risk in spouses [33–36]. The risk of OPC in partners of patients with cervical cancer was assessed in a registry-based study [33] published in 2000, a point in time when the role of HR-HPV in OPC was still being elucidated. Using the Swedish Family cancer database, Hemminki et al. [33] have noted that husbands of cervical cancer patients have an increased risk of tonsil and tongue cancer, with respective standardized incidence ratio (SIR)[1] of 2.4 and 2.7. However, this study is limited by the fact that it did not take into account tobacco and alcohol consumptions, the traditional risk factors of tonsil and tongue cancer.

More recently, concurrent cases of HPV-driven OPC occurring in couples have been described [34–36] (Table 1). Andrews et al. [34] have reported on 2 couples in which both the husband and the wife were diagnosed within a 1 year interval with HPV-driven OPC. These individuals were aged from 51 to 58 years old and were engaged 10 to 15 years before the diagnosis was made. Analyses of the viral genomes demonstrated the same HPV16 variant in tumors of both the husband and wife in both couples. Similar observations were noted by Haddad et al. [35], who also found that both spouses were affected by the same HPV16 variant. The probability to observe by chance a pair of OPCs (incidence in the general population: 6–15/100,000), caused by a HR-HPV and particularly by the same HPV16 variant in spouses is extremely low. These findings demonstrate that these partners shared exposure to the same virus. The exposure was likely from one spouse to the other although the co-infection from an exposure to a third person/persons having this same virus cannot be completely ruled out.

[1] The standardized incidence ratio (SIR) is an estimate of the occurrence of cancer in a population relative to what might be expected if the population had the same cancer experience as some larger comparison population designated as "normal" or average.

Prevalence and concordance of HPV infection in sexual partner of patient with HPV-related cancer

Given that few studies have directly examined the risk of HPV-driven cancers in partners, an alternative strategy is to assess the rates of HR-HPV infections. Indeed this may serve as a proxy to estimate if their cancer risk is greater than that of the general population. As there are significant differences between oral and anogenital HPV infections in term of epidemiology and natural history, the prevalence and concordance of HPV infection in sexual partner of patient with HPV-related cancer will be discussed according to the affected anatomic site.

It is well established that genital HPV-infection is frequent in asymptomatic men whose sexual partners had cervical HPV-infection [37–39]. Moreover, genotype concordance is more frequent than expected by chance (25–65% of cases), highlighting the highly contagious nature of HPV infections [37–39]. Several studies have specifically assessed penile HPV-infection in healthy partners of women with CIN II/III or cervical cancer [40–52] (Table 3). Reported rates of penile infections varied widely, but in some studies it exceeded those found in the general population. Moreover, up to 70% of these cases had histologically proven HPV-related penile lesions [44], although their risk of progression to an invasive cancer is extremely low. However these findings are difficult to analyze due to several limitations including the use of many different HPV sampling/detection methods and small sample sizes (see Table 3). Additionally, there are significant differences in the definition of partners that may confound the results. As well as a lack of good estimates of population expected HPV infection rates.

Rates of oral high-risk HPV-infection in partners of patients with CIN or HPV-driven OPC are variable [53–57], but seem comparable to those of the general population [53–56]. These data should be treated cautiously as very few studies (see Table 4) have addressed this issue and each with obvious weaknesses such as limited number of patients and methodological variations. Interestingly one of them [57] showed a surprisingly high number of cervical dysplasia and HPV-related malignancies in partners of patients with HPV-related OPC. In this study, the authors examined 164 patients with HPV-related OPCs and 93 of their current sexual partners. Among the 93 partners, 8 reported a medical history of cervical dysplasia and 1 of cervical cancer. Additionally, 6 patients stated that they had a former partner affected with an HPV-related (or potentially related) cancer. These findings were mostly self-reported by partners/patients and not systematically checked by the authors and thus there are inherent recall biases, but they support the assumption of an increased risk of HPV-related malignancies in spouses.

Implications for counseling of partners

A diagnosis of HPV-driven malignancy is not only a cancer diagnosis, with all the associated psychological implications, but also conveys that the cancer was caused by a viral exposure in the past that may have also affected partners current and past. Explaining the diagnosis of an HPV-driven cancer with patients is a sensitive issue, and it is important that correct information is conveyed to avoid fear, blame, and misconceptions. Firstly, virtually all humans are exposed to HPV at some point in their life. Secondly, HPV-driven cancers develop typically many years after exposure and partners would have shared exposures over many years perhaps decades.

It is important to recall that according to some guidelines related to HR-HPV cervical infection management, there is no evidence to support sexual partner notification although some women may benefit from having an informed discussion with their spouses about their diagnosis, which can foster partner support

Table 3
Penile HPV-infection in partners of patients with cervical dysplasia or cancer.

Reference (country/year)	Women (index cases)	No. male partners	Control group (no.)	Sampling/Testing method	Penile HR HPV-infection rate	Penile HPV16-infection	HPV-infection rate in controls
Lopez diez et al. [40] (Spain/2016)	CIN II/III	125	No	Scraping/PCR	63/125 (50.4%)	30/63 (47.6%)	–
Bar et al. [41] (Israel/2007)	CIN III	74	No	Scraping/PCR	13/74 (17.6%)	NA	–
Giraldo et al. [42] (Brazil/2006)	LSIL with HR-HPV	54	No	Scraping/PCR	14/54 (25.9%)	NA	–
Martin-Ezquerra et al. [43] (Spain/2011)	CIN II/III	91	No	Scraping[1] Urine[2] HC-II	8/62 (12.9%)[1] 22/78 (28%)[2]	NA	–
Bleeker et al. [44] (Netherlands/2005)	CIN	238	Yes(n = 118)	Scraping PCR	81/170 (59.4%)	47/101 (46.5%)	HPV: 25.3% HPV16: 19%
Rosenblatt et al. [45] (Brazil/2003)	CIN I-III	30	Yes(n = 60)	Scarping HC	3/30 (10%)	NA	8%
Campion et al. [46] (UK/1988)	CIN III	50	Yes(n = 25)	Biopsy[3] Scraping[4] Histology/HC	23/50 (46%)[3] 15/50 (30%)[4]	10/15 (66.6%)	HPV: 12% HPV16: 4%
Guzman et al. [47] (Mexico/2008)	CIN	21	Yes(n = 32)	Scraping PCR	4/21 (19%)	NA	6%
Barrasso et al. [48] (France/1987)	CIN	32	No	Scraping Blot-hybridization	9 (28.1%)	9 (28.1%)	–
Gupta et al. [49] (India/2006)	ICC	30	No	Scraping PCR	NA	9 (30%)	–
Franceschi et al. [50] International/2002	ICC CIS	611	Yes(n = 533)	Scraping PCR	41 (6.7%)	30 (4.9%)	HR-HPV: 4.3% HPV16: 2.8%

CIN: cervical intra epithelial neoplasia, ICC: invasive cervical carcinoma, CIS: carcinoma in situ, PCR: Polymerase chain reaction, HC: hybrid capture, NA: not available.
Rates of penile HPV-infections varied widely across these studies. The lacks of control groups in most studies, variation in the sampling methods and in the assay used to identify HPV make the analysis of these data complicated.
In the study of Martin Ezquerra 2 sampling methods were performed: scraping (1) and urine HC-II (2). The penile HR HPV-infection rates were respectively 12.9% (1) and 28% (2). Actually the number 1 and 2 were used to indicate to which methods the results are related. Similarly in the study of Campion et al the number "3" has been attributed to biposy and 4 to scraping.

Table 4
Oral HPV-infection in partners of patients with cervical, oropharyngeal or anal dysplasia/carcinoma.

Reference	No. partners	Sampling method	HPV testing method	Oral HR-HPV infection rate
Partners of cervical dysplasia/carcinoma patients				
Uken et al. [53]	60	Brushing	PCR	3/60 (5%)
Tatar et al. [54]	34	Oral rinse	PCR	6/34 (17%)[a]
Marques et al. [55]	22	Brushing	PCR	3/22 (13.6%)
Partners of oropharyngeal cancer patients				
D'Souza et al. [57]	93	Oral rinse	PCR	2/93 (2.1%)
Tsao et al. [56]	128	Brushing	PCR	17/128 (13.3%)
Partners of anal dysplasia/carcinoma patients				
Prendes et al. [72][b]	66	Oral rinse	PCR	7 (11%)

[a] 3 infections were related to HR-HPV, 1 to LR-HPV and 2 were not genotyped.
[b] The study cohort included 49 HIV-positive patients.

[58]. On the other hand, it has been reported that a significant fraction of health professionals still encourage women with abnormal pap-test or with a positive cervical HPV-DNA test to notify their partners [59] even if this has probably limited impact on HPV-infection control. Indeed most of these infections clear spontaneously and there is currently no specific treatment in case of persistent HR-HPV infection (ie chronic carrier).

Regarding a partner's HPV-driven cancer risk, although no firm conclusion can be drawn, data suggest that this risk is slightly but significantly increased in comparison to the general population. This is even more likely because multiple anatomical sites could be at risk of malignancies but most studies performed to date have focused on only one anatomical site. Future studies should assess the global risk of HPV-driven cancer in partners taking into account both anogenital and oropharyngeal sites.

From a practical standpoint, discussing this issue with patients and their partners is difficult as this risk remains hypothetical and needs confirmation. Indeed although the increased relative risk[2] of HPV-related cancer in the spouse is usually around 2–3, the increase in absolute risk,[3] although potentially underestimated, is only around 1–3% compared to the general population (Table 2). Moreover, this risk is even lower if not non-existent in vaccinated individuals (e.g. prophylactic vaccination against HPV). Therefore the message should be tailored to the individual's circumstances. It is important to point out that long term sexual partners have likely

[2] The relative risk is the ratio of the probability of an event occurring in an exposed group to the probability of the event occurring in a comparison, non-exposed group.
[3] The absolute risk is the probability of the occurrence of an event in a population relative to its exposure to a specific hazard or pathogen. Absolute risk is risk stated without any context whatsoever. Example: The absolute risk of lung cancer in a country is the ratio between the number of lung cancer diagnosed during a year and the number of inhabitant. Adding context (e.g. age, smoking history, industrial exposure, etc.) is used to define a person's relative risk of suffering a particular condition.

shared their HPV infection before the occurrence of cancer and therefore it is probably not necessary to change sexual behaviors in established couples. Conversely, appropriate protection (condoms or other protection barriers) should be discussed with new partners.

Finally, there are no standardized screening for HPV-related cancers with the exception of cervical cancers, and efforts to establish anal cancer screening paradigms in HIV positive individuals and men who have sex with men. Female partners of patients with an HPV-driven cancer should be advised that maintaining routine cervical cancer screening is one means to reduce their small but potentially elevated increased risk [60]. With regard to cancer risk at other HPV-related sites, no recommendation can be made as there are no currently recommended screening paradigms for non-cervical HPV-related cancers in asymptomatic relationships.

Direction for future research

To date, all studies that have assessed the risk of HPV-driven cancer in spouses were performed retrospectively using registries. The quality of the studies is therefore overall low and the risk of bias is high. It is clear that prospective studies are needed, but setting up such studies raises several methodological, practical or ethical questions.

Firstly, it is important to determine which population will be the most relevant. Indeed the prevalence of HPV infection and the associated risk of HPV-related malignancy varies according to the disease site and the subject gender. Most previous works have focused on partners of men with penile cancers; however this cancer is rare (0.1–1/100,000 per year) [61,62] and is caused by HR-HPV in only 40–50% of cases [31]. Another option is to focus on female partners of men with HPV-driven OPCs. OPC's are more frequent than penile cancers (1.4–6.4/100,000/year) [62], their incidence is increasing and they are caused by HR-HPVs in 60–80% in several western countries. Moreover HPV16, which is the most aggressive genotype, represents nearly 90% of all HPV-driven OPC cases) [3,4]. Cervical cancer screening, which is overall standardized and well organized in most developed countries, might be used to assess prospectively the risk of cervical cancer in female partners of patients with OPC. This approach might be well accepted by participants, particularly in the long run, as the benefit of generalized cervical cancer screening is widely supported. However, this strategy does not address the issue entirely. Indeed, it does not assess the risk of HPV-related OPC in partners of women with an HPV-related cancer or premalignancy, and men are much more likely to develop HPV-related OPC than women. Additionally, this will lead to underestimate the global risk as sexual practices are generally collinear (e.g. oral and genital intercourse are not mutually exclusive). Consequently it would be more relevant to take into account all at risk sites where HR-HPV can cause cancer to obtain a more precise evaluation of the risk as well as increase study power and implications. This evaluation can be performed by regular comprehensive clinical examination or medical surveys.

Secondly, determining the adequate duration of such a study is an important question. Monitoring partners for at least 10 years after the identification of the index case will be needed but the risk of lost to follow up will be significant. Defining appropriately what a "partner" is another potential issue. In the literature, the duration of the relationship to define a couple varies widely and this may have a critical impact on outcomes. Indeed, HPV-driven neoplasms are preceded by a phase of abortive infection during which there is theoretically no production of viral particles and consequently the infectious risk is limited or zero [5,9]. Moreover, in recent couples, partners HPV-infection might be related to previous relationship. Consequently, it might be more relevant to focus on couples that have a stable relationship for at least 5–10 years or on past partners. Another important issue is related to the choice of the best comparator. Observed outcomes in the cases can be directly compared with a matched control group (healthy individuals whose partners are not affected by HPV-related cancer) or with the expected rates in the general population using cancer registries. Although, the use of a control group is desirable for methodological reasons, it increases the costs of the study and it unclear whether these "control" individuals will accept a long term follow-up or screening interventions. A potential solution could be to enrich the cases population with patients at risk for developing HPV-related cancers, for example using HPV serum biomarkers. There is mounting evidence that individuals with high levels of E6 HPV16 antibodies are at higher risk of developing an HPV-related cancer and particularly at the oropharyngeal site [63–66] Focusing the screening campaigns on these individuals could reduce the number of participants needed to screen and hence the costs of screening studies by increasing the absolute and relative risk of HPV-related cancer compared to the general population. This would also improve the cost-efficiency and acceptability of such risk-adapted screening strategies in the long run.

Ethical issues will need to be addressed. Is it acceptable to monitor individuals whose couple has separated during the study? If oral/genital HPV testing is performed during follow-up, should the results be communicated to the partners if a test that was previously negative turns out positive? Indeed, the detection of an HPV-infection that was not present previously might raise sensitive questions within the couple (and potentially induce suspicion and mistrust as this is a sexually transmitted disease), although this might solely be related to variation in HPV biomarkers levels or in diagnostic sensitivity.

All of these questions highlight the difficulties to assess properly the risk incurred by partners. However, answering definitively this issue is clinically relevant. If the risk is not increased, it will be possible to reassure patients and their partners. Otherwise, preventive measures should be considered in this at risk population. To date, cervical cancer is the only HPV-related cancer for which there are effective secondary prevention measures. However, it is conceivable that in the future these individuals might be tested for persistent HR-HPV infection and benefit, under certain conditions, from therapeutic vaccination aiming to treat HR-HPV infections. Indeed, such treatments are currently under development [67,68].

Conclusions

This systematic review suggests the potential existence of a small increased risk in HPV-related cancers among spouses of patients with HPV-related cancer. However this eventuality shall not be the source of unjustified concerns as it is important to emphasize several limitations including the reduced number of publications on that subject and methodological issues. This article represents a synthesis of the available data and a basis for further reflection. It is obvious that this issue warrants further investigation to confirm these findings using methodologically robust designs, and, if confirmed, the development of risk-adapted screening strategies. Of course controlling HR-HPV infection by prophylactic vaccination would be the ideal solution, however this implies a sufficient coverage at the global level.

Conflict of interest

No financial disclosures from any authors.

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