HHS Public Access

Author manuscript

*Gynecol Oncol*. Author manuscript; available in PMC 2015 July 10.

Published in final edited form as:

*Gynecol Oncol*. 2011 June 1; 121(3): 532–536. doi:10.1016/j.ygyno.2011.02.032.

# Risk Factors for HPV Infection among American Indian and White Women in the Northern Plains

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## Abstract

**Objective—**American Indian (AI) women living in the Northern Plains have high incidence and mortality rates for cervical cancer. We assessed risk factors for human papillomavirus (HPV) infection among AI and White women.

**Methods—**We tested cervical samples for HPV infection obtained from women ages 18-65 years attending 2 rural AI reservation clinics in South Dakota (*n = 235*) and an urban clinic serving predominantly White women (*n = 246*). Patients self-reported information on HPV risk factors. We used percentages and chi-square tests to compare risk factors, and logistic regression with HPV status as the outcome to quantify the association between HPV and risk factors.

**Results—**AI women had more risk factors than White women, including younger age, less education, less vegetable consumption, more sexual partners, younger age at first sexual experience and first pregnancy, and more pregnancies (*p* values ≤ 0.003). AI women more often endorsed recreational drug use, history of sexually transmitted diseases, and current smoking; White women reported more alcohol consumption (*p* values < 0.001). In multivariate analysis, younger age and current smoking were associated with higher odds of HPV infection in AI women, whereas a higher number of sexual partners was associated with higher odds of HPV infection in White women.

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CONFLICT OF INTEREST STATEMENT

Dr. Schmidt-Grimminger reports that he is on the speakers list for Merck and GlaxoSmithKline, which pay him to give talks on HPV vaccination. None of the other authors have any conflicts of interest of any kind to report.

**Conclusions—**AI women have a high burden of risk factors for HPV disease, and associations with HPV infection appear to differ by community. Knowledge of specific risk factors in AI populations may provide targets for public health officials to decrease HPV infection and disease.

### Keywords

cervical cancer; American Indian; risk factors; screening; health disparities; human papillomavirus

In 2008, cervical cancer was diagnosed in 11,070 women in the U.S., and caused 3,870 deaths.[1] Human papillomavirus (HPV), a sexually transmitted infection, is implicated in most cervical cancer cases.[2-4] Compared to Whites, members of racial and ethnic minority groups suffer disproportionately from HPV infection, with higher cervical cancer incidence and lower survival rates. This is especially true for American Indian (AI) women, for whom incidence rates are ominously increasing.[5-9]

Preventing HPV infection is a primary focus of programs aimed at reducing cervical cancer incidence and mortality. Modifiable and non-modifiable risk factors for HPV infection, as conventionally established, include demographic and socioeconomic factors, sexual activity, and lifestyle habits.[10] Modifiable risk factors are especially desirable targets for health behavior interventions. Because health behaviors vary by race and ethnicity, understanding risk factor patterns is critical to designing effective interventions in specific communities. Despite their high cervical cancer rates, very little is known about the prevalence of HPV infection and its risk factors among AI women. Our previous research found a high prevalence of HPV infection among AI women living in the Northern Plains, but this work neither included a control group nor assessed epidemiologic risk factors for HPV.[11]

The objectives of the present study, therefore, were to: 1) compare patterns of HPV risk factors between AIs living on rural reservations and urban White women presenting for gynecological examinations in South Dakota; and 2) quantify the association between these risk factors and HPV infection in the rural reservation and urban communities.

## METHODS

### Setting

This study was conducted in 2 reservation clinics operated by the Indian Health Service and in 1 urban clinic located in the city of Sioux Falls, South Dakota. Both reservation sites are large, rural, extremely economically disadvantaged, and located in South Dakota. According to the 2004 census, 38,000 tribal members were living within reservation boundaries at Site 1. In fiscal year 2002, 4,406 women between the ages of 15 and 64 received services at the Indian Health Service Unit at Site 1.[12] Site 2 had 21,245 tribal members living within reservation boundaries in 2004.[13] In fiscal year 2002, 3,100 women between the ages of 15 and 64 received services at the Indian Health Service Unit at Site 2.

The urban site is a multi-specialty obstetrics and gynecology clinic serving South Dakota and parts of Minnesota, Iowa, and Nebraska, with approximately 30,000 outpatient visits annually. In 2003, the population of Sioux Falls was 133,834, and only 6% of residents lived below the poverty line.[14] The urban population is predominantly White (92%), with small

numbers of Latino (2%), African American (2%), AI (2%), and Asian American (1%) residents.[15]

## Participants

All sexually active women ages 16 to 65 with an intact uterus presenting for routine gynecologic exams were identified by nurses. Whenever an appropriately trained study staff member was in the clinic, all eligible patients were invited to participate in our study. Once the patient consented, the survey was administered by the staff member in a private setting. Because 99% of women attending the rural reservation clinics self-identified as AI, and 96% of women attending the urban clinic self-identified as White, hereafter we refer to these groups as AI and White.

The project was approved by the institutional review boards of the University of South Dakota and the University of Washington, as well as by the Aberdeen Area Tribal Review Board and the individual participating tribes. Tribal approval included review by the tribal Health and Human Service Committees and formal resolutions from the tribal councils.

## Survey Development

With permission, we modified a published survey created to identify HPV risk factors among AI women in a high-risk gynecology clinic.[16] Modifications included altering demographic questions to allow direct comparison to the Behavioral Risk Factor Surveillance System data collected in South Dakota. For content validity, the modified survey was reviewed and refined on the basis of the expert opinions of Indian Health Service healthcare providers working in the local AI communities. Focus groups were conducted with women from the AI communities to evaluate questions about sexual history and ensure that data collection was performed with appropriate cultural sensitivity. In addition to providing feedback on the sexual history questions, focus group members also requested that a question about household income be removed from the original survey.

## HPV Analysis

Samples were processed according to a previously described protocol.[17] The integrity of the extracted DNA was confirmed by using standard 1% agarose gel electrophoresis followed by staining with ethidium bromide. DNA extracts were stored at – 20° C until amplification by PCR. HPV DNA was amplified by using the L1 consensus primer system. The Roche Linear Array assay was used to test for specific types of HPV.

## Risk Factors and Outcome

Self-reported multi-category risk factors were age in years (18-24, 25-34, 35-44, ≥ 45), highest education level attained (K-11th grade, high school graduate/GED, some college or technical school, ≥ college graduate), number of vegetable servings consumed in the past 7 days (0-3, 4-6, 1/day, ≥ 2/day), number of days alcohol was consumed in the past month (0, 1-2, 3-9, 10-30), total lifetime number of sexual partners (1, 2-5, 6-9, ≥ 10), age in years at first sexual experience (11-16, 17-19, ≥ 20), and total number of pregnancies (0, 1, 2, ≥ 3). Binary risk factors (coded yes or no) were multiple sexual partners in the past 3 months, any recreational drug use, not using a condom during the most recent sexual experience,

previous diagnosis of sexually transmitted disease, and current smoking. Too few women reported never receiving a Pap smear for that variable to be considered in the analysis. The outcome for our analysis was clinically determined HPV status (infected, not infected).

### Statistical Analysis

Although patients as young as 16 years old were recruited into the study, we restricted our analysis to women ≥ 18 years old, given low numbers of 16-17 year olds. We also required patients to have valid data for all variables included in the analysis. We used chi-square tests to evaluate the correlation of all study variables with exclusion criteria. Preliminary data analyses indicated that the 2 AI samples were sufficiently similar to combine them into a single sample for this analysis (results not shown). We used percentages to describe risk factors and HPV status separately for the AI and White patients, with chi-square tests to compare the distribution of each variable between the 2 groups.

We used logistic regression to model the association between HPV infection and risk factors. First, we performed univariate models to estimate the unadjusted association of each risk factor with HPV infection. For factors with ≥ 3 categories, we compared the ordinal model, which assumed a linear trend across categories, to the nominal model, which did not apply linear constraints to the relationship. For all multi-category risk factors, we found no statistically significant difference between the ordinal and nominal models; therefore, we present only the former for simplicity and ease of interpretation. Too few White patients endorsed either multiple sexual partners in the past 3 months or history of drug use for those variables to be included in the analysis for White patients. Similarly, estimates associated with history of drug use in AI patients were too unstable to be included in the regression models. Our final regression model included all risk factors simultaneously, with the association between HPV infection and each risk factor adjusted for the influence of all other risk factors. All logistic regression models were conducted separately for AI and White patients. Results are presented as point estimates with 95% confidence intervals, and we considered an alpha error rate of 0.05 as the threshold for statistical significance.

## RESULTS

Overall, 510 of 558 (91%) women approached completed the surveys, yielding 258 of 294 (88%) from the AI clinics and 252 of 264 (95%) from the White clinic. We excluded 11 women who were younger than 18 years old, and 3 who were missing HPV status. We further excluded 51 women who were missing data for one or more HPV risk factors. Our final sample comprised 205 (80%) of the 258 AI women and 239 (95%) of the White women with completed surveys. The higher percentage of excluded AI women was primarily due to more missing values for the binary indicators of monogamy (13 vs. 6 missing values) and previous diagnosis of sexually transmitted disease (19 vs. 7 missing values) compared to the White sample. Chi-square tests comparing included and excluded women were not statistically significant for any study variable.

The table shows the frequency distributions of HPV prevalence and each risk factor separately for the AI and White women. AI women had approximately twice the rate of HPV infection compared to their White counterparts. A higher percentage of AI women

tested positive for infection by oncogenic HPV types (30% vs. 16%, $p < 0.001$). Overall, AI women exhibited a wider variety of HPV infections, and 7 HPV types were detected only in AI patients. In contrast, White women showed less variation in prevalent infections, and just 1 HPV type was detected only in White patients.

The AI women showed patterns consistent with higher HPV risk for most of the multi-category risk factors, including younger age, less education, less vegetable consumption, more sexual partners, younger age at first sexual experience, and more pregnancies, whereas higher alcohol consumption was the only risk factor endorsed more frequently by White women. Of the binary risk factors, AI women were more likely to report having multiple sexual partners in the past 3 months, and more likely to endorse recreational drug use, previous diagnosis of sexually transmitted disease, and current smoking.

Risk factors were differently associated with odds of HPV infection in the AI and White women. In the univariate logistic regression models for AI women (results not graphed), lower odds of infection were associated with older age ($p < 0.001$), higher education levels ($p = 0.04$), and more pregnancies ($p = 0.002$). Higher odds of infection were associated with using a condom during the most recent sexual experience ($p = 0.01$) and with current smoking ($p = 0.04$). Except for smoking, all statistically significant univariate associations in the AI sample were confounded by age. In the multivariate adjusted regression model (Figure), only age (odds ratio = 0.5, 95% confidence interval = 0.3-0.7, $p < 0.001$) and current smoking (odds ratio = 2.0, 95% confidence interval = 1.1-3.7, $p = 0.04$) remained statistically significant for the AI patients. For White women, the univariate logistic regression models (results not graphed) showed higher odds of HPV infection associated with higher lifetime number of sexual partners ($p = 0.001$) and previous diagnosis of sexually transmitted disease ($p = 0.004$). In the multivariate adjusted regression model, only higher lifetime number of sexual partners (odds ratio = 1.6, 95% Confidence Interval = 1.1-2.5, $p = 0.02$) was associated with higher odds of HPV infection (Figure).

## DISCUSSION

Native women living in the Northern Plains have a significantly higher risk of dying from cervical cancer than the general population.[18] We found that the HPV prevalence among AI women was twice that observed in the White cohort. These findings are congruent with a recent report in which the overall HPV infection rate was twice as high in a lower socioeconomic group as it was in a higher socioeconomic group (23% versus 12%).[19] The most important risk factor for cervical cancer is persistent HPV infection, although other factors contribute, including younger age, lower socioeconomic status, earlier sexual debut, multiple sexual partners, hormonal contraception, other sexually transmitted infections, multiple childbirths, smoking, immunosuppression, and poor nutrition.[20]

Interestingly, our study found that conventional HPV risk factors differed between the AI and White cohorts. The AI group had higher rates of all sexual risk factors except for condom use, whereas their education level, which was used in our analyses as a proxy for socioeconomic status, was lower than for White women. Although not understood, the association of low socioeconomic status with risk of incident cancer is well-recognized.[21]

Likewise, AI women reported lower daily vegetable consumption than their White counterparts. Not surprisingly, the quality, selection, and availability of fresh fruits and vegetables on the 2 reservations is substantially less than in supermarkets located in urban settings in South Dakota. Of note, a case-control study that assessed dietary intake of nutrients and vitamins among AI women living in the Southwest concluded that low intake of vitamin C, folate, and vitamin E increased the risk of cervical dysplasia.[22]

Surprisingly, in the multivariate regression models none of the conventional sexual risk factors were significantly associated with higher odds of HPV infection among AI women. Only younger age and smoking were significant risk factors for HPV infection in the AI population, while more sexual partners remained a significant risk factor for Whites. This finding suggests that other unrecognized or unmeasured risk factors may be at work among AIs, and that interventions targeting conventional risk factors, such as sexual behavior, might not be effective in these communities. Public health efforts to identify female smokers in reservation communities may offer a point of intervention by simultaneously identifying those at elevated risk for HPV infection.

This study has several notable limitations. First, the age distribution of our AI sample was skewed toward a younger population, likely contributing to the increased overall prevalence of HPV infection. However, adjusting for age in the multivariate logistic regression model largely mitigates this concern in the inferential analysis. Second, our sample included only women who presented for routine gynecological examinations, so we cannot extrapolate our results to women who do not receive regular cervical cancer screening or regular healthcare. A related concern is that, given logistical and staffing limitations, we were not able to collect information on either a random or a consecutive sample of women at either clinic. Nevertheless, we have no reason to suspect that any study variable would correlate with the availability of study staff at the clinics, so we do not believe this limitation seriously biases our results or conclusions.

In sum, ours is the first epidemiologic survey of cervical cancer risk factors in a population of AI women. The higher HPV prevalence in AI women and their higher rates of conventional risk factors, compared to Whites, portray a population with a greater overall risk profile for cervical cancer. Nevertheless, except for younger age and current smoking, conventional risk factors were not significantly associated with higher odds of HPV infection in our AI sample. Our results underscore the need for further research to determine which risk factors drive these high rates of HPV infection and to better inform efforts to reduce the burden of HPV among AI women.

## ACKNOWLEDGMENTS

Many thanks for their time and interest to the tribal and private clinics and their staff and to all the women who participated in this study. We also acknowledge Raymond Harris, PhD, for his thoughtful and detailed editing, and Laura Koutsky, PhD, for her scientific review. This work was supported by the National Cancer Institute (grant number U01CA114642 to Dr. Buchwald), which supports Native People for Cancer Control, a Community Networks Program.

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## RESEARCH HIGHLIGHTS

- AI women had approximately twice the rate of HPV infection compared to their White counterparts.
- Risk factors were differently associated with odds of HPV infection in the AI and White women.
- We had an excellent participation rate in both the AI and Caucasian population with 88% of the AI and 95% of the Caucasian population participating.

## PRECIS

AI women had approximately twice the rate of HPV infection compared to their White counterparts. Risk factors were differently associated with odds of HPV infection in AI and White women.

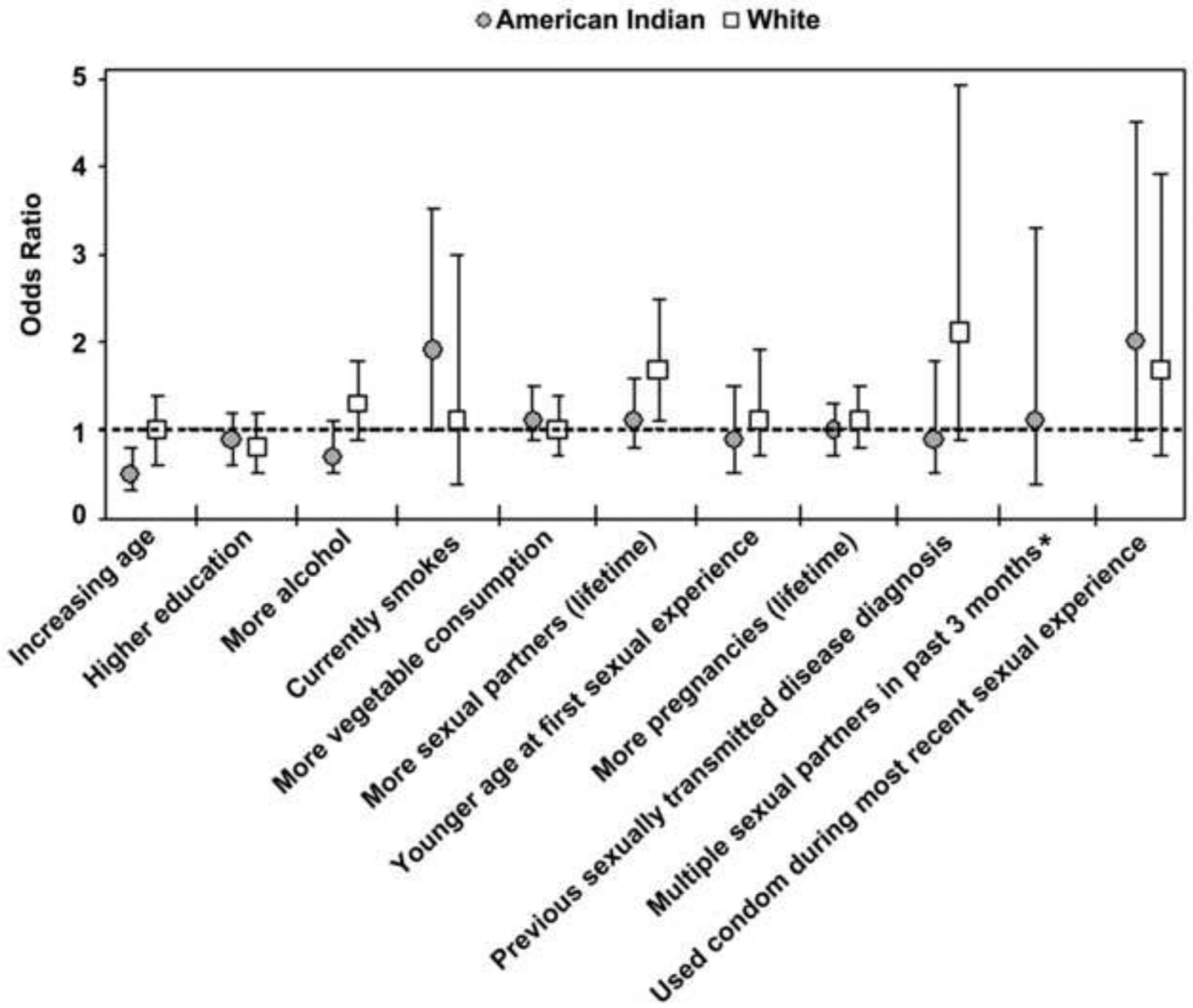


**Figure.**

Odds ratios with 95% confidence intervals for HPV infection in 205 American Indian patients and 239 White patients in South Dakota. Results are from multivariate adjusted regression models, and each odds ratio is adjusted for the influence of all other risk factors in the figure.

[NOTE] * Too few patients reported non-monogamous relationships to evaluate this risk factor for the White sample.

## Table

Distribution of HPV prevalence and selected HPV risk factors for 205 rural reservation-based AI and 239 urban White women in South Dakota.

| | American Indian* % (95% CI) | White* % (95% CI) | Chi-square *p* value |
|---|---|---|---|
| **HPV Status** | | | |
| Positive | 47 (41 – 54) | 24 (19 – 30) | < 0.001 |
| **Multi-Category Factors** | | | |
| ***Age*** | | | |
| 18 – 24 years | 26 (20 – 32) | 13 (8 – 18) | 0.003 |
| 25 – 34 years | 33 (27 – 40) | 34 (29 – 41) | |
| 35 – 44 years | 25 (20 – 32) | 29 (23 – 35) | |
| ≥ 45 years | 16 (11 – 22) | 24 (19 – 30) | |
| ***Education*** | | | |
| K – 11th grade | 18 (13 – 24) | 2 (1 – 5) | < 0.001 |
| High school/GED | 27 (22 – 34) | 11 (8 – 16) | |
| Some college | 43 (37 – 50) | 38 (32 – 44) | |
| ≥ College graduate | 11 (8 – 16) | 49 (42 – 55) | |
| ***Vegetable Servings in Past Week*** | | | |
| 0 – 3 per week | 32 (26 – 38) | 18 (13 – 23) | 0.001 |
| 4 – 6 per week | 18 (13 – 24) | 30 (25 – 36) | |
| 1 per day | 28 (22 – 34) | 29 (23 – 35) | |
| ≥ 2 per day | 22 (17 – 29) | 24 (19 – 30) | |
| ***Alcohol in Past Month*** | | | |
| 0 days | 58 (51 – 64) | 24 (19 – 30) | < 0.001 |
| 1 – 2 days | 29 (23 – 35) | 30 (24 – 36) | |
| 3 – 9 days | 11 (8 – 16) | 40 (34 – 47) | |
| 10 – 30 days | 2 (1 – 6) | 6 (4 – 10) | |
| ***Lifetime Sexual Partners*** | | | |
| 1 | 8 (5 – 12) | 23 (19 – 29) | < 0.001 |
| 2 – 5 | 51 (44 – 58) | 49 (43 – 55) | |
| 6 – 9 | 17 (13 – 23) | 16 (11 – 21) | |
| ≥ 10 | 24 (19 – 30) | 12 (9 – 17) | |
| ***Age at First Sexual Experience*** | | | |
| 11 – 16 years | 48 (41 – 55) | 33 (27 – 39) | < 0.001 |
| 17 – 19 years | 42 (35 – 49) | 44 (38 – 51) | |
| ≥ 20 years | 10 (7 – 15) | 23 (18 – 28) | |
| ***Number of Pregnancies*** | | | |
| 0 | 16 (12 – 22) | 31 (25 – 37) | < 0.001 |
| 1 | 14 (10 – 20) | 19 (14 – 24) | |
| 2 | 18 (13 – 23) | 21 (17 – 27) | |
| ≥ 3 | 52 (45 – 59) | 29 (24 – 35) | |
| **Binary Factors** | | | |

| | American Indian* % (95% CI) | White* % (95% CI) | Chi-square *p* value |
|---|---|---|---|
| Multiple sexual partners past 3 months | 9 (6 – 14) | 2 (1 – 5) | 0.002 |
| Any recreational drug use | 9 (6 – 14) | < 1 (0 – 3) | < 0.001 |
| No condom used during most recent sexual experience | 80 (73 – 85) | 82 (76 – 86) | 0.58 |
| Sexually transmitted infection history | 51 (44 – 58) | 14 (10 – 19) | < 0.001 |
| Current smoking | 48 (42 – 55) | 13 (9 – 17) | < 0.001 |

* American Indian sample combined from 2 clinics located on separate reservations; White sample from a single urban clinic; CI = confidence interval; HPV = human papillomavirus.