Short Communication

Family History and Environmental Risk Factors for Colon Cancer

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Abstract

Background: We analyzed the joint effect of environmental risk factors and family history of colorectal cancer on colon cancer. Methods: We used data from a case-control study conducted in northern Italy between 1992 and 1996 including 1225 cases with colon cancer and 4154 controls. We created a weighed risk factor score for the main environmental risk factors in this population (positive family history, high education, low occupational physical activity, high daily meal frequency, low intake of fiber, low intake of calcium, and low intake of β-carotene). Results: Compared with the reference category (subjects with no family history of colorectal cancer and in the lowest tertile of the risk factor score), the odds ratios of colon cancer were 2.27 [95% confidence interval (CI) = 1.89–2.73] for subjects without family history and in the highest environmental risk factor score, 3.20 (95% CI = 2.05–5.01) for those with family history and low risk factor score, and 7.08 (95% CI = 4.68–10.71) for those with family history and high risk factor score. The pattern of risk was similar for men and women and no meaningful differences emerged according to subsite within the colon. Conclusions: Family history of colorectal cancer interacts with environmental risk factors of colon cancer. (Cancer Epidemiol Biomarkers Prev 2004;13(4):658–661)

Background

Subjects who have a family history of colon cancer in first-degree relatives are at ~2–3-fold increased risk of colon cancer (1–4). Several known autosomal dominant inherited syndromes, such as familial adenomatous polyposis and hereditary nonpolyposis colorectal cancer (HNPPC) (5, 6), are associated with a high penetrant phenotype (7). Other less penetrant but more frequent genes may be involved in the inherited predisposition to colorectal cancer (8). Some studies indicate that non-HNPPC familial colorectal cancer is difficult to characterize genetically, given its heterogeneity, low penetrance, and possible recessive mode (4, 9, 10).

Previous studies that have examined environmental factors for colon cancer in separate strata of subjects with and without family history (a proxy for genetically determined susceptibility) found no consistent difference in the relative risk among subjects according to family history of the disease (11–14). However, a case-control study (15) that analyzed the joint effects of family history of colorectal cancer and several adult life dietary risk factors showed that subjects with family history of colorectal cancer and in the highest tertile of the risk factor score were at substantial increased risk of colorectal cancer [odds ratio (OR) = 5.5].

The aim of this study was to investigate the joint effect of familial propensity and adult life style risk factors on colon cancer risk using data from a large case-control study conducted between 1992 and 1996 in Italy.

Subjects and Methods

Between 1992 and 1996, we conducted a case-control study of colorectal cancer in six Italian areas (the provinces of Pordenone and Gorizia in northeastern Italy, the urban areas of Milan and Genoa and the province of Forlì in the North, and Latina and the urban areas of Naples in the Center and South; Refs. 3, 14). We enrolled 1225 cases (688 men and 537 women; median age 62 years) with incident, histologically confirmed colon cancer. The controls were 4154 subjects (2073 men and 2081 women; median age 58 years) residing in the same geographical areas and admitted to the same hospitals where cases had been identified for acute conditions unrelated to known or likely risk factors for...
colorectal cancer. Of these, 23% were admitted for trauma, 28% for other orthopedic disorders, 20% for acute surgical conditions, 19% for eye diseases, and 10% for miscellaneous other illnesses, such as ear, nose, throat, skin, and dental conditions. Fewer than 4% of cases and controls approached for interview refused to participate.

Trained interviewers used a structured questionnaire during hospital admission when the disease was diagnosed to obtain information on general sociodemographic factors and life-style habits, including diet, physical activity, and family history of colorectal cancer in first-degree relatives. Information on diet referred to the previous 2 years and was based on the same validated food frequency questionnaire comprising 78 foods, food groups, or recipes and allowing the estimation of energy intake as well as of several micronutrients (16, 17).

In addition to a positive family history, the major risk factors for colon cancer in this Italian population were high education, low occupational physical activity, high daily meal frequency, low intake of fiber, low intake of calcium, and low intake of β-carotene (18). We categorized these variables according to approximate tertiles, except meal frequency with two categories (upper two-thirds and lower third).

ORs of colon cancer and the corresponding 95% confidence intervals (CI) were derived from unconditional multiple logistic regression models. The regression equations included terms for age, study center, sex (when appropriate), education, number of meals, occupational physical activity, fiber, calcium intake, β-carotene, and total energy intake.

Following the approach described by Katsouyanni et al. (19), we defined a risk score to consider the overall impact of the risk factors that operate at overlapping time intervals in life and then evaluated the joint impact of family history and risk factors. We assigned a value of 1 to subjects at high risk with respect to a particular factor and 0 otherwise. We summed these risk factors using weights corresponding to the excess OR (defined as the OR – 1) as derived from this study. The values for the risk score range from 0 to 2.27 (median value = 0.81). All subjects were distributed into three categories defined by approximate tertiles (cut points = 0.68 and 1.05).

### Results

A total of 134 cases (11.9%) and 146 controls (3.5%) reported history of colorectal cancer in first-degree relatives. The multivariate OR of colon cancer for those with a family history of the disease was 3.29 (95% CI = 2.57–4.23). Table 1 shows the distribution of cases and controls according to sex and the risk factors considered and the corresponding OR of colon cancer.

We subsequently evaluated the joint effects of the adult life risk score and family history with the six possible combined categories of exposure, taking as

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Men Cases/controls</th>
<th>OR (95% CI)</th>
<th>Women Cases/controls</th>
<th>OR (95% CI)</th>
<th>Total Cases/controls</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Education (yr)</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>&lt;7</td>
<td>306/1057</td>
<td>1c</td>
<td>315/1219</td>
<td>1c</td>
<td>621/2276</td>
<td>1c</td>
</tr>
<tr>
<td>7–11</td>
<td>210/629</td>
<td>1.41 (1.13–1.75)</td>
<td>121/527</td>
<td>1.23 (0.95–1.59)</td>
<td>331/1156</td>
<td>1.30 (1.10–1.53)</td>
</tr>
<tr>
<td>≥12</td>
<td>170/380</td>
<td>1.74 (1.34–2.25)</td>
<td>97/313</td>
<td>1.78 (1.32–2.40)</td>
<td>267/693</td>
<td>1.74 (1.44–2.11)</td>
</tr>
<tr>
<td>Number of meals</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;4</td>
<td>529/1620</td>
<td>1c</td>
<td>305/1368</td>
<td>1c</td>
<td>834/2988</td>
<td>1c</td>
</tr>
<tr>
<td>≥4</td>
<td>158/452</td>
<td>1.17 (0.94–1.45)</td>
<td>232/709</td>
<td>1.39 (1.13–1.73)</td>
<td>390/1161</td>
<td>1.31 (1.13–1.52)</td>
</tr>
<tr>
<td>Occupational physical activity</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>233/873</td>
<td>1c</td>
<td>91/350</td>
<td>1c</td>
<td>324/1223</td>
<td>1c</td>
</tr>
<tr>
<td>Intermediate</td>
<td>186/580</td>
<td>1.18 (0.94–1.50)</td>
<td>247/1000</td>
<td>1.18 (0.89–1.57)</td>
<td>433/1580</td>
<td>1.18 (0.99–1.41)</td>
</tr>
<tr>
<td>Low</td>
<td>268/616</td>
<td>1.44 (1.14–1.82)</td>
<td>199/726</td>
<td>1.55 (1.22–2.13)</td>
<td>467/1342</td>
<td>1.43 (1.19–1.72)</td>
</tr>
<tr>
<td>Fiber intake (g/day)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High (≥24.46)</td>
<td>231/776</td>
<td>1c</td>
<td>166/636</td>
<td>1c</td>
<td>397/1412</td>
<td>1c</td>
</tr>
<tr>
<td>Intermediate (18.31–24.45)</td>
<td>227/720</td>
<td>1.01 (0.78–1.30)</td>
<td>178/653</td>
<td>1.02 (0.77–1.37)</td>
<td>405/1373</td>
<td>1.02 (0.84–1.23)</td>
</tr>
<tr>
<td>Low (&lt;18.31)</td>
<td>230/577</td>
<td>1.18 (0.84–1.65)</td>
<td>193/792</td>
<td>1.08 (0.74–1.56)</td>
<td>423/1369</td>
<td>1.13 (0.88–1.45)</td>
</tr>
<tr>
<td>Calcium intake (mg/day)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High (≥1288.5)</td>
<td>240/727</td>
<td>1c</td>
<td>163/685</td>
<td>1c</td>
<td>403/1412</td>
<td>1c</td>
</tr>
<tr>
<td>Intermediate (953.9–1288.4)</td>
<td>212/672</td>
<td>0.96 (0.75–1.21)</td>
<td>169/698</td>
<td>1.27 (0.96–1.68)</td>
<td>381/1370</td>
<td>1.05 (0.88–1.25)</td>
</tr>
<tr>
<td>Low (&lt;953.9)</td>
<td>236/674</td>
<td>1.03 (0.78–1.35)</td>
<td>205/698</td>
<td>1.81 (1.32–2.49)</td>
<td>441/1372</td>
<td>1.29 (1.06–1.58)</td>
</tr>
<tr>
<td>β-carotene intake (µg/day)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High (≥6611)</td>
<td>183/705</td>
<td>1c</td>
<td>170/707</td>
<td>1c</td>
<td>353/1412</td>
<td>1c</td>
</tr>
<tr>
<td>Intermediate (4541–6610)</td>
<td>226/697</td>
<td>1.29 (1.00–1.66)</td>
<td>193/675</td>
<td>1.24 (0.95–1.64)</td>
<td>419/1372</td>
<td>1.25 (1.04–1.51)</td>
</tr>
<tr>
<td>Low (&lt;4541)</td>
<td>279/671</td>
<td>1.67 (1.23–2.28)</td>
<td>174/699</td>
<td>1.10 (0.78–1.55)</td>
<td>453/1370</td>
<td>1.37 (1.09–1.72)</td>
</tr>
</tbody>
</table>

*In some strata, the sum does not add up to the total because of missing values.

*Estimates from unconditional multiple logistic regression models, including terms for age, sex (when appropriate), center, total energy intake, and all the factors shown in table.

*Reference category.
referred those subjects without family history of colon cancer and with the lowest score, as shown in Table 2. Among subjects with no family history, the risk of colon cancer increased in the subsequent tertiles of the risk factor score (OR = 2.27 for subjects with no family history and in the highest tertile of the score). Among subjects with family history, the OR of colon cancer increased from 3.20 for those with low environmental risk factor score to 7.08 (95% CI = 4.68–10.71) for those in the highest tertile of the score. The pattern of risk was similar for men and women (Table 2). No meaningful or consistent differences emerged in the analysis according to subsite within the colon (data not shown).

Discussion

In agreement with previous observations (11–15, 20–23), our results show that family history, taken here as a proxy for genetically determined predisposition to cancer, influences the risk of colon cancer and that environmental factors appear to multiply familial risk. A potential limitation of the present study is the use of family history as a proxy for genetic susceptibility. Although this is an imperfect surrogate for genetic predisposition to cancer, the number of cases and controls unequivocally characterized as genetically susceptible is limited as to permit the analysis of the interaction between the genetic propensity and environmental risk factors (21, 24).

Another potential problem for the association observed is the possibility that dietary and other environmental risk factors are correlated within families (i.e., shared eating habits in the family) and hence may account for part of the risk attributed to family history (25). In the present data set as well as in a previous study (15), the environmental risk factor score was, however, not correlated with family history of colon cancer. Simple familial clustering of environmental factors is, however, unlikely to account for the familial aggregation of disease (26, 27).

Most other problems with the study design and the lifestyle and dietary questionnaire have been addressed elsewhere (3, 12, 26). With reference to possible selection bias, chronic diseases potentially related to diet modification were excluded, and the participation of cases and controls was almost complete. Separate analysis according to the type of hospital controls yielded similar results. The similar catchment areas and the same interview setting for cases and controls are reassuring against potential information bias, and cases and controls did not differ with regard to the mean number of first-degree relatives. Moreover, the dietary questionnaire used has a satisfactory validity and reproducibility (16, 17, 28).

It has been suggested that there are two distinct categories of colon cancer according to the location of the tumor in the proximal or distal segments of the large bowel. There are morphological and physiological differences between right and left colon and in the incidence of right and left colon cancers (29, 30). Different environmental, genetic, and molecular factors for right and left colon cancers are under study (31). In the present data set, the power was limited for subsite analysis, but no appreciable difference in the combination of familial and environmental factors was observed across colon subsites. This is not surprising given the lack of consistent evidence of differential role of risk factors in various subsites (32).

The combination of familial and environmental factors showed no appreciable interaction under a multiplicative model (33). On a public health perspective, however,
this would translate into a positive interaction on an additive model with large scope for prevention (19). These findings imply that subjects with a family history of colorectal cancer may greatly benefit by control of environmental risk factors.

Acknowledgments
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References