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Association of Diet Quality and Dietary Components with Clinical Resolution of HPV

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Abstract

Nutrient deficits have been repeatedly linked to cervical human papillomavirus (HPV) persistence, cervical neoplasia, and cervical cancer in case-control studies. This study sought to examine the relationship between overall diet quality and dietary components with the spontaneous resolution of cervical HPV over one year. A prospective observational cohort study was performed. Women with low-grade cervical cytology and/or positive HPV test completed a 24-hour dietary recall, from which the Healthy Eating Index (HEI)-2010, a score of overall diet quality, and scores in dietary categories were calculated. Participants were managed clinically according to national management guidelines. Those whose subsequent testing demonstrated normalization of cytology and/or HPV testing ("HPV resolution") were compared to those whose abnormalities persisted or progressed ("HPV non-resolution"). Twenty-six women were included in the HPV resolution group and 38 in the non-resolution group. They were observed for a median of 428 and 412 days, respectively ($p=0.09$). There was no difference in overall diet quality between the groups. Intake of total and whole fruit, and seafood/plant protein were associated with HPV resolution in a logistic regression model (all $p<0.05$). These finding could have important implications for the counseling and management of individuals with HPV infection of the cervix.

Keywords

Papillomavirus infections; Cervical Intraepithelial Neoplasia; Healthy Diet; Plant-Based Diet

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Introduction

There are more than 12,000 new cervical cancers each year in the United States and more than 570,000 worldwide.[1,2] Human papillomavirus (HPV) infection of the cervix causes nearly all cases of cervical cancer. HPV infection spontaneously resolves in 90% of cases, but persists in the remaining 10%, and may progress to precancerous high-grade cervical intraepithelial neoplasia (CIN2+) and, over time, cervical cancer.[3]

Case-control studies investigating the relationship between nutrition and cervical cancer have documented lower odds of cervical cancer in women with higher intakes or serum levels of numerous individual nutrients, including vitamins A, C, E, B12, α-carotene, β-carotene, lutein, folate, zinc, and dietary fiber.[4–10] Total fruit and vegetable intake as assessed by food frequency questionnaire was associated with decreased odds of cervical cancer in a case-control study of women in New York.[8] Higher daily intake of whole fruits, again assessed by food frequency questionnaire, was associated with a 17% decreased risk of developing invasive cervical cancer in a prospective study of European women undergoing cervical cancer screening.[11]

Further studies have linked individual nutritional factors with a decreased risk of cervical intraepithelial neoplasia (CIN) and HPV persistence. Higher serum concentrations of folate, lycopene, and α- and γ-tocopherols were associated with decreased odds of high-grade cervical dysplasia in case-control studies in China and Brazil. [12–14] A case-control study conducted in the United States compared women with persistent HPV infection to those with transient HPV infection, and concluded that higher circulating cis-lycopene concentrations were protective against HPV persistence.[15] Another case-control study conducted in Brazil demonstrated that consumption of certain carotenoids (cryptoxanthin, lutein/zeaxanthin) and vitamin C, as measured by food frequency questionnaire, was associated with lower odds of HPV persistence.[16] Certain whole foods, including papaya and dark green and yellow fruits and vegetables, were also linked to a decreased risk of high-grade neoplasia and lower risk of persistent HPV infection in these case-control investigations.[13,17,15,16]

A single study has evaluated the relationship of overall diet quality, rather than specific individual nutrients or foods, to cervical neoplasia. This cross-sectional study of women with abnormal cervical cytology did not show an association between Mediterranean, Western, or “prudent” diet patterns with the risk of CIN2 or worse.[18] Two randomized trials administered vitamin D or folate to women with low-grade CIN for 6 months each. Both led to a higher rate of regression of neoplasia compared to placebo.[19,20] In another small randomized trial, intake of β-carotene and vitamin C did not lead to regression of low-grade CIN.[21]

There is consistent evidence that nutrient deficits are linked to cervical HPV persistence, cervical neoplasia, and cancer. However, no single nutrient has emerged as a target for further study or therapeutic intervention. We hypothesized that overall diet quality could be a better predictor of the behavior of cervical HPV infection than individual nutrient or food intakes. We aimed to explore the role of diet quality in the spontaneous clearance of cervical

HPV infection in a clinical setting. We assessed the associations of overall diet quality and dietary components with clinical resolution of HPV over time.

Materials and Methods

A prospective cohort study was performed. Women aged 21 and older with cervical cytology of low-grade squamous intraepithelial lesion (LSIL), atypical squamous cells of undetermined significance (ASC-US) with positive high-risk HPV test (hrHPV), or normal cervical cytology with positive hrHPV were identified through the electronic health record. Participants were a convenience sample of individuals who were subsequently referred to the study by their healthcare providers. Participants were enrolled from September 2015 through May 2017, within 3 months of cervical cytology being performed. Women had to be able to speak and read English to participate. There were no other exclusion criteria. Written informed consent was obtained from all participants and maintained by the investigators. The Tulane University and Louisiana State University IRBs approved this study prior to study start.

At enrollment, height and weight were recorded and body mass index (BMI) was calculated. Participants completed an online 24-hour dietary recall. The National Cancer Institute's Automated Self-Administered 24-hour Recall-2014 (ASA24–2014) was utilized in 2015, and the ASA24–2016 was used after its introduction in 2016. Participants self-administered paper questionnaires which assessed demographic characteristics and substance use. The first 60 participants were asked to provide blood samples for vitamin C (ascorbic acid), calcium, folate, vitamin D binding protein, vitamin A (retinol), vitamin E (α-tocopherol), carotenoids (α-carotene, β-carotene, lutein, lycopene, β-cryptoxanthin, zeaxanthin) and fatty acid profile. These were analyzed using commercially available kits.

Participants were followed via electronic medical record review from the date of enrollment through the end of the study period in September 2018. Medical history was collected from the medical record. Participants were managed clinically by their treating medical practitioners according to national management guidelines.[22] Cytology, hrHPV results, and patient age, presentation and history were considered in determining appropriate follow-up. Some participants underwent colposcopy and biopsy following initial cytology ("early colposcopy"), while others were observed with repeat cytology with or without hrHPV testing at approximately 1 year after initial cytology ("second round testing"). Of individuals who underwent early colposcopy, some were diagnosed with CIN2+ on biopsy. These were censored at the time of diagnosis of CIN2+ and were not further followed. Participants who had CIN1 or less on biopsy at early colposcopy underwent repeat cytology and hrHPV testing at approximately 1 year after initial cytology ("second round testing"). Of those with persistent abnormalities on second round testing, some underwent colposcopy with biopsy at approximately 1 year from index cytology ("late colposcopy"), while others did not, with a plan for continued observation with cervical cytology with or without hrHPV testing. Results of biopsies performed with late colposcopy were recorded. Participants were not further followed after the second round of testing. Cytology was classified according to the Bethesda System (2014). The Roche Cobas HPV Test was utilized, which reports results

of HPV-16, HPV-18 and HPV-other high risk type. Positive results of any of these were considered hrHPV-positive.

The planned primary analysis was to determine if overall diet quality was associated with clinical resolution of HPV over one year. Clinical resolution was defined as a negative hrHPV test at approximately 1 year (at least 6 months) after prior positive hrHPV test or abnormal cytology, or normal cytology without hrHPV testing at approximately 1 year (at least 6 months) after prior abnormal cytology. Non-resolution of HPV was defined as a positive hrHPV test, abnormal cytology, or CIN1 or worse (CIN1+) on cervical biopsy at approximately 1 year (at least 6 months) after prior positive hrHPV test or abnormal cytology, or cervical biopsy demonstrating CIN2 or worse (CIN2+) at any time point.

Overall diet quality was determined by calculating the Healthy Eating Index (HEI) score from ASA24. The HEI is a dietary index developed by the US Department of Agriculture and the National Cancer Institute, which aligns with the US Dietary Guidelines for Americans. It is intended to be calculated from the ASA24, and has been extensively validated and shown to be a reliable measure of diet quality.[23] HEI-2010 was computed rather than the more recent HEI-2015, because most participants completed the ASA24–2014, from which the HEI-2010 is calculated. The HEI-2010 has 12 components that sum to a maximum total score of 100. “Adequacy” points are given for adequate consumption of food in nine categories: total fruit, whole fruit, total vegetables, greens and beans, whole grains, dairy, total protein foods, seafood and plant proteins, and fatty acids; “moderation” points are given for sufficiently low levels of intake of three categories: refined grains, sodium, and empty calories, which includes solid fats, alcohol, and added sugars. The seafood/plant protein category includes seafood, beans, peas, nuts, seeds, and soy products excluding beverages.

The relationship of the total HEI-2010 score and each of the 12 dietary components to clinical resolution of HPV was assessed. Percentage of participants in the upper half of diet quality for each dietary component (percentage that had >50% of maximum points in each food category) was compared between the HPV resolution and non-resolution groups. Chi-squared analysis was used.

Differences in HPV resolution were examined by potential confounding factors: age, race, income, education, HIV status, use of immunosuppressant medications, current or prior smoking status, history of abnormal cytology, current use of hormonal contraception, and history of sexually transmitted infection (STI), including gonorrhea, chlamydia, trichomoniasis, syphilis, or genital warts. Differences in these factors between the HPV resolution and non-resolution groups were assessed using Student’s t-test for continuous variables and Pearson’s chi-squared test for categorical factors. When the assumptions of these tests were not met, the nonparametric Wilcoxon rank sum test and Fisher’s exact test were used. Those factors found to have an association with HPV resolution with $p<0.10$ were considered to be possible confounders.

The relationship of the following additional clinical factors with HPV resolution were similarly evaluated: BMI, obesity (BMI ≥30), category 3 obesity (BMI ≥40), presence

of diabetes mellitus, current pregnancy, current or prior alcohol overuse (defined as >3 drinks/day or >7 days/week),[24] and current or prior regular illicit drug use. Participants who were pregnant at enrollment or follow up were considered pregnant.

The relationships between HPV resolution and indicators of diet quality (HEI score and 12 dietary components), and between HPV resolution and the additional clinical factors were further assessed using multiple logistic regression models, which included the previously identified possible confounders.

Spearman's correlation coefficient was calculated to measure correlation between serum levels and intake levels for each nutrient for which both results were obtained, including vitamin C, calcium, folate, vitamin A, vitamin E, α-carotene, β-carotene, lutein and zeaxanthin, lycopene, and β-cryptoxanthin.

A sample size calculation showed that inclusion of 75 women would provide 80% power to detect a 10-point difference in HEI scores between the clinical HPV resolution and non-resolution groups with an alpha of 0.05%. Inclusion of 90 women allowed for an 20% loss-to-follow up rate after one year. Due to unanticipated problems with recruitment, 77 women were enrolled in this study. Only the first 60 were asked to provide blood samples due to budgetary limitations.

Results

Seventy-seven women were enrolled. Thirteen participants were removed from the analysis due to inadequate or absent follow-up data. This left 64 participants for analysis (Figure 1). Of these, 41 underwent early colposcopy, while 23 were observed with second round testing alone. Ten of those who underwent early colposcopy were diagnosed with CIN2+ and were counted among the HPV non-resolution group and were not further followed. Thirty-one were followed after early colposcopy with second round testing. At the time of second round testing, 26 individuals demonstrated clinical resolution of HPV, and 28 had persistent abnormalities. Of those with persistent abnormalities, 19 underwent late colposcopy. CIN2+ was diagnosed in 5 of these individuals. Total number demonstrating CIN2+ from both early and late colposcopy was 15. Those with positive hrHPV test, abnormal cytology, or CIN1+ on cervical pathology at second round testing, and those that ever had CIN2+, were combined to form the non-resolution of HPV group, which ultimately consisted of 38 individuals (Figure 1).

Duration of follow up was calculated from date of initial cytology until diagnosis of CIN2+, or if the individual never developed CIN2+, until the date of biopsies following second round testing. If no biopsies were performed, the date of the second round of cytology and/or HPV testing was used as the endpoint. Median follow up was 428 days in the HPV resolution group and 412 days in the non-resolution group (p=0.09).

Demographics and selected medical history characteristics are listed in Table 1. These factors did not differ significantly by HPV status. Early colposcopy with biopsy, which could affect HPV clearance, was not associated with clinical resolution of HPV (p=0.61). Caloric intake did not differ significantly between the groups (Table 2). In the unadjusted

primary analysis, overall diet quality as measured by total HEI-2010 score was not significantly different in the HPV resolution and non-resolution groups: mean score of 50.1 (standard deviation (SD) 15.6) versus 45.8 (SD 13.6), p=0.24. In the HPV resolution group, 46% of participants received >50% of the maximum points in the whole fruit category, compared to 18% of participants in the non-resolution group (p=0.02). 73% of women in the HPV resolution group received >50% of the maximum points in the seafood/plant protein category, while 40% of women in the non-resolution group met this target (p<0.01). Results were similar when continuous intakes were used (data not shown).

Age, length of follow-up, and education (more than high school versus high school or less) were included in regression models as potential confounders, as all had p<0.10 in the univariate analysis. In this model, overall diet quality as measured by HEI-2010 was not a significant predictor of HPV status (p=0.44). Intake of whole fruit and seafood/plant protein each remained associated with clinical resolution of HPV (both p<0.05). In addition, intake total fruit (which includes fruit juice) was associated with clinical resolution of HPV in the multivariate model. Intake of total vegetables and total dairy were *inversely* associated with clinical resolution of HPV in the multivariate model, but not in the univariate analysis (Table 2).

Clinical resolution of HPV infection was not significantly associated with BMI, obesity, category 3 obesity, diabetes, current pregnancy, current or prior alcohol overuse, or current or prior regular illicit drug use (Table 3). BMI was not correlated with caloric intake (r=−0.09, p=0.49).

Blood samples were obtained from 51 participants. Nine participants who were asked to provide blood samples refused to do so. Correlation between serum nutrient values and intake values as assessed by the ASA24 is shown in Table 4. Vitamin C, calcium, folate, vitamin A, α-carotene, β-carotene, lutein + zeaxanthin, and β-cryptoxanthin demonstrated a very weak correlation; calcium, lycopene had a strong correlation, and vitamin E had a very strong correlation. Association between serum nutrient values and HPV resolution was not assessed due to small sample size.

Discussion

This small prospective study of dietary factors associated with clinical resolution of HPV demonstrated no significant association between overall diet quality and HPV resolution over more than a year of follow-up. The mean HEI-2010 scores of 50.1 and 45.8 in the groups both fell within the “poor” diet range (<51).[25] From 2009–2010, the national average HEI-2010 score was 57.8; as such, the diet quality of this population lagged behind the national average.[24] Estimated caloric requirements for adult women range from 1600 to 2400 kilocalories per day. As both groups had mean calorie counts of fewer than 1600, participants in both groups were at risk of having nutritionally inadequate diets.

One other investigation has evaluated the relationship of overall diet quality with high-grade cervical intraepithelial neoplasia, and did not find an association between overall dietary pattern and CIN2+.[18] That study differed significantly in methodology: it was cross-

sectional, while the present study was prospective. We investigated the dietary milieu prior to the development of significant neoplasia, while that study looked for dietary differences after the development of CIN2+. Different nutritional assessment tools and dietary quality scales were also used. Similar results despite differing methodology may point to the conclusion that no relationship exists between overall diet quality and HPV resolution.

Intake of total and whole fruit and seafood/plant protein were associated with HPV resolution in this study. In a case-control study of HPV-positive women in Brazil, women who consumed papaya once or more per week had a lower risk of persistent HPV infection.[16] In a later case-control study of the same population of HPV-positive women, those who consumed papaya once or more per week were 81% less likely to have incident cervical neoplasia.[17] In another case-control investigation of women with differing grades of cervical neoplasia, participants with the highest consumption of dark green and yellow fruits and vegetables were 48% less likely to have CIN3.[13] While no linkages between seafood and plant protein sources and the behavior of HPV have been described, an inverse association between fish intake and colorectal cancer incidence has been documented.[26]

Intake of total vegetables and total dairy were *inversely* associated with clinical resolution of HPV in the multivariate analysis, but not in the univariate analysis. The finding of the multivariate analysis is in conflict with prior evidence of an association between higher levels of vegetable consumption and HPV clearance in a population of HPV-positive women in Arizona, USA.[15] Another population-based study in Europe showed no association between vegetable intake and the formation of carcinoma in situ of the cervix.[11] No prior studies have evaluated the relationship between intake of dairy products and HPV infection of the cervix.

Taken together, the findings of this and prior studies suggest that greater intake of fruit, and perhaps also seafood and plant proteins, may contribute to the clearance of HPV, or prevent the progression of cervical neoplasia. Data regarding vegetable intake has been mixed. An inverse association between intake of dairy products and HPV resolution requires further investigation. Future prospective studies are needed to confirm these findings, and to determine where in the course of cervical HPV infection the increased or decreased intake of these food groups is most likely to be effective in altering the clinical outcome.

There are several mechanisms by which these dietary factors could influence the course of HPV infection of the cervix. Antioxidant nutrients neutralize the action of reactive oxygen species, which damage lipids, proteins, and nucleic acids of epithelial cells. A deficiency in these compounds could serve as a cofactor in HPV persistence and malignant transformation.[27] Carotenoids, tocopherols, and ascorbic acid are potent antioxidants. β-carotene is also the precursor to retinoid acid, which is crucial in modulating epithelial cell growth and differentiation.[8] In addition, tocopherols and ascorbic acid may enhance mucosal immune responses to infection.[11] Folic acid also possesses some antioxidant properties.[8,28]

This study had several limitations. It was underpowered to detect a difference between the groups in the primary outcome. As noted above, participants in both groups had “poor” diet quality and low calorie intakes, which may have impacted the outcome. Due to small sample

size, results could not be stratified by HPV type at enrollment. Development of CIN2+ and HPV persistence without progression to high-grade neoplasia could not be analyzed as separate endpoints, and were instead considered together in the HPV non-resolution group. The relationship between serum nutrient values and HPV resolution status could not be assessed. Performing these multiple analyses would have increased probability of type I error.[29] The HEI-2010 did not allow differentiation between seafood versus plant protein sources. The period of follow-up fell within the window within which some HPV infections may not yet have resolved, even if eventually destined to clear. A study with a follow-up period extending beyond the 2 years within which HPV is expected to clear would have better identified patients with non-resolution of HPV. The rate of current or former illicit drug use was high. This may have introduced risk factors for HPV non-resolution which were not controlled for in the analysis. Smoking and history of previous cervical neoplasia were not associated with HPV resolution, though these are known to be risk factors for HPV persistence. Low smoking rates and high rates of previous neoplasia in this population may have contributed to these findings.

Though multiple possible confounding factors were considered, it remains a possibility that dietary intakes are a marker for socioeconomic factors or health behaviors which were not measured in this investigation, but influenced the outcome. Individuals with higher fruit intakes may have higher health literacy, improved access to healthcare, lower degree of chronic stress or lack of certain environmental exposures; such factors were not assessed and may be the underlying cause for the observations in this and previous studies.

The use of a single 24-hour dietary recall questionnaire as the primary assessment of diet quality carries some limitations. Multiple assessments would have provided a more complete picture of each individual's dietary habits. Both groups had low energy intakes; this may be explained by the fact that users of dietary assessment tools are known to under-report their energy intakes by up to 10–20%.[30] In this investigation, degree of correlation between nutrient intake and serum levels was low. Other studies have had similar findings.[31] This may be due to incomplete assessment of true dietary intake by the tool utilized in this study, faulty recollection on the part of participants, or fluctuation in serum values, which can vary from day to day.[30] Despite these limitations, self-reported dietary data are still considered a valuable tool to assess nutritional intake, and capture information which cannot be captured by measurement of biomarkers alone.[32,33]

The current investigation meaningfully contributes to the literature on diet quality and its association with HPV resolution over time. It demonstrated no significant association between overall diet quality and clinical resolution of HPV. However, it suggested an association between intake of fruit and seafood and plant protein with HPV resolution. An inverse association between vegetable intake and HPV resolution was suggested, which differs from the findings of prior studies. An inverse association between consumption of dairy and HPV resolution was also suggested. Further prospective assessments of the relationship between these dietary components and persistent HPV infection, high-grade cervical neoplasia, and cervical cancer are needed. If confirmed, these findings could have important implications for the counseling and management of women with HPV infections of the cervix.

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Study data were collected and managed using REDCap electronic data capture tools hosted at Tulane University.[34] REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.

Disclosure of interest statement

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References

1. United States Cancer Statistics: Data Visualizations. Centers for Disease Control and Prevention. https://gis.cdc.gov/Cancer/USCS/DataViz.html. Accessed May 15, 2019.
2. Cervical cancer. World Health Organization. https://www.who.int/cancer/prevention/diagnosis-screening/cervical-cancer/en/. Accessed May 15, 2019.
3. Moscicki AB, Schiffman M, Burchell A, Albero G, Giuliano AR, Goodman MT, Kjaer SK, Palefsky J. Updating the natural history of human papillomavirus and anogenital cancers. Vaccine 2012;30 Suppl 5:F24–33. [PubMed: 23199964]
4. Zhang X, Dai B, Zhang B, Wang Z. Vitamin A and risk of cervical cancer: a meta-analysis. Gynecol Oncol 2012;124(2):366–73. [PubMed: 22005522]
5. Kim J, Kim MK, Lee JK, Kim JH, Son SK, Song ES, Lee KB, Lee JP, Lee JM, Yun YM. Intakes of vitamin A, C, and E, and beta-carotene are associated with risk of cervical cancer: a case-control study in Korea. Nutr Cancer 2010;62(2):181–9. [PubMed: 20099192]
6. Myung SK, Ju W, Kim SC, Kim H. Vitamin or antioxidant intake (or serum level) and risk of cervical neoplasm: a meta-analysis. Bjog 2011;118(11):1285–91. [PubMed: 21749626]
7. Guo L, Zhu H, Lin C, Che J, Tian X, Han S, Zhao H, Zhu Y, Mao D. Associations between antioxidant vitamins and the risk of invasive cervical cancer in Chinese women: A case-control study. Sci Rep 2015;5:13607. [PubMed: 26337940]
8. Ghosh C, Baker JA, Moysich KB, Rivera R, Brasure JR, McCann SE. Dietary intakes of selected nutrients and food groups and risk of cervical cancer. Nutr Cancer 2008;60(3):331–41. [PubMed: 18444167]
9. Zhou X, Meng Y. Association between serum folate level and cervical cancer: a meta-analysis. Arch Gynecol Obstet 2016;293(4):871–7. [PubMed: 26319154]
10. Xie Y, Wang J, Zhao X, Zhou X, Nie X, Li C, Huang F, Yuan H. Higher serum zinc levels may reduce the risk of cervical cancer in Asian women: A meta-analysis. J Int Med Res 2018;46(12):4898–4906. [PubMed: 30370809]
11. Gonzalez CA, Travier N, Lujan-Barroso L, Castellsague X, Bosch FX, Roura E, Bueno-de-Mesquita HB, Palli D, Boeing H, Pala V and others. Dietary factors and in situ and invasive cervical cancer risk in the European prospective investigation into cancer and nutrition study. Int J Cancer 2011;129(2):449–59. [PubMed: 20853322]
12. Zhao W, Hao M, Wang Y, Feng N, Wang Z, Wang W, Wang J, Ding L. Association between folate status and cervical intraepithelial neoplasia. Eur J Clin Nutr 2016;70(7):837–42. [PubMed: 27026426]
13. Tomita LY, Longatto Filho A, Costa MC, Andreoli MA, Villa LL, Franco EL, Cardoso MA. Diet and serum micronutrients in relation to cervical neoplasia and cancer among low-income Brazilian women. Int J Cancer 2010;126(3):703–14. [PubMed: 19642096]

14. Wang JT, Ding L, Jiang SW, Hao J, Zhao WM, Zhou Q, Yang ZK, Zhang L. Folate deficiency and aberrant expression of DNA methyltransferase 1 were associated with cervical cancerization. Curr Pharm Des 2014;20(11):1639–46. [PubMed: 23888945]
15. Sedjo RL, Roe DJ, Abrahamsen M, Harris RB, Craft N, Baldwin S, Giuliano AR. Vitamin A, carotenoids, and risk of persistent oncogenic human papillomavirus infection. Cancer Epidemiol Biomarkers Prev 2002;11(9):876–84. [PubMed: 12223432]
16. Giuliano AR, Siegel EM, Roe DJ, Ferreira S, Baggio ML, Galan L, Duarte-Franco E, Villa LL, Rohan TE, Marshall JR and others. Dietary intake and risk of persistent human papillomavirus (HPV) infection: the Ludwig-McGill HPV Natural History Study. J Infect Dis 2003;188(10):1508–16. [PubMed: 14624376]
17. Siegel EM, Salemi JL, Villa LL, Ferenczy A, Franco EL, Giuliano AR. Dietary consumption of antioxidant nutrients and risk of incident cervical intraepithelial neoplasia. Gynecol Oncol 2010;118(3):289–94. [PubMed: 20691333]
18. Barchitta M, Maugeri A, Quattrocchi A, Agrifoglio O, Scalisi A, Agodi A. The Association of Dietary Patterns with High-Risk Human Papillomavirus Infection and Cervical Cancer: A Cross-Sectional Study in Italy. Nutrients 2018;10(4).
19. Vahedpoor Z, Jamilian M, Bahmani F, Aghadavod E, Karamali M, Kashanian M, Asemi Z. Effects of Long-Term Vitamin D Supplementation on Regression and Metabolic Status of Cervical Intraepithelial Neoplasia: a Randomized, Double-Blind, Placebo-Controlled Trial. Horm Cancer 2017;8(1):58–67. [PubMed: 28050798]
20. Asemi Z, Vahedpoor Z, Jamilian M, Bahmani F, Esmaillzadeh A. Effects of long-term folate supplementation on metabolic status and regression of cervical intraepithelial neoplasia: A randomized, double-blind, placebo-controlled trial. Nutrition 2016;32(6):681–6. [PubMed: 26853484]
21. Mackerras D, Irwig L, Simpson JM, Weisberg E, Cardona M, Webster F, Walton L, Ghersi D. Randomized double-blind trial of beta-carotene and vitamin C in women with minor cervical abnormalities. Br J Cancer 1999;79(9–10):1448–53. [PubMed: 10188889]
22. Massad LS, Einstein MH, Huh WK, Katki HA, Kinney WK, Schiffman M, Solomon D, Wentzensen N, Lawson HW. 2012 updated consensus guidelines for the management of abnormal cervical cancer screening tests and cancer precursors. J Low Genit Tract Dis 2013;17(5 Suppl 1):S1–s27. [PubMed: 23519301]
23. Guenther PM, Kirkpatrick SI, Reedy J, Krebs-Smith SM, Buckman DW, Dodd KW, Casavale KO, Carroll RJ. The Healthy Eating Index-2010 is a valid and reliable measure of diet quality according to the 2010 Dietary Guidelines for Americans. J Nutr 2014;144(3):399–407. [PubMed: 24453128]
24. 2015–2020 Dietary Guidelines for Americans, 8th Edition. U.S. Department of Health and Human Services and U.S. Department of Agriculture. http://health.gov/dietaryguidelines/2015/guidelines/. Accessed May 15, 2019.
25. Hurley KM, Oberlander SE, Merry BC, Wrobleski MM, Klassen AC, Black MM. The healthy eating index and youth healthy eating index are unique, nonredundant measures of diet quality among low-income, African American adolescents. J Nutr 2009;139(2):359–64. [PubMed: 19074210]
26. Aglago EK, Huybrechts I, Murphy N, Casagrande C, Nicolas G, Pischon T, Fedirko V, Severi G, Boutron-Ruault MC, Fournier A and others. Consumption of Fish and Long-chain n-3 Polyunsaturated Fatty Acids Is Associated With Reduced Risk of Colorectal Cancer in a Large European Cohort. Clin Gastroenterol Hepatol 2019.
27. Georgescu SR, Mitran CI, Mitran MI, Caruntu C, Sarbu MI, Matei C, Nicolae I, Tocut SM, Popa MI, Tampa M. New Insights in the Pathogenesis of HPV Infection and the Associated Carcinogenic Processes: The Role of Chronic Inflammation and Oxidative Stress. J Immunol Res 2018;2018:5315816. [PubMed: 30225270]
28. Joshi R, Adhikari S, Patro BS, Chattopadhyay S, Mukherjee T. Free radical scavenging behavior of folic acid: evidence for possible antioxidant activity. Free Radic Biol Med 2001;30(12):1390–9. [PubMed: 11390184]
29. Ranganathan P, Pramesh CS, Buyse M. Common pitfalls in statistical analysis: The perils of multiple testing. Perspect Clin Res 2016;7(2):106–7. [PubMed: 27141478]

30. Elmadfa I, Meyer AL. Developing suitable methods of nutritional status assessment: a continuous challenge. Adv Nutr 2014;5(5):590s–598s. [PubMed: 25469404]

31. Burrows TL, Rollo ME, Williams R, Wood LG, Garg ML, Jensen M, Collins CE. A Systematic Review of Technology-Based Dietary Intake Assessment Validation Studies That Include Carotenoid Biomarkers. Nutrients 2017;9(2).

32. Subar AF, Freedman LS, Tooze JA, Kirkpatrick SI, Boushey C, Neuhouser ML, Thompson FE, Potischman N, Guenther PM, Tarasuk V and others. Addressing Current Criticism Regarding the Value of Self-Report Dietary Data. J Nutr 2015;145(12):2639–45. [PubMed: 26468491]

33. Pennant M, Steur M, Moore C, Butterworth A, Johnson L. Comparative validity of vitamin C and carotenoids as indicators of fruit and vegetable intake: a systematic review and meta-analysis of randomised controlled trials. Br J Nutr 2015;114(9):1331–40. [PubMed: 26349405]

34. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, McLeod L, Delacqua G, Delacqua F, Kirby J and others. The REDCap consortium: Building an international community of software platform partners. J Biomed Inform 2019;95:103208. [PubMed: 31078660]

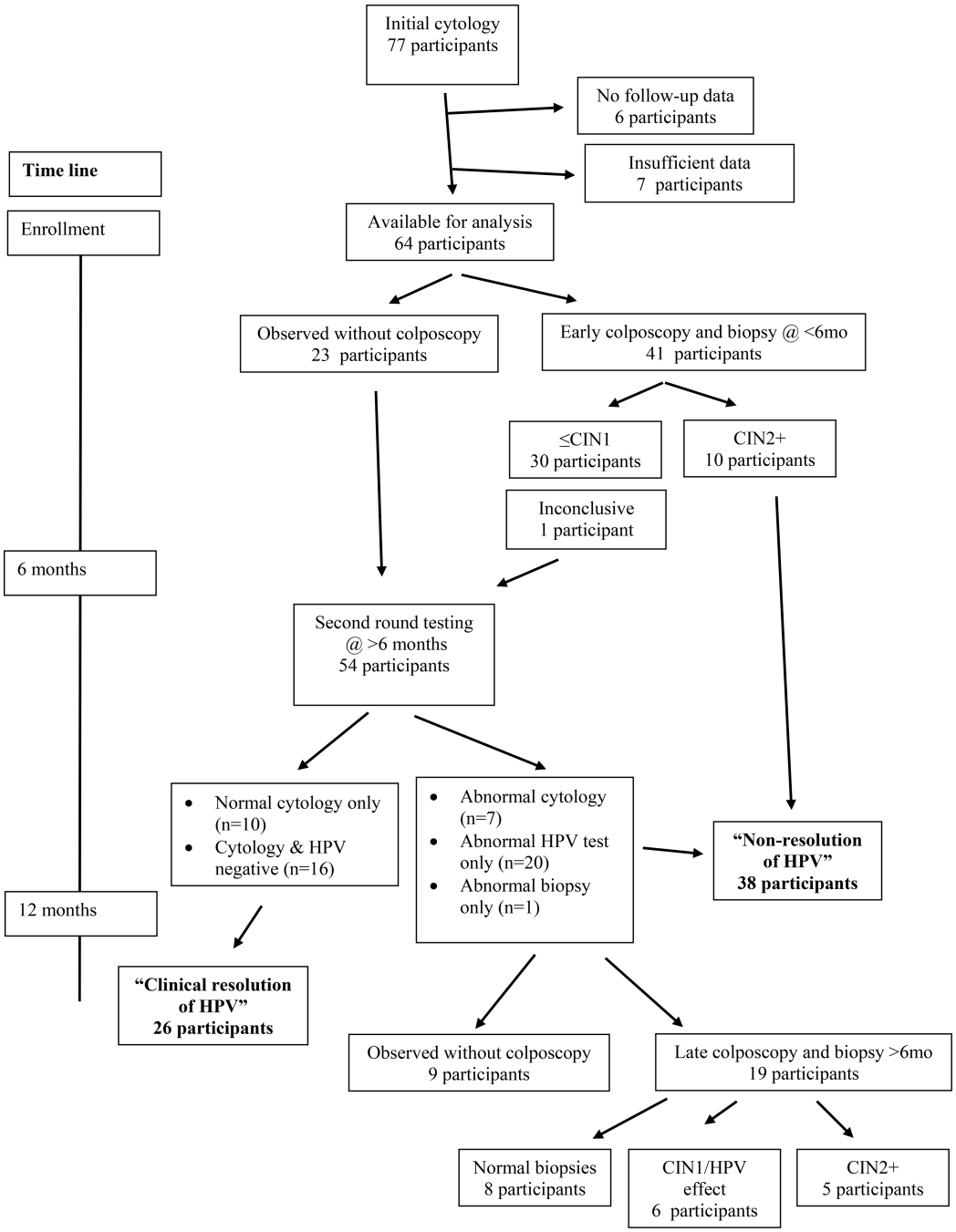

Figure 1.
Study flow chart

Table 1.

Demographic and medical history characteristics

	Clinical resolution of HPV[1] (n=26)	Non-resolution of HPV[2] (n=38)	p-value[3]
Length of follow up (median, IQR)	428 (211)	412 (320)	0.09
Age (mean ±SD)	34.3 (±9.5)	39.9 (±13.4)	0.07
African-American (%)	11 (42%)	22 (58%)	0.98
Income <$10K/year (%)	5 (23%)	13 (36%)	0.29
Education more than high school(%)	22 (85%)	25 (66%)	0.09
HIV-positive (%)	1 (4%)	3 (8%)	0.64
Use of immunosuppressant medications (%)	0 (0%)	1 (3%)	1.0
Current smoker (%)	2 (8%)	7 (18%)	0.22
Former smoker (%)	5 (19%)	7 (18%)	0.89
History of abnormal cervical cytology (%)	17 (65%)	21 (55%)	0.42
Hormonal contraception user (%)	11 (48%)	12 (35%)	0.34
Ever diagnosed with STI (%)	15 (58%)	15 (40%)	0.15

[1]Clinical resolution of HPV was defined as a negative hrHPV test at least 6 months after prior positive hrHPV test or abnormal cytology, or normal cytology without HPV testing at least 6 months after prior abnormal cytology

[2]Non-resolution of HPV was defined as a positive hrHPV test, abnormal cytology, CIN1 or worse (CIN1+) on cervical pathology at least 6 months after prior positive HPV test or abnormal cytology, or cervical pathology results demonstrating CIN2 or worse (CIN2+) at any time point

[3]p-values were calculated using Student's t-test for continuous variables and Pearson's chi-squared test for categorical factors. When the assumptions of these tests were not met, the nonparametric Wilcoxon rank sum test and Fisher's exact test were used. $P<0.05$ was considered statistically significant. $P<0.10$ was considered a possible confounder and was included in multivariate regression model

Table 2.

Association of Healthy Eating Index (HEI) total and component scores and clinical resolution of HPV

HEI value	Clinical resolution of HPV[1] (n=24)	Non-resolution of HPV[2] (n=38)	Unadjusted p-value[3]	Adjusted p-value[4]
Kilocalories (mean ±SD)	1406.6 (±719.5)	1474.0 (±840.4)	0.74	0.25
HEI total score (±SD)	50.1 (±15.6)	45.8 (±13.6)	0.24	0.44
Participants receiving >50% of maximum points in each category (%)				
Adequacy				
Total vegetables	11 (42%)	21 (55%)	0.31	*0.05*
Greens and beans	8 (31%)	10 (26%)	0.70	0.88
Total fruit (includes fruit juice)	12 (46%)	11 (29%)	0.16	*0.04*
Whole fruit	12 (46%)	7 (18%)	*0.02*	*0.03*
Whole grain	3 (12%)	7 (18%)	0.46	0.10
Total dairy	6 (23%)	15 (40%)	0.17	*0.04*
Total protein	23 (89%)	32 (84%)	0.63	0.72
Seafood & plant protein	19 (73%)	15 (40%)	*<0.01*	*0.01*
Fatty acids [5]	18 (69%)	20 (53%)	0.18	0.09
Moderation				
Sodium	12 (46%)	16 (42%)	0.75	0.08
Refined grains	17 (65%)	23 (61%)	0.69	0.86
Solid fats, alcohol, added sugars	16 (62%)	24 (63%)	0.90	0.64

[1] Clinical resolution of HPV was defined as a negative hrHPV test at least 6 months after prior positive hrHPV test or abnormal cytology, or normal cytology without HPV testing at least 6 months after prior abnormal cytology.

[2] Non-resolution of HPV was defined as a positive hrHPV test, abnormal cytology, CIN1 or worse (CIN1+) on cervical pathology at least 6 months after prior positive HPV test or abnormal cytology, or cervical pathology results demonstrating CIN2 or worse (CIN2+) at any time point.

[3] p-values were calculated using Student's t-test or Pearson's chi-squared test. $p<0.05$ was considered statistically significant

[4] Data were analyzed using logistic regression. Adjusted models were adjusted for age, education, and length of follow-up $p<0.05$ was considered statistically significant

[5] Points given for ratio of polyunsaturated fatty acids (PUFAs) + monounsaturated fatty acids (MUFAs) to saturated fatty acids (SFAs) > 2.5

Table 3.

Factors not associated with clinical resolution of HPV

	Clinical resolution of HPV[1] (n=26)	Non-resolution of HPV[2] (n=38)	Unadjusted p-value[3]	Adjusted p-value[3]
Body mass index (mean ±SD)	30.4 (±7.9)	29.3 (±6.4)	0.53	0.92
Obesity (%)	11 (42.3%)	15 (39.5%)	0.82	0.83
Category 3 obesity (%)	3 (11.5%)	3 (7.9%)	0.63	0.97
Diabetes mellitus (%)	0 (0%)	4 (10.5%)	0.14[4]	-----
Pregnancy (%)	2 (7.7%)	4 (10.5%)	0.70	0.63
Current alcohol overuse (%)	3 (11.5%)	1 (2.6%)	0.18	0.55
Prior alcohol overuse (%)	2 (7.7%)	4 (10.5%)	0.70	0.92
Current regular illicit drug use (%)	7 (26.9%)	6 (15.8%)	0.28	0.46
Prior regular illicit drug use (%)	14 (53.9%)	13 (34.2%)	0.28	0.21

[1] Clinical resolution of HPV was defined as a negative hrHPV test at least 6 months after prior positive hrHPV test or abnormal cytology, or normal cytology without HPV testing at least 6 months after prior abnormal cytology

[2] Non-resolution of HPV was defined as a positive hrHPV test, abnormal cytology, CIN1 or worse (CIN1+) on cervical pathology at least 6 months after prior positive HPV test or abnormal cytology, or cervical pathology results demonstrating CIN2 or worse (CIN2+) at any time point

[3] Data were analyzed using logistic regression. Adjusted models were adjusted for age, education, and length of follow-up

[4] Logistic model did not converge; p-value from Fisher's Exact Test

Table 4.

Correlation between serum and ASA24 nutrient values

Nutrient	rho[1]	P-value
Vitamin C	0.52	<0.01
Calcium	0.23	0.10
Folate	0.33	0.01
Vitamin A	0.43	<0.01
Vitamin E	0.01	0.94
α-carotene	0.35	<0.01
β-carotene	0.36	<0.01
Lutein + zeaxanthin	0.43	<0.01
Lycopene	0.07	0.64
β-cryptoxanthin	0.36	<0.01

[1]Spearman's correlation coefficient