# Oral Human Papillomavirus Infection in HIV-Positive and HIV-Negative Individuals

by

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## Preface

A version of Chapter 4 (HIV-Infected Individuals Are at Increased Risk of Oral HPV Infection: Findings from the Epidemiology of Papillomavirus Infections Study) will be submitted for publication. The full list of authors is: Mikiko Senga, James Riddell IV, Heather M. Walline, Carl F. Marrs, Mary Reyes, Norman D. Hogikyan, Carol R. Bradford, Mark E. Prince, Leon Golson, Jimena Lockluck, and Thomas E. Carey.

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# List of Abbreviations

| | |
|---|---|
| ACR | American College of Rheumatology |
| ANOVA | Analysis of variance |
| ARA | American Rheumatism Association |
| ARHP | Association of Rheumatology Health Professionals |
| CD4 | Cluster of differentiation 4 |
| DNA | Deoxyribonucleic acid |
| dsDNA | Double-stranded deoxyribonucleic acid |
| EPI | Epidemiology of Papillomavirus Infections |
| HAART | Highly active antiretroviral therapy |
| HARC | HIV/AIDS Resources Center |
| HIV | Human immunodeficiency virus |
| HNC | Head and neck cancer |
| HNSCC | Head and neck squamous cell carcinoma |
| HPV | Human papillomavirus |
| HR | High-risk HPV |
| IARC | International Agency for Research on Cancer |
| LR | Low-risk HPV |
| MALDI-TOF | Matrix Assisted Laser Desorption Ionization-Time of Flight |
| MDCH | Michigan Department of Community Health |
| MSM | Men who have sex with men |
| NHANES | National Health and Nutrition Examination Survey |
| OPSCC | Oropharyngeal squamous cell carcinoma |
| OR | Odds ratio |
| ORF | Open reading frame |
| p53 | Protein 53 (also known as tumor protein 53) |
| PBS | Phosphate-buffered saline |
| PCR | Polymerase chain reaction |
| pRB | Retinoblastoma protein |
| RNA | Ribonucleic acid |
| SLE | Systemic lupus erythematosus |
| SPH | School of Public Health |
| SPORE | Specialized Program of Research Excellence |
| STD | Sexually transmitted disease |
| TAE | Tris-acetate ethylenediaminetetraacetic acid |
| UM | University of Michigan |
| WHO | World Health Organization |

## Abstract

**Background:** Recent studies have shown that human papillomavirus (HPV) is an etiologic agent for oropharyngeal squamous cell carcinomas (OPSCC). Although individuals with HIV are presumably at increased risk of developing OPSCC, it is unknown to what extent the HIV status contributes to prevalence of oral HPV infections. This study was conducted to evaluate the prevalence and risk factors in three diverse groups in Washtenaw and surrounding counties in Michigan.

**Methods:** Participants were recruited to form three study groups: 1) HIV-positive patients seen at the University of Michigan Health System; 2) HIV-negative individuals tested at an HIV screening clinic; and 3) self-reported HIV-negative individuals. Oral rinse samples were collected from participants and were tested for presence and type of HPV DNA with PGMY09/11 primers and Sanger sequencing. In addition, HPV type and copy number were examined by HPV MultiPlex PCR-MassArray for 15 discrete high-risk HPV types (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68 and 73) and 3 low-risk HPV types (HPV 6, 11, and 90). Study participants completed a survey to ascertain medical, social, and behavioral risk factors. Clinical information pertaining to HIV disease status was collected for HIV patients.

**Results:** The total of 266 community-based participants (107 HIV-infected, 69 tested HIV-negative, and 90 self-reported HIV-negative) were enrolled. The overall crude prevalence of oral HPV DNA was 10.5%. The HIV-infected group had the highest prevalence (20.1%), followed by the self-reported HIV-negative group (5.6%) and the

HIV-negative group that received HIV testing (1.4%). Male partner's circumcision status was significantly associated with oral HPV infection (aOR=3.85). In univariate analysis, male gender, lifetime number of vaginal sex partners, and higher viral load were associated with increased risk of oral HPV infection.

**Conclusion:** The data supports previous findings that higher prevalence of oral HPV infection is observed in HIV-positive individuals compared to HIV-negative individuals.

**CHAPTER 1**

**Introduction**

**Overview**

Individuals with HIV infection are at increased risk of developing a variety of virally induced tumors, including those associated with human papillomavirus (HPV) (1-4). Recent studies have shown that HPV is an etiologic agent for a rapidly growing subset of head and neck squamous cell carcinomas, particularly oropharyngeal squamous cell carcinomas (5-9). However, to date, very little is known about the natural history of HPV infection in the oral cavity of HIV-positive and HIV-negative individuals. Of note, it is unknown to what extent HIV infection contributes to acquisition of active infection or persistent and/or recurrent oral co-HPV infections. Given that oropharyngeal cancer rates are expected to surpass that of cervical cancer by 2020 (10), not only is there a critical need to investigate the HPV infection rates in HIV positive and negative populations from the clinical standpoint, but it is also important to understand specific molecular and behavioral risk factors that affect oral HPV incidence and prevalence for prevention and screening purposes.

One of the major challenges in oral cancer prevention is that, unlike screening for HPV-related cervix cancer, no standard screening methods for oral cancer currently exist. To this end, this dissertation research was conducted to identify individuals with risk of oropharyngeal cancer using HPV as proxy, and to document the effectiveness of

Multiplex PCR MassArray, a high-throughput assay for HPV detection that has been developed by colleagues at the University of Michigan Cancer Center (11, 12).

To test the central hypothesis that HIV-positive individuals are more likely to be susceptible to oral HPV infection compared to HIV-negative individuals due to their immunosuppression and high-risk behaviors, this study was conducted to investigate clinical, molecular, and behavioral factors in transmission of oral HPV in three study groups: 1) HIV-positive patients seen at the University of Michigan Health System; 2) HIV-negative individuals tested at an HIV screening clinic; and 3) self-reported HIV-negative individuals from the general public. The specific aims and corresponding hypothesis are as follow:

1) To determine and compare the prevalence, HPV type distribution and risk factors of oral HPV infection in HIV-positive and -negative groups. This aim tested the hypotheses that higher prevalence of oral HPV infection will be observed in HIV individuals than in both reference groups (i.e. HIV-negative individuals tested at an HIV screening clinic and self-reported HIV-negative individuals from the general public), and that more high-risk HPV types and higher viral copy numbers will be observed in HIV-positive individuals compared to HIV-negative groups. Furthermore, it was hypothesized that prevalence of HPV infections will be related to certain high risk behaviors and, in HIV-positive individuals, degree of immunodeficiency.

2) To evaluate the validity of the questionnaire that was used for aim #1 by assessing the informational concordance between self-reported data and data abstracted from medical records. The aim is to test the hypothesis that the patient survey is a better data source for certain items whereas the medical record is a better source for others.

**The Organization of the Dissertation**

This dissertation takes an unconventional format such that the two chapters that immediately follow this overview will be comprised of the literature review (Chapter 2) and overall study methods (Chapter 3), respectively. Chapter 4 will present the overall findings of the study, and Chapter 5 will specifically discuss the methods used to validate the questionnaire that was used in the study by assessing concordance of patients' self-reported knowledge and physicians' documented knowledge of selected clinical and behavioral information. Chapter 6 will take a drastic shift to provide a systematic literature review of the global incidence and prevalence of systemic lupus erythematosus (SLE). Although this systematic literature review is not directly part of the epidemiological research of oral HPV infection, SLE is an autoimmune disease that is presumed to have important relevance to HPV. My epidemiological study consisted of an immunocompromised population (i.e., HIV-infected patients), but it is hypothesized that patients with autoimmune disease may mimic HIV-infected populations. This is because autoimmune disease patients, such as those with SLE, are often prescribed immunosuppressant therapy. Therefore, it was important to document the global burden of SLE to establish a baseline for future HPV research in this unique population.

Chapter 7 will serve as the final chapter and conclude with the summary of results,

public health implications, and future directions for research.

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# CHAPTER 2

## Background and Significance

### Human Papillomavirus

Human papillomavirus (HPV) is an encapsulated, non-enveloped double-stranded DNA virus. There are five major HPV genera in the Papillomaviridae family: Alpha-papillomavirus, Beta-papillomavirus, Gamma-papillomavirus, Mu-papillomavirus, and Nu-papillomavirus (1). The viral genome is about 8,000 base pairs in length, and consists of eight genes that are categorized into either early (E) or late (L) regions which reflects the temporality of their expression in relation to cell cycle (2, 3). Genes expressed early in the HPV cycle are generally involved in viral replication as well as gene expression regulation (3-5). The E6 and E7 proteins have received much interest because of their ability to disrupt the function of tumor suppressor proteins, p53 and pRb, respectively (6-8). While E6 and E7 are expressed in both oncogenic and non-oncogenic HPV types, the high risk of E6 and E7 differ in that high risk E6 contains introns that result in alternate splice forms (9, 10), higher E7 expression (11) and oncogenesis that are absent in low risk HPV types (12, 13). The genes of the L region (i.e., L1 and L2) code for capsid proteins. L1 is the most conserved region, and represents 80% of protein in the viral capsids (14).

Approximately 120 different genotypes have been identified to date (15, 16). The subtypes have been classified based on phylogenic position and ability to infect mucosal or cutaneous surfaces (5, 16). The International Agency for Research on Cancer (IARC) at the World Health Organization (WHO) has further categorized HPV subtypes into high-risk (HR) and low-risk (LR) according to carcinogenicity (17-19). Oncogenic HPV types are: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, and 73 (17-19). Thirteen HPV types are considered non-oncogenic: 6, 11, 26, 40, 42, 53, 54, 55, 61, 62, 64, 66, 67, 69, 70, 71, 72, 81, 82, 83, 84, CP6108, and IS39 (20). Other HPV types have not been classified to date.

**HPV-associated Cancers in the Head and Neck Region in HIV-uninfected Populations**

Head and neck cancer (HNC) is the sixth most common cancer in the world (21), and ranks as the eighth most common cause of cancer death (22). Malignancies of the lip, oral cavity, nose, and paranasal sinuses, nasopharynx, oropharynx, hypopharynx, and larynx all fall within the category of HNC (23). Squamous cell carcinomas are the most frequent malignancy in the head and neck region (24, 25). Traditional risk factors for cancer, such as alcohol consumption and tobacco smoking, are the most important risk factors for head and neck squamous cell carcinoma (HNSCC) (26).

With a decline in smoking rates, HNCs have decreased over time in the United States and Europe (27-29). In the meanwhile, a growing subset of HNC, particularly oropharyngeal squamous cell carcinomas (OPSCC) of the base of tongue and tonsil, has been observed (30, 31). In fact, the incidence of oropharyngeal cancer is expected

to surpass the incidence of cervical cancer by 2020 (32). It has also been noted that the steady increase in OPSCC in the United States tends to affect men who lack significant smoking or drinking history and are on average 9 years younger than the typical HNSCC patient (30, 33, 34). Similar observations have been made in European countries (34-38). These trends have suggested that there is an alternative etiology for this particular set of HNC.

HPV has been implicated in the pathogenesis of HNSCC. Ragin and Taioli conducted a meta-analysis reporting the prevalence of HPV in cancers that have the primary site in the head and neck region (39). In this meta-analysis, HPV prevalence ranged from 0 to 40.5%, with the tonsil having the highest prevalence, followed by oropharynx. Further, Hobbs et al. calculated the odds of finding HPV type 16 stratified by head and neck anatomical site, and found that the tonsil had the greatest odds of oral HPV16 prevalence, followed by other oropharynx sites, oral cavity, and larynx (40). These findings strengthen the idea that oral cavity/oropharynx is a good reservoir for HR HPV. Indeed, not only is HPV type 16 the most commonly found HR HPV type in HPV-positive tumors in the head and neck region (41-45), but it is also the most common infection in the oral cavity (1, 20, 46). Other HR HPV types in the oral cavity include HPV types 66 and 51, mimicking the distribution of HPV types in the cervix (47).

Despite its oncogenic property, HPV is associated with better prognosis and survival in HPV-positive OPSCCs when compared to HPV-negative oropharynx tumors (48). HPV-associated HNCs have 72% reduction in mortality compared to their HPV-negative counterparts (49). The progression of HPV-positive HNSCCs and OPSCCs was 60% and 52% lower than corresponding HPV-negative tumors at these sites.

Further, recurrence was 59% and 63% less for individuals with HPV-positive HNSCCs and OPSCCs, respectively, compared to HPV-negative counterparts (49, 50). It must be noted, however, that patients with HPV-associated HNSCCs are often younger (51). Therefore, favorable clinical outcome may in part be attributed to their younger age.

Leemans et al. (52) summarized the major differences between HPV-positive and HPV-negative HNSCC. HPV-negative HNSCCs are decreasing in incidence, have smoking and excessive alcohol use as the primary risk factors, affect older age, have evidence for field cancerization, have frequent TP53 mutations, and have poor prognosis (52). On the contrary, HPV-positive HNSCCs are increasing in incidence, are associated with oral sex, affect younger population, have infrequent TP53 mutations, are primarily found in the oropharynx, and have favorable prognosis and survival. Based on such a comprehensive review comparing HPV-positive and HPV-negative HNSCCs, it has become quite clear that HPV-positive and HPV-negative tumors represent distinct epidemiologic, clinicopathological, and molecular entities (28, 31, 48, 53-61).

**HPV Infection in HIV-uninfected Populations**

Since there is mounting evidence to suggest that the increasing incidence of OPSCCs is due to HPV, which is a sexually transmitted disease (STD), epidemiologic investigations have focused on identifying specific behaviors that are associated with the risk of oral HPV infection. HPV is the most common STD in the United States with approximately 5 million new infections occurring annually (62, 63). More than 50% of sexually active adults have been infected with one or more genital HPV types, and by

the age of 50, more than 80% of women will have acquired at least one genital HPV

type (64)

Prevalence and incidence of HPV in the genital region has been studied

extensively. According to a systematic literature review of HPV infection in women in the

United States, the prevalence varied from 10 to 90%, and the incidence ranged from 7

to 20% (65). The prevalence also varied among American men, ranging from 1.3 to

72.9% (66). The incidence of HPV infection in men was 29% over 12 months (67).

However, in a different population, namely college men, the incidence of over a 24-

month period was as high as 62.4% (68). While the variations in rates are partly due to

age distribution in the study populations and HPV detection methods, the transient

nature of HPV infection makes it difficult to accurately estimate the occurrence and type

distribution of the virus.

The burden of non-head and neck cancers that are associated with HPV is

significant. Cervical cancer is the most common cancer in women worldwide with

470,000 new cases each year, and more than half of these result in death (69). The

incidence of anal cancer is low relative to cervical cancer as the rate of anal cancer in

the general population is approximately 2 per 100,000 per year (70). However, the rates

are much higher in at-risk populations, specifically men who have sex with men (MSM)

and immunocompromised individuals (71-76). The proportion of cancers positive for

HPV16 is greater among anal cancer cases (i.e., over 70%) than cervical cancer cases

(i.e., over 50%) (77). On the contrary, penile cancer occurs less frequently than cervical

and anal cancers as it represents less than 1% of new cancers among the U.S. men.

Moreover, the link between HPV and penile cancer has not been demonstrated

convincingly. It has been reported that at least 40% of penile cancers were HPV

positive, and HPV16 and 18 accounted for over 70% of these HPV-positive cases (78).

The difference in rates may be due to the virus' capability to harbor in the genital area

and overall hygiene. For example, it has been demonstrated that circumcision serves as

a protective factor for penile cancer (79).

In the oral cavity of healthy individuals, the prevalence is less than that observed

in OPSCC patients. Whereas HPV prevalence in OPSCCs has ranged from 2.9% in

Australia, Cuba, and Sudan (80) to 80.4% in Japan (81), HPV prevalence in healthy

populations has ranged from 0% in a very small study sample in the United Kingdom

(82) to 20.7% in Brazil (83). Globally, the prevalence of oral HPV infection is estimated

to be 4.5% among healthy individuals (84). Carcinogenic HPV types were seen in 3.5%

of this global population, with the prevalence of HPV 16 in the oral cavity being only

1.3% (84). The prevalence appears to be affected by the economic status of countries;

the prevalence of any HPV type in developing countries (7.3%) is two-fold higher than

that in developed countries (3.6%) (84). Further, the prevalence of HPV 16 is 4.3%

among healthy individuals in developing countries, whereas it is only 0.7% in developed

countries (84).

In comparing the prevalence between oral HPV infection and genital HPV

infection, specifically in the cervix, oral HPV infection rates appear to be lower. Oral

HPV prevalence is five to ten-fold lower than cervicovaginal HPV prevalence (47).

Gillison et al. recently conducted the first nationwide study of oral HPV infection in the

United States using the data from the National Health and Nutrition Examination Survey

(NHANES), reporting an oral HPV prevalence of approximately 7% (85). The

prevalence among women in this study is 3.6%, which is nearly ten-fold lower than the average prevalence of HPV in the cervical and vaginal region, which is approximately 34% (86, 87). Among men in the general population, oral HPV prevalence is 10% whereas the prevalence in their genital region is generally over 20% (66).

A single risk factor for oral HPV infection has not been identified, but a combination of risk factors plays a role in oral HPV infection. There is a great deal of evidence to suggest that the risk factors for oral HPV infection are similar to those in genital HPV infection. Prevalence of oral HPV infection increases with number of partners (85, 88) and lack of condom use (85). Open-mouth kissing was recently added as another risk factor (88, 89). Tobacco smoking, marijuana use, and excessive alcohol consumption have been known to be positively associated with oral HPV infection (56, 90). Chronic inflammation in the oral cavity arising from poor hygiene has also been documented as a risk factor for oral HPV infection (91). Although there have been only a handful of studies, co-infection with other infectious agents, including bacteria and viruses, has been suggested. Previously, oral HPV infection was detected in conjunction with Epstein Barr virus (92) and herpesvirus (93, 94). Although not statistically significant, there was also concomitant infection with the following types of bacteria: *Dialister pneumosintes, Filifactor alocis, Porphyromonas gingivalis, Olsenella uli*, and *Pyramidobacter piscolens* (93).

Despite the aforementioned similarities between genital and oral HPV infection, HPV infection in the oral cavity has notable differences from that in the genital region in terms of risk factors. As with HPV-positive HNSCC, oral HPV infection in non-cancer

populations is associated with young age (85, 88, 95), higher socioeconomic status, higher education, and white race (96).

Although autoinoculation has not been reported as a risk factor of oral HPV infection, this is still possible in theory. The same HPV types in the hand or fingernails as those in the genital area have been observed in both men and women (68, 97, 98). In the study by Partridge et al., HPV types detected were HPV 26 and HPV 36 (68). Winer et al. reported HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 53, 56, 66, and 82, in addition to numerous LR HPV types (98). Widdice et al. also reported a wide range of HPV types, including types 6, 16, 31, 35, 39, 42, 51, 52, 53, 58, 59, 61, 62, 66, 67, 70, 73, 84, and CP6108 (97). With all these results combined, it is clear that a variety of mucosal HPV types could be found on the skin. Such findings suggest that there is a potential that HPV could be self-inoculated to the oral cavity.

**HPV-associated Non-HNCs in HIV-infected Populations**

The prevalence of oral HPV infection is thought to be exacerbated in HIV-positive populations because of immunosuppression. HPV-related tumors are known to be associated with immunosuppression in individuals with immunodeficiency diseases and in organ transplant recipients (99-101). An increased incidence of HPV-related cancers has also been documented in men who have sex with men (MSM) and HIV-positive populations, suggesting that there is an increased risk of HPV transmission and oncogenesis in these individuals (71, 73, 74, 102, 103).

Compared to the general population, individuals with HIV are at increased risk of developing several cancers linked to HPV because of high HPV prevalence and HPV-

associated cellular abnormalities. HIV-infected women are two to three times more likely than HIV-uninfected women to have detectable levels of cervical HPV DNA (104-108). In addition, HIV-infected women were more likely to have a higher HPV detection rate than HIV-uninfected women, and the detection rates depended on the level of CD4 count (109). Similar differences between HIV-positive and HIV-negative women regarding cancer risk have been observed even in younger women. A three-fold risk of HPV infection and squamous intraepithelial lesions was reported in HIV-infected adolescent females compared to HIV-uninfected adolescent females (110, 111). Likewise, HIV-infected men have approximately a three-fold higher risk of being infected with HPV than HIV-uninfected men, and such risk is observed primarily in the anus among men who have sex with men (71, 103).

Given the higher prevalence rates of HPV in the HIV population in the context of immunosuppression, it is not surprising to find higher rates of HPV-associated cancers. The incidences of cervical and anal cancers steadily increase as CD4 count declines (112, 113). A risk of developing invasive cervical cancer is five- to 15-fold greater in women with HIV (114, 115). Low CD4 count (109) and high HIV viral load are significantly associated with HPV DNA detection in cervical squamous intraepithelial neoplasia (116). In addition to the influence of immunosuppression on cancer risk, it has also been reported that HIV-infected individuals are less likely to have received cervical cancer screening (115, 117-119), making this group even more vulnerable.

HIV-infected men are also at higher risk of HPV-associated cancers. Although studies directly comparing the rates of penile cancer in HIV-infected and -uninfected men are rare, it has been noted that HIV-infected men are more likely to have HR HPV

on their penis than HIV-negative men (120). High rates of HR HPV (i.e., 78, 36 and 30% in the anus, penis and mouth, respectively) have been observed in HIV-positive men (121). Moreover, HIV-infected men have roughly 37-fold higher risk of anal cancer than the general population (122). These anogenital carcinomas associated with oncogenic HPV suggest a gradual loss of control over HPV-infection with progressing immunosuppression.

**HPV-associated HNCs in HIV Populations**

Given that immunosuppression and risky sexual risk behaviors have contributed to greater risks of anogenital cancers in HIV-positive individuals compared to HIV-negative individuals, it is hypothesized that HIV-positive individuals are also at an increased risk of HNCs. This notion especially holds because evidence strongly suggests that HPV-associated HNCs, particularly OPSCCs, are sexually transmitted. However, it remains unclear whether HIV-infected individuals are indeed at a greater risk. Further, it is unknown to what extent HNC incidence and prevalence are affected by HIV disease progression.

To date, a limited number of studies have compared HNC rates between HIV-positive and HIV-negative populations. Modest risk of HNCs has been observed among HIV-infected populations compared to HIV-negative counterparts in large studies. In a meta-analysis of the head and neck cancers in developed countries between 1980 and 2007, HIV-infected individuals had a two-fold increase (21). This and another meta-analysis cited a two-fold increase, when specifically assessing the cancer rates in the oropharynx (21, 123). Such findings are comparable to studies performed in the United

States. Three investigators have compared the incidence rates of oropharyngeal cancers between HIV-positive and HIV-negative populations, and the incidence ratios ranged from 1.4 to 1.8 (124-126). In tonsillar cancers, the incidence ratio was 2.6 times higher in the HIV-positive population in the United States (122). The largest difference was observed in Switzerland, where the HIV-positive population had a four-fold increase in the cancers of the lip, oral cavity, and pharynx compared to the HIV-negative population (127).

The extent to which immune effects may play a role in new and recurrent HNCs in HIV populations remains unknown. Furthermore, the role of highly active antiretroviral therapy (HAART) in oral HPV infection is unknown. The literature indicates that the incidence of HPV-related anogenital cancers has not declined with antiretroviral therapy (103). In the oral cavity, HAART use has been associated with persistence of oral HPV infection (128). Given that the incidence of HPV-associated diseases have not declined in the HAART era and that HAART may actually prolong HPV infection, HPV-associated oral cancers may increase over time in the HIV-population. It is troubling that there is already some evidence pointing to this direction (129-132).

**Oral HPV-infection in HIV-infected Populations**

Because cancer is a rare event, much of the work on HPV-associated HNC has focused on epidemiologic studies using oral HPV infection as a proxy. In the HIV population, the prevalence of oral HPV infection has ranged from 14 to 45% (88, 94, 95, 128, 133-146). In the United States, where the prevalence of oral HPV infection in the general population is 7% (85), the oral HPV prevalence in HIV-positive populations has

been 33%, on average (95, 134, 136, 138, 140, 144, 145, 147). The average oral HPV prevalence rates among HIV-positive individuals were 28.5% and 26.5% in Italy and South Africa, respectively (94, 139, 141, 142). There was one study each in Australia and Spain, for which the prevalence was 16% and 19% (146).

The prevalence of oncogenic HPV in HIV populations has also varied. In a review conducted by Beachler and D'Souza, the prevalence of oncogenic HPV ranged between 12 and 26% (147). This is significantly higher than the 3.7% observed in the U.S. general population (85). Also in the same review, the prevalence of HPV 16, which has been found in over 80% of oropharyngeal cancers (80, 84), ranged from not being detected at all to as high as 6.1% in the HIV-positive populations (147). Since the prevalence of HPV 16 in the U.S. general population is 1% (85), it could imply that HIV-positive individuals may incur a risk that is as high as six-fold.

The risk factors that were previously described to have an association with HNC must be taken into account in the investigation of oral HPV infection, especially in HIV-positive populations. This is because HIV and HPV share similar risk factors for infection. An increased number of sexual partners for vaginal, oral, and anal sex has been associated with oral HPV infection (85, 95, 133, 134, 136), as well as HPV-associated HNC (90). Barrier use during oral sex is a protective factor (85). Sexual orientation appears to be associated, but the specific sexual preference that is responsible for oral HPV infection has not been identified, as the data are conflicting (85, 94, 136). Smoking (85, 88, 148, 149), alcohol consumption (90), and marijuana use (90) that are often associated with risky sexual behaviors are also known to be risk factors for oral HPV infection.

As observed in HPV-associated HNCs, oral HPV infection has distinct risk factors that are not observed in HPV-negative HNCs.  These risks include male gender (85, 95, 136), high socioeconomic status (96), and education (96, 150). It remains unclear as to why these risks are prominent in oral HPV infection.

**HPV Detection**

As described earlier, there is tremendous heterogeneity in the oral HPV prevalence rates. Other than the differences arising from population demographics, risk factors, and study design (i.e., cross-sectional, case-control, cohort, or clinical trial), the heterogeneity is largely caused by the methods employed in these studies. Sources of variability include method of specimen collection, processing methods, and detection methods. Regarding specimen collection, oral rinses have an advantage of sampling the entire oral cavity, maximizing potential for detection (56, 89, 128, 133, 136, 143, 151); however, this method offers no information about the site of oral HPV infection. Site-specific sampling targets a potential or actual site of oncogenesis, but the sensitivity may not be as high (152-154). Detection of oral HPV infection is further affected by sample purification method since contaminants that inhibit polymerase chain reaction (PCR) could underestimate the prevalence of HPV infection (155).  Finally, there is a variety of HPV detection methods that are currently available or in development (table 2.1). The use of different approaches has contributed to significant heterogeneity in HPV infection rates.

**Table 2.1. Molecular Diagnostic Methods for HPV Detection.**
Adapted from "Molecular Diagnostics of Human Papillomavirus," by A. Arney and K. M. Bennett, 2010, *LabMedicine, 41,* p. 523-530. Copyright 2010 by WebMD LLC. Adapted with permission. (156)

| Test | Principle | Comments | Low-Risk Strains | High-Risk Strains |
|---|---|---|---|---|
| Reverse Line Blot (Roche) | Target amplification; genotyping; consensus PCR and line blot | Research use only | 6, 11, 61, 62, 64, 67, 69, 72, 81, 89 | 16,18, 26, 31, 33, 35, 39, 40, 42, 45, 51 to 59, 66, 68, 73, 82, 83, 84 |
| LINEAR ARRAY HPV Genotyping Test (Roche) | Target amplification; genotyping; PCR followed by line hybridization | CE-Marked for use in Europe | 6, 11, 40, 42, 53, 54, 55, 61, 62, 64, 67, 69, 70, 71, 72, 81, 84, IS39, CP6108 | 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68, 73, 82, 83 |
| INNO-LiPA HPV Genotyping Extra (Innogenetics) | Target amplification; genotyping; SPF10 primers at L1 region, reverse hybridization | CE-Marked for use in Europe | 6, 11, 40, 43, 44, 54, 70 | 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 69, 71, 73, 74, 82 |
| AMPLICOR HPV (Roche) | Target amplification; detection; PCR and nucleic acid hybridization | CE-Marked for use in Europe | N/A | 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68 |
| PapilloCheck (Greiner Bio-One) | Target amplification of E1 for genotyping; PCR/DNA-array | CE-Marked for use in Europe | 6, 11, 40, 42, 43, 44 | 16, 18, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 70, 73, 82 |
| Multiplex HPV Genotyping Kit (Multimetrix) | Target amplification; genotyping; PCR and fluorescent bead array | Research use only | 6, 11, 42, 43, 44, 70 | 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73, 82 |
| GenoID Real-Time HPV Assay (GenoID) | Target amplification for detection or semi-genotyping; real-time PCR | CE-Marked for use in Europe | 6, 11, 42, 43, 44 (Lightcycler only) | 16, 18, 31, 33, 35, 39, 45, 51,52, 56, 58, 59, 66, 68 |
| Digene Hybrid Capture II (HC2) HR HPV DNA Test (Digene/Qiagen) | Signal amplification for detection; hybrid capture, semi-quantitative | FDA-approved | N/A | 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68 |
| Digene Hybrid Capture II (HC2) HPV DNA Test (Digene/Qiagen) | Signal amplification for detection; hybrid capture, semi-quantitative | FDA-approved | 6, 11, 42, 43, 44 | 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68 |
| CareHPV (Qiagen) | Signal amplification for detection; rapid test related to HC2 | For use in developing countries | N/A | 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68 |
| Cervista HPV HR (Hologic) | Signal amplification for detection; Invader technology | FDA-approved | N/A | 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68 |
| Cervista HPV 16/18 (Hologic) | Signal amplification for genotyping; Invader technology | FDA-approved | N/A | 16, 18 |

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# CHAPTER 3

## Study Methods

### Infrastructure of the Study

Prior to the inception of the study, collaboration with the following organizations was established to enable recruitment of three different populations: The University of Michigan (UM) School of Public Health (SPH) Department of Epidemiology; UM Medical School Department of Otolaryngology; and UM Division of Infectious Diseases within Department of Internal Medicine; and the HIV/AIDS Resources Center (HARC), a community-based non-profit organization in Ypsilanti, Michigan. Recruitment, enrollment, and data collection described below were performed between May 2012 and August 2013. Specimen processing, HPV detection, and data management were performed in parallel to maximize efficiency. This chapter describes the overall framework of study activities that pertain to all aims of this dissertation.

### Identification of Study Subjects

After IRB approval was obtained, recruitment of study participants took place at three different sites: UM HIV/AIDS Treatment Program within the Division of Infectious Diseases, HARC, and the School of Public Health. Since each site had its own business operational style, recruitment strategies were tailored for each study group.

*Recruitment of HIV-infected Patients*

The following two methods were utilized to recruit HIV-positive participants:

1) Active, in-person method: HIV patients were recruited from the UM HIV/AIDS Treatment Program within the Division of Infectious Diseases. Health care providers in the HIV Clinic informed current and newly diagnosed HIV-seropositive patients of the opportunity to participate in the study in compliance with IRB regulation and approval. Once patients expressed their interest in participating in the study, they were referred to the study staff for further screening for eligibility. (See eligibility criteria below.)

2) Passive, in-person method: The recruitment announcements were placed in clinic rooms and on the UM clinical research volunteer's website (www.umclinicalstudies.org). (Appendix 1). In this method, potentially interested participants who are HIV-positive contacted the Principal Investigator (PI), Mikiko Senga, to determine eligibility. If they met the eligibility, the PI arranged to obtain written informed consent during their regular visit at the HIV Clinic.

Once eligibility was confirmed, informed consent was obtained in a private clinic room, and study activities followed.

*Individuals Tested HIV-negative*

Individuals with an HIV-negative test result were recruited using an active, in-person method. All recruitment activities for this study group took place at HARC. The Michigan Department of Community Health (MDCH) requires that any new HIV cases be reported for surveillance purposes. Therefore, to maintain compliance with this requirement, test counselors at HARC obtained MDCH consent to report any new HIV

cases identified through this study to the Michigan State Health Department. Test counselors proceeded to perform HIV testing and counseling per HARC's HIV testing protocol. Individuals who received an HIV-negative test result were informed by the test counselors about the opportunity to participate in the study. Potentially interested participants were then referred to the study staff  for more information and to screen for their eligibility.

Once eligibility was confirmed, informed consent was obtained in a private office room, and study activities followed.


*Self-reported HIV-negative Individuals*

Individuals with self-reported HIV-negative status were recruited online. The recruitment announcement was posted on the UM clinical research volunteer's website ([www.umclinicalstudies.org](www.umclinicalstudies.org)). As of March 2012, there were over 10,350 potential research participants registered in this website. This registry was the chosen method of recruitment for this study population because these potentially eligible research participants reflected Michigan demographics due to similarities in age, gender, race, and ethnicity between Michigan residents and individuals registered on this website.

In an active, online recruitment method, the Principal Investigator screened the registry for potential study volunteers based on eligibility criteria, and contacted them directly to assess their interest in participating. In a passive, online recruitment method, interested individuals with the self-reported HIV-negative status contacted the Principal Investigator to determine eligibility.

Once eligibility was confirmed, informed consent was obtained in a private room at UM SPH, and study activities followed.

**Eligibility Criteria**

*HIV-infected Patients*

Patients who have been treated in the University of Michigan Health System (UMHS) were considered for enrollment if they fulfilled the following eligibility criteria:

(1) HIV seropositive;

(2) Age of 18 years or older; and

(3) Ability and willingness to provide written informed consent.

*Individuals Tested HIV-negative*

Individuals who were tested for HIV through HARC, and had an HIV-negative test result were deemed eligible. In addition, the following criteria had to be met:

(1) HIV seronegative;

(2) Age of 18 years or older; and

(3) Ability and willingness to provide written informed consent.

*Self-reported HIV-negative Individuals*

Healthy volunteers, who responded to the online recruitment announcement on the UM Clinical Research Volunteer's website (www.umclinicalstudies.org), were considered for enrollment if they fulfilled the following eligibility criteria:

(1) HIV negative by self report;

(2) Age of 18 years or older; and

(3) Ability and willingness to provide written informed consent.

**Consent Process**

After participant eligibility was confirmed, informed consent was obtained using the consent forms approved by UM IRBMED B1 (IRB# HUM00047989). (Appendices 2 & 3). Participants were informed of the study purpose, overall study design, study activities (i.e. specimen collection and survey administration) and corresponding risks and benefits, the right to withdraw participation, types of information collected, ways in which the information may be used, confidentiality of information, and protection of research participants. Participants were given ample time and opportunities to ask questions prior to deciding whether or not they wanted to enroll in the study.

**Data Collection**

Data collection consisted of multiple components. During the study visit, biological samples (i.e. saliva and oral rinses) were collected. Additionally, a survey was administered to each participant to ascertain social and health behaviors. After the study visit, HIV-positive participants' medical records were reviewed, and laboratory experiments were performed to produce HPV-related data. Each of the aforementioned data collection activities is described in detail below.

*Oral Specimen Collection (All study groups)*

Saliva was collected by asking participants to expectorate their saliva into commercially available kits (i.e. Oragene DISCOVER OGR-500 and Oragene RNA RE-100). Participants who had difficulty generating saliva were provided with a 2"x2" Parafilm square that could be chewed on to stimulate saliva production. After 1mL of saliva was collected, the collection tubes were sealed with a cap containing RNA stabilizing solution. The kit was designed such that, as the cap screwed onto the collection tube, the seal containing RNA stabilizing solution would break, allowing this solution and the saliva to mix. The saliva sample was stored at -4°C until further processing.

After saliva was collected, oral rinse was collected. Participants were asked to swish and gargle 10 mL of SCOPE mouthwash 30 seconds, and then expectorate into a sterile, 50 mL conical tube. The oral rinse sample was stored at -4°C until further processing.

*Social Behaviors and Family History Survey (All study groups)*

All study participants were asked to complete a questionnaire that consisted of questions related to demographic information, alcohol, tobacco, and other drug use, sexual practices, diet, environmental exposures, oral hygiene, general hygiene, cancer history, and general health. (Appendices 4 & 5). In addition, HIV patients were asked questions related to their HIV disease status, such as CD4 count, viral load, and medication adherence. For women, Pap smear history was asked. For men, Pap smear history of their current partner was asked. Participants completed the questionnaire in a

quiet, private room. They were asked to label their questionnaire with their unique study identification number. As an added measure of privacy, the participants were provided a manila envelope into which the completed questionnaire was enclosed. For participants who could not read, study staff read and recorded responses to survey questions.

*Medical Record Abstraction (Only HIV-Patients)*

IRB approval allowed for collection of selected clinical information that is relevant to the oral HPV infection. The information was abstracted from only HIV-positive study participants' medical record. The medical record review was conducted only for HIV patients because there was no guarantee that participants in other study groups (i.e. HARC clients and self-reported HIV-negative individuals from the UM Clinical Research Volunteers registry) had been seen in the University of Michigan Health System. Using Careweb, the UMHS's electronic medical record system, HIV viral load, CD4 cell count, CD4 cell nadir, current HIV medications, sexually transmitted diseases (STD), previous cancer diagnosis, and evidence of non-oral HPV-associated diseases were abstracted from patients' medical records.

**Participant Reimbursement**

Participants were compensated $10 in cash at the end of the study visit. Cash was the chosen method of reimbursement to protect the identity of participants, especially given the sensitive study populations.

**Laboratory Methods**

*DNA Isolation and Purification*

The oral rinse specimens were transferred into a 15-mL tube and centrifuged at 3,000 × *g* for 10 minutes at 4°C. The supernatant was decanted. The pellet was resuspended in 10 mL phosphate-buffered saline (PBS), and centrifugation was repeated. The supernatant was pipeted out. The pellet was resuspended in 1 mL Puregene Cell Lysis Solution and mixed by inverting 50 times. The sample was incubated at 37°C for 15 minutes. After incubation, the sample was digested with DNase-free RNase A (5 µg/ml) for 30 minutes at 37°C. Puregene Proteinase K was added to a final concentration of 0.5 mg/mL, and mixed by inverting three times. The sample was vortexed vigorously at high speed for 20 seconds to mix. The sample was digested overnight at 55°C.

On the following day, the sample was heat inactivated at 95°C for 10 minutes, and was cooled to room temperature. 340 µL of Protein Precipitation solution was added to each sample. The sample was vortexed vigorously for 20 seconds at high speed. The sample was then incubated for 10 minutes on ice to ensure a tight pellet in the next step. The sample was centrifuged for 10 minutes at 2000 x g (3300 rpm). In a new 15-mL tube, 1 mL of isopropanol and 2 µL of glycogen solution were combined, and the tube was placed on ice. After centrifugation, the supernatant containing the DNA was poured into the new 15-mL tube, containing isopropanol and glycogen solution, leaving behind the precipitated protein pellet. The samples were mixed by inverting gently 50 times. The samples were centrifuged for 5 minutes at 2000 x g (3300 rpm). The supernatant was carefully discarded, and the tube was drained by inverting

on a clean piece of absorbent paper, taking care that the pellet remained in the tube. One milliliter of 70% ethanol was added to the tube and inverted several times to wash the DNA pellet. The tube was centrifuged for one minute at 2000 x g (3300 rpm). The supernatant was carefully discarded. The tube was drained on a clean piece of absorbent paper, taking care that the pellet remained in the tube. The tube was air-dried for 10 minutes. 50 μL DNA Hydration Solution was added to the tube containing DNA and vortexed for 5 seconds at medium speed to mix. The samples were incubated at 65°C for 1 hour to dissolve the DNA. The samples were incubated at room temperature overnight with gentle shaking. Following the overnight incubation, the samples were centrifuged briefly and transferred to a 1.5-ml Eppendorf tube and stored at -80°C (1).

*Quantification of DNA Concentration*

To measure DNA concentration, a Qubit® 2.0 Fluorometer (Invitrogen) was used. To prepare the samples for measurement, an appropriate volume of Qubit® working solution was made by diluting the Qubit® dsDNA BR reagent 1:200 in Qubit® dsDNA BR buffer. Then two assay standards were created by aliquoting 190 μL of Qubit® working solution into two 0.5-mL PCR tubes and 10 μL of each Qubit® standard (i.e. Standard #1 and Standard #2) were added to the appropriate tube. The standards were mixed by vortexing a few seconds. The remaining working solution was aliquoted into the appropriate number of new 0.5-mL PCR tubes to accommodate the number of DNA samples. One microliter of DNA was combined with 199 μL of the working solution in each tube to make the volume in each assay tube equal to 200 μL. All sample tubes were vortexed for a few seconds and incubated at room temperature for 2 minutes. The

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samples were read using the Qubit® 2.0 Fluorometer, selecting dsDNA Broad Range as the assay type. If a sample had a DNA concentration too low to be quantified with Qubit® dsDNA Broad Range assay (i.e. less than 500 ng/mL), the process was repeated using Qubit® dsDNA High Sensitive assay.

*HPV Detection*

Isolated DNA was tested for presence and type of HPV using two different detection methods: 1) Multiplex PCR MassArray, and 2) PCR followed by sequencing.

1) HPV Multiplex PCR MassArray: DNA samples were assayed in quadruplicate using a validated, ultra-sensitive method utilizing real-time competitive polymerase chain reaction, followed by probe-specific single base extension and matrix-assisted laser desorption/ionization-time of flight mass spectroscopy with separation of products on a matrix-loaded silicon chip array. Multiplex PCR amplification of the E6 region of 15 discrete high-risk HPV types (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68 and 73), 3 low-risk HPV types (HPV 6, 11, and 90), and a human GAPDH control was processed to saturation, followed by a shrimp alkaline phosphatase quenching. Amplification reactions included synthetic competitor oligonucleotides identical to each natural amplicon except for a single nucleotide difference. This method of amplification suppressed background and false-positive signal generation. Multiplex single base extension reactions employed probes that identified unique sequences in the E6 region of each hrHPV type, extending at the single distinguishable base of wild type and competitor amplicons. Each hrHPV type and its competitor were recognized by mass in assay-defined profiles when analyzed on the MALDI-TOF mass spectrometer (2).

2) HPV-L1-PCR followed by sequencing: Consensus PCR targeting the L1 region of the HPV viral genome was performed on all DNA samples using PGMY 09/11 primers (3). Gel electrophoresis was performed with a 1.5% agarose gel containing 0.25 ug/mL ethidium bromide in 1X TAE buffer at 90V for 80 minutes. The PCR products with 450bp fragments were purified with QIAquick PCR Purification Kit (Qiagen) according to the manufacturer's protocol and were sequenced using Sanger method to identify the HPV type.

These two detection methods were used because, in theory, the combined approach would yield a higher frequency of samples detected. The HPV multiplex PCR MassArray is ideal for high throughput testing of multiple samples resulting in immediate identification of the HPV types present in each sample. While the use of PGMY 09/11 L1 consensus primer is currently the gold standard for detection of HPV types not represented in the Multiplex assay, it is not as sensitive as HPV Multiplex PCR MassArray, and it requires a second sequencing step to identify the HPV type. However, since we did not want to restrict HPV detection to the 18 HPV types in the HPV Multiplex PCR MassArray, the DNA samples that were detected to contain HPV were sequenced. Sequencing, in return, allowed for detection of a wider range of low risk and cutaneous HPV types.

**Statistical Analysis**

Prevalence of oral HPV infections was calculated for each study group. The $\chi^2$ test or the Fisher's exact test, where appropriate, was used to test for heterogeneity. Logistic regression models were used to estimate odds ratios (ORs) and 95%

confidence intervals (CIs) for associations between demographic and exposure variables from the survey and medical record abstraction and the presence of oral HPV DNA. HPV DNA positivity was defined as any positive test result for at least one of the 18 genotypes detected by HPV Multiplex PCR MassArray or any HPV genotype detected from sequencing. Tests for trend were conducted across ordered groups. Variables that were significant in univariate analysis were evaluated in a multiple logistic regression model, as were variables that were considered to be relevant based on *a priori* knowledge. The final model was created by the inclusion of variables with potential biological significance, as well as those that remained statistically significant after adjustment. P-values less than 0.05 were considered statistically significant, and all p-values reported were 2-sided. All analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC).

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# CHAPTER 4

## HIV-Infected Individuals Are at Increased Risk of Oral HPV Infection: Findings from the Epidemiology of Papillomavirus Infections Study

### Abstract

**Background:** Recent studies have shown that human papillomavirus (HPV) is an etiologic agent for oropharyngeal squamous cell carcinomas (OPSCC). Although individuals with HIV are presumably at increased risk of developing OPSCC, it is unknown to what extent the HIV status contributes to acquisition, persistence, and/or recurrent oral HPV infections. This study was conducted to investigate whether HIV-positive individuals are more likely to be infected with oral HPV compared to HIV-negative individuals.

**Methods:** Participants were recruited to form three study groups: 1) HIV-positive patients seen at the University of Michigan Health System; 2) HIV-negative individuals tested at an HIV screening clinic; and 3) self-reported HIV-negative individuals from Washtenaw and neighboring counties in Michigan. Oral rinse samples were collected from participants and were tested for presence and type of HPV DNA with PGMY09/11 primers and Sanger sequencing. In addition, HPV type and copy number were examined by HPV MultiPlex PCR-MassArray for 15 discrete high-risk HPV types (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68 and 73) and 3 low-risk HPV types (6, 11, and 90). Study participants completed a survey to ascertain medical, social, and

behavioral risk factors. Clinical information pertaining to HIV disease status was collected for HIV-infected patients.

**Results:** A total of 266 community-based participants (107 HIV-infected, 69 tested HIV-negative, and 90 self-reported HIV-negative) were enrolled. The overall crude prevalence of oral HPV DNA was 10.5%. The HIV-infected group had the highest prevalence (20.1%), followed by the self-reported HIV-negative group (5.6%) and the HIV-negative group that received HIV testing (1.4%). Male partner's circumcision status was significantly associated with oral HPV infection. Among the HIV patients, higher viral load was associated with increased risk of oral HPV infection.

**Conclusion:** The data supports previous findings that prevalence of oral HPV infection is higher in HIV-positive individuals compared to HIV-negative individuals.

## Introduction

Human papillomavirus (HPV) is an etiologic agent that is associated with a subset of head and neck cancers, specifically oropharyngeal squamous cell carcinomas (OPSCC) (1-5). In the United States, the incidence of oropharyngeal cancer is expected to surpass the incidence of cervical cancer by 2020 (6). It is hypothesized that the lack of validated screening method for oral cancer and changes in sexual behavior are responsible for the shift in this trend. However, the natural history of oral HPV infection is not well understood, and independent risk factors for oral HPV infection remain unexplored.

Compared to the general population, in which the prevalence of male and female oral HPV infection has been estimated to be approximately 7% and 1%, respectively (7),

oral HPV detection rates in HIV-positive individuals appear to be greater, with prevalence ranging from 14 to 39 % (8-13). The elevated risk of oropharyngeal cancer among HIV-infected individuals may be due to higher rates of tobacco and alcohol use (8, 14-16), the shared sexual risk factors between HIV and HPV, and sexual preferences (9, 12, 13, 17, 18). While severity of immunosuppression appears to be a risk factor (9, 10, 12), reductions in HPV-related malignancies or oral HPV prevalence in the post-HAART era have not been observed (10, 19-21).

To date, the majority of studies comparing oral HPV infection rates between HIV-positive and HIV-negative populations have been performed in inner-city populations. To expand knowledge about oral HPV infection in other populations, we investigated the prevalence and type distribution of oral HPV infection, and identified risk factors for oral HPV infection among HIV-positive and HIV-negative individuals in a midwestern college population that has relatively high educational and socioeconomic status. To our knowledge, this is the first study to compare oral HPV prevalence in HIV-positive individuals with the use of two HIV-negative groups as reference.

## Methods

**Study Population**

We conducted a cross-sectional study between May 2012 and August 2013 to examine the prevalence of oral HPV infection in an HIV-infected population compared to two different HIV-negative populations with different risk factors for HIV acquisition. HIV-infected patients were recruited from the HIV/AIDS Treatment Program at the University of Michigan. To form a comparable HIV-negative group with similar risk factors,

individuals who referred themselves for screening and tested HIV-negative were recruited at a community health organization (HIV/AIDS Resources Center in Ypsilanti, MI [HARC]). In addition, self-reported HIV-negative individuals in Washtenaw County, Michigan, and surrounding counties were recruited through the University of Michigan's Clinical Studies electronic registry. For all study groups, partners of index study participants were recruited and enrolled whenever this was possible. The study was approved by the Institutional Review Board of the University of Michigan Medical School (application number HUM00047989), and written informed consent was obtained from all participants.

**Social Behaviors and Family History Survey (All study groups)**

All study participants were asked to complete a questionnaire that consisted of questions related to demographic information, alcohol, tobacco, and other drug use, sexual practices, diet, environmental exposures, oral hygiene, general hygiene, cancer history, and general health. In addition, HIV-infected patients were asked questions related to their HIV disease status, such as CD4 cell count, HIV viral load, and medication adherence. For women, Pap smear history was asked. For men, Pap smear history of their current partner (if female) was asked. Few men had received anal pap smears.

**Medical Record Abstraction (HIV-infected Patients)**

Selected clinical information that is relevant to oral HPV infection was abstracted from the medical records. The information was abstracted from only HIV-infected study

participants' medical records. The medical record review was conducted only for HIV

patients because there was no guarantee that participants in other study groups (i.e.

HARC clients and self-reported HIV-negative individuals from the UM Clinical Research

Volunteers registry) had been seen in the University of Michigan Health System. Using

Careweb, the UMHS's electronic medical record system, HIV viral load, CD4 cell count,

CD4 cell nadir, current HIV medications, sexually transmitted diseases (STD), previous

cancer diagnosis, and evidence of non-oral HPV-associated diseases were abstracted

from patients' medical records.

## Specimen Collection (All study groups)

Oral rinse samples were collected from study participants using a validated

method as previously described (22). Ten mL of mouthwash was swished and gargled

for 30 seconds, and expectorated into a sterile tube. Specimens were refrigerated at

4°C until processed. The oral rinse samples were centrifuged at 3,000g for 10 min at

4°C. The supernatant was decanted, and the pellet was resuspended in 10 ml of

phosphate-buffered saline. The centrifugation was repeated and DNA isolation

immediately followed.

## DNA Isolation (All study groups)

DNA was extracted using Puregene DNA Purification Kit according to the

manufacturer's protocol. This kit was chosen because it has been shown that other

methods have resulted in a greater loss of DNA during the purification process. These

methods included: proteinase K digestion (PKD) and heat inactivation; PKD and ethanol

precipitation (EP); PKD, phenol-chloroform extraction, and EP; and the QIAamp DNA

Blood Midi kit. In addition, DNA obtained from these methods may result in PCR

inhibition (23). Replicate study Isolated DNA was stored at -80°C until HPV detection

and genotyping were conducted.


**HPV Detection (All study groups)**

Isolated DNA was tested for presence and type of HPV using two different

detection methods: 1) Multiplex PCR MassArray, and 2) PCR followed by sequencing.

1) HPV Multiplex PCR MassArray: DNA samples were assayed in quadruplicate

using a validated, ultra-sensitive method utilizing real-time competitive polymerase

chain reaction, followed by probe-specific single base extension and matrix-assisted

laser desorption/ionization-time of flight mass spectroscopy with separation of products

on a matrix-loaded silicon chip array. Multiplex PCR amplification of the E6 region of 15

discrete high-risk HPV types (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68

and 73), 3 low-risk HPV types (HPV 6, 11, and 90), and a human GAPDH control was

processed to saturation, followed by shrimp alkaline phosphatase quenching.

Amplification reactions included synthetic competitor oligonucleotides identical to each

natural amplicon except for a single nucleotide difference. This suppressed background

and false-positive signal generation. Multiplex single base extension reactions

employed probes that identified unique sequences in the E6 region of each hrHPV type,

extending at the single distinguishable base of wild type and competitor amplicons.

Each hrHPV type and its competitor were recognized by mass in assay-defined profiles

when analyzed on the (Matrix Assisted Laser Desorption Ionization-Time of Flight)

MALDI-TOF mass spectrometer (24) thus identifying the presence and type of HPV in the sample.

2) HPV-L1-PCR followed by sequencing: Consensus PCR targeting the L1 region of the HPV viral genome was performed on all DNA samples using PGMY 09/11 primers (25). Gel electrophoresis was performed with a 1.5% agarose gel containing 0.25 ug/mL ethidium bromide in 1X TAE buffer at 90V for 80 minutes. The PCR products with 450bp fragments were purified with QIAquick PCR Purification Kit (Qiagen) according to the manufacturer's protocol and were sequenced using Sanger method to identify the HPV type.

HPV types detected from these two detection methods were categorized into high-risk (oncogenic) and low-risk (non-oncogenic) types according to the classification established by the World Health Organization's International Agency for Research Center (26-28).

**Statistical Analysis**

Prevalence of oral HPV infections was calculated for each study group. The demographic characteristics of HIV-positive and HIV-negative groups were compared using $\chi^2$ test or the Fisher's exact test, where appropriate, for categorical variables, whereas ANOVA was used for continuous variables. Logistic regression models were used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for associations between demographic and exposure variables from the survey and medical record review and the presence of oral HPV DNA. HPV DNA positivity was defined as any positive test result for at least one of the 18 genotypes detected by HPV Multiplex PCR

MassArray or any HPV genotype detected from sequencing. Tests for trend were conducted across ordered groups. Variables that were significant in univariate analysis were evaluated in multiple logistic regression models. Variables that were considered to be relevant based on *a priori* knowledge were also included. The final multivariate model for the overall study included gender, lifetime number of vaginal sex partners, and male partner circumcision. Study group could not be included in the final multivariate model because of small numbers of HPV detected in the "tested HIV-negative" and the "self-reported HIV-negative" groups. An attempt was made to include HIV status in the final multivariate model; however, the number of HPV detected in the HIV-negative population was still too small, even after combining the two HIV-negative groups. For the HIV-infected group, the final multivariate model included gender, lifetime number of vaginal sex partners, male partner circumcision status, and HIV RNA load. Because such a small number of HPV-positive individuals was detected in the HIV-negative groups, meaningful models could not be created after stratification. Therefore, separate multivariate models were created for all three study groups combined. The final multivariate model for this included gender, lifetime number of vaginal sex partners, and male partner circumcision status. P-values less than 0.05 were considered statistically significant, and all p-values reported were 2-sided. All analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC).

## Results

**Participant Characteristics**

A total of 266 individuals participated in the study, 107 of whom were HIV-infected patients, 69 who tested HIV-negative, and 90 self-reported HIV-negative individuals. The characteristics of the study population, stratified by study site, are shown in table 1. All three study groups were primarily White (>50%). While HIV-positive and self-reported HIV-negative groups were similar in median age (47 years vs. 45 years, respectively), the "tested HIV-negative" group was considerably younger (28 years). A majority of HIV-positive and "tested HIV-negative" groups were male, while self-reported HIV-negative had a roughly equal proportion of male and female participants. Overall, participants were well-educated, with more than 85% having completed high school. The HIV-positive group was more likely to have smoked cigarettes at least once (60%) and to currently smoke marijuana. The highest proportion of current drinkers was among "tested HIV-negative" individuals.

Table 2 describes characteristics related to sexual behavior. In the HIV-positive group, nearly 70% of men were men who have sex with men (MSM) and 16% were bisexual, whereas all 18 women were heterosexual. In the "tested HIV-negative" group, a majority of men (61%) were also MSM, and a majority of women reported being heterosexual. Both self-reported HIV-negative men and women were predominantly heterosexual. HIV-positive men reported the youngest average age at first anal intercourse and at first oral sex.

**Prevalence of HPV DNA by Study Group**

Two hundred sixty six oral rinses were collected. To date, all 266 have been tested for HPV infection using PGMY 09/11 L1 consensus primers. These samples were determined as evaluable based on the presence of β-globin. Of these 266 samples, 228 (105 HIV-positive, 52 tested HIV-negative, and 71 self-reported HIV-negative) were also tested for HPV infection via multiplex PCR MassArray. The remainder has not been tested due to time constraints. With the PGMY and PCR MassArray results combined, oral HPV infections were detected in 20.1% (22/107) of HIV-positive individuals, 1.4% (1/69) of individuals that tested HIV-negative, and 5.6% (5/90) of self-reported HIV-negative individuals. The overall prevalence of oral HPV infection in the study was 10.5% (table 3). Eight individuals had more than one HPV type. Of the 28 HPV DNAs detected in the oral rinses from the whole group, 75% (21/28) were high-risk, and 14.3% (4/28) were low-risk types. In the HIV-positive group, 75% (17/22) of HPV DNAs detected were high-risk HPV types (hrHPV) while 14% (3/22) were low-risk HPV types (lrHPV). The remaining 27% (4/22) were unclassifiable because they are not known to belong to either category at this present time (26-28). These percentages exceed 100% because there were six HIV-positive individuals who were infected with more than one HPV type. Of the hrHPV types detected in this study group, 59% (10/17) were HPV 16. In the "tested HIV-negative" group, the only HPV-positive case that was detected was not a mucosal high-risk or low-risk type. In the self-reported HIV-negative group, 80% (4/5) oral HPVs were hrHPV while 20% (1/5) were lrHPV. There was also one sample that contained and unclassifiable HPV type and also, contained HPV type 31. Of 28 HPV-positive samples, 24 were detected by multiplex

PCR MassArray, and 4 additional samples were detected by L1 PCR and sequencing. Two of 28 DNA-positive samples were type-concordant between two detection methods (data not shown). In all study groups, HPV was detected more frequently in males.

As shown in table 4, gender, lifetime number of vaginal sex partners, and male partner circumcision were associated with oral HPV infection in univariate analysis. The odds of oral HPV infection were significantly higher among men (OR, 3.6; 95% CI, 1.1-12.4). The odds of oral HPV infection were significantly higher with increasing number of vaginal sex partners (OR, 3.4; 94% CI, 1.53-7.69). Having an uncircumcised male partner significantly increased the odds of oral HPV infection by nearly four-fold (OR, 3.93, 95% CI, 1.36-11.39). Alcohol use, which was marginally significant, had a protective effect against oral HPV infection (p=0.058, for trend). In addition to these factors, among HIV-positive individuals, the odds of oral HPV infection significantly increased with increasing HIV viral load (p=0.041, for trend) (table 5).

In multivariate analysis, the only variable that was significantly associated with oral HPV infection was male partner circumcision (table 6). In the HIV-positive group, having an uncircumcised partner significantly elevated the odds of oral HPV infection (OR, 4.54; 95% CI, 1.44-14.31). Similarly, in the overall study, the same variable increased the risk of oral HPV infection (OR, 3.85; 95% CI,1.28-11.56). The odds of oral HPV infection with increasing lifetime number of vaginal sex partners were marginally significant in both the HIV-positive group (OR, 3.12; 95% CI, 0.85-11.53) and the study as a whole (OR, 2.91; 95% CI, 0.82-10.35). Among HIV-positive individuals, the odds of oral HPV infection tended to increase with higher viral load, specifically over 100,000

copies/µl (OR, 16.24; 95% CI, 0.88-305.08); this relationship was marginally significant (p=0.063).

**Concordance between Sexual Partners**

Fourteen couples participated in the study. The characteristics of the couples and their HPV status are shown in table 7. Of the 14 couples, oral HPV infection was detected in only one pair. Both partners were HIV-positive and MSM. The partners' HPV DNA genotypes were not concordant, with partner A having three different types (HPV 32, 42, and 66) while partner B had four different types (HPV 13, 16, 52, and 74).

## Discussion

In the present cross-sectional study, HIV-positive individuals are significantly at increased risk of oral HPV infection compared to HIV-negative individuals. The prevalence of 20.1% in the HIV-positive group was within the range of previously reported HPV detection rates in HIV-positive populations, although this study was on the lower end of the spectrum (8-13, 17, 21, 29-38). In addition, hrHPV was more prevalent in the HIV-positive group than in HIV-negative groups. In this study, prevalence of hrHPV among HIV-positive individuals was 15.9%, which was in line with previous literature (9, 12, 29, 30, 34). Also consistent with the literature, HPV 16 was the most commonly detected hrHPV type (7-9, 12, 13, 21). However, provided that the prevalence of oral HPV 16 among HIV-infected adults has ranged from 0 to 6.1%, at 9.3%, the prevalence of HPV 16 in our study was the highest ever reported in an HIV-positive population (39). In contrast, the prevalence of lrHPV among HIV-positive

individuals (4.4%) was considerably lower than previously reported (8, 10, 11, 31). In addition to the classified hrHPV and lrHPV mucosal types (26-28), we detected 12 other HPV types that are considered mucosal and/or cutaneous from sequencing.

Given that we utilized two highly robust methods of HPV detection that included sequencing, it is unclear as to why the prevalence of oral HPV infection in our HIV-positive group is in the lower margin of previously reported prevalence ranges among HIV-positive populations in the United States, yet the prevalence of HPV 16 in the oral cavity of our HIV-positive patients is the highest documented. Since reduced CD4 count is associated with increased oral HPV prevalence (9, 12, 21, 29), the relatively low prevalence of oral HPV infection in our HIV-positive group may be explained by the larger proportion of immunocompetent HIV-positive patients who are very adherent with their antiviral medication regimens.

Despite the low overall prevalence of oral HPV infection in our HIV-positive individuals, a high prevalence of oral HPV 16 was observed. To explain the high prevalence of oral HPV 16, we hypothesize this may be partly due to risky behaviors practiced among MSM, specifically anal-to-oral sex. It has been shown that prevalence of genital HPV 16 is high among MSM (34, 40, 41). Our findings did not support an association between oral HPV infection and oral or anal sex as well as corresponding number of partners. Likewise, the lack of condom use for these behaviors was not associated with oral HPV infection. Since anal-to-oral sex was not assessed in this study, this could be an area that could be further explored.

This study compared oral HPV prevalence in HIV-positive individuals with the use of two HIV-negative reference groups. Due to the small sample size, we could not

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stratify the HIV-negative groups to thoroughly assess risk factors. However, it is important to note that higher oral HPV prevalence was observed among self-reported HIV-negative individuals than those who tested HIV-negative. This observation is counter-intuitive because one would expect that the "tested HIV-negative" group would be at higher risk since it is assumed that those who voluntarily seek out HIV testing must have had some level of risk to seek testing. However, it is quite possible that this group that was presumed to be of high risk may actually be the more conscientious group (e.g., repeat testers for HIV who had more exposure to sexual health education) compared to the self-reported HIV-negative group. Therefore, assessing knowledge and attitudes regarding sexual health could have explained this difference. In addition, the "tested HIV-negative" group was considerably younger than the HIV-positive group and the "self-reported HIV-negative" group. Oral HPV infection has been associated with increasing age (7). The younger average age of the "tested HIV-negative" group could explain the lower prevalence of the infection in this group compared to the "self-reported HIV-negative" group.

In reviewing the overall study findings, several factors that have previously been associated with oral HPV infection were not found to be significant in this study. For example, tobacco smoking, which was associated with oral HPV infection in a few studies (7, 17, 42), was not associated in the study, most likely due to a small number of heavy smokers in a study that consisted of 266 participants. Further, in previous studies, men had higher risk of oral HPV infection than women (6, 12, 43). However, we did not observe this in our study, nor did we observe an association between oral HPV infection and previously reported factors, including oral or anal sex (7, 8, 12, 17, 44);

corresponding number of partners (7, 9, 12, 29, 30); condom use for these sexual

behaviors (7); sexual orientation (29, 31, 34, 45, 46); and open-mouth kissing (17, 47).

Surprisingly, alcohol consumption had a protective effect against oral HPV infection

although this association was not statistically significant. This effect was possibly driven

by the larger proportion of drinkers in the "tested HIV-negative" group which incidentally

was our youngest study group since risk of oral HPV infection is associated with

increasing age (7, 12, 17). Alternatively, to explain a similar finding, Pickard and

colleagues (47) cited that alcohol may denature HPV viral capsid and prevent infection

(47, 48).

To our knowledge, this is the first study to report an association between oral

HPV infection and male partner circumcision. Lack of circumcision has been associated

with penile cancers (49-53), and 95% of penile cancers are squamous cell carcinoma,

of which HPV accounts for 22 to 66% (49). Lack of circumcision has been associated

with HIV transmission in the African continent, leading public health experts to propose

adult male circumcision as a means of intervention (54-56). Given the reported

association between oral sex and oral HPV infection (7, 12, 17), our finding implies that

circumcision could also reduce HPV transmission by removing the likely penile reservoir

for HPV.

There are a few limitations. The most obvious is the total sample size and power,

limiting the analysis of stratification by study group to compare oral HPV risk factors.

Second, the cross-sectional design did not allow us to establish a temporal relationship.

Third, the convenience sample of well-controlled HIV-positive patients at the University

of Michigan and HIV-negative individuals from Washtenaw county and surrounding

counties is dissimilar to the types of urban populations frequently studied in the United States.

Despite these limitations, our study has notable strengths. The study may represent middle America more appropriately; there was little variation in the HIV-positive population based on stable HIV disease status; and yet we still observed much higher incidence of oral HPV infection in this population. Our data is consistent with significantly previous reports of higher risk of oral HPV infection in HIV-positive individuals than in HIV-negative individuals (ref). Whether this is due to HIV status increasing risk of infection or to other risk factors is unknown. This is the first study to report that male circumcision may play a role in the transmission of oral HPV infection. Future studies will improve the understanding of risk factors for oral HPV infection, and should be carried out in a variety of populations to better investigate those factors associated with HPV-associated cancer. Ultimately developing specific preventative strategies to prevent oral HPV infection and developing screening tools may be of benefit in the future.

**Table 4.1: Characteristics of the Enrolled Study Population, by Study Group**

| Characteristics | Overall | HIV+ | | Tested HIV- | | Self-reported HIV- | |
|---|---|---|---|---|---|---|---|
| | | n | % | n | % | n | % |
| Total | 266 | 107 | 40.2 | 69 | 26.0 | 90 | 33.8 |
| | | | | | | | |
| Gender | | | | | | | |
| Female | 75 | 18 | 16.8 | 18 | 26.1 | 39 | 43.3 |
| Male | 191 | 89 | 83.2 | 51 | 73.9 | 51 | 56.7 |
| | | | | | | | |
| Age (median) | 41.5 | 47 (19-75) | | 28 (18-83) | | 45 (18-83) | |
| Female | 41 | 52.5 (33-63) | | 32 (19-64) | | 45 (18-83) | |
| Male | 45 | 46 (19-75) | | 26 (18-83) | | 44 (19-82) | |
| | | | | | | | |
| Race | | | | | | | |
| Asian | 12 | 1 | 0.93 | 5 | 7.25 | 6 | 6.67 |
| Black | 53 | 31 | 28.97 | 13 | 18.84 | 9 | 10.00 |
| Hispanic | 5 | 4 | 3.74 | 1 | 1.45 | 0 | 0.00 |
| Native American | 2 | 1 | 0.93 | 0 | 0.00 | 1 | 1.11 |
| White | 165 | 63 | 58.88 | 37 | 53.62 | 65 | 72.22 |
| Other | 24 | 4 | 3.74 | 12 | 17.39 | 8 | 8.89 |
| Unknown | 5 | 3 | 2.80 | 1 | 1.45 | 1 | 1.11 |
| | | | | | | | |
| Education | | | | | | | |
| < High school | 18 | 12 | 11.21 | 3 | 4.41 | 3 | 3.33 |
| High school graduate | 55 | 23 | 21.50 | 16 | 23.53 | 16 | 17.78 |
| Some college | 88 | 39 | 36.45 | 21 | 30.88 | 28 | 31.11 |
| College graduate | 55 | 24 | 22.43 | 10 | 14.71 | 21 | 23.33 |
| Advanced degree | 45 | 7 | 6.54 | 16 | 23.53 | 22 | 24.44 |
| Unknown | 4 | 2 | 1.86 | 2 | 2.94 | . | . |
| | | | | | | | |
| Marital Status | | | | | | | |
| Married | 56 | 19 | 17.76 | 4 | 5.80 | 33 | 36.67 |
| Living as married | 22 | 10 | 9.35 | 4 | 5.80 | 8 | 8.89 |
| Single | 145 | 61 | 57.01 | 52 | 75.36 | 32 | 35.56 |
| Widowed | 8 | 4 | 3.74 | 1 | 1.45 | 3 | 3.33 |
| Divorced | 33 | 12 | 11.21 | 8 | 11.59 | 13 | 14.44 |
| Unknown | 2 | 1 | 0.93 | . | . | 1 | 1.11 |
| | | | | | | | |
| Place lived longest | | | | | | | |
| USA | 246 | 101 | 94.39 | 61 | 88.41 | 84 | 93.33 |
| Other countries | 15 | 4 | 3.74 | 6 | 8.70 | 5 | 5.56 |
| Unknown | 5 | 2 | 1.87 | 2 | 2.90 | 1 | 1.11 |
| | | | | | | | |
| Tobacco use | | | | | | | |
| Current smoker | 55 | 27 | 25.23 | 18 | 26.09 | 10 | 11.11 |
| Former smoker | 77 | 36 | 33.64 | 11 | 15.94 | 30 | 33.33 |
| Never smoker | 133 | 43 | 40.19 | 40 | 57.97 | 50 | 55.56 |
| Unknown | 1 | 1 | 0.93 | . | 0.00 | . | 0.00 |
| | | | | | | | |
| Alcohol use | | | | | | | |
| Current drinker | 166 | 59 | 55.14 | 53 | 76.81 | 54 | 60.00 |
| Former drinker | 75 | 38 | 35.51 | 9 | 13.04 | 28 | 31.11 |
| Never drinker | 23 | 10 | 9.35 | 6 | 8.70 | 7 | 7.78 |
| Unknown | 2 | . | . | 1 | 1.45 | 1 | 1.11 |
| | | | | | | | |
| Marijuana use | | | | | | | |
| Current user | 60 | 34 | 31.78 | 19 | 27.54 | 7 | 7.78 |
| Former user | 93 | 35 | 32.71 | 22 | 31.88 | 36 | 40.00 |
| Never user | 113 | 38 | 35.51 | 28 | 40.58 | 47 | 52.22 |
| | | | | | | | |
| Other substance use | | | | | | | |
| No | 245 | 96 | 89.72 | 62 | 89.86 | 87 | 96.67 |
| Yes | 19 | 11 | 10.28 | 7 | 10.14 | 1 | 1.11 |
| Cocaine | 10 | 7 | N/A | 2 | N/A | 1 | N/A |
| Heroin | 1 | 1 | N/A | 0 | N/A | 0 | N/A |
| Unknown | 2 | 0 | 0.00 | 0 | 0.00 | 2 | 2.22 |

**Table 4.2: Characteristics Related to Sexual Behavior, by Study Group**

| Characteristics | HIV+ | | Tested HIV- | | Self-reported HIV- | |
|---|---|---|---|---|---|---|
| | M<br>n (%) | F<br>n (%) | M<br>n (%) | F<br>n (%) | M<br>n (%) | F<br>n (%) |
| **Sexual Preference** | | | | | | |
| Sex with men | 62(69.66) | 18(100.00) | 31(60.78) | 15(83.33) | 5(9.80) | 38(97.44) |
| Sex with women | 13(14.61) | 0(0.00) | 16(31.37) | 0(0.00) | 43(84.31) | 1(2.56) |
| Sex with men and women | 14(15.73) | 0(0.00) | 4(7.84) | 3(16.67) | 2(3.92) | 0(0.00) |
| Unknown | 0(0.00) | 0(0.00) | 0(0.00) | 0(0.00) | 1(1.96) | 0(0.00) |
| **Age at first vaginal sex, mean (range)** | 15.8<br>(3-27) | 16.5<br>(7-21) | 17.4<br>(9-26) | 17.8<br>(11-30) | 17.7<br>(12-28) | 18.6<br>(10-24) |
| **Lifetime number of vaginal sex partners** | | | | | | |
| 0-5 | 70(78.65) | 16(88.89) | 39(76.47) | 17 (94.44) | 25(49.02) | 38(97.44) |
| ≥ 6 | 19(21.35) | 2(11.11) | 12(23.53) | 1(5.56) | 26(50.98) | 1(2.56) |
| **Condom use during vaginal sex** | | | | | | |
| Never | 21(23.60) | 2(11.11) | 5(9.80) | 3(16.67) | 7(13.73) | 5(12.82) |
| Rarely | 14(15.73) | 6(33.33) | 6(11.76) | 4(22.22) | 13(25.49) | 12(30.77) |
| Most of the time | 20(22.47) | 7(38.89) | 11(21.57) | 6(33.33) | 24(47.06) | 11(28.21) |
| All the time | 10(11.24) | 2(11.11) | 8(15.69) | 4(22.22) | 2(3.92) | 4(10.26) |
| Unknown | 24(26.97) | 1(5.56) | 21(41.18) | 1(5.56) | 5(9.80) | 7(17.95) |
| **Age at first oral sex, mean (range)** | 17.5<br>(4-52) | 23.6<br>(16-40) | 18.2<br>(2-35) | 18<br>(1-32) | 19.6<br>(13-38) | 21.6<br>(10-45) |
| **Lifetime number of oral sex partners** | | | | | | |
| 0-5 | 80(89.89) | 18(100.00) | 40(78.43) | 17(94.44) | 31(60.78) | 38(97.44) |
| ≥ 6 | 9(10.11) | 0(0.00) | 11(21.57) | 1(5.56) | 20(39.22) | 1(2.56) |
| **Condom use during oral sex** | | | | | | |
| Never | 57(64.04) | 9(50.00) | 38(74.51) | 9(50.00) | 38(74.51) | 24(61.54) |
| Rarely | 21(23.60) | 2(11.11) | 9(17.65) | 6(33.33) | 3(5.88) | 6(15.38) |
| Most of the time | 7(7.87) | 0(0.00) | 1(1.96) | 1(5.56) | 2(3.92) | 0(0.00) |
| All the time | 1(1.12) | 1(5.56) | 1(1.96) | 0(0.00) | 0(0.00) | 0(0.00) |
| Unknown | 3(3.37) | 6(33.33) | 2(3.92) | 2(11.11) | 8(15.69) | 9(23.08) |
| **Age at first anal sex, mean (range)** | 18.9<br>(0-50) | 30.3<br>(21-40) | 23.9<br>(9-70) | 21.6<br>(17-32) | 23.7<br>(13-35) | 22.9<br>(1-30) |
| **Lifetime number of anal sex partners** | | | | | | |
| 0-5 | 89(100.00) | 18(100.00) | 48(94.12) | 18(100.00) | 50(98.04) | 39(100.00) |
| ≥ 6 | 0(0.00) | 0(0.00) | 3(5.88) | 0(0.00) | 1(1.96) | 0(0.00) |
| **Condom use during anal sex** | | | | | | |
| Never | 10(11.24) | 5(27.78) | 4(7.84) | 5(27.78) | 8(15.69) | 7(17.95) |
| Rarely | 30(33.71) | 3(16.67) | 10(19.61) | 2(11.11) | 2(3.92) | 2(5.13) |
| Most of the time | 32(35.96) | 0(0.00) | 20(39.22) | 3(16.67) | 5(9.80) | 0(0.00) |
| All the time | 9(10.11) | 0(0.00) | 10(19.61) | 1(5.56) | 7(13.73) | 1(2.56) |
| Unknown | 8(8.99) | 10(55.56) | 7(13.73) | 7(38.89) | 29(56.86) | 29(74.36) |
| **Age at first kiss, mean (range)** | 16.6<br>(3-30) | 15.3<br>(1-20) | 16.2<br>(6-25) | 16.8<br>(5-30) | 16.3<br>(10-27) | 17.2<br>(10-35) |
| **Lifetime number of kissing partners** | | | | | | |
| 0-5 | 70 (78.65) | 18(100.00) | 30(58.82) | 16(88.89) | 23(45.10) | 37(94.87) |
| ≥ 6 | 19(21.35) | 0(0.00) | 21(41.18) | 2(11.11) | 28(54.90) | 2(5.13) |

**Table 4.3: HPV Prevalence and Type Distribution, by Study Group**

| | Overall (n=266) | | HIV+ (n=107) | | Tested HIV- (n=69) | | Self-reported HIV- (n=90) | |
|---|---|---|---|---|---|---|---|---|
| | n | Prevalence (%) | n | Prevalence (%) | n | Prevalence (%) | n | Prevalence (%) |
| All | 28* | 10.5 | 22* | 20.1 | 1* | 1.4 | 5* | 5.6 |
| Male | 25 | 9.4 | 19 | 17.8 | 1 | 1.4 | 5 | 5.6 |
| Female | 3 | 1.1 | 3 | 2.8 | 0 | 0.0 | 0 | 0.0 |
| High-risk mucosal | 21* | 7.9 | 17* | 15.9 | 0 | 0.0 | 4* | 4.4 |
| 16 | 13 | 4.9 | 10 | 9.3 | 0 | 0.0 | 3 | 3.3 |
| 18 | 1 | 0.4 | 1 | 0.9 | 0 | 0.0 | 0 | 0.0 |
| 31 | 1 | 0.4 | 0 | 0.0 | 0 | 0.0 | 1 | 1.1 |
| 33 | 2 | 0.8 | 2 | 1.9 | 0 | 0.0 | 0 | 0.0 |
| 39 | 1 | 0.4 | 1 | 0.9 | 0 | 0.0 | 0 | 0.0 |
| 52 | 1 | 0.4 | 1 | 0.9 | 0 | 0.0 | 0 | 0.0 |
| 56 | 1 | 0.4 | 1 | 0.9 | 0 | 0.0 | 0 | 0.0 |
| 58 | 1 | 0.4 | 1 | 0.9 | 0 | 0.0 | 0 | 0.0 |
| 59 | 1 | 0.4 | 1 | 0.9 | 0 | 0.0 | 0 | 0.0 |
| Low-risk mucosal | 4* | 1.5 | 3* | 2.8 | 0* | 0.0 | 1* | 1.1 |
| 6 | 2 | 0.8 | 1 | 0.9 | 0 | 0.0 | 1 | 1.1 |
| 11 | 1 | 0.4 | 1 | 0.9 | 0 | 0.0 | 0 | 0.0 |
| 42 | 2 | 0.8 | 2 | 1.9 | 0 | 0.0 | 0 | 0.0 |
| 53 | 1 | 0.4 | 1 | 0.9 | 0 | 0.0 | 0 | 0.0 |
| 66 | 1 | 0.4 | 1 | 0.9 | 0 | 0.0 | 0 | 0.0 |
| 70 | 1 | 0.4 | 1 | 0.9 | 0 | 0.0 | 0 | 0.0 |
| Other | 8* | 3.0 | 6* | 5.6 | 1* | 1.4 | 1* | 1.1 |
| 2 | 1 | 0.4 | 1 | 0.9 | 0 | 0.0 | 0 | 0.0 |
| 2a | 1 | 0.4 | 1 | 0.9 | 0 | 0.0 | 0 | 0.0 |
| 13 | 1 | 0.4 | 1 | 0.9 | 0 | 0.0 | 0 | 0.0 |
| 27 | 1 | 0.4 | 1 | 0.9 | 0 | 0.0 | 0 | 0.0 |
| 27b | 1 | 0.4 | 1 | 0.9 | 0 | 0.0 | 0 | 0.0 |
| 32 | 1 | 0.4 | 2 | 1.9 | 0 | 0.0 | 0 | 0.0 |
| 44 | 1 | 0.4 | 0 | 0.0 | 1 | 1.4 | 0 | 0.0 |
| 55 | 1 | 0.4 | 0 | 0.0 | 1 | 1.4 | 0 | 0.0 |
| 57b | 1 | 0.4 | 1 | 0.9 | 0 | 0.0 | 0 | 0.0 |
| 74 | 1 | 0.4 | 1 | 0.9 | 0 | 0.0 | 0 | 0.0 |
| 90 | 2 | 0.8 | 1 | 0.9 | 0 | 0.0 | 1 | 1.1 |
| 107 | 1 | 0.4 | 1 | 0.9 | 0 | 0.0 | 0 | 0.0 |

*The number of individuals with oral HPV infection, using which the prevalence was calculated. There were 6 persons in HIV+ group, 1 person in HIV- group, and 1 person in self-reported HIV- group who were infected with more than one HPV type. The rest of the table show HPV type distribution and corresponding prevalence.

**Table 4.4: Risk Factors for Oral HPV Infection, Univariate Analysis**

| Variable | Univariate OR (CI) | Variable | Univariate OR (CI) |
|---|---|---|---|
| Sex | | Condom use during oral sex | |
|   Female | REF |   Most of the time | REF |
|   Male | 3.61 (1.06-12.36) |   Rarely | 0.92 (0.17-5.11) |
|   p-value | 0.028 |   Never | 0.45 (0.09-2.28) |
| Current age (in years) | |   p for test for trend | 0.128 |
|   < 30 | REF | Age at first anal sex | |
|   30-39 | 1.18 (0.30-4.64) |   ≥ 18 | REF |
|   40-49 | 1.90 (0.57-6.35) |   < 18 | 0.86 (0.45-2.17) |
|   50-59 | 3.78 (1.20-11.90) |   p-value | 0.704 |
|   ≥ 60 | 0.72 (0.13-3.87) | Lifetime number of anal sex partners | |
|   p for test for trend | 0.324 |   0 | REF |
| Tobacco use | |   1-3 | 1.26 (0.43-3.70) |
|   Never smoker | REF |   ≥ 4 | 1.32 (0.39-4.89) |
|   Former smoker | 1.51 (0.62-3.67) |   p for test for trend | 0.648 |
|   Current smoker | 1.24 (0.44-3.48) | Condom use during anal sex | |
|   p for test for trend | 0.54 |   All the time | REF |
| Second-hand smoking | |   Most of the time | 3.57 (0.42-30.49) |
|   No | REF |   Rarely | 6.07 (0.73-50.76) |
|   Yes | 0.52 (0.22-1.27) |   Never | 3.09 (0.33-30.49) |
|   p-value | 0.279 |   p for test for trend | 0.358 |
| Alcohol use | | Age at first kiss | |
|   Never drinker | REF |   ≥ 16 | REF |
|   Former drinker | 0.49 (0.15-1.65) |   < 16 | 1.41 (0.64-3.10) |
|   Current drinker | 0.33 (0.11-1.03) |   p-value | 0.387 |
|   p for test for trend | 0.065 | Lifetime number of kissing partners | |
| Age at first vaginal sex | |   0-5 | REF |
|   ≥ 16 | REF |   ≥ 6 | 1.88 (0.83-4.23) |
|   < 16 | 1.72 (0.78-3.78) |   p-value | 0.124 |
|   p-value | 0.179 | Male partner circumcision | |
| Lifetime number of vaginal sex partners | |   Yes | REF |
|   0-5 | REF |   No | 3.93 (1.36-11.39) |
|   ≥ 6 | 3.43 (1.53-7.69) |   p-value | 0.011 |
|   p-value | 0.002 | Study group | |
| Condom use during vaginal sex | |   Self-reported HIV- | REF |
|   All the time | REF |   Tested HIV- | 0.25 (0.03-2.19) |
|   Most of the time | 0.74 (0.17-3.17) |   p-value | 0.211 |
|   Rarely | 1.76 (0.44-7.07) |   HIV positive | 4.40 (1.59-12.16) |
|   Never | 1.46 (0.36-6.36) |   p-value | 0.004 |
|   p for test for trend | 0.270 | Sexual Preference* | |
| Age at first oral sex | |   Sex with women | REF |
|   ≥ 16 | REF |   Sex with men | 1.12 (0.43-2.89) |
|   < 16 | 1.78 (0.81-3.92) |   p-value | 0.821 |
|   p-value | 0.150 |   Sex with men and women | 2.66 (0.76-9.32) |
| Lifetime number of oral sex partners | |   p-value | 0.124 |
|   0-5 | REF | | |
|   ≥ 6 | 1.93 (0.77-4.89) | | |
|   p-value | 0.158 | | |

* Only men were included in this analysis

**Table 4.5: Characteristics Related to HIV Disease Status and Risks Associated with Oral HPV Infection, Univariate Analysis**

| Characteristics | N | % | Univariate OR (CI) |
|---|---|---|---|
| Nadir CD4 count (cells/µl), median (IQR) | 553 | (389-847) | |
| ≥ 200 | 72 | (69.90) | REF |
| < 200 | 31 | (30.10) | 1.86 (0.70-4.95) |
| p-value | | | 0.216 |
| CD4 count (cells/µl), median (IQR) | 553 | (389-847) | |
| ≥ 200 | 103 | (88.35) | REF |
| < 200 | 12 | (11.65) | 1.32 (0.27-6.54) |
| p-value | | | 0.734 |
| HIV viral load (copies/µl), median (IQR) | 0 | (0-39) | |
| Undetectable | 244 | (91.73) | REF |
| 40-99,999 | 20 | (7.52) | 2.40 (0.74-7.79) |
| ≥ 100,000 | 2 | (0.75) | 9.61 (0.58-158.78) |
| p-value | | | 0.041 |
| Current ART Therapy | | | |
| Yes | 97 | (90.65) | REF |
| No | 10 | (9.35) | 0.96 (0.19-4.89) |
| p-value | | | 0.964 |

**Table 4.6: Risk Factors for Oral HPV Infection, Multivariate Analysis**

| Variable | Multivariate OR (CI) | p-value |
|---|---|---|
| All 3 Groups Included | | |
| Sex | | |
|   Female | REF | |
|   Male | 2.59 (0.67-10.00) | 0.166 |
| Lifetime number of vaginal sex partners | | |
|   0-5 | REF | |
|   ≥ 6 | 2.91 (0.82-10.35) | 0.099 |
| Male partner circumcision | | |
|   Yes | REF | |
|   No | 3.85 (1.28-11.56) | 0.016 |
| HIV Group Only | | |
| Sex | | |
|   Female | REF | |
|   Male | 2.33 (0.59-9.17) | 0.227 |
| Lifetime number of vaginal sex partners | | |
|   0-5 | REF | |
|   ≥ 6 | 3.12 (0.85-11.53) | 0.088 |
| Male partner circumcision | | |
|   Yes | REF | |
|   No | 4.54 (1.44-14.31) | 0.001 |
| HIV viral load (copies/µl) | | |
|   Undetectable | REF | |
|   40-99,999 | 1.78 (0.30-10.42) | 0.524 |
|   ≥ 100,000 | 16.24 (0.88-305.08) | 0.063 |

**Table 4.7: Concordance of Oral HPV Infection between Partners**

| Couple | Gender | HIV Status | HPV Status (Type) | Sexual Preference |
|--------|--------|-----------|-------------------|-------------------|
| 1 | Male | HIV- | Negative | Heterosexual |
|   | Female | HIV- | Negative | Heterosexual |
| 2 | Male | HIV+ | Negative | Heterosexual |
|   | Female | HIV- | Negative | Heterosexual |
| 3 | Male | HIV- | Negative | MSM |
|   | Male | HIV- | Negative | Bisexual |
| 4 | Male | HIV- | Negative | Heterosexual |
|   | Female | HIV- | Negative | Heterosexual |
| 5 | Male | HIV- | Negative | Heterosexual |
|   | Female | HIV- | Negative | Heterosexual |
| 6 | Male | HIV- | Negative | MSM |
|   | Male | HIV- | Negative | MSM |
| 7 | Male | HIV- | Negative | Heterosexual |
|   | Female | HIV- | Negative | Heterosexual |
| 8 | Male | HIV- | Negative | Heterosexual |
|   | Female | HIV- | Negative | Heterosexual |
| 9 | Male | HIV+ | Negative | Heterosexual |
|   | Female | HIV+ | Negative | Heterosexual |
| 10 | Male | HIV+ | Negative | MSM |
|    | Male | HIV+ | Negative | MSM |
| 11 | Male | HIV+ | Negative | Bisexual |
|    | Female | HIV- | Negative | Heterosexual |
| 12 | Male | HIV+ | Positive (66, 32, 42) | MSM |
|    | Male | HIV+ | Positive (16, 13, 52, 74) | MSM |
| 13 | Male | HIV+ | Negative | MSM |
|    | Male | HIV- | Negative | MSM |
| 14 | Male | HIV+ | Negative | MSM |
|    | Male, | HIV- | Negative | MSM |

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# CHAPTER 5

## Assessment of Informational Concordance
## between HIV Patients and Physicians

### Abstract

**Background:** For research studies collecting self-reported data, the validity of data is often unknown, especially when studies involve sensitive populations. Whenever possible, it is important to cross-check the data with other data sources.

**Methods:** This study was nested within a cross-sectional study that investigated the prevalence of oral HPV infection in HIV-positive and HIV-negative individuals in Michigan. A self-administered questionnaire was completed by all study participants. For HIV-infected participants, medical records were abstracted for selected variables that are known to be associated with HPV infection and for information related to HIV disease status. Concordance, sensitivity, and specificity were assessed between the data from the self-report and the medical records.

**Results:** Of 266 participants in the main cross-sectional study, 106 HIV-positive individuals were eligible for the nested analsis. Therefore, information from the medical records was obtained from these 106 study participants. Overall there was good concordance between the self-reported data and the medical records. The items that had substantial agreement were related to the family history of cancer. The items that

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were least likely to be concordant were patients' condom use, alcohol consumption, and marijuana use.

**Conclusion:** Our findings indicate that concordance varied depending on questionnaire items The self-administered questionnaire tended to be more reliable for questions that were more sensitive in nature, while the medical records were more reliable for items that required laboratory testing and confirmation of disease status.

## Introduction

Epidemiological studies often utilize questionnaires to gather self-reported information from study participants. In such studies, the validity relies heavily on the quality of the data that study participants provide. There is a variety of sources that may undermine the quality of self-reported information. While a recall bias due to time lapse is a well-known source of error (1-3), personal characteristics, such as age, socioeconomic status, education, patient's medical knowledge, and anxiety level have also been associated with accuracy of self-reported information (3-6). Biases may also stem from sources other than study participants, including questionnaire content/wording, interviewing technique, and environment in which a study is conducted (1, 3, 4, 7-9). Further, it has been suggested that trust in the healthcare system may affect participation in research studies (10).

Important work has been done to compare informational concordance between physicians and patients. A vast majority have focused on healthcare utilization (11-19), diagnostic tools (7, 20-23), specific diseases (24, 25), and medication use (26-29). However, little research has been done on the validity of self-reporting for disease

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classification in research studies (30, 31), even though self-reported information could also play a role in improving the quality of care.

HIV-positive individuals are at risk of co-infection with different sexually transmitted diseases (STDs). This is partly due to the shared sexual behavioral factors (32) as well as other behaviors, such as substance use, that are associated with risky sexual behaviors (33-35). Assessing risky behaviors in conjunction with HIV co-infection is not only important from the patient treatment perspective, but also from the prevention standpoint. However, because providers must ask sensitive questions regarding patient behavior, it is challenging to accurately assess the patient's risk for other diseases. There are studies that have evaluated which source of data (i.e., physicians vs. patients) is more reliable (24, 36, 37). However, such a question has not been thoroughly explored in HIV-positive populations.

Our group recently completed a cross-sectional study consisting of HIV-infected individuals in a university hospital setting to investigate the prevalence and risk factors for oral HPV infection. Since this study gathered information through participant self-report and medical record review, we performed sub-analysis to assess the agreement between these two data sources.

## Methods

### Study Population

This analysis is nested within our cross-sectional study to investigate the prevalence of oral HPV infection in HIV-infected population compared to two different HIV-negative populations. HIV-infected patients were recruited from the HIV/AIDS

Treatment Program at the University of Michigan (UM) between May 2012 and August 2013. Two HIV-negative study groups were formed: individuals who tested HIV-negative at HIV/AIDS Resources Center (HARC), a community health organization serving several counties in Michigan; and self-reported HIV-negative individuals in the UM Clinical Research Volunteers registry. The study was approved by the Institutional Review Board of the University of Michigan Medical School (application number HUM00047989), and written informed consent was obtained from all participants.

**Social Behaviors and Family History Survey**

A questionnaire was administered to all study participants. The following information was collected: demographic factors, alcohol, tobacco, and other drug use, sexual practices, diet, environmental exposures, oral hygiene, general hygiene, cancer history, and general health. In addition, the HIV-infected participants were asked about their HIV disease status and medication adherence. Participants completed the questionnaire in a quiet, private room, and were asked to place the questionnaires into a plain envelope upon completion.

**Medical Record Abstraction**

Selected clinical information that was relevant to oral HPV infection was abstracted from medical records based on *a priori* knowledge. These are tobacco, alcohol, and marijuana use, sexually transmitted diseases, condom use, previous cancer diagnosis, and evidence of non-oral HPV-associated diseases. Additionally, the following clinical and laboratory information pertaining to HIV was abstracted: HIV viral

load, CD4 cell count, CD4 cell nadir, and current HIV medications. The medical record review was conducted for only HIV-infected patients because the participants in other study groups (i.e., HARC clients and self-reported HIV-negative individuals from the UM Clinical Research Volunteers registry) are not necessarily seen in the University of Michigan Health System and medical records for these groups were therefore unavailable.

**Statistical Analysis**

Although our questionnaire consisted of a wide range of questions, our analysis in this study was focused on the items that could be obtained from the medical records, since many of the variables in our questionnaire are not typically asked by the clinicians as part of the standard of care. Therefore, we focused our abstraction on three main domains which are as follow: substance use, health status, and family history of cancer.

We report the demographic characteristics and frequency of the aforementioned questionnaire items. To assess the degree of overlap between patient self-reported data and corresponding items in the medical records, we computed the percent total agreement, defined as the sum of percent agreement on positives and negatives. To evaluate concordance, Cohen's kappa statistic was computed (38). Since the p-value for kappa indicates whether the estimated kappa is not due to chance (39), 95% confidence intervals were generated to evaluate the degree of agreement.

Due to the assumption that either data source could serve as the gold standard and that which data source should serve as the gold standard depends on the nature of

the question, the sensitivity and specificity were calculated twice. The first approach considered the self-reported data as the gold standard, and second approach considered the medical records as the gold standard. The sensitivity and specificity were calculated for only dichotomous variables. For condom use, the answer choices in our survey was ordinal (i.e., always, almost always, rarely, and never), but such a way of reporting was not available in the medical records. Therefore, this variable was dichotomized by considering the responses in the "always" and "almost always" categories as using condoms, whereas the responses in the "rarely" and "never" categories were defined as not using condoms.  All statistical analysis was performed using SAS version 9.3 (SAS Institute, Cary, NC).

## Results

### Participant Characteristics

Of 266 individuals who participated in the study, 107 were HIV-infected patients. Medical records were available from 106 HIV-infected patients. One patient was newly diagnosed and therefore did not have sufficient information in the medical records to be included in our analysis. The characteristics of the study population are shown in table 1. The majority of participants are white (59%) and male (83%). They are well-educated, with 87% having completed high school. The median age was 47 (52.5 in women, 46 in men), and 57% were single.

**Concordance**

Table 2 describes the frequencies of self-reported and abstracted data items, their corresponding agreement in percentages, kappa values, and 95% confidence intervals. In addition, two sets of sensitivity, and specificity are reported, one assuming the patient self-reported data is the gold standard, and the other assuming the medical records is the gold standard.

Overall, there was good agreement between the self-reported data and the medical records. There was over 80% total agreement on the majority of the items, and only four items had less overlap. These latter items, namely condom use, alcohol consumption, marijuana use, and skin warts, had total agreement percentages of 48%, 61%, 63%, and 66%, respectively.

Concordance was also good according to kappa. Patient's mother's cancer status (kappa=0.84) had almost perfect agreement. Substantial concordance (kappa between 0.61 and 0.80) was observed in tobacco smoking, tobacco chewing, patients' CD4 count ever falling below 200, patient's father's cancer status, patient's own cancer status, and patient's children's cancer status. Items with moderate concordance (kappa between 0.41 and 0.60) were HPV vaccine status, genital warts, genital herpes, syphilis, marijuana use, other substance use, patient's sister's cancer status, and patient's brother's cancer status. There was a fair degree of concordance (kappa between 0.21 and 0.40) in alcohol consumption and cigar use. Slight agreement (kappa between 0.01 and 0.20) was observed among chlamydia, oral herpes, skin warts, and HIV medication adherence. Concordance was the lowest in condom use, and this agreement was less than by chance.

**Sensitivity and Specificity**

There was a great variety in the sensitivity and specificity between the two gold standards (table 3). High sensitivity and high specificity were observed in both the self-reported data and the medical records for the following items: tobacco chewing, chlamydia, HIV-medication adherence, and ever having CD4 count fall below 200. Low sensitivity and low specificity were observed in both data sources for condom use. When the self-reported data was considered as the gold standard, sensitivity was considerably lower than that of the medical records for the following variables: cigar use, other substance use, syphilis, genital warts, skin warts, and the receipt of HPV vaccine. The specificity was comparable between the two data sources for all variables except other substance use and skin warts. Specificity for other substance use in the self-reported data was lower than in the medical records. On the contrary, it was higher for skin warts in the self-reported data than the medical records.

With regard to the family history of cancer, sensitivity varied again between the two data sources, but specificity was comparable across all variables. Sensitivity ranged from 50 to 100% when the self-reported data was considered the gold standard, and it ranged from 43% to 86% when the medical records were used as the gold standard.

## Discussion

Moderate to substantial agreement between the self-reported data and the medical records was observed in this study. The questionnaire offered a greater abundance of information relevant to the EPI study than the medical records. Since the purpose of the questionnaire was to ascertain the risk factors for oral HPV infection, the

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information for which was asked in the questionnaire may not have been covered extensively in the medical records. Further, the same questionnaires were administered to all our study participants, ensuring consistency of the information captured. However, the extent of information in the medical records varied by physicians. In addition, the survey questions were worded to cover the lifetime of patients; however, our medical records do not necessarily account for this, and we had no access to outside medical records for patients who are concurrently seeking or previously sought care at other institutions. Therefore, missing data may have contributed to the discrepancies in the frequency of the reported items.

Among the items in the substance use category, there was substantial agreement between the self-reported data and the medical records for tobacco smoking and tobacco chewing. However, there was only fair agreement for cigar use and alcohol consumption, and moderate agreement for marijuana use and substance use. Cigar use is a rare event in the current generation (i.e., there were only two individuals identified in the medical records), and for rare findings, low kappa values may not necessarily reflect overall agreement (39). Regarding alcohol consumption, marijuana use, and other substance use, discordance may have resulted from the social desirability effect. It is well-known that behaviors that are perceived to be socially undesirable may be underreported (1, 40, 41). As an added explanation as to why the sensitivity was particularly low for "other substance use" question, the way in which this question was posed may have been an issue. This question required an open-ended response, and it has been reported that the open-ended format can decrease agreement (42). Further, in studies examining the sensitivity of recollection of drug use, sensitivity was higher for

questions about medications used for a specific indication than for the open-ended

questions (9). It is important to note that the variables assessed in this category are

dynamic in nature. Behaviors could have changed over time between the time they

were reported in the medical records and the time the self-administered survey was

completed. Therefore, a time lag could in part explain the discordance.

In the health category, sensitivity was higher for all items, except condom use,

when the medical records were considered as the gold standard. With regard to STDs,

a possible explanation for such a trend is that STDs are often asymptomatic and require

laboratory testing for accurate diagnosis. If infected individuals are not aware of their

STD status, this could lead to underreporting. Even if they are symptomatic, they may

misclassify symptoms for another disease. These hypotheses may explain the low

sensitivity when self-reported data was used as the gold standard. Previously, it has

been suggested that for diseases that require testing for diagnosis, self-reporting is

highly accurate (30). This reasoning probably holds for our observations, given that very

high specificity was observed in all questionnaire items regarding STDs and HPV

vaccination status. Further, these high specificity values were comparable to those of

the medical records, when the self-reported data were used as the gold standard.

Therefore, the lack of patients' awareness of the disease and vaccination status may

have contributed to moderate agreement according to the kappa statistics.

The highly discordant reporting regarding condom use is troubling. It is unlikely

that dichotomizing this variable led to such a low percentage of total agreement and a

low kappa value; in fact, dichotomizing should have boosted the values since it reduced

opportunities for misclassification. Patients are likely to know that physicians expect

patients to report consistent condom use, and that if patients report otherwise, this will lead to extensive counseling. Therefore, social undesirability should be high when responding to physicians. Likewise, such biases are prevalent in questions associated with condom use (43-46). Thus we attribute discordant results due to recall bias and social desirability bias.

For the family history of cancer, the agreement ranged from "moderate" to "almost perfect." The percentage of individuals who self-reported the presence of cancer agreed with the medical records was 90%, which is consistent with a study previously done in an HIV-positive population (31). The sensitivity in our study was higher. The difference could be explained by a higher proportion of white participants and lower prevalence of substance use in our population, as these factors are associated with more accurate reporting (30, 31). Although the study in question did not measure the participants' level of education, this factor may also explain the difference since higher education attainment is associated with improved self-reporting of cancer diagnoses (47). As for the concordance rates, sensitivity, and specificity of family members' cancer status, the accuracy of reporting may have been influenced by the degree in which the study participants are affected by their family members' disease. It has been reported that the individuals who correctly reported disease status were most likely to  be first-degree relatives, such as parents, siblings, and offsprings (48).

There are important implications of validation studies such as this study. From the research standpoint, reliance on patient self-reporting without validation can lead to misclassification of disease, which in turn may affect outcomes of a study. Consistent with previous studies, our study indicates that accuracy of self-reporting differs by

disease classification. The data from our study suggests that medical records are a more reliable source of information for STDs. This study of concordance between self-reported data and medical records also has clinical significance, as the results could serve as an indicator of the level of patient-physician interaction. Improving communication and efforts to educate some patients regarding their own health status is encouraged.

Our study had important limitations. First, given the small sample size, the results must be interpreted with caution. Second, even if the percent total agreement and kappa values were perfect, we cannot be certain of the veracity of the information provided. By definition, sensitivity is the proportion of individuals who have the disease that report having the disease, and specificity is the proportion of individuals who do not have the disease that report not having the disease (49). However, in reality just as there is a possibility that individuals have always told the truth (i.e., to their medical providers and in our study questionnaires), it is also possible that individuals consistently provided false information. Therefore, misclassification of information is inevitable. Third, there was considerable variability in physician reporting of patients' medical information. Even though we utilized two independent individuals to extract relevant information from the medical records to ensure a thorough review, we recognize that some information was not available because of the degree of thoroughness in physician clinic notes. Lastly, the findings from this study cannot be generalized to other HIV-positive populations across the United States due to demographic differences.

In spite of these limitations, we identified preferred data sources for each of the questionnaire items. The self-administered questionnaire was more reliable for the items related to substance use, while the medical records were more accurate in the reporting of health-related items. Both sources of data were equally reliable in reporting the family history of cancer. Since concordance between patient self-reporting and medical records could vary depending on the domain and item of questions asked, recall ability, and disease area (1, 30, 50-52), additional research is needed to include a wider range of questions and domains while carefully designing the study and questionnaires to minimize bias.

**Table 5.1: Study Participant Characteristics**

| Characteristics | n | % |
|---|---|---|
| Total | 107 | 40.2 |
| Gender | | |
|   Female | 18 | 16.8 |
|   Male | 89 | 83.2 |
| | | |
| Age (median) | 47 (19-75) | |
|   Female | 52.5 (33-63) | |
|   Male | 46 (19-75) | |
| | | |
| Race | | |
|   Asian | 1 | 0.93 |
|   Black | 31 | 28.97 |
|   Hispanic | 4 | 3.74 |
|   Native American | 1 | 0.93 |
|   White | 63 | 58.88 |
|   Other | 4 | 3.74 |
|   Unknown | 3 | 2.80 |
| | | |
| Education | | |
|   < High school | 12 | 11.21 |
|   High school graduate | 23 | 21.50 |
|   Some college | 39 | 36.45 |
|   College graduate | 24 | 22.43 |
|   Advanced degree | 7 | 6.54 |
|   Unknown | 2 | 1.86 |
| | | |
| Marital Status | | |
|   Married | 19 | 17.76 |
|   Living as married | 10 | 9.35 |
|   Single | 61 | 57.01 |
|   Widowed | 4 | 3.74 |
|   Divorced | 12 | 11.21 |
|   Unknown | 1 | 0.93 |

**Table 5.2: Measures of Concordance**

| Item | Frequency Reported | | Measures of Concordance | |
| --- | --- | --- | --- | --- |
| | Patient Only | Physician Only | % Total Agreement | Kappa (CI) |
| **Substance Use** | | | | |
| Tobacco smoking | | | | |
| Current smoker | 27 | 30 | 85.7 | 0.78 (0.68-0.88) |
| Former smoker | 36 | 34 | | |
| Never smoker | 43 | 42 | | |
| Cigar use | | | | |
| Former user | 14 | 2 | 91.3 | 0.34 (-0.01-0.69) |
| Never user | 91 | 79 | | |
| Tobacco chewing | | | | |
| Former user | 102 | 89 | 95.0 | 0.73 (0.51-0.96) |
| Never user | 4 | 3 | | |
| Marijuana use | | | | |
| Current user | 34 | 33 | 62.9 | 0.44 (0.31-0.56) |
| Former user | 35 | 13 | | |
| Never user | 38 | 59 | | |
| Other substance use | | | | |
| Current user | 11 | 6 | 91.5 | 0.43 (0.12-0.73) |
| Never user | 96 | 100 | | |
| Alcohol consumption | | | | |
| Current drinker | 59 | 59 | 61.3 | 0.38 (0.27-0.50) |
| Former drinker | 38 | 11 | | |
| Never drinker | 10 | 36 | | |
| **Health** | | | | |
| Chlamydia | | | | |
| Yes | 22 | 1 | 79.3 | 0.08 (-0.07-0.23) |
| No | 77 | 93 | | |
| Genital herpes | | | | |
| Yes | 11 | 11 | 90.8 | 0.48 (0.19-0.77) |
| No | 89 | 94 | | |

| | | | | |
|---|---|---|---|---|
| **Oral herpes** | | | | |
| Yes | 11 | 7 | 86.3 | 0.17 (-0.11-0.45) |
| No | 86 | 98 | | |
| **Syphilis** | | | | |
| Yes | 19 | 12 | 83.3 | 0.45 (0.22-0.69) |
| No | 80 | 91 | | |
| **Genital warts** | | | | |
| Yes | 20 | 20 | 88.0 | 0.58 (0.37-0.80) |
| No | 82 | 86 | | |
| **Skin warts** | | | | |
| Yes | 35 | 5 | 66.0 | 0.07 (-0.06-0.19) |
| No | 66 | 101 | | |
| **Condom use** | | | | |
| Yes | 61 | 42 | 48.4 | -0.11 (-0.35-0.13) |
| No | 45 | 23 | | |
| **HPV vaccine** | | | | |
| Received | 10 | 5 | 92.9 | 0.58 (0.26-0.90) |
| Not received | 61 | 101 | | |
| **HIV medication adherence** | | | | |
| Take medicines everyday | 98 | 83 | 82.8 | 0.13 (-0.08-0.35) |
| Do not take medicines everyday | 6 | 18 | | |
| **Ever had CD4 count below 200** | | | | |
| Yes | 47 | 51 | 84.7 | 0.70 (0.54-0.85) |
| No | 41 | 53 | | |
| **Family History of Cancer** | | | | |
| Patient's cancer status | 25 | 20 | 89.7 | 0.69 (0.52-0.86) |
| Father's cancer status | 21 | 22 | 89.3 | 0.71 (0.53-0.89) |
| Mother's cancer status | 21 | 21 | 94.6 | 0.84 (0.71-0.98) |
| Brother's cancer status | 4 | 4 | 90.0 | 0.44 (-0.01-0.90) |
| Sister's cancer status | 7 | 7 | 89.4 | 0.49 (0.11-0.87) |
| Children's cancer status | 1 | 2 | 90.0 | 0.62 (-0.04-1.00) |

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## Table 5.3: Sensitivity and Specificity

| Item | Patient self-report as Gold Standard | | Physician-report as Gold Standard | |
|---|---|---|---|---|
| | Sensitivity | Specificity | Sensitivity | Specificity |
| **Substance Use** | | | | |
| Tobacco smoking | | | | |
| Current smoker | - | - | - | - |
| Former smoker | | | | |
| Never smoker | | | | |
| Cigar use | | | | |
| Former user | 22.2 | 100 | 100.0 (n=2) | 91.0 |
| Never user | | | | |
| Tobacco chewing | | | | |
| Former user | 80.0 | 96.6 | 72.7 | 97.7 |
| Never user | | | | |
| Marijuana use | | | | |
| Current user | - | - | - | - |
| Former user | | | | |
| Never user | | | | |
| Other substance use | | | | |
| Current user | 36.4 | 63.4 | 66.7 | 93.0 |
| Never user | | | | |
| Alcohol consumption | | | | |
| Current drinker | - | - | - | - |
| Former drinker | | | | |
| Never drinker | | | | |
| **Health** | | | | |
| Chlamydia | | | | |
| Yes | 94.7 | 100.0 (n=0) | 100.0 (n=1) | 79.1 |
| No | | | | |
| Genital herpes | | | | |
| Yes | 45.5 | 96.6 | 62.5 | 93.3 |
| No | | | | |

| | | | | |
|---|---|---|---|---|
| Oral herpes | | | | |
| Yes | 18.2 (n=2) | 95.2 | 33.3 (n=2) | 90.0 |
| No | | | | |
| Syphilis | | | | |
| Yes | 42.1 | 96.1 | 72.7 | 86.9 |
| No | | | | |
| Genital warts | | | | |
| Yes | 50.0 | 98.6 | 90.9 | 87.7 |
| No | | | | |
| Skin warts | | | | |
| Yes | 8.57 (n=3) | 96.9 | 60.0 | 66.3 |
| No | | | | |
| Condom use | | | | |
| Yes | 61.5 | 38.5 | 57.1 | 31.8 |
| No | | | | |
| HPV vaccine | | | | |
| Received | 44.4 | 100.0 (n=4) | 100.0 (n=4) | 92.4 |
| Not received | | | | |
| HIV medication adherence | | | | |
| Take medicines everyday | 84.2 | 50.0 (n=2) | 97.6 | 11.76 |
| Do not take medicines everyday | | | | |
| Ever had CD4 count below 200 | | | | |
| Yes | 83.0 | 86.8 | 88.6 | 80.5 |
| No | | | | |
| **Family History of Cancer** | | | | |
| Patient's cancer status | 68.0 | 96.3 | 85.0 | 90.8 |
| Father's cancer status | 84.2 | 90.8 | 72.7 | 95.2 |
| Mother's cancer status | 90.0 | 95.8 | 85.7 | 97.2 |
| Brother's cancer status | 50.0 (n=2) | 94.4 | 50.0 (n=2) | 94.4 |
| Sister's cancer status | 75.0 | 90.7 | 42.9 | 97.5 |
| Children's cancer status | 100 (n=1) | 88.9 | 50.0 (n=1) | 100.0 |

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# CHAPTER 6

# Incidence and Prevalence of Systemic Lupus Erythematosus from around the World: A Systematic Literature Review

## Abstract

**Background:** Systemic lupus erythematosus (SLE) is an autoimmune disease that has received little public health attention. We conducted a systematic literature review to investigate the global pattern of incidence and prevalence of SLE.

**Methods:** Four electronic databases were searched to identify cohort and cross-sectional studies, published from 1990-2010, describing incidence and/or prevalence of SLE. Crude incidence and prevalence rates and corresponding 95% confidence intervals were computed based on the number of cases and population at risk. Results were stratified by continent, and by physician-confirmed diagnosis versus self-report. Heterogeneity was assessed by exact likelihood ratio tests. Pooled estimates were calculated when heterogeneity was not detected, weighted by denominator.

**Results:** Of 11,870 screened articles, 65 (49 prevalence & 32 incidence) from 5 continents met eligibility criteria and were included in the analysis. Studies from all regions yielded annual incidence rates between 0.3 and 8.7 per 100,000 and prevalence between 1.1 and 534.9 per 100,000. High incidence was observed in the United States, Caribbean, Brazil, and Sweden. Prevalence was much higher in the United States than in Europe and Asia. Prevalence was also higher among studies with self-reported physician-diagnosed SLE cases compared to physician confirmed cases.

**Conclusions:** There was considerable variability in both incidence and prevalence across different regions. To allow for improved comparison of studies, multiple sources of discrepancy must be considered: study design, case ascertainment method, type of surveillance, race, gender, and method of case classification.

## Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease with a significant impact on morbidity, mortality, and quality of life. Although the etiology of disease is not well-understood, the production of autoantibodies, which mediate tissue damage, appears to interact with and is triggered by certain genetic and environmental factors. SLE displays variable manifestations affecting almost every organ, contributing to cutaneous, joint, internal, neurologic, and hematologic problems. However, clinical manifestations of SLE vary in individuals. Severity and recurrence of disease may also differ from patient to patient. Furthermore, there are considerable geographic and ethnic variations with SLE disproportionately affecting women of childbearing age and those who are African Americans, Afro-Caribbeans, and Asians (1, 2).

Incidence and prevalence are often used as simple measures to describe epidemiology of disease. However, in SLE, accurately quantifying incidence and prevalence has proven to be complicated for a number of reasons. First, since SLE is a relatively rare, complex disease, research studies classically focus on the tertiary care setting due to practicality. This introduces biases since the patient populations are often highly selective due to factors such as health care utilization patterns, socioeconomic status, and race, and thus may not fully represent the spectrum of disease. Second, case definition is not always consistent among studies. Some studies have classified

individuals as having SLE based on retrospective review of medical records while some others have developed separate case definitions for their research purposes. However, most research investigations utilize the American College of Rheumatology (ACR) SLE criteria for determination of eligibility. One issue with this criteria is that when these criteria were evaluated in external populations as opposed to the original test population, the sensitivities were as low as 78% (versus 96% in the test population) (3, 4). This problem leads to the systematic exclusion of lupus patients who may have mild, early or atypical presentations, but who nonetheless should be advocated for and included in research. Third, studies use different case ascertainment methods. Most studies turn to hospital admission and billing databases, records from rheumatology clinics, and academic registries to identify SLE cases. Multiple sources are often used, and cases are confirmed upon review of medical records or patient examination by a rheumatologist. However, rigorous case ascertainment does not always take place due to limited resources, inability to contact patients, or unavailability of medical records. Furthermore, self-report of a physician-diagnosed SLE lacks precision (5).

The reports of incidence and prevalence of SLE described in literature are obviously conflicting, and no systematic literature review has been conducted to date. The objective of this review is to establish the best estimates of incidence and prevalence of SLE in different parts of the world. Specifically, self-reported incidence and prevalence rates will be compared to non-self-reported incidence and prevalence rates.

## Methods

### Identification of Studies

We identified studies describing the incidence and/or prevalence of SLE, published between 1990 and 2010. The following electronic databases were used for our primary search: 1) Medline/Pubmed (1947 - July 2010), 2) Scopus (1823 - July 2010), 3) ISI Web of Science (1900 - July 2010), and 4) Embase (1947 - July 2010). Google Scholar was used to supplement the search. For each database, a customized search strategy was formulated in consultation with a medical librarian. The combination of the search terms are presented in Table 1. No language restrictions were applied. All electronic database searches were conducted on July 3, 2010. Review articles published within the last 20 years on the epidemiology of autoimmune diseases, including SLE, were also identified. Reference lists from all relevant articles were hand searched for additional articles that were not captured by the electronic database searches. When articles could not be located through the University of Michigan libraries or its affiliates, we made every effort to obtain the original article from the authors.

Studies were eligible for inclusion in the review if they were cohort or cross-sectional studies reporting incidence and/or prevalence of SLE. SLE cases in patients of all ages were included. Both self-reported cases of physician-diagnosed SLE and non self-reported cases (e.g. hospital chart review, population-based registries, physician diagnosis, etc.) were included. Studies were excluded if: (1) they were non-human studies; (2) they consisted of lupus diagnoses that were not SLE; (3) their results were not based on primary data; (4) they were not published within the past 20 years; and (5)

they did not assess general arthritis or rheumatic conditions without specifically screening for lupus. Serial reports from the same study were excluded; only the most recent or most comprehensive data available from a given series were utilized to avoid over-weighing of a single study. Studies which restricted their study population to include only a specialized population (e.g. environmentally exposed clusters or other high risk groups) were also excluded.

A primary reviewer screened the titles and abstracts of all publications identified by the literature search, based on the predetermined eligibility criteria. Articles were rejected if they clearly did not meet the eligibility criteria. The full-text of all remaining articles that possibly or definitely met the eligibility criteria were obtained and reviewed to further screen these articles. A secondary reviewer was consulted in cases where article eligibility was unclear. Four articles were translated to English. We used a standardized data extraction form to extract the data, including (1) administrative details: author(s); year of publication; journal title; article title; year(s) in which the study was conducted; study objective; Pubmed identification number; (2) details of the study: study design; geographic location of study; type of surveillance (For our review, active surveillance was defined as the identification of cases via medical chart review, door-to-door visits, and medical/physical evaluations conducted directly by study investigators. We considered studies to have used passive surveillance if (a) they relied on voluntary reporting mechanisms for case identification (b) they used randomization to search for cases; (c) they reported cases as a result of secondary data analysis; or (d) they reported cases that arose from questionnaires that relied on participants' willingness to return the questionnaire); (3) details of study population: demographic information

(race/ethnicity, sex, age distribution); patient inclusion and exclusion criteria; classification criteria for diagnosis of SLE; validation of SLE diagnosis; (4) details of outcomes: incidence rate (crude and age- and/or sex-adjusted rates if available); prevalence rate (crude and age- and/or sex-adjusted rates if available); actual number of incident SLE cases; actual number of prevalent SLE cases; population denominator to calculate the incidence and/or prevalence rates (i.e. population at risk); and (5) types of biases.

**Analysis**

We computed crude incidence and prevalence rates and corresponding 95% confidence intervals (CIs) based on the number of cases and the population at risk reported in the articles. Where no crude data were available, age- and/or sex-adjusted estimates were used to derive the incidence and prevalence rates. Where data were given from more than one time period, the most recent figures were used. Where multiple study sites were presented in one article, the data were compiled to compute an overall estimate for the country the article represented. For the articles without the actual number of cases, we derived the best estimate of the numerator by using other available data (i.e. incidence and/or prevalence rates and the population size.) Similarly, when the population at risk was not given, the best estimate of the denominator was derived from other information given (i.e. incidence and/or prevalence rates and the number of identified cases). In the event the denominator could not be inferred, the best estimate of the population size was obtained from an appropriate population census. We report the incidence rate as a number of new cases per 100,000 of the population

per year and the prevalence rate as a cross-sectional estimate of the number of cases per 100,000 of the population. We also report the incidence and prevalence rates as presented in the original articles. Our results are stratified by the geographic region. We generated forest plots according to region where the symbols, which were weighed by denominator, represent point estimate, and the horizontal line represents the CIs. Exact 95% CIs were calculated based on binomial distribution. We followed recommendations by Schriger et al. (2010) to order the forest plots by effect size (6). We assessed heterogeneity using the chi-square test with α = 0.05 for statistical significance. As we observed the presence of statistical heterogeneity due to differences in geographic region, we present the results according to these sub-groups. Where studies were comparable, we calculated pooled estimates using denominator as the weight. Data management and analysis were conducted using R 2.11.1. software (R Development Core Team, 2010) and Stata version 11 (Stata Corp., College Station, TX). Heterogeneity was computed using StatXact (StatXact9 for Windows, Cytel Software, Cambridge, MA).

## Results

**Description of studies**

We identified 11,870 publications from the electronic searches, of which we determined 74 articles to be potentially eligible based on initial screening. Of these, 61 met eligibility criteria. 8 additional articles were identified from reference lists, of which 4 met eligibility criteria. Thus, in total, 65 articles were included in this review as outlined in the flow chart. (Figure 1). Of these, 49 described prevalence and 32 described

incidence. The studies of incidence and prevalence are summarized in Tables 2 and 3, respectively.

**Incidence**

Overall, studies from all regions yielded annual incidence rates from 0.3 to 8.7 per 100,000. All studies reported the incidence of SLE using non self-reported physician-diagnosed SLE as a case finding method. Significant heterogeneity existed among all studies (p<0.01), and stratification by continent did not resolve heterogeneity. In Asia, there were 3 studies with annual incidence ranging from 0.3 to 3.1 per 100,000. 2 studies (7, 8) used cohort design and utilized hospital records or databases while one study (9) was a cross-sectional survey-based study. Removing the latter study resulted in similar estimates (p=0.53). There was one study in Australia for which incidence could be calculated (10). With 13 new cases among Aborigines between 1986 and 1990 this study reported incidence of at least 11/100,000. In Europe, annual incidence ranged from 0.4 to 4.9 per 100,000 among 17 studies. 13 of these were cohort studies (11-23) and 4 were cross-sectional studies (24-27). Further stratification by study design, country, and surveillance type did not impact heterogeneity. There were 10 studies in North America where incidence varied between 0.4 and 6.0 per 100,000. 7 of these studies were cohort studies (28-34) and 3 were cross-sectional studies (35-37). Only stratification by sub-region within North America (i.e. USA, Canada, and Caribbean) resulted in two Caribbean studies (31, 35) being similar (p=0.98). Two studies that used passive surveillance were also similar (p=0.24) despite the difference in study population (29, 36). There was one study in South America (38) reporting annual

incidence of 8.7/100,000. Out of 32 studies there were 5 population-based studies (11, 19, 22, 26, 37). A graphical summary of incidence studies is displayed in Figure 2.

**Prevalence**

Overall, there were 49 studies with prevalence rates ranging from 1.1 to 534.9 per 100,000. 43 articles reported non self-reported prevalence which spanned from 1.5 to 158.7 per 100,000 (8, 10, 13, 14, 16, 18, 19, 23-27, 29-32, 35, 36, 39-63). Among non self-report studies, there were 2 studies (14, 24) that reported age-adjusted estimates, and there was 1 study (29) that adjusted for both sex and age. With the exception of studies describing non self-reported prevalence in Australia, there was strong evidence of heterogeneity for all geographic region and reporting type combinations (all p<0.001, Australia p=0.071). Upon stratification of non self-reported studies by continent, 8 studies were found in Asia, 4 in Australia, 18 in Europe, and 13 in North America. Prevalence in Asia ranged from 3.4 to 47.2 per 100,000. One of the 8 studies in Asia was performed among men and women, but only female cases were found (40). In Australia, it ranged from 45.4 to 88.4 per 100,000. A pooled prevalence estimate for the 4 Australian studies was 49.4/100,000. Prevalence in Europe varied from 1.5 to 70.7 per 100,000. We could not derive an overall crude prevalence for one of the studies (64) in Europe because it reported age- and sex stratified results, and we could not obtain denominator for each group. North America exhibited the widest range, extending from 3.6 to 158.7 per 100,000. 6 studies (40, 42, 45, 49, 50, 59) examined prevalence of SLE based on self-reported symptoms but no physician diagnosis. In addition to these studies, we found 4 studies (65-68) that also relied on self-reported

symptoms for SLE case detection; however, we did not include these studies in our analysis because their study instruments covered a broad spectrum of rheumatic diseases without a specific focus on SLE. A graphical summary of prevalence studies is displayed in Figure 3.

There were 6 articles describing self-reported physician-diagnosed prevalence of SLE (5, 69-74). All studies with the self-report method were cross-sectional studies. Since significant heterogeneity was observed among all self-reported studies, we stratified the studies by country. We found 2 studies in Europe and 4 studies in North America, and stratification could not recover heterogeneity. The lowest self-reported prevalence rate of 1.1 per 100,000 was reported in Greece (70). The highest self-reported prevalence rate of 534.9 per 100,000 was reported in a study conducted in the United States that used random-digit telephone dialing and involved no follow-up in-person examination of patients by a rheumatologist (71). Aside from one study in Europe, all studies consisted of study population ≥16 years old. All studies in Europe had lower prevalence rates than all studies in North America.

## Discussion

This review included 65 studies on prevalence and incidence of SLE from 5 continents. No studies from Africa were found. Significant heterogeneity across all studies in examining both incidence and prevalence was observed, and thus required us to stratify our results. Our comparison of studies included stratification by geographic region and by self- vs. non-self report of physician-diagnosed SLE cases, as it is fairly well established that heterogeneity may be due to differences in study methodology and

population. To the best of our knowledge, this review represents the first systematic attempt to summarize the global incidence and prevalence of SLE.

Our findings were consistent with previous reviews done on this topic, highlighting disparities of SLE (1, 2, 75, 76). As expected, the highest annual incidence rates (>4/100,000) were observed in studies consisting of Aborigines (Australia), populations with a high proportion of individuals of African descent (Curaçao and Martinique), and migrants (United States). Countries with moderate (between 2 and 4 per 100,000) and low (<2/100,000) annual incidence rates were in Europe. Similarly, the global prevalence rates were the highest in the migratory populations in the United States, followed by Caribbean countries. European and Asian countries had much lower prevalence than the United States. These observations may be explained by a variation in demographic composition, with the United States and Caribbean countries having a higher proportion of people of African descent. These results still must be interpreted with caution, since the rates not only varied within different continents but also within the same country.

Since previous reviews have stratified results by gender, we took a different approach in our analysis by comparing self- to non-self report of physician-diagnosed SLE. Despite the small number of studies using the self-report method, we found that prevalence was higher among studies with self-reported SLE cases than those with non physician-confirmed cases in North America. Interestingly, the opposite was observed in Europe. This difference may have implications on case findings in the context of health disparities. Despite its obvious drawbacks (1), self-reporting could serve as a useful tool in detecting individuals in heterogeneous populations that need access to care and/or in

areas where rheumatologists are not easily accessible. We did not stratify by age because cases are not detected as often in children.

Numerous factors are likely to have contributed to the broad spectrum of results. While the most recently accepted classification method of SLE is the 1997 updated ACR criteria (77), the studies that we identified in this review used different classification criteria. This review included the 1982 ACR criteria and ARA criteria, in addition to the 1997 updated ACR criteria, because the studies spanned 20 years. Ascertainment of cases ranged from patient physical examination performed by rheumatologists to coding of SLE diagnosis in administrative databases to medical chart review. Surveillance method and source of data may also have impacted case findings. Finally, as there is usually a lag time between the initial onset of symptoms and the diagnosis meeting at least four criteria, incident cases are more prone to measurement error.

Given variability between studies, we could not perform meta-analyses, including pooled estimation of incidence and prevalence. Although we were able to extract or derive raw numbers for the incident and prevalent cases from the majority of the articles to calculate our crude estimates, some studies reported adjusted estimates, making it difficult for real comparison. Publication bias is another issue in that studies with positive results may be more likely to be published. We attempted to prevent this bias by searching for articles using Internet search engines (e.g., Google) and for conference abstracts in dating between 2006 and 2009 in the ACR/ARHP Annual Scientific Meetings Conference database. Several abstracts were retrieved but excluded because they were later published in a journal.

The findings summarized in the present review demonstrated considerable variability in both incidence and prevalence across different regions. This variability may arise from a variety of sources including study design, case ascertainment method, type of surveillance, race, gender, and method of case classification. Future studies accounting for these factors could greatly improve case findings.

## Acknowledgements

**Table 6.1: Search terms used for five major databases and conference abstracts**

| Database | Search Terms | Items Found |
|---|---|---|
| Medline/Pubmed | "Lupus Erythematosus, Systemic/epidemiology*" AND "Prevalence" AND ("humans" AND "1990/05/31"[PDAT] : "2010/06/01"[PDAT]) | 412 |
| | "Lupus Erythematosus, Systemic/epidemiology*" AND "Incidence" AND ("humans" AND "1990/05/31"[PDAT] : "2010/06/01"[PDAT]) | 250 |
| | "Incidence" AND "Prevalence" AND "Lupus Erythematosus, Systemic/epidemiology" AND ("humans" AND "1990/05/31"[PDAT] : "2010/06/01"[PDAT]) | 86 |
| | "Autoimmune Diseases/epidemiology" OR "Autoimmunity" AND lupus | 2,963 |
| | "Lupus Erythematosus, Systemic/epidemiology" AND ("humans" AND Review[ptyp] AND "2005/06/03"[PDat] : "2010/06/01"[PDat]) | 75 |
| | "Lupus Erythematosus, Systemic/epidemiology*"[Mesh] AND "Prevalence"[Mesh] AND ("humans"[MeSH Terms] AND "1990/05/31"[PDAT] : "2010/06/01"[PDAT]) | 376 |
| | "Lupus Erythematosus, Systemic/epidemiology*"[Mesh] AND "Incidence"[Mesh] AND ("humans"[MeSH Terms] AND "1990/05/31"[PDAT] : "2010/06/01"[PDAT]) | 250 |
| | "Incidence"[Mesh] AND "Prevalence"[Mesh] AND "Lupus Erythematosus, Systemic/epidemiology"[Mesh] AND ("humans"[MeSH Terms] AND "1990/05/31"[PDAT] : "2010/06/01"[PDAT]) | 56 |
| | "Autoimmune Diseases/epidemiology"[Mesh] OR "Autoimmunity"[Mesh] AND lupus | 3,796 |
| | "Lupus Erythematosus, Systemic/epidemiology"[Mesh] AND ("humans"[MeSH Terms] AND Review[ptyp] AND "2005/06/03"[PDat] : "2010/06/01"[PDat]) | 106 |
| Scopus | ("systemic lupus erythematosus" AND "prevalence" AND "epidemiology") AND PUBYEAR AFT 1990 AND ( LIMIT-TO(EXACTKEYWORD,"Systemic lupus erythematosus" ) OR LIMIT-TO(EXACTKEYWORD,"Human" ) OR LIMIT-TO(EXACTKEYWORD,"Prevalence" ) OR LIMIT-TO(EXACTKEYWORD,"Humans" ) ) | 157 |
| | ("systemic lupus erythematosus" AND "incidence" AND "epidemiology") AND PUBYEAR AFT 1990 AND ( LIMIT-TO(EXACTKEYWORD,"Human" ) OR LIMIT-TO(EXACTKEYWORD,"Systemic lupus erythematosus" ) OR LIMIT-TO(EXACTKEYWORD,"Humans" ) OR LIMIT-TO(EXACTKEYWORD,"Incidence" ) ) | 130 |
| | ("systemic lupus erythematosus" AND "incidence" AND "prevalence" AND "epidemiology") AND PUBYEAR AFT 1990 AND ( LIMIT-TO(EXACTKEYWORD,"Systemic lupus erythematosus" ) OR LIMIT-TO(EXACTKEYWORD,"Human" ) OR LIMIT-TO(EXACTKEYWORD,"Prevalence" ) OR LIMIT-TO(EXACTKEYWORD,"Incidence" ) OR LIMIT-TO(EXACTKEYWORD,"Humans" ) ) | 61 |
| ISI Web of Science | Topic=("systemic lupus erythematosus") AND Topic=(prevalence) AND Topic=(epidemiology) Timespan=1990-2010. Databases=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH | 193 |
| | Topic=("systemic lupus erythematosus") AND Topic=(incidence) AND Topic=(epidemiology) Timespan=1990-2010. Databases=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH | 109 |
| | Topic=("systemic lupus erythematosus") AND Topic=(incidence) AND Topic=(prevalence) AND Topic=(epidemiology) Timespan=1990-2010. Databases=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH | 55 |
| Embase | 'systemic lupus erythematosus'/exp OR 'systemic lupus erythematosus' AND ('prevalence'/exp OR 'prevalence') AND ('epidemiology'/exp OR epidemiology) AND [humans]/lim AND [1990-2010]/py | 1,604 |
| | 'systemic lupus erythematosus'/exp OR 'systemic lupus erythematosus' AND ('incidence'/exp OR 'incidence') AND ('epidemiology'/exp OR epidemiology) AND [humans]/lim AND [1990-2010]/py | 936 |
| | 'systemic lupus erythematosus'/exp OR 'systemic lupus erythematosus' AND ('prevalence'/exp OR 'prevalence') AND ('incidence'/exp OR 'incidence') AND ('epidemiology'/exp OR epidemiology) AND [humans]/lim AND [1990-2010]/py | 255 |
| Google Scholar | "systemic lupus erythematosus" | 294,000 |
| | "systemic lupus erythematosus" "prevalence" | 49,200 |
| | "systemic lupus erythematosus" "incidence" | 64,600 |
| | "systemic lupus erythematosus" "incidence" "prevalence" | 22,700 |
| | "systemic lupus erythematosus" "prevalence", limit to 1990-2010 | 9,950 |
| | "systemic lupus erythematosus" "incidence", limit to 1990-2010 | 13,100 |
| | "systemic lupus erythematosus" "incidence" "prevalence", limit to 1990-2010 | 5,470 |

| Conference Abstracts | | |
|---|---|---|
| Year | Search term: "Incidence lupus" | Search term: "Prevalence lupus" |
| 2009 | 31 hits (1 relevant abstract) | 60 hits (1 relevant abstract) |
| 2008 | 31 hits (1 relevant abstract) | 58 hits (1 relevant abstract) |
| 2007 | 23 hits (0 abstract) | 55 hits (1 relevant abstract) |
| 2006 | 37 hits (1 relevant abstract) | 67 hits (2 relevant abstracts) |

**Figure 6.1: Flow Diagram of the Literature Search Process**

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┌────────────────────────────┐
│ Potentially relevant       │
│ articles identified for    │
│ initial screening          │
│ (n=11,870)                 │
└────────────────────────────┘
         │            ┌────────────────────────────────┐
         │ ──────────▶│ Excluded (n=11,688)            │
         │            │ • Clearly not meeting          │
         │            │   eligibility criteria         │
         │            │   (n=6,280)                    │
         │            │ • Duplicates (n=5,408)         │
         ▼            └────────────────────────────────┘
┌────────────────────────────┐
│ Studies retrieved from     │
│ more detailed evaluation   │
│ (n=182)                    │
└────────────────────────────┘
         │            ┌────────────────────────────────┐
         │ ──────────▶│ Studies excluded from          │
         │            │ systematic review              │
         │            │ • Failed to meet eligibility   │
         │            │   criteria                     │
         │            │ (n=108)                        │
         ▼            └────────────────────────────────┘
┌────────────────────────────┐   ┌──────────────────────────┐
│ Potentially appropriate    │   │ Additional articles      │
│ articles to be included in │- -│ identified from article  │
│ the systematic review      │   │ references (n=8)         │
│ (n=74)                     │   └──────────────────────────┘
└────────────────────────────┘
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Excluded (n=13)
• Failed to meet
• eligibility criteria
  (n=3)
• Serial reports from
  the same study
  (n=8)
• Unable to locate
  potentially eligible
  articles (n=2)

Excluded (n=4)
• Failed to meet
  eligibility criteria
  (n=3)
• Serial report from
  the same study
  (n=1)

Studies Analyzed in systematic review (n= 65: 61 from original search + 4 from hand-search)

## Table 6.2: Incidence of SLE, by Geographic Region

| Continent | Author, year | Study period | Location | Age | Ethnicity | Case source(s) | Total no. of cases | Denominator for computing incidence | Annual incidence per 100,000 (CI) | Annual incidence per 100,000 in original paper |
|---|---|---|---|---|---|---|---|---|---|---|
| Asia | Mok et al. (2008) | 2000-2006 | Hong Kong | All | Chinese | Hospital database | 442 | 14,258,065* | 3.1 (2.8-3.4) | 2.8 (used most recent data in 2006) |
| | Iseki et al. (1994) | 1972-1991 | Japan | 5-77 | All | Clinical, hospital records | 34 | 1,223,395 | 2.8 (1.9-3.9) | 2.37* |
| | Fujikawa et al. (1997) | 1994 | Japan | All | All | Hospitals survey | 906 | 29,910,000 | 0.3 (0.2-0.4) | 0.47 |
| Australia | Anstey et al. (1993) | 1984-1991 | Australia | All | Aborigines | Clinical, hospital records; physicians survey | 13 | 24,900 | 12 (2.5-35.2) | 11 |
| Europe | Somers et al. (2007) | 1990-1999 | UK | All | All | General Practice Research Database | 1638 | 33,666,320 | 4.9 (4.6-5.1) | 4.87 |
| | Stahl-Hallengren et al. (2000) | 1981-1991 | Sweden | >15 | White | Clinical, hospital records, patients evaluation | 41 | 172,300 | 4.6 (2.0-9.1) | 4.8 |
| | Jonsson et al. (1990) | 1981-1986 | Sweden | ≥15 | All | Clinical, hospital records; physicians survey | 38 | 200,470 | 4 (1.7-7.9) | 4 |
| | Johnson et al. (1995) | 1991-1992 | England | ≥18 | All | Clinical, hospital records; physicians survey | 33 | 872,877 | 3.8 (2.6-5.3) | 3.8 |
| | Hopkinson et al. (1993) | 1989-1990 | Nottingham, England | All | All | Clinical, hospital records; physicians survey | 23 | 613,700 | 3.7 (2.4-5.6) | 3.7 |
| | Voss et al. (1998) | 1980-1994 | Denmark | >15 | All | Community diagnostic retrieval system | 14 | 387,841 | 3.6 (2-6.1) | 3.6 (used the most recent data) |
| | Gudmundsson et al. (1990) | 1975-1984 | Iceland | All | All | Clinical, hospital records; physicians survey | 76 | 227,742 | 3.5 (1.5-6.9) | 3.3 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Nightingale et al. (2006) | 1992-1998 | Nationwide, UK | All | All | Clinical, hospital, prescription records | 390 | 12,911,216 | 3 (2.7-3.3) | 3.02 |
| | Eilertsen et al. (2009) | 1978-2006 | Norway | All | All | Hospital registries | 139 | 177,640 | 2.8 (0.9-6.6) | 2.8 |
| | Nossent et al. (2001) | 1978-1996 | Norway | 16-80 | All | Community and tertiary hospitals registry, national mortality DB, general practitioners | 83 | 177,033 | 2.8 (0.9-6.6) | 2.6 (adult estimate) |
| | Govoni et al.(2006) | 1996-2002 | Italy | ≥16 | All | Hospital, clinical records; National Health Care System | 9* | 346,826 | 2.6 (1.2-4.9) | 2.6 (used the most recent data) |
| | Lopez et al. (2003) | 1992-2003 | Spain | All | All | Clinical, hospital records | 116 | 1,073,971 | 2.1 (1.4-3.2) | 2.15 |
| | Alamanos et al. (2003) | 1982-2001 | Greece | All | All | Clinical, hospital records | 9* | 488,435 | 1.8 (0.8-3.5) | 1.9 |
| | Laustrup et al. (2009) | 1995-2002 | Denmark | ≥15 | All | Population-based registry, patients survey, examination by rheumatologist | 4 | 385,093 | 1 (0.3-2.7) | 1.04 |
| | Kaipiainen-Seppanen et al. (1996) | 1980-1990 | Finland | <16 | All | Drug reimbursement certificates, hospital records | 7 | 270,000 | 0.7 (0.1-2.7) | 0.8 |
| | Huemer et al. (2001) | 1997-1998 | Austria | ≤16 | All | Hospital registries | 6 | 618,311 | 0.5 (0.1-1.4) | 0.48 |
| | Pelkonen et al. (1994) | 1983-1986 | Finland | <16 | All | Hospital-based registry, National Hospital Discharge Register | 15 | 1,016,619 | 0.4 (0.1-1) | 0.37 |
| North America | Klein et al. (2010) | 1998-2004 | California, USA | 10-62 | All | Insurance database | 299 | 5,000,000 | 6 (5.3-6.7) | 6 |
| | Uramoto et al. (1999) | 1980-1992 | Minnesota, USA | All | All | Electronic database by the Rochester Epidemiology Project | 48 | 70,745** | 5.7 (1.5-14.5) | 5.56 (used the most recent data) |
| | Naleway et al. (2005) | 1991-2001 | Wisconsin, USA | 14-90 | All | Community clinic electronic records | 44 | 77,280 | 5.2 (1.4-13.3) | 5.2 |

| | Nossent et al. (1992) | 1980-1989 | Curacao | All | All | Hospitl registries, national mortality database | 68 | 146,500 | 4.8 (1.9-9.8) | 4.63 |
|---|---|---|---|---|---|---|---|---|---|---|
| | Deligny et al. (2002) | 1990-1999 | Martinique | All | All | Hospital records, physicians survey, death registry | 180 | 381,427* | 4.7 (2.8-7.5) | 4.7 |
| | Bernatsky et al. (2007) | 1994-2003 | Canada | All | All | Administrative data: billing codes, hospitalization data and procedure data | 219 | 7,492,300 | 2.9 (2.5-3.3) | 3 |
| | McCarty et al. (1995) | 1985-1990 | Pennsylvania, USA | All | All | Clinical, hospital records; physicians survey | 191 | 8,018,694 | 2.4 (2.1-2.7) | 2.4 |
| | Peschken et al. (2000) | 1980-1996 | Manitoba, Canada | All | North American Indians & Caucasians | Physicians survey | 37 | 128,685 | 2.3 (0.5-6.8) | Ranges from 0.0 to 7.4 |
| | Malleson et al. (1996) | 1991-1993 | Canada | ≤16 | All | Physicians survey | 52 | 4168731** | 0.6 (0.4-0.9) | 0.28 |
| | Denardo et al. (1994) | 1984-1992 | Northeast, USA | ≤18 | All | Hospital/clinical registries | 55* | 13,207,000 | 0.4 (0.3-0.5) | 0.4 |
| South America | Pereira Vilar et al. (2002) | 2000 | Brazil | >15 | All | Clinical, hospital, laboratory records | 43 | 493,239 | 8.7 (6.3-11.7) | 8.7 |

Eilertsen had incidence data that were split into 2 time periods; however, prevalence estimate was from the entire observation period. Therefore, we report the incidence to reflect the whole study period also.
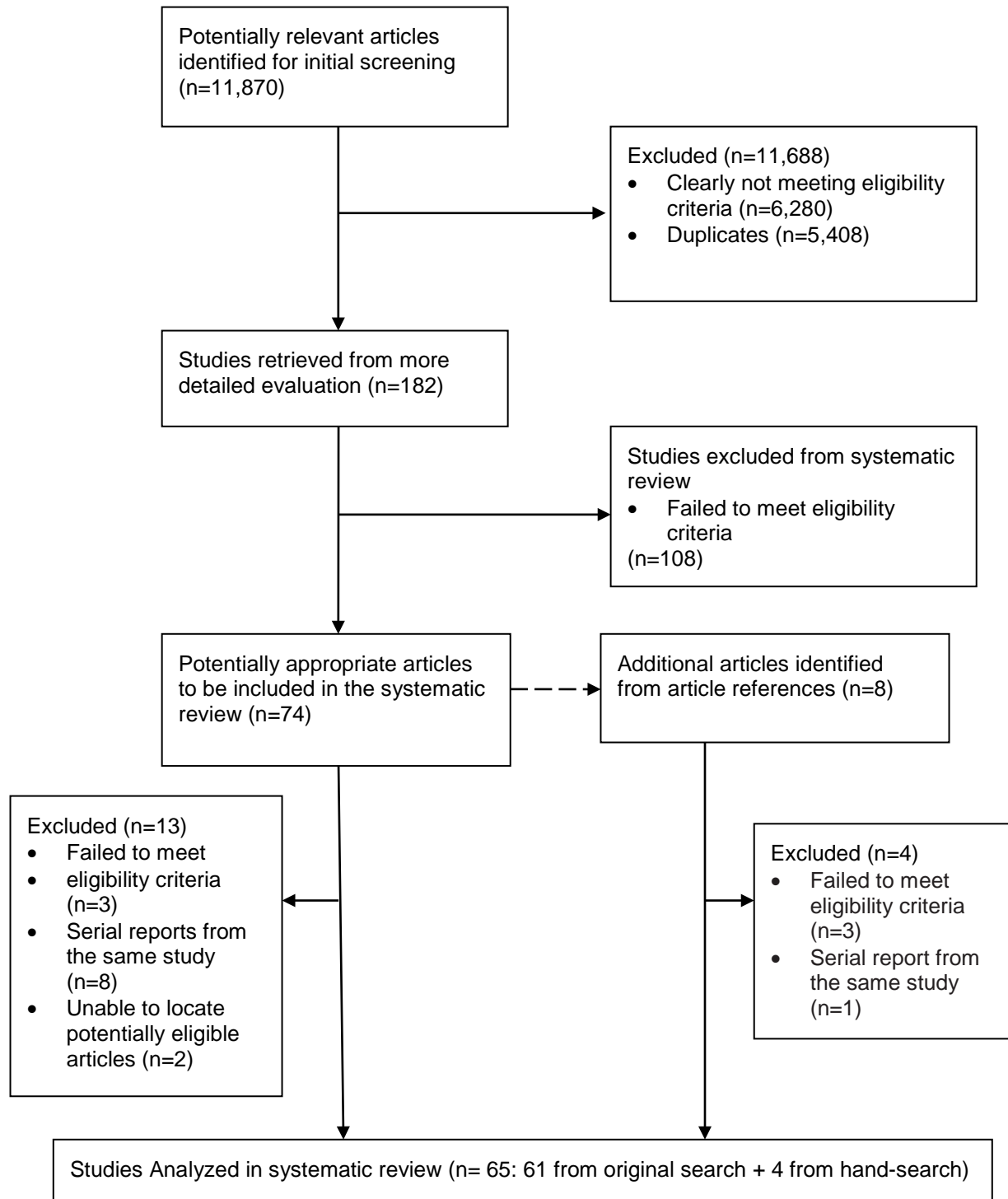
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## Table 6.3: Prevalence of SLE, by Geographic Region

| Continent | Author, year | Study period | Location | Age | Ethnicity | Case source(s) | Total no. of cases | Denominator for computing prevalence | Prevalence per 100,000 (CI) | Prevalence per 100,000 in original paper |
|---|---|---|---|---|---|---|---|---|---|---|
| Asia | Iseki et al. (1994) | 1972-1991 | Japan | 5-77 | All | Clinical, hospital records | 462 | 1223395 | 37.8 (34.4-41.4) | 37.76* |
| | Wang et al. (1997) | 1974-1990 | Malaysia | All | Chinese, Malay, Indians | Clinical, hospital records | 539 | 1253488* | 43 (39.4-46.8) | 43 |
| | Wigley et al. (1994) | Unknown | China | ≥20 | Chinese | Patients survey, physician examination | 4 | 9720 | 41.2 (11.2-105.3) | 41* |
| | Al-Arfaj et al. (2002) | Unknown | Saudi Arabia | 1-85 | All | Patients survey, examination by rheumatologist | 2 | 10372 | 19.3 (2.3-69.6) | 19.28 |
| | Chou et al. (1994) | Unknown | Taiwan | >20 | All | Patients survey, examination by rheumatologist | 1 | 8998 | 11.1 (0.3-61.9) | 11.1* |
| | Huang et al. (2004) | 1995-1999 | Taiwan | <16 | All | The Major Illness/Injury Registry | 365 | 5775640 | 6.3 (5.7-7.0) | 6.3 |
| | Karadsheh et al. (2000) | 1969-1997 | Jordan | 9-60 | All | Clinical, hospital records | 76 | 2235294* | 3.4 (2.7-4.3) | 3.4 |
| | Malaviya et al. (1993) | Unknown | India | Unknown | All | ANA screening, questionnaire | 3 | 91888 | 3.3 (0.7-9.5) | 3.2 |
| Australia | Anstey et al. (1993) | 1984-1991 | Australia | All | Aborigines | Clinical, hospital records; physicians survey | 22 | 24900 | 88.4 (55.4-133.7) | 52 |
| | Grennan et al. (1995) | 1993 | Australia | All | Aborigines | Clinical, hospital records; physicians survey | 23 | 45305 | 50.8 (32.2-76.2) | 50.77* |
| | Segasothy et al. (2001) | 1990-1999 | Australia | 6-53 | Aborigines & Caucasian Australians | Hospital records; physicians survey | 24* | 50000 | 48 (30.8-71.4) | 48* |
| | Bossingham et al. (2003) | 1996-1998 | Australia | 7-74 | Caucasians & Aborigines | Clinical, hospital records | 108 | 238000 | 45.4 (37.2-54.8) | 45.3 |

| Europe | Benucci et al. (2005) | 2002 | Italy | >18 | All | Clinical records, patients evaluation | 23 | 32521 | 70.7 (44.8-106.1) | 71 |
|---|---|---|---|---|---|---|---|---|---|---|
| | Stahl-Hallengren et al. (2000) | 1981-1991 | Sweden | >15 | White | Clinical, hospital records, patients evaluation | 119* | 174952 | 68.0 (56.4-81.4) | 68 (used most recent data) |
| | Eilertsen et al. (2009) | 1978-2006 | Norway | All | All | Hospital registries | 114 | 177640 | 64.2 (52.9-77.1) | 64.1 |
| | Govoni et al. (2006) | 1996-2002 | Italy | ≥16 | All | Hospital, clinical records; National Health Care System | 201 | 346826 | 58.0 (50.2-66.5) | 57.9 |
| | Andrianakos et al. (2003) | 1996-1999 | Greece | >18 | All | Clinical, hospital records | 7* | 14233 | 49.2 (19.8-101.3) | 49.18* |
| | Nightingale et al. (2007) | 1992-1998 | Nationwide, UK | All | All | Clinical, hospital, prescription records | 666 | 1635169 | 40.7 (37.7-43.9) | 40.7 (most recent) |
| | Alamanos et al. (2003) | 1982-2001 | Greece | All | All | Clinical, hospital records | 178 | 488435 | 36.4 (31.3-42.2) | 39.51 |
| | Gudmundsson et al. (1990) | 1975-1984 | Iceland | Al | All | Clinical, hospital records; physicians survey | 86 | 239498 | 35.9 (28.7-44.3) | 35.9 (age-adjusted) |
| | Lopez et al. (2003) | 1992-2003 | Spain | All | All | Clinical, hospital records | 367 | 1073971 | 34.2 (30.8-37.9) | 34.12 |
| | Eaton et al. (2007) | 1977-2001 | Denmark | All | All | The National Hospital Register of Denmark | 1732 | 5472032 | 31.7 (30.2-33.2) | 31.65* |
| | Laustrup et al. (2009) | 1995-2002 | Denmark | ≥15 | All | Population-based registry, patients survey, examination by rheumatologist | 109 | 385155 | 28.3 (23.2-34.1) | 28.3 |
| | Johnson et al. (1995) | 1991-1992 | England | ≥18 | All | Clinical, hospital records; physicians survey | 242 | 872877 | 27.7 (24.3-31.4) | 27.7 |
| | Samanta et al. (1992) | 1989 | Leicester, UK | >20 | All | Hospital records, physicians survey, histopathology reports, Lupus Society survey, ANA reports | 50 | 191469 | 26.1 (19.4-34.4) | 26.1 |
| | Gourley et al. (1997) | 1992-1993 | Ireland | All | All | Clinical records; physicians, patients survey; patients | 415 | 1631800 | 25.4 (23.0-28.0) | 25.4 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Hopkinson et al. (1993) | 1989-1990 | Nottingham, England | All | All | Clinical, hospital records; physicians survey | 147 | 610000 | 24.1 (20.4-28.3) | 24 (age-adjusted) |
| | Voss et al. (1998) | 1980-1994 | Denmark | >15 | All | Community diagnostic retrieval system | 84 | 387841 | 21.7 (17.3-26.8) | 21.7 |
| | Dadoniene et al. (2006) | 2004 | Lithuania | All | All | Population-based registry | 76 | 470451 | 16.2 (12.7-20.2) | 16.2 |
| | Mazur et al. (1995) | Unknown | Moldova | Adults | All | Clinical, hospital records | 116 | 3222222 | 3.6 (3.0-4.3) | 3.6 |
| | Zink et al. (2001) | 1993-1998 | Germany | ≥15 | All | Clinical, hospital records | 1221 | 80000000 | 1.5 (1.4-1.6) | 1.51* |
| | Anagnostopoulos et al. (2010) | 2007-2008 | Greece | Adults | All | Patients survey, examination by rheumatologist | 2 | 176433 | 1.1 (0.1-4.1) | 1.13* |
| North America | Lahita et al. (1995) | Unknown | Nationwide, USA | ≥16 | All | Telephone survey | 19 | 3552 | 534.9 (322.3-834.1) | 534.9* |
| | Ward et al. (2004) | 1988-1994 | Nationwide, USA | ≥18 | All | Self-reported physician diagnosis from NHANES III | 40 | 20050 | 199.5 (142.6-271.6) | 241 (self-report only) |
| | Molina et al. (2007) | 2003 | Puerto Rico | All | All | Insurance database | 877 | 552733 | 158.7 (148.3-169.5) | 159 |
| | Uramoto et al. (1999) | 1980-1992 | Minnesota, USA | All | All | Electronic database by the Rochester Epidemiology Project | 86* | 70745** | 121.6 (97.2-150.1) | 122 (age- and sex-adjusted) |
| | Hochberg et al. (1995) | Unknown | USA excluding Alaska | ≥18 | All | Telephone survey | 5 | 4304 | 123.9 (40.3-289.0) | 124 (validated) |
| | Chakravarty et al. (2007) | 2000 | California, USA | ≥18 | All | Hospitalization databases | 532* | 463948* | 114.7 (105.1-124.8) | 114.67* (both states) |
| | Balluz et al. (2001) | 1997 | Arizona, USA | Adults | Hispanic | Patients survey, examination by rheumatologist | 20 | 19489 | 102.6 (62.7-158.4) | 103 |
| | Boyer et al. (1991) | 1970-1984 | Alaska | All | Native Americans | Clinical, hospital records | 9 | 9770 | 92.1 (42.1-174.8) | 91.7 |
| | Naleway et al. (2005) | 1991-2001 | Wisconsin, USA | 14-90 | All | Community clinic electronic records | 64 | 77280 | 82.8 (63.8-105.7) | 82.8 |

| Post et al. (1998) | 1996 | Moorpark, California | 34-67 | All | Patients survey, physicians survey | 20 | 29310 | 68.2 (41.7-105.4) | 68.23 |
|---|---|---|---|---|---|---|---|---|---|
| Deligny et al. (2002) | 1990-1999 | Martinique | All | All | Hospital records, physicians survey, death registry | 245 | 381427* | 64.2 (56.4-72.8) | 64.2 |
| Bernatsky et al. (2007) | 1994-2003 | Canada | All | All | Administrative data: billing codes, hospitalization data and procedure data | 3825 | 7492300 | 51.1 (49.4-52.7) | 51 (billing & hospitalizati on data combined) |
| Nossent et al. (1992) | 1980-1989 | Curacao | All | All | Hospitl registries, national mortality database | 69 | 146500 | 47.1 (36.6-59.6) | 47.6 |
| Maskarinec et al. (1995) | 1988-1989 | Hawaii, USA | All | All | Physicians survey, patients survey | 454 | 1086124 | 41.8 (38.0-45.8) | 41.8 |
| Peschken et al. (2000) | 1980-1996 | Manitoba, Canada | All | North American Indians & Caucasians | Physicians survey | 257 | 1100295 | 23.4 (20.6-26.4) | 22.1 |
| Balkaran et al. (2004) | 1992-2001 | Trinidad | 5-17 | All | Clinical, hospital records | 33 | 168860* | 19.5 (13.5-27.4) | 19.54* |
| Houghton et al. (2006) | 2004 | British Columbia, Canada | <18 | All | Clinical, hospital records | 40 | 1098485** | 3.6 (2.6-5.0) | 3.64* |

**Figure 6.2: SLE Incidence Distribution, by Geographic Region**
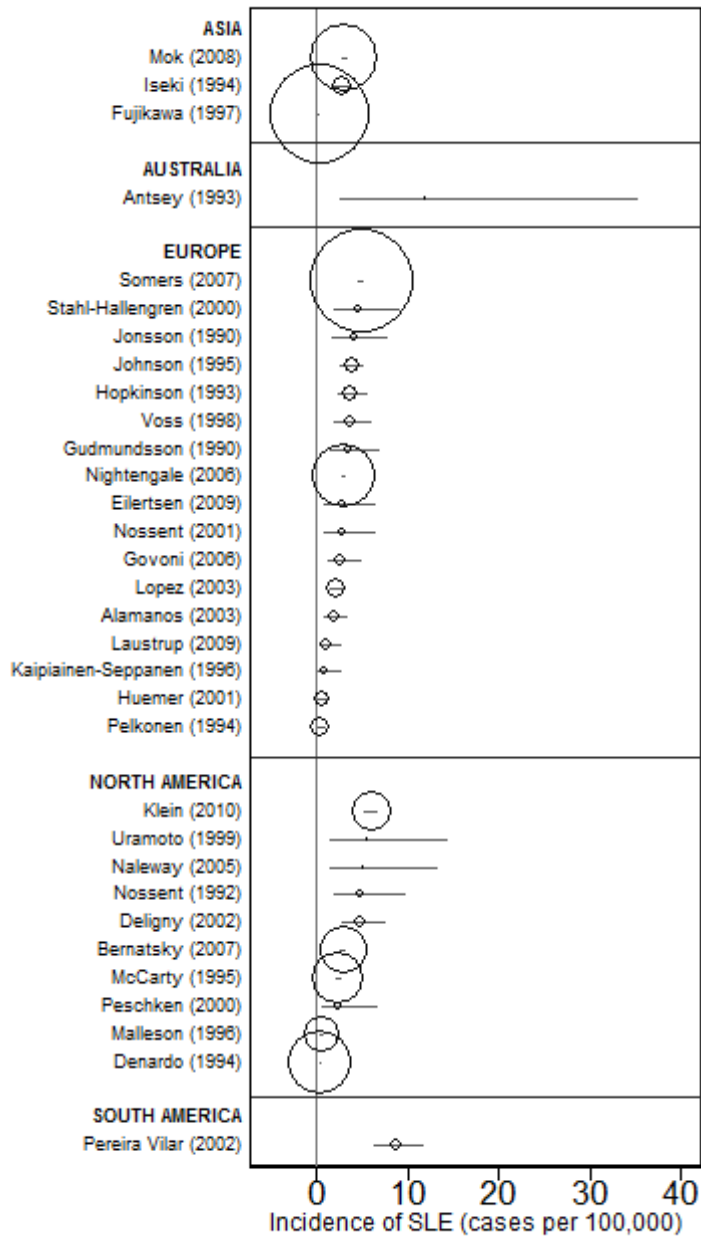
**Figure 6.3: SLE Prevalence Distribution, by Geographic Region**



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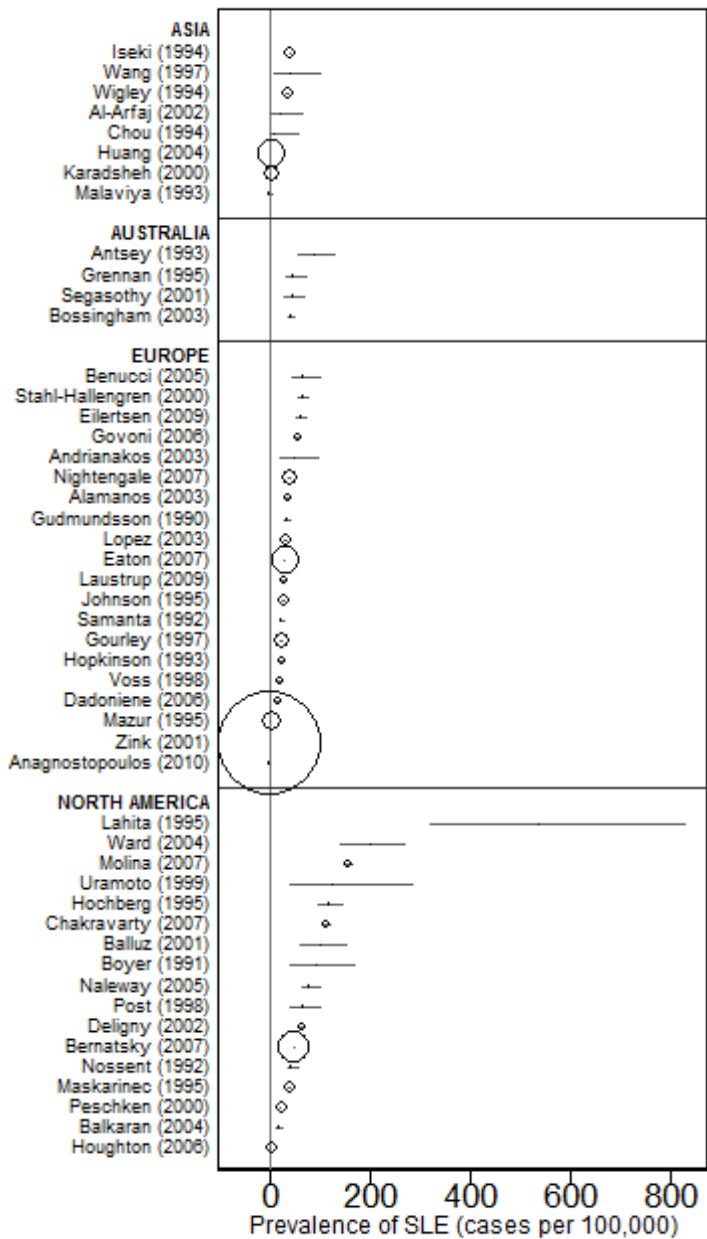
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# CHAPTER 7

## Conclusions and Future Directions

### Summary of Study Results

The overarching goal of this dissertation was to describe the prevalence, type distribution, and risk factors of oral HPV infection in three populations: 1) HIV-positive patients seen at the University of Michigan; 2) HIV-negative individuals with confirmed HIV-negative status; and 3) self-reported HIV-negative individuals. By making such comparisons, the study was intended to improve the understanding of risks of oropharyngeal cancers in HIV-positive and HIV-negative individuals, using oral HPV infection as a proxy.

Chapter 4 presented the overall findings from the study. As hypothesized, the prevalence of oral HPV infection was the highest in the HIV-positive group. This finding is consistent with previous studies comparing HIV-positive and HIV-negative populations (1-5). Previously reported risk factors, such as increasing age (3-8), sexual orientation (9, 10), lifetime number of sexual partners (5, 6, 11, 12), certain sexual behaviors (5, 6, 9), open-mouth kissing (11, 12), alcohol consumption (9), smoking (5, 6, 8, 9), lower CD4 count (3, 6, 8), and current HIV therapy (8) were not significantly associated with oral HPV infection in this study. However, there were variables that were significantly associated with oral HPV infection in the univariate analyses that were

consistent with previous literature. These risk factors included male gender (3, 5, 6), lifetime number of vaginal sex partners (5, 11, 12), and HIV viral load (6). In this study, it was found for the first time that male partner's circumcision status significantly affects the risk of oral HPV infection. Like Pickard and colleagues (11), the decreased odds of oral HPV infection with alcohol consumption was observed in this study.

Another interesting finding from this study is that the HIV-negative population that was presumed to be at higher risk actually had lower oral HPV prevalence than the HIV-negative population that was presumed to have the lowest risk. Specifically speaking, HARC participants were selected to be in the "tested HIV-negative" group, under the assumption that those seeking HIV testing may have shared risk factors with HIV-positive individuals. Therefore, forming this "tested HIV-negative" group was a way minimize confounding by creating a group that is comparable to the HIV-positive group. Even though the sample sizes of each study group were small, the study findings suggest that, in this particular study population, the "tested HIV-negative" individuals may have lower risk of oral HPV infection. Factors that could account for this observation are younger age, access to free counseling, health education, and condom use. Frequent clients at HARC have multiple opportunities to receive to these resources, further increasing the level of knowledge and awareness related to prevention of STDs. In addition, the "tested HIV-negative" group was about 20 years younger than the HIV-infected and the self-reported HIV negative groups. Since increasing age is associated with oral HPV infection (5), the younger age in the "tested HIV-negative" group may also explain the lower prevalence observed in this group.

Given that the great majority of our HIV-positive participants were immunocompetent and highly adherent to their HIV therapy, it remains unknown whether HIV-related immunosuppression is a risk factor for oral HPV infection. In this study, lower CD4 count was not associated with oral HPV infection; however, increasing HIV viral load increased the risk. This suggests that viremia, which also may have a deleterious effect on immune function, may be associated with increased oral HPV prevalence. Despite its association with increased oral HPV infection, viremia could be confounded by risky sexual behaviors, lack of medication adherence, and older age. However, such interactions could not be assessed due to a small number (n=2) of HIV-infected participants with HIV viral load ≥100,000 copies/µL, and remain an important area to be explored in future studies.

Chapter 5 assessed the concordance of information between patient self-report and medical chart review for HIV-infected study participants. This assessment served as a validation tool to determine the accuracy of the findings reported in chapter 4. Consistent with previous literature, it was found that the degree of agreement between the two data sources largely depends on the type of questions and disease classification (13, 14). Since this study consisted of HIV-infected individuals, questions related to STDs were the main focus of the questionnaire. With that being said, sensitivity was higher when the medical records were used as the gold standard, because accurate reporting depended on diagnostic tools (13). However, high specificity of STD reporting in both data sources suggests that the negative STD status is often correctly reported. As with previous studies, accurate reporting of condom use continues to be problematic (15-18). Despite the variability in concordance, sensitivity,

and specificity between to the data sources, it is unlikely that these discrepancies affected the overall study results regarding oral HPV risk calculation for HIV-infected participants. The errors were minimized because the clinical data abstracted from the medical records were utilized in the statistical models.

Chapter 6 highlighted the global incidence and prevalence of SLE between 1990 and 2010. Due to significant heterogeneity of incidence and prevalence across geographic regions, the pooled estimates were not computed. However, the systematic literature review determined that SLE disproportionately affects women of childbearing age and individuals of African origin. There were several notable reasons that may have contributed to the variability in incidence and prevalence across the world and even within a same country. First, incidence and prevalence were affected by demographic factors. For example, the studies with higher proportions of women and individuals of African descent had higher incidence and/or prevalence. Likewise, studies performed in children had lower rates of SLE since the average onset of SLE is 31 years old (19). Second, the accuracy in incidence and prevalence depended on the study design. While a cohort design allowed for changes in incidence and prevalence to be observed over time, a cross-sectional design provided only a snapshot, limiting the amount of data for this analysis. Third, surveillance method may have affected case finding, as active surveillance typically leads to more cases found. Fourth,  case definition and ascertainment method may have affected incidence and prevalence estimates. Broader case definition and less stringent ascertainment methods are likely to have led to more cases being identified. Fifth, it is likely that differences in case reporting mechanism resulted in misclassification. For example, physician-diagnosed reporting of SLE is more

accurate than patient self-reporting. Lastly, incidence and prevalence may have been underestimated in circumstances where undiagnosed cases in a community had not reached the healthcare system for screening and diagnosis. It is also possible that some other cases may have received care outside of the catchment area. Therefore, catchment area of a study may have affected incidence and prevalence rates.

Although SLE itself has not been identified as a risk factor for oral HPV infection, it has been reported that SLE increases the risk of HPV in the genital region and HPV-associated cancers (20-22). Given that patients with SLE are often prescribed immunosuppressant drugs, the findings from the HIV-infected population in the EPI Study may extend to other individuals with immunodeficiency. Further, there may be important implications related to the immunogenicity of HPV vaccines in this population, which in turn could have consequences on the HPV incidence and prevalence as well as HPV-associated cancers.

**Public Health Implications**

Because the study was conducted in Michigan, where HIV incidence and prevalence are considerably lower than the vast majority of the world, it is expected that the findings from the EPI Study would have even greater implications for future prevention and control of HPV infection and head and neck cancers in other geographic regions, particularly in areas where oral HPV infection rates may be more amplified due to higher HIV incidence and prevalence.

Unlike cervical cancer, there are currently no standard, validated methods for oral cancer screening. Due to the anatomic location and lack of screening methods, oral

cancers are diagnosed at later stages, often with distant metastases (23). Until an

effective oral cancer screening method is developed, prevention strategies must focus

on risk reduction. This dissertation identified male circumcision as a potential tool to

decrease the risk of oral HPV infection. It is well-documented that male circumcision

significantly decreases the risk of HIV acquisition and transmission (24). It has also

been reported that male circumcision could reduce prevalence and viral load of penile

HPV (25, 26). However, this practice is controversial and is not widely accepted due to

religious and/or cultural beliefs (27). Therefore, more commonly accepted sexual

prevention measures should continue to be encouraged.

The implications of validation studies such as the one performed as part of this

dissertation are profound. As mentioned, there is variability in the degree of

concordance, sensitivity, and specificity depending on the questionnaire items.

Research studies that rely on self-report without validation could incur errors due to

misclassification of disease status, leading to incorrect inferences regarding study

outcomes. In clinical practice, patient-physician concordance could influence a variety of

outcomes, including decision-making related to HIV treatment and medication

adherence (28). Therefore, the findings from this dissertation encourages good patient-

physician relationship and communication to improve patient's knowledge and

awareness about his/her conditions. By doing so, the patient's quality of care could be

maximized.

**Strengths and Limitations**

One of the notable strengths of this dissertation is the unique epidemiological study design. Two HIV-negative groups were utilized for comparison to the HIV-positive group. The use of two HIV-negative groups as a reference has not been done in previous studies. By evaluating the prevalence in three populations, this study was able to more clearly demonstrate that patients with HIV infection have an increased risk of oral HPV infection compared to HIV-negative populations. Further, it was learned that an HIV-negative population that was presumably at risk actually had lower oral HPV prevalence than the HIV-negative population that presumably had the least risk. Such findings emphasize the importance of replicating similar epidemiological studies in other populations. Another strength of this dissertation is that a validation study was performed to evaluate the accuracy of data. Since this study consisted of primary data collection, it was especially important to compare the participant self-reported data to the medical records. Overall, there was good agreement between the two data sources. For the laboratory component of this research, two detection methods were utilized, which led to more HPV infections being detected. This approach also allowed for detection of concomitant HPV infections. The method-specific strengths of the multiplex PCR-MassArray were that it allowed for detection and identification of multiple high-risk HPV types and represented low risk-types, HPV 6, 11, and 90, using only 10 ng/µL of sample in a high throughput assessment.. The second method uses multiple primer sets, PGMY09/11 (29) to detect additional HPV types which can then be assessed by sequencing. This allowed for detection of HPV types that were not included in the multiplex PCR-MassArray assay, leading to a greater variety of HPV types detected. As

demonstrated previously, the use of more than one detection method greatly improves the detection rates (30), and this approach was essential in a study with such a small sample size.

There are several limitations. The most obvious is the limited sample size and power. In studies among cancer-free populations that had small sample sizes (i.e., less than 200 study participants), it has been reported that the HPV prevalence appeared to have an inversely proportional relationship to the study sample size (31). This suggests that, while the prevalence reported in this dissertation may be elevated, the findings from this study cannot be generalized to other populations because the study relied on the convenience sample of HIV-positive patients at the University of Michigan and HIV-negative individuals from Washtenaw and surrounding counties. The characteristics of this study population were unique. Of note, the HIV-positive participants were mostly MSM, and the study participants were receiving HAART therapy and responding well to treatment with CD4 cell counts in the normal range. Little variation in the HIV disease status means that the effect of immunosuppression on oral HPV infection could not be thoroughly assessed.  Lastly, causal relationship could not be established due to the cross-sectional design.

**Future Directions**

Despite considerable progress in improving the understanding of HPV-associated OPSCC, it is clear that more research, particularly prospective studies, is needed to evaluate the natural history of oral HPV infection. There are now several variables that are associated with oral HPV infection. Since there is considerable

variability in HPV prevalence which likely arises from differences in the variety of behavioral risk factors, further research is needed determine independent factors that affect the acquisition, persistence, and recurrence of oral HPV infection.

The long term clinical implications for individuals who have had HPV DNA detected in their oral cavities is unknown. A potential way to improve the understanding of the clinical significance of oral HPV infection is to examine the state of viral activation by assessing viral transcripts. For example, since the expression of E6 and E7 oncoproteins is required for maintenance of transformation (32), it could imply that individuals having such a status may have persistent HPV infection that may require monitoring over time. Partial transcripts with high levels of E6 and E7 and low levels of E1 and E2 may imply that viral transformation has occurred (33), and individuals with these conditions should be surveilled for possible oral cancer.

A multi-site case-control study investigating the risk of HNCs is currently underway through the Head & Neck Cancer Specialized Program of Research Excellence (SPORE). However, because there are so few studies that have compared HNCs between HIV-positive and HIV-negative populations, more research is need to better understand the clinical implications of HNCs in the HIV population.

From the research standpoint, there is a need to improve the tools to effectively capture data, both in the field and in the laboratory. This dissertation clearly demonstrated the importance of validated questionnaires, especially for covering sensitive topics such as HPV and HIV. The improvement must also take place in the laboratory. Currently, tests for HPV detection is expensive, labor-intensive, and time-consuming. Although high-throughput technology has been developed for HPV

detection (34), the cost remains an issue. In this study, detection method was base on

DNA; however, as proposed above, gene expression analysis could provide more

detailed information that may have direct clinical application. For oral cancer screening

to have meaningful impact on public health, it must become widely accessible and used.

To this end, it is imperative that detection tools be efficient and cost-effective.

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**Appendices**

# University of Michigan Clinical Research

**Title:**              The Etiology of Papillomavirus Infections (EPI) Study

**Abbreviated Title:**    The Etiology of Papillo...

**Condition Category:**   Cancer - Head & Neck:Ear, Nose and Throat Conditions:HIV/AIDS

**Purpose:**              The purpose of the study is to compare human papillomavirus infection in the saliva obtained from HIV patients as well as HIV-negative individuals.

**Study Description:** Human papillomavirus (HPV) is a known cause of cervical cancer, and is associated with head and neck cancer, particularly cancer in the mouth. It is believed that HPV is seen in excess in people living with HIV/AIDS compared to the general population, thereby possibly increasing their risk of oral cancer, but more research is needed. To test this hypothesis, the study is seeking volunteers to provide saliva and complete a survey every 3~6 months over 2 years.

**Eligibility:**

**Age Range:**  From 18 To 999 years

**Gender:**    Both Female and Male

**Ethnicity:**  All

**Race:**  All

**Smoking:**  Both Smoking and No-Smoking

**This study is seeking:**  Both Healthy Subjects and Patients with Specified Condition

**Other Eligibility Factors**

**Tags:**    HIV/AIDS
cancer screening
head and neck cancer
human papillomavirus (HPV)
oral cancer

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**Location of Study Visits:**   Ann Arbor, MI
Ypsilanti, MI

**Principal Investigator:**   Senga, Mikiko

**Compensation:**                    $26-$100

**Expected Recruitment End Date:**   26-APR-13

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## Enrollment Information

**Contact for this study:**   Mikiko Senga / Mary Reyes
(734) 647-9830
msenga@umich.edu

**PLEASE NOTE:** Study Coordinators and Research Nurses cannot give medical advice over the phone. If you have specific questions regarding your health care, please call your primary care physician.

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| For University of Michigan Staff |
| --- |
| **IRB Number:** HUM00047989 |
| **Formal Title:** HIV/HPV Oral Rinse Study |
| **GCRC Study:** No |
| **Cancer Center Study:** No |

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Appendix 4.2: Epidemiology of Papillomavirus Infections Study consent form for HIV patients

# UNIVERSITY OF MICHIGAN
# CONSENT TO BE PART OF A RESEARCH STUDY

## INFORMATION ABOUT THIS FORM

You may be eligible to take part in a research study.  This form gives you important information about the study.  It describes the purpose of the study, and the risks and possible benefits of participating in the study.

Please take time to review this information carefully.  After you have finished, you should talk to the researchers about the study and ask them any questions you have.  You may also wish to talk to others (for example, your friends, family, or other doctors) about your participation in this study.  If you decide to take part in the study, you will be asked to sign this form.  *Before you sign this form, be sure you understand what the study is about, including the risks and possible benefits to you.*

## 1.   GENERAL INFORMATION ABOUT THIS STUDY AND THE RESEARCHERS

**1.1   Study title: The Etiology of Papillomavirus Infections (EPI) Study**

**1.2   Company or agency sponsoring the study:** University of Michigan

**1.3   Names, degrees, and affiliations of the researchers conducting the study:**

Mikiko Senga, Department of Epidemiology, School of Public Health
James Riddell IV, M.D., Department of Internal Medicine, Medical School
Thomas E. Carey, Ph.D., Department of Otolaryngology; Medical School
Gregory T. Wolf, M.D., F.A.C.S., Department of Otolaryngology; Medical School
Heather Walline, Department of Otolaryngology; Medical School

## 2.   PURPOSE OF THIS STUDY

**2.1  Study purpose:**

The purpose of this study is to examine saliva samples from both HIV positive and negative individuals and look for DNA associated with human papillomavirus (HPV).  Additionally, questionnaires will be requested of study participants.

## 3.   INFORMATION ABOUT STUDY PARTICIPANTS (SUBJECTS)

Taking part in this study is completely **voluntary**.  You do not have to participate if you don't want to.  You may also leave the study at any time.  If you leave the study before it is finished, there will be no penalty to you, and you will not lose any benefits to which you are otherwise entitled.

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## 3.1  Who can take part in this study?

HIV-positive and HIV-negative subjects will be asked to take part in this study.  HIV patients seen at the University of Michigan and their partners may be asked to participate in this study, regardless of HIV status. HIV-negative individuals seeking HIV testing and counseling at HIV/AIDS Resource Center (HARC) and HIV-negative individuals from the community may also participate in the study. Each subject must be at least 18 years of age and willing to return for required follow-up visits, outlined below.

## 3.2  How many people (subjects) are expected to take part in this study?

It is expected that 100 HIV-positive subjects will participate in this study at the University of Michigan.  Up to 100 partners of HIV-positive individuals will be included in this study. 100 HIV-negative subjects are expected to participate.

## 4.  INFORMATION ABOUT STUDY PARTICIPATION

## 4.1  What will happen to me in this study?

At your initial visit for the study, the study staff will provide you with a questionnaire that you will be asked to complete either by yourself or with the help of staff.  You will be asked to complete this survey in the privacy of a research room with a staff member.  Or you may be asked to take the survey home and mail it back once you complete it with pre-paid postage to the study coordinator.   This survey will be linked to you only through a study number and will not bear your name.

At each visit, you will be asked to spit your saliva into a collection cup, or swish an oral rinse in your mouth and spit it into a cup.  This oral sample will be banked for future testing, should you provide your consent.  At each visit after your initial visit, you will be asked to complete a shorter questionnaire, asking if there have been any changes in the answers you gave in the questionnaire at your initial visit.   Again, this questionnaire will be done in the privacy of an exam room, either by yourself or with the help of staff.

The researchers in this study would like to bank your oral sample for future testing.  If you withdraw your consent for this study, every effort will be made to destroy any remaining sample.  However, the researchers are requesting to keep the oral rinse sample(s) you have already provided.  If you are in agreement with banking your samples for future use by the researchers, please indicate here:

---

**Yes, I am in agreement with the banking of my oral samples for future testing:**

**Initials:_____    Date:\_\_\_\_\_**


**No, I do not agree that the researchers can bank my oral samples for future testing:**

**Initials:_____    Date:_____**

---

## 4.2  How much of my time will be needed to take part in this study?

The initial visit will take longer, as you will be asked to complete a more detailed questionnaire. The total estimated time for this visit is 1 hour.  Follow-up visits may be scheduled along with

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your routine care visits and will either add an additional 30 minutes to your routine visit in a separate research room, or will take 30 minutes on its own in a research exam room.

## 4.3 When will my participation in the study be over?

Your participation in this study will be over once you have completed all follow-up visits, should you agree to return, for approximately 2 years.  Each visit will be 3-4 months apart, timed with your routine care visits. You may participate in as little as one visit or as many as 6 visits (i.e. up to 3 times per year for 2 years).

## 5.  INFORMATION ABOUT RISKS AND BENEFITS

### 5.1  What risks will I face by taking part in the study?  What will the researchers do to protect me against these risks?

The known or expected risks are:

- **Saliva collection:** If you are asked to provide saliva using the oral rinse method, the oral rinse may sting your mouth and produce an unfavorable taste.
- **Questionnaire(s):**  There is a risk that the questionnaire may contain questions that make you feel uncomfortable or uneasy.  If at any time you feel uncomfortable, you may notify the staff member administering the questionnaire and you will be permitted to skip questions or portions of the survey that bring your discomfort.

### 5.2  What happens if I get hurt, become sick, or have other problems as a result of this research?

The researchers have taken steps to minimize the risks of this study.  Even so, you may still have problems or side effects, even when the researchers are careful to avoid them. Please tell the researchers listed in Section 10 about any injuries, side effects, or other problems that you have during this study.

### 5.3  If I take part in this study, can I also participate in other studies?

 *Being in more than one research study at the same time, or even at different times, may increase the risks to you.  It may also affect the results of the studies*.  You should not take part in more than one study without approval from the researchers involved in each study.

### 5.4  How could I benefit if I take part in this study?  How could others benefit?

You may not receive any personal benefits from being in this study.

Future individuals who are HIV positive and diagnosed with head and neck cancer may benefit if a better screening method is developed after this research is completed.

### 5.5  Will the researchers tell me if they learn of new information that could change my willingness to stay in this study?

Yes, the researchers will tell you if they learn of important new information that may change your willingness to stay in this study. If new information is provided to you after you have joined the study, it is possible that you may be asked to sign a new consent form that includes the new information.

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## 6.  OTHER OPTIONS

**6.1  If I decide not to take part in this study, what other options do I have?**

This study is not providing any care. You can receive the same treatment without being in this study.

## 7.  ENDING THE STUDY

**7.1  If I want to stop participating in the study, what should I do?**

You are free to leave the study at any time.  If you leave the study before it is finished, there will be no penalty to you. You will not lose any benefits to which you may otherwise be entitled.  If you choose to tell the researchers why you are leaving the study, your reasons for leaving may be kept as part of the study record. If you decide to leave the study before it is finished, please tell one of the persons listed in Section 10 "Contact Information" (below).

**7.2  Could there be any harm to me if I decide to leave the study before it is finished?**

If you want to withdraw from the study at any time, you are free to do so, even if you do not give a reason. If you do withdraw, your usual medical care will not be affected in any way. If necessary for your medical care, your study doctor may advise you to have some follow-up tests.

If you withdraw from the study, no new information (data) about you will be added to the database. The researchers would still like to be able to examine the oral samples you provided if you decide to leave the study before it is finished.

**7.3  Could the researchers take me out of the study even if I want to continue to participate?**

Yes. There are many reasons why the researchers may need to end your participation in the study.  Some examples are:

- ✓ The researcher believes that it is not in your best interest to stay in the study.
- ✓ You become ineligible to participate.
- ✓ Your condition changes and you need treatment that is not allowed while you are taking part in the study.
- ✓ You do not follow instructions from the researchers.
- ✓ The study is suspended or canceled.

## 8.  FINANCIAL INFORMATION

**8.1  Who will pay for the costs of the study? Will I or my health plan be billed for any costs of the study?**

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There are no costs to participants associated with being in this study.

By signing this form, you do not give up your right to seek payment if you are harmed as a result of being in this study.

### 8.2  Will I be paid or given anything for taking part in this study?

Yes, you will be paid $10 per study visit.

### 8.3  Who could profit or financially benefit from the study results?

None of the personnel involved in this study could profit or benefit financially from the study results.

## 9.  CONFIDENTIALITY OF SUBJECT RECORDS AND AUTHORIZATION TO RELEASE YOUR PROTECTED HEALTH INFORMATION

The information below describes how your privacy and the confidentiality of your research records will be protected in this study.

### 9.1  How will the researchers protect my privacy?

Your research information will be stored in a locked cabinet.  All specimens will be coded before they are analyzed, and the research personnel who analyze the specimens will not be able to link them with any of your identifying information or medical history.  All data regarding your oral rinse sample will be stored in a password-protected database with barcoding of each sample to further enhance the privacy of your sample.

### 9.2  What information about me could be seen by the researchers or by other people? Why?  Who might see it?

Signing this form gives the researchers your permission to obtain, use, and share information about you for this study, and is required in order for you to take part in the study.  Information about you may be obtained from any hospital, doctor, and other health care provider involved in your care, including:

- Hospital/doctor's office records, including test results (X-rays, blood tests, urine tests, etc.)
- Alcohol/substance abuse treatment records
- Your AIDS/HIV status
- All records relating to your illness, the treatment you have received, and your response to the treatment
- Billing information

There are many reasons why information about you may be used or seen by the researchers or others during or after this study.  Examples include:

- The researchers may need the information to make sure you can take part in the study.
- The researchers may need the information to check your test results or look for side effects.
- University, Food and Drug Administration (FDA), and/or other government officials may need the information to make sure that the study is done in a safe and proper manner.

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- Study sponsors or funders, or safety monitors or committees, may need the information to:
    o Make sure the study is done safely and properly
    o Learn more about side effects
    o Analyze the results of the study
- Insurance companies or other organizations may need the information in order to pay your medical bills or other costs of your participation in the study.
- The researchers may need to use the information to create a databank of information about your condition or its treatment.
- Information about your study participation may be included in your regular UMHS medical record.
- If you receive any payments for taking part in this study, the University of Michigan accounting department may need your name, address, social security number, payment amount, and related information for tax reporting purposes.
- Federal or State law may require the study team to give information to government agencies. For example, to prevent harm to you or others, or for public health reasons.

The results of this study could be published in an article, but would not include any information that would let others know who you are.


### 9.3  What happens to information about me after the study is over or if I cancel my permission?

As a rule, the researchers will not continue to use or disclose information about you, but will keep it secure until it is destroyed.  Sometimes, it may be necessary for information about you to continue to be used or disclosed, even after you have canceled your permission or the study is over.  Examples of reasons for this include:

- To avoid losing study results that have already included your information

- To provide limited information for research, education, or other activities  (This information would not include your name, social security number, or anything else that could let others know who you are.)

- To help University and government officials make sure that the study was conducted properly

As long as your information is kept within the University of Michigan Health System, it is protected by the Health System's privacy policies.  For more information about these policies, ask for a copy of the University of Michigan Notice of Privacy Practices.  This information is also available on the web at http://www.med.umich.edu/hipaa/npp.htm. Note that once your information has been shared with others as described under Question 9.2, it may no longer be protected by the privacy regulations of the federal Health Insurance Portability and Accountability Act of 1996 (HIPAA).


### 9.4  When does my permission expire?

Your permission expires at the end of the study, unless you cancel it sooner. You may cancel your permission at any time by writing to the researchers listed in Section 10 "Contact Information" (below).

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## 10.  CONTACT INFORMATION

### 10.1  Who can I contact about this study?

Please contact the researchers listed below to:

- Obtain more information about the study
- Ask a question about the study procedures or treatments
- Talk about study-related costs to you or your health plan
- Report an illness, injury, or other problem (you may also need to tell your regular doctors)
- Leave the study before it is finished
- Express a concern about the study

> Principal Investigator: Mikiko Senga
> Mailing Address: 1500 E. Medical Center Drive, 3210 Taubman CenterAnn Arbor, MI 48109-5378
> Telephone: 734-647-9830
>
> Study Coordinator: Mary Reyes
> Mailing Address: 1500 E. Medical Center Drive, 3120 Taubman CenterAnn Arbor, MI 48109-5378
> Telephone: 734-647-9830

You may also express a concern about a study by contacting the Institutional Review Board listed below, or by calling the University of Michigan Compliance Help Line at 1-888-296-2481.

> University of Michigan Medical School Institutional Review Board (IRBMED)
> 2800 Plymouth Road
> Building 200, Room 2086
> Ann Arbor, MI 48109-2800
> Telephone: 734-763-4768
> Fax: 734-763-1234
> e-mail: irbmed@umich.edu

If you are concerned about a possible violation of your privacy, contact the University of Michigan Health System Privacy Officer at 1-888-296-2481.

*When you call or write about a concern, please provide as much information as possible, including the name of the researcher, the IRBMED number (at the top of this form), and details about the problem.  This will help University officials to look into your concern.  When reporting a concern, you do not have to give your name unless you want to.*

## 11.  RECORD OF INFORMATION PROVIDED

### 11.1  What documents will be given to me?

Your signature in the next section means that you have received copies of all of the following documents:

- This "Consent to be Part of a Research Study" document.  (*Note: In addition to the copy you receive, copies of this document will be stored in a separate confidential research file and may be entered into your regular University of Michigan medical record.*)

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## 12.  SIGNATURES

**Research Subject:**

*I understand the information printed on this form.  I have discussed this study, its risks and potential benefits, and my other choices with _____.  My questions so far have been answered.  I understand that if I have more questions or concerns about the study or my participation as a research subject, I may contact one of the people listed in Section 10 (above).  I understand that I will receive a copy of this form at the time I sign it and later upon request.  I understand that if my ability to consent for myself changes, either I or my legal representative may be asked to re-consent prior to my continued participation in this study.*

Signature of Subject: _____  Date: _____

Name (Print legal name):  _____

Patient ID:_____  Date of Birth: _____

**Principal Investigator (or Designee):**

*I have given this research subject (or his/her legally authorized representative, if applicable) information about this study that I believe is accurate and complete.  The subject has indicated that he or she understands the nature of the study and the risks and benefits of participating.*

Name: _____  Title: _____

Signature: _____  Date of Signature: _____

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Appendix 4.3: Epidemiology of Papillomavirus Infections Study consent form for HIV-negative participants

# UNIVERSITY OF MICHIGAN
# CONSENT TO BE PART OF A RESEARCH STUDY

## INFORMATION ABOUT THIS FORM

You may be eligible to take part in a research study.  This form gives you important information about the study.  It describes the purpose of the study, and the risks and possible benefits of participating in the study.

Please take time to review this information carefully.  After you have finished, you should talk to the researchers about the study and ask them any questions you have.  You may also wish to talk to others (for example, your friends, family, or other doctors) about your participation in this study.  If you decide to take part in the study, you will be asked to sign this form.  *Before you sign this form, be sure you understand what the study is about, including the risks and possible benefits to you.*

## 1.  GENERAL INFORMATION ABOUT THIS STUDY AND THE RESEARCHERS

**1.1  Study title: The Etiology of Papillomavirus Infections (EPI) Study**

**1.2  Company or agency sponsoring the study:** University of Michigan

**1.3  Names, degrees, and affiliations of the researchers conducting the study:**

Mikiko Senga, Department of Epidemiology, School of Public Health
James Riddell IV, M.D., Department of Internal Medicine, Medical School
Thomas E. Carey, Ph.D., Department of Otolaryngology; Medical School
Gregory T. Wolf, M.D., F.A.C.S., Department of Otolaryngology; Medical School
Heather Walline, Department of Otolaryngology; Medical School

## 2.  PURPOSE OF THIS STUDY

**2.1  Study purpose:**

The purpose of this study is to examine saliva samples from both HIV positive and negative individuals and look for DNA associated with human papillomavirus (HPV).  Additionally, questionnaires will be requested of study participants.

## 3.  INFORMATION ABOUT STUDY PARTICIPANTS (SUBJECTS)

Taking part in this study is completely **voluntary**.  You do not have to participate if you don't want to.  You may also leave the study at any time.  If you leave the study before it is finished, there will be no penalty to you, and you will not lose any benefits to which you are otherwise entitled.

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### 3.1  Who can take part in this study?

HIV-positive and HIV-negative subjects will be asked to take part in this study.  HIV patients seen at the University of Michigan and their partners  may be asked to participate in this study, regardless of HIV status. HIV-negative individuals seeking HIV testing and counseling at HIV/AIDS Resource Center and HIV-negative individuals from the community may also participate in the study. Each subject must be at least 18 years of age and willing to return for required follow-up visits, outlined below.

### 3.2  How many people (subjects) are expected to take part in this study?

It is expected that 100 HIV-positive subjects will participate in this study at the University of Michigan.  Up to 100 partners of HIV-positive individuals will be included in this study. 100 HIV-negative subjects are expected to participate.

## 4.  INFORMATION ABOUT STUDY PARTICIPATION

### 4.1  What will happen to me in this study?

The study staff will provide you with a questionnaire that you will be asked to complete either by yourself or with the help of staff.  You will be asked to complete this survey in the privacy of a research room with a staff member.  Or you may be asked to take the survey home and mail it back once you complete it with pre-paid postage to the study coordinator.   This survey will be linked to you only through a study number and will not bear your name.

You will be asked to spit your saliva into a collection cup, or swish an oral rinse in your mouth and spit it into a cup.  This oralsample will be banked for future testing, should you provide your consent. At each visit after your initial visit, you will be asked to complete a shorter questionnaire, asking if there have been any changes in the answers you gave in the questionnaire at your initial visit.   Again, this questionnaire will be done in the privacy of an exam room, either by yourself or with the help of staff.

The researchers in this study would like to bank your oral sample for future testing.  If you withdraw your consent for this study, every effort will be made to destroy any remaining sample.  However, the researchers are requesting to keep the oral rinse sample(s) you have already provided.  If you are in agreement with banking your samples for future use by the researchers, please indicate here:

**Yes, I am in agreement with the banking of my oral samples for future testing:**

**Initials:_____     Date:_____**


**No, I do not agree that the researchers can bank my oral samples for future testing:**

**Initials:_____     Date:_____**

### 4.2  How much of my time will be needed to take part in this study?

The initial visit will take longer, as you will be asked to complete a more detailed questionnaire.  The total estimated time for this visit is 1 hour.  Each follow-up visit, which is scheduled every 3-4 months, will take about 30 minutes.

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## 4.3 When will my participation in the study be over?

Your participation in this study will be over once you have completed all follow-up visits, should you agree to return for approximately 2 years.  Each visit will be 3-4 months apart. You may participate in as little as one visit or as many as 6 visits (i.e. up to 3 times per year for 2 years).

### 5.   INFORMATION ABOUT RISKS AND BENEFITS

## 5.1  What risks will I face by taking part in the study?  What will the researchers do to protect me against these risks?

The known or expected risks are:

- **Saliva collection:** If you are asked to provide saliva using the oral rinse method, the oral rinse may sting your mouth and produce an unfavorable taste.
- **Questionnaire(s):**  There is a risk that the questionnaire may contain questions that make you feel uncomfortable or uneasy.  If at any time you feel uncomfortable, you may notify the staff member administering the questionnaire and you will be permitted to skip questions or portions of the survey that bring your discomfort.

## 5.2  What happens if I get hurt, become sick, or have other problems as a result of this research?

The researchers have taken steps to minimize the risks of this study.  Even so, you may still have problems or side effects, even when the researchers are careful to avoid them. Please tell the researchers listed in Section 10 about any injuries, side effects, or other problems that you have during this study.

## 5.3  If I take part in this study, can I also participate in other studies?

*Being in more than one research study at the same time, or even at different times, may increase the risks to you.  It may also affect the results of the studies*.  You should not take part in more than one study without approval from the researchers involved in each study.

## 5.4  How could I benefit if I take part in this study?  How could others benefit?

You may not receive any personal benefits from being in this study.

Future individuals who are HIV positive and diagnosed with head and neck cancer may benefit if a better screening method is developed after this research is completed.

## 5.5  Will the researchers tell me if they learn of new information that could change my willingness to stay in this study?

Yes, the researchers will tell you if they learn of important new information that may change your willingness to stay in this study. If new information is provided to you after you have joined the study, it is possible that you may be asked to sign a new consent form that includes the new information.

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## 6.  OTHER OPTIONS

### 6.1  If I decide not to take part in this study, what other options do I have?

This study is not providing any care. You can receive the same treatment without being in this study.

## 7.  ENDING THE STUDY

### 7.1  If I want to stop participating in the study, what should I do?

You are free to leave the study at any time.  If you leave the study before it is finished, there will be no penalty to you. You will not lose any benefits to which you may otherwise be entitled.  If you choose to tell the researchers why you are leaving the study, your reasons for leaving may be kept as part of the study record. If you decide to leave the study before it is finished, please tell one of the persons listed in Section 10 "Contact Information" (below).

### 7.2  Could there be any harm to me if I decide to leave the study before it is finished?

If you want to withdraw from the study at any time, you are free to do so, even if you do not give a reason. If you do withdraw, your usual medical care will not be affected in any way. If necessary for your medical care, your study doctor may advise you to have some follow-up tests.

If you withdraw from the study, no new information (data) about you will be added to the database. The researchers would still like to be able to examine the oral samples you provided if you decide to leave the study before it is finished.

### 7.3  Could the researchers take me out of the study even if I want to continue to participate?

Yes. There are many reasons why the researchers may need to end your participation in the study.  Some examples are:

- ✓ The researcher believes that it is not in your best interest to stay in the study.
- ✓ You become ineligible to participate.
- ✓ Your condition changes and you need treatment that is not allowed while you are taking part in the study.
- ✓ You do not follow instructions from the researchers.
- ✓ The study is suspended or canceled.

## 8.  FINANCIAL INFORMATION

### 8.1  Who will pay for the costs of the study? Will I or my health plan be billed for any costs of the study?

There are no costs to participants associated with being in this study.

By signing this form, you do not give up your right to seek payment if you are harmed as a result of being in this study.

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## 8.2  Will I be paid or given anything for taking part in this study?

Yes, you will be paid $10 for your participation.

## 8.3  Who could profit or financially benefit from the study results?

None of the personnel involved in this study could profit or benefit financially from the study results.

| 9.  CONFIDENTIALITY OF SUBJECT RECORDS AND AUTHORIZATION TO RELEASE YOUR PROTECTED HEALTH INFORMATION |
| --- |

The information below describes how your privacy and the confidentiality of your research records will be protected in this study.

## 9.1  How will the researchers protect my privacy?

Your research information will be stored in a locked cabinet.  All specimens will be coded before they are analyzed, and the research personnel who analyze the specimens will not be able to link them with any of your identifying information or medical history.  All data regarding your oral rinse sample will be stored in a password-protected database with barcoding of each sample to further enhance the privacy of your sample.

## 9.2  What information about me could be seen by the researchers or by other people? Why?  Who might see it?

Signing this form gives the researchers your permission to obtain, use, and share information about you for this study, and is required in order for you to take part in the study.  Information about you may be obtained from any hospital, doctor, and other health care provider involved in your care, including:

- Hospital/doctor's office records, including test results (X-rays, blood tests, urine tests, etc.)
- Alcohol/substance abuse treatment records
- Your AIDS/HIV status
- All records relating to your illness, the treatment you have received, and your response to the treatment
- Billing information

There are many reasons why information about you may be used or seen by the researchers or others during or after this study.  Examples include:

- The researchers may need the information to make sure you can take part in the study.
- The researchers may need the information to check your test results or look for side effects.
- University, Food and Drug Administration (FDA), and/or other government officials may need the information to make sure that the study is done in a safe and proper manner.
- Study sponsors or funders, or safety monitors or committees, may need the information to:
  - Make sure the study is done safely and properly
  - Learn more about side effects
  - Analyze the results of the study

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- Insurance companies or other organizations may need the information in order to pay your medical bills or other costs of your participation in the study.
- The researchers may need to use the information to create a databank of information about your condition or its treatment.
- Information about your study participation may be included in your regular UMHS medical record.
- If you receive any payments for taking part in this study, the University of Michigan accounting department may need your name, address, social security number, payment amount, and related information for tax reporting purposes.
- Federal or State law may require the study team to give information to government agencies. For example, to prevent harm to you or others, or for public health reasons.

The results of this study could be published in an article, but would not include any information that would let others know who you are.

### 9.3  What happens to information about me after the study is over or if I cancel my permission?

As a rule, the researchers will not continue to use or disclose information about you, but will keep it secure until it is destroyed.  Sometimes, it may be necessary for information about you to continue to be used or disclosed, even after you have canceled your permission or the study is over.  Examples of reasons for this include:

- To avoid losing study results that have already included your information

- To provide limited information for research, education, or other activities  (This information would not include your name, social security number, or anything else that could let others know who you are.)

- To help University and government officials make sure that the study was conducted properly

As long as your information is kept within the University of Michigan Health System, it is protected by the Health System's privacy policies.  For more information about these policies, ask for a copy of the University of Michigan Notice of Privacy Practices.  This information is also available on the web at http://www.med.umich.edu/hipaa/npp.htm. Note that once your information has been shared with others as described under Question 9.2, it may no longer be protected by the privacy regulations of the federal Health Insurance Portability and Accountability Act of 1996 (HIPAA).

### 9.4  When does my permission expire?

Your permission expires at the end of the study, unless you cancel it sooner. You may cancel your permission at any time by writing to the researchers listed in Section 10 "Contact Information" (below).

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Consent Subtitle: HIV/HPV oral rinse consent (partner)
Consent Version: 27Sep2011

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## 10.  CONTACT INFORMATION

### 10.1  Who can I contact about this study?

Please contact the researchers listed below to:

- Obtain more information about the study
- Ask a question about the study procedures or treatments
- Talk about study-related costs to you or your health plan
- Report an illness, injury, or other problem (you may also need to tell your regular doctors)
- Leave the study before it is finished
- Express a concern about the study

> Principal Investigator: Mikiko Senga
> Mailing Address: 1500 E. Medical Center Drive, 3210 Taubman Center
> Ann Arbor, MI 48109-5378
> Telephone: 734-647-9830
>
> Study Coordinator: Mary Reyes
> Mailing Address: 1500 E. Medical Center Drive, 3120 Taubman Center
> Ann Arbor, MI 48109-5378
> Telephone: 734-647-9830

You may also express a concern about a study by contacting the Institutional Review Board listed below, or by calling the University of Michigan Compliance Help Line at 1-888-296-2481.

> University of Michigan Medical School Institutional Review Board (IRBMED)
> 2800 Plymouth Road
> Building 200, Room 2086
> Ann Arbor, MI 48109-2800
> Telephone: 734-763-4768
> Fax: 734-763-1234
> e-mail: irbmed@umich.edu

If you are concerned about a possible violation of your privacy, contact the University of Michigan Health System Privacy Officer at 1-888-296-2481.

*When you call or write about a concern, please provide as much information as possible, including the name of the researcher, the IRBMED number (at the top of this form), and details about the problem.  This will help University officials to look into your concern.  When reporting a concern, you do not have to give your name unless you want to.*

## 11.  RECORD OF INFORMATION PROVIDED

### 11.1  What documents will be given to me?

Your signature in the next section means that you have received copies of all of the following documents:

- This "Consent to be Part of a Research Study" document.  (*Note: In addition to the copy you receive, copies of this document will be stored in a separate confidential research file and may be entered into your regular University of Michigan medical record.*)

IRB Standard Consent Template Version 10-14-10
DO NOT CHANGE THIS FIELD-IRB USE ONLY

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Consent Subtitle: HIV/HPV oral rinse consent
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## 12.  SIGNATURES

**Research Subject:**

*I understand the information printed on this form.  I have discussed this study, its risks and potential benefits, and my other choices with _____.  My questions so far have been answered.  I understand that if I have more questions or concerns about the study or my participation as a research subject, I may contact one of the people listed in Section 10 (above).  I understand that I will receive a copy of this form at the time I sign it and later upon request.  I understand that if my ability to consent for myself changes, either I or my legal representative may be asked to re-consent prior to my continued participation in this study.*

Signature of Subject: _____   Date: _____

Name (Print legal name): _____

Patient ID:_____   Date of Birth: _____

**Principal Investigator (or Designee):**

*I have given this research subject (or his/her legally authorized representative, if applicable) information about this study that I believe is accurate and complete.  The subject has indicated that he or she understands the nature of the study and the risks and benefits of participating.*

Name: _____   Title: _____

Signature: _____   Date of Signature: _____

IRB Standard Consent Template Version 10-14-10
DO NOT CHANGE THIS FIELD-IRB USE ONLY

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Consent Subtitle: HIV/HPV oral rinse consent
(partner)
Consent Version: 27Sep2011

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## University of Michigan Etiology of Papillomavirus Infections (EPI) Study (Male)

Date completed ___-___-_____ (mm-dd-yyyy)
Study ID: _____

<u>Instructions</u>:

Thank you for your willingness to participate in the EPI Study. This study is to understand the role of human papillomavirus (HPV), a virus which causes cervical cancer, in people with and without HIV.

Please complete the survey by checking the appropriate answer and filling in the blanks as requested. You may feel that some questions do not apply to you, and that is okay.

All of your answers are strictly confidential, and your responses will not affect your clinical care you receive from your doctor(s) at the University of Michigan Health Systems.

1. <u>Demographics</u>

**A. What is your gender?**

    __ Male
    __ Female <u>(STOP. Please ask for the correct version of the questionnaire)</u>

**BI. Race (check one only)**

    __ White, not Hispanic origin
    __ Hispanic
    __ Black, not Hispanic origin
    __ Native Hawaiian or other Pacific Islander
    __ Asian
    __ Native American/Alaskan Nation
    __ Other, specify _____
    __ Unknown / I prefer not to answer

**BII. Additional Race/Ethnicity** (If you consider yourself multiracial, check all additional categories that apply in this question). Do not include what you reported in BI.

    __ White, not Hispanic origin
    __ Hispanic
    __ Black, not Hispanic origin
    __ Native Hawaiian or other Pacific Islander
    __ Asian
    __ Native American/Alaskan Nation
    __ Other, specify _____
    __ Unknown/I prefer not to answer

**C. Highest school grade completed (check one)**

    __ 8th or less
    __ 9-11th grade
    __ High school graduate/GED
    __ Vocational/technical school
    __ Associate degree/some college
    __ Bachelor's degree
    __ Advanced degree
    __ Other, specify _____
    __ I prefer not to answer

**D. Marital status**

    __ Married        __ Divorced/Separated
    __ Widowed      __ Living as married
    __ Single          __ I prefer not to answer

**E. Religion during childhood**

    __ Protestant
    __ Catholic
    __ Jewish
    __ Mormon/Latter Day Saints
    __ Muslim/Islam
    __ None
    __ Other, specify _____
    __ I prefer not to answer

# University of Michigan Etiology of Papillomavirus Infections (EPI) Study (Male)

Date completed ___-___-_____ (mm-dd-yyyy)
Study ID: _____

F. Where were you born?

     __ USA, specify the 2 letter state code _____
     __ Other country, specify _____

G. Where did you live longest?

     __ USA, specify the 2 letter state code _____
     __ Other country, specify _____

## 2. Cigarette history

A. Have you smoked at least 100 cigarettes (5 packs) during your lifetime?
     __ No (Skip to #3)
     __ Yes, but quit (answer B-E)
     __ Yes, currently smoke (answer B-E)
B. Age you began smoking cigarettes      _____
C. Number of years you smoked cigarettes      _____
D. Average # of cigarettes smoked per day      _____
E. If quit, age you stopped smoking completely      _____

## 3. Cigar history

A. Have you ever smoked cigars during your lifetime?
     __ No (Skip to #4)
     __ Yes, but quit (answer B-E)
     __ Yes, currently (answer B-E)
B. Age you began smoking cigars      _____
C. Number of years you smoked cigars      _____
D. Average number of cigars smoked per day      _____
E. If quit, age stopped smoking cigars completely_____

## 4. Chewing tobacco history

A. Have you ever chewed tobacco during your lifetime?
     __ No (Skip to #5)
     __ Yes, but quit (answer B-E)
     __ Yes, currently chew (answer B-E)
B. Age began chewing tobacco      _____
C. Number of years having chewed tobacco      _____
D. Average times chewed tobacco per day      _____
E. If quit, age stopped chewing completely      _____

## 5. Pipe smoking history

A. Have you ever smoked pipes during your lifetime?
     __ No (Skip to #6)
     __ Yes, but quit (answer B-E)
     __ Yes, currently smoke (answer B-E)
B. Age you began smoking pipes      _____
C. Number of years you smoked pipes      _____
D. Average # of pipes you smoked per day      _____
E. If quit, age you stopped smoking it completely _____

## 6. Snuff history

A. Have you ever snorted or smoked snuff during your lifetime?
     __ No (Skip to #7)
     __ Yes, but quit (answer B-E)
     __ Yes, currently use snuff (answer B-E)
B. Age you began using snuff      _____
C. Number of years you used snuff      _____
D. Average times you used snuff per day      _____
E. If quit, age you stopped using it completely      _____

## 7. Marijuana history

A. Have you ever smoked marijuana during your lifetime?
     __ No (Skip to #8)
     __ Yes, but quit (answer B-E)
     __ Yes, currently smoke (answer B-E)
B. Age you began smoking marijuana      _____
C. Number of years you smoked marijuana      _____
D. Average times you smoked marijuana per day _____
E. If quit, age you stopped smoking it completely _____

## 8. Other substance use

A. Do you use any drugs other than marijuana?
     __ No (Skip to #9)
     __ Yes

B. What substance do you use? _____

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# University of Michigan Etiology of Papillomavirus Infections (EPI) Study (Male)

Date completed ___-___-_____ (mm-dd-yyyy)
Study ID: _____

## 9. Sexual practices

### A. What is your sexual preference?
__ Sex with a man
__ Sex with a woman
__ Sex with a man or woman

### B. At what age did you become sexually active?
_____

## 10. Vaginal intercourse

### A. Have you ever had vaginal intercourse?
__ No (Skip to #11)
__ Yes
__ Don't know

### B. Number of women with whom you had vaginal intercourse
_____

### C. Did you use condoms during vaginal intercourse?
__ Never __ Most of the time
__ Rarely __ All of the time

### D. If you answered never, rarely, or most of the time to 10C, during what age range did you most frequently have unprotected sex?
__ Under age 18 __ Age 18-22
__ Age 23-29 __ Age 30-39
__ Age 40-49 __ Over age 50

### E. When was the last time you had vaginal intercourse?
__ Within the past day
__ Within the past week
__ Within the past month
__ More than one month ago

### F. Have you ever had vaginal sex with someone who had warts on her vagina?
__ No
__ Yes

## 11. Oral sex

### A. Have you ever performed oral sex?
__ No (Skip to #12)
__ Yes

### B. At what age did you first perform oral sex? _____

### C. Number of partners of each gender on whom oral sex was performed
Male _____
Female _____

### D. Did you use condoms during oral sex?
__ Never __ Most of the time
__ Rarely __ All of the time

### E. If you answered never, rarely, or most of the time to 11D, during what age range did you most frequently have unprotected oral sex?
__ Under age 18 __ Age 18-22
__ Age 23-29 __ Age 30-39
__ Age 40-49 __ Over age 50

### F. When was the last time you had oral intercourse?
__ Within the past day
__ Within the past week
__ Within the past month
__ More than one month ago

### G. Have you ever had oral sex with someone who had warts on his/her genitals?
__ No
__ Yes
__ Don't know

## 12. Anal sex

### A. Have you ever engaged in anal intercourse?
__ No (Skip to #13)
__ Yes

### B. At what age did you first engage in anal intercourse? _____

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# University of Michigan Etiology of Papillomavirus Infections (EPI) Study (Male)

Date completed ___-___-_____ (mm-dd-yyyy)
Study ID: _____

C. Number of partners of each gender with whom you engaged in anal intercourse
Male _____
Female _____

D. Did you use condoms during anal intercourse?
__ Never          __ Most of the time
__ Rarely         __ All of the time

E. If you answered never, rarely, or most of the time to 12D, during what age range did you most frequently have unprotected anal sex?
__ Under age 18   __ Age 18-22
__ Age 23-29      __ Age 30-39
__ Age 40-49      __ Over age 50

F. When was the last time you had anal intercourse?
__ Within the past day
__ Within the past week
__ Within the past month
__ More than one month ago

G. Have you ever had anal sex with someone who had warts on his/her anus?
__ No
__ Yes

13. French kissing

A. Have you ever engaged in deep kissing (aka "French kissing" or kissing with tongue)?
__ No (Skip to #14)
__ Yes

B. At what age did you begin deep kissing?
_____

C. Number of partners of each gender with whom you engaged in deep kissing
Male _____
Female _____

D. During what age range did you most frequently engage in deep kissing?
__ Under age 18   __ Age 18-22
__ Age 23-29      __ Age 30-39
__ Age 40-49      __ Over age 50

E. When was the last time you French kissed someone?
__ Within the past day
__ Within the past week
__ Within the past month
__ More than one month ago

F. Have you ever kissed or French kissed someone who had a wart on his/her mouth?
__ No
__ Yes

14. Other sexual practices

A. Do you ever use your saliva as lubricant during sex?
__ No
__ Yes

B. Do you ever use your partner's saliva as lubricant during sex?
__ No
__ Yes

C. Do you masturbate?
__ No
__ Yes

D. If yes, how often?
__ Once a day
__ Within the past week
__ Within the past month
__ More than one month ago

# University of Michigan Etiology of Papillomavirus Infections (EPI) Study (Male)

Date completed ___-___-_____ (mm-dd-yyyy)
Study ID: _____

E. Do you wash your hands after you masturbate?
  __ No
  __ Yes, always
  __ Yes, sometimes
  __ Yes, rarely

15. <u>Sexual Health</u>

A. Have you ever had an <u>anal</u> pap smear?
  __ No
  __ Yes
  __ Don't know

B. Have you ever had an abnormal <u>anal</u> pap smear?
  __ No
  __ Yes
  __ Don't know

C. If your partner is female, what kind(s) of birth control do you and your partner use?
  __ Cervical cap
  __ Female condom
  __ Male condom
  __ Dental dam
  __ Diaphragm
  __ Spermicides
  __ Pills

D. If your partner is female, has she ever had an abnormal <u>cervical</u> pap smear?
  __ No
  __ Yes
  __ Don't know

E. Have you ever had syphilis?
  __ No
  __ Yes
  __ Don't know

F. Have you ever had chlamydia?
  __ No
  __ Yes
  __ Don't know

G. Have you ever had genital herpes?
  __ No
  __ Yes
  __ Don't know

H. Have you ever had oral herpes?
  __ No
  __ Yes
  __ Don't know

I. Do you exchange sex for money?
  __ No
  __ Yes
  __ Don't know

J. Do you exchange sex for drugs?
  __ No
  __ Yes
  __ Don't know

16. <u>General health history</u>

A. Have you had your tonsils out?
  __ No
  __ Yes
  __ Don't know

B. Have you ever had warts on your hands or feet?
  __ No
  __ Yes
  __ Don't know

C. Have you ever had warts in your genital area?
  __ No
  __ Yes
  __ Don't know

# University of Michigan Etiology of Papillomavirus Infections (EPI) Study (Male)

Date completed ___-___-_____ (mm-dd-yyyy)
Study ID: _____

D. Have you ever had any of the following types of cancer?
__ Nose
__ Mouth, throat, tongue, or voice box
__ Tonsil
__ Kaposi's sarcoma
__ Lymphoma
__ Anal
__ Cervical
__ Penile
__ Skin
__ Other:_____

E. How many times <u>a week</u> do you brush your teeth?
____ times a week

F. How many <u>times a day</u> do you brush your teeth?
____ times a day

G. How many times <u>a week</u> do you use mouthwash?
____ times a week

H. How many times <u>a day</u> do you use mouthwash?
_____ times a day

I. What kind of mouthwash do you use?
__ Alcohol-based
__ Non alcohol-based
__ I do not use any kind of mouthwash
__ Don't know

J. Do you wash your hands after you had any contact with someone?
__ No
__ Yes, always
__ Yes, sometimes
__ Yes, rarely

K. Do you wash your hands after you go to the bathroom?
__ No
__ Yes, always
__ Yes, sometimes
__ Yes, rarely

L. Do you share eating utensils with another person?
__ No
__ Yes, always
__ Yes, sometimes
__ Yes, rarely

M. Do you share a drink from the same bottle/cup with someone?
__ No
__ Yes, always
__ Yes, sometimes
__ Yes, rarely

N. Have you ever received an HPV vaccine?
__ No
__ Yes
__ Don't know

O. If yes, when did you receive this vaccine?
Date: _____/_____/_____
          Month     Day      Year

P. Have you ever had or been told that you had infectious mononucleosis (or "mono")?
__ No
__ Yes
__ Don't know

Q. If yes, when did you have mono?
Date: _____/_____/_____
          Month     Day      Year

R. Are you circumcised?
__ No
__ Yes
__ Don't know

S. If you have a male sexual partner, is he circumcised?
__ No
__ Yes
__ Don't know

# University of Michigan Etiology of Papillomavirus Infections (EPI) Study (Male)

Date completed ___-___-_____ (mm-dd-yyyy)
Study ID: _____

## 17. <u>Drinking history</u>
<u>Note</u>: One drink is equivalent to 1 oz. of liquor, 5 oz. of wine, or 12 oz. of beer

A. Have you ever consumed alcohol?
    __ No (Skip to #18)
    __ Yes, but quit
    __ Yes, currently

B. At what age did you begin drinking alcohol?
    _____

C. Number of years you have consumed alcohol
    _____

D. Frequency of consumption of beverages containing alcohol <u>while you were under the age of 18</u> (please check only one)
    __ Never
    __ Less than monthly
    __ 2-4 times per month
    __ 2-4 times per week
    __ 4 or more times per week

E. Number of drinks containing alcohol on a typical day when drinking <u>while you were under the age of 18</u> (please check only one)
    __ 1 or 2      __ 3 or 4
    __ 5 or 6      __ 7-9
    __ 10 or more

F. Frequency of consumption of beverages containing alcohol <u>while you were between age 18-22</u> (please check only one)
    __ Never
    __ Less than monthly
    __ 2-4 times per month
    __ 2-4 times per week
    __ 4 or more times per week

G. Number of drinks containing alcohol on a typical day when drinking <u>while you were between age 18-22</u> (please check only one)
    __ 1 or 2      __ 3 or 4
    __ 5 or 6      __ 7-9
    __ 10 or more

H. Frequency of consumption of beverages containing alcohol <u>while you were between age 23-29</u> (please check only one)
    __ Never
    __ Less than monthly
    __ 2-4 times per month
    __ 2-4 times per week
    __ 4 or more times per week

I. Number of drinks containing alcohol on a typical day when drinking <u>while you were between age 23-29</u> (please check only one)
    __ 1 or 2      __ 3 or 4
    __ 5 or 6      __ 7-9
    __ 10 or more

J. Frequency of consumption of beverages containing alcohol <u>while you were between age 30-39</u> (please check only one)
    __ Never
    __ Less than monthly
    __ 2-4 times per month
    __ 2-4 times per week
    __ 4 or more times per week

K. Number of drinks containing alcohol on a typical day when drinking <u>while you were between age 30-39</u> (please check only one)
    __ 1 or 2      __ 3 or 4
    __ 5 or 6      __ 7-9
    __ 10 or more

# University of Michigan Etiology of Papillomavirus Infections (EPI) Study (Male)

Date completed ___-___-_____ (mm-dd-yyyy)
Study ID: _____

L. Frequency of consumption of beverages containing alcohol <u>while you were between age 40-49</u> (please check only one)
__ Never
__ Less than monthly
__ 2-4 times per month
__ 2-4 times per week
__ 4 or more times per week

M. Number of drinks containing alcohol on a typical day when drinking <u>while you were between age 40-49</u> (please check only one)
__ 1 or 2        __ 3 or 4
__ 5 or 6        __ 7-9
__ 10 or more

N. If you quit, age you stopped drinking completely
_____

18. <u>Dietary factors:</u>
A. How much water do you drink per day?
__ One 8 oz glass
__ Two 8oz glasses
__ Three 8oz glasses
__ Four 8oz glasses
__ Five 8oz glasses
__ Six 8oz glasses
__ Seven 8oz glasses
__ Eight 8oz glasses
__ More than eight 8oz glasses

B. How many drinks that contain caffeine do you drink per day?
__ None
__ One 8 oz glass
__ Two 8oz glasses
__ Three 8oz glasses
__ Four 8oz glasses
__ Five 8oz glasses
__ Six 8oz glasses
__ Seven 8oz glasses
__ Eight 8oz glasses
__ More than eight 8oz glasses

C. Do you chew nicotine gum?
__ Yes
__ No
__ Don't know

19. <u>Second-hand smoking exposure</u>
A. Have you ever been exposed to second-hand smoking?
__ No (answer E, F, G, H)
__ Yes

B. Where did this exposure take place and for about how long?
__ Work        ____ hours/day for ____ years
__ Home        ____ hours/day for ____ years
__ Other       ____ hours/day for ____ years

C. At what age did your second-hand smoking exposure begin?  _____

D. If exposure ceased, at what age? _____

E. Did your mother use any tobacco while she was pregnant with you?
__ Yes
__ No
__ Don't know

F. Did your mother use any marijuana while she was pregnant with you?
__ Yes
__ No
__ Don't know

G. Did your father use any tobacco while your mother was pregnant with you?
__ Yes
__ No
__ Don't know

# University of Michigan Etiology of Papillomavirus Infections (EPI) Study (Male)

Date completed ___-___-_____ (mm-dd-yyyy)
Study ID: _____

H. Did your father use any marijuana while your
mother was pregnant with you?
     __ Yes
     __ No
     __ Don't know

I. Did your parents or other family members smoke in
your home when you were growing up?
     __ Yes
     __ No
     __ Don't know

J. Did your parents or anyone else use marijuana in
your home when you were growing up
     __ Yes
     __ No
     __ Don't know

20. <u>Exposure to chemicals</u>

A. Do you work in any of the following job categories?
     __ Mining
     __ Oil industry, including gas stations
     __ Welding
     __ Work involving smoke
     __ Soft wood work
     __ Hard wood work

B. Are you exposed to any of the following chemicals
or substances on a regular basis?
     __ Diesel exhaust
     __ Asbestos
     __ Dust
     __ Welding
     __ Smoke at work
     __ Wood work

21. <u>HIV Patients Only</u>:

A. How old were you when you first tested
positive for HIV?
     _____ years old

B. Do you take your medications every day?
     __ No
     __ Yes
     __ Don't know

C. Has your CD4 count ever been below 200?
     __ No
     __ Yes
     __ Don't know

# University of Michigan Head & Neck Oncology Program
## Social Behaviors and Family History Form

Date completed ___-___-_____ (mm-dd-yyyy)

Form ID _____          Resp. No. _____

Instructions: Complete the information by checking the appropriate answer and filling in the blanks as requested.

## 22. Family history

A. **How many of the following family members (living and dead) do you have?** Include only those who are blood-related.

____ Brothers          ____ Sisters          ____ Sons          ____ Daughters

B. **Are you adopted?**

____ No          ____ Yes (In 11C, complete the question only for your children)

C. Check the box under blood relatives for each family member who developed cancer and give an estimate of the age that the first cancer was diagnosed.  For each relative with cancer, check off all types of cancer that apply.

| Blood relative with cancer | Age when first cancer diagnosed | Type of Cancer | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | Lung | Breast | Colon | Prostate | Head & Neck | Non-Melanoma skin | Other (check and specify) |
| __ Father | | ____ | ____ | ____ | ____ | ____ | ____ | __ specify _____ |
| __ Mother | | ____ | ____ | ____ | xxxxxx | ____ | ____ | __ specify _____ |
| __ Brother #1<br>__ Brother #2<br>__ Brother #3<br>__ Brother #4 | | ____<br>____<br>____<br>____ | ____<br>____<br>____<br>____ | ____<br>____<br>____<br>____ | ____<br>____<br>____<br>____ | ____<br>____<br>____<br>____ | ____<br>____<br>____<br>____ | __ specify _____<br>__ specify _____<br>__ specify _____<br>__ specify _____ |
| __ Sister #1<br>__ Sister #2<br>__ Sister #3<br>__ Sister #4 | | ____<br>____<br>____<br>____ | ____<br>____<br>____<br>____ | ____<br>____<br>____<br>____ | xxxxxx | ____<br>____<br>____<br>____ | ____<br>____<br>____<br>____ | __ specify _____<br>__ specify _____<br>__ specify _____<br>__ specify _____ |
| __ Child #1<br>__ Child #2<br>__ Child #3<br>__ Child #4 | | ____<br>____<br>____<br>____ | ____<br>____<br>____<br>____ | ____<br>____<br>____<br>____ | ____<br>____<br>____<br>____ | ____<br>____<br>____<br>____ | ____<br>____<br>____<br>____ | __ specify _____<br>__ specify _____<br>__ specify _____<br>__ specify _____ |

# University of Michigan Etiology of Papillomavirus Infections (EPI) Study (Female)

Date completed ___-___-_____ (mm-dd-yyyy)
Study ID: _____

Instructions:

Thank you for your willingness to participate in the EPI Study. This study is to understand the role of human papillomavirus (HPV), a virus which causes cervical cancer, in people with and without HIV.

Please complete the survey by checking the appropriate answer and filling in the blanks as requested. You may feel that some questions do not apply to you, and that is okay.

All of your answers are strictly confidential, and your responses will not affect your clinical care you receive from your doctor(s) at the University of Michigan Health Systems.

## 1. Demographics

### A. What is your gender?

__ Male (STOP. Please ask for the correct version of the questionnaire)
__ Female

### BI. Race (check one only)

__ White, not Hispanic origin
__ Hispanic
__ Black, not Hispanic origin
__ Native Hawaiian or other Pacific Islander
__ Asian
__ Native American/Alaskan Nation
__ Other, specify _____
__ Unknown / I prefer not to answer

### BII. Additional Race/Ethnicity (If you consider yourself multiracial, check all additional categories that apply in this question). Do not include what you reported in BI.

__ White, not Hispanic origin
__ Hispanic
__ Black, not Hispanic origin
__ Native Hawaiian or other Pacific Islander
__ Asian
__ Native American/Alaskan Nation
__ Other, specify _____
__ Unknown/I prefer not to answer

### C. Highest school grade completed (check one)

__ 8th or less
__ 9-11th grade
__ High school graduate/GED
__ Vocational/technical school
__ Associate degree/some college
__ Bachelor's degree
__ Advanced degree
__ Other, specify _____
__ I prefer not to answer

### D. Marital status

__ Married          __ Divorced/Separated
__ Widowed       __ Living as married
__ Single           __ I prefer not to answer

### E. Religion during childhood

__ Protestant
__ Catholic
__ Jewish
__ Mormon/Latter Day Saints
__ Muslim/Islam
__ None
__ Other, specify _____
__ I prefer not to answer

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# University of Michigan Etiology of Papillomavirus Infections (EPI) Study (Female)

Date completed ___-___-_____ (mm-dd-yyyy)
Study ID: _____

**F. Where were you born?**

    __ USA, specify the 2 letter state code _____
    __ Other country, specify _____

**G. Where did you live longest?**

    __ USA, specify the 2 letter state code _____
    __ Other country, specify _____

## 2. Cigarette history

**A. Have you smoked at least 100 cigarettes (5 packs) during your lifetime?**
    __ No (Skip to #3)
    __ Yes, but quit (answer B-E)
    __ Yes, currently smoke (answer B-E)
B. Age you began smoking cigarettes _____
C. Number of years you smoked cigarettes _____
D. Average # of cigarettes smoked per day _____
E. If quit, age you stopped smoking completely _____

## 3. Cigar history

**A. Have you ever smoked cigars during your lifetime?**
    __ No (Skip to #4)
    __ Yes, but quit (answer B-E)
    __ Yes, currently (answer B-E)
B. Age you began smoking cigars _____
C. Number of years you smoked cigars _____
D. Average number of cigars smoked per day _____
E. If quit, age stopped smoking cigars completely_____

## 4. Chewing tobacco history

**A. Have you ever chewed tobacco during your lifetime?**
    __ No (Skip to #5)
    __ Yes, but quit (answer B-E)
    __ Yes, currently chew (answer B-E)
B. Age began chewing tobacco _____
C. Number of years having chewed tobacco _____
D. Average times chewed tobacco per day _____
E. If quit, age stopped chewing completely _____

## 5. Pipe smoking history

**A. Have you ever smoked pipes during your lifetime?**
    __ No (Skip to #6)
    __ Yes, but quit (answer B-E)
    __ Yes, currently smoke (answer B-E)
B. Age you began smoking pipes _____
C. Number of years you smoked pipes _____
D. Average # of pipes you smoked per day _____
E. If quit, age you stopped smoking it completely _____

## 6. Snuff history

**A. Have you ever snorted or smoked snuff during your lifetime?**
    __ No (Skip to #7)
    __ Yes, but quit (answer B-E)
    __ Yes, currently use snuff (answer B-E)
B. Age you began using snuff _____
C. Number of years you used snuff _____
D. Average times you used snuff per day _____
E. If quit, age you stopped using it completely _____

## 7. Marijuana history

**A. Have you ever smoked marijuana during your lifetime?**
    __ No (Skip to #8)
    __ Yes, but quit (answer B-E)
    __ Yes, currently smoke (answer B-E)
B. Age you began smoking marijuana _____
C. Number of years you smoked marijuana _____
D. Average times you smoked marijuana per day _____
E. If quit, age you stopped smoking it completely _____

## 8. Other substance use

**A. Do you use any drugs other than marijuana?**
    __ No (Skip to #9)
    __ Yes

**B. What substance do you use? _____**

# University of Michigan Etiology of Papillomavirus Infections (EPI) Study (Female)

Date completed ___-___-_____ (mm-dd-yyyy)
Study ID: _____

## 9. Sexual practices

A. What is your sexual preference?
- A. __ Sex with a man
- B. __ Sex with a woman
- C. __ Sex with a man or woman

B. At what age did you become sexually active?
_____

## 10. Vaginal intercourse

A. Have you ever had vaginal intercourse?
- __ No (Skip to #11)
- __ Yes
- __ Don't know

B. Number of partners of each gender with whom you had vaginal intercourse
Male _____
Female _____

C. Did you use condoms during vaginal intercourse?
- __ Never
- __ Rarely
- __ Most of the time
- __ All of the time

D. If you answered never, rarely, or most of the time to 10C, during what age range did you most frequently have unprotected sex?
- __ Under age 18
- __ Age 23-29
- __ Age 40-49
- __ Age 18-22
- __ Age 30-39
- __ Over age 50

E. When was the last time you had vaginal intercourse?
- __ Within the past day
- __ Within the past week
- __ Within the past month
- __ More than one month ago

F. Have you ever had vaginal sex with someone who had warts on his penis (if your partner was male) or her vagina (if your partner was female)?
- __ No
- __ Yes

## 11. Oral sex

A. Have you ever performed oral sex?
- __ No (Skip to #12)
- __ Yes

B. At what age did you first perform oral sex? _____

C. Number of partners of each gender on whom oral sex was performed
Male _____
Female _____

D. Did you use condoms during oral sex?
- __ Never
- __ Rarely
- __ Most of the time
- __ All of the time

E. If you answered never, rarely, or most of the time to 11D, during what age range did you most frequently have unprotected oral sex?
- __ Under age 18
- __ Age 23-29
- __ Age 40-49
- __ Age 18-22
- __ Age 30-39
- __ Over age 50

F. When was the last time you had oral intercourse?
- __ Within the past day
- __ Within the past week
- __ Within the past month
- __ More than one month ago

G. Have you ever had oral sex with someone who had warts on his/her genitals?
- __ No
- __ Yes
- __ Don't know

# University of Michigan Etiology of Papillomavirus Infections (EPI) Study (Female)

Date completed ___-___-_____ (mm-dd-yyyy)
Study ID: _____

## 12. Anal sex

A. Have you ever engaged in anal intercourse?
　　__ No (Skip to #13)
　　__ Yes

B. At what age did you first engage in anal intercourse? _____

C. Number of partners of each gender with whom you engaged in anal intercourse
　　Male _____
　　Female _____

D. Did you use condoms during anal intercourse?
　　__ Never　　　　__ Most of the time
　　__ Rarely　　　　__ All of the time

E. If you answered never, rarely, or most of the time to 12D, during what age range did you most frequently have unprotected anal sex?
　　__ Under age 18　　__ Age 18-22
　　__ Age 23-29　　　__ Age 30-39
　　__ Age 40-49　　　__ Over age 50

F. When was the last time you had anal intercourse?
　　__ Within the past day
　　__ Within the past week
　　__ Within the past month
　　__ More than one month ago

G. Have you ever had anal sex with someone who had warts on his/her anus?
　　__ No
　　__ Yes

## 13. French kissing

A. Have you ever engaged in deep kissing (aka "French kissing" or kissing with tongue)?
　　__ No (Skip to #14)
　　__ Yes

B. At what age did you begin deep kissing?
　　_____

C. Number of partners of each gender with whom you engaged in deep kissing
　　Male _____
　　Female _____

D. During what age range did you most frequently engage in deep kissing?
　　__ Under age 18　　__ Age 18-22
　　__ Age 23-29　　　__ Age 30-39
　　__ Age 40-49　　　__ Over age 50

E. When was the last time you French kissed someone?
　　__ Within the past day
　　__ Within the past week
　　__ Within the past month
　　__ More than one month ago

F. Have you ever kissed or French kissed someone who had a wart on his/her mouth?
　　__ No
　　__ Yes

## 14. Other sexual practices

A. Do you ever use your saliva as lubricant during sex?
　　__ No
　　__ Yes

B. Do you ever use your partner's saliva as lubricant during sex?
　　__ No
　　__ Yes

C. Do you masturbate?
　　__ No
　　__ Yes

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Date completed ___-___-_____ (mm-dd-yyyy)
Study ID: _____

**D. If yes, how often?**
__ Once a day
__ Within the past week
__ Within the past month
__ More than one month ago

**E. Do you wash your hands after you masturbate?**
__ No
__ Yes, always
__ Yes, sometimes
__ Yes, rarely

## 15. Sexual Health

**A. Have you ever had an anal pap smear?**
__ No
__ Yes
__ Don't know

**B. Have you ever had an abnormal anal pap smear?**
__ No
__ Yes
__ Don't know

**C. Have you ever used birth control?**
__ No
__ Yes
__ Don't know

**D. Are you currently on birth control?**
__ No
__ Yes (answer E)
__ Don't know

**E. What kind(s) of birth control do you use?**
__ Cervical cap
__ Female condom
__ Male condom
__ Dental dam
__ Diaphragm
__ Spermicides
__ Pills

**F. Have you ever had a cervical pap smear?**
__ No
__ Yes
__ Don't know

**G. How often do you have a cervical pap smear?**
__ More than once a year
__ Once a year
__ Once every two years
__ Once every five years
__ Once every

**H. Have you ever had an abnormal cervical pap smear?**
__ No
__ Yes
__ Don't know

**I. Have you ever had syphilis?**
__ No
__ Yes
__ Don't know

**J. Have you ever had chlamydia?**
__ No
__ Yes
__ Don't know

**K. Have you ever had genital herpes?**
__ No
__ Yes
__ Don't know

**L. Have you ever had oral herpes?**
__ No
__ Yes
__ Don't know

**M. Do you exchange sex for money?**
__ No
__ Yes
__ Don't know

# University of Michigan Etiology of Papillomavirus Infections (EPI) Study (Female)

Date completed ___-___-_____ (mm-dd-yyyy)
Study ID: _____

N.  Do you exchange sex for drugs?
  __ No
  __ Yes
  __ Don't know

16. General health history

A.  Have you had your tonsils out?
  __ No
  __ Yes
  __ Don't know

B.  Have you ever had warts on your hands or feet?
  __ No
  __ Yes
  __ Don't know

C.  Have you ever had warts in your genital area?
  __ No
  __ Yes
  __ Don't know

D.  Have you ever had any of the following types of cancer?
  __ Nose
  __ Mouth, throat, tongue, or voice box
  __ Tonsil
  __ Kaposi's sarcoma
  __ Lymphoma
  __ Anal
  __ Cervical
  __ Penile
  __ Skin
  __ Other:_____

E.  How many times a week do you brush your teeth?
  _____ times a week

F.  How many times a day do you brush your teeth?
  _____ times a day

G.  How many times a week do you use mouthwash?
  _____ times a week

H.  How many times a day do you use mouthwash?
  _____ times a day

I.  What kind of mouthwash do you use?
  __ Alcohol-based
  __ Non alcohol-based
  __ I do not use any kind of mouthwash
  __ Don't know

J.  Do you wash your hands after you had any contact with someone?
  __ No
  __ Yes, always
  __ Yes, sometimes
  __ Yes, rarely

K.  Do you wash your hands after you go to the bathroom?
  __ No
  __ Yes, always
  __ Yes, sometimes
  __ Yes, rarely

L.  Do you share eating utensils with another person?
  __ No
  __ Yes, always
  __ Yes, sometimes
  __ Yes, rarely

M.  Do you share a drink from the same bottle/cup with someone?
  __ No
  __ Yes, always
  __ Yes, sometimes
  __ Yes, rarely

N.  Have you ever received an HPV vaccine?
  __ No
  __ Yes
  __ Don't know

O.  If yes, when did you receive this vaccine?
  Date: _____/_____/_____
          Month    Day    Year

# University of Michigan Etiology of Papillomavirus Infections (EPI) Study (Female)

Date completed ___-___-_____ (mm-dd-yyyy)
Study ID: _____

P. Have you ever had or been told that you had infectious mononucleosis (or "mono")?
__ No
__ Yes
__ Don't know

Q. If yes, when did you have mono?
Date: _____/_____/_____
        Month    Day    Year

R. Have you ever been pregnant?
__ No
__ Yes
__ Don't know

S. How many children have you given birth to?
__ 0            __ 4
__ 1            __ 5
__ 2            __ more than 5
__ 3

T. If you have a male sexual partner, is he circumcised?
__ No
__ Yes
__ Don't know

17. Drinking history
Note: One drink is equivalent to 1 oz. of liquor, 5 oz. of wine, or 12 oz. of beer

A. Have you ever consumed alcohol?
__ No (Skip to #18)
__ Yes, but quit
__ Yes, currently

B. At what age did you begin drinking alcohol?
_____

C. Number of years you have consumed alcohol
_____

D. Frequency of consumption of beverages containing alcohol while you were under the age of 18 (please check only one)
__ Never
__ Less than monthly
__ 2-4 times per month
__ 2-4 times per week
__ 4 or more times per week

E. Number of drinks containing alcohol on a typical day when drinking while you were under the age of 18 (please check only one)
__ 1 or 2            __ 3 or 4
__ 5 or 6            __ 7-9
__ 10 or more

F. Frequency of consumption of beverages containing alcohol while you were between age 18-22 (please check only one)
__ Never
__ Less than monthly
__ 2-4 times per month
__ 2-4 times per week
__ 4 or more times per week

G. Number of drinks containing alcohol on a typical day when drinking while you were between age 18-22 (please check only one)
__ 1 or 2            __ 3 or 4
__ 5 or 6            __ 7-9
__ 10 or more

H. Frequency of consumption of beverages containing alcohol while you were between age 23-29 (please check only one)
__ Never
__ Less than monthly
__ 2-4 times per month
__ 2-4 times per week
__ 4 or more times per week

# University of Michigan Etiology of Papillomavirus Infections (EPI) Study (Female)

Date completed ___-___-_____ (mm-dd-yyyy)
Study ID: _____

I. Number of drinks containing alcohol on a typical day when drinking <u>while you were between age 23-29</u> (please check only one)

    __ 1 or 2        __ 3 or 4
    __ 5 or 6        __ 7-9
    __ 10 or more

J. Frequency of consumption of beverages containing alcohol <u>while you were between age 30-39</u> (please check only one)

    __ Never
    __ Less than monthly
    __ 2-4 times per month
    __ 2-4 times per week
    __ 4 or more times per week

K. Number of drinks containing alcohol on a typical day when drinking <u>while you were between age 30-39</u> (please check only one)

    __ 1 or 2        __ 3 or 4
    __ 5 or 6        __ 7-9
    __ 10 or more

L. Frequency of consumption of beverages containing alcohol <u>while you were between age 40-49</u> (please check only one)

    __ Never
    __ Less than monthly
    __ 2-4 times per month
    __ 2-4 times per week
    __ 4 or more times per week

M. Number of drinks containing alcohol on a typical day when drinking <u>while you were between age 40-49</u> (please check only one)

    __ 1 or 2        __ 3 or 4
    __ 5 or 6        __ 7-9
    __ 10 or more

N. If you quit, age you stopped drinking completely

    _____

18. <u>Dietary factors:</u>
A. How much water do you drink per day?
    __ One 8 oz glass
    __ Two 8oz glasses
    __ Three 8oz glasses
    __ Four 8oz glasses
    __ Five 8oz glasses
    __ Six 8oz glasses
    __ Seven 8oz glasses
    __ Eight 8oz glasses
    __ More than eight 8oz glasses

B. How many drinks that contain caffeine do you drink per day?
    __ None
    __ One 8 oz glass
    __ Two 8oz glasses
    __ Three 8oz glasses
    __ Four 8oz glasses
    __ Five 8oz glasses
    __ Six 8oz glasses
    __ Seven 8oz glasses
    __ Eight 8oz glasses
    __ More than eight 8oz glasses

C. Do you chew nicotine gum?
    __ Yes
    __ No
    __ Don't know

19. <u>Second-hand smoking exposure</u>
A. Have you ever been exposed to second-hand smoking?
    __ No (answer E, F, G, H)
    __ Yes

B. Where did this exposure take place and for about how long?
    __ Work    ____ hours/day for ____ years
    __ Home    ____ hours/day for ____ years
    __ Other    ____ hours/day for ____ years

C. At what age did your second-hand smoking exposure begin? _____

# University of Michigan Etiology of Papillomavirus Infections (EPI) Study (Female)

Date completed ___-___-_____ (mm-dd-yyyy)
Study ID: _____

D. If exposure ceased, at what age? _____

E. Did your mother use any tobacco while she was pregnant with you?
　　__ Yes
　　__ No
　　__ Don't know

F. Did your mother use any marijuana while she was pregnant with you?
　　__ Yes
　　__ No
　　__ Don't know

G. Did your father use any tobacco while your mother was pregnant with you?
　　__ Yes
　　__ No
　　__ Don't know

H. Did your father use any marijuana while your mother was pregnant with you?
　　__ Yes
　　__ No
　　__ Don't know

I. Did your parents or other family members smoke in your home when you were growing up?
　　__ Yes
　　__ No
　　__ Don't know

J. Did your parents or anyone else use marijuana in your home when you were growing up
　　__ Yes
　　__ No
　　__ Don't know

20. Exposure to chemicals

A. Do you work in any of the following job categories?
　　__ Mining
　　__ Oil industry, including gas stations
　　__ Welding
　　__ Work involving smoke
　　__ Soft wood work
　　__ Hard wood work

B. Are you exposed to any of the following chemicals or substances on a regular basis?
　　__ Diesel exhaust
　　__ Asbestos
　　__ Dust
　　__ Welding
　　__ Smoke at work
　　__ Wood work

21. HIV Patients Only:

A. How old were you when you first tested positive for HIV?
　　____ years old

B. Do you take your medications every day?
　　__ No
　　__ Yes
　　__ Don't know

C. Has your CD4 count ever been below 200?
　　__ No
　　__ Yes
　　__ Don't know

# University of Michigan Head & Neck Oncology Program
## Social Behaviors and Family History Form

Date completed ___-___-_____ (mm-dd-yyyy)

Form ID _____          Resp. No. _____

<u>Instructions</u>: Complete the information by checking the appropriate answer and filling in the blanks as requested.

22. <u>Family history</u>

A. **How many of the following family members (living and dead) do you have?** Include only those who are blood-related.

____ Brothers          ____ Sisters          ____ Sons          ____ Daughters

B. **Are you adopted?**

____ No          ____ Yes (In 11C, complete the question <u>only for your children</u>)

C. Check the box under blood relatives for each family member who developed cancer and give an estimate of the age that the <u>first</u> cancer was diagnosed.  For each relative with cancer, <u>check off</u> all types of cancer that apply.

| Blood relative with cancer | Age when first cancer diagnosed | Type of Cancer | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | Lung | Breast | Colon | Prostate | Head & Neck | Non-Melanoma skin | Other (check and specify) |
| __ Father | | ____ | ____ | ____ | ____ | ____ | ____ | __ specify _____ |
| __ Mother | | ____ | ____ | ____ | xxxxxx | ____ | ____ | __ specify _____ |
| __ Brother #1<br>__ Brother #2<br>__ Brother #3<br>__ Brother #4 | | ____<br>____<br>____<br>____ | ____<br>____<br>____<br>____ | ____<br>____<br>____<br>____ | ____<br>____<br>____<br>____ | ____<br>____<br>____<br>____ | ____<br>____<br>____<br>____ | __ specify _____<br>__ specify _____<br>__ specify _____<br>__ specify _____ |
| __ Sister #1<br>__ Sister #2<br>__ Sister #3<br>__ Sister #4 | | ____<br>____<br>____<br>____ | ____<br>____<br>____<br>____ | ____<br>____<br>____<br>____ | xxxxxx | ____<br>____<br>____<br>____ | ____<br>____<br>____<br>____ | __ specify _____<br>__ specify _____<br>__ specify _____<br>__ specify _____ |
| __ Child #1<br>__ Child #2<br>__ Child #3<br>__ Child #4 | | ____<br>____<br>____<br>____ | ____<br>____<br>____<br>____ | ____<br>____<br>____<br>____ | ____<br>____<br>____<br>____ | ____<br>____<br>____<br>____ | ____<br>____<br>____<br>____ | __ specify _____<br>__ specify _____<br>__ specify _____<br>__ specify _____ |