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

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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.
| 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                                                              |

Table 1. — Food groups used in analysis.

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 sociodemographic 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
body mass index (BMI) was calculated by the formula \( \text{weight (kg)} / \text{height}^2 (\text{m}^2) \). 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 of data were evaluated by Kolmogorov-Smirnov test. To compare qualitative and quantitative vari-

| 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/m²), 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%)             |         |
| Residence N (%)                               |                          |                         |                      |         |
| Urban                                         | 379 (96.5%)              | 256 (98.5%)             | 122 (92.5%)          |         |
| Rural                                         | 14 (3.5%)                | 4 (1.5%)                | 10 (7.5%)            |         |
| 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)            |         |
| 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%)           |         |
| 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%)           |         |
| 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%)             |         |
| 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%)                | 42 (5%)                 | 17 (12.9%)           | 0.0001  |
| HPV infection                                  | 361 (92.1%)              | 260 (100%)              | 101 (76.5%)          |         |
| NO                                            | 31 (7.9)                 | 260 (100%)              | 101 (76.5%)          |         |
| Yes                                           | 31 (7.9)                 | 31 (23.5%)              |                     |         |
| First pregnancy age, median (IQR)             | 20 (5)                   | 21 (6)                  | 19 (4)               | 0.0001  |
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|          |        |          |        |
| median low               | 2.95     | 1.71-5.09 | 2.23     |        |
| median high              | 0.001 < 1 |        | 0.01     | 1.77-4.24 |
| 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.

Variables 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 intercorrelation 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 dairy, French fries, mayonnaise, soft drinks, sugars, refined grains, solid oil, nuts and, boiled potato” increased the risk of CC. In consistency 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 scavenging 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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