Influence of dietary factors on colorectal cancer survival

X Dray, M-C Boutron-Ruault, S Bertrais, D Sapinho, A-M Benhamiche-Bouvier, J Faivre

Background: Diet has been identified as a major determinant of colorectal cancer (CRC) but little is known of its influence on CRC survival.

Aims: To study the influence of dietary factors on survival in patients who had undergone potentially curative CRC surgery.

Patients: Among 171 patients included in a case control study of CRC aetiological factors, 10 year survival data on 148 patients who underwent resection of the tumour for potential cure were obtained from a Registry of Digestive Tumours.

Methods: Tertiles of food and nutrient intakes were entered into Cox proportional hazards survival models, controlling for age, sex, tumour stage, and tumour location.

Results: Only five year survival was influenced by the pre-diagnosis diet. High energy intake, as a result of high carbohydrate, protein, and lipid intake, was strongly related to increased survival. Five year relative risk of death for the highest versus the two lowest tertiles of energy intake was 0.18 (95% confidence interval 0.07; 0.44). This effect was similar in both sexes, for the colon and for the rectum. It was stronger in patients with N+/M+ tumours (relative risk 0.06) than in those with less advanced tumours (relative risk 0.37; stage-energy interaction term non-significant). No specific food or nutrient could be identified as having prognostic significance.

Conclusions: Whether high energy intake selects less severe tumoral clones or modifies antitumoral immunity remains unclear. Larger series need to be investigated before conducting intervention studies but our findings should prompt nutritional follow up in CRC patients.

Colon cancer (CRC) is one of the most common cancers in the Western world. It is widely accepted that environmental factors, especially dietary factors, are involved in the aetiology of CRC. High intakes of fat, red meat, refined sugar, and energy have been associated with an increased risk of CRC.\(^\text{1,2}\) On the other hand, vegetable consumption is often related to a decreased risk of CRC.\(^\text{3,4}\) CRC survival is poor, with an overall 5 year survival rate of approximately 45%.\(^\text{5}\) Stage at diagnosis and possibility of resection of the tumour for cure are the main prognostic factors. Sex, age at the time of diagnosis,\(^\text{6}\) tumour site,\(^\text{7}\) and socioeconomic status\(^\text{8}\) have also been discussed as determinants of survival. Although the relationship between diet and CRC has been extensively studied, its influence on survival has been examined in only one study to date,\(^\text{9}\) while diet was associated with the prognosis of cancers of the lung,\(^\text{10}\) prostate,\(^\text{11}\) and breast.\(^\text{12}\) The aim of this study was to assess the influence of pre-diagnosis diet on five and 10 year survival of patients who underwent resection of CRC for potential cure.

PATIENTS AND METHODS

Study population

A case control study on the relationship between colorectal neoplasms and diet was conducted between 1985 and 1987 in the Côte d’Or area (Burgundy, France) to investigate risk factors in colorectal tumours. The present study included the colorectal cancer (CRC) cases from the case control study. Details of the studied population have been presented elsewhere.\(^\text{13}\) Briefly, patients were recruited from all gastroenterologists (public and private practices) in the area covered by a registry of digestive tumours. To meet a well defined eligibility, patients had to be residents of the Côte d’Or area, aged 30–79 years old, and had to present with a histologically proven primary CRC for the first time. Criteria for exclusion were polyposis coli, inflammatory bowel disease, previous colectomy, and previous cancer. Histopathological diagnosis was performed in the two laboratories that centralised all pathological examinations in the area and collaborated with the Registry of Digestive Tumours of the Côte d’Or. A total of 171 CRC cases (109 men, 62 women) were included in the case control study, with a participation rate of 79.9%. Palliative surgery, absence of surgery, and death within one month of tumour resection (even when curative) were additional exclusion criteria in the present study.

Data ascertainment

Individual and clinical data were obtained from medical files and recorded in the Registry of Digestive Tumours of the Côte d’Or. Tumour location was classified according to the International Classification of Diseases for Oncology, 9th revision, as colonic or rectal cancer. Stage at diagnosis was coded according to Dukes’ classification,\(^\text{14}\) and correspondence with the TNM classification\(^\text{15}\) was as follows: Dukes’ A, tumour infiltrating the submucosa or the lamina propria (T1-T2 N0 M0); Dukes’ B, tumour extending into the subserosa or into non-peritonealised, pericolic, or perirectal tissue (T3 N0 M0) or directly infiltrating other organs or structures and/or perforating the visceral peritoneum (T4 N0 M0); Dukes’ C, metastasis in regional lymph nodes (N+); and Dukes’ D, distant metastasis (M+). Information on familial history of CRC, type of surgery, and adjuvant treatments was also obtained. Possibility of resection of the tumour for potential cure was defined as macroscopic resection of all tumoral tissue. Follow up data (vital status and, when relevant, date of death) were obtained regularly from the Registry of Digestive Tumours of the Côte d’Or through medical and administrative sources.

Abbreviations: CRC, colorectal cancer; BMI, body mass index; RR, relative risk.
Dietary and lifestyle data were assessed with special care. Before the case control study was set up, a pilot study was performed to compare and validate two diet history methods (a questionnaire by meal and a questionnaire with a list of foods) for assessing current dietary intake. This pilot study resulted in a two hour detailed qualitative and quantitative questionnaire concerning diet in the year preceding diagnosis. The questionnaire followed the pattern of meals throughout the day. It was administered within three months of diagnosis at the subject’s home by a specially trained dietician who also coded the data. Nutritional data were transformed into a mean daily intake of nutrients, using a compilation food composition table worked out for the needs of the study, which included 318 simple foods and 188 mixed dishes. Tertiles of foods, nutrients, total energy, and alcohol free energy intakes were computed separately by sex. Tobacco consumption (summarised in pack-years) and alcohol intake (g/day) were also assessed. Physical activity was recorded as low (totally sedentary lifestyle), high (recreational or occupational activity requiring strenuous physical activity), or moderate. Information on weight and height was obtained from subjects at the time of interview. Body mass index (BMI) was calculated as weight/(height$^2$) and tertiles of BMI were computed.

Statistical analysis

All data were entered into a computer based data file. Descriptive statistics (mean, SD, tertiles) were calculated for all dietary variables. Associations ($\chi^2$ test) and interactions (Mantel-Haenszel $\chi^2$ test) were tested for all adjustment variables. Death from any cause within five and 10 years of diagnosis was the end point. A multivariate Cox proportional hazards model was applied using SAS (8th version). The hypothesis of proportionality of risk over time was assessed for each covariate using the graphical method and, when needed, by testing the statistical significance of an interaction term between the explanatory variable and time. Kaplan-Meier survival curves and crude log rank tests were calculated for all variables before multivariate analysis. Because patients with Dukes’ A and B tumours had very similar survival curves and because patients with Dukes’ D tumours resected for potential cure were rare (four patients) and had a crude five year survival (25.0%) comparable with Dukes’ C patients (28.1%), the tumour stage variable was set as Dukes’ A-B in one group and Dukes’ C-D in another group. In multivariate survival analysis, the relative risk of death (RR) estimates for nutrient intake and their 95% confidence intervals (95% CI) were adjusted for age, sex, tumour location (rectum or colon), and stage (Dukes’ A-B or C-D). Energy intake was also entered into the models as an adjustment variable, except for nutrients presenting with Pearson correlation coefficients (p) with an energy intake over 0.80 to avoid co-adjustment.

**RESULTS**

Among the 171 patients included in the initial case control study, 19 had undergone palliative surgery or no surgery, one had undergone potential curative surgery but died seven days after surgery, and three had undetermined tumour stage. These 23 patients were therefore excluded from the survival study. The characteristics of the remaining 148 patients (97 men, 51 women) are presented in table 1. None was lost to follow up.

### Five year survival

Forty six patients (31.1%) died within five years of diagnosis. In univariate analysis, tumour stage was the strongest variable related to five year survival as 20 (17.9%) of 112 Dukes’ A-B patients and 26 (72.2%) of 36 Dukes’ C-D patients died within five years (p<0.0001). Six (12.0%) of 50 patients with a high energy intake, 22 (45.8%) of 48 patients with a moderate energy intake, and 18 (36.0%) of 50 patients with a low energy intake died within five years (p=0.0007). Age under 65 years (p=0.17), female sex (p=0.25), and colonic location of the tumour (p=0.22) were also associated with better five year survival, but these relationships were not statistically significant. There was a significant association between age and...
energy intake ($p=0.001$) but no significant interaction regarding survival ($p=0.14$). No other association was found between adjustment variables, in particular between energy intake and tumour stage ($p=0.18$) or between BMI, physical activity, and energy intake.

The adjusted RRs of death within five years of diagnosis obtained using the Cox model are presented in tables 2–4. We found significant interactions in terms of survival between sex and tumour location ($p=0.05$) and between tumour stage and BMI ($p=0.03$). Interaction terms were allocated in the multivariate model for further analyses. Tumour stage was the strongest prognostic factor, with the effect being greater in patients with colon tumours than in those with rectal tumours. We also observed better survival in women with Dukes’ A-B rectal tumours (compared with men with Dukes’ A-B colonic tumours) and in patients with Dukes’ C-D rectal tumours. Energy intake was significantly associated with survival, with the effect being stronger in patients with advanced than in those with non-advanced tumours, although the interaction term was not statistically significant: five year adjusted RR for high energy intake was 0.37 (95% CI 0.12; 1.12) ($p=0.08$) for Dukes’ A-B patients ($n=112$ patients, $n^*=20$ deaths) and 0.06 (95% CI 0.01; 0.30) ($p<0.001$) for Dukes’ C-D patients ($n=36$ patients, $n^*=26$ deaths). The effect of energy intake on survival was similar in both sexes. The corresponding risk for male patients ($n=97$ patients, $n^*=33$ deaths) was 0.20 (95% CI 0.06; 0.61) ($p=0.005$) and was 0.18 (95% CI 0.03; 0.96) ($p=0.04$) for female patients ($n=51$ patients, $n^*=13$ deaths).

Tumour location did not significantly influence the impact of energy intake on survival: five year adjusted RR of death for high energy intake was 0.21 (95% CI 0.06; 0.68) ($p=0.01$) in patients with colon tumours ($n=88$ patients, $n^*=24$ deaths) and 0.15 (95% CI 0.03; 0.69) ($p=0.01$) in patients with rectal tumours ($n=60$ patients, $n^*=22$ deaths).

Because tobacco and alcohol consumption were rare in women, these variables were only examined in men. They had no statistically significant effect on survival. Physical activity and BMI were not statistically related to five year survival. Patients with a familial history of CRC had slightly decreased survival compared with their counterparts (RR 0.63 (95% CI 0.22; 1.79); $p=0.39$). Adjuvant treatments had no significant effect on five year prognosis (RR 0.47 (95% CI 0.28; 1.80); $p=0.71$). Energy intake was strongly correlated with intake of carbohydrates (correlation coefficient $p=0.90$), proteins ($p=0.90$), lipids ($p=0.85$ and $p=0.86$, respectively). Therefore, energy intake was not entered into the models as an adjustment variable when studying these variables. When controlling for age, sex, stage, tumour site, and interaction terms, all macronutrients (glucids, lipids, proteins) were significantly associated with survival, with the effect being

Table 2  Adjustment variables. Multivariate survival analysis [Cox model]. $n=148$ patients

<table>
<thead>
<tr>
<th>Adjustment variable</th>
<th>Group comparison</th>
<th>5 year RR of death</th>
<th>95% CI</th>
<th>$p$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Women v men</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colonic tumour</td>
<td></td>
<td>0.39 (0.15; 0.99)</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>Rectal tumour</td>
<td></td>
<td>1.61 (0.48; 5.39)</td>
<td>0.44</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>$\geq 65$ v $&lt;65$ year</td>
<td>1.28 (0.67; 2.45)</td>
<td>0.45</td>
<td></td>
</tr>
<tr>
<td>Tumour stage</td>
<td>Dukes’ C-D v Dukes’ A-B</td>
<td>15.21 (6.03; 38.38)</td>
<td>$&lt;0.0001$</td>
<td></td>
</tr>
<tr>
<td>Colonic tumour</td>
<td></td>
<td>3.80 (1.50; 9.65)</td>
<td>0.005</td>
<td></td>
</tr>
<tr>
<td>Rectal tumour</td>
<td></td>
<td>0.18 (0.07; 0.44)</td>
<td>0.0002</td>
<td></td>
</tr>
</tbody>
</table>

RR, relative risk; 95% CI, 95% confidence interval; CRC, colorectal cancer; H v 2L, highest tertile compared with the two lowest tertiles.

Table 3  Five year relative risk of death according to specific foods [controlled for age, sex, tumour stage, tumour location, and energy intake]

<table>
<thead>
<tr>
<th>Food</th>
<th>1st tertile (Ref)</th>
<th>2nd tertile</th>
<th>3rd tertile</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR 95% CI</td>
<td>RR 95% CI</td>
<td>RR 95% CI</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meat</td>
<td>1.0</td>
<td>1.32 (0.59; 2.95)</td>
<td>1.64 (0.75; 3.58)</td>
</tr>
<tr>
<td>Delicatessen</td>
<td>1.0</td>
<td>1.28 (0.64; 2.58)</td>
<td>0.93 (0.40; 2.14)</td>
</tr>
<tr>
<td>Fish</td>
<td>1.0</td>
<td>2.07 (1.00; 4.26)</td>
<td>1.24 (0.58; 2.65)</td>
</tr>
<tr>
<td>Eggs</td>
<td>1.0</td>
<td>0.66 (0.30; 1.45)</td>
<td>1.10 (0.52; 2.33)</td>
</tr>
<tr>
<td>Fats</td>
<td>1.0</td>
<td>1.44 (0.73; 2.83)</td>
<td>0.79 (0.31; 2.02)</td>
</tr>
<tr>
<td>Vegetables</td>
<td>1.0</td>
<td>1.03 (0.47; 2.29)</td>
<td>1.09 (0.49; 2.45)</td>
</tr>
<tr>
<td>Fruits</td>
<td>1.0</td>
<td>0.81 (0.38; 1.70)</td>
<td>0.84 (0.37; 1.88)</td>
</tr>
<tr>
<td>Rice and pasta</td>
<td>1.0</td>
<td>0.97 (0.44; 2.14)</td>
<td>0.97 (0.44; 2.15)</td>
</tr>
<tr>
<td>Bread</td>
<td>1.0</td>
<td>1.41 (0.67; 2.97)</td>
<td>1.01 (0.43; 2.33)</td>
</tr>
<tr>
<td>Sweet products</td>
<td>1.0</td>
<td>0.95 (0.45; 2.03)</td>
<td>1.02 (0.48; 2.16)</td>
</tr>
<tr>
<td>Tea and coffee</td>
<td>1.0</td>
<td>1.69 (0.78; 3.64)</td>
<td>1.46 (0.64; 3.22)</td>
</tr>
<tr>
<td>Dairy products</td>
<td>1.0</td>
<td>0.53 (0.24; 1.15)</td>
<td>0.63 (0.30; 1.33)</td>
</tr>
</tbody>
</table>

Ref, Reference; RR, relative risk; 95% CI, 95% confidence interval; *Test for linear trend.
strongest for lipids, especially saturated and monounsaturated fatty acids. When controlling for energy intake, no other specific nutrients (controlled for age, sex, tumour stage, tumour location, and interaction terms (Cox model). n=148 patients. 95% CI, 95% confidence intervals. controlling for age, sex, stage, tumour location, and interaction terms (energy intake groups (highest (H) versus two lowest (2L) tertiles), after controlling for rectal versus colonic location 3.12 (95% CI 1.32;7.35), 3.12 (95% CI 1.32;7.35), p=0.01), but not tumour stage, age, or sex. None of the energy, food, or nutrient intake variables were related to survival between five and 10 years.

DISCUSSION
In our series, five year survival in patients operated on for cure of CRC was influenced by the pre-diagnosis diet. While controlling for known prognostic factors, high energy intake, as a result of high lipid, protein, and carbohydrate intake, was strongly related to increased survival.

Because our population was included in a cancer registry, we had precise data on the tumours (histopathological diagnosis, stage, location, and treatment) and exhaustive and prolonged follow up data. Dietary data were collected with the objective of limiting potential bias due to the retrospective assessment of prognostic factors: a pilot study validated a questionnaire specifically designed for CRC risk factors, and the home face to face detailed interview was performed shortly after diagnosis by trained dieticians. As adjuvant treatments were rare at the time of inclusion (1985–1987), they did not interact with our results. Such a study would be more difficult to design today as chemotherapy and radiation therapies significantly modify the course of the disease. Stage was included a priori as an adjustment variable and our results confirm the importance of tumour extension on five year survival. Tumour location was found to be a significant interaction factor for five year survival in our study and has been mentioned as a significant prognostic factor in previous studies. Moreover, rectal location was the only significant Tumour location was found to be a significant interaction factor for five year survival in our study and has been mentioned as a significant prognostic factor in previous studies. Moreover, rectal location was the only significant 10 year prognostic factor, making it necessary to adjust for this parameter. Sex and age were included in our multivariate models because of their prognostic roles in overall and CRC specific survival, and because they influence dietary intake.

As intakes of most nutrients tend to be positively associated with total energy intake, we decided to control for energy intake in our multivariate models. In addition, total energy intake had already been identified as a prognostic factor in survival between five and 10 years after diagnosis
Ten years after diagnosis, 70 patients (47.3%) were dead while none was lost to follow up. Within the 10 year period, the hypothesis of proportionality of risk was not verified for tumour stage or energy intake. A separate survival analysis was therefore performed on those who had survived the first five years. The assumption of proportionality of risk was verified for all variables in this group. During this period, only tumour location had a significant prognostic role (RR of death for rectal versus colonic location 3.12 (95% CI 1.32;7.35),
Nevertheless, for some variables which are strongly correlated with energy intake, this method could lead to co-
adjustment, and we avoided it for macronutrients and some fatty acids. We computed both total and alcohol free energy
intakes, but alcohol free energy intake was kept for further analysis, as alcohol has been shown to be a separate risk fac-
tor for colorectal tumours. In this study, alcohol by itself was not associated with survival.

Some limitations of our data set must be discussed. Our study was initially designed to assess risk factors, not
prognostic factors, which led to collection of the pre-diagnosis diet. However, some authors have shown that pre- and
post-diagnosis diets tended to be similar in cancer patients, suggesting that high energy intake may truly influence the
course of the disease.

We cannot exclude recall bias as dietary intake was retrospectively assessed. This bias may be reinforced in
patients presenting with a digestive cancer and interviewed for their dietary habits. In CRC, for some variables (tobacco and
alcohol consumption and CRC familial history) it has been shown that dietary intake may change after diagnosis. Reac-
tion to tumour stage have not been found for energy intake in studies of CRC aetiological factors. In our population, we did not observe
any statistically significant interaction between tumour stage and energy intake.

Another limitation of our study is potential selection bias. As a common feature of retrospective assessment of risk fac-
tors of death, only surviving patients participated in the dietary interview, and among them 20.1% refused. Looking for
a potential effect of diet on CRC survival, we decided not to include incurable patients. Extrapolation of our results to palli-
ative treated patients should therefore not be attempted. However, progress in chemotherapy has led to longer survival of
patients with high pre- and post-diagnosis dietary intake would form greater body stores of nutrients, they may live longer than their counterparts who are able to eat less. According to this interpretation, dietary intake and body stores would reinforce immunity and could have an indirect effect on cancer recurrence or growth. However, we did not observe any association between CRC survival and BMI. Experiments tend to support an opposing phenomenon, as energy restriction increases the natural killer cell activity involved in antitumour immunity. But such experiments were conducted in healthy patients. Moreover, it has been proved that natural killer cell activity is specifically linked to some polyunsaturated fatty acids and not to global energy intake. Longer survival because of reinforced anti-
tumour immunity due to greater nutrient intake and body stores should be observed with other cancers. It has been observed in prostate cancer but not in breast cancer where, on the contrary, high energy intake was associated with decreased survival. But in these cancers, fatty acid intake, which is strongly correlated with energy intake, could have a specific prognostic role because of its influence on hormonal metabolism.

In conclusion, high energy intake was strongly associated with prolonged survival in patients who underwent potential curative surgery for CRC. This prognostic effect was stronger in advanced than in local stage disease and may be specifically related to CRC mortality. Biological explanations for this phenomenon remain unclear. Larger series should be used to investigate dietary influence on CRC survival before intervention studies are conducted, but our results should prompt nutritional evaluation and follow up in CRC patients.

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References

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