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HPV infection by anatomical site among Greek men and women: A systematic review

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Abstract

Objectives—We systematically reviewed the literature on anal, penile, cervical, and oropharyngeal HPV infection in Greece to provide a comprehensive overview of HPV prevalence and to explore the reporting of HPV in Greek men and women.

Methods—A total of 5 databases, including PubMed and Scopus, were searched up until January 1st, 2015 for studies looking at HPV prevalence, incidence, or risk factors by anatomical site.

Results—We identified 50 eligible studies for inclusion. The majority of them were cervical studies (n=26) followed by head and neck studies (n=13) with only two studies exclusively focusing on anal sites and two at penile sites. The remaining studies examined prevalence from multiple sites. Most studies looked at small, high-risk populations and HPV prevalence ranged from 2.5%–43.4% for cervical studies; 0%–91% for head and neck studies; 54.6%–78.4% for anal studies and 20.3%–66.7% for penile studies. Age, smoking, and number of sexual partners were commonly assessed risk factors.

Conclusion—There were significant gender and anatomic site disparities in the reporting of HPV prevalence. Given the relationship between HPV infection and the increasing incidence of anal cancer in men, more research is needed to reveal the prevalence of HPV at these sites in Greek men especially given reports of the declining health of the Greek population.

Keywords

HPV; Greece; anal; cervical; penile; oropharyngeal; prevalence; men; women

Introduction

Human papillomavirus (HPV) has more than 100 subtypes identified to date, with subtypes classified into low-risk types (e.g. HPV 6, 11, 42) that are implicated in anogenital warts in

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both males and females and high-risk types (e.g. HPV 16, 18, 31) that have been linked to cervical cancer and other cancers (CDC, 2014; Muñoz et al., 2003). Because of the high prevalence of human papillomavirus and its association with cervical cancer, there have been numerous studies in Greece focusing on HPV prevalence and risk factors in women. However, growing evidence suggests that HPV can also cause significant disease in men. Not only are HPV positive men able to transmit the virus to their female sexual partners, but HPV has also been implicated in oropharyngeal cancers, anal cancers, and penile cancer in men (Kreimer et al., 2005; Moscicki & Palefsky, 2011; Nyitray et al., 2014). The role of HPV in these cancers is especially significant in high-risk populations, including HIV-positive persons or men who have sex with men (MSM) (Backes et al., 2009; Hoots et al., 2009). Previous epidemiologic studies have demonstrated a high prevalence of the virus (>12.4%) among low-risk men and an even greater prevalence among high-risk men (30.9%) (Dunne et al., 2006; Hebnnes et al., 2014).

Examining HPV in both women and men in Greece is crucial at this point in time for several reasons. First, the rate of smoking in Greece is one of the highest in Europe (~40%). Studies have found a correlation between smoking and HPV positivity, which may impact the development of dysplasia and cancer following infection (Antonsson et al., 2014; Kjellberg et al., 2000; Roura et al., 2014). Second, the recent economic crisis in Greece has resulted in a 50% increase in the incidence rate of HIV infections from 2010 to 2011 (Ifanti et al., 2013). Overall, the economic crisis has also resulted in a significant increase in the number of people below the poverty line and those reporting severe material deprivation (HS, 2013). Recent data suggests increased rates of homelessness are associated not just with increased HIV risk among injecting drug users, but also increased STI risk in general (HS, 2013; Tsang et al., 2015). This economic stress could jeopardize decision-making or access to STI preventative measures among Greek men and women, especially since condom use has been linked to a reduction in risk of HPV infection (Pierce Campbell et al., 2013).

For these reasons, we systematically reviewed the literature to identify all articles that have looked at HPV prevalence at cervical, anal, penile, vaginal and oropharyngeal sites where the gender of participants is reported. To our knowledge there has been no previous systematic review of HPV epidemiology in Greece, in contrast with other European countries and the Americas where there are several systematic reviews (Anderson et al., 2013; Giorgi Rossi et al., 2012; Stier et al., 2015). The objectives of this paper are to determine the extent to which previous studies have looked at HPV prevalence in men, to evaluate potential risk factors prevalent in the Greek population, and to provide a comprehensive summary of the current information available on HPV in Greece. We expect to find underreporting of HPV prevalence in Greek men, especially high-risk men. As the majority of studies included in this review were published before the beginning of the economic crisis, its findings serve as a benchmark upon which future epidemiologic and interventional studies can build to limit HPV transmission among Greek men and women.

Methods

We used the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines for this systematic review (Moher et al., 2010). The purpose of the PRISMA guideline is to ensure the high quality of systematic reviews and meta-analyses.

Data sources

The database search was completed up to January 1st, 2015 and the following databases were included: PubMed, Scopus, Web of Science, CINAHL and Cochrane (Figure 1). The detailed search strategy that was used for the PubMed database can be found in Appendix A of this review. Similar search strategies were used for other databases.

Study Selection and Data Abstraction

The following were the criteria for study inclusion:

1. Population included a specific Greek or Greek-Cypriot subset
2. Anal, cervical, penile, vaginal, or oropharyngeal HPV infection with risk, incidence, and/or prevalence defined as outcome variables in symptomatic and/or asymptomatic individuals
3. Gender of study participants was reported in manuscript
4. Reporting was quantitative and was conducted in part or in whole in Greece
5. Publication as a full manuscript in English or Greek

Since we were interested in extracting data on HPV prevalence in the Greek population, we only included studies that reported quantitative data. Moreover we excluded studies that did not report the gender of study participants because we were interested in assessing the availability of data on HPV by gender. We did not exclude studies on the basis of date of publication.

After conducting the search and retrieving the articles, two reviewers (S.T., L.H.) independently reviewed the title and abstract of each study to determine if the inclusion criteria were met and scored the study as “Include”, “Do not include” or “Uncertain”. For the studies that were marked as “Uncertain”, the reviewers identified the source of the uncertainty and reviewed the entire article to make a final determination of eligibility (Figure 1). Senior authors (A.K., J.S.) reviewed a subset of articles and differences in decisions around inclusion were resolved as a group. The two reviewers then read through all the studies marked for inclusion and excluded those that did not meet the inclusion criteria upon full text review. The following data were abstracted: date of publication, location, study type, number tested, gender distribution, age distribution, sampling location (cervical, anal etc.), subtype-specific HPV prevalence, and any risk factors assessed.

The studies were then separated based on the location of sampling into cervical, anal, penile, and oropharyngeal and analyzed separately to determine the range of HPV prevalence reported at these sites for both symptomatic and asymptomatic subjects in Greece. Risk

factors reported by individual studies were also analyzed in aggregate to determine the most common risk factors for HPV infection.

Quality assessment

Two reviewers (S.T., L.H.) independently went through each article that was to be included in this review and scored them according to a modified risk of bias tool that has been previously reported for assessing bias in systematic reviews of prevalence studies (Hoy et al., 2012) (Table B-1). The modified risk of bias tool includes 10 items that address four domains of bias in studies and a summary risk of bias assessment (Hoy, et al., 2012). The questions are designed to determine internal validity (5 questions) and external validity (5 questions). After each reviewer scored the articles, the inter-rater agreement was calculated and found to indicate substantial agreement ($k=0.635$). A linear regression was performed to determine trends in quality over time. The reviewers discussed any differences in ratings and arrived at a consensus (Table B-2). Moreover, a third reviewer (J.S.) re-scored 10% of the articles for purposes of quality assurance. All statistical analyses were performed using STATA Version 13.0.

Results

Overall study characteristics and quality

Our search identified 72 articles that potentially met the inclusion criteria. After reading through the full-text of each article, a total of 50 articles were selected for final inclusion (Figure 1). A large proportion of the studies were cross-sectional studies ($n=24$) that were completed at a single hospital or outpatient clinic in Greece. Only 3 studies were case-control studies and the remaining were either retrospective sample testing or diagnostic studies. Studies generally did not employ a random sampling method, but rather they consecutively sampled patients attending a particular clinic during a given time period, or enrolled participants based on availability of archived biopsied tissues. Moreover, the average risk of bias score for the studies was 6.6 out of 10 indicating that the overall quality for the studies was low. Based on linear regression analysis there was a strong, albeit not statistically significant, trend of increasing quality over time ($r=0.238$, $p=0.089$).

The majority of the studies investigated HPV prevalence in specific groups that cannot be generalized to the larger Greek population. In particular, only 7 studies included representative screening populations at multiple sites but most of these were done in women. Moreover, we found that there are a limited number of studies looking exclusively at HPV in men. We identified 2 studies including only men in their sample compared to 30 studies including only women. The remaining studies included both sexes. Interestingly, out of all the studies that included men ($n=20$), only 2 studies specifically reported the distribution of MSM in their population and a single study reported HPV prevalence separately for HIV positive and HIV negative men (Gomousa-Michael et al., 2000; Hadjivassiliou et al., 2007; Mavrogianni et al., 2011). All three of these studies restricted their samples to the anogenital area.

HPV Prevalence at cervical sites

We identified 30 studies looking at cervical HPV prevalence in our review and the majority of them (n=26) sampled exclusively from a cervical site (Tables 1, 4). In addition to numerous smaller studies of specific populations, nine large studies including at least 1000 patients have been done in Greece (Agorastos et al., 2014; Agorastos et al., 2004; Agorastos et al., 2009; Argyri, Papaspyridakos, et al., 2013; Diamantopoulou et al., 2013; Panotopoulou et al., 2007; Spathis et al., 2012; Tsiodras et al., 2010; Tsiodras et al., 2011). Six of these larger studies report HPV prevalence rates that range from 15.7% to 43.4% (Argyri et al., 2013; Diamantopoulou, et al., 2013; Panotopoulou, et al., 2007; Spathis, et al., 2012; Tsiodras, et al., 2010; Tsiodras, et al., 2011). The remaining three studies report HPV prevalence rates among asymptomatic women ranging from 2.5–5.9% (Agorastos, et al., 2014; Agorastos, et al., 2004; Agorastos, et al., 2009). While some of them were done at a single hospital or clinic, five of them drew their sample populations from multiple geographic locations (Agorastos, et al., 2014; Agorastos, et al., 2004; Agorastos, et al., 2009; Spathis, et al., 2012; Tsiodras, et al., 2011).

Earlier studies found that the most prevalent HPV strains were typically 16, 6, 11, and 18 which is consistent with prior studies on HPV and the strains included in current HPV vaccines (Agorastos et al., 1995; Diakomanolis et al., 2001; Dokianakis et al., 1999; Hassan et al., 2001; Koffa et al., 1995; Konidaris et al., 2007; Kroupis et al., 2007; Labropoulou et al., 1996; Lambropoulos et al., 1994; Malamou-Mitsi V., 2002; Prokopakis et al., 2002). However, more recent large studies using more comprehensive typing methods have demonstrated a high prevalence of such strains as 53, 31, 42, 41, 51, 59, and 35 (Agorastos, et al., 2014; Agorastos, et al., 2009; Argyri, et al., 2013; Argyri, et al., 2013; Michala et al., 2012; Papachristou et al., 2009; Stamataki et al., 2010).

Common risk factors assessed by the various studies included age, number of sexual partners, age of sexual debut, income level, and smoking status. The one relationship that remained consistent and significant across studies was the relationship between age and HPV prevalence. Multiple studies found that HPV prevalence was highest in younger women, with prevalence rates declining with increasing age (Agorastos, et al., 1995; Agorastos, et al., 2004; Agorastos, et al., 2009; Argyri, et al., 2013; Argyri, et al., 2013; Kroupis, et al., 2007; Papachristou, et al., 2009; Stamataki, et al., 2010; Tsiodras, et al., 2010; Tsiodras, et al., 2011). Other studies found that multiple sexual partners increased HPV risk (Konidaris, et al., 2007; Michala, et al., 2012; Stamataki, et al., 2010; Tsiodras, et al., 2011). Lastly, smoking, a factor found to be associated with the development of cervical cancer in previous studies, was found to be significantly associated with HPV in only two studies included in this review (Kjellberg, et al., 2000; Konidaris, et al., 2007; Michala, et al., 2012; Roura, et al., 2014).

HPV Prevalence at Head and Neck sites

We identified a total of 13 studies in our systematic review that examined head and neck sites (Table 2). Specific anatomic locations included oral mucosa (n=7), esophagus (n=2), larynx (n=2), adenoids/tonsils (n=2), and parotids (n=1) (Aggelopoulou et al., 1999; Blioumi et al., 2014; Bouda et al., 2000; Gorgoulis et al., 1999; Kouvousi, et al., 2013; Lambropoulos

et al., 1997; Laskaris et al., 2014; Lyronis I., 2005; Lyronis, et al., 2008; Mammas, et al. 2012; Mammas, et al., 2006; Tsimplaki et al., 2014; Vageli, et al., 2007). Only 5 studies included asymptomatic patients (Blioumi, et al., 2014; Bouda, et al., 2000; Lambropoulos, et al., 1997; Lyronis I., 2005; Lyronis, et al., 2008). The remaining studies focused on testing patients with dysplasia, hyperplasia or cancer. The number of participants ranged from 9 to 258 patients, but was generally limited. Overall, for adult asymptomatic patients, the HPV prevalence at oral sites ranged from 0% to 56% while for adult symptomatic patients it ranged from 11.3% to 91%. The only study that included an asymptomatic screening population found an HPV prevalence rate of 9.5% (Lambropoulos, et al., 1997). This particular study had a low risk of bias and included a wide age range of patients. Moreover, two studies specifically enrolled children (ages 2–14) with tonsillar/adenoid hyperplasia and found prevalence rates of 8.5% and 8.4% (Mammas, et al., 2012; Mammas, et al., 2006). Interestingly, six studies reported HPV prevalence separately for men and women (Blioumi, et al., 2014; Bouda, et al., 2000; Laskaris, et al., 2014; Lyronis, et al., 2008; Mammas, et al., 2006; Tsimplaki, et al., 2014). In all of these studies, with the exception of one, women had a higher HPV prevalence than men (Bouda, et al., 2000).

The oropharyngeal studies also identified several risk factors including age, heavy smoking, and alcohol use. The two studies which specifically enrolled children found that younger age correlated to HPV infection (Mammas, et al., 2012; Mammas, et al., 2006). This same result was also found by another adult study, which examined specimens from patients with oral malignancies and/or dysplasia (Blioumi, et al., 2014). These results seem to conflict with the study that included the asymptomatic screening population and which found that increasing age correlated with higher prevalence (Lambropoulos, et al., 1997). However, this study only looked at asymptomatic patients and hence HPV-age correlation could differ between patients who are asymptomatic and patients who have abnormal cytology. Three studies also found a significant correlation between HPV infection and smoking (Bouda, et al., 2000; Gorgoulis, et al., 1999; Laskaris, et al., 2014). The major HPV subtypes found in head and neck sites were 6, 16, and 18. However, many studies used techniques that are not able to identify all subtypes, hence there may be missing data on the actual type specific distribution of HPV at these sites (Table 2).

HPV Prevalence at anal sites

To our knowledge only four studies on the prevalence of HPV in anal or perianal sites have been done in Greece at this point in time (Tables 3,4) (Alexandrou et al., 2014; Labropoulou, et al., 1994; Mavrogianni, et al., 2011; Valari et al., 2011). One study enrolled patients with perianal warts and included a high-risk population (Mavrogianni, et al., 2011). The overall prevalence was found to be 78.4%, which is much higher than that reported by other studies in Europe and the United States (Dunne, et al., 2006). The study also reported that MSM with perianal warts were more likely to develop intranal warts compared to non-MSM. Another study that was of particular interest looked at women with suspected cervical, vulvar, or vaginal HPV related pathology and studied HPV positivity at both cervical and anal sites (Valari, et al., 2011). They found that cervical pathology was associated with anal HPV infection and concluded that women with abnormal colposcopy findings may also be at risk for anal malignancies.

HPV Prevalence at penile sites

A total of five studies investigated the prevalence of penile HPV in Greek men (Tables 3,4) (Gomousa-Michael et al., 1997; Gomousa-Michael, et al., 2000; Hadjivassiliou, et al., 2007; Labropoulou, et al., 1994; Yapijakis, et al., 2008). One study, which looked at men visiting a dermatologist for penile lesions, stratified its subjects on the basis of HIV status and it was the only one to do so from all the studies included in this systematic review (Gomousa-Michael, et al., 2000). HPV prevalence was higher in HIV positive men compared to HIV negative men (66.7% vs. 50%). A second study included a larger population of 550 men with genital warts and 64 asymptomatic men with HPV positive female partners (Hadjivassiliou, et al., 2007). The reported prevalence rate was higher (50.9%) for the patients with genital warts than it was for the asymptomatic patients (20.3%). The study included 56 MSM subjects who were found to be more likely to be HPV positive compared to non-MSM ($p<0.001$) (Hadjivassiliou, et al., 2007). Another study in this category enrolled high-risk women and their male sexual partners who had abnormal urethral cytology (Gomousa-Michael, et al., 1997). The sites sampled include the penile urethra for men and the cervix for women. The study reported there was a synchronous HPV infection in 50% of sexual partners indicating that HPV positivity may be transferred between partners (Gomousa-Michael, et al., 1997).

HPV prevalence at vaginal/vulvar sites

Two studies looked at women with vaginal and/or vulvar intraepithelial neoplasia or cancer (Tables 3,4) (Anastasiadis et al., 2000; Tsimplaki et al., 2012). Both studies were limited because of the small and non-random population, as well as the fact that HPV testing methods were not documented in the paper. Hence we are not confident in the prevalence rates reported. Only one of these studies looked at age as an independent risk factor for HPV infection and found that younger women with vulvar or vaginal neoplasia were at a higher risk for HPV infection (Tsimplaki, et al., 2012).

Discussion

Although HPV has typically been associated with cervical cancer and disease in women, emerging evidence has revealed the importance of HPV in other cancers in both genders. A recent systematic review on HPV in head and neck cancer in Europe found that the prevalence of the virus in patients with relevant cancers was 40% (Abogunrin, et al., 2014). This represents a serious burden of disease, but also an opportunity for prevention. With the availability of a vaccine against HPV, it is possible to screen for and prevent HPV related cancers at multiple anatomic sites.

Over half of the studies in this review investigated HPV prevalence in women at cervical sites alone (26/50), with 4 additional studies looking at cervical HPV prevalence as one of multiple anatomical sites. Therefore, the body of research on cervical HPV prevalence in Greece is well developed. Many of the large studies have found HPV prevalence rates among women to be quite high, ranging from 15.7% to 43.4% (Table 1). However, studies done by Agorastos et. al report prevalence rates among women at a much lower rate, ranging from 2.5% to 5.9% (Agorastos, et al., 2014; Agorastos, et al., 2004; Agorastos, et al., 2009).

These studies tended to draw from multiple sites across a wide range of geographic locations, as opposed to a single large site or sites exclusively in Athens. This may provide a better representation of HPV prevalence amongst the general population of Greek women.

The development of technologies that allow a wider range of HPV strains to be typed has been significant. More recent studies have revealed high-risk strains, such as HPV types 31, 35, 51, and 59, present in the Greek population in addition to the well-known types 16 and 18. These additional high-risk types can also lead to the development of various cancers, and are not included in the HPV vaccines currently used by the Greek National Health program (Control, 2015; Muñoz, et al., 2003). More data on the prevalence of these less-studied high-risk types would help guide screening and vaccination policy for women in Greece.

What is needed moving forward, as noted by the LYSISTRATA study, is to further investigate attitudes towards HPV vaccination amongst Greek women in order to expand vaccination programs and continue to increase prevention of cervical cancer (Agorastos, et al., 2014). The LYSISTRATA study reported that fear of adverse side effects was likely a major cause of the current low HPV vaccination rates amongst Greek women (Agorastos, et al., 2014). No data is available on vaccine uptake nationwide, but a recent study amongst female post-secondary students found that only 25% were vaccinated despite the fact that the vaccine is provided free of charge. Of those, 85% reported insufficient information or fear of adverse side effects as the major reason for not vaccinating (Michail, 2014). More education on the HPV vaccine by both physicians and public health officials could serve to remedy this issue and lead to higher vaccine uptake amongst Greek women.

The remaining studies investigated HPV prevalence at a variety of anatomical sites in both men and women. Studies that investigated HPV prevalence at head and neck sites were the most numerous after cervical studies. Studying the epidemiology of HPV at these sites is particularly important given that previous studies have linked HPV infection to head and neck cancers (Kreimer, et al., 2005). However, there has only been one study in Greece with an asymptomatic screening population, and this study included a relatively small sample size (n=169) (Lambropoulos, et al., 1994). The remaining head and neck HPV studies were single center studies and focused on patients with head and neck cancers (Table 2). As a result, the findings of these studies cannot be generalized to the population at large. The same applies for studies looking at anal and penile sites in Greece, which enrolled patients with existing anal and/or penile lesions or cancer (Alexandrou, et al., 2014; Gomousa-Michael, et al., 1997; Gomousa-Michael, et al., 2000; Hadjivassiliou, et al., 2007; Labropoulou, et al., 1994; Mavrogianni, et al., 2011). An understanding of the epidemiology of HPV at these sites in asymptomatic individuals is needed in order to identify risk factors for infection and determine the cost-effectiveness of vaccination in the general population. Multi-center epidemiological studies investigating HPV prevalence at penile, anal, and head and neck sites should be conducted in order to fill this gap.

Overall, only 7 studies included samples from anal or penile areas in men, with only two of these looking exclusively at HPV prevalence in men (Gomousa-Michael, et al., 1997; Gomousa-Michael, et al., 2000; Hadjivassiliou, et al., 2007; Labropoulou, et al., 1994; Mavrogianni, et al., 2011; Valari, et al., 2011; Yapijakis, et al., 2008). In light of the recent

evidence supporting the role of HPV in cancers in men, there is an obvious gap in the data currently available on HPV prevalence in Greece (Dunne, et al., 2006; Hebnnes, et al., 2014). This is important since a meta-analysis looking specifically at men in Europe (including one study in Greece), found an overall HPV prevalence rate of 12.4% (Hebnnes, et al., 2014). Additionally, there is an even greater lack of knowledge on HPV prevalence in high-risk Greek men, such as MSM or HIV positive men. Such studies would be useful in making appropriate public health plans for preventing associated morbidity and mortality from anal, penile and oropharyngeal cancers in men.

As previously mentioned, several factors make this an important time to be examining HPV rates amongst both men and women in Greece. The high rates of smoking, recent economic crisis, and recent increase in HIV prevalence may all contribute to increased HPV risk (Antonsson, et al., 2014; HS, 2013; Ifanti, et al., 2013; Kjellberg, et al., 2000; Roura, et al., 2014). In the post-crisis era people are more likely to be at higher risk for acquiring STIs (Tsang, et al., 2015). In order to assess these risks and develop future HPV and cancer prevention programs, better data on HPV prevalence both amongst the highest risk populations and the general population is necessary.

Together, these factors highlight that it is critical to better understand the role of HPV in Greece. This systematic review has revealed that there are gaps in the reporting of HPV prevalence in Greece and we suggest that more research is needed on the prevalence of HPV in men at anal and penile sites. The current body of knowledge on HPV prevalence at oropharyngeal sites should also be expanded for both men and women. Filling these gaps will help inform public health programming and might aid in the detection and prevention of HPV-related cancers at oropharyngeal, anal, and penile sites. Moving forward, large, population-based studies of HPV prevalence at multiple anatomic sites are needed in order to accurately characterize HPV prevalence amongst men and women in Greece and develop appropriate public health programming to detect and prevent HPV related cancers.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Flowchart for selection of studies reporting HPV prevalence in Greece

Table 1

Studies reporting HPV prevalence in Greece from cervical sites (n=26)

Author, Year	Location and type of Study	Population	Age Range	Anatomical location of sample and sampling method	Methods of HPV detection	HPV Prevalence (% & fraction)	HPV types detected (In order of most prevalent to least)	Risk factors ^a	ROB Score
Lambrouopoulos et. al., 1994	Thessaloniki, Greece, Cross-sectional	Asymptomatic Greek Women (n=202)	17–45	Cervix, cytobrush scraping	PCR	41.8% (83/202)	16, 18, 16/18	None	5
Agorastos et. al., 1995	Thessaloniki, Greece Cross-sectional	Asymptomatic Greek Women (n=226)	20–55	Cervix, cytobrush scraping of endo and ecto-cervix	PCR, Dot-blot	36.3% (82/226)	16, 18	Age <35 (p=0.0095), rural residence (p=0.0038), IUD use (p=0.0319), history of PID (p=0.009976), frequent washing of the genitals (p=0.0319), and a history of atypical pap findings (p=0.0348)	8
Koffa et. al., 1995	Athens, Greece Retrospective study	Women with evidence of LSIL, CIN 1 or HPV (n=50)	NR	Cervix, cervical smear	Multiplex PCR	42% (21/50)	16, 11, 18, 33, 6/11	None	6
Labroupoulou et. al. 1996	Athens, Greece Retrospective study	Women with HSIL or invasive cancer (n=64)	18–46	Cervical	Southern blot hybridization and PCR	89% (57/64)	6, 11, 16, 18, 31, 33, 35, 39, 45, 51, unclassified	None	7
Dokianakis et. al., 1999	Athens, Greece Retrospective	Women with CIN III or carcinoma of the cervix (n=88)	NR	Cervix, cervical smears from lesions	Multiplex PCR	63% (55/88)	18, 16, 33, other	None	6
Diakomanolis et. al., 2001	Athens, Greece Cross-sectional	Adolescents referred to Colposcopic Unit for cytological or cervical abnormality (n=78)	15–20	Cervix, colposcopy directed biopsy	Not detailed	28.2% (22/78)	Not reported	No relationship between HPV and smoking or oral contraceptive use	6
Hassan et. al., 2001	Athens, Greece Cross-sectional	Adolescents referred to Colposcopic Unit for cytological or cervical abnormality (n=51)	15–20	Cervix, cytobrush smears	PCR	54.9% (28/51)	16, 18, 11, 31, 33, 16/18, 11/16, 11/31	None	8
Malamou-Mitsi et. al. 2002	Ioannina, Greece Retrospective	Greek women with LSIL, HSIL, or cytological evidence of HPV infection (n=42)	24–60	Cervix, PE tissue sample	PCR (QIAamp® procedure), RFLP	71.3% (30/42)	16, 31, 33, 56, 61, undetermined	None	6
Prokopakis et. al. 2002	Heraklion, Greece Retrospective	Greek women with cervicitis or intraepithelial neoplasia (n=47)	NR	Cervix, PE tissue sample	PCR-RFLP, multiplex PCR	36% (17/47)	18, 16	No relationship to smoking and alcohol consumption	6

Author, Year	Location and type of Study	Population	Age Range	Anatomical location of sample and sampling method	Methods of HPV detection	HPV Prevalence (% & fraction)	HPV types detected (In order of most prevalent to least)	Risk factors ^a	ROB Score
Agorastos et. al. 2004	Thessaloniki, Themi, Mihaniona, Corfu, Veria and Serres, Cross-sectional	Greek women attending outpatient gynecological clinics (n=1296)	17–67	Cervix, cytobrush sample	PCR-RLB	2.5% (32/1296)	16	Age<27 years, nulliparity	8
Konidaris et. al. 2007	Athens, Greece	Greek women with cervical cancer, other gynecological cancer and, benign dysplasias (n=195)	18–82	Cervix, tissue samples	ISH for typing of HPV 6, 11, 16, 18, 31, 33 and 51	51.8% (101/195)	6/11, 16/18, 16/18 & 31/33/51, 31/33/51., multiple types	Multiple sexual partners (p=0.06), smoking (p=0.0001)	7
Kroupis et. al. 2007	Athens, Greece Cross-sectional	Greek women with pre-neoplastic cervical lesions (n=841)	16–72	Cervix, ThinPrep Pap-test	PCR	60% (504/841)	16, 53, 6, 31, 51, other	Younger age (p=0.0001)	7
Panotopoulou et. al. 2007	Athens, Greece Case-control	Greek women with ASCUS, LSIL HSIL, or squamous cell cervical carcinoms n=997) and asymptomatic Greek women (n=639)	18–48	Cervix, cytobrush scraping	PCR	A: 24.60% (169/639) AC: 75.4% (752/997)	11, 18, 6, 16, 31, 33, multiple types	None	7
Mammas et. al. 2008	Larissa, & Heraklion, Greece Cross-sectional	Women from Greece (n=38) and Crete (n=37) with LSIL or HSIL	31–61	Cervix, colposcopy specimens	PCR	100% (75/75)	6, 18, other	None	7
Agorastos et. al. 2009	Multicenter Cross-sectional	Women from Greece (n=4139) attending outpatient gynecological clinics	20–59	Cervix, Digene brush scrapings	Hybrid Capture® 2, RFLP-PCR	5.9% (245/4139)	16, 53, 31, 35, 51, 18	Age 20–29	8
Papachristou et. al. 2009	4 clinics in Athens Greece, Cross-sectional	Asymptomatic Greek women (n=217) and women with ASCUS, LSIL, HSIL, or genital warts (n=103) attending gynecologic or infectious disease clinics in Athens	16–71	Cervix, Cervex brush scraping	Amplicor® HPV test, Linear Array HPV genotyping test	157/320 (49.1%)	6, 16, 42, 51, 31, 52, 62, 66, 53, 84, 59, 18, 56, 61	Younger age (p=0.104), multiple sexual partners (P<0.001), previous abnormal pap smear (p=0.01), nulliparity (p=0.001)	6
Tsiodras et. al. 2010	Athens, Greece Cross-sectional	Women attending outpatient gynecological clinics in Athens (n=1270)	Mean = 34.2	Cervix, Bruns-like brush scraping	Hybrid Capture 2, PCR	19% (241/1270)	Multiple types, 11, 6, 18, 16, 3, 31, other type	None	8

Author, Year	Location and type of Study	Population	Age Range	Anatomical location of sample and sampling method	Methods of HPV detection	HPV Prevalence (% & fraction)	HPV types detected (In order of most prevalent to least)	Risk factors ^a	ROB Score
Stamataki et. al. 2010	Athens, Greece Cross-sectional	Women attending a gynecological outpatient clinic (n=225)	16–45	Cervix, wooden Ayre spatula and cervical brush	PCR (Clinical Array® kit)	22.7% (51/225)	16, 53, 18	Younger age (p=0.03), lower monthly income (p=0.01), multiple sexual partners (p<0.001), alcohol consumption (p=0.04)	7
Tsiodras et. al. 2011	10 Hospitals across Northern and Southern Greece, Cross-sectional	Asymptomatic Greek women (n=1348) and women with ASCUS, LSIL, HSIL, and cervical cancer (n=952) attending outpatient gynecological clinics	Mean = 42.2	Cervix, ThinPrep liquid based preparation	CLART® HPV2 Kit	A: 39.5% (532/1348), AC: 82.67% (787/952)	16, 6, 18, 11	Younger age (p<0.001), sexual debut before age 19 (p<0.001), increasing number of sexual partners (p<0.001), shorter relationships (p<0.001)	9
Nasioutziki et. al. 2011	Thessaloniki, Greece Retrospective diagnostic	Women with current or previous HPV infection or cervical intraepithelial lesion (n=226)	25–45	Cervix, cytobrush and plastic Ayre spatula scrapings	Hybrid Capture® 2	40% (91/226)	Not reported	None	7
Michala et. al. 2012	Athens, Greece Cross-sectional	Sexually active adolescents attending health or gynecological clinics with LSIL and HSIL (n=45) or without abnormal cytology (n=85)	13–19	Cervix, Spatula and endocervical brush scrapings, Cervix brush scraping	PapilloCheck® HPV DNA Microarray kit	A: 26% (22/85) AC: 93.3% (42/45)	41, 51, 59, 16, 53, 31, 39, 66, 18, 33, 6, 43, 56, 11, 44, 45, 52, 58, 73, 82, 40, 68	Smoking (p=.0001), increased number of sexual partners (p=0.007), inadequate use of contraception (p=0.027)	7
Spathis et. al. 2012	Athens & Ioanina, Greece Cross-sectional	Greek women with CIN I, II, or III or cervical cancer (n=597) or asymptomatic Greek women (n=576) attending colposcopy	19–81	Cervix, liquid based cytology sample	CLART® HPV2 Kit	A: 40.5% (33/576), AC: 70.02% (418/597)	16, 18	None	7
Argyri et. al. 2013	Athens, Greece Cross-sectional	Caucasian women attending an outpatient gynecological clinic (n=3170)	14–70	Cervix, ecto-and endocervical cytobrush scrapings	PCR, PapilloCheck® HPV kit	33.1% (1049/3170)	Multiple types, 42, 16, 51, 53, 56, 59, 31, 39, 66, 44, 52, 33, 45, 6, 18, 68, 58, 40, 11, 43, 82, 70, 35, 73	Younger age (p<0.001)	8
Argyri et. al. 2013	Athens, Greece Cross-sectional	Greek women attending an outpatient gynecological clinic (n=849)	18–60	Cervix, cervical cell scrapings	PCR, PapilloCheck® HPV kit	41.3% (351/849)	42, 16, 51, 53, 56, 59, 31, 44, 39, 66, 52, 18, 33, 45, 6, 68, 73, 40, 11, 58, 43, 82, 70, 35	None	7

Author, Year	Location and type of Study	Population	Age Range	Anatomical location of sample and sampling method	Methods of HPV detection	HPV Prevalence (% & fraction)	HPV types detected (In order of most prevalent to least)	Risk factors ^a	ROB Score
Diamantopoulou et. al. 2013	Western Athens, Greece Cross-sectional	Women attending a gynecological clinic (n=2845)	18–65	Cervix, Brooms-like brush scraping	Papillomavirus Clinical Arrays® Kit, CLART® HPV2 Kit	43.4% (1234/2845)	Not reported	None	9
Agorastos et. al. 2014	Hospitals across Greece, Cross-sectional	Greek women attending outpatient clinics (n=5107)	18–59	Cervix, brush scraping	Hybrid Capture® II, Abbot Real Time® HPV test, PCR	5.8% (295/5107)	16, 31, 35, 53, 18, 51, 56, 58, 52, 39, 66, 45, 33, 59, 68	None	8

Notes: HPV: Human papillomavirus; ROB: Risk of bias; LSIL: Low-grade squamous intraepithelial lesions; HSIL: High-grade squamous intraepithelial lesions; CTIN: Carcinoma in-situ; ASCUS: Atypical squamous cells of undetermined significances; PCR: Polymerase Chain Reaction; RFLP: Restriction fragment length polymorphism; A: Asymptomatic patients; AC: abnormal cytology patients; PE: Paraffin embedded; NR: Not reported;

^a Only risk factors with statistical significance were included

Table 2

Studies reporting HPV prevalence in Greece from head and neck sites (n=13)

Author, Year	Location and type of study	Population	Age Range	Anatomical location of sample and sampling method	Methods of HPV detection	HPV Prevalence (% & fraction)	HPV types detected (In order of most prevalent to least)	Risk factors ^c	ROB Score
Lambropoulos et. al. 1997	Thessaloniki, Greece	Cross-sectional	14–85	Buccal mucosa using sterile cytobrushes	PCR and Southern Blot Hybridization	9.5% (16/169) ^a	6, 16, 11	Increasing age was associated with a higher prevalence	8
Gorgoulis et. al. 1999	Athens, Greece	Retrospective	NR	FFPE laryngeal specimens (surgical, biopsy)	Nested PCR and NISH	13% (20/154) ^a	6, 16, 18, 33	Heavy smoking was correlated with higher HPV prevalence	6
Aggelopoulou et. al. 1999	Athens, Greece	Retrospective	NR	PE tissue blocks from sites of oral malignancy	PCR and agarose gel electrophoresis	49% (50/102) ^a	16, 18	None	6
Bouda et. al., 2000	Athens, Greece	Retrospective	AC: 27–84 (52.7) A: 24–65 (48.3)	PE tissue blocks from sites of oral malignancy and oral cytologic scrapes from healthy subjects	Nested and type-specific PCR, and NISH	AC: 91% (48/53) M: 87% (27/31) F: 95.5% (21/22) A: 0% (0/16)	16, 18, 6/16, 16/18, 6, 33, 16/33, 18/33, Multiple	Smoking was correlated with HPV infection	6

Author, Year	Location and type of study	Population	Age Range	Anatomical location of sample and sampling method	Methods of HPV detection	HPV Prevalence (% & fraction)	HPV types detected (In order of most prevalent to least)	Risk factors ^c	ROB Score
Lyronis et. al., 2005	Crete, Greece Case-control	Greek residents who had undergone esophageal biopsies that were case-matched to asymptomatic patients. ^b Male (n=52) Female (n=8)	46–100	PE biopsy tissue specimens from the esophageal mucosa	PCR using type specific primers	AC: 6/27 (22.2%) ^a A: 17/30 (56%) ^a	16, 18	No link to smoking, alcohol, EBV	6
Mammas et. al., 2006	Crete, Greece Prospective	Children with benign tonsillar and adenoid hyperplasia Male (n=47) Female (n=59)	2–14	PE adenoid and tonsillar specimens	PCR using general and type specific primers	8.5% (9/106) M: 10.6% (5/47) F: 6.8% (4/59)	16, 11	HPV positive children were more likely to be younger (p=0.006)	6
Vageli et. al., 2007	Larissa, Greece Prospective	Patients with parotid tumors Male (n=7) Female (n=2)	11–70	FFPE biopsy specimens	Multiple, real time and in situ PCR	77.8% (7/9) M: 85.7% (6/7) F: 50% (1/2)	16, 18	None	6
Lyronis et al., 2008	Heraklion, Crete Case-control	Hospitalized patients (n=30) with esophageal squamous cell carcinoma (ESCC) and matched controls (n=32) Male (n=51) Female (n=11)	46–100 (67)	PE esophageal specimens from biopsy both with and without ESCC	PCR with type specific primers (6, 11, 16, 18, 33 only)	AC: 56.7% (17/30) ^a A: 18.8% (6/32) ^a	No typing	HPV was correlated with risk for esophageal cancer (OR=5.66, P<0.003)	6
Mammas et. al., 2012	Athens, Greece Cross-sectional	Young patients treated in the children's hospital Male (n=88) Female (n=102)	2–14	PE biopsy specimen of oral mucosa	PCR using general primers	8.4 % (16/190) ^a	16, 11, 33	HPV was correlated with younger age	6

Author, Year	Location and type of study	Population	Age Range	Anatomical location of sample and sampling method	Methods of HPV detection	HPV Prevalence (% & fraction)	HPV types detected (In order of most prevalent to least)	Risk factors ^c	ROB Score
Kouvousi et al., 2013	Athens, Greece Prospective	Patients with SCC of the oral cavity visiting an outpatient clinic Male (n=33) Female (n=12)	19–82 (51.9)	Samples collected with a brush by swabbing the oral mucosa	PapilloCheck® HPV Screening kit	11.1% (4/45) ^a	16, 18, 31, 33, 45	None	6
Bloumi et al., 2014	Thessaloniki, Greece Retrospective tissue samples	Archival specimens from oral SCC (n=63), oral leukoplakias w/ dysplasia (n=57), oral leukoplakias w/o dysplasia (n=53), oral fibroma (n=50) and normal tissues extracted during surgery (n=35) Male (n=127) Female (n=131)	12–94 (53)	FFPE biopsy tissue specimens from patients with and without oral malignancy	NPCR, immunohisto-chemical ISH, TEM	32.9% (85/258) M: 32.3% (41/127) F: 32.8% (43/131)	16, 13, 56, 13/16, 66, 16/56	HPV was correlated with younger age	5
Tsimplaki et al., 2014	Athens, Greece Retrospective tissue samples	Hospitalized patients with non-metastatic SCC of the oral tongue Male (n=39) Female (n=14)	19–75 (51)	Tissue obtained from biopsy of oral SCC	PapilloCheck® HPV Screening kit	11.3% (6/53) M: 5.1% (2/39) F: 28.6% (4/14)	16, 6, 18	HPV was correlated with abstinence from alcohol and smoking (p=0.013)	6
Laskaris et al., 2014	Pireaus, Greece Prospective tissue samples	Hospitalized patients with laryngeal SCC Male (n=38) Female (n=16)	21–88 (62.6)	Tissue samples obtained from biopsies of untreated laryngeal SCC	PapilloCheck® HPV Screening kit	18.5% (10/54) M: 15.8% (6/38) F: 25.0% (4/16)	16, 18, 51, 33, 6	Tobacco use: absence correlates with HPV infection	6

Notes: HPV: Human papillomavirus; ROB: Risk of bias; SCC: squamous cell carcinoma; FFPE: formalin-fixed paraffin embedded; PE: paraffin embedded; ISH: in situ hybridization; TEM: transmission electron microscopy; NPCR: nested polymerase chain reaction AC: abnormal cytology patients; A: asymptomatic patients; M: male; F: female; EBV: Epstein-Barr virus; NR: Not reported;

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These studies do not breakdown HPV prevalence by gender;
A total of 8 patients were unaccounted for in this study;
Only risk factors with statistical significance were included

Table 3

Studies reporting HPV prevalence in Greece from anal, penile and vulvar sites (n=5)

Author, Year	Location and type of study	Population	Age Range (mean)	Anatomical location of sampling method	Methods of HPV detection	HPV Prevalence (% & fraction)	HPV types detected (In order of most prevalent to least)	Risk factors ^b	ROB Score
Anastasiadis et. al., 2000	Thrace, Greece Retrospective Chart Review	Referred female patients (n=34) with vulvar intraepithelial neoplasia or invasive cancer	41–87 (54.7)	Vaginal and cervical Papsmears	NR	Invasive Cancer: 8.3% (1/12) CIS-VIN: 59.1% (13/22)	None	None	5
Gomousa-Michael et. al., 2000	Athens, Greece Cross-sectional	HIV positive (n=30) and HIV negative (n=40) males visiting a dermatologist for penile lesions Male (n=70)	Mean: 30	Imprint smears from penile lesions (6 per participant)	PCR and ISH, immunocyto-chemistry	HIV (-): 50% (20/40) HIV (+): 66.7% (20/30)	HIV (-): 6, 11, 16/18, 31/33/35 HIV (+): 16/18, 31/33/35, 6, 11	High-risk HPV infection was correlated with being HIV positive	6
Hadjiyassiliou et. al., 2007	Athens, Greece Cross-sectional	Male patients with genital warts (n=550; MSM=56) and asymptomatic (n=64) with HPV infected female partners	13–78	Cytobrush sampling of penile urethra. Perianal area was sampled if warts were present	Hybrid Capture® 2	AC: 50.9% (280/550) A: 20.3% (13/64)	Low risk, high risk	MSM were more likely to be HPV positive (p=0.0007)	6
Mavrogianni et. al., 2011	Athens, Greece Cross-sectional	Patients with perianal warts referred for evaluation of intranal disease Males (n=52; MSM=32) Females (n=13)	19–64 (31)	Cytobrush sampling of anal canal	PCR	78.4% ^a (56/65)	6, 11, 53, 16, 33, 51, 59	MSM were more likely to develop intranal warts	6
Alexandrou et. al., 2014	Athens, Greece Prospective	Patients diagnosed with anal or perianal SCC Males (n=5) Females (n=6)	31–89 (61)	PE tissue biopsies from anal canal and perianal region	PCR and CLART® HPV 2 kit	54.6% (6/11) M: 40% (2/5) F: 66.7% (4/6)	16, 61/73, 6/51, 6, 6/44, 61	None	6

Notes: HPV: Human papillomavirus; ROB: Risk of bias; CIS-VIN: carcinoma in situ-vaginal intraepithelial neoplasia; PCR: Polymerase-chain reaction; ISH: in situ hybridization; HIV: Human immunodeficiency virus; MSM: Men who have sex with men; AC: Abnormal cytology patients; SCC: squamous cell carcinoma; A: asymptomatic; M: male; F: female; PE: Paraffin embedded; NR: Not reported;

These studies do not breakdown HPV prevalence by gender;
Only risk factors with statistical significance were included

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Table 4
Studies reporting HPV prevalence in Greece from multiple anatomical sites (n=6)

Author, Year	Location and type of study	Population	Age Range	Anatomical location of sample and sampling method	Methods of HPV detection	HPV Prevalence (% & fraction)	HPV types detected (In order of most prevalent to least)	Risk factors ^b	ROB Score
Labropoulou et al. 1994	Athens, Greece Prospective tissue samples	Patients with recurrent condyloma acuminata Male (n=20) Female (n=6)	Mean: 24	Biopsies taken from warts in the vulva and penis/ anus	PCR and Southern Blot	73.1% (19/26) ^a	6, 11, multiple	None	6
Gomousa-Michael et al., 1997	Athens, Greece Diagnostic study	Females with previous positive HPV or SIL cytology and their male partners with abnormal urethral cytology Male (n=20) Female (n=20)	NR	Cytobrush sampling of penile urethra for males and cervix for women	Immunohisto-chemistry and ISH	Males: 20% (16/20) Females: 45% (9/20)	6/11, 31/33/35, 16/18	Synchronous HPV infection was found in 50% of sexual partners	5
Yapijakis et al., 2008	Athens, Greece (multicenter) Observational	Male patients (n=13) with lesions in the oral cavity or condyloma acuminata and female patients (n=250) with abnormal pap smear	18–64	Cervical, penile, and oral scrapings	PCR using general primers	81.7% (215/263) ^a	High risk, Intermediate risk, Low risk	None	6

Author, Year	Location and type of study	Population	Age Range	Anatomical location of sample and sampling method	Methods of HPV detection	HPV Prevalence (% & fraction)	HPV types detected (In order of most prevalent to least)	Risk factors ^b	ROB Score
and/or oral lesions									
Valari et. al., 2011	Ioannina, Greece Cross-sectional	Women (n=235) with suspected or confirmed HPV related pathology of cervix, vagina, or vulva	Mean: 34.3	Liquid based cytology samples from the cervix and anus	Clinical Arrays® HPV and flow cytometry	Cervical: 55.7% (131/235) Anal: 46.5% (109/235)	NR	Cervical pathology was linked to risk for anal HPV infection	7
Tsimplaki et. al., 2012	Athens, Greece Retrospective tissue samples	Sample (n=56) tissue sections from VAIN, VIN, or vaginal SCC (VaSCC) and vulvar SCC (VuSCC).	VAIN: 46.2 VIN: 35 VaSCC: 61.3 VuSCC: 62.5	Paraffin-embedded tissue specimens from biopsy of vagina or vulva	PapilloCheck® HPV DNA Microarray	VAIN: 56% (10/18) VIN: 71.4% (20/28) VaSCC: 50% (2/4) VuSCC: 50% (3/6)	16 and multiple others	HPV infection was higher in younger women with VIN (p=0.001) and VAIN (p=0.006)	6
Adamopoulou et. al., 2013	Athens, Greece Cross-sectional	Sexually active women referred for screening (n=43)	20–57 (33.8)	Cervical smears and saliva from oral cavity	PCR, NPCR	Cervical: 51.2% (PCR) 60.5% (NPCR) Oral: 11.6% (PCR) 44.2% (NPCR)	16, 31, 58	None	6

Notes: HPV: Human papillomavirus; ROB: Risk of bias; SIL: squamous intraepithelial lesion; ISH: in-situ hybridization; VAIN: vaginal intraepithelial neoplasia; VIN: vulvar intraepithelial neoplasia; SCC: Squamous cell carcinoma; PCR: polymerase-chain reaction; NPCR: nested polymerase chain reaction; ISH: in-situ hybridization; NR: Not reported;

^a These studies do not breakdown HPV prevalence by gender;

^b Only risk factors with statistical significance were included