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Review article

Airborne human papillomavirus (HPV) transmission risk during ablation procedures: A systematic review and meta-analysis

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ABSTRACT

Background: Human Papillomavirus (HPV) is associated with development of oropharyngeal cancer. Aim of this review was to assess airborne transmission risk of infectious particles from HPV lesions to airway mucosa of medical staff during established ablation procedures.
Methods: A systematic review of human and animal studies, published before 09/2020, relevant to airborne HPV transmission. Controlled studies reporting prevalence of HPV-associated upper airway (nasal/oral/pharyngeal) disease in staff performing ablation procedures (laser, loop electrosurgical excision [LEEP], cryosurgery) on HPV lesions were included in meta-analysis. Additionally, we aimed for a comprehensive systematic overview of studies regarding occupational risk of airborne HPV transmission and safety measures during ablation procedures.
Results: A total of n = 30 original studies report outcomes related to HPV transmission risk in medical staff conducting ablation procedures. HPV DNA detection in ablation smoke (n = 7), matching HPV genotypes on ablated HPV lesions and face/airways of medical staff after ablation (n = 2), and evidence for infectivity of papillomavirus in ablation smoke (n = 3, animal models only) were reported. Three case reports describe occupational HPV disease of upper airway mucosa. Three controlled studies assessed warts (in CO_2 laser-users only); when pooling all controls (general population, non-laser users), nasal/oral/pharyngeal lesion sites were more common amongst laser-users (OR = 5.75; 95%CI[1.55, 21.38]; $p < .001$).
Discussion: Airborne HPV dispersal with matching “high-risk” HPV-genotypes in airways of medical staff after ablations (LEEP and CO_2-laser) and cases of HPV-associated upper airways neoplasms based on exposure to laser and LEEP smoke are documented. Upper airway mucosa is a more common anatomical site for warts in CO_2 laser users compared to controls. Simple safety measures greatly reduce HPV contamination and transmission risk.

1. Background

Human Papillomavirus (HPV) is a highly contagious and commonly sexually transmitted human pathogen. The majority of known HPV genotypes are harmless or considered “low-risk” types (e.g. HPV-6 and HPV-11), which primarily cause benign cutaneous warts and anogenital lesions. Papillomatosis of the oropharyngeal and laryngobronchial system has also been attributed to infection with low-risk HPV genotypes. High-risk genotypes (e.g. HPV-16 and HPV-18) on the other hand are primarily involved in the development of cervical cancer and other urogenital malignancies in both women and men. Also, despite introduction of vaccines against relevant HPV genotypes, an increasing prevalence of HPV-16-positive oropharyngeal cancers has been reported over the past decades. (Berman and Schiller, 2017).

Physical ablation procedures are established treatment options in benign and pre-cancerous HPV-associated lesions. Laser ablation, electrosurgery, e.g. loop electrical excision (LEEP), and cryosurgical procedures, e.g. application of liquid nitrogen, are effective treatment options conducted by dermatologists, gynaecologists, urologists and surgeons worldwide. While HPV is highly contagious in direct skin to skin contact and thus the use of protective gloves is generally established amongst healthcare workers, it appears unclear whether infectious virus particles are mobilized from HPV-associated lesions into the ambient air during surgical manipulation. These concerns are particularly relevant

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from an occupational health perspective, since several HPV genotypes have been classified as human carcinogens by the International Agency for Research on Cancer (IARC). While it has been argued that most HPV-associated neoplasms suitable for physical ablation are induced by low-risk HPV genotypes, it is important to note, that multiple high- and low-risk HPV genotypes have been shown to coexist even in benign neoplasms, particularly in the anogenital region (Ingles et al., 2015; Kwon et al., 2016; Azevedo et al., 2017). Further, and potentially interrelated, even low-risk HPV-associated lesions bear a risk for the development of malignancy. (Papapanagiotou et al., 2017; Syrjanen, 2018; Georgescu et al., 2018).

This knowledge highlights the importance of prevention regarding potential airborne HPV transmission in exposed medical staff regardless of HPV genotype and further raises the questions (Berman and Schiller, 2017): is airborne transmission of infectious HPV particles during ablation procedures possible and (Ingles et al., 2015) does it lead to an elevated risk for HPV lesions of the upper airways in medical staff?

2. Methods

A systematic literature review regarding risk for HPV transmission during physical ablation procedures in HPV-associated lesions, defined as [1] airborne dispersion of papillomavirus during ablation and/or [2] HPV-related upper airway disease in medical staff conducting ablations was carried out using PubMed (MEDLINE), Embase, and The Cochrane Library interchangeably using the keywords ("human papillomavirus" OR "HPV") AND ("laser ablation" OR "electrosurgery" OR "electrosurgical" OR "cryotherapy" OR "surgical smoke" OR "loop electrical excision" OR "aerosol") OR "cryosurgery") OR "cryosurgical" OR "surgical fume" OR "surgical plume" OR "LEEP") AND ("transmission" OR "occupational"). Additionally, related scientific article recommendations at the respective official homepages of the European Union Information Agency for Occupational Safety and Health (EU-OSHA) (https://osha.europa.eu/) and the US National Institute of Occupational Safety and Health (NIOSH), Center of Disease Control (https://www.cdc.gov/), were reviewed. All articles and article types (original articles, reviews, meta-analyses, case reports, and letters) published before September 2020 were screened regardless of language. Additionally, if reported, occupational safety measures were reviewed in regards to their feasibility and effectiveness in this setting. Only controlled studies (S) reporting prevalence of upper airways warts (nasal, oral, pharyngeal mucosa) (O) in medical staff (P) conducting established physical ablation procedures (laser, loop electrosurgical excision [LEEP], cryosurgery) (I) versus controls, who do not conduct ablation procedures (C), were eligible for qualitative synthesis. For the quantitative meta-analysis, odds ratios with Haldane-Anscombe correction were calculated that reflected the odds of having upper airways warts in medical staff as compared to controls. The pooled effect was derived following Mantel and Haenszel (1959) and tested for homogeneity using Tarone's (1985) test (Mantel and Haenszel, 1959; Tarone, 1985). The risk of bias analysis of all studies included in meta-analysis was conducted by using the "Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies" (National Institutes of Health, 2014), an appraisal tool for critical methodological quality evaluation of cross sectional studies. (Downes et al., 2016).

2.1. *Role of the funding source*

There was no funding source for this study

3. Results

A total of n = 315 articles were identified and screened for relevance; n = 28 original articles reported outcomes related to airborne HPV transmission risk during established physical ablation procedures (PRISMA Flow Diagram, Supplementary Figure 1). Eight studies (n = 8) reported work-place contamination associated with physical ablation procedures.

All studies (n = 14) assessing airborne dispersion of papillomavirus during ablation procedures in animals and/or humans, including five studies on infectiousness of papillomavirus particles in ablation smoke (Table 1).

Ten studies identified HPV DNA in ablation smoke derived from CO2 laser, electrocoagulation and/or LEEP in vapour samples (Best et al., 2020; Garden et al., 2002; Kashima et al., 1991; Neumann et al., 2018; Sawchuk et al., 1989; Zhou et al., 2019) or filters(Best et al., 2020; Ferenczy et al., 1990; Sood et al., 1994) of a local air exhaustion system. Four studies did not identify HPV DNA in smoke generated by CO_2 laser (Abramson et al., 1990; Ilmarinen et al., 2012; Subbarayan et al., 2020; Wisniewski et al., 1990) or erbium:YAG (Hughes and Hughes, 1998) laser. Three studies found corresponding HPV genotypes(16, 18, 24), i.e. matching the respective HPV genotypes of the ablated patient lesions, in the nasolabial fold and upper airways (nasal cytobrush, nasal swab) of medical staff following CO_2, electrocoagulation and/or LEEP ablation. In a prospective pilot study, high-risk HPV were found in LEEP generated smoke. HPV-16,-39,-53 genotypes caught in exhaust suction tubes during the procedure were matching those from the four resected intraepithelial neoplastic cervix (CIN) lesions (Neumann et al., 2018). Recently, HPV DNA assessed in surgical smoke and in nasal swabs from surgical staff before and after LEEP ablation of CIN lesions showed HPV genotypes in LEEP smoke which corresponded with those identified in the respective ablated CIN tissue samples. HPV DNA load was increasing with positional distance of the smoke evacuation device from the ablation site. The authors further identified HPV DNA in the nasal cavities of 2 surgeons after LEEP procedure, which again corresponded with HPV genotypes found in the respective ablated tissues; however, this nasal HPV DNA was not traceable in follow up (3–6 month) (Zhou et al., 2019). HPV DNA was found in 32% of nasolabial fold swipes and in 16% of nasal cytobrush specimens of gynaecologists conducting several consequent CO_2 laser and electrocoagulation sessions on genital warts; new HPV DNA was found in one additional case after smoke exposure. All conjunctival samples taken before and after ablation procedures were negative for HPV DNA (Bergbrant et al., 1994). No data was found on airborne HPV DNA dispersal risk during cryotherapy. Contamination of cryoguns with HPV is highly dependent on cleaning methods (Strauss et al., 2003) and herpes simplex virus was shown to "survive" up to 12h on cotton-tipped applicators. (Burke et al., 1986).

Very few studies have documented infectious potency of dispersed papillomavirus from ablation procedures and so far only in animal models. Bovine papillomavirus collected from CO_2 laser smoke (conducted in several ranges of clinically used laser settings) during wart treatment in cattle induced cutaneous fibropapillomas when reinoculated into skin of calves (Garden et al., 2002; Sawchuk et al., 1989). This had previously not been achieved in a comparable experimental setting conducted on heifers (Wisniewski et al., 1990). Similar findings were reported by Sawchuk et al., who described infectiousness of HPV particles derived from CO_2 laser vapour and electrocoagulation smoke during ablation of bovine warts via Bioassay *in vitro* (Sawchuk et al., 1989). In another experimental setting, CO_2 laser smoke generated during ablation of detached laryngeal papilloma samples did not infect cultured cell lines (Kunachak et al., 1996). In a murine model, surgical smoke from mouse tail warts ablated with KTP laser was consistently capable of transmitting mouse papillomavirus (MmuPV1) to uninfected mice. (Best et al., 2020).

We identified three (n = 3) case reports describing four case histories of HPV associated upper airway disease due to surgical smoke exposure (Table 2). In 1990, a 44-year old surgeon who had treated rectal lesions and anogenital condylomas using a Nd:YAG laser over the course of 3 years, developed laryngeal papillomatosis associated with HPV subtypes 6 and 11 (Hallmo and Naess, 1991). He had used a surgical mask, gloves and eye protection, but no specific smoke evacuation system. In 2003, a 28 year old gynaecology nurse, who had repeatedly assisted in

Table 1
Studies on airborne dispersal of HPV DNA during established ablation procedures for treatment of HPV-associated lesions.

Study	Design	Procedure	Ablated Material	Findings	Safety Measures	Recommendations
Garden JM et al. 1988	Human Model	CO_2 laser	plantar or mosaic verrucae	intact HPV DNA in 2/7 laser vapour samples		
Sawchuk WS et al. 1989	Human Model	CO_2 laser	human plantar warts	HPV DNA positive in 5/8 laser vapour samples	Simple surgical mask integrated into smoke evacuation system	Standard surgical mask was capable of removing virtually all laser- or electrocoagulation-derived virus (close fitting form!)
	Animal Model	Electro-coagulation	human plantar warts	HPV DNA positive in 4/7 electrocoagulation-derived vapour samples		
		CO_2 laser Electro-coagulation	bovine warts	infectious (Bioassay) bovine papillomavirus in vapour from both modalities; higher virus load in laser vapour		
Ferenczy A et al. 1990	Human Model	CO_2 laser	condylomata and cervical intraepithelial neoplasias (CIN)	HPV-6 DNA positive on pre-filter (1/5)		
Wisniewski PM et al. 1990	Human Model	CO_2 laser	cervical intraepithelial neoplasias (CIN II), koilocytes	No HPV DNA in laser vapour (Southern Blot)	Tissue debris found on inner glasses surface of one surgeon	Well-fitting surgical masks, sufficient smoke evacuation, (safety goggles with side protection?)
	Animal Model	CO_2 laser	Bovine papilloma lesions from dairy cattle	no tumour growth on cattle exposed to laser vapour heifers		
Abramson et al. 1990	Human Model	CO_2 laser	Laryngeal papilloma	No HPV DNA found in Southern Blot of laser vapour samples unless direct contact with lesion was made		
Kashima HK et al. 1991	Human Model	CO_2 laser	laryngeal papillomatosis	HPV-6/HPV-11 identified in (17/27) in vapour, corresponding HPV subtype to tissue		
Bergbrant IM et al. 1994	Human Model	CO2 laser Electro-coagulation	Genital warts	HPV DNA in 32% of nasolabial fold and 16% of nasal cytobrush samples, post ablation 5/, samples pre-ablation with one additional case after ablation		Approved face masks, evacuation of air, thorough decontamination of PPE after each session
Sood et al. 1994	Human Model	LEEP	CIN	39/49 HPV positive tissue samples, HPV DNA identified on filters in 18/49 sessions, HPV genotypes in tissue matching filter DNA		
Hughes PSH et al. 1998	Human Model	erbium: YAG laser	verrucae vulgares	No HPV DNA in abundant "fluffy" laser plume on handpiece after ablation		
Zhou Q et al. 2019	Human Model	LEEP	cervical intraepithelial neoplasias (CIN)	40/134 HPV DNA in smoke samples 2 positive nasal swabs (HPV-16 and HPV-58)		
Garden JM et al. 2002	Animal Model	CO_2 laser	Bovine papillomavirus-induced cutaneous fibropapillomas	papillomavirus DNA in laser smoke (in all tested clinically used parameter settings of laser) tumor development at all laser smoke-inoculated sites, virus type matching DNA in laser smoke		
Ilmarinen et al. 2012	Human Model	CO_2 laser	Laryngeal papilloma	intact HPV DNA on gloves of 1/5 surgeons and 3/5 nurses, no HPV DNA detected in oral mucosa or on surgical masks		
Neumann K et al. 2017	Human Model	LEEP	high-grade squamous intraepithelial lesion (HSIL) of cervix uteri	4/24 HPV DNA in smoke samples (HPV 16, 39, 53)		Efficient suction device, respiratory masks, standard as mandatory for laser ablations (e.g. FFP2 masks); HPV vaccination in LEEP involved professionals?
Best SR et al. 2019	Animal Model	KTP laser	MmuPV1 tail warts	Papillomavirus DNA in KTP laser smoke and in laser filter, wart induction in uninfected mice challenged with surgical byproducts		
Subbarayan RS et al. 2020	Animal Model	Electro-cautery	Mouse tail intradermally injected with plasmid DNA (transformed from plasmid expressing HPV p16 E6/E7 genes)	No HPV DNA detected in electrocautery fume samples		
	Human Model	Electro-cautery (robotic Bovie)	oropharyngeal squamous cell carcinoma HPV-16-positive oropharyngeal squamous cell carcinoma (n = 3)	No HPV DNA detected in electrocautery fume and samples collected from suction apparatus, surgical mask, and equipment (robotic arm)		
Hu X et al. 2020	Human Model	LEEP, laser, others	cervical lesions	42/469 HPV DNA (HPV 16, 31, 33, 55, 56, 58, 59) in operators nasal swabs after electrosurgical procedures, HPV positive rate decreases when wearing masks		Efficient suction, surgical masks and N95 respirators, efficient smoke evacuation systems

Table 2
Reports on HPV-associated occupational disease due to exposure to ablation procedures.

Study	Design	Procedure	Ablated Material	Findings	Safety Measures	Recommendations
Hallmo P. et al. 1991	Case report	Nd:YAG Laser	anogenital condylomata	laryngeal papillomatosis (HPV-6 and 11)	“ordinary” smoke evacuator, conventional mask, gloves, eye protection	Equipment which provides optimal protection
Calero L et al. 2003	Case report	CO_2 laser electro-cautery	anogenital condylomata	laryngeal papillomatosis	No efficient smoke evacuation, no mask?	Disposable gowns, surgical caps, gloves, standard surgical mask, 1 cm suction distance, frequent filter change
Rioux M et al. 2013	Case Reports	CO_2 laser LEEP (one case)	cervical and vulvar lesions	HPV 16 positive tonsillar squamous cell carcinoma HPV 16 positive base of tongue cancer	Many procedures performed without proper ventilation or mask	Portable smoke evacuators with High Efficiency Particulate Air (HEPA) filter or equivalent, suction within 2 inches from surgical site, use of respirators (N95 grade or higher)

electrocautery and CO_2 laser treatments of anogenital condylomata without proper protective equipment, developed laryngeal papillomatosis. Based on expert evaluation by a virological institute, her case was legally accepted as an occupational disease based on suspected airborne HPV transmission in Germany (Calero and Brusis, 2003). There are two reported cases of HPV-16-positive oropharyngeal squamous cell cancers in gynaecologists. Both had over 20 years of practice in performing physical ablation procedures, particularly CO_2 laser and LEEP, in HPV associated lesions of the cervix and vulva. They were male, 53 and 62 year old respectively, and appeared to have no other relevant risk factors for HPV-16 infection. (Rioux et al., 2013).

Four cross-sectional controlled studies ($n = 4$) aimed to assess the prevalence of HPV infection in the upper airways of medical personnel conducting ablation procedures. The methodological quality assessment of these studies is presented in supplementary table 1, in consideration of their potential eligibility for meta-analysis. A recent study, by Hu X. el al collected questionnaire-based data and nasal swab samples from 700 gynecologist ($n = 469$ exposed to electrosurgical smoke, out of which $n = 356$ were performing LEEP), at 67 hospitals in China (Hu et al., 2020). HPV DNA was significantly more prevalent in nasal epithelia of staff performing any kind of electrosurgery compared to non-exposed staff (Table 3a) and prevalence rates correlated with years of exposure. Highest prevalence rates were found for staff conducting electrosurgery for over 15 years (17.33%), followed by 10–15 years (13.21%), 5–10 years (7.22%) and 0–5 years (6.15%). HPV-16 was the most prevalent genotype in the nasal swabs of the electrosurgery group (76.19%). In a 3 months follow up, 56.52% of the positively tested gynecologists still exhibited the same HPV genotypes in their nasal swabs; no HPV DNA was detected in the group of positively tested gynecologists still participating in the study after 24 months. Due to basic differences in study design (e.g. ablation method, no HPV-associated lesions reported), this study was not eligible for pooling with the other three cross-sectional studies presented below.

Finally, out of these four, three ($n = 3$) cross-sectional studies reported prevalence of warts at any anatomical site, including nasal/oropharyngeal warts, in medical staff conducting laser ablations. All were questionnaire-based evaluations predominantly conducted in dermatologists and gynaecologists, with a history of CO_2 laser use. (Table 3b).

In a recent study conducted amongst employees of dermatology and gynaecology departments in Denmark, HPV was identified in nasal swabs and/or oral rinse in 5.8% of 287 participants, who had had any experience with CO_2 laser ablation of genital warts; a rate of 1.7% was reported in those with no laser experience. The prevalence of mucosal HPV increased when CO_2 laser treatments had been conducted for at least 5 years. An inclusion criterion in this study was omission from treatment of HPV-related disease for at least 24h prior to participation. HPV-6 or 11 were not detected in any of the mucosal samples, whereas high-risk HPV 16 or 18 genotypes were identified in four samples (Kofoed et al., 2015). HPV prevalence in oral and nasal mucosa of medical staff conducting electrosurgical ablation, LEEP or cryotherapy of genital warts did not appear elevated when compared to those who did not conduct any of these procedures (Kofoed et al., 2015). Another comparative questionnaire-based study by Gloster et al. found no significant difference in the prevalence of warts in surgical staff performing CO_2 laser procedures, regardless of smoke exposure duration in years, when compared to a general patient-population. In this study, the most common self-reported wart sites amongst laser surgeons after “hands” were “face” and “nasopharynx”; a significantly higher incidence of “nasopharyngeal warts” was reported by laser surgeons compared to controls (13% vs. 0,6%) (Gloster and Roenigk, 1995). Lobraico et al. only found a higher prevalence of hand warts in dermatologists which

Table 3
Cross-sectional controlled studies on the prevalence of (a) HPV DNA and (b) HPV-associated upper airway lesions in medical staff exposed to ablation smoke.

Study	Design	Cases	Controls	Anatomical Site	Method	Cases	Controls	
Hu X et al. 2020 (China)	Cross-sectional Questionnaire based	LEEP Electrosurgery	No LEEP No electrosurgery	Nasal swabs	*LEEP* *Electrosurgery*	**36**/356 **42**/469	**10**/344 4/231	**10,1% vs 2,9%** **9,0% vs 1,7%**

(b)

				Warts any anatomical site		face			upper airways *(nasal, oral, pharyngeal)*		
Study	Design	Cases	Controls	Cases	Controls	Cases	Controls		Cases	Controls	
Gloster HM et al. 1995 (U.S.)	Cross-sectional Questionnaire based	CO_2 laser users	Patient-population	31	6124	**8**/31	n.r.	**N/A**	**4**/31	**37**/6124	**12,9% vs 0,6%**
Lobraico RV et al. 1989 (U.S.)	Cross-sectional Questionnaire based	CO_2 laser users	Non-laser users	26	390	**6**/26	**21**/390	**23% vs 5,3%**	**0***/26	**2**/390	**N/A**
Kofoed K et al. 2015 (Denmark)	Cross-sectional Questionnaire based	CO_2 laser users	Non-laser users	39	29	n.r.	n.r.	**N/A**	**2**/39	**1**/29	**5,1% vs 3,4%**

*missing explicit report was assumed as no cases; n.r … not reported (missing data); N/A … not available.

the authors attributed to insufficient use of preventive equipment (Lobraico, 1989). They only explicitly described nasal or oral warts in non-laser-users (0,5%), implying that none of the 26 CO_2 laser using specialists (n = 902) with warts had reported upper airway lesions.

The calculated scores indicated a suitable (fair) overall quality of the considered papers, i.e. susceptible to some bias but not sufficient to invalidate its results, and allowed for data pooling. Pooling data from all three studies indicated a significantly elevated risk (OR = 5.75; 95%CI [1.55, 21.38]; $p = .005$) for any oral or nasopharyngeal lesions amongst CO_2 users with warts. (Fig. 1). Tarone's test for heterogeneity failed to corroborate a homogeneous effect across all three studies ($\chi^2 = 8.28$, $df = 2$, $p = .02$). Limiting the analyses to studies using only medical staff as controls, showed a homogenous ($\chi^2 = 0.19$, $df = 1$, $p = .66$) effect that did not reach statistical significance (OR = 1.23; 95%CI[0.13, 12.08]; $p = .86$).

4. Discussion

Airborne dispersal of low-risk and high-risk HPV DNA during ablation of HPV-associated lesions is well-documented, with matching HPV genotypes in surgical smoke and corresponding tissue treated with LEEP and CO_2 laser (Kashima et al., 1991; Neumann et al., 2018; Sood et al., 1994; Weyandt et al., 2011). Studies which did not find HPV DNA in surgical smoke were mainly conducted in ablation of laryngeal papillomatosis (Abramson et al., 1990; Kunachak et al., 1996; Dodhia et al., 2018); thus, these findings might, to some extent, be explained by lesion-specific differences in viral load and tissue mass of airway papilloma when compared to e.g. anogenital neoplasms (Goon et al., 2017). Accordingly, all reported cases of occupational HPV-associated disease up to date have exclusively been found in healthcare workers treating anogenital lesions (Hallmo and Naess, 1991; Calero and Brusis, 2003; Rioux et al., 2013). Further, detection of HPV DNA in surgical smoke seems impaired when less sensitive analytical methods, like Southern blot hybridization, were used instead of PCR (Abramson et al., 1990; Wisniewski et al., 1990). As most research has been conducted in CO_2 laser, electrocoagulation and LEEP-derived surgical smoke, little data exists for other laser types like APC, YAG and KTP lasers. In an animal study, smoke generated by KTP laser was shown to transmit highly infectious papillomavirus particles in mice (Best et al., 2020). However, it remains unclear how differences in physical properties of various laser ablation procedures impact disruption of HPV specimen dispersal, compromising its detection (Hughes and Hughes, 1998). Interestingly, CO_2 laser ablation settings did not appear to have an impact neither on positive nor on negative study outcomes (Kunachak et al., 1996). Also, no data exists on airborne HPV dispersal during cryosurgery, likely because no surgical smoke is generated during these procedures. Potential airborne dispersal of preserved HPV particles however remains of interest in this context, since herpes simplex virus was shown to "survive" up to 12h on cotton-tipped applicators used in cryoablation (Burke et al., 1986). Due to the associated preservation of infectious material in cryotherapy, adherence to hygiene recommendations is essential to avoid transmission. In general, safety recommendations derived from literature are largely consistent with standard safety measures established for medical contact with HPV lesions and conduction of physical ablation procedures, but users must be aware of their importance. These include the use, but also correct disposal, of examination gloves, aprons, caps and appropriate (regularly cleaned or disposable) eye protection. Closely positioned local smoke exhaustion systems and highly efficient filters as well as appropriate room ventilation are central to virus transmission control along with adherence to established HPV related hygiene guidelines. Fortunately, the use of N95 masks and, to some extent, even surgical masks were shown to effectively reduce contamination of nasal epithelia with HPV DNA. Occupational safety recommendations are summarized in Supplementary File 1.

Actual transmission of HPV DNA from surgical smoke to face and nasal mucosa of medical staff during LEEP and CO_2 laser ablation has also been documented (Neumann et al., 2018; Zhou et al., 2019; Bergbrant et al., 1994). However, infectious potential of papillomavirus in surgical smoke has so far only been demonstrated in animal models, particularly for LEEP, CO_2 laser and KTP laser ablations (Garden et al., 2002; Sawchuk et al., 1989). In one study on detached laryngeal papilloma tissue, CO_2 laser smoke did not infect cultured cell lines; however, HPV DNA was not explicitly described in the ablated tissue or employed smoke samples. (Kunachak et al., 1996).

A recent study by Hu X. el al found a significantly higher prevalence of HPV DNA in nasal swab samples of 469 gynecologists regularly conducting electrosurgery, particularly LEEP, correlating with years of exposure (Hu et al., 2020). Here, the high-risk HPV-16 genotype was

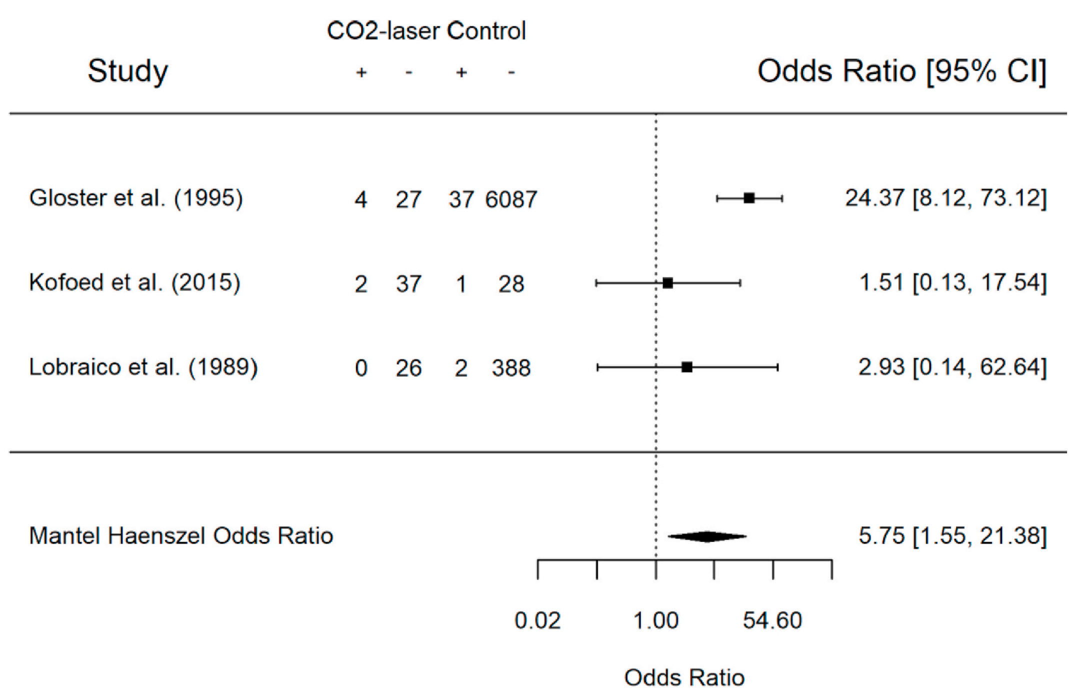

Fig. 1. Forest plots of meta-analysis regarding prevalence of reported oral/nasal/pharyngeal lesions amongst CO_2 laser users versus controls with any warts.

most prevalent in the nasal epithelia of gynecologists exposed to surgical smoke. 3 months later, more than half of them still exhibited the same HPV genotypes on their nasal mucosa. 24 months later, and while some positively tested participants had withdrawn from the study, no HPV DNA was be detected in the nasal mucosa of the remaining gynecologists. The authors thus concluded a transient nasal HPV infection. However, it has to be noted that none of the previously negative gynecologists was tested again in the follow ups.

While one other study also identified high-risk HPV-16, and HPV-58, in nasal mucosa of medical staff after LEEP, no HPV DNA was again found in follow-up (Zhou et al., 2019). This finding appears in line with the overall low detection rates of HPV DNA on nasal and oral mucosa in medical staff conducting ablation procedures in Denmark (Kofoed et al., 2015). While low-risk HPV 6 and 11 were not detected in any of the mucosal samples in this study, high-risk HPV 16 or 18 genotypes were present in four samples. Interestingly, a higher prevalence of "nasopharyngeal warts" were reported by CO_2 laser surgeons compared to non-laser using controls (1,2% vs. 0,8%) in this study. Further, in subjects with warts, facial lesions and, most importantly, upper airways lesions were more common in CO_2 laser users compared to non-users (5, 1% vs 3,4%) (Kofoed et al., 2015) and compared to general population (13% vs. 0,6%). (Gloster and Roenigk, 1995) (Table 3).

Despite case reports of occupational HPV upper airways neoplasms induced by surgical smoke (Hallmo and Naess, 1991; Calero and Brusis, 2003; Rioux et al., 2013), studies on mucosal HPV prevalence in medical staff in relation to surgical smoke exposure are scarce and heterogeneous. This situation is further compromised by technical difficulties in providing a seamless sampling of HPV from all relevant mucosal sites (e. g. tonsillar crypts) (Kofoed et al., 2015), and forecasting HPV-associated disease.

4.1. Limitations

This review presents an assessment of published data on airborne HPV transmission risk during ablation procedures and potentially associated occupational infection and HPV related disease. The detailed analysis and weighted discussion of existing literature in favour of positive findings is based on occupational safety and health consideration. A major limitation of the studies used for meta-analysis is the possible reporting bias. Further, qualitative synthesis was limited due to control group heterogeneity of the eligible studies. While OR was still elevated after excluding the study by Gloster et al. which used patients as controls, thus taking into account only medical staff as controls, p-values did not reach statistical significance.Further, a lack of baseline HPV status, ideally even before surgical smoke exposure, would be desirable but is often not feasible. Hu X et al. (2020) showed that the same HPV DNA genotypes might "persist" in nasal mucosa in most of the positively tested staff 3 months later, but not 24 months later. These results imply that HPV particles are most likely repeatedly deposited in and cleared from the nasal mucosa in ablation smoke exposed staff. Thus, a single sampling time point might be insufficient. Longitudinal studies including baseline HPV status and objective evaluation of HPV-associated lesions in medical staff with and without ablation smoke exposure are needed to estimate risk and confirm causality.

5. Conclusion

Taken together, each ablation procedure can lead to workplace contamination and HPV particles are indeed dispersed in surgical smoke generated by CO_2 laser and LEEP. While an associated infection risk is currently only documented in animal models, published data indicates that CO_2 laser users have a higher risk for warts of the upper airways compared to controls. Both aspects are relevant knowledge for physicians and cannot be dismissed from an occupational health perspective.

In summary, while even high-risk HPV transmission by surgical smoke is indeed feasible, infection risk remains controversial in humans. Identification of relevant occupational HPV transmission by surgical smoke is impeded by other transmission routes associated with workplace hygiene and contamination. It is further masked by increasing age and sexual activity, which might further reduce readiness of medical staff to report potential cases of occupational disease. Despite the widespread incidence of HPV, it still remains a goal of occupational health and safety to minimize workplace associated transmission risks and thus allow healthcare workers to manage their HPV risk behaviour at their own discretion.

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Declaration of competing interest

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