

## RESEARCH ARTICLE

# Case-Control Study of Diet in Patients with Cervical Cancer or Precancerosis in Wufeng, a High Incidence Region in China

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### Abstract

**Purpose:** To investigate the diet of patients with cervical cancer and precancerosis in the Wufeng area, a high-incidence region in China. **Methods:** In the case group, 104 patients diagnosed with cervical cancer or cervical intraepithelial neoplasias (CINII/III) were recruited from the Wufeng area. Nine hundred thirty-six healthy women were selected from the same area as the matched controls. A questionnaire, which included questions about general lifestyle conditions, smoking and alcohol status, source of drinking water, green tea intake, and diet in the past year, was presented to all participants. **Results:** Green tea intake ( $P=0.022$ ,  $OR=0.551$ , 95%  $CI=0.330-0.919$ ) and vegetable intake ( $P=0.035$ ,  $OR=0.896$ , 95%  $CI=0.809-0.993$ ) were identified as protective factors against cervical cancer or CINII/III. There was no indication of any associations of other lifestyle factors (smoking status, alcohol status, source of drinking water) or diet (intake of fruit, meat/egg/milk, soybean food, onion/garlic, staple food and pickled food) with cervical cancer. **Conclusions:** The results suggest that eating more fresh vegetables and drinking more green tea may help to reduce the risk of cervical cancer or CINII/III in people of the Wufeng area.

**Keywords:** Diet - cervical cancer - high-incidence region - green tea

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### Introduction

Cervical cancer is the second most common malignant tumour in the world in women between the ages of 15 and 44 years old; almost 80% of all cases occur in less developed countries (Parkin, 2001). Every year, approximately 530,000 new cases are detected worldwide; 585,278 incident cases and 327,899 deaths attributable to cervical cancer are predicted for 2010 (Ferlay, 2010). China has one of the highest incidence rates of cervical cancer in the world, with 135,000 new cases being detected every year (Andersson et al., 2001).

The Wufeng area is located in the south-western part of the Hubei province of central China, a mountainous area. Due to the location, the local economy is undeveloped and the rate of migration is low. The population of the Wufeng area is approximately 200 thousand, and over 80% are of the Tu Minority. Gynecologic diseases and breast diseases are the major local public health problems (Zhang et al., 2012). The Wufeng area has one of the highest incidences of cervical cancer in China. As recently as the 1970s, it

had the highest incidence in the country.

Human papilloma virus (HPV) infection is a necessary cause of invasive cervical cancer worldwide (Walboomers et al., 1999). However, only a few HPV-infected women are unable to clear the virus and develop persistent HPV infection. The incidence of cervical cancer is related to many risk factors. In addition to HPV infection, long-term use of oral contraceptives, high parity, smoking and diet are considered to be cofactors (Moreno et al., 2002; Garcia-Closas et al., 2005; Tomita et al., 2010; MacLaughlan et al., 2011). The study of the relationship between nutritional factors and cervical cancer is complicated because of its multifactorial aetiology; many of the identified risk factors may influence dietary intake as well as nutrient status (Potischman et al., 1996). It was found that a diet rich in plant-based nutrients may play an important role in reducing the risk of cervical cancer (Ghosh et al., 2008), and thiamine, riboflavin, folate, and vitamin B12 may play a protective role against cervical cancer (Hernandez et al., 2003). A South Korean matched case-control study also supports the hypothesis

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that increasing the intake of antioxidant vitamins such as vitamins A, C, and E and beta-carotene can decrease the risk of cervical cancer (Kim et al., 2010). Among low-income Brazilian women, a healthy and balanced diet, which can provide high serum levels of antioxidants, may reduce the risk of cervical neoplasia (Hernandez et al., 2003).

In the last 10 years, the relationship between green tea and different cancers has been an area of interest for many investigators. Green tea has been shown to inhibit the occurrence of cancers (Zou et al., 2002; Mao et al., 2011; Khan et al., 2012; Nguyen et al., 2012) such as gastric, breast, and prostate. A recent study implicates a potential mechanism of action for green tea compounds in the suppression of HPV-related cervical cells (Zou C et al., 2010). It has also been shown that catechin hydrate has a potential benefit for cervical cancer prevention (Al-Hazzani et al., 2011). However, observational data are needed to evaluate whether green tea reduces the risk of cervical cancers.

Many studies have suggested the risk of pickled food to many malignant diseases, such as oesophageal, gastric, colorectal and bladder cancers (Radosavljevic et al., 2005; Islami et al., 2009; Sun et al., 2010; Squires et al., 2010). However, studies of the relationship between cervical cancer and pickled food are limited, and the relationship is not clear. To investigate the relationship between dietary factors and cervical cancer in the Wufeng area, we performed an analysis of data from a 1:9 matched case-control study of cervical carcinoma in women from the Wufeng area.

## Materials and Methods

### Participants

A matched case-control comparison (1:9) was designed in this study. Manual fitting procedures were used. Patients were diagnosed with cervical intraepithelial neoplasias (CINII and CINIII) or cervical cancer between 2006 and 2008. The cases came from three towns in Wufeng, Hubei Province (Caihua Town, Fujiayan Town and Changleping Town). Each case was matched to 9 healthy women according to age, age of first sexual intercourse, parity and contraceptives (matching factors were divided into several groups, as shown in Table 1). Nine controls were selected at random from the eligible matched participants in the screening. This study included only married women (common-law partners) without a history of cervical cancer, cervical intraepithelial neoplasias or cervical excision. This study protocol was reviewed by the Ethics Committee of Tongji hospital, Huazhong University of Science and Technology (<http://clinicaltrials.gov>; NCT01267851).

### Lifestyle and Diet Questionnaires

The questionnaires were implemented in person by professionally trained investigators. The contents of the questionnaire included questions about general lifestyle conditions, smoking and alcohol status, source of drinking water, green tea intake, and diet in the past year. A history of green tea intake was defined as drinking more

than 50 g of dry tea monthly for least 2 years. The Food Frequency Questionnaire (FFQ) measured the dietary intake of women in the Wufeng area including vegetables, fresh fruits, meat/egg/milk, soybean foods, onion/garlic, staple foods, and pickled foods. In our study, participants were asked to indicate how frequently food items were consumed (daily, weekly or monthly). Both the diet and lifestyle questionnaires were available in Chinese.

### Statistical Analysis

The questionnaire answers were recorded twice and verified three times. After the logic and outlier verification, the rate of logic and outlier errors were ensured to be less than 0.2%, and the defect rate of the data was less than 5.0% and was filled using the EM Mode. A conditional logistic regression was performed as both as a univariate and multivariate analysis to identify independent variables. Statistical analysis was performed using the SPSS13.0 software package. All P values were derived from two-sided statistical tests, and statistical significance was defined as  $P < 0.05$ .

## Results

### Study Participants

In the case group, 40 of the 102 patients were diagnosed with CINII, 41 patients with CINIII, and 23 patients with cervical cancer. The mean age was  $43.52 \pm 7.45$  years in the case group, while it was  $43.76 \pm 7.20$  years in the control group. The case and control groups were similar with respect to age, parity, age of first intercourse, and contraceptive use, as shown in Table 1.

### Lifestyle Factors

The relationship between lifestyle factors (source of drinking water, smoking status, alcohol status and green tea intake) and cervical cancer or CINII/III was concluded from both univariate and multivariate analysis (Tables 2

**Table 1. Matching Criteria of Cases and Controls\***

	Case group		Control group		P
	n	%	n	%	
Age (years)					1.0
28-30	6	5.8	54	5.8	
31-35	8	7.7	72	7.7	
36-40	17	16.3	153	16.3	
41-45	33	31.7	297	31.7	
46-50	22	21.2	198	21.2	
51-55	11	10.6	99	10.6	
56-61	7	6.7	63	6.7	
Parity					1.0
1	28	26.9	252	26.9	
2	67	64.4	603	64.4	
3-5	9	8.7	81	8.7	
The age of first intercourse (years)					1.0
16-20	44	42.3	396	42.3	
21-29	60	57.7	540	57.7	
Contraceptive use					1.0
Never	98	94.2	882	94.2	
Ever	6	5.8	54	5.8	

\*Descriptive analysis was performed with chi-square tests for categorical variables; P, P value

**Table 2. Adjusted Odds Ratios (ORs) and 95% Confidence Intervals (CIs) for Risk of Cervical Cancer with Smoking status, Alcohol Status, Source of Drinking Water and Green Tea Intake**

	case	control	P	OR	95%CI
Smoking status					
Ever	7	68	0.84	0.92	0.41-2.06
Never	97	868		1.00	
Alcohol status					
Ever	8	51	0.35	1.44	0.67-3.10
Never	96	885		1.00	
Source of drinking water				0.49	
Cellar/pond/shallow well	14	126	0.79	1.10	0.53-2.28
Lake/river	3	10	0.12	3.00	0.75-12.06
Deep well/spring	69	622	0.73	1.10	0.64-1.90
Tap water	18	178		1.00	
Green tea intake					
Yes	79	786	0.04	0.60	0.37-0.98
No	25	150		1.00	

P, P value; OR, odds ratio; CI, confidence interval; P <0.05 is considered significant

**Table 3. Association of Cervical Cancer Risk with Dietary Habit**

In the past year, the frequency of eating food (times/week)	P		
	P	OR	95%CI
Vegetable	0.00	0.91	0.86-0.97
Fruit	0.37	0.95	0.85-1.06
Meat/egg/milk	0.42	0.98	0.93-1.03
Soybean food	0.08	0.95	0.89-1.01
Onion/garlic	0.09	0.96	0.92-1.01
Staple food	0.00	0.94	0.91-0.98
Pickled food	0.06	0.96	0.92-1.00

P, P value; OR, odds ratio; CI, confidence interval; P <0.05 is considered significant

and 4). The results suggested that green tea intake was a protective factor against cervical cancer or CINII/III (P=0.022, OR=0.551, 95% CI: 0.330-0.919). In this study, smoking and drinking history were not directly associated with the incidence of cervical cancer or CINII/III (P≥0.05). Different sources of drinking water (three untreated sources of drinking water: cellar/pond/shallow well, lake/river, or deep well/spring; one treated source of drinking water: tap water) were not significantly associated with cervical cancer or CINII/III (P≥0.05).

#### Dietary Habit

The relationship between dietary habit and cervical cancer or CINII/III was also concluded from both univariate (Table 3) and multivariate analyses (Table 4). The frequency of fresh vegetable intake in the case group was 11 times/week, and in the control group it was 13 times (P=0.002). The frequency of staple food intake in the case group was 18 times, and in the control group it was 20 times (P=0.004). Multivariate analysis suggested that more fresh vegetables may decrease the risk of cervical cancer or CINII/III (P=0.035, OR=0.896, 95% CI: 0.809-0.993). However, intake of fruit, meat/egg/milk, soybean foods, onion/garlic, staple foods or pickled foods was not associated with cervical cancer or CINII/III (P≥0.05).

**Table 4. Adjusted Odds Ratios (ORs) and 95% Confidence Intervals (CIs) for Risk of Cervical Cancer**

	B	P	Adjusted OR	95%CI
Source of drinking water		0.27		
Cellar/pond/shallow well	0.18	0.65	1.20	0.55-2.60
Lake/river	1.46	0.05	4.30	1.00-18.43
Deep well/spring	0.26	0.39	1.30	0.72-2.36
Smoking status	-0.30	0.51	0.74	0.31-1.79
Alcohol status	0.50	0.25	1.64	0.71-3.80
Green tea intake	-0.60	0.02	0.55	0.33-0.92
Vegetable	-0.11	0.04	0.90	0.81-0.99
Fruit	-0.08	0.23	0.93	0.82-1.05
Meat/egg/milk	0.01	0.88	1.01	0.93-1.09
Soybean food	-0.04	0.36	0.96	0.89-1.05
Onion/garlic	0.04	0.39	1.04	0.96-1.12
Staple food	-0.04	0.08	0.96	0.92-1.01
Pickled food	0.01	0.66	1.01	0.95-1.08

P, P value; B, partial regression coefficient; OR, odds ratio; CI, confidence interval; OR adjusted for body mass index (BMI); P <0.05 is considered significant

## Discussion

Although HPV infection is a well-known crucial risk for CIN and cervical cancer, other cofactors also have some effects. Studies have shown that some diet habits may promote high-risk HPV carriers to develop CIN (Hwang et al., 2010). In this study, results indicated that dietary habits might influence the incidence of cervical cancer in women of the Wufeng area.

Green tea is now recognised as the most effective beverage to prevent tumour progression due to the epigallocatechin gallate (EGCG), epicatechin gallate (ECG), epigallocatechin (EGC) and epicatechin (EC) that it contains (Fujiki, 2005). Recently, a study in Japan showed that green tea could be used as a synergist for anti-cancer drugs (Suganuma et al., 2011). Our study also suggested that women drinking green tea have a lower risk of developing cervical cancer. Because green tea is produced in large quantities in the Wufeng area, it can be consumed by the women there as a daily beverage.

A low intake of fresh vegetables and fruit may contribute to persistent infection of HPV (Sedjo et al., 2002). A European study showed that a high intake of fruit helped to reduce the risk of CIN, but consumption of vegetables did not play a significant role in the prevention of cervical cancer (Gonzalez et al., 2011). Our study concluded that a high intake of fresh vegetables, but not fruit, had a protective effect against cervical cancer or CINII/III. The Wufeng area is a less developed area with limited transportation facilities; local residents have enough fruit to eat only during high-yield periods (3-4 months every year), with very little fruit supplied during the rest of the year. Thus, neither the case or control group had adequate consumption of fruit. However, the number of cases examined in this study may be not adequate. No obvious evidence was found to show the effects of fruit against cervical cancer. More quantitative data should be collected for further research to prevent bias.

Pickled food contains nitrites, which can lead to some malignant neoplasms of the digestive system. The effect

of pickled food on cervical cancer is not clear. In the Wufeng area, most people eat a large quantity of pickled food due to the traditional diet and low economic status. However, in our study, the results showed that pickled food intake was not significantly related to cervical cancer or CINII/III. One limitation of our study was small size of the cervical cancer case group. Thus, further multicentre trials with more samples are warranted to confirm these findings.

Our study implies that cervical cancer is the result of multiple genetic and lifestyle factors working together to increase risk. The results suggest that eating more fresh vegetables and drinking more green tea may help to reduce the risk of cervical cancer or CINII/III in the Wufeng area. Popularisation of disease prevention knowledge can make favourable changes.

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