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Human papillomavirus association in epithelial cancers: a systematic review of the literature

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Abstract

Background: The role of Human Papillomavirus (HPV) in cervix cancers is well established with immunisation commenced in most developed countries. The role of HPV in uterine cervix cancers is well established with immunisation programmes commenced in most developed countries. Despite numerous publications on HPV association with cancers affecting multiple body sites, there is substantial amount of controversy over HPV immunisation as a preventive measure. The aim of this study was to establish the evidence for HPV-associated cancers in regions other than the cervix and question whether the evidence would support a global immunisation programme against HPV irrespective of gender or geography.

Methods: A systematic review of previous studies. Searching MEDLINE (1962-April 2011), Embase (1988-April 2011), and Cochrane Library (to April 2011) identified published articles.

Results: 651 of 13,090 identified studies were eligible for inclusion. The overall median prevalence of HPV in cancers was 31%. This varied considerably by cancer type with the median prevalence for bladder cancer (12%), compared to that for anal/colorectal cancers (61.5%). Upper aerodigestive and gastrointestinal tract cancers had the largest number of studies and reported median prevalence of 33.3% and 30.1%, respectively.

Conclusions: Our assessment that 1 in 3 cancers are HPV-associated can be interpolated to 2.12 million cancers annually worldwide. If we were to not consider HPV-associated cancer as a disease of single anatomical subsites, but to consider it as a disease of the entire human body the current available evidence on incidence may support a global immunisation programme.

Keywords: Human papillomavirus, cancer, immunisation, cervix

Introduction

The Human Papillomavirus (HPV) was first described in the early 1960's and originally was believed to be associated exclusively with benign diseases [1-2]. Since then the methods of detection and association with diseases have been extensively researched and improved. The HPVs are a group of double-stranded DNA viruses, which are principally spread by sexual contact [3]. There are many different types of HPV which have been associated with both benign and malignant diseases. The benign and premalignant conditions include cutaneous warts, leukoplakia, erythroplakia and recurrent respiratory papillomatosis (RRP); while HPV associated cancers have been found in all regions of the human body [1-4].

HPVs are the principal oncogenic viruses in humans and their roles in cervical carcinogenesis and premalignant lesions are well established. HPV genotypes are subdivided into oncogenic (high-risk) and benign (low-risk) genotypes. Oncogenic genotypes include 16, 18, 31, 33 and 45, and benign include 6 and 11 [2-3]. HPV 16 and 18 are the two most common oncogenic genotypes causing 70-100% of all cervical cancers worldwide [5-6].

HPVs can infect the cutaneous and mucosal epithelium. HPV infects epithelial cells that undergo terminal differentiation and so encode multiple mechanisms to override the normal regulation of differentiation to produce progeny virions. Two viral oncoproteins, E6 and E7, alter cell cycle control by inactivating the two tumour suppressor proteins, p53 and Rb, thus leading to carcinogenesis [7-8]. Recent data suggest that E6 and E7 also play a major role in the inhibition of the host cell innate immune response to HPV [7].

The evidence collected over the last three decades suggests that HPV-associated malignant disease is rising despite the falling incidence in aetiological factors such as smoking. Whilst the role of HPV in uterine cervix cancers has been established, there is growing evidence for its role in the aetiopathogenesis of cancers involving other systems. In the United Kingdom an immunisation programme against HPV has commenced aimed at adolescent females [9]. This review aims to establish the incidence of HPV-associated cancers outwith the uterine cervix and discuss whether the evidence supports global immunisation against HPV.

Methodology

Search strategy

Published articles were identified by an electronic search of the Medline (1962 to April 2011), Embase (1988 to April 2011),

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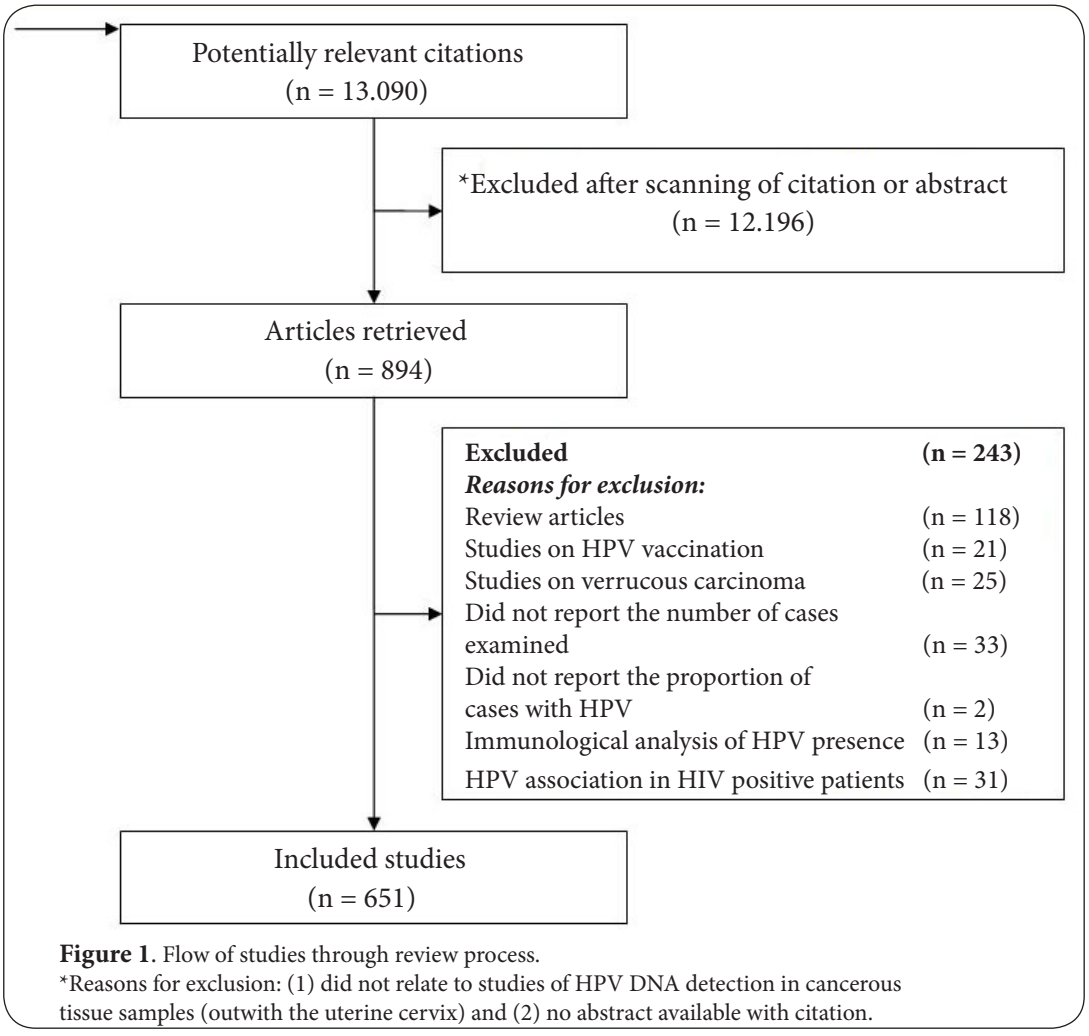

Figure 1. Flow of studies through review process.
*Reasons for exclusion: (1) did not relate to studies of HPV DNA detection in cancerous tissue samples (outwith the uterine cervix) and (2) no abstract available with citation.

and Cochrane Library (to April 2011). Combinations of MeSH terms and text words were used including: 'HPV in cancer' or 'HPV in benign disease' or 'HPV in precancerous lesions'. The search included all articles published in the English language. The search results yielded 13.090 papers. This was refined using each of the following keywords: head and neck, larynx, pharynx, oral cavity, oropharyngeal, nasopharynx, sinonasal, hypopharynx, oesophagus, trachea, lungs, heart, kidney, liver, pancreas, gall bladder, colorectal, skin, urinary bladder, prostate, genital tract, ano-rectal, vagina, penile and vulvar. Bibliographies and references of included studies were also searched.

Study selection

A shortlist of all publications was achieved by two authors (MSM & RAC). All abstracts were reviewed independently by these two authors and a refined list of publications was created and full articles were retrieved for detailed analysis and data extraction. All publications based on appropriate studies were included using specific inclusion and exclusion criteria. Publications deemed suitable based on the inclusion criteria were subjected to a further systematic examination and analysis for suitability by two authors (MSM & RAC). If no consensus was achieved, studies were assessed by the senior author (SM).

Inclusion criteria

- Studies that included assessment of the HPV DNA positiv ity in tissue samples.
- Studies involving subjects with squamous cell carcinoma or adenocarcinoma.
- Case-series analysis (retrospective or prospective).
- Case-control or cohort studies.

Exclusion criteria

- HPV DNA detection in verrucous carcinoma.
- Immunological analysis of HPV presence.
- HPV association in HIV positive patients.
- Review articles on HPV association in carcinoma.
- Studies on precancerous or benign lesions.

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Table 1.Characteristics of the selected studies.

		Number of studies (%)
All studies		651
Study Type	Case-Series	482 (74)
	Case-Control	167 (26)
	Other	2 (0.3)
Cancer Type	Head & Neck	338 (52)
	GI Tract	149 (23)
	Bronchopulmonary	48 (7)
	Bladder Cancer	47 (7)
	Anal / Colorectal	38 (6)
	Prostate Cancer	26 (4)
	*Genital	5 (1)
Study Year	Pre-1994	92 (14)
	1995-1999	154 (24)
	2000-2004	153 (24)
	Post-2005	252 (39)
Country setting	Europe	249 (38)
	Asia	214 (33)
	N America	117 (18)
	C or S America	36 (6)
	Africa	25 (4)
	Australasia	8 (1)
HPV Detection Method	PCR (+ other tests)	542 (83)
	ISH +/- ICH	97 (15)
	Southern Blot	12 (2)
HPV Genotype	Oncogenic (16/18 only)	577 (94)
	Oncogenic (16/18/31/33/35/51)	18 (3)
	Mixed (6/11/16/18/31/33/35)	17 (3)

ISH: In-situ hybridisation techniques. ICH: Immunohistochemistry.
*Two recent systematic reviews on male and female genital cancers exist; current review only includes most recent studies.

- Papers without abstracts.

Quality assessment of studies

There is currently no formally accepted method for quality assessment of observational studies. We have performed a quality assessment of the included case series studies using a methodological tool previously used for clinical guidelines issued by the National Institute for Clinical Excellence [10]. For case control or cohort studies, we used the Newcastle-Ottawa Scale used for the quality assessment of non-randomised studies [11]. The assessment tools were applied by two independent reviewers (MSM & RAC).

Data extraction

All abstracts were reviewed and a refined list of publications was created and full articles were retrieved for detailed analysis and data extraction. Where not stated in the articles, results were calculated where possible from the given data. Where available, information on the incidence of relevant cancers was obtained from the World Health Organisation (WHO) figures (WHO Cancer Report 2008) [12]. Results presented according to the study type and specific findings. Due to journal limitations on the permitted quotable references and the large number of publications on the subject, we have only listed those references that are most relevant to the specific objective of our paper. However we are happy to provide the full reference list used in our analysis on request.

Statistical analysis

All statistical analysis conducted by one author (CM). We summarised study characteristics as proportions and compared groups using the chi-squared test across the following explanatory variables: study methodological type; type of cancer site; study year; country setting; HPV detection type and HPV genotype. Median values and inter-quartile ranges (IQR) were reported for characteristics due to the skewed nature of the underlying distributions.

Results

The search strategy initially identified 13,090 potential citation with 894 articles extracted for consideration (**Figure 1**).

One-hundred and eighteen review articles were excluded from primary analysis. There were 21 studies which reported on HPV immunisation and 25 on verrucous carcinoma which were also excluded. Thirty-one studies were in HIV positive populations and 13 others used immunological analysis for the presence of HPV and so were excluded. Of the remaining studies 33 did not report the number of cases examined and a further 2 did not report the proportion of cases with HPV so these were also excluded, leaving 651 studies.

Description of studies

The median number of patients per study was 104 (IQR 60-132) and these were performed in 53 different countries with 5 studies across multiple countries. Almost three-quarters of the studies were case series reports with head and neck (52%) and gastro-intestinal (GI) tract (23%) the most common cancer type. The number of studies reporting on HPV is increasing and studies are conducted across the world. Polymerase Chain Reaction (PCR) assays either alone or in combination with other tests were used in the majority of studies (83%) with HPV genotype 16/18 the most commonly sought target (see **Table 1**).

Incidence of HPV by Cancer type

The studies were grouped into 7 different cancer types (by anatomic region) with the number of subjects and HPV prevalence reported (see **Table 2**). The median prevalence of HPV was 31% (IQR 15.7-50%). This varied considerably by cancer type with the median prevalence for bladder cancer of 12% (IQR 0-34.8%) compared to that for anal or colorectal cancers at 61.5% (IQR 40-82%). Head & neck cancers had the largest number of studies and reported a median prevalence of 33.3% (IQR 20-50%) with GI tract the next largest set of studies with a median prevalence of 30.1% (IQR 10-56.1%).

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Table 2. Number of subjects and prevalence of HPV by cancer type.

		No. studies	No subjects (Median, IQR)	HPV Prevalence (Median, IQR)
All cancers	All Studies	651	104 (60-132)	31% (15.7-50)
	Studies n>=50	517 (79%)	116 (90-139)	31.1% (15-50)
Head & Neck	All Studies	338	104 (60-136)	33.3% (20-50)
	Studies n>=50	268 (79%)	119 (92-142)	33.15% (20.3-50)
GI Tract	All Studies	149	100 (49-125)	30.1 (11.5-54.5)
	Studies n>=50	109 (73%)	113 (93-137)	33% (10-56.1)
Bronchopulmonary	All Studies	48	104 (66-120.5)	19.5% (6.85-44.05)
	Studies n>=50	40 (83%)	110 (96-125)	18% (5.85-43.1)
Bladder Cancer	All Studies	47	106 (60-134)	12% (0-34.8)
	Studies n>=50	38 (81%)	118.5 (73-148)	15.35% (2.5-36.5)
Anal / Colorectal	All Studies	38	106 (60-128)	61.5% (40-82)
	Studies n>=50	34 (89%)	112.5 (82-129)	67% (42-82.1)
Prostate Cancer	All Studies	26	111.5 (75-130)	13.5 (0-41)
	Studies n>=50	23 (88%)	112 (89-131)	14 (0-41)
Genital**	All Studies	5	118 (67-152)	31% (31-55.1)

**All studies had 50 or more subjects.

Table 3. Number of subjects and prevalence of HPV for Head & Neck cancer by study characteristics.

		No. studies (%)	No subjects (Median, IQR)	HPV Prevalence (Median, IQR)
All studies		338	104 (60-136)	33.3% (20-50)
Study Type	Case-Series	269 (80)	106 (66-136)	32.4% (20-50)
	Case-Control	68 (20)	91.5 (59-135)	36% (21.9-49.75)
	Other	1 (0.3)	139	38%
Study Year	Pre-1994	36 (11)	78 (44-116)	23.75% (11-50)
	1995-1999	71 (21)	108 (82-142)	26% (20-45.6)
	2000-2004	93 (28)	102 (62-136)	36.4% (21-50)
	Post-2005	138 (41)	113 (60-141)	36% (25-57)
Country setting	Europe	144 (43)	112 (73-140)	35.6 (22.35-50)
	Asia	85 (25)	104 (60-135)	33.6% (19-58.8)
	N America	75 (22)	100 (63-127)	26.1% (20-50)
	C or S America	21 (6)	117 (44-124)	37.3 (21.5-48.5)
	Africa	7 (2)	60 (34-136)	17.3% (2-60)
	Australasia	4 (1)	71 (54-103.5)	39.5% (24.75-42)
HPV Detection	PCR (+ other tests)	301 (89)	104 (60-137)	33.3% (21-50)
Method	ISH and / or ICH	33 (10)	93 (70-135)	38.8% (16.4-54)
	Southern Blot	4 (1)	88 (40.5-131.5)	30% (5-52.25)
HPV Genotype	Oncogenic (16/18 only)	331 (98)	104 (60-137)	33.3% (21-50)
	Oncogenic (16/18/31/33/35/51 combination)	2 (1)	121.5 (107-136)	11.3% (2.6-20)
	Mixed (6/11/16/18/31/33/35)	4 (1)	130.5 (68.5-135.5)	45.2% (25.2-75)

Repeating the descriptive analysis but restricting the studies to only those with greater than 50 subjects showed minimal differences both in overall HPV prevalence and by cancer type (see **Table 2**).

Description of head & neck HPV

The 338 studies on head & neck cancer were described in greater detail (see **Table 3**). The majority were case-series studies but there was little difference in HPV prevalence between these and the case-control studies (36% vs 32.4%). HPV prevalence has increased based on year of study publication rising from 23.75% to 36% for the most recent studies. The median HPV prevalence by continent was similar for Europe, Asia, Central or South America and Australasia but lower in North America and especially in Africa.

There was little difference in HPV prevalence by method of detection but testing for HPV oncogenic genotypes 16/18/31/33/35/51 combinations had an 11% median prevalence compared to 33.3% for testing for oncogenic 16/18 only.

Discussion

Our study has shown that there is a large and increasing body of work looking at HPV prevalence across a range of different

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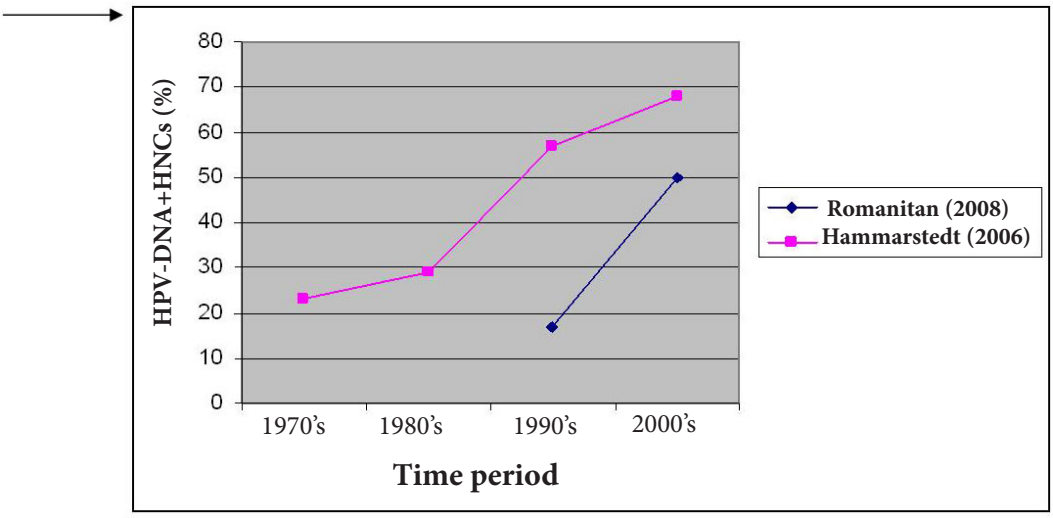

Figure 2. Time-series studies showing a dramatic increase in HPV-positive cancers from 1970s to 2000s. Both studies analysed only tonsillar carcinoma specimen by PCR method. [21-22] *HNCs: Head & neck cancers. Graphs plotted from the given data in the articles for comparison and illustration.*

cancers, although head & neck cancers are the most commonly studied as might be expected. The reported HPV prevalence in these studies is high overall at almost 1 in 3 patients but does vary according to type of cancer. HPV prevalence would seem to be increasing based on the year of publication with a 12% rise from papers pre 1994 to post 2005 reporting on head and neck cancer.

Strengths & Weaknesses of the study

As our study clearly demonstrates, oncogenic HPV DNA has been detected in malignant tissue samples from a multitude of anatomical subsites except the heart and the kidney [3]. There is however wide variation in HPV DNA detection rates in malignant tissue from the same subsite across the published literature. Notable factors include geography, the study population type and DNA detection methods employed, with PCR being the most sensitive. To minimise the variables we only included studies where DNA detection methods were used. Studies based on immunological and immunohistochemical analysis of HPV presence were excluded as the sensitivity of such methods is low [13]. For the purposes of this study we also excluded publications on the malignant condition, verrucous carcinoma, as the disease process is very slow behaving more like a benign process and to its rarity. Studies on immunosuppressed patients for example those infected with the Human Immunodeficiency Virus were excluded to keep the study population as uniform as possible.

Our finding that the published HPV prevalence is rising, is supported by a dramatic increase in incidence of oncogenic HPV-associated cancers, particularly in younger adults with history of no smoking and relatively low alcohol intake, which has been attributed to changing sexual behaviours by many authors [14-19]. During their lifetime, about 75% of sexually active individuals will be exposed to HPV [20]. **Figure 2** summarises graphically the data published by Romanitan et al., (2008) and Hammerstedt et al., (2006), clearly demonstrates increasing incidence in HPV-positive cancers related to the head and neck region [21-22]. This has been paralleled by a decreasing incidence in HPV-unrelated (head & neck) cancers. Chaturvedi et al., (2008) too have clearly demonstrated these two phenomena in their study of HPV-related (n=17.625) and HPV-unrelated (n=28.144) oropharynx cancers over the 1973-2004 period [23]. HPV-associated cancers represent a distinct subgroup of tumours with distinct aetiology and biology, such as increased sensitivity to radiotherapy and significantly better prognosis as compared with HPV-unrelated cancers [24].

Clinical implications

Most HPV is spread by sexual contact. In a study looking at a college-aged population, it was found that once sexual activity was initiated, even without intromissive intercourse, the incidence of infection increased over time [25]. Therefore, proscribing sexual contact could reduce HPV transmission but this is not a realistic objective.

Cervical screening programmes exist in the USA, UK and other developed countries to identify and treat cancerous and precancerous cervical lesions. Until recently, no highly effective primary prevention strategy to reduce the risk of HPV associated diseases existed. However, a quadrivalent HPV vaccine, which protects against the most frequently implicated oncogenic and benign HPV genotypes (HPV 6, 11, 16, and 18), is now available. In addition, a bivalent HPV vaccine that protects against oncogenic HPV genotypes 16 and 18 is also available. The vaccine is composed of HPVL1-capsid protein virus-like particles, which are not live; they contain no viral DNA, so they are neither infectious nor oncogenic [26]. Results

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of recent studies among women not previously infected with vaccine-type HPV genotypes appear to show prophylactic HPV immunisation to be highly efficacious (90-100%) in preventing HPV infection and premalignant gynaecological diseases [27]. Evidence for disease regression in premalignant/dysplastic cervical disease has also been observed with the use of the vaccine [27].

Our assessment that 1 in 3 cancers are HPV-associated can be interpolated to 2.12 million cancers annually worldwide (range 1.0–3.2 million) based on the WHO annual figures of all cancers. This is an estimation based on the median detection rate for all non-cervical cancers corresponding to available studies and takes into account that all cervical cancers are HPV-associated. This compares to tuberculosis, a disease with an active global immunisation programme, which can also affect multiple anatomical subsites and with an annual incidence of 9.27 million new cases [28]. These figures could support a global immunisation programme for HPV.

What needs to be established however is whether intervention by way of immunisation results in a corresponding reduction in HPV-associated malignant and premalignant diseases outwith the uterine cervix. The acquisition of data to prove this will take years. One suggestion would be to study the response of HPV-proven dysplastic lesions in multiple accessible subsites such as the oral cavity to immunisation. If the data acquired is as was demonstrated in cervical cancer [27] the authors firmly believe that this will lead to a "tipping-point" of evidence that could justify the reasoning for a global immunisation programme against HPV-associated diseases. Further research is vital.

While the current incidence figures may support a global immunisation programme and were future research to show a favourable tissue response to the vaccine, the authors still acknowledge that the distribution of HPV-associated cancers by anatomical subsite is variable world-wide. For example, oral malignancies are more common in the Far East than in the Western world but the incidence of other HPV-associated cancers in the Far East may be lower. In short the question is whether the HPV-associated malignant and premalignant diseases overall for a certain country or region justifies the institution of an immunisation programme. Individual health boards may choose to establish local incidence figures before embarking upon an immunisation programme.

HPV association in benign and pre-cancerous disease

Lastly, whilst this paper sets to establish the evidence from the perspective of HPV-associated cancers, it must be noted that there are important benign and precancerous diseases exhibiting HPV association. They include leukoplakia, lichen planus and RRP. The findings are discussed here as it lends further support to the idea of a global immunisation programme against HPV. The strongest association is noted with RRP (50-100%) with HPV 6 and 11 being the predominant genotypes detected [29]. The proportions of HPV positive leukoplakia and lichen planus range from 14.8-80% and 0-75%, respectively [30-31].

Conclusions

If we were to not consider HPV-associated malignant disease as a disease of single anatomical subsites, but to consider it as a disease of the entire human body, the current available evidence on incidence arguably supports a global immunisation programme. Further studies to establish favourable HPV-infected tissue response to HPV immunisation both *in vitro* and *in vivo* is vital and the evidence available now certainly justifies this process.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Authors' contributions	MSM	CM	RAC	REM	SM
Research concept and design	√	--	√	--	√
Collection and/or assembly of data	√	--	--	--	√
Data analysis and interpretation	√	√	√	--	√
Writing the article	√	--	--	--	--
Critical revision of the article	--	√	--	√	√
Final approval of article	√	√	√	√	√
Statistical analysis	--	√	--	--	--
Other (please specify)……	--	--	--	--	--

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