



Current nutritional considerations for prevention of cervical cancer

Benjamin A. Cox, OMSIV, William T. Crow, DO, Lyn Johnson, DO

From LECOM-Bradenton, College of Medicine, Bradenton, FL.

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The purpose of this research (1983-2010) was to examine the nutritional influences on the development of cervical neoplasia and thereby formulate a strategy for prevention. Articles retrieved from Ovid: Medline and Alt HealthWatch Databases were reviewed. The major topics of review include the role of micronutrients found in foods, herbs, and dietary supplements and their effects on cervical cancer. Results show that a significant body of research suggests that a diet rich in fruits and vegetables may protect against cervical cancer. In addition, protective effects have specifically been observed for dietary and plasma nutrients including but not limited to folate, B₁₂, vitamin C, vitamin A, vitamin E (tocopherols), lycopene, and fiber. However, many women in the United States are not currently meeting the USDA recommendations for intake of some of these nutrients. Physician may suggest to patients at risk for cervical cancer that a diet rich in fruits and vegetables may reduce their risk of disease. In addition, for patients who find such a diet challenging, physicians may recommend dietary supplementation to ensure patients' nutritional needs are being met. Additional research into the role of herbs in the prevention of cervical cancer is warranted.

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Epidemiology of cervical cancer and significance of prevention

As the second most common female tumor worldwide, cervical cancer and its prevention continue to be of concern to the primary care physician. Annual rates have declined by more than 75% in the past 50 years since the widespread introduction of regular cervical cytology screening. In 1993, the World Bank estimated the cost of prevention versus the cost of treatment of cervical cancer and determined that the cost of treating invasive cervical cancer was \$2600 per year compared with \$100 per year to screen eligible women every 5 years.¹ The majority of these cases however continue to occur in medically underserved areas.² It has long been postulated that the rational use of cytological screening

services is the key to reducing the rates of invasive cervical cancer.³

Etiology of cervical cancer

Cervical cancer begins as precursor lesions of the cervix, which have the ability to progress to more severe stages of cervical intraepithelial neoplasia (CIN) or to spontaneously revert back to normal tissue.⁴ It has yet to be fully determined why some preinvasive lesions regress, whereas others remain dormant or progress to even more invasive lesions. Prospective studies have shown that persistent human papillomavirus (HPV) infection significantly increased the risk of developing progressive CIN compared with women who were only transiently infected.⁵ Additional risk factors include smoking, multiple sexual partners, and genetic predisposition. Although it is not known for certain what stages

Corresponding author: Benjamin A. Cox, OMSIV, College of Medicine, OMSIV, c/o 2012, Bradenton, FL 34211.

E-mail address: Benjamin.cox@med.lecom.edu.

Table 1 USDA guidelines for recommended daily intake and upper limit for females >19 years old^{19,21}

Nutrient	RDI	UL	Significant food source
Folate	400 μ g/d	1000 μ g/d	Deep green leaves, spinach, mustard greens, beans, oranges
B ₁₂	2.4 μ g/d	Not Determined	Meat, eggs, milk
Vitamin C	75 mg/d	2000 mg/d	Peppers, citrus, broccoli, kiwi, papaya, mango, leafy greens
Vitamin A	700 μ g/d	3000 μ g/d	Carrots, pumpkin, squash, kale, sweet potato
Vitamin E (i.e., tocopherol)	15 mg/d	1000 mg/d	Nuts, seeds, avocado, turnip greens, tomato
Fiber	31 g/d	Not determined	Beans, mixed vegetables, berries, apples, pears

RDI = recommended daily intake; UL = upper limit.

nutritional factors have an impact, it is believed that nutritional status is a co-factor in this progression.⁶

Materials and methods

The databases searched were Ovid Medline and Alt Health-Watch. The search headers were: cervical cancer, cervical neoplasia, nutrition, vitamins, herbs, and folate. The articles obtained were cross-referenced and studies including multiple search headers were reviewed (1983-2010).

Results

Diet and lifestyle

Although oncogenic HPV (primarily subtypes 16 and 18) infection is the main etiologic factor for cervical neoplasia, infection alone is insufficient to result in disease.⁷ This is supported by the observation of the relatively high prevalence of HPV infection compared with the relatively low incidence of CIN and cervical cancer. Nutritional co-factors may be necessary for the progression of neoplasia from virally infected tissue. A significant body of research suggests that a diet rich in fruits and vegetables may protect against various cancers.^{3,4,8-14} In addition, protective effects have specifically been observed for dietary and plasma nutrients including but not limited to folate, B₁₂, vitamin C, vitamin A, vitamin E (tocopherols), and fiber.^{9-13,15-20} High-quality food sources of these nutrients and their Recommended Daily Intake (RDI) are found in [Table 1](#).

In one study, higher levels of vegetable consumption was associated with a 54% decreased risk of HPV persistence. In addition, women with the highest levels of cis-lycopene had a 56% reduction in HPV persistence compared with women with the lowest levels. This suggests that increased vegetable consumption, particularly vegetables rich in cis-lycopene, may be protective against HPV.⁷ Results of a hospital-based case-control study of cervical cancer found that a higher intake of dietary fiber, vitamin C, vitamin E, vitamin A, alpha-carotene, beta-carotene, folate, lutein, and lycopene were related to a significantly decreased odds ratio of

cervical cancer. A diet high in these nutrients may play an important role in the reduction of cervical cancer risk.¹¹ Increasing levels of alpha-carotene, beta-cryptoxanthin, and lutein/zeaxanthin were associated with decreasing risk of CIN II/III.

When the role of alcoholic drinks was examined, there was a positive dose-responsive association between total alcohol intake and high-grade squamous intraepithelial lesions, indicating that excessive alcohol consumption may be related to the development of cervical cancer.¹³ In addition, a profound risk reduction of cervical cancer by 44% has been observed in women who exercise more than three to four times per week.¹⁹

Folate

Folate deficiency (erythrocyte levels <140 ng/mL) may affect up to 10% of the United States population and approximately 50% of low-income and African-American women. These are the same women who are at the greatest risk for cervical cancer.²² Incidence and mortality rates are nearly twice as great among African American women compared with white women in the United States.²³ In addition, it has been estimated by national surveys that 85% of females aged 14 to 18 years consume less than the recommended 400 μ g/day of folate.²⁴

Folate has received much attention because epidemiologic studies have supported its protective role and there are plausible explanatory mechanisms about how this occurs.⁸ In 1998, the FDA mandated the fortification of grain products with folate to reduce the risk of neural tube defects. As a result, some subgroups of the population have had sustained levels exceeding the body's physiologic need. Observation of these groups produced no credible evidence of any adverse health effects. Interestingly, these studies have found that higher folate levels are associated with a significantly lower risk of CIN, especially when vitamin B₁₂ levels are sufficient. Women with supraphysiological plasma folate and sufficient B₁₂ levels had 70% reduction of CIN II+ compared with those with low folate and insufficient B₁₂ levels.²⁵

It is believed that folate levels modulate HPV persistence and thereby influence cancer risk.⁸ It was found that women with HPV-16 seropositivity had a five-fold greater risk of

having cervical dysplasia if they also had diminished red blood cell folate levels. These studies suggest that the effect of diminished folate status on carcinogenesis does not require frank folate deficiency similar to levels that would result in anemia. Only modest diminution in folate levels is all that is necessary to cause such an effect.¹⁶ Studies indicate that less than adequate levels of folate in the diet increase the risk of cervical cancer. This has been found to be particularly true in individuals who consume alcohol on a regular basis.⁴ Oral contraceptive use, a well-known independent risk factor for cervical cancer, has been associated with compromised folate status.⁶ Studies have found that folic acid supplementation can improve CIN I and II in women who take oral contraceptives.¹⁷

Antioxidants

Several studies of nutrient levels and cervical cancer risk have demonstrated a significant inverse relationship among dietary consumption of vitamin C, vitamin E, beta-carotene, dark green and yellow vegetables, the risk for CIN, and cervical cancer.^{10,18,19} Antioxidant activity has been shown to reduce HPV transcription in the cervical cell line HeLa, an immortal human cell line used in laboratory research.^{8,18}

A study reviewing the specific role of antioxidant vitamins in cervical cancer found that both vitamin C and vitamin E reduce the risk of cervical cancer.¹⁰ Mean plasma levels of carotenoids and alpha-tocopherols have been found to be significantly lower in women with CIN and cervical cancer. This supports the potential role of antioxidant deficiency in the pathogenesis of CIN and carcinoma of the cervix.¹⁴ The carotenoid lycopene may also play a protective role in the early stages of carcinogenesis.²³ Levels of the antioxidant coenzyme Q10 (ubiquinone) have also been inversely correlated to the incidence of CIN and cervical carcinoma.²⁶ Smoking, an independent risk factor for cervical cancer, has been associated with lower vitamin C and carotenoid status including beta-carotene.^{6,14}

Retinoids

It has been known for several decades that vitamin A can suppress the behavior of malignant cells, prevent the activity of tumor promoters, and prevent the onset of cancer.²⁷ It is believed that retinoids control differentiation and apoptosis of cervical epithelial cells, and therefore low levels of retinoids could increase the risk of oncogenic progression.^{28,29} Laboratory studies suggest that by inhibiting the differentiation of HPV immortalized cervical cell lines, retinoids may reduce the extent of viral oncogene transcription and thus slow the neoplastic process.³⁰

In clinical trials, topical application of all-trans-retinoic acid (tretinoin) has been shown to enhance the regression of cervical intraepithelial neoplasia. In cell culture studies, at physiologic concentrations, all-trans-retinoic acid has been found to inhibit the proliferation of cells harboring HPV.²⁰

Similarly, in a randomized phase III trial, topical beta-trans-retinoic acid was found to be effective in reversing moderate CIN. Complete histological regression was seen in 43% of the treatment group compared with 27% in the placebo group.¹⁷ Another study determined that an increased intake of foods high in vitamin A, particularly retinol, may reduce the risk of in situ cervical cancer, and at the highest levels may inhibit progression to invasion.⁹

Phytotherapy

Phytotherapy is the use of natural plant extracts in the treatment of disease. A recent meta-analysis of adjuvant phytotherapy in the treatment of cervical cancer concluded that it may improve the efficacy and safety of conventional therapy in clinical treatments.³¹ Of the 10 most frequently used herbs, there were five found to improve survival rate and tumor remission rate. These were *Poria*, *Radix glycyrrhizae*, *Radix angelicae sinensis*, *Rhizoma atractylodis macrocephalae*, and *Radix ginseng*.³¹ Experiments have found that these herbs may inhibit the proliferation of tumor cells by induction of apoptosis, and enhancing immune function via mediation of cytokines.³¹ Extracts from the coumarin-containing plant *Micromelum minutum* have been found to be cytotoxic to cervical cancer cell lines.³²

Conclusions

Despite the observed decline in incidence, women continue to seek information concerning the relationships between cancer risk and specific foods and nutrients, such as antioxidants, supplements, phytochemicals, and omega-3 fatty acids. Participants in a recent study most often turned to magazines, friends, and family members when they sought this information.³³ These findings present an opportunity for primary care physicians to enhance their leadership role in creating and disseminating evidence-based information to meet the expressed needs of women who may be at increased risk for CIN. Physicians may suggest to patients at risk for cervical cancer that a diet rich in fruits and vegetables, particularly leafy greens such as spinach, kale, turnip greens, and collard greens, may reduce their risk of disease. In addition, for patients who find such a diet challenging, physicians should recommend dietary supplementation to ensure patients' nutritional needs are being met. The possible epidemiological effects are prospectively favorable for both current and future generations of women as this research is being incorporated into clinical applications. Future studies of the effects of diet and nutrient supplementation on cervical cancer are most certainly warranted.

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