

Oral Contraceptive Exposure, Folate and Vitamin B12 Status in Relation to High-Risk HPV and Cervical Cytological Abnormality among Sudanese Women

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Abstract:

Background: Persistent high-risk human papillomavirus (hrHPV) infection is necessary for most cervical cancers, but hormonal and nutritional factors may modify viral persistence or lesion progression. Evidence concerning oral contraceptive pills (OCPs), folate and vitamin B12 is limited in conflict-affected African settings.

Objective: To examine relationships of current OCP use OCP duration, folate and vitamin B12 status with hrHPV positivity and cervical cytological severity among Sudanese women.

Methods: A cross-sectional study included 200 women recruited through post-war health-service clusters. OCP exposure was recorded by current-use status and duration category. Serum folate and vitamin B12 were classified as low, normal or not done. Cervical specimens underwent liquid-based cytology and consensus hrHPV PCR. Associations were assessed by chi-square tests.

Results: 92 women (46.0%) reported Current OCP use. Low folate occurred in 55 (27.5%) and low vitamin B12 in 42 (21.0%). HPV positivity was 35.9% among current users and 29.6% in the no/past group, but the association was not significant ($\chi^2=0.62$, $p=0.431$). OCP duration showed a non-monotonic borderline relationship with abnormal cytology ($\chi^2=8.32$, $p=0.080$). Folate status was associated with hrHPV positivity ($\chi^2=8.46$, $p=0.015$) and Bethesda category ($\chi^2=36.40$, $p<0.001$), whereas vitamin B12 was not associated with hrHPV positivity ($\chi^2=1.65$, $p=0.439$).

Conclusion: Current OCP use and vitamin B12 showed no significant associations. Folate was a promising correlate, but missing measurements and the cross-sectional design preclude causal inference and require prospective confirmation.

Keywords: oral contraceptive pills; folate; vitamin B12; high-risk human papillomavirus; cervical cytology; cervical intraepithelial neoplasia; Sudan; post-war health services

1. INTRODUCTION

Persistent infection with carcinogenic human papillomavirus is the central causal pathway for cervical precancer and cancer, but only a minority of infections persist and progress. This difference has stimulated investigation of cofactors that may influence

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acquisition, immune clearance, persistence or epithelial transformation (Bosch et al. 2002; Schiffman et al. 2007). Oral contraceptive exposure and one-carbon micronutrients are biologically plausible modifiers, although the epidemiological evidence is inconsistent.

The relationship between oral contraceptive pills and cervical disease is difficult to isolate because OCP use is correlated with age, parity, partnership patterns, health-service attendance and screening. Pooled and case-control studies have reported increasing cancer risk with prolonged use, especially among HPV-positive women, and decreasing risk after cessation (Moreno et al. 2002; Smith et al. 2003; International Collaboration of Epidemiological Studies of Cervical Cancer 2007). More recent analyses that control for HPV have produced less consistent results and emphasize residual confounding, outcome heterogeneity and limitations of cross-sectional exposure measurement (Marks et al. 2011; Anastasiou et al. 2022).

Folate and vitamin B12 participate in one-carbon metabolism, nucleotide synthesis and methyl-donor generation. Deficiency may affect DNA repair, methylation and immune competence, providing a plausible connection with HPV persistence and cervical transformation. Several studies have linked lower folate status with persistent HPV or higher-grade cervical lesions, but other investigations have reported null results (Sedjo et al. 2002, 2003; Piyathilake et al. 2004, 2007, 2009; Zhao et al. 2016; Yang et al. 2018). Evidence for vitamin B12 is weaker and may depend on functional deficiency, binding proteins and interaction with folate.

These questions are particularly relevant in Sudan, where nutritional insecurity, displacement and disrupted screening can coexist. The present analysis examined current OCP use, duration of exposure, serum folate and serum vitamin B12 in relation to consensus hrHPV positivity and Bethesda cytological severity. The working hypotheses were that prolonged OCP exposure and low micronutrient status would be associated with greater HPV positivity or cytological abnormality, while acknowledging that a cross-sectional design cannot establish temporality or persistence.

2. MATERIALS AND METHODS

A descriptive analytical cross-sectional study was conducted as part of a broader doctoral investigation and reported in accordance with STROBE principles (von Elm et al. 2007). This manuscript is restricted to hormonal and micronutrient exposures and their relationships with molecular and cytological outcomes; technical genotyping results are reported separately to minimize duplicate publication.

Two hundred women were recruited consecutively through functioning post-war health-service clusters in Sudan: Soba, other hospitals or clinics, health centers and private clinics. Participants attended for routine screening, gynecological evaluation, follow-up of previous abnormalities, suspicious lesions or cervicitis/STI-related care. Women aged at least 18 years were included after informed consent when LBC material and the minimum analytical dataset were available. Previous total hysterectomy, current treatment for established cervical cancer, inability to consent, insufficient records and clinically unsuitable sampling were exclusion criteria.

A structured questionnaire and clinical-record abstraction captured current and past OCP use, formulation where known, duration, other hormonal methods, barrier-method use, folate supplementation, age, parity, smoking, screening history and selected

clinical factors. Current OCP status was analyzed as current versus no/past use for the principal HPV comparison. Duration categories were 0, 1-12, 13-36, 37-60 and more than 60 months. Because exposure was self-reported and past users were combined with non-current users in the principal analysis, residual misclassification was possible.

Cervical specimens were collected into LBC preservative, stained by the Papanicolaou method and reported according to the Bethesda System (Nayar and Wilbur 2015). Abnormal cytology comprised ASC-US, LSIL, HSIL, AGC and SCC. Residual LBC material underwent DNA extraction, beta-globin internal-control testing and broad consensus HPV PCR using MY09/MY11, GP5+/GP6+ or SPF10. Consensus results were recorded as positive, negative or invalid.

Venous blood was processed by routine laboratory methods. Serum folate and vitamin B12 were measured on the available calibrated immunoassay platform with internal quality-control material and categorized as low, normal or not done according to the laboratory reference intervals used during the study. Serum concentrations reflect circulating status and recent intake; red-cell folate, homocysteine and methylmalonic acid were not available. Hemoglobin and mean corpuscular volume were recorded as contextual measures.

Frequencies and percentages described categorical variables; means, standard deviations, medians and ranges described continuous variables. Pearson chi-square tests evaluated current OCP use versus consensus HPV positivity, OCP duration versus abnormal cytology, folate status versus HPV positivity, vitamin B12 status versus HPV positivity, and folate status versus Bethesda category. Yates correction was applied to the 2x2 OCP analysis. Statistical significance was $p < 0.05$; p values from 0.05 to 0.10 were considered borderline. Missing or not-done categories were retained to reproduce the thesis analysis, and their potential influence was examined critically in interpretation.

Ethical considerations

Ethical approval was obtained or maintained through the relevant institutional and clinical authorities. Participants provided informed consent, records were coded and access was restricted. Women with clinically significant findings were referred for appropriate evaluation and management.

3. RESULTS

3.1 Oral contraceptive and micronutrient profile

Current OCP use was reported by 92 women (46.0%), 29 (14.5%) reported past-only use and 79 (39.5%) reported no current exposure. Combined OCPs were the most frequent known formulation. Intermediate duration groups were well represented, but only 13 women reported 1-12 months and 27 reported more than 60 months. Folate was low in 55 women (27.5%), vitamin B12 was low in 42 (21.0%), and only 20.5% reported folate supplementation (Table 1; Figure 1).

Table 1. Oral contraceptive, behavioral and micronutrient characteristics (n=200).

Variable	Category	n (%)
Current OCP use	Yes	92 (46.0)
Current OCP use	No	79 (39.5)
Current OCP use	Past only	29 (14.5)
OCP type	Combined	75 (37.5)

Variable	Category	n (%)
OCP type	Progestin-only	28 (14.0)
OCP duration	0 months	79 (39.5)
OCP duration	1-12 months	13 (6.5)
OCP duration	13-36 months	41 (20.5)
OCP duration	37-60 months	40 (20.0)
OCP duration	>60 months	27 (13.5)
Barrier method	Never	116 (58.0)
Folate supplementation	Yes	41 (20.5)
Folate status	Low	55 (27.5)
Folate status	Normal	132 (66.0)
Folate status	Not done	13 (6.5)
Vitamin B12 status	Low	42 (21.0)
Vitamin B12 status	Normal	147 (73.5)
Vitamin B12 status	Not done	11 (5.5)

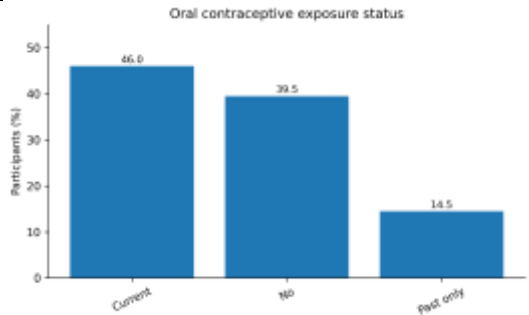


Figure 1. Distribution of current, absent and past-only oral contraceptive exposure.

3.2 Current OCP use and hrHPV positivity.

Consensus HPV positivity was numerically higher among current OCP users than among women with no current use or past-only use (35.9% versus 29.6%). The difference was small and not statistically significant ($\chi^2=0.62$, $df=1$, $p=0.431$) (Table 2). Current exposure alone therefore did not provide evidence of an independent cross-sectional relationship with detectable hrHPV in this cohort.

Table 2. Current oral contraceptive use versus consensus HPV positivity (row percentages).

OCP status	HPV negative	HPV positive
Current	59 (64.1%)	33 (35.9%)
No/Past	76 (70.4%)	32 (29.6%)

Yates-corrected $\chi^2=0.62$, $df=1$, $p=0.431$.

3.3 OCP duration and cytological abnormality

Abnormal cytology increased from 24.1% in the zero-month group to 41.5% at 13-36 months and 42.5% at 37-60 months but then decreased to 18.5% among women reporting more than 60 months. The overall association was borderline ($\chi^2=8.32$, $df=4$, $p=0.080$) and lacked a monotonic duration-response pattern (Table 3; Figure 2).

Table 3. Duration of oral contraceptive exposure versus abnormal cytology (row percentages).

OCP duration	NILM	Abnormal cytology
0 months	60 (75.9%)	19 (24.1%)
1-12 months	9 (69.2%)	4 (30.8%)
13-36 months	24 (58.5%)	17 (41.5%)
37-60 months	23 (57.5%)	17 (42.5%)
>60 months	22 (81.5%)	5 (18.5%)

$\chi^2=8.32$, $df=4$, $p=0.080$. Abnormal cytology includes ASC-US, LSIL, HSIL, AGC and SCC.

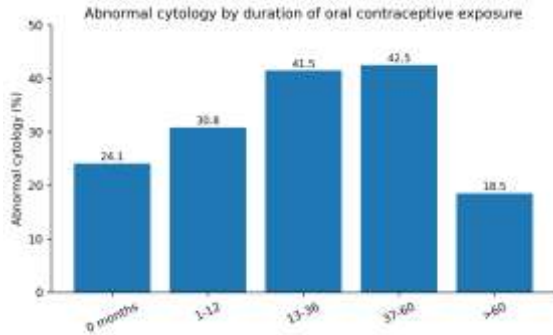


Figure 2. Non-monotonic proportion of abnormal cytology across OCP-duration categories.

3.4 Micronutrient status, hrHPV and Bethesda severity

HPV positivity was 41.8% in the low-folate group and 31.8% in the normal-folate group. The overall three-category association, including the not-done group, was significant ($\chi^2=8.46$, $df=2$, $p=0.015$). Vitamin B12 status was not associated with HPV positivity ($\chi^2=1.65$, $df=2$, $p=0.439$) (Table 4, Panel A; Figure 3).

Folate status was also associated with Bethesda category ($\chi^2=36.40$, $df=10$, $p<0.001$). Low folate was accompanied by a larger HSIL proportion than normal folate (23.6% versus 12.1%), whereas NILM predominated in the normal group. The not-done category contained three ASC-US cases and no LSIL or HSIL, indicating that missingness was not randomly distributed across cytology categories (Table 4, Panel B; Figure 4).

Table 4. Micronutrient status in relation to consensus HPV positivity and Bethesda category.

Panel A. Folate and vitamin B12 status versus consensus HPV result.

Micronutrient status	HPV negative	HPV positive
Folate low	32 (58.2%)	23 (41.8%)
Folate normal	90 (68.2%)	42 (31.8%)
Folate not done	13 (100.0%)	0 (0.0%)
Vitamin B12 low	30 (71.4%)	12 (28.6%)
Vitamin B12 normal	96 (65.3%)	51 (34.7%)
Vitamin B12 not done	9 (81.8%)	2 (18.2%)

Folate: $\chi^2=8.46$, $df=2$, $p=0.015$. Vitamin B12: $\chi^2=1.65$, $df=2$, $p=0.439$.

Panel B. Folate status versus Bethesda category.

Folate status	NILM	ASC-US	LSIL	HSIL	AGC	SCC
Low	32 (58.2%)	2 (3.6%)	8 (14.5%)	13 (23.6%)	0	0
Normal	96 (72.7%)	0	16 (12.1%)	16 (12.1%)	2 (1.5%)	2 (1.5%)
Not done	10 (76.9%)	3 (23.1%)	0	0	0	0

$\chi^2=36.40$, $df=10$, $p<0.001$. Row percentages are shown.

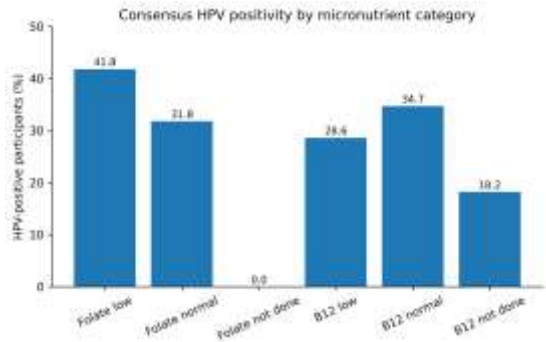


Figure 3. Consensus HPV positivity according to folate and vitamin B12 categories.

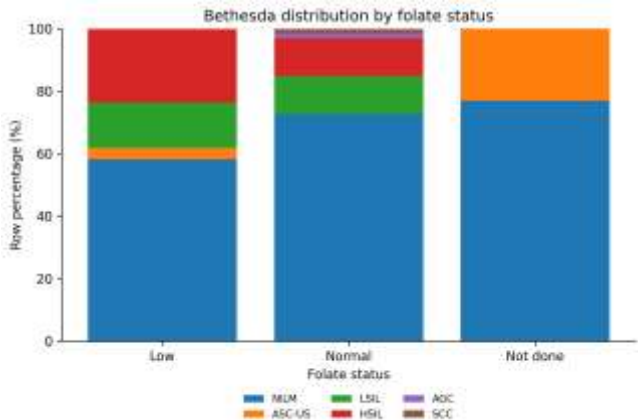


Figure 4. Bethesda cytology distribution according to folate status.

4. DISCUSSION

The analysis did not support a simple model in which current OCP use or low vitamin B12 independently predicted detectable hrHPV. OCP duration showed a borderline but non-monotonic relationship with abnormal cytology, whereas folate status showed statistically significant relationships with both HPV positivity and Bethesda severity. The hierarchy of evidence is therefore mixed: the OCP and B12 results are negative or inconclusive, and the folate signal is biologically plausible but vulnerable to missing-category and confounding effects.

HPV positivity was six percentage points higher among current OCP users, but the difference did not reach statistical significance. This finding is compatible with the

inconsistent literature. Marks et al. (2011) reported an association between recent long-term combined OCP use and prevalent HPV, whereas Anastasiou et al. (2022) found no consistent independent effect after controlling for HPV and other confounders. The present result concerns detectable infection at one time point, not persistence, high-grade progression or invasive cancer, and it should not be directly compared with studies of long-term cancer risk.

Several factors could have attenuated a true effect. Current use is a crude proxy for cumulative hormonal exposure. The no/past category combines women with different exposure histories. Formulation, adherence and time since cessation were incompletely characterized. OCP use is also associated with age, parity, partnership patterns and screening contact. None of these factors was adjusted in the reported chi-square test. The non-significant result therefore indicates insufficient evidence in this sample rather than proof of no biological effect.

The highest abnormal-cytology proportions occurred at 13-60 months, but the proportion fell sharply beyond 60 months. The absence of a monotonic gradient weakens a straightforward dose-response interpretation. The pattern may represent random variation, discontinuation after symptoms or an abnormal result, differences in age and screening history, or misclassification of cumulative duration. Dividing 200 participants into five categories also reduced cell sizes and statistical power.

Large, pooled analyses have reported higher cervical cancer risk with prolonged current hormonal-contraceptive use and decreasing risk after cessation (International Collaboration of Epidemiological Studies of Cervical Cancer 2007). Moreno et al. (2002) and Smith et al. (2003) similarly identified duration-related effects. Those studies evaluated cancer or longer-term outcomes, whereas the present endpoint grouped ASC-US through SCC in a cross-sectional cohort. Differences in design and outcome are sufficient to explain the weaker, borderline result.

The folate findings are biologically coherent. Folate is required for thymidylate and purine synthesis and contributes to methyl-donor generation. Deficiency could impair DNA repair, alter methylation and affect immune responses relevant to viral clearance. Piyathilake et al. (2004, 2007, 2009) linked folate status with hrHPV natural history and CIN risk, while Zhao et al. (2016), Yang et al. (2018), Peitz et al. (2024) and Jin et al. (2024) reported inverse associations between folate exposure and HPV-related outcomes.

The present association nevertheless requires guarded interpretation. The overall HPV chi-square test retained a not-done group in which no HPV-positive cases were recorded; this structure may have contributed materially to the p value. Serum folate is sensitive to recent intake and is less stable than red-cell folate as a marker of longer-term status. Cross-sectional measurement cannot determine whether low folate preceded persistent infection or shared determinants such as diet, socioeconomic disadvantage, inflammation and displacement. In addition, hrHPV may mediate the relationship between folate and cytological severity. A future adjusted model should include age, smoking, parity, OCP duration, socioeconomic factors and HPV status.

Vitamin B12 was not associated with HPV positivity, and the low-B12 group did not show a higher positivity proportion than the normal group. This negative result is informative because it prevents generalization from folate to all one-carbon nutrients. Serum B12 can be influenced by binding proteins and may not reflect functional deficiency; methylmalonic acid or homocysteine would provide complementary

information. B12 may also act through interaction with folate rather than as an independent predictor.

Published evidence is mixed. Sedjo et al. (2002) reported associations between methylation-related nutrients and HPV persistence, but a subsequent analysis found no relationship between folate, B12, homocysteine and persistence or dysplasia (Sedjo et al. 2003). Berenson and Rahman (2012) observed lower B12 concentrations during hormonal contraception without consistent clinical deficiency. The present null result therefore fits the uncertainty of the field.

The findings do not justify changing contraceptive counselling or recommending folate as treatment for HPV. OCP decisions should remain based on established contraceptive indications, contraindications and patient preference. Nutritional assessment may be appropriate where deficiency is suspected, but supplementation should follow clinical standards rather than the expectation of clearing HPV. The research implication is stronger: prospective cohorts should measure OCP formulation and cumulative exposure accurately, repeat HPV testing to define persistence, use red-cell folate and functional B12 markers, and estimate adjusted odds ratios with cluster-aware methods.

Strengths and limitations

Strengths include simultaneous measurement of OCP exposure, serum micronutrients, LBC cytology and hrHPV in a post-war Sudanese cohort, together with explicit reporting of significant and non-significant results. Limitations include cross-sectional design, clinic enrichment, reduced sample size, unequal cluster sizes, self-reported OCP duration, incomplete formulation and adherence information, serum rather than red-cell folate, absence of functional B12 markers, missing measurements, sparse cytology categories, multiple testing and lack of multivariable adjustment. These limitations are especially important for the folate findings and the borderline OCP-duration pattern.

5. CONCLUSION

Current oral contraceptive use was not significantly associated with consensus hrHPV positivity, and duration showed only a non-monotonic borderline relationship with abnormal cytology. Vitamin B12 status was also unrelated to hrHPV detection. Folate status was associated with HPV positivity and Bethesda severity, but the missing-data category, cross-sectional measurement and lack of adjusted modelling prevent causal interpretation. The appropriate conclusion is that folate is a promising research correlate rather than an established preventive or therapeutic factor. Prospective, adequately powered and cluster-aware studies with repeated HPV testing and improved nutritional biomarkers are required.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ETHICAL APPROVAL

Ethical approval was obtained or maintained through the relevant institutional and clinical authorities. All participants provided informed consent, confidentiality was protected through coded identifiers, and women with clinically significant abnormalities were referred for appropriate evaluation and management.

DATA AVAILABILITY

The aggregate data supporting the findings are presented in the manuscript. De-identified participant-level data may be available from the corresponding author upon reasonable request and subject to institutional and ethical approval.

AUTHOR CONTRIBUTIONS

Hala Mahmoud Elhag Mohamed conducted the doctoral investigation, participated in data and specimen collection, laboratory work, data curation and thesis drafting. Mohammed Siddig Abdelaziz Mohammed and Ali Sid Ahmed provided doctoral supervision, methodological guidance and critical review. Mutaz Mohamed Ibrahim Ali contributed conceptualization of the hormonal and micronutrient publication domain, manuscript redesign, statistical interpretation, journal-targeted scientific editing and correspondence. All authors reviewed and approved the final manuscript.

REFERENCES

1. Anastasiou, E., K. J. McCarthy, E. L. Gollub, L. Ralph, J. H. H. M. van de Wijert, and H. E. Jones. 2022. "Hormonal Contraception and Cervical Dysplasia/Cancer Controlling for Human Papillomavirus Infection: A Systematic Review." *Contraception* 107: 1-9.
2. Berenson, A. B., and M. Rahman. 2012. "Effect of Hormonal Contraceptives on Vitamin B12 Level and the Association of the Latter with Bone Mineral Density." *Contraception* 86 (5): 481-487.
3. Bosch, F. X., A. Lorincz, N. Muñoz, C. J. L. M. Meijer, and K. V. Shah. 2002. "The Causal Relation between Human Papillomavirus and Cervical Cancer." *Journal of Clinical Pathology* 55 (4): 244-265.
4. Husain, N. E., A. Burhan, I. A. I. Ahmed, S. I. Mohammed, and N. Hammad. 2022. "Women's Cancers in Sudan with a Focus on Cervical Cancer: Turmoil, Geopolitics, and Opportunities." *ecancermedalscience* 16: 1433.
5. International Collaboration of Epidemiological Studies of Cervical Cancer. 2007. "Cervical Cancer and Hormonal Contraceptives: Collaborative Reanalysis of Individual Data for 16,573 Women with Cervical Cancer and 35,509 Women without Cervical Cancer from 24 Epidemiological Studies." *Lancet* 370 (9599): 1609-1621.
6. Jin, S., F. Lin, L. Yang, and Q. Zhang. 2024. "Association between Dietary Folate Intake and HPV Infection: NHANES 2005-2016." *PLOS ONE* 19 (7): e0306636.
7. Marks, M., P. E. Gravitt, S. B. Gupta, et al. 2011. "The Association of Hormonal Contraceptive Use and HPV Prevalence." *International Journal of Cancer* 128 (12): 2962-2970.
8. Moreno, V., F. X. Bosch, N. Muñoz, et al. 2002. "Effect of Oral Contraceptives on Risk of Cervical Cancer in Women with Human Papillomavirus Infection: The IARC Multicentric Case-Control Study." *Lancet* 359 (9312): 1085-1092.
9. Nayar, R., and D. C. Wilbur, eds. 2015. *The Bethesda System for Reporting Cervical Cytology*. 3rd ed. Cham: Springer.
10. Peitz, J. G., C. A. Adebamowo, and S. N. Adebamowo. 2024. "Association between Serum Folate and Vaginal High-Risk Human Papillomavirus Infections in United States Women." *Journal of Nutrition* 154 (3): 583-589.
11. Piyathilake, C. J., O. L. Henao, M. Macaluso, et al. 2004. "Folate Is Associated with the Natural History of High-Risk Human Papillomaviruses." *Cancer Research* 64 (23): 8788-8793.

12. Piyathilake, C. J., M. Macaluso, I. Brill, D. C. Heimburger, and E. E. Partridge. 2007. "Lower Red Blood Cell Folate Enhances the HPV-16-Associated Risk of Cervical Intraepithelial Neoplasia." *Nutrition* 23 (3): 203-210.
13. Piyathilake, C. J., M. Macaluso, R. D. Alvarez, W. C. Bell, D. C. Heimburger, and E. E. Partridge. 2009. "Lower Risk of Cervical Intraepithelial Neoplasia in Women with High Plasma Folate and Sufficient Vitamin B12 in the Post-Folic Acid Fortification Era." *Cancer Prevention Research* 2 (7): 658-664.
14. Schiffman, M., P. E. Castle, J. Jeronimo, A. C. Rodriguez, and S. Wacholder. 2007. "Human Papillomavirus and Cervical Cancer." *Lancet* 370 (9590): 890-907.
15. Sedjo, R. L., P. Inserra, M. Abrahamsen, et al. 2002. "Human Papillomavirus Persistence and Nutrients Involved in the Methylation Pathway among a Cohort of Young Women." *Cancer Epidemiology, Biomarkers & Prevention* 11 (4): 353-359.
16. Sedjo, R. L., B. M. Fowler, A. Schneider, S. M. Henning, K. Hatch, and A. R. Giuliano. 2003. "Folate, Vitamin B12, and Homocysteine Status: Findings of No Relation between Human Papillomavirus Persistence and Cervical Dysplasia." *Nutrition* 19 (6): 497-502.
17. Shere, M., P. Bapat, C. Nickel, B. Kapur, and G. Koren. 2015. "Association between Use of Oral Contraceptives and Folate Status: A Systematic Review and Meta-Analysis." *Journal of Obstetrics and Gynaecology Canada* 37 (5): 430-438.
18. Smith, J. S., J. Green, A. Berrington de González, et al. 2003. "Cervical Cancer and Use of Hormonal Contraceptives: A Systematic Review." *Lancet* 361 (9364): 1159-1167.
19. von Elm, E., D. G. Altman, M. Egger, S. J. Pocock, P. C. Gøtzsche, and J. P. Vandenbroucke. 2007. "The Strengthening the Reporting of Observational Studies in Epidemiology Statement: Guidelines for Reporting Observational Studies." *Lancet* 370 (9596): 1453-1457.
20. World Health Organization. 2021. *WHO Guideline for Screening and Treatment of Cervical Pre-Cancer Lesions for Cervical Cancer Prevention*. 2nd ed. Geneva: WHO.
21. Yang, J., A. Yang, Z. Wang, et al. 2018. "Interactions between Serum Folate and Human Papillomavirus with Cervical Intraepithelial Neoplasia Risk in a Chinese Population-Based Study." *American Journal of Clinical Nutrition* 108 (5): 1034-1042.
22. Yenigul, N. N., et al. 2021. "Can Serum Vitamin B12 and Folate Levels Predict HPV Penetration in Patients with ASC-US?" *Nutrition and Cancer* 73 (4): 602-608.
23. Zhao, W., M. Hao, Y. Wang, et al. 2016. "Association between Folate Status and Cervical Intraepithelial Neoplasia." *European Journal of Clinical Nutrition* 70 (7): 837-842.