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Original Research

Dietary patterns and risk of cervical cancer: A case-control study

Marziyeh Najafi[1], Zahra Nazari[1], Roya Shamsi[1], Omid Nikpayam[2,3], Alireza Bahrami[1], Azita Hekmatdoost[1], Ehsan Hejazi[1]

[1]*Department of Clinical Nutrition and Dietetics, School of Nutrition Sciences and Food Technology, Shahid Beheshti University of Medical Sciences, Tehran, Iran*

[2]*Students Research Committee, Tabriz University of Medical Sciences, Tabriz, Iran*

[3]*Department of Clinical Nutrition, Faculty of Nutrition and Food Science, Tabriz University of Medical Sciences, Tabriz, Iran*

Summary

Objective: Cervical cancer (CC) is the second most frequent malignancy. Infections with the human papillomavirus have a crucial role in the Pathology of CC. The association of nutrient and dietary pattern with CC have been reported in few studies. This study was conducted to evaluate the relationship between dietary patterns and CC situations in the Iranian population. *Method:* This is a case-control study in which totally 260 controls and 132 patients aged 30-79 were included as control, and case groups. Dietary data were evaluated by 147-items semi-quantitative food frequency questionnaire. Multivariate logistic regression was used to estimate the relationship between dietary patterns and risk of cervical cancer. *Results:* Statistical analysis investigated two dietary patterns (healthy and unhealthy). Two dietary patterns covered 17.76% of total variance of dietary intake. Higher adherence of the unhealthy dietary pattern was associated with increased risk of CC (OR = 2.23, 95% CI = 1.77-4.24); however, there was no association between healthy dietary pattern and CC (OR = 1.91, 95% CI = 0.90-3.20). *Conclusion:* Our results indicate that unhealthy dietary pattern is significantly associated with CC.

Key words: Dietary patterns; Cervical cancer; Case-control; Healthy dietary pattern; Unhealthy dietary pattern.

Introduction

Cervical cancer (CC) is the second most frequent malignancy and the third cause of cancer-related death among women [1]. Although most of the mortalities occur in the under-developing countries, CC is still a major public health in developed countries because approximately 58000 new case-patients are annually diagnosed and 24000 deaths happen yearly in Europe [2]. Infections with the human papillomavirus have a crucial role in the pathology of CC [3]; however, other risk factors were reported in previous studies including sex in adolescence [4], multiple sexual partners [5], pregnancy in adolescence [6] and long-term use of oral contraceptives [7].

Although the association of nutrient and dietary pattern with CC have been reported in few studies, the attention to the effects of food groups and food pattern in the pathology of CC has increased recently. Some dietary factors such as fruits can prevent progression of papillomavirus and change occurrence of the epithelial of cervix, but certain foods provide a situation that papillomavirus cause adverse effects on the host [8]. Also, a study in 2012 demonstrated that green tea and vegetables had beneficial effects against CC [9]. Another study in 2016 indicated that people with high scores for semi-western diet (bread, dairy products, eggs, and soft drinks and relatively higher fat intake ratio) had a higher risk of cervical intraepithelial neoplasia [10].

Most of the studies focus on nutrients or food groups [8-12]; however, people in each meal consume a combination of various foods and nutrients. Furthermore, it is better to evaluate food patterns in the patients for investigating the effects of diet on the CC situation.

Due to the lack of sufficient information about the role of dietary patterns in the CC patients in the world, especially in Iran, this study was conducted to evaluate the relationship between dietary patterns and CC situations in the Iranian population.

Methods

Subjects

This case-control study was conducted from December 2018 to December 2019 in two referral hospitals in Tehran. CC cases were patients who had been diagnosed with endoscopy and pathologic confirmation. CC patients who had been diagnosed three months before the interview, aged 30-79, and who were volunteers included in the study. CC cases were patients that confirmed their disorder and referred to the hospital for therapeutic measures.

Controls were selected randomly from patients aged 30-79 admitted to the same hospitals as cases for diseases unrelated to neoplastic conditions at the same time span. Subjects had no history of any diet related chronic diseases and malignancy.

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Table 1. — *Food groups used in analysis.*

Food groups	Food items
Refined grains	lavash bread, baguette bread, macaroni, rice, others
Unrefined grains	barbari bread, sangak bread, taftoon bread, wholemeal bread, barley, oatmeal, others
Vegetables	All kind of cabbage, spinach, lettuce, cucumber, eggplant, onions, green Beans, peas, stewed vegetable, Pumpkin, Mushrooms, pepper, Turnip, Corn, Garlic, other vegetables, others
Tomato	Tomato, tomato products
Carrot	Carrot, carrot juice
Boiled potato	Boiled potato
French fries	French fries
Fruits	Cantaloupe, watermelon, melon, sloe, apple, apricot, yellow and red plum, cherry, sour cherry, nectarine, peach, pear, fresh fig, date, grape, kiwi, pomegranate, strawberry, banana, persimmon,fresh berry , pineapple, citrus, nuts
Fruit juice	Packed juice
Low fat dairies	Low fat milk, skim milk, others
High fat dairies	High-fat milk, high-fat yogurt, cream cheese, cream, ice cream, others
Red meat and viscera	Beef, mutton, mincemeat, visceral meat
Processed meat	Salami, sausages, hamburger, visceral meat
Poultry	chicken
Fish	Fish, tuna
Egg	Egg
Legumes	Lentils, cotyledons, beans, pea, broad beans, mung beans, soybeans, others
Sweets and desserts	Cookies, sweet, chocolate, Cakes, muffins, honey, jam, sugar cube, sugar, candy, Halva, other
Solid oil	Solid vegetable oil, animal oil, rump
Liquid oil	Any kind of liquid oil except olive oil
Animal butter	Animal butter
Sugar	Sugar, cheese sugar, sugar cube, candy
Olive	Olive, olive oil
Mayonnaise	Mayonnaise sauce
Snacks	Biscuits, chips, puff, others
Nuts	Almonds, peanuts, walnuts, pistachios, hazelnuts, all kinds of seeds, others
Soft drinks	Carbonated drinks
Tea	Black tea
Coffee	Coffee, nescafe

In total 260 controls and 132 patients which matched by weight were included in this study. All participants signed an informed consent. Present study was approved by the Ethics Committee of National Nutrition & Food Technology Research Institute, Shahid Beheshti University of Medical Sciences with the ethic code of IR.SBMU.NFTRI.REC.1399.006.

Assessment of dietary intake and physical activity

Dietary intake of participants during the year before the diagnosis of CC in case group or control group was assessed by face to face interview using a valid and reliable semi-quantitative, 147-item food frequency questionnaire (FFQ) [13]. Participants were questioned about their consumption frequency on a day, week, month, and year for each food item in FFQ, all intakes then were converted to the daily frequency. Eventually, household measures were used to convert the food items to the frequency daily grams. Energy and nutrients values of food were calculated by Nutritionist 4 software. The Iranian food composition table was used for some food items that did not exist in the Nutritionist 4. Alcohol in the Iranian population is forbidden due to religious beliefs, in the present study the consumption of alcohol was not asked and this item was not included in the analysis.

Physical activity of all participants was assessed by a valid and reliable metabolic equivalent of task (MET) questionnaire, which asked about the time of various physical activity during the day [14] then total MET for each person calculated.

Anthropometric measurements

During an interview, a general questionnaire was completed for all patients that were asked about the socio-demographic characteristics, family history of cancer, smoking habits, economic status, physical activity, comorbidity, drug history, and used supplements. Anthropometric indexes, including weight, height were assessed and

Table 2. — *Baseline characteristic of patients.*

Variables	Total patients (n = 392)	Control group (n = 260)	Case group (n = 132)	*p*-value
Age (year), median (IQR)	48 (17)	42 (16)	54 (11)	0.0001 >
Weight (kg), median (IQR)	68 (18)	68 (18)	67 (18)	0.709
Height (cm), median (IQR)	160 (8)	161 (7)	160 (7)	0.0001 >
BMI (kg/m^2), median (IQR)	25.96 (5.99)	26.10 (5.96)	25.96 (5.66)	0.243
Smoking N (%)				
No	382 (97.2%)	257 (98.8%)	124 (93.9%)	
Yes	11 (2.8%)	3 (1.2%)	8 (6.1%)	0.005
Residence N (%)				
Urban	379 (96.5%)	256 (98.5%)	122 (92.5%)	
Rural	14 (3.5%)	4 (1.5%)	10 (7.5%)	0.002
Education level N (%)				
Illiterate	30 (7.7%)	6 (2.4%)	23 (17.4)	
Low education	270 (68.7%)	176 (76.6%)	94 (71.2)	
High education	93 (23.6%)	78 (30%)	15 (11.4)	0.0001 >
Marriage status N (%)				
Married	308 (78.5%)	204 (78.6%)	103 (78%)	
Single	43 (10.9%)	41 (15.7%)	2 (1.5%)	
widow	42 (10.6%)	15 (5.7%)	27 (20.5%)	0.0001 >
History of cancer in first degree relatives N (%)				
No	244 (62.2%)	179 (69.8%)	65 (49.2%)	
yes	148 (37.8%)	81 (31.2%)	67 (50.8%)	0.0001 >
History of cervical cancer in first degree relatives N (%)				
No	383 (97.7%)	260 (100%)	125 (93.2%)	
Yes	9 (2.3%)	0 (0%)	9 (6.1%)	0.0001 >
Common ways of cooking food N (%)				
Fried	53 (13.5%)	31 (11.9%)	22 (16.7%)	
Boiled	81 (20.7%)	49 (18.8%)	32 (24.2%)	
Grilled	2 (0.5%)	1 (0.4%)	1 (0.8%)	
Steamer	7 (1.8%)	5 (1.9%)	2 (1.5%)	
Combination	249 (63.5%)	174 (66.9%)	75 (56.8%)	0.352
OCP usage				
No	236 (60.2%)	150 (57.7%)	86 (65.2%)	
Yes	156 (39.9%)	110 (42.3%)	46 (34.2%)	0.154
IUD usage				
NO	324 (82.7%)	225 (86.5%)	99 (75%)	0.004
Yes	68 (17.3%)	35 (13.5%)	33 (25%)	
Immune system defect				
NO	371 (94.7%)	256 (97.5%)	115 (87.1%)	
Yes	21(5.3%)	4(2.5%)	17 (12.9%)	0.0001 >
HPV infection	361 (92.1%)			
NO	31 (7.9)	260 (100%)	101(76.5%)	
Yes		0 (0%)	31(23.5%)	0.0001 >
First pregnancy age, median (IQR)	20 (5)	21 (6)	19 (4)	0.0001 >

body mass index (BMI) was calculated by the formula weigh (kg)/height^2 (m^2). Weight was measured without shoes, and wearing light clothes using Seca digital scale with a precision of 0.1 kg, and height was assessed barefoot with a meter attached on the wall with precision of 1 cm.

Statistical analysis

All statistical analysis was performed by IBM statistical package software for social science (SPSS), version 21. Data were expressed as mean ± SD and frequency (percentage) respectively, quantitative and qualitative variables. The normality off data were evaluated by Kolmogorov-Smirnov test. To compare qualitative and quantitative vari-

Table 3. — *Factor loading matrix of food group in dietary pattern.*

Food group	Healthy pattern	Unhealthy pattern
Vegetables	0.766	.
Tomato	0.699	.
Fruits	0.548	.
Legumes	0.473	.
Carrot	0.399	.
Olive and olive oil	0.359	.
Snack	.	0.576
High fat dairies	.	0.563
French fries	.	0.445
Mayonnaise	.	0.427
Soft drinks	.	0.425
Sugars	.	0.416
Refined grains	.	0.41
Solid oil	.	0.398
Nuts	.	0.391
Boiled potato	.	0.325
Total variance	9.18%	8.58%

Table 4. — *Odds ratios and 95% confidence intervals for cervical cancer by higher scores on the dietary patterns (median low vs. median high).*

Dietary pattern	OR[1]	95% CI	OR[2]	95% CI
Healthy dietary pattern				
median low	1		1	
median high	1.91	1.33-3.22	1.7	0.90-3.20
p-value for trend	0.01		0.09	
Unhealthy dietary pattern	1		1	
median low	2.95	1.71-5.09	2.23	1.77-4.24
median high	0.001 >		0.01	
p-value for trend				

OR and 95% CI obtained from logistic regression. [1]*adjusted for age.* [2]*adjusted for age, history of cancer in first degree relatives, physical activity, marriage status, smoking, OCP usage, IUD usage, immune system defect, herpes zoster infection, first pregnancy age, number of pregnancies.*

ables between two groups, chi-square test and independent sample *t*-test were used respectively. To determine the dietary patterns, initially items of FFQ questionnaire were categorized into 29 food groups according to the composition and nutrient content, and their constituent ingredients (Table 1). Principal component analysis (PCA) was performed based on 29 food groups. Varimax rotation was used to improve interpolation and minimizing correlation between factors. The Bartlett test of sphericity was used to determine correlation between variables and the Kaiser-Mayer-Olkin test was used to assess the adequacy of sample size. The dietary patterns were selected based on the screen plot (eigenvalue > 1). Post-rotated factor loadings prescribed two dietary patterns and these patterns were labeled according each food group with highest loading on each pattern. Food groups with positive and negative loading in each pattern showed direct and inverse relationship with the pattern respectively. By summing each food group intake, the factor score for each pattern was calculated; then, they were weighted according to factor loading so that every participant received an individual factor score for each identified pattern [15]. Dietary patterns were categorized according to the median of factor scores. Binary Logistic regression was performed to obtain odds ratio (OR) and 95% confidence interval (CI) of CC by higher scores on dietary patterns. The median low score dietary patterns were considered as reference group. Dietary patterns were considered as independent variables, and risk of CC as dependent one. p-values < 0.05 were considered as statistical significant.

Results

The life style and social demographic characteristics of all participants (132 case and 260 control) are shown in Table 2. Statistical analysis showed that all baseline variables were different between cases and controls except weight ($p = 0.709$), BMI ($p = 0.243$), common methods of cooking ($p = 0.352$), and oral contraceptive pill (OCP) ($p = 0.154$). Patients in this study were matched according to their body weight. Stability of factor analysis in present study was approved by Bartlett test of sphericity (< 0.001) and the Kaiser-Mayer-Olkin (0.622). According to factor analysis, two dietary patterns were identified; factor loading matrix of food group in each dietary pattern was expressed in Table 3. Two dietary patterns covered 17.76% of total variance of dietary intake. The features of first dietary pattern was high consumption of vegetables, tomato, fruits, legumes, carrot, olive and olive oil, which are labeled as "Healthy diet". Second dietary pattern was named as "Unhealthy diet" due to higher consumption of snack, high fat dairies, French fries, mayonnaise, soft drinks, sugars, refined grains, solid oil, nuts and, boiled potato. The odds ratio (OR) and 95% confidence interval (CI) for cervical cancer according to median of factor scores for two identified dietary patterns indicated in Table 4.

After adjusting for age, the healthy dietary pattern was inversely associated with risk of CC (OR = 1.91, 95% CI = 1.33-3.22). However, this association was not seen after adjusting for other confounders including: history of cancer in first degree relatives, physical activity, marriage status, smoking, OCP usage, IUD usage, immune system defect, herpes zoster infection, first pregnancy age, number of pregnancies (OR = 1.91, 95% CI = 0.90-3.20).

Higher intake of the unhealthy dietary pattern was associated with increased risk of CC (OR = 2.23, 95% CI = 1.77-4.24).

Discussion

The results of present case-control study indicated that adherence to the unhealthy dietary pattern containing low vegetables, fruits and high simple carbohydrate, fat, energy significantly increase the risk of CC. While there was no significant association between the healthy dietary pattern and risk of CC after adjusting for confounding factors.

This case-control study showed unhealthy dietary pattern containing "snack, high fat dairies, French fries, mayonnaise, soft drinks, sugars, refined grains, solid oil, nuts and, boiled potato" increased the risk of CC. In consistence with this finding, a study in Italy reported that adhering to the western dietary pattern elevated the risk of papillomavirus infection [16]. Also, Seo *et al.*, in a case-control study, showed that following the semi-western diet increases the risk of cervical epithelial neoplasia [10]. It seems that saturated fatty acids (SFA), n-6 polyunsaturated fatty acids (n-6 PUFA) and simple carbohydrate in these diets are responsible for the unfavorable effects. Previous studies showed that SFA, n-6 PUFA and simple carbohydrate contribute in inflammation [17-19]. Although the exact etiology of CC is unrecognized, the role of inflammation in the pathogenesis of CC has been reported [20]. Chronic inflammation is involved in the different procedure of cell, transformation, survival, proliferation, invasion, and metastasis. Also, many inflammatory cytokines increased in the patients with CC such as tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-18 (IL-18) [21]. Besides, unhealthy diet contains low vegetables, fruits and fibers, these food groups are a rich source of various vitamins and polyphenolic compounds, which may contribute in protection against CC. Polyphenols had anti-oxidant characteristics that release oxidative stress and inflammation in the body [22]. Previous studies have reported that oxidative stress had a major role in the pathogenesis of CC. Oxidative stress is recognized by elevation of ROS, which caused DNA mutation, genomic instability and eventually promoted cancer [23]. Polyphenols in the fruits and vegetables had desirable effects on oxidative situations and inflammation via scavenge of ROS [22, 24]. In addition, a clinical trial study showed that enhanced consumption of vegetables and fruit, 8 to 10 servings per day, for one year caused an increase in the level of serum carotenoids, which reduces risk of CC [25].

The findings of this study are suggestive of the fact that high consumption of vegetables and fruits may reduce the risk of CC; although, the association between healthy diet and CC was not significant. Barchitta *et al.* showed that the risk of CC was lower in patients with high score of prudent dietary pattern, containing high fruits and vegetables compared to others patients [16]. Moreover, Herrero *et al.* in a large case-control study indicated that patients who observed highest consumption of fruit and fruit juice were associated with decreased risk of CC [26]. Although findings of another case-control study suggested that frequently consumption of dark green or yellow vegetables and fruit juices was related to a reduced risk of CC [27], a study in South Korea, expressed that there was no relation between green and white vegetables and cervical intraepithelial neoplasia [10].

The strengths of this study are the following: up to our knowledge this is the first study in Iran, which evaluated the dietary pattern in CC patients, using validate questionnaires with the ability to control potential confounders.

This case-control study contains several limitations first: selection bias, we tried to enroll new cases to minimize this error. Second: recall bias, using trained interviewer completing FFQ for all patients diminished this bias.

According to the results of this study, it is concluded that healthy dietary pattern, which is recognized by high consumption of vegetables and fruits declines the risk of CC, whereas unhealthy dietary pattern is associated with CC risk.

Abbreviations

BMI: body mass index; CC: Cervical cancer; CI: confidence interval; FFQ: food frequency questionnaire; IL-1: interleukin-1; IL-6: interleukin-6; IL-8: interleukin-8; IL-18: interleukin-18; MET: metabolic equivalent of task; n-6 PUFA: n-6 polyunsaturated fatty acids; OCP: oral contraceptive pill; OR: odds ratio; PCA: principal component analysis; SFA: saturated fatty acids; TNF-α: tumor necrosis factor-α.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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Corresponding Author:
EHSAN HEJAZI, Ph.D.
Department of Clinical Nutrition and Dietetics, School of Nutrition Sciences and Food Technology, Shahid Beheshti University of Medical Sciences, Tehran, Iran
e-mail: ehsanhejazi@sbmu.ac.ir