PAPILLEX Ingredient Research Summary

There is evidence that diet and nutrition are modifiable risk factors for HPV and its related conditions including cervical cancer. In recent years, attention paid to micronutrients in gynecology has increased, especially regarding Human papillomavirus (HPV) infection. We performed a review of the human literature up until 2022, aiming to clarify the effects of micronutrients, minerals, and vitamins on the history of HPV infection and the development of cervical cancer. We included studies having as their primary objective the evaluation of dietary supplements. Different natural compounds and micronutrients demonstrated a potential protective role against cervical cancer by intervening in different stages of the natural history of HPV infection, development of cervical dysplasia, and invasive disease. Healthcare providers should be aware of and incorporate the literature evidence in counseling. Further well-designed investigations to give clear indications for clinical practice are warranted.

Ingredient	Data for Ingredient	Reference
Lycopene and Carotenoids	A 50% (OR=1.5) increased risk for developing oncogenic HPV was observed in women with low dietary carotenoid status. The OR of developing any type of HPV in women with low dietary intake of combined carotenoids was 2.4. Low levels of carotenoids may increase risk of persistent HPV infection.	https://www.ncbi.nlm.nih.gov/pubmed/20661820
	Researchers followed a cohort of women over time, assessing serum levels of retinol, carotenoids, and tocopherols, along with cervical cell samples and HPV DNA analysis. The study found that higher levels of specific carotenoids and tocopherols were associated with quicker clearance of type-specific HPV infections, particularly during the initial 120 days.	https://aacrjournals.org/cancerres/article/67/12/5987/533146/Hawaii-Cohort-Study-of-Serum-Micronutrient
	There is a 54% decreased risk of HPV persistence with higher levels of vegetable consumption. A 56% reduction in HPV persistence was seen in women with higher cis-lycopene concentrations compared to women with lowest concentrations. Higher vegetable consumption and higher levels of circulating cis-lycopene may be protective against HPV persistence.	https://www.ncbi.nlm.nih.gov/pubmed/12223432
	In a case-control study conducted in Xinjiang, China, involving 358 adults (158 cases and 200 controls), researchers assessed serum levels of carotenoids. The results showed that higher serum concentrations of certain carotenoidsand α-tocopherol were linked to a reduced risk of cervical cancer. Specifically, a 1-standard deviation increase in total carotenoid levels was associated with a 29% lower risk, and a 1-standard deviation increase in total tocopherol levels was associated with a 25% lower risk of cervical cancer.	https://www.ncbi.nlm.nih.gov/pubmed/25854393

	The study aimed to investigate the anticancer effects and mechanisms of lycopene in human cervical carcinoma (HeLa) cells. The results indicate that lycopene enhances the sensitivity of HeLa cells to cisplatin by reducing cell viability, increasing the expression of pro-apoptotic protein Bax, decreasing anti-apoptotic protein Bcl-2, suppressing the NF-KB signaling pathway, and activating the Nrf2-mediated antioxidant response. These findings suggest a potential role for lycopene in improving the efficacy of cervical cancer treatment.	https://pubmed.ncbi.nlm.nih.gov/32718121/
	Significantly positive associations were seen in 143 subjects with HPV-positive status between vitamin A, vitamin E, iron, β-carotene, and folate. Diet may be a factor in improved prognosis for those with HPV-positive HNSCC.	https://www.ncbi.nlm.nih.gov/pubmed/21667401
	Increasing concentrations of serum lycopene were negatively associated with CIN1, CIN3, and cervical cancer. Increasing concentrations of serum α- and γ-tocopherols, as well as higher dietary intakes of dark green and deep yellow vegetables and fruit was associated with a nearly 50% decreased relative risk of CIN3.	https://www.ncbi.nlm.nih.gov/pubmed/19642096
	Epidemiological studies indicate that human exposure to isothiocyanates and indoles through cruciferous vegetable consumption may decrease cancer risk dependent on genetic variation in elimination of isothiocyanates. Small human trials suggest I3C supplementation may be beneficial in treating conditions related to HPV, including CIN.	https://www.ncbi.nlm.nih.gov/pubmed/17317210
	Sulforaphane was shown to induce downregulation of β-catenin in human carcinoma stem cells by inhibiting the viability through apoptosis.	https://www.ncbi.nlm.nih.gov/pubmed/23902242
	Sulforaphane (SF), a compound in broccoli, activates protective enzymes against carcinogens through NRF2 transcription factor induction. This research conducted tests on cell lines, mouse models, and human volunteers. SF induced NRF2 expression in cell lines and functional target gene activation. In mice, SF reduced tongue tumor incidence and volume. 7 out of 10 human subjects consuming SF-rich extract showed NRF2 gene upregulation, with systemic SF exposure	https://aacrjournals.org/cancerres/article/75/15_Supplement/894/605214/Abstract-894-Sulforaphane-as-a-chemopreventive

Broccoli sprout extract (indole-3-carboniol, DIM, sulphoraphane)	The study investigated the impact of 3,3'-diindolylmethane (DIM) on cervical lesions, estrogen metabolism, and immune function in K14-HPV16 mice. DIM increased estrogen C-2 hydroxylation and serum IFN-γ levels. Wild-type mice without DIM displayed hyperplasia, while DIM-fed mice had a normal epithelium. Transgenic mice without DIM showed abnormalities, including dysplastic cells, while DIM-fed transgenic mice exhibited mild hyperplasia. DIM demonstrated an inhibitory effect on E6/E7 oncogene-induced cervical lesions, marked by reduced cervical dysplasia and enhanced immune response.	https://aacrjournals.org/cebp/article/18/11/2957/67537/Diindolylmethane-Inhibits-Cervical-Dysplasia
	In a study involving 30 patients with confirmed CIN II-III, participants were randomly assigned to receive a placebo or oral doses of 200 or 400 mg/day of I-3-C for 12 weeks. Patients with persistent CIN underwent further treatment if necessary. Results showed that no patients in the placebo group experienced complete regression of CIN, whereas 4 out of 8 patients in the 200 mg/day group and 4 out of 9 patients in the 400 mg/day group showed complete regression based on biopsy at 12 weeks. The relative risk (RR) for complete regression was 0.50 for the 200 mg/day group and 0.55 for the 400 mg/day group, indicating a protective effect of I-3-C.	https://www.ncbi.nlm.nih.gov/pubmed/10926790
	The study aimed to identify the minimum effective dose of diindolylmethane (DIM) to prevent the progression from cervical dysplasia to carcinoma in situ caused by human papilloma virus (HPV) in K14-HPV16 mice. Mice were given five doses of DIM (0–2,500 ppm) in their diet. Results showed that 62% of mice receiving 1,000 ppm DIM remained dysplasia-free after 20 weeks, compared to 16% with no DIM and 18% with 500 ppm. Importantly, 1,000 ppm of 3,3'-DIM completely suppressed cervical cancer development	https://aacrjournals.org/cancerpreventionresearch/article/4/6/890/49872/Results-from-a-Dose-Response-Study-Using-3-3
	In mice prone to cervical-vaginal cancer induced by chronic 17β-estradiol exposure, the phytochemical indole-3-carbinol (I3C), administered at physiological doses, demonstrated preventive effects.	https://aacrjournals.org/cancerres/article/59/16/3991/505373/Indole-3-Carbinol-Prevents-Cervical-Cancer-in

	A clinical study investigated the efficacy of Indole-3-Carbinol (I3C) in treating recurrent respiratory papillomatosis (RRP). Among 33 patients receiving I3C after surgical removal, 33% experienced remission, 30% showed reduced papillomatous growth requiring less surgery, and 36% had no clinical response. No patients experienced worsening of RRP, and there were no I3C-related side effects	https://www.sciencedirect.com/science/article/abs/pii/S0892199703001620
	Sulforaphane suppresses EZH2 expression in skin cancer cells through a proteasome-dependent mechanism. EZH2 is enhanced by HPV E7 oncoprotein and acts to promote proliferation and differentiation into a malignan transformation induced by the HPV. EZH2 can be controlled by certain therapeutics designed to promote differentiation into a benign state and prevent recurrent disease by inhitbiting incorporation of HPV into the genome.	https://www.ncbi.nlm.nih.gov/pubmed/28818106
Vitamin B9 (Folate)	A folate deficiency was associated with an increased risk of squamous cell carcinoma of the cervix and cervical intraepithelial neoplasia in subjects who were HPV 16 positive.	https://www.ncbi.nlm.nih.gov/pubmed/25422218
	Low levels of serum folate may increase the risk of cervical intraepithelial neoplasia progression. There may also be a relationship between low serum folate and high-risk HPV infection in promoting CIN development.	https://www.ncbi.nlm.nih.gov/pubmed/27026426
	This meta-analysis comprised 6 case-control studies	https://
	Serum folate is inversely associated with risk of higher-	https://academic.oup.com/
	724 women participating in a cervical cancer screening in	https://
	HPV 16 infection, FHIT methylation, and folate deficiency	https://
	Forty patients with persistent HPV infections and cervical	https://www.mdpi.com/
	Significantly positive associations were seen in 143	https://
	A randomized, double-blind, placebo-controlled trial involved 58 women aged 18 to 55 years assigned to receive either 5 mg/day of folate supplements or a placebo for 6 months. Regression of CIN1: A higher percentage of women in the folate group experienced regression of CIN1 (83.3%) compared to the placebo group (52.0%).	https://pubmed.ncbi.nlm.nih.gov/26853484/

Camelia sinensis	This study examined the impact of green tea polyphenols on cervical lesions in 51 patients and compared them to a control group of 39 untreated patients. Various treatment methods, including vaginal and oral approaches, led to a 69% response rate among treated patients, whereas the untreated control group showed only a 10% response rate	https://www.ncbi.nlm.nih.gov/pubmed/14512803
	Epigallocatechin gallate and polyphenols E showed inhibition of immortalized cervical epithelial and cancer cell growth in vitro. Apoptosis induction and cell cycle changes through p53 and p21 were seen in a dose-dependent matter. HPV-E7 was also decreased by these green tea compounds.	https://www.ncbi.nlm.nih.gov/pubmed/20686382
	Clinical intervention trials, such as those using Polyphenon®E (PSV), a standardized GTC preparation approved for genital warts treatment, have demonstrated efficacy in anogenital warts and potentially other HPV-related conditions. (−)-Epigallocatechin gallate (EGCG), a major component of PSV, likely underlies its mechanism of action, involving apoptosis induction and inflammation reduction.	https://www.mdpi.com/1420-3049/25/11/2588
	Forty patients with persistent HPV infections and cervical lesions were divided into two groups. The treated group received a combination of 200 mg epigallocatechin gallate (EGCG), 400 µg folic acid (FA), 1 mg vitamin B12, and 50 mg hyaluronic acid (HA) for 12 weeks, while the control group received no treatment. Results showed that 17 out of 20 women in the treatment group achieved full viral clearance with no cytological or histological evidence of lesions.	https://www.mdpi.com/2077-0383/12/6/2171
	TriCurin, a blend of curcumin, resveratrol, and epicatechin gallate, exhibits potent anti-tumor effects in HPV-positive head and neck squamous cell carcinoma (HNSCC). The study demonstrates TriCurin's ability to inhibit cell viability, clonogenic survival, and tumorsphere formation, induce apoptosis, and modulate key molecular markers. In a pre-clinical animal model, TriCurin significantly inhibits tumor growth by 85%, showcasing its potential as a promising therapeutic agent for managing HPV-positive HNSCC.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5601119/

	The study investigated the effects of combining epigallocatechin gallate, folic acid, vitamin B12, and hyaluronic acid on HPV-positive cervical cancer cells (HeLa)(17). The combination induced a significant increase in apoptosis and p53 gene expression, while decreasing E6/E7 gene expression, a marker of HPV infection	https://pubmed.ncbi.nlm.nih.gov/37318498/#:~:text=Conclusions%3A%20This%20study%20provides%20for,HPV%2Dinfected%20cervical%20HeLa%20cells.
	IEGCG demonstrated inhibition of growth in a time- and concentration-dependent manner in HPV16 and HPV18 positive cells. Additionally, EGCG induced cell cycle arrest and apoptosis. The study suggests that EGCG may have potential applications in the prevention and treatment of cervical cancer by regulating key genes involved in the disease.	https://www.ncbi.nlm.nih.gov/pubmed/19784588
	The study aimed to investigate the inhibitory effects of epigallocatechin-3-gallate (EGCG) on cervical carcinoma cell lines infected with different high-risk human papillomavirus (HPV) subtypes and its impact on microRNA (miR) expression. EGCG significantly inhibited HeLa cell growth in a dose- and time-dependent manner, with an IC50 of 90.74 and 72.74 μg/ml at 24 and 48 h, respectively. The study identified significant changes in miR expression in response to EGCG treatment	https://www.spandidos-publications.com/etm/17/3/1742
	EGCG has shown in vitro abilities in anti-proliferation, anti-metastasis, and proapoptosis of cervical cancer cells in inhibiting cervical cancer. Human epidemiological and clinical data is limited.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6225117/
	EGCG prevents the carcinogenesis of cervical cancer, inducing apoptosis and inhibiting telomerase activity.	https://www.ncbi.nlm.nih.gov/pubmed/14751158
	High social and economical class subjects with diets rich in carotenoids and vitamin C, low smoking and alcohol consumption, as well as predominant monogamy and regular use of condoms were associated with the negative HPV results in all samples.	https://www.ncbi.nlm.nih.gov/pubmed/20339693
	There is a U shaped association between serum vitamin C and HPV infection in American women: a cross-sectional study with a total of 2174 women, 18–59 years of age. When vitamin C levels were sufficient, a negative correlation with HPV infection was observed (OR 0.7, 95% CI: 0.52–0.94).	https://link.springer.com/article/10.1186/s12905-022-01993-7

Vitamin C	The meta-analysis aimed to evaluate the association between vitamin C intake and cervical neoplasia (CN) risk. Twelve studies, including one prospective cohort study and 11 case-control studies, were analyzed, revealing a significant overall association between vitamin C intake and reduced CN risk. Subgroup analyses by vitamin C dose showed consistent risk reduction, and a dose-dependent relationship was observed, suggesting an inverse association between vitamin C intake and CN risk.	https://www.tandfonline.com/doi/abs/10.1080/01635581.2016.1115101
	This study investigated the relationship between antioxidant vitamin intakes and cervical cancer risk in Korea. It found that lower intakes of vitamins A, β-carotene, and C were associated with higher cervical cancer risks	https://www.tandfonline.com/doi/abs/10.1080/01635580903305326
	The study investigated the impact of vitamin C on cervical cancer cells infected with HPV. Vitamin C was found to downregulate HPV transcription, stabilize the P53 protein, and modulate apoptotic markers, enhancing sensitivity to chemotherapy drugs like cisplatin and etoposide.	https://www.sciencedirect.com/science/article/abs/pii/S0006291X01945930
	There is a possibility of using antioxidant supplementation as prophylactic agents for prevention and treatment of cervical cancer in a population of study subjects from India. Vitamin E and C levels in plasma were significantly lower in cervical cancer patients, genotyping showing high positive rates for HPV-16 and 18.	https://www.ncbi.nlm.nih.gov/pubmed/22320976
Astragalus membranaceus	In an in vitro study, an astragalus injection into cervical immortalized epithelial cells showed an inhibiting effect on their growth, regulating immune cell contents, and arresting cell cycles and related protein expression. Astragalus can reduce cell viability in a dose-dependent matter.	https://www.ingentaconnect.com/content/doaj/10071237/2016/00000022/00000004/art00005/supp-data;jsessionid=1w7jgv1h9ebe6.x-ic-live-03
	Researchers conducted a study to investigate the effectiveness of combining Astragalus membranaceus (AM), a traditional Chinese herbal medicine, with recombinant human interferon alpha 2b (IFN) against herpes simplex virus. The study utilized AM in suppository and ointment forms, along with IFN produced with high purity. Results demonstrated that the combination of AM and IFN in suppository and ointment forms exhibited significantly higher anti-herpes simplex virus activity compared to IFN alone.	https://europepmc.org/article/med/12526333

	The study explored how astragalus polysaccharide (APS) enhances the sensitivity of cervical cancer (CC) HeLa cells to carboplatin (CBP) by regulating the PI3K/Akt pathway. APS + CBP treatment significantly inhibited proliferation, increased apoptosis, and induced G2/M phase cell cycle arrest.	https://www.ejgo.net/articles/10.22514/ejgo.2023.093
	Astragalus membranaceus was shown to be synergic to interferon therapy which has a significant effect on HPV-16 detection.	https://www.ncbi.nlm.nih.gov/pubmed/2173655
Selenium	In a randomized, double-blind, placebo-controlled trial involving 58 women with CIN1, daily supplementation of 200 µg Se yeast led to a higher percentage of CIN1 regression (88% vs. 56% in placebo).	https://pubmed.ncbi.nlm.nih.gov/26439877/
	The study included 40 patients and 40 controls, finding that the mean serum selenium level in the genital warts group was lower than in the control group (83.92±35.43 vs. 93.62±26.29 ng/ml, respectively).	https://jmums.mazums.ac.ir/article-1-20223-en.html
	While no significant difference was observed in mean selenium values between cases with CIN and controls, subgroup analysis revealed a significant reduction in selenium levels with increasing severity of CIN, particularly in CIN III lesions, suggesting a potential link between reduced serum selenium, increased oxidative stress, and the development of high-grade CIN.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6857890/
	A meta-analysis of 12 studies investigated the relationship between serum selenium levels and cervical cancer, revealing significantly lower selenium levels in cervical cancer cases compared to controls and higher selenium levels after treatment. The findings suggest that higher serum selenium levels may be associated with a protective effect against cervical cancer.	https://link.springer.com/article/10.1007/s12011-017-0982-6
	This study explored the protective effects of antioxidant selenomethionine (SeMet) against HPV-18-induced changes in embryonic cells. HPV-18 exposure reduced trophoblast nuclei size and viability, but supplementation with SeMet prevented these effects and lowered apoptosis.	https://www.hindawi.com/journals/ijrmed/2015/562567/
	Selenium dioxide (SeO2) demonstrated anti-tumor properties in high-risk HPV subtypes of cervical carcinoma cell lines (HeLa and Caski). SeO2 induced morphological changes, inhibited cell proliferation, and increased apoptosis in a dose-dependent manner with higher sensitivity observed in the HPV16+ cell line (Caski) compared to HPV18+ (HeLa).	http://journal11.magtechjournal.com/Jwk_jcyxylc/EN/abstract/abstract12396.shtml

	This study investigated selenium's anticancer effects on TC-1 cells and a mouse model. Selenium inhibited cell growth, induced apoptosis, and arrested the cell cycle. It also regulated genes related to important pathways. In a mouse model, selenium effectively suppressed tumor growth, suggesting its potential for inducing anti-cancer effects.	https://www.jcpjournal.org/journal/view.html?pn=search&uid=249&vmd=Full
	Low serum concentrations of selenium and nickel, as well as high serum concentrations of arsenic may be related to HPV infection and CIN2+ prevalence in rural China.	https://www.ncbi.nlm.nih.gov/pubmed/30257641
Ganoderma lucidum	All active compounds found in ganoderma lucidum reduced cell growth in human cervical cancer cells.	https://www.ncbi.nlm.nih.gov/pubmed/26292672
	Cytotoxic activity of extracted compounds from ganoderma lucidum was remarkable against human cervical cancer cell lines.	https://www.ncbi.nlm.nih.gov/pubmed/26899240
	Among 472 individuals with oral swabs for gingivitis, 61 tested positive for HPV16 or HPV18. Twenty patients were treated with Laetiporus sulphureus (group 1), while 41 received a combination of Trametes versicolor and Ganoderma lucidum (group 2) for 2 months. After the treatment period, group 2 showed a significant clearance rate of 88% (compared to 5% in group 1, $p < 0.001$).	https://pubmed.ncbi.nlm.nih.gov/25271984/
	Ganoderma lucidum polysaccharide (GLP) at 200 μg/mL for 48 hours exhibited anti-cervical cancer effects by reducing invasion, migration, and promoting apoptosis(37). GLP altered apoptosis-related protein expression, modulated epithelial-mesenchymal markers, and inhibited JAK/STAT5 pathways, suggesting its potential therapeutic role	https://karger.com/pha/article-abstract/105/7-8/461/267808/Ganoderma-Lucidum-Polysaccharide-an-Extract-from?redirectedFrom=fulltext
	Aqueous extracts of ganoderma lucidum produced inhibition of proliferation of HPV transformed cells by inducing apoptosis and cell cycle arrest in transformed cervical cells.	https://www.ncbi.nlm.nih.gov/pubmed/24941039
	The a-tocopherol succinate isomer of vitmain E showed reduction in immunosuppression by myeloid derived suppresor cells, as well as anti-tumour effects of high potency against HPV-16 using the transfer of antigen-specific CD8+ T cells through necrosis induction of TC-1	https://www.ncbi.nlm.nih.gov/pubmed/25072795

Vitamin E	There is a possibility of using antioxidant supplementation as prophylactic agents for prevention and treatment of cervical cancer in a population of study subjects from India. Vitamin E and C levels in plasma were significantly lower in cervical cancer patients, genotyping showing high positive rates for HPV-16 and 18.	https://www.ncbi.nlm.nih.gov/pubmed/22320976
	Significantly positive associations were seen in 143 subjects with HPV-positive status between vitamin A, vitamin E, iron, β-carotene, and folate. Diet may be a factor in improved prognosis for those with HPV-positive HNSCC.	https://www.ncbi.nlm.nih.gov/pubmed/21667401
	The analysis incorporated 15 case-control studies with a total of 3741 cases and 6328 controls. The findings indicated that higher vitamin E intake was associated with a reduced risk of cervical neoplasia	https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0183395
	The study, using data from the National Health and Nutrition Examination Survey (2013-2016), investigated the association between dietary vitamin E intake and genital and oral HPV infection in 5809 participants aged 18–59 years. Results revealed an inverse linear relationship between vitamin E consumption and overall high- and low-risk HPV infections, suggesting a potential protective effect	https://www.mdpi.com/2072-6643/15/17/3825
	Increasing concentrations of serum lycopene were negatively associated with CIN1, CIN3, and cervical cancer. Increasing concentrations of serum α- and γ-tocopherols, as well as higher dietary intakes of dark green and deep yellow vegetables and fruit was associated with a nearly 50% decreased relative risk of CIN3.	https://www.ncbi.nlm.nih.gov/pubmed/19642096
Zinc Sulfate	This meta-analysis investigated the relationship between zinc deficiency and cervical dysplasia. The study suggested that zinc deficiency could be associated with an increased risk of cervical dysplasia and highlighted the importance of zinc in cervical health.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6300959/
	The study investigated the therapeutic effects of a zinc-citrate compound (CIZAR®) in women with high-risk human papillomavirus (HR-HPV) infection. Women treated with twice-weekly self-administered intra-vaginal infusion of 0.5 mM zinc citrate solution (CIZAR®) for 12 weeks showed a significant clearance rate of HR-HPV (64.47%) compared to spontaneous clearance in the control group (15.25%).	https://www.sciencedirect.com/science/article/abs/pii/S0090825811003234

Zinc Sulfate	80 zinc-sufficient women aged 21 to 55 with positive HPV DNA tests and abnormal cervical cytology (ASCUS or LISL) were randomly divided into a case group (n=40) and a control group (n=40). Oral Zinc Sulfate treatment for 3 months was found to reduce the risk of persistent HPV infection and progression of cervical lesions (OR = 0.130; 95% CI 0.04-0.381; p < 0.001).	https://pubmed.ncbi.nlm.nih.gov/35485687/
	Zinc tetra-ascorbo-camphorate (C14), demonstrated potent in vitro anti-human papillomavirus (HPV) activity, particularly in inhibiting the adsorption of HPV-16-pseudovirus (PsVs) on COS-7 cells. The inhibitory concentration (IC50) of C14 ranged between 2.9 and 8.3 µM, with therapeutic indexes ranging from >410 to >3,300	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8203719/