Adherence to a healthy Nordic food index is associated with a lower incidence of colorectal cancer in women: The Diet, Cancer and Health cohort study

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Abstract
Colorectal cancer (CRC) is a multi-factorial disease, the incidence of which is related in particular to a ‘Western’ diet and lifestyle but also to genetic and hormonal factors(1,2). It has been estimated that more than 40% of CRC cases in Western countries could be prevented by appropriate food, nutrition, physical activity and body weight(3).

Emerging evidence of a probable protective role of the Mediterranean dietary pattern against cancer, especially in cohorts in the USA(4), has led to the suggestion that American and northern European populations should adapt to this diet. In the large National Institutes of Health-American Association of Retired Persons Diet and Health Study (NIH-AARP) Diet and Health Study in the USA, a cohort study of 3110 incident cases of CRC and 5 years of follow-up, compliance with a Mediterranean diet was associated with a 28% lower incidence of CRC in men but not in women(5). In a more recent study in the USA, based on the Nurses’ Health Study and the Health Professionals Follow-up Study of 1432 cases of CRC, no significant effect of the Mediterranean diet was found on the incidence of CRC(6). In a Danish intervention study, the dropout rate was much higher in the group assigned to the Mediterranean diet than in that assigned to a low-fat diet, suggesting that participants might more readily comply with a ‘traditional’ diet than with a foreign diet(7,8). In countries outside the Mediterranean region, promotion of a healthy diet based on local items might be more relevant and feasible(9).

As the Nordic diet is in general rich in unhealthy foods, such as margarine and sugar, it would not be relevant to study the health effects of the overall Nordic diet(10). This diet does, however, also include a range of foods with anticipated health-promoting effects, such as whole-grain cereals and fish. In order to determine whether selected healthy food items were therefore associated with a lower incidence of CRC in women. The protective effect was of the same magnitude as previously found for the Mediterranean diet, suggesting that healthy regional diets should be promoted in order to ensure health; this will also preserve cultural heredity and the environment.

Key words: Colorectal cancer: Colon cancer: Dietary index: Nordic diet: Scandinavian

Abbreviations: CRC, colorectal cancer; IRR, incidence rate ratio.

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items in the Nordic diet have positive health effects, we evaluated a healthy Nordic food index consisting of six items that are part of traditional Nordic cuisine: fish, cabbage, rye bread, oatmeal, apples and pears, and root vegetables. In a previous study, adherence to a healthy Nordic food index was associated with lower total mortality\(^{(13)}\). Moreover, a diet rich in whole-grain products, including rye bread and oatmeal, was associated with a lower incidence of colon cancer among men\(^{(12)}\). The aim of the study reported here was to elucidate whether adherence to a healthy Nordic food index was associated with a lower incidence of CRC in a cohort of Danish men and women.

### Materials and methods

#### Study population

The Danish Diet, Cancer and Health prospective cohort study was initiated in 1993. During 1993–7, 80996 men and 79729 women aged 50–64 years were invited to participate in the study, representing 19\% of the Danish population in that age group. Those invited also had to have been born in Denmark, have no diagnosis of cancer registered in the Danish Cancer Registry and live in the municipality of Copenhagen, Frederiksberg, Aarhus, Hinnerup or Hørning at the time of invitation. The participation rate was 37\% for women and 34\% for men, resulting in a cohort of 57053\(^{(13)}\). The study was approved by the relevant scientific committees and the Danish Data Protection Agency, and all the participants gave written consent. All participants filled in a questionnaire including questions on social factors, health status, reproductive factors and lifestyle at the study centres; anthropometric measurements (height, weight and waist circumference) were made by a laboratory technician\(^{(13)}\).

Of the 57053 members of the Diet, Cancer and Health cohort, 572 were excluded because of a diagnosis of cancer before baseline. Another thirty-seven were excluded because they did not fill in the questionnaire, 564 were excluded because of missing information on variables of interest for this study: fish intake, rye bread intake, anthropometrics, education, smoking status, use of non-steroidal anti-inflammatory drugs and use of hormone replacement therapy (for women). The resulting cohort consisted of 55880 participants, of whom 29216 were women and 26664 were men.

#### Case ascertainment and selection

All participants were followed-up from the date of their visit to the centre by the personal identification number assigned to all Danish inhabitants. They were followed-up until censoring, which was the date of diagnosis of any cancer (except non-melanoma skin cancer), date of death, date of emigration or end of follow-up (31 December 2009). Information on cancer was obtained by linkage with the Danish Cancer Registry, which holds information on all cancer cases in Denmark\(^{(13)}\).

There were 1035 incident cases of CRC between baseline and the end of follow-up, but ten were excluded because of missing information on the questionnaire, leaving 1025 cases for the present study. CRC cases were identified as codes C18–C20 in the 10th revision of the International Statistical Classification of Diseases, Injury and Causes of Death (ICD-10), which include all first incident primary adenocarcinomas; proximal colon cancers, of the caecum, appendix, ascending colon, hepatic flexure, transverse colon and splenic flexure (C18:0–C18:5); and distal colon cancers, of the descending (C18:6) and sigmoid colon (C18:7). Overlapping (C18:8) and unspecified lesions (C18:9) of the colon and cancers of the rectosigmoid junction (C19) were grouped with all colon cancers only. Cancers of the rectum (C20) were assessed both separately and with all colon cancer as CRC (C18–C20).

### Dietary assessment

Before their visit to the study centre, the participants were asked to fill in a 192-item FFQ, which has been validated\(^{(15,16)}\). The participants were asked to report their habitual intake of food items within the past 12 months in twelve categories ranging from never to more than eight times a day. The intakes of specific foods were calculated with the software program FoodCalc\(^{(17)}\). At the study centre, the FFQ were scanned optically and checked for missing values and reading errors. Uncertainties were cleared up with the participants by the laboratory technician during the visit\(^{(13)}\).

The healthy Nordic food index was based on traditional Nordic foods chosen \textit{a priori} on the basis of expected health benefits. The food items had to be present naturally in the Nordic countries, to already be an essential part of the Nordic diet, and information on the food items should be available from the FFQ. The food items used as exposure variables in the study were fish, cabbage, rye bread, oatmeal, apples and pears, and root vegetables. Information on intake of fish, cabbage, apples and pears, and root vegetables was obtained from multiple questions in the FFQ, whereas intake of oatmeal and rye bread was derived from one question each. Intake of fish was based on answers to twenty-three questions on a variety of fish and fish products eaten as hot meals or in open sandwiches. Information on intake of the Brassicaceae cauliflower, brussels sprouts, broccoli, kale, white cabbage and red cabbage was derived from answers to six questions. Consumption of apples and pears was inferred from the answers to two questions. That of root vegetables was derived from several questions on the intake of raw and cooked vegetables separately and as part of a recipe; carrots were the main root vegetables consumed.

The healthy Nordic food index was scored in accordance with those for the Mediterranean diet constructed by Trichopoulou et al\(^{(18,19)}\). Here, 1 point was given for an intake equal to or greater than the sex-specific median for each food category. As information on oatmeal and rye bread intake was derived from only one question each, it could not be divided into equal groups; the cut-off values were therefore defined from sex-specific spline curves with boundaries at predefined questionnaire categories.

In the scoring, 1 point was given for intake as follows: for men, fish ≥42 g/d; cabbage ≥14 g/d; rye bread ≥113 g/d; oatmeal ≥50 g/d; apples and pears ≥56 g/d; root vegetables
Statistical analyses

Cox proportional hazard models were used to estimate incidence rate ratios (IRR), with age as the underlying time axis. All quantitative variables were entered linearly into the Cox model\(^\text{20}\). Linearity of the associations was evaluated graphically by linear splines with three boundaries placed at quartiles of cases\(^\text{21}\). Time under study was the time-dependent variable and modelled as a linear spline with boundaries at 1, 2 and 3 years after entry into the study to allow for different underlying hazards during the first years of follow-up.

All the estimates are presented as both crude unadjusted and adjusted estimates. Overall, three adjustments were made. Of these, one adjustment was made for factors known to be associated with CRC: alcohol intake (any consumption, yes/no and g/d), smoking status (current, former, never), use of hormone replacement therapy (current, former, never), schooling (low: ≤7 years, medium: 8–10 years, and high: ≥10 years), participation in sports activities (yes/no), use of non-steroidal anti-inflammatory drugs (yes/no; yes: taken at least once a month within the past 10 years), participation in sports activities (yes/no), use of non-steroidal anti-inflammatory drugs (yes/no; yes: taken at least once a month within the past year), waist circumference (cm) and meat intake (g/d of red and processed meat). Another adjustment was made with the same factors and also energy (kJ/d, excluding alcohol). A final adjustment was made for Ca (dietary, dietary supplements), vitamin D (dietary, dietary supplements) and dietary fibre.

Exclusion of cases diagnosed within the first year and within the first 2 years after baseline did not change the results, and these were therefore included in the analysis.

Competing risk tests were performed to determine whether cases of colon and of rectum cancer and cases of distal and of proximal colon cancer could be merged\(^\text{22}\). We used the likelihood test for interactions between the healthy Nordic food index and categories of BMI (≤25, 25–30 and >30 kg/m\(^2\)) for men and women (\(P\) values >0.77).

SAS statistical software release 9.1 (SAS Institute, Inc.) on a TextPad platform was used for all statistical analyses. The PHREG procedure was used for the Cox proportional hazard models and the UNIVARIATE and FREQ procedures for the descriptive analyses.

Results

During a median of 13 years of follow-up, colon or rectal cancer was diagnosed in 567 men and 458 women.

Table 1 shows the median intakes of the food groups of the healthy Nordic food index, with the 5th and 95th percentiles, for all participants and for cases stratified by sex. For men, no differences were observed. Women with CRC had slightly lower intakes of fish, cabbage, root vegetables, apples and pears than all participants.

The baseline distribution of possible confounders for the entire cohort and for people with 0–1 points (poor adherence), 2–3 points (medium adherence) and 4–6 points (good adherence) are shown in Table 2. Participants who scored high on the healthy Nordic food index had had longer schooling, were less likely to be smokers and had a smaller waist circumference than participants with lower scores. Furthermore, participants with high scores had a greater energy intake and more frequently participated in sports.

Adherence to the healthy Nordic food index was associated with a lower incidence of CRC for women, and the same tendency was found for men before adjustment for potential confounders (Table 3). When the index was assessed as a linear variable, a 1-point increase was associated with a non-significant, 5% lower incidence of CRC for men (crude IRR, 0.95; 95% CI 0.89, 1.01; \(P = 0.08\)) and a statistically significant, 9% lower incidence of CRC for women (crude IRR, 0.91; 95% CI 0.85, 0.98; \(P = 0.01\)). Adjustment for potential confounding factors removed the association for men but not for women (adjusted IRR, 0.91; 95% CI 0.84, 0.99; \(P = 0.02\)). In the crude model, both men and women with 5–6 points had a considerably lower incidence of CRC than those with

Table 1. Intake of items in a healthy Nordic food index of colorectal cancer cases and all participants in the Danish Diet, Cancer and Health cohort (Medians and percentiles)

<table>
<thead>
<tr>
<th>Healthy Nordic food index component (g/d)</th>
<th>(\text{All (n 26 664)})</th>
<th>Cases (n 567)</th>
<th>(\text{All (n 29 216)})</th>
<th>Cases (n 458)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(\text{Men})</td>
<td>(\text{Women})</td>
<td>(\text{Men})</td>
<td>(\text{Women})</td>
</tr>
<tr>
<td>Fish</td>
<td>42</td>
<td>12</td>
<td>42</td>
<td>11</td>
</tr>
<tr>
<td>Cabbage</td>
<td>14</td>
<td>2</td>
<td>15</td>
<td>3</td>
</tr>
<tr>
<td>Rye bread(^*)</td>
<td>63</td>
<td>20</td>
<td>63</td>
<td>20</td>
</tr>
<tr>
<td>Oatmeal(^*)</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Apples and pears</td>
<td>56</td>
<td>4</td>
<td>56</td>
<td>2</td>
</tr>
<tr>
<td>Root vegetables</td>
<td>16</td>
<td>2</td>
<td>15</td>
<td>3</td>
</tr>
<tr>
<td>Food index score, points</td>
<td>3</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

\(^*\) Information on intake from a single question; therefore, medians do not divide participants into equal groups.

P5, 5th percentile; P95, 95th percentile.
Table 2. Baseline characteristics of all participants in the Diet, Cancer and Health cohort and by healthy Nordic food index scores of 0–1 points (poorest adherence), 2–3 points and 4–6 points (best adherence) (Medians, number of participants, percentiles and percentages)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Food index score</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>0–1</td>
<td>2–3</td>
</tr>
<tr>
<td>n</td>
<td>26 664</td>
<td>6608</td>
<td>11 966</td>
</tr>
<tr>
<td>%</td>
<td>100</td>
<td>25</td>
<td>45</td>
</tr>
<tr>
<td>Cases</td>
<td>567</td>
<td>142</td>
<td>273</td>
</tr>
<tr>
<td>Age (years)</td>
<td>56</td>
<td>50–64</td>
<td>55</td>
</tr>
<tr>
<td>Schooling (%)</td>
<td>35</td>
<td>41</td>
<td>35</td>
</tr>
<tr>
<td>Short (≤ 7 years)</td>
<td>42</td>
<td>42</td>
<td>40</td>
</tr>
<tr>
<td>Medium (8–10 years)</td>
<td>24</td>
<td>17</td>
<td>23</td>
</tr>
<tr>
<td>Long (&gt;11 years)</td>
<td>24</td>
<td>17</td>
<td>23</td>
</tr>
<tr>
<td>Smoking status (%)</td>
<td>26</td>
<td>22</td>
<td>25</td>
</tr>
<tr>
<td>Never</td>
<td>35</td>
<td>28</td>
<td>35</td>
</tr>
<tr>
<td>Past</td>
<td>40</td>
<td>50</td>
<td>40</td>
</tr>
<tr>
<td>Current (kg/m²)</td>
<td>26</td>
<td>21–33</td>
<td>26</td>
</tr>
<tr>
<td>Alcohol intake (g/d)</td>
<td>19</td>
<td>2–80</td>
<td>21</td>
</tr>
<tr>
<td>Intake of red and processed meat (g/d)</td>
<td>49</td>
<td>38</td>
<td>48</td>
</tr>
</tbody>
</table>

P5, 5th percentile; P95, 95th percentile.
0–1 points. For women, a 35% lower incidence was found even after adjustment (adjusted IRR, 0·65; 95% CI 0·46, 0·94). For men, a statistically significant, 31% lower incidence was found in the crude model, but the association was no longer significant after adjustment for risk factors. Further adjustment for Ca, vitamin D and dietary fibre did not change the estimates (results not shown).

Even though competing risk tests showed that it was acceptable to merge colon and rectum cancer (women, \( P = 0·15 \); men, \( P = 0·22 \)) and proximal and distal colon cancer (women, \( P = 0·62 \); men, \( P = 0·40 \)), the subtypes were also evaluated separately (Table 4). In the crude analyses, a lower incidence of distal colon cancer was found for men, but the association was no longer significant after adjustment for total energy. For women, a lower incidence of rectum cancer was found (adjusted IRR, 0·83; 95% CI 0·71, 0·96).

None of the individual food items of the healthy Nordic diet was found to be solely responsible for the protective effect of the food index (results not shown), although consumption of rye bread tended to be associated with a lower incidence among men. For women, an intake of cabbage above or equal to the median was associated with a lower incidence of CRC (crude IRR, 0·80; 95% CI 0·66, 0·96), but this statistically significant association disappeared after inclusion of the other dietary items in the model (mutual adjustment).

Discussion

In this prospective cohort study, adherence to a healthy Nordic food index was associated with a lower incidence of CRC among women. The magnitude of the protective effect was in the same range as that found for the Mediterranean diet\(^5\)\(^6\). A score of 5–6 points (best adherence) to the diet was associated with a 35% lower incidence of CRC for women; a similar tendency was found for men but was no longer significant after adjustment for potential confounders.

The strengths of this study include the sample size (>1000 cases) and the long follow-up (median, 13 years). Further, a validated FFQ was used to assess intake\(^15\)\(^16\) and detailed information on potential confounding factors was obtained from an additional questionnaire. The prospective follow-up and minimal loss to follow-up because of linkage to the Danish Cancer Registry are further strengths\(^14\). The potential limitations of the study include the assessment of diets from a single FFQ administered at baseline; therefore, any changes in diet during the long follow-up were not captured. Residual confounding due to incomplete adjustment for the potential confounding factors or the effects of unknown confounders cannot be ruled out. An additional limitation is that the FFQ was not designed to capture intake of other traditional Nordic food items, such as rapeseed oil and berries, and these items could not be included in the index. If they had been added to the index, an even stronger association might have been found.

Adherence to the healthy Nordic food index was associated with a lower incidence of CRC, in accordance with our expectation, which was based on the hypothetical relationships of all the food items in the index to decreased cancer incidence.
In the large European Prospective Investigation into Cancer and Nutrition study, fish intake was associated with a lower incidence of CRC (per 100 g increase, hazard ratio = 0.46; 95% CI 0.27, 0.77)23. Isothiocyanate, which is found in cruciferous vegetables such as cabbage, is probably protective against CRC24. Rye bread contains large quantities of whole-grain rye, which has a high fibre content; the evidence for a protective effect of fibre against cancer was classified as ‘convincing’ in the Continuous Update Project of the World Cancer Research Fund/American Institute for Cancer Research25. Furthermore, cereal fibre in particular has been associated with a lower incidence of CRC26. In line with our earlier study of whole-grain products in a smaller set of CRC cases, we did not find a lower incidence of CRC associated with rye bread or oatmeal intake for women12, whereas women with high intake of rye bread in a Swedish cohort had a lower incidence of colon cancer27. We did find a tendency for a protective effect of rye bread in men, which concurs with earlier findings12. Rye might have a greater protective effect against CRC than other types of whole grain. In a randomised crossover trial, rye bread increased the concentration of butyrate to a greater extent than white wheat bread in men28. Butyrate, which is a fermentation product of the colonic bacteria, may be one of the compounds responsible for the protective effect of whole grain against CRC29. Other studies suggest that intake of oats reduces the risk for CRC because of their high content of fibre and the content of the polyphenols avenanthramides, which attenuate the proliferation of colon cancer cells in vitro30. Most of the intake of root vegetables in the present study was from carrots, a rich source of β-carotene, which has been associated with a lower incidence of CRC51, even though the evidence is not consistent32. Proanthocyanidins, present in apples and pears, have been suggested to be chemopreventive33. Furthermore, the healthy Nordic food index might be associated with an overall healthy lifestyle and with other healthy dietary patterns.

Although a traditional Nordic food index has not previously been related to the incidence of CRC, two large cohort studies have been conducted in the USA on the Mediterranean diet, one of which found a moderate decrease in the incidence of CRC among participants with strong adherence to the Mediterranean diet5,6. The size of the effect seen is comparable to that found in the present study, where a healthy Nordic food index is used.

We found a reduced incidence of CRC among women but only a tendency to a lower incidence among men. The reason for this sex difference is difficult to identify. The well-known protective effect of oestrogens against CRC may play a role34, and there may be sex differences in the aetiology of this cancer5. There might have been misclassification by sex; however, this is unlikely to have influenced the results, because in the validation study of the FFQ, the validity was better for men than for women35. Furthermore, sex differences in the estimated risks for CRC were also found in studies of the Mediterranean diet5,35. In terms of generalisability, this study included only people aged 50–64 years at baseline and only people living in the Copenhagen and Aarhus areas. Additionally, the cohort underrepresented people of low

| Table 4. Incidence rate ratios (IRR, linear, per 1-point increase) and numbers of cases of colon and rectum cancer according to healthy Nordic food index |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| Cancer site                     | No. of cases    | IRR 95% CI      | No. of cases    | IRR 95% CI      | No. of cases    | IRR 95% CI      | No. of cases    | IRR 95% CI      |
| Colon                           | 341             | 0.93 0.86, 1.01 | 324             | 0.99 0.87, 1.12 | 298             | 0.97 0.88, 1.07 |
| Proximal                        | 193             | 0.98 0.93, 1.05 | 193             | 0.99 0.93, 1.07 | 193             | 0.99 0.93, 1.07 |
| Distal                          | 157             | 0.85 0.77, 0.96 | 134             | 0.97 0.87, 1.09 | 134             | 0.97 0.87, 1.09 |
| Other                           | 51              | – – – – –       | 51              | – – – – –       | 51              | – – – – –       |
| Rectum                          | 226             | 0.97 0.88, 1.07 | 226             | 0.97 0.88, 1.07 | 226             | 0.97 0.88, 1.07 |

* Crude. † Adjusted for covariates: alcohol intake, smoking status, use of hormone replacement therapy (women only), schooling, sports, use of non-steroidal anti-inflammatory drugs, waist circumference and meat intake (processed and red).
‡ Model 2 plus energy.
socio-economic status(13). Therefore, caution should be used in extrapolating the results.

CRC has been associated with lower socio-economic status in Denmark(46). As people find it easier to comply with a diet that is familiar to them than with the Mediterranean diet(7), adherence to a healthy Nordic diet might be better for lower socio-economic groups, which are usually difficult to reach. As CRC is one of the commonest cancers in the Western world, with a 5-year survival of approximately 60%(37), advocating local traditional diets could have a great impact on public health. The results of this study suggest that it would be useful to evaluate the health benefits of other regional diets, instead of promoting a Mediterranean diet worldwide.

In conclusion, we found that female participants with high scores on intake of a regional diet based on healthy Nordic food items had a lower incidence of CRC. Attempts should be made to promote a healthy regional diet, instead of promoting a Mediterranean diet worldwide; this might ensure the compliance of people of lower socio-economic status and also ensure cultural diversity, respect for heritage and protection of the environment.

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