The Association between Lifestyle, Occupational, and Reproductive Factors and Colorectal Cancer Risk

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Abstract

Objective: Association of lifestyle, reproductive and environmental factors has been investigated with increased risk of colorectal cancer in different studies. We explored evidence and investigated association between various risk factors and colorectal cancer. Methods: This case-control study was conducted on 155 colorectal cancer patients and 150 hospital-controls. We obtained detailed lifestyle, occupational, reproductive information from both groups. Chi-Square test and Logistic regression model were used to evaluate the risk factors of colorectal cancer. Results: The results showed that frequent intake of fruits, chicken, fish and alcohol drinking were associated with risk for colorectal cancer. Agricultural occupation (OR=7.003, 95% CI=2.19-22.38) and industrial exposure (OR=1.97, 95% CI=0.91-4.22) were associated significantly with risk for colorectal cancer. Regarding reproductive factors, women who reported less than 3 pregnancies was associated with an increased risk of colorectal carcinoma (OR=2.88, 95% CI=1.15-7.17). We did not find significant association between other reproductive factors and colorectal cancer risk in women after adjusting for demographic factors. Conclusion: In this case-control study we observed that agricultural occupation, industrial exposure and high consumption of fish and less than 3 pregnancies in women were associated with an increased risk of colorectal carcinoma.

Keywords: Colorectal cancer- lifestyle- occupation- risk factors

 Refuge to represent the full content. Venue to the potential to reduce or increase morbidity and mortality in cancer survivors (Calle et al., 2003). Pregnancy leads to substantial changes in the hormonal milieu, which may be protective against colorectal cancer. Also experimental studies indicate that estrogen may play a protective role in colorectal carcinogenesis either indirectly by reducing secondary bile acids and insulin-like growth factor-I or directly by regulating cell growth in the colonic epithelium and inhibiting cell proliferation of colorectal tumors by binding to the estrogen receptor (Martineti et al., 2005). These features reasonably led that we investigate occupational, lifestyle and reproductive factors in relation to colorectal cancer risk.

Materials and Methods

Study Population

This case-control study was conducted on 155 patients with colorectal cancer and 150 hospital-based controls who referred to Pars hospital in Tehran, Iran during 2015-2016. The patients were older than 18 years and without psychiatric disorders and with ability to complete the self-administered questionnaires. Also

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patients were eligible if they were diagnosed one year before interview date with primary malignancy in the colon or rectum. Patients with anal cancer and Crohn’s disease were excluded. All controls were chosen based on frequency-matched to patients on age (± 5-years) and sex. After consent, the patients and controls completed following questionnaires: The short demographic characteristics, lifestyle, medical, occupational, family and reproductive histories of study population with colorectal cancer. This study was approved by the Ethic Committee of Qom University of medical sciences.

**Medical History**
Data on medical conditions were derived from self-reported medical history (i.e. rectal bleeding and chronic constipation) at least one year prior to the diagnosis date for patients and one year prior to study date for controls. Body mass index (BMI; kg/m2) was calculated from height.

**Reproductive History**
Information on menstrual and reproductive factors was obtained from 58 female colorectal cancer patients and 61 female controls. Women were completed the reproductive histories questionnaire including Age at menarche, age at first birth, number of pregnancies and average duration of lactation for each baby.

**Occupational History and Exposures**
Participants who reported jobs of farming for the longest duration in their lifetime or non-farming were completed Information including occupation history. Exposure to industrial materials was defined as being in contact with any of following substances for at least 8 hours a week for a year (yes vs. no): solvents, paint thinners, printer’s inks or dyes, paints, lacquer, pigments, motor oils, gasoline, petroleum, car exhaust, diesel fuel, fumes, natural gas, tar, mineral oil, hydrochloric acid, bleach or cleansers, dry cleaning fluids, leather, tanning solutions, rubber products, glues, plastics, resins, sawdust, wood dust, coal dust, metals, radioactive materials, or asbestos.

**Lifestyle History**
At the baseline interview, all lifestyle factors were collected by self-report. Participants completed a questionnaire including consumption frequency of the vegetable, fruit, red meat, chicken and fish. Also questions on other lifestyle factors including alcohol drinking, tobacco consumption and physical exercise were completed.

**Statistical Analysis**
For data analysis, variables differences between the patients and controls were assessed by Chi-square test. Logistic regression model was used to calculate the odds ratio (OR) and 95% confidence intervals (95% CI). The associations between cancer and risk factors were shown by odds ratio. Data were analyzed using IBM SPSS software version 21. Level of significant was considered at P < 0.05.

**Results**
The analysis was based on 155 patients (92 men and 58 women), and 150 controls (89 men and 61 women). The mean age of patients was 54.36 ± 11.78 years with a range 25-83, and the mean age of controls was 54.05 ± 11.28 years with a range 24-74. Some demographic and medical histories were significantly different across the patients and controls groups such as residence distribution (P=0.002), Rectal bleeding (P<0.0001) and Chronic constipation (P=0.001). There was any significant difference between patients and control groups according to age and sex (Table 1).

Lifestyle factors were evaluated and results of univariate analysis showed that alcohol drinking, fruits consumption, chicken consumption and fish consumption were associated with risk for colorectal cancer (Table 2). In multivariate analysis after adjusting other lifestyle factors and demographic factors, chicken (OR=0.15, 95% CI=0.05-0.45) and fish consumption (OR=5.74, 95% CI=2.18-15.11) were significantly correlated with colorectal cancer risk. Based on the crude OR estimated by the logistic model, there were significant associations between agricultural occupation and industrial exposure with colorectal cancer risk (Table 2). Based on the adjusted OR, agricultural occupation was significantly correlated with colorectal cancer risk.

| Factor                              | Number patients | Number controls | p-value |
|-------------------------------------|-----------------|-----------------|---------|
| Gender                              |                 |                 |         |
| Female                              | 58 (48.7)       | 61 (51.3)       | 0.723   |
| Male                                | 92 (50.8)       | 89 (49.2)       |         |
| BMI                                 | 25.85 ± 3.99    | 26.58 ± 3.69    | 0.103   |
| age                                 | 54.36 ± 11.78   | 54.05 ± 11.28   | 0.817   |
| Educational level                   |                 |                 |         |
| <High school                        | 27 (46.6)       | 31 (53.4)       | 0.665   |
| High school graduation              | 66 (50)         | 66 (50)         |         |
| University                          | 58 (53.7)       | 50 (46.3)       |         |
| Residence                           |                 |                 |         |
| Rural                               | 5 (20.8)        | 19 (79.2)       | 0.002   |
| Urban                               | 150 (53.4)      | 131 (46.6)      |         |
| Family history of any cancer        |                 |                 |         |
| Yes                                 | 75 (49)         | 78 (51)         | 0.326   |
| No                                  | 66 (55)         | 54 (45)         |         |
| Family history of colorectal cancer |                 |                 |         |
| Yes                                 | 25 (47.2)       | 28 (52.8)       | 0.407   |
| No                                  | 114 (53.5)      | 99 (46.5)       |         |
| Rectal bleeding                     |                 |                 |         |
| Yes                                 | 93 (86.1)       | 15 (13.9)       | <0.001  |
| No                                  | 48 (31)         | 107 (69)        |         |
| Chronic constipation                |                 |                 |         |
| Yes                                 | 53 (70.7)       | 22 (29.3)       | 0.001   |
| No                                  | 93 (47.4)       | 103 (52.6)      |         |

Numbers and row percentages (in parentheses); Discrepancies in the totals are due to missing covariate values.
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We did not find significant association between reproductive factors, including age at menarche, age at first birth, number of pregnancies and average duration of lactation with colorectal cancer risk in women after adjusting for demographic factors (Table 3). Nevertheless, we observed in univariate analysis that women who reported less than 3 pregnancies was associated with an increased risk of colorectal carcinoma among women correlated with colorectal cancer risk (OR=7.003, 95% CI=2.19-22.38).

Table 2. Association of Life Style Factor and Occupational History of Study Population with Colorectal Cancer

| Life style factors          | Number of patients | Number of controls | Crude OR (95% CI) | p-value | Adjusted OR (95% CI) | p-value |
|----------------------------|--------------------|--------------------|-------------------|---------|----------------------|---------|
| Tobacco consumption        |                    |                    |                   |         |                      |         |
| Yes                        | 32 (44.4)          | 40 (55.6)          | 0.71 (0.42-1.21)  | 0.21    | 0.20 (0.06-1.63)     | 0.15    |
| No                         | 123 (52.8)         | 110 (47.2)         | (reference)       |         | (reference)          |         |
| Habit of alcohol drinking  |                    |                    |                   |         |                      |         |
| Yes                        | 19 (30.6)          | 43 (69.4)          | 0.34 (0.19-0.63)  | 0.001   | 0.37 (0.12-1.16)     | 0.09    |
| No                         | 136 (56)           | 107 (44)           | (reference)       |         | (reference)          |         |
| Habit of smoking           |                    |                    |                   |         |                      |         |
| current smoker             | 10 (43.5)          | 13 (56.5)          | 0.74 (0.31-1.76)  | 0.49    | 1.20 (0.27-5.31)     | 0.8     |
| former smoker              | 18 (51.4)          | 17 (48.6)          | 1.02 (0.50-2.08)  | 0.95    | 0.83 (0.24-2.82)     | 0.76    |
| Never smoker               | 114 (50.9)         | 110 (49.1)         | (reference)       |         | (reference)          |         |
| habitual physical exercise |                    |                    |                   |         |                      |         |
| None                       | 73 (59.3)          | 50 (40.7)          | 1.57 (0.89-2.78)  | 0.11    | 2.44 (0.92-6.44)     | 0.07    |
| Max 2 h/week               | 40 (47.6)          | 44 (52.4)          | 0.98 (0.53-1.81)  | 0.95    | 1.49 (0.60-3.68)     | 0.38    |
| >2 h/week                  | 38 (48.1)          | 41 (51.9)          | (reference)       |         | (reference)          |         |
| Vegetables consumption frequency |                |                    |                   |         |                      |         |
| Frequent consumption       | 14 (37.8)          | 23 (62.2)          | 0.62 (0.30-1.29)  | 0.2     | 0.71 (0.16-3.04)     | 0.64    |
| Moderate consumption       | 38 (57.6)          | 28 (42.4)          | 1.40 (0.79-2.46)  | 0.2     | 1.66 (0.67-4.07)     | 0.26    |
| Rare/no consumption        | 94 (49.2)          | 97 (50.8)          | (reference)       |         | (reference)          |         |
| Fruits consumption frequency |                  |                    |                   |         |                      |         |
| Frequent consumption       | 48 (40.3)          | 71 (59.7)          | 0.29 (0.11-0.77)  | 0.013   | 0.76 (0.23-2.51)     | 0.65    |
| Moderate consumption       | 87 (56.1)          | 68 (43.9)          | 0.59 (0.21-1.43)  | 0.22    | 0.68 (0.21-2.19)     | 0.52    |
| Rare/no consumption        | 16 (49.2)          | 7 (50.8)           | (reference)       |         | (reference)          |         |
| Red meat consumption frequency |                |                    |                   |         |                      |         |
| Frequent consumption       | 102 (54.3)         | 86 (45.7)          | 1.30 (0.52-3.21)  | 0.56    | 3.23 (0.88-11.90)    | 0.077   |
| Moderate consumption       | 39 (44.8)          | 48 (55.2)          | 0.89 (0.34-2.32)  | 0.81    | 2.06 (0.46-9.12)     | 0.33    |
| Rare/no consumption        | 10 (47.6)          | 11 (52.4)          | (reference)       |         | (reference)          |         |
| Chicken consumption frequency |                 |                    |                   |         |                      |         |
| Frequent consumption       | 102 (47.4)         | 113 (52.6)         | 0.41 (0.19-0.88)  | 0.023   | 0.15 (0.05-0.45)     | <0.001  |
| Moderate consumption       | 25 (55.6)          | 20 (44.4)          | 0.57 (0.22-1.44)  | 0.23    | 0.51 (0.10-2.50)     | 0.414   |
| Rare/no consumption        | 24 (68.6)          | 11 (31.4)          | (reference)       |         | (reference)          |         |
| Fish consumption frequency |                    |                    |                   |         |                      |         |
| Frequent consumption       | 40 (71.4)          | 16 (28.6)          | 3.12 (1.54-6.30)  | 0.001   | 5.74 (2.18-15.11)    | <0.001  |
| Moderate consumption       | 57 (44.2)          | 72 (55.8)          | 0.99 (0.58-1.67)  | 0.96    | 2.69 (1.17-6.19)     | 0.019   |
| Rare/no consumption        | 44 (44.4)          | 55 (55.6)          | (reference)       |         | (reference)          |         |
| occupational history factors |                  |                    |                   |         |                      |         |
| Occupation                 |                    |                    |                   |         |                      |         |
| Farming- related           | 33 (86.8)          | 5 (13.2)           | 7.94 (2.9-21.09)  | <0.001  | 7.003 (2.19-22.38)   | 0.001   |
| Non- farming               | 103 (45.4)         | 124 (54.6)         | (reference)       |         | (reference)          |         |
| Industrial exposure        |                    |                    |                   |         |                      |         |
| Yes                        | 39 (56.5)          | 30 (43.5)          | 2.007 (1.09-3.66) | 0.024   | 1.97 (0.91-4.22)     | 0.082   |
| No                         | 46 (39.3)          | 71 (60.7)          | (reference)       |         | (reference)          |         |

a, Also adjusted for age (continuous); gender (male, female); residence (rural, urban)
Table 3. Association of Menstrual and Reproductive Factors of Study Population with Colorectal Cancer

| Factors                        | Number | Crude OR (95% CI) | p-value | Adjusteda OR (95% CI) | p-value |
|-------------------------------|--------|-------------------|---------|-----------------------|---------|
| Age at menarche               |        |                   |         |                       |         |
| <14                           | 30 (51.7) | 28 (48.3) | 0.70 (0.31-1.55) | 0.38 | 0.80 (0.29-2.23) | 0.67 |
| >=14                          | 26 (60.5) | 17 (39.5) | (reference) |         |                       |       |
| Number of pregnancies         |        |                   |         |                       |         |
| <3                            | 49 (59) | 34 (41) | 2.88 (1.15-7.17) | 0.023 | 1.43 (0.46-4.41) | 0.53 |
| >=3                           | 9 (33.3) | 18 (66.7) | (reference) |         |                       |       |
| Average duration of lactation |        |                   |         |                       |         |
| (months/child)                |        |                   |         |                       |         |
| <6                            | 21 (47.7) | 23 (52.3) | 1.15 (0.52-2.53) | 0.71 | 1.33 (0.47-3.76) | 0.57 |
| >=6                           | 26 (44.1) | 33 (55.9) | (reference) |         |                       |       |
| Age at first birth (years)    |        |                   |         |                       |         |
| <25                           | 39 (46.4) | 45 (53.6) | 3.46 (0.91-13.14) | 0.068 | 1.64 (0.32-8.32) | 0.54 |
| >=25                          | 3 (20) | 12 (80) | (reference) |         |                       |       |

a. Also adjusted for age (continuous); BMI; residence (rural, urban); Only female study participants were included in the analyses; and column total may be different due to missing data.

(OR=2.88, 95% CI=1.15-7.17).

Discussion

This study illustrated the role of lifestyle, occupational and reproductive factors in colorectal cancer etiology in a developing country. In this case-control study we observed that agricultural occupation, industrial exposures, alcohol drinking, fruits consumption, chicken consumption, fish consumption and number of pregnancies were associated with risk of colorectal cancer. The etiology of colorectal cancer is rather poorly understood, and the mechanism for the various dietary factors is likely to differ. Evidence from this study indicates that the risk of colorectal cancer is decreased by alcohol drinking. Marmot et al., (2007) found similar result to ours that the consumption of alcohol is associated with lower risk of colorectal cancer. The epidemiological evidence has been complemented by recent molecular evidence on mechanisms that could explain the association in this study (Boffetta and Hashibe, 2006). Most previous studies have found an association between alcohol drinking and colorectal cancer that contrast with our finding (Moskal et al., 2007) which alcohol is not a carcinogen itself, but acts as a tumor promoter and co-carcinogen. Alcohol also acts as a solvent and thus might increase the exposure to other carcinogens by increasing the penetration of carcinogens into the cell (Marmot et al., 2007).

In this study, red meat consumption was not associated with colorectal cancer risk, but this was in contrast with other study. The four studies were reported an increased risk of colorectal cancer with increased consumption of red meat (Aykan, 2015; Bernstein et al., 2015; Carr et al., 2016; Domingo and Nadal, 2017). This difference may be attributed to our sample size.

We found that high consumption of chicken and fruit were associated with decreased risks of colorectal cancer. Fruits and vegetables are good source of components of fiber and folic acid, reported to have anti-carcinogenic effects (Ryan-Harshman and Aldoori, 2007). Terry et al., (2001) examined fruit, vegetable, and fiber intake and risk of colorectal cancer among Swedish women, and similar to our findings they reported that high consumption of fruit was associated with a 32% reduction in risk of colorectal cancer. Levi et al., (2001) found a significant inverse relationship between fiber intake and risk of colorectal cancer (odds ratio 0.57, 95% confidence interval 0.47–0.68). van Duijnhoven et al., (2009) suggested that the association of fruit and vegetables with CRC risk may be a reflection of increased intake of other food groups.

A protective effect of poultry (usually chicken) consumption was reported in one study only Willett et al., (1990), and similar to our findings. In the other studies, poultry intake was not significantly associated with colorectal cancer risk (Järvinen et al., 2001; Carr et al., 2016; Ward et al., 2016; Wu et al., 2016). Angelo et al., (2016) that found higher consumption of beef, chicken was associated with increased risks of colorectal cancer in brazil contrast with our finding. It is also important to conduct epidemiological studies that allow clearly establish if the consumption of poultry is associated or not with an increased risk of CRC. In this study high consumption of fish was associated with increased risks of colorectal cancer. Other studies reported a significant positive association between smoked and salted fish with risk of colorectal cancer and suggested that this finding may have been due to the nitrosamine content of these types of fish (Knekt et al., 1999; Cross and Sinha, 2004) Our findings may also be limited by the information of questionnaire for these types of fish intake. In Japan, one study observed that the high consumption of fish may be associated to a lower risk of the colorectal cancer (Lee et al., 2008) that contrast with our finding. Fish intake was not associated with colorectal cancer risk in the most recently published prospective (English et al., 2004; Kobayashi et al., 2004).

Our research has shown that agricultural occupation, industrial exposures and rural residence distribution were associated with a higher risk of colorectal cancer. Our findings are in agreement with research regarding
the role of occupational exposures in colorectal cancer risk that exposed to industrial materials was associated with 2-4 times higher risk for large bowel cancer in Canada and China (Dumas et al., 2000; Roos et al., 2005). Rural residency and agricultural occupations have been associated with a lower risk of colorectal cancer when compared to urban residency and non-agricultural occupation (Wang et al., 2002). Geographical distribution of high colorectal cancer incidence tends to be parallel with regions of high agricultural activity in the U.S (Carozza et al., 2008). We think that intense environmental pollution and agricultural occupation may help to explain a higher risk of colorectal cancer.

No significant associations were found for reproductive factors and colorectal cancer risk in women, that is consistent with most of the study (Akhter et al., 2008; Kabat et al., 2008). We observed in univariate analysis that demonstrated inverse associations of higher pregnancy with colorectal cancer risk. It has been hypothesized that hormonal changes associated with pregnancy might interact with bile-acid or estrogen receptors, resulting in a reduced risk for colorectal cancer (Potter, 1995). Pregnancy leads to substantial changes in the hormonal milieu, which may be protective against colorectal cancer. For example, during gestation, production of ovarian estradiol ceases and the predominant estrogen in circulation is estrone (Melmed et al., 2015). Whereas estradiol has been demonstrated to have proliferative properties in colorectal cancer cell lines (Di Domenico et al., 1996), estrone has been shown to exert anti-proliferative effects in colorectal tissues (English et al., 1999).

In conclusion, we observed that agricultural occupation, industrial exposure and fish consumption in colorectal cancer patients and less than 3 pregnancies in women were associated with an increased risk of colorectal carcinoma.

In addition, we lacked more detailed data on other reproductive factors, such as age at birth of last child, breastfeeding history, and abortion history, which have been linked with colorectal cancer. The other limitation of our study was the relatively small number of female, which made the model we used underpowered for associations.

Also further prospective studies that directly assess dose-response relationship, the actual levels in exposed and non-exposed individuals in relation to colorectal cancer risk would be highly informative. Future studies should focus on investigating the biological mechanisms of environmental, industrial, and reproductive factors in colorectal carcinogenesis and other health conditions are urgently needed.

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