Dietary fibre in food and protection against colorectal cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC): an observational study

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Summary

Background Dietary fibre is thought to protect against colorectal cancer but this view has been challenged by recent prospective and intervention studies that showed no protective effect.

Methods We prospectively examined the association between dietary fibre intake and incidence of colorectal cancer in 519 978 individuals aged 25–70 years taking part in the EPIC study, recruited from ten European countries. Participants completed a dietary questionnaire in 1992–98 and were followed up for cancer incidence. Relative risk estimates were obtained from fibre intake, categorised by sex-specific, cohort-wide quintiles, and from linear models relating the hazard ratio to fibre intake expressed as a continuous variable.

Findings Follow-up consisted of 1 939 011 person-years, and data for 1065 reported cases of colorectal cancer were included in the analysis. Dietary fibre in foods was inversely related to incidence of large bowel cancer (adjusted relative risk 0·75 [95% CI 0·59–0·95] for the highest versus lowest quintile of intake), the protective effect being greatest for the left side of the colon, and least for the rectum. After calibration with more detailed dietary data, the adjusted relative risk for the highest versus lowest quintile of fibre from food intake was 0·58 (0·41–0·85). No food source of fibre was significantly more protective than others, and non-food supplement sources of fibre were not investigated.

Interpretation In populations with low average intake of dietary fibre, an approximate doubling of total fibre intake from foods could reduce the risk of colorectal cancer by 40%.

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Introduction

Whether dietary fibre (non-starch polysaccharides) lowers the risk of colorectal cancer is debatable. In reports from large prospective studies in the USA, Finland, and Sweden, no protective effects of fibre were seen.[1–3] In addition, results of large intervention trials have shown that supplements of bran, soluble fibre, or vegetables have not reduced recurrence rates of adenomatous colorectal polyps.[4–6] Death rates for colorectal cancer in vegetarians are no different from those in non-vegetarians.[7]

These findings of no effect have challenged consensus recommendations, drawn from a large body of epidemiological and experimental findings, that population intakes of fibre should be increased to reduce the risk of colorectal cancer.[8,9] However, all prospective studies of diet and cancer have been done in single populations in whom dietary habits are more or less homogeneous, so that the extent of measurement error would have obscured all but very large underlying associations with diet.[10,11] Measurement error can be reduced by studying populations with diverse dietary practices, thus increasing the between-person variance in diet, and enabling measurement error to be kept to a minimum.[10] Such was the approach behind the large prospective collaborative project done in ten different European countries, the European Prospective Investigation of Cancer and Nutrition (EPIC).[12] Other reports[13,14] have shown the heterogeneity of dietary intakes of foods supplying dietary fibre in this collaborative cohort. For example, there is over a three-fold range in total average population consumption of fruit and vegetables (excluding potatoes) between centres in Sweden and in southern Spain.[13,14]

Methods

Participants

The EPIC cohort consists of subcohorts recruited from 22 centres from Denmark, France, Germany, Greece,

Italy, the Netherlands, Norway, Spain, Sweden, and the UK, allowing comparisons between regions with very different rates of cancer occurrence and distribution of lifestyle and food habits. We administered food-related questionnaires and lifestyle and personal questionnaires and obtained anthropometric measurements from all participants at the time of enrolment. The methods have been reported in full by Riboli and colleagues.[15]

The 519 978 eligible participants were mostly aged 25–70 years and recruited from the general population residing in a specific geographical region—a town or a province. Exceptions were the French cohort (based on female members of the health insurance for state school employees), the Utrecht cohort, Netherlands (based on women attending breast cancer screening), the Ragusa cohort, Italy (based on blood donors and their spouses), and most of the Oxford cohort, UK (based on vegetarian and health-conscious volunteers).

Procedures

As a result of several studies done in the early 1990s,[12] we measured diet by country-specific questionnaires designed to capture local dietary habits and to provide high compliance. For calibration, we obtained a second dietary measurement from an 8% random sample (36 000 individuals) of the cohort using a computerised 24-h diet recall method developed ad hoc.[16] The extensive lifestyle questionnaires included questions on education and socioeconomic status, occupation, history of previous illness and disorders or surgical operations, lifetime history of consumption of tobacco and alcoholic beverages, and physical activity.

Follow-up was based on population cancer registries in seven of the participating countries: Denmark, Italy, the Netherlands, Spain, Sweden, the UK, and Norway. In France, Germany, and Greece, we used a combination of methods including health insurance records, cancer and pathology registries, and active follow-up through participants and their next-of-kin. Mortality data were also obtained from either the cancer registry or mortality registries at the regional or national level. By June, 2002, for all centres using cancer registry data, reports to the IARC represented complete follow-up until December, 1998, or December, 1999. For France and Germany—countries using individually based follow-up—the end of the follow-up was 2002, when the last known contact, or date of diagnosis, or death was available. We included the results from all centres except for Greece and Norway (because of the small numbers of cases accruing there from a short follow-up time).

We used the 10th revision of the International Statistical Classification of Diseases, Injuries and Causes of Death (ICD). Mortality data were coded following the rules of ICD-10, and cancer incidence data following ICD-0-2. Cancer of the rectum included tumours in the rectosigmoid junction (C19) and rectum (C20). We excluded anal canal tumours. Right colon tumours included the caecum, appendix, ascending colon, hepatic flexure, transverse colon, and splenic flexure (C18.0–18.5). Left colon tumours included the descending and sigmoid colon (C18.6–18.7). We included all incident cases of colorectal cancer ICD-0-2 C18, C19, C20 with dietary data for the period of complete follow-up, but excluded prevalent cases.

Statistical analysis

To convert the weight of foods derived from the food questionnaires to daily fibre intakes, participating countries used country-specific food tables, incorporating analyses for dietary fibre or plant polysaccharides, which are based on different definitions and analytical techniques and give different values for common foods.[17] To assess the possible effects of sex and different analytical procedures for fibre analysis, we used sex-specific, and sex-and-country-specific quintiles of dietary fibre in the analysis. Daily fibre intake—derived from the Englyst and the Southgate methods[18]—was calculated in the UK cohorts. There was no significant difference between the estimates of relative risk for colorectal cancer using these methods, and we used sex-specific quintiles and the Englyst non-starch polysaccharide values for the UK cohorts. Data for individuals in the top and bottom 1% of the ratio of energy intake to estimated energy requirement (calculated from age, sex, and bodyweight)[19] and from the top 1% of sex-specific fibre intakes, were excluded from the analysis to reduce the effect on the analysis of implausible extreme values.

Analyses were done with Cox's regression and were stratified by centre to control for centre effects related to different methods of fibre analysis,[17] follow-up procedures, and questionnaire design. The 20 French administrative regions were condensed into four geographical regions (northeast, northwest, south, and south coast). The five Italian centres were combined into one, as were the four Spanish centres, because of small numbers of cases in each centre. The UK Oxford centre was divided into two, for general population and health conscious participants. Age was used as the primary time variable in all Cox's regression models, with year of follow-up and sex included as covariates. The analysis focused on dietary fibre—with other dietary variables included as covariates—and anthropometric variables. These quantitative variables were categorised according to sex-specific quintiles defined over the entire cohort. We analysed the data using variables as categorical and as continuous, scored from 1 to 5 according to the interquintile interval in which an observation lay. Trend tests were calculated on the basis of these quintile based scores. Categorical relative risks were calculated from the hazard ratio.[20]

For the purpose of making isoenergetic comparisons, we included weight in all models. Estimated total energy intake was included to control partly for the error in the estimated intake of fibre, since there is high correlation between the errors of estimation of different dietary components. To improve this error correction, estimated energy intake was divided into energy from fat and energy from non-fat sources, since it is mostly the non-fat components of the diet that contribute to fibre intake. Models were run including non-fat energy and with and without energy from fat, and the results did not differ; models including both non-fat and fat energy were included in the results. Partial correlations (adjusting for age and centre) for fibre with energy excluding fat were 0·473 in men and 0·529 in women, and with energy from fat were 0·037 in men and –0·030 in women. Smoking and physical exercise had no significant effect, and these were therefore not included in the models. To control for body size and obesity, we included weight and height in the models.

	Large bowel cancer cases			Cohort numbers			Fibre intake (g per day)		
	Men	Women	All	Men	Women	All	Men	Women	All
Country									
France	0	166	166	0	71 874	71 874	·· (··)	22·92 (6·94)	22·92 (6·94)
Italy	35	49	84	13 508	30 489	43 997	24·93 (9·12)	22·02 (7·29)	22·92 (8·01)
Spain	41	33	74	15 025	24 910	39 935	29·12 (8·34)	23·35 (7·08)	25·52 (8·08)
UK	94	112	206	23 905	55 957	79 862	20·00 (7·50)	20·39 (7·06)	20·27 (7·20)
Netherlands	14	86	100	9 998	28 913	38 911	26·77 (7·61)	22·55 (5·49)	23·63 (6·38)
Germany	59	34	93	22 137	29 354	51 491	23·83 (7·51)	21·55 (6·41)	22·53 (7·00)
Sweden	110	122	232	22 840	29 519	52 359	21·33 (7·78)	19·08 (6·47)	20·06 (7·16)
Denmark	58	52	110	26 599	29 181	55 780	20·48 (6·70)	19·51 (6·51)	19·97 (6·62)
Age (years)									
<35	1	0	1	7 637	18 404	18 404	23·32 (8·73)	20·53 (7·13)	21·35 (7·74)
35–44	13	21	34	22 172	53 336	53 336	24·67 (8·72)	21·85 (7·02)	22·68 (7·67)
45–54	91	188	279	48 118	118 198	118 198	23·08 (8·35)	21·59 (6·90)	22·02 (7·38)
55–64	225	300	525	46 853	90 319	90 319	22·48 (7·86)	21·51 (6·80)	21·84 (7·20)
⩾65	81	145	226	9 232	19 940	19 940	20·64 (7·29)	21·09 (6·74)	20·95 (6·92)
All	411	654	1065	134 012	300 197	300 197	22·98 (8·26)	21·52 (6·90)	21·97 (7·38)

Values are number of participants or mean (SD).

Table 1: **Description of the EPIC cohort**

To correct for centre-specific bias and for regression dilution within each centre-sex stratum, the 24-h recall nutrient values were regressed on the main study dietary questionnaire values, within each centre, for men and women separately, thus providing sex-specific and centre-specific regression coefficients.[21,22] This analysis was a multivariate procedure, including fibre, energy from fat, and energy from non-fat sources simultaneously. For every individual in the main study, we obtained adjusted values of these three variables by applying both the intercept and slope variables of the appropriate sex-specifc and centre-specific regression to the main study questionnaire values: adjusted value=intercept+slope (observed questionnaire value). Use of both the intercept and slope variables, age-specific and centre-specific, ensured that centre-specific bias was addressed, as was that of regression dilution. We then ran Cox's regression models with the adjusted values for each individual. The SE of the de-attenuated coefficient was calculated with bootstrap sampling in the calibration and disease models consecutively.[23] 300 repetitions gave a sufficiently stable estimate of the SE of the corrected regression coefficient. The p value for trend for the de-attenuated β was obtained by dividing the de-attenuated β by the bootstrap-derived SE approximating the standard normal distribution.

Role of the funding source

EPIC was funded jointly by the European Commission funding authorities listed in the acknowledgments. These funding authorities agreed to fund our proposed design and running of the study, but had no role in the subsequent management of the study or in the writing of the report. The report was not submitted to them for approval before publication.

Results

Since 1992, we have obtained 1 939 011 person-years (average 4·5 years) of follow-up. Our study is based on 1065 incident colorectal cancer cases with complete and satisfactory data as described above. Of these, 706 tumours were located in the colon (287 right side, 286 left side, 133 overlapping or unspecified) and 359 in the rectum. Histological confirmation was available for 1035 cases. Table 1 shows numbers of colorectal cancer tumours according to country, age and sex, and country-specific, sex-specific, and age-specific intakes of fibre.

Table 2 shows baseline characteristics by sex-specific quintiles of fibre intake. Height, weight, and body-mass index did not differ by much across quintiles despite some significant trends due to the very large sample size. Across the quintiles of fibre there was a significant

	Quintile					p
	1	2	3	4	5	
Women						
Fibre (g per day)	12·64 (2·27)	17·45 (1·03)	20·89 (0·99)	24·69 (1·28)	31·91 (3·97)	··
Number in each quintile	60 043	60 074	60 003	60 038	60 039	··
Age (years)	50·98 (10·66)	51·37 (10·09)	51·51 (9·93)	51·32 (9·85)	51·04 (9·77)	0·588
Weight (kg)	65·35 (11·75)	65·74 (11·70)	65·70 (11·56)	65·71 (11·52)	65·69 (11·71)	<0·0001
Height (m)	1·62 (0·07)	1·62 (0·07)	1·62 (0·07)	1·62 (0·07)	1·62 (0·07)	<0·0001*
Body-mass index (kg/m^2)	24·98 (4·38)	25·06 (4·35)	25·00 (4·32)	24·97 (4·34)	25·01 (4·48)	0·570
Energy from fat (MJ)	2·40 (0·79)	2·73 (0·85)	2·94 (0·91)	3·17 (0·98)	3·52 (1·12)	<0·0001
Non-fat energy (MJ)	4·16 (1·04)	4·85 (1·07)	5·33 (1·14)	5·83 (1·22)	6·72 (1·45)	<0·0001
Men						
Fibre (g per day)	12·77 (2·41)	18·03 (1·17)	21·97 (1·15)	26·51 (1·55)	35·61 (5·30)	··
Number in each quintile	26 810	26 796	26 806	26 798	26 802	··
Age (years)	53·23 (10·22)	53·38 (9·75)	52·79 (9·80)	51·94 (9·89)	50·35 (9·88)	<0·0001
Weight (kg)	81·09 (12·10)	81·45 (11·99)	81·29 (11·81)	81·17 (11·77)	80·86 (11·87)	0·237
Height (m)	1·75 (0·07)	1·75 (0·07)	1·75 (0·07)	1·75 (0·07)	1·75 (0·08)	<0·0001*
Body-mass index (kg/m^2)	26·42 (3·59)	26·50 (3·56)	26·45 (3·57)	26·44 (3·62)	26·56 (3·72)	0·0002
Energy from fat (MJ)	2·88 (0·96)	3·30 (1·02)	3·59 (1·12)	3·88 (1·20)	4·29 (1·38)	<0·0001
Non-fat energy (MJ)	5·26 (1·44)	6·11 (1·40)	6·69 (1·46)	7·33 (1·56)	8·38 (1·82)	<0·0001

Values are mean (SD). *Differences were highly significant but in the order of 3 mm across quintile 1–5.

Table 2: **Baseline characteristics by quintile of fibre intake**

	Quintile					Hazard ratio (95% CI) for each quintile increase	p
	1	2	3	4	5		
Colorectal cancers							
Number	237	234	200	200	194	..	
Hazard ratio (95% CI)	1·00	0·94 (0·78–1·13)	0·77 (0·63–0·95)	0·76 (0·61–0·95)	0·75 (0·59–0·95)	0·923 (0·873–0·976)	0·005
Colon cancers							
Number	156	158	131	130	131	..	
Hazard ratio (95% CI)	1·00	0·95 (0·75–1·19)	0·75 (0·58–0·96)	0·71 (0·55–0·94)	0·72 (0·54–0·97)	0·908 (0·848–0·972)	0·006
Left colon cancer (n=286)	1·00	0·66 (0·46–0·93)	0·55 (0·37–0·80)	0·51 (0·34–0·77)	0·65 (0·43–0·99)	0·891 (0·804–0·989)	0·030
Right colon cancer (n=287)	1·00	1·21 (0·84–1·71)	0·93 (0·63–1·37)	0·89 (0·59–1·35)	0·73 (0·46–1·19)	0·911 (0·819–1·013)	0·087
Rectal cancers							
Number	81	76	69	70	63	..	
Hazard ratio (95% CI)	1·00	0·92 (0·66–1·27)	0·83 (0·59–1·18)	0·85 (0·59–1·24)	0·80 (0·53–1·22)	0·952 (0·864–1·048)	0·319

Cox's regression using age, weight, height, sex, non-fat energy, energy from fat, and stratified by centre.

Table 3: **Numbers of cancers and hazard ratios by quintile of sex-specific total fibre intake**

trend with energy derived from non-fat sources. This trend reflected the contribution of the non-fat components of the diet that contribute to fibre intake, such as cereals and fruit. The trend with fat energy was also significant but less pronounced, reflecting lower correlations between fat energy and fibre.

Table 3 shows the number of cancers by quintile and the hazard ratios. The hazard ratio for colorectal cancer for the highest quintile was 0·75 (95% CI 0·59–0·95)—a significant reduction in risk. The trend in hazard ratio across quintiles was also significant (p=0·005), the regression coefficient (β=0·080) predicting an 8% reduction in risk for each quintile increase in fibre. These associations did not significantly differ when analysed according to less than 2, 2–4, and more than 4 years of follow-up. Trend effects were significant for colon cancer (p=0·006) and the reduction in hazard ratio in the top quintile was also significant, 0·72 (0·54–0·97). Neither the trend across quintiles nor the hazard ratio in the highest quintile showed significant differences for rectal cancer (0·80; 0·53–1·22). The protective effect of fibre was no greater for the left-sided colon (0·65; 0·43–0·99) than the right-sided colon (0·73; 0·46–1·19). Further analyses showed that fibre was equally protective in women and men and that adjustment for red and processed meat did not affect these results (data not shown).

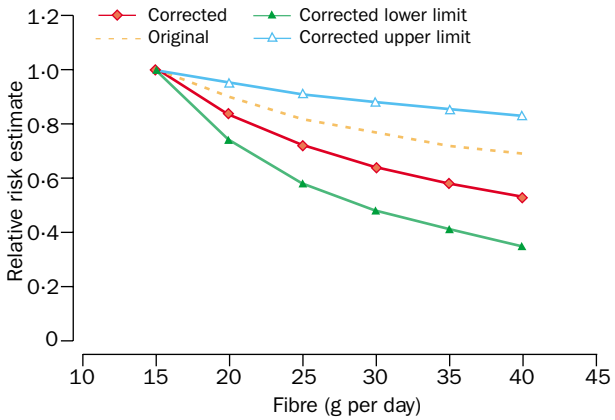

Figure 1: **Relative risk for colorectal cancer according to dietary fibre intake**
Calculated from Cox's regression using age, weight, height, sex, non-fat energy, energy from fat. Original estimates are calculated from the hazard ratio[20] for each quintile increase in energy adjusted fibre (table 3).

Figure 1 shows the continuous and de-attenuated risks for colorectal cancer according to the energy adjusted values of total fibre intake. The β coefficient estimate for log fibre intake based on the observed values was –0·38 (SE 0·13, p=0·002), whereas that for the calibrated values was –0·64 (SE 0·23, p=0·005).

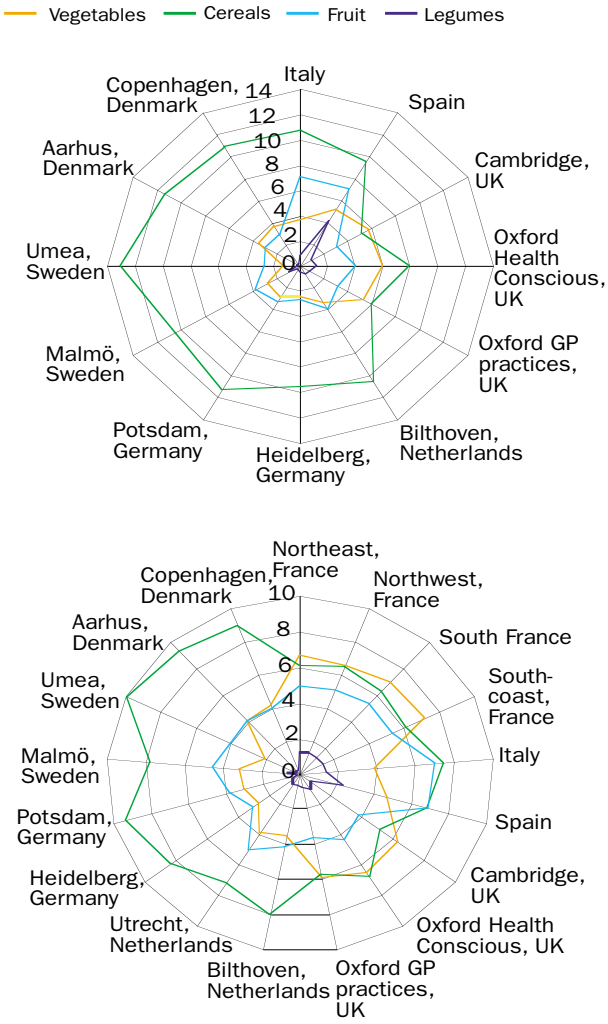

Figure 2: **Average dietary fibre intake in g per day from different food sources for men (upper) and women (lower)**
Calculated from the dietary questionnaires for each of the centres used in this analysis. The vegetables category excludes potatoes, legumes, soy products, and tomato products. The cereals category excludes cakes and biscuits.

	Quintile					Hazard ratio for each quintile increase	p
	1	2	3	4	5		
Cereal fibre (g)	4·72 (2·28)	6·61 (2·82)	7·93 (3·31)	9·35 (3·91)	12·05 (5·71)	..	
Hazard ratio (95% CI)	1·00	0·89 (0·74–1·08)	0·85 (0·69–1·03)	0·88 (0·71–1·08)	0·78 (0·62–0·98)	0·950 (0·901–1·002)	0·060
Vegetable fibre (g)	2·83 (1·72)	3·77 (2·10)	4·42 (2·42)	5·11 (2·81)	6·48 (3·85)	..	
Hazard ratio (95% CI)	1·00	0·94 (0·77–1·15)	0·95 (0·77–1·16)	1·00 (0·81–1·24)	0·88 (0·70–1·11)	0·983 (0·932–1·035)	0·517
Legumes fibre (g)	0·45 (0·68)	0·65 (0·92)	0·85 (1·14)	1·14 (1·47)	1·73 (2·17)	..	
Hazard ratio (95% CI)	1·00	1·02 (0·83–1·26)	1·10 (0·91–1·34)	1·18 (0·97–1·43)	1·04 (0·84–1·30)	1·025 (0·976–1·077)	0·311
Fruit fibre (g)	2·21 (1·56)	3·41 (2·00)	4·29 (2·38)	5·36 (2·87)	7·76 (4·40)	..	
Hazard ratio (g)	1·00	0·69 (0·57–0·85)	0·76 (0·63–0·92)	0·82 (0·66–0·99)	0·78 (0·64–0·97)	0·967 (0·922–1·015)	0·174

Analyses are done with Cox's regression using age, weight, height, sex, non-fat energy, energy from fat, and stratified by centre.

Table 4: **Intakes of fibre and colorectal cancer by quintile of sex-specific source of fibre intake**

This linear decrease in risk corresponds to a relative risk of 0·58 (0·41–0·85) for colorectal cancer incidence at a mean of 35 g dietary fibre (the highest quintile) compared with the baseline mean fibre intake of 15 g in the lowest quintile. Further analysis showed that adjustment for alcohol did not affect these results (data not shown).

Figure 2 shows sources of fibre intake in men and women by the centres used in this analysis. Cereals were the main sources of fibre in the Netherlands, Germany, Sweden, and Denmark, whereas vegetables were most important in France and the UK. Fruit was an important source of fibre in Italy and Spain. Legumes and potatoes contributed small amounts and were more important in Spain, the Netherlands, and Denmark than in other regions, but consumption in other regions averaged 2 g or less. Mean fibre from cakes and biscuits, tomato sauces, and soya products averaged less than 1 g per day.

Table 4 shows that effects for food sources of fibre were not as consistent as those for total fibre. The trends in risks associated with cereal fibre, and fruit, legume, and vegetable sources of fibre were not significant, nor did they differ significantly from each other. Analyses for fibre from cakes and biscuits, potatoes, tomato pastes, and soya products were also not significant.

Discussion

Fibre is one of the most important, if controversial, factors thought to prevent colorectal cancer, with well established biological mechanisms underlying the hypothesis. When entering the large bowel, fibre increases stool weight, reduces transit time, dilutes colonic contents, and stimulates bacterial anaerobic fermentation. This process reduces contact between the intestinal contents and mucosa, and leads to production of short-chain fatty acids, acetate, propionate, and butyrate, which reduce pH and the conversion of primary to secondary bile acids.[24] Butyrate is a major source of energy for the distal colon and in cell lines it reduces cell proliferation and induces apoptosis, factors that are associated with inhibition of the transformation of the colonic epithelium to carcinoma.[24–27]

Our results showed that total dietary fibre consumption was inversely associated with colorectal cancer risk. However, we only studied fibre in foods. Foods supplying fibre also contribute many other nutrients and phytochemicals that have been linked to cancer protection and which could account for the protective effects seen.[8,9] Thus, our results cannot be extrapolated to any potential benefit of dietary supplements or additives containing fibre alone. The association was stronger for colon cancer, especially left-sided colon cancer, than for rectal cancer. The fact that the association was mainly with colon cancer rather than rectal cancer might be expected, since the rectum is empty most of the time,[28] reducing the diluting, antiproliferative, and nutritive effects attributed to fibre.

When fibre intake from the dietary questionnaire was calibrated with intake from the 24-h recall, the Cox's proportional hazard model showed an even greater reduction in risk, with a 40% reduction of risk when average intakes increased from the lowest to highest quintile of fibre intake (figure 1). CIs around the estimates are large, so that the risk may have been reduced by as little as 15 or as great as 60%. Even a moderate increase in fibre intake by those consuming the least in most populations would have significant effects on cancer prevention, and supports recommendations to increase population intakes of fibre in those populations consuming low amounts to reduce high rates of colorectal cancer.[8,9] Although minor differences in hazard ratios were seen between different sources of fibre, they were not significant, so that, on the basis of current data, no firm statement can be made as to whether any one source of dietary fibre is more protective than others.

Three other epidemiological studies have investigated prospectively the role of fibre in colon cancer protection.[1–3] However, only the US Nurses Health Study,[1] was based on a number of colorectal cancer cases as large as in the EPIC study, allowing separate analyses of colon and rectal cancers, and for multivariate analysis including several potential confounding factors. However, in the US nurses cohort, no associations between fibre intake from any source and colon and rectal cancers or adenomas were identified. This difference might reflect lower and less varied fibre intakes in the US Nurses cohort than in our cohort. In EPIC, the mean values in the lowest and highest fifth of the distribution of daily fibre intake are 12·6 g (SD 2·3) and 33·1 g (14·7) respectively. The corresponding figures for the US Nurses study are 9·8 g (1·7) to 24·9 g (5·5) so that about 30% of the EPIC cohort were consuming substantially more fibre than the mean of the highest quintile of the US Nurses study. Cereal fibre is very low in the US Nurses study, the median in the highest fifth of the distribution (4·8 g per day) approximating the mean in the lowest fifth in EPIC (4·7 g per day; 2·28).

Our findings for the potential for reducing colorectal cancer incidence by increasing fibre intake as foods have been adjusted for measurement error by calibrating intake obtained from the food questionnaire against a method that measures specific intake over a single day. We have used this information to calibrate both the

centre means and to deattenuate the individual values on a sex-specific and centre-specific basis by standard methods;[21,22] the crude risks underestimated the protective effects of fibre on colorectal cancer risks when compared with the corrected risks (figure 1). However even the deattenuated risks are probably underestimated since these standard methods assume absence of correlations of errors between the reference and the food intake questionnaire.[10,11] Furthermore, our results are for a limited period of follow-up and the association could strengthen when longer exposure times are assessed. The potential for protection by fibre from foods in populations with current low intakes might therefore be even greater than our findings, which predict a 40% reduction in colorectal cancer risk when intakes of fibre are approximately doubled.

Contributors

E Riboli is overall coordinator of the EPIC study, which he designed and implemented in collaboration with R Kaaks, N Slimani, and the main investigators in the collaborating centres: N E Day, S A Bingham, F Clavel-Chapelon, H Boeing, A Tjønneland, K Overvad, C Martinez, M Dorronsoro, C A Gonzalez, T J Key, A Trichopoulou, P Vineis, R Tumino, H B Bueno de Mesquita, P H M Peeters, G Berglund, G Hallmans, and E Lund. N Slimani, E Kesse, A Nieters, A Naska, V Krogh, and G Skeie supervised the collection and analysis of dietary data. N E Day, S A Bingham, R Luben, P Ferrari, and T Norat analysed the data. S A Bingham wrote the report, taking into account the comments and suggestions of the co-authors.

Conflict of interest statement

None declared.

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References

1 Fuchs CS, Giovannucci E, Colditz, GA, et al. Dietary fiber and the risk of colorectal cancer and adenoma in women. *N Engl J Med* 1999; **340:** 169–76.

2 Terry P, Giovannucci E, Michels KB, et al. Fruit, vegetables, dietary fiber, and risk of colorectal cancer. *J Natl Cancer Inst* 2001 **93:** 525–33.

3 Pietinen P, Malila N, Virtanen M, et al. Diet and the risk of colorectal cancer in a cohort of Finnish men. *Cancer Causes Control* 1999; **10:** 387–96.

4 Schatzkin A, Lanza E, Corle D, et al. Lack of effect of low fat high fiber diet on the recurrence of colorectal adenomas. *N Engl J Med* 2000; **342:** 1149–55.

5 Alberts DS, Martinez ME, Roe DJ, et al. Lack of effect of a high fiber cereal supplement on the recurrence of colorectal adenomas. *N Engl J Med* 2000; **342:** 1156–62.

6 Bonithon-Kopp C, Kronborg O, Giacosa A, et al. Calcium and fibre supplementation in prevention of colorectal adenoma recurrence: a randomised intervention trial. *Lancet* 2000; **356:** 1300–06.

7 Key TJ, Fraser GE, Thorogood M, et al. Mortality in vegetarians and non-vegetarians: a collaborative analysis of 8300 deaths among 76 000 men and women in five prospective studies. *Publ Health Nutr* 1998; **1:** 33–41.

8 WCRF-AICR. Food, nutrition and the prevention of cancer: a global perspective. Washington DC: American Institute for Cancer Research, 1997.

9 COMA Working Group on Diet and Cancer. Nutritional aspects of the development of cancer. UK Department of Health Report on Health and Social Subjects No 48. London: HMSO, 1998.

10 Day NE, McKeown N, Wong MY, Welch A, Bingham S. Epidemiological assessment of diet: a comparison of a 7-day diary with a food frequency questionnaire using urinary markers of nitrogen, potassium and sodium *Int J Epidemiol* 2001; **30:** 309–17.

11 Kipnis V, Midthune D, Freedman LS, et al. Empirical evidence of correlated biases in dietary assessment instruments and its implications. *Am J Epidemiol* 2001; **153:** 394–403.

12 Riboli E, Kaaks R. The EPIC project: rationale and study design. *Int J Epidemiol* 1997; **26** (suppl)**:** S6–14.

13 Agudo A, Slimani N, Ocke MC, et al. Consumption of vegetable, fruit and other plant foods in the EPIC cohorts from ten European countries. *Publ Health Nutr* 2002; **5:** 1179–96.

14 Wirfalt E, McTaggart A, Pala V, et al. Food sources of carbohydrates in a European cohort of adults. *Publ Health Nutr* 2002; **5:** 1197–216.

15 Riboli, E, Hunt, KJ, Slimani N, et al. EPIC: study populations and data collection. *Publ Health Nutr* 2002; **5:** 1113–24.

16 Slimani N, Kaaks R, Ferrari P, et al. EPIC Calibration Study: rationale, design and population characteristics. *Publ Health Nutr* 2002; **5:** 1125–46.

17 Deharveng G, Charrondiere UR, Slimani N, Southgate DAT, Riboli E. Comparison of nutrients in the food composition tables in the nine European countries participating in EPIC. *Eur J Clin Nutr* 1999; **53:** 60–79.

18 Holland B, Welch AA, Unwin D, Buss DH, Paul AA, Southgate DAT. McCance and Widdowson's the composition of foods. London: Royal Society of Chemistry and MAFF, 1991.

19 Department of Health. Dietary reference values for food energy and nutrients for the United Kingdom. UK Department of Health Report on Health and Social Subjects No 41. London: Stationery Office, 1991.

20 Breslow NE, Day NE. Statistical methods in cancer research. Volume II: the design and analysis of cohort studies (IARC Sci Publ No 82). Lyon: International Agency for Research on Cancer, 1987.

21 Kaaks R, Riboli E, Van Staveren W. Calibration of dietary-intake measurements in prospective cohort studies *Am J Epidemiol* 1995; **142:** 548–56.

22 Rosner B, Willett WC, Spiegelman D. Correction of logistic-regression relative risk estimates and confidence-intervals for systematic within-person measurement error. *Stat Med* 1989; **8:** 1051–69.

23 Rosner B, Gore R. Measurement error correction in nutritional epidemiology based on individual foods, with application to the relation of diet to breast cancer. *Am J Epidemiol* 2001; **154:** 827–35.

24 Bingham S. Mechanisms and experimental evidence relating dietary fibre and starch to protection against large bowel cancer. *Proc Nutr Soc* 1990; **49:** 153–71.

25 Boffa LC, Luption JR, Mariani MR, et al. Modulation of colonic cell proliferation, histone acetylation and luminal short chain fatty acids by variation of dietary fibre (wheat bran) in rats. *Cancer Res* 1992; **52:** 5906–12.

26 Chai F, Evdoukiou A, Young GP, Zalewski PD. Involvement of p21 and its cleavage by DEVD-caspase during apoptosis of colorectal cancer cells induced by butyrate. *Carcinogenesis* 2000; **21:** 7–14.

27 Domon-Dell C, Wang Q, Kim S, Kedinger M, Evers BM, Freund JN. Stimulation of the intestinal Cdx2 homeobox gene by butyrate in colon cancer cells. *Gut* 2002; **50:** 525–29.

28 McNeil NI, Rampton DS. Is the rectum usually empty? *Dis Colon Rectum* 1981; **24:** 596–99.