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The relationship between dietary fat intake and risk of colorectal cancer: evidence from the combined analysis of 13 case-control studies

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The objective of this study was to examine the effects of the intake of dietary fat upon colorectal cancer risk in a combined analysis of data from 13 case-control studies previously conducted in populations with differing colorectal cancer rates and dietary practices. Original data records for 5,287 cases of colorectal cancer and 10,470 controls were combined. Logistic regression analysis was used to estimate odds ratios (OR) for intakes of total energy, total fat and its components, and cholesterol. Positive associations with energy intake were observed for 11 of the 13 studies. However, there was little, if any, evidence of any energy-independent effect of either total fat with ORs of 1.00, 0.95, 1.01, 1.02, and 0.92 for quintiles of residuals of total fat intake (*P* trend = 0.67) or for saturated fat with ORs of 1.00, 1.08, 1.06, 1.21, and 1.06 (*P* trend = 0.39). The analysis suggests that, among these case-control studies, there is no energy-independent association between dietary fat intake and risk of colorectal cancer. It also suggests that simple substitution of fat by other sources of calories is unlikely to reduce meaningfully the risk of colorectal cancer. *Cancer Causes and Control* 1997, **8**, 215-228

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Introduction

The strong positive association between fat disappearance data and rates of colorectal cancer both internationally and with secular international trends[1] has led to the hypothesis that dietary fat is associated with increased risk of this disease. Early animal studies[2-4] were generally supportive of this hypothesis in demonstrating a promotional or co-carcinogenic effect of dietary fat intake on chemically induced colon carcinogenesis. However, more recent animal studies[5,6] have suggested that total energy intake may be more relevant than dietary fat in promoting colon carcinogenesis.

Among epidemiologic studies that have examined the postulated association with fat intake, there have been very few cohort studies in which fat consumption has been estimated based on a reasonably complete dietary instrument and in which appropriate adjustment for total energy intake has been carried out.[7-9] The critical importance of energy adjustment in dietary epidemiologic studies has been pointed out by Willett and others.[10,11] There have been, however, more case-control studies that have estimated individual fat intake based on adequate dietary methodology than there have been cohort studies with such adequate methodology. In this paper, we report results with respect to fat intake based on the combined analysis of the original data from 13 previously conducted case-control studies, in which sufficient dietary data were collected to enable individual estimates of the intake of fat, total energy, and a number of other nutrients to be made. The strong, consistent, inverse association with dietary fiber seen in these data has previously been reported.[12] Given the high positive correlation between fat and total energy intakes, the particular focus of the present analysis is the estimation of any energy-independent association between fat intake and risk of colorectal cancer.[11]

Materials and methods

Studies and data

Details of the 13 case-control studies included in the present analysis are summarized in Table 1. More specific details relating to case and control ascertainment, and the collection of dietary and other data in these studies are provided in the original references given in Table 1.

The process used to identify relevant studies and to obtain the necessary data has been described previously.[12] The 13 studies described in Table 1,[13-39] to the best of our knowledge, form a complete set of case-control studies of colorectal cancer completed by 1989 in which dietary data were adequate to permit individual nutrient estimates, with the exception of one study from New York State (United States)[40] and one study in Sweden; [41] we were unaware of the existence of the latter study at the time the current analysis was initiated.

Individual data records for each study subject were provided by the original study investigators for subsequent data processing and analysis. Nutrient estimates were based on food composition tables specific to each particular study.

The estimated total energy intake for subjects in the Singapore study was multiplied by a factor of 1.25, to take account of the fact that the questionnaire in that study was not designed to assess intake of simple sugars and hence, on average underestimated energy intake by about 20 percent.[31] Inferences were little changed when the Singapore data were excluded, and hence this approximation appears to have introduced no major bias.

Statistical Analysis

A standard recoding procedure was used to convert the data from the various studies to a common format for the combined analysis. Not all dietary variables were available for all the studies. In particular, cholesterol data were not available for three studies and individual component fat data (*i.e.*, saturated, monounsaturated, or polyunsaturated fat) for two of these. Values for nutrient variables which were more than three times the standard deviation (SD) from the mean for that particular nutrient in each particular study on the log scale were excluded from all analyses to minimize the possibility of including 'outliers' which could affect results using continuous variables. This excluded only a very small number of observations.

Combined analyses for total energy intake was based on 12,963 study subjects with valid energy, cholesterol, and fiber intakes; the two latter variables are confounders of the energy association.[12] Combined analyses relating to the fat variables were adjusted for energy, cholesterol, and fiber intakes, and hence were based on the 12,869 subjects with valid data for all these variables. Analyses of height, weight, and body mass index (BMI) (wt/ht^2) did not require adjustment for any of the dietary variables and included 13,322 subjects. Two studies did not have height or weight data. Appendix Table 1 shows the distribution of cases and controls for these various combined analyses and for the subgroup analyses by gender, age group, and cancer site.

Unconditional logistic regression was used to estimate ORs, 95 percent confidence intervals (CI) and *P*-values. All *P*-values quoted are two-tailed. For all analyses, data were stratified into the 130 possible combinations of study (13 categories), gender (two categories), and age-group (five-year categories: 0-44, 45-54, 55-64, 65-74, and 75+). The use of 10-year age intervals was dictated by the fact that this was all that was available for one large study, but finer stratification on age for the other studies had essentially no impact on the results. All analyses included

indicator variables for those strata relevant to the particular analysis. Since the number of study subjects in each stratum was large, use of unconditional logistic regression leads to essentially unbiased estimates.[42]

As has been pointed out by several authors,[10,11] it is important to take account of total energy intake in analyzing associations with nutrients. In particular, if an association with total energy exists, this will lead inevitably to an association with all nutrients that contribute to energy intake. Adjustment for energy intake leads to effect estimates for nutrients which are independent of their energy content, *i.e.*, represent any specific energy independent effect of that nutrient.[11] In addition, adjustment for total energy intake may improve the precision of the estimates for other nutrients.[11]

When nutrients are treated as continuous variables in statistical analyses, three alternative methods for energy adjustment have been proposed.[10,43-45] In practice, all three approaches are based on the same underlying statistical model and lead to identical estimates for the specific energy-independent effect of the nutrient.[11] It should be noted that some previous reports have presented results in which the effect of fat includes both any energy effect and any specific non-energy effect without differentiating the two potential effects (for example see reference[43]).

There remains an important issue in presenting the results for analyses based on continuous variables, namely the size of the unit in which to present ORs. In this paper, we have used as units the difference in nutrient-residual means between the lowest and highest quintile of intake for all study subjects combined. Nutrient residuals are obtained by regressing the nutrient on total energy intake[10] and thus represent the variation in nutrient intake conditional upon total energy intake. Thus, the unit we have used approximates the difference in nutrient intake between highest and lowest quintiles for individuals with the same underlying total energy intake and thus represents a change which might be feasible for an individual without changing her/his total energy intake.[11] However, it should be noted that, given the substantial variation in dietary practices across the various populations represented in our analysis, the nutrient-residual units presented are somewhat greater than those that would be observed in an homogeneous population; they thus represent a more extreme difference than that which might be achieved within, as opposed to across, populations. It should also be noted that the choice of units has no impact on the corresponding *P*-value and thus does not affect the assessment of the possible contribution of chance to any particular association. For variables such as total energy intake itself, height, and weight, where the residuals approach does not apply, the units used are the difference in means between lowest and highest quintile of the variable itself. Clearly, this does not represent a change which is likely to be feasible for any individual, and should be interpreted simply as the difference in risk between the two groups of individuals who are at the tail ends of the distribution of those variables.

Table 1. Case-control studies of diet and colorectal cancer included in analysis

Study	Location	Years data collected	Type of control[a]	No. of subjects			Reference
				Cases	Controls	Total	
Argentina	La Plata	1985-87	P	110	220	330	(13,14)
Australia I	Adelaide	1979-81	P	220	438	658	(15,16)
Australia II	Melbourne	1980-81	P	715	727	1,442	(17-23)
Belgium	Liège and Oost-Vlaanderen	1978-83	P	818	2,848	3,666	(24)
Canada	Calgary and Toronto	1976-78	H & P	542	1,077	1,619	(25)
China	Hangzhou and Ningbo	1981-86	P	432	1,296	1,728	(26)
France	Marseille	1979-84	H	399	399	798	(27,28)
Greece	Athens	1979-80	H	100	100	200	(29,30)
North American Chinese	Los Angeles, USA San Francisco, USA Vancouver, Canada	1981-86	P	473	1,192	1,665	(26)
Singapore	Singapore	1985-87	H	203	426	629	(31)
Spain	Majorca	1984-88	H & P	286	498	784	(32,33)
United States I	Los Angeles (CA)	1984-88	P	746	746	1,492	(34,35,36,37)
United States II[b]	Utah	1979-83	P	243	503	746	(38,39)
All studies combined				5,287	10,470	15,757	

[a] H = hospital, P = population

[b] Some additional study subjects have been included in the present analysis who were not available for the original analysis of these data (refs. 32,33).

When the results for the nutrients are presented in terms of categorical variables, the approach used is first to form residuals for the nutrient, then categorize those residuals and finally include total energy intake as a continuous additional variable in the regression model. This procedure leads to unbiased estimates of the ORs of the energy independent effect of the nutrient in contrast to the procedure of categorizing the nutrient itself and then adjusting for total energy intake.[11] Categories have been chosen to give approximately equal numbers of study subjects in each of the quintiles; in practice this means that analyses restricted to subgroups, *e.g.*, study-specific or gender-specific results will not have a uniform distribution of subjects across those categories, but using a common standard for all analyses permits the direct comparison of risk estimates for a given category across all subgroups. Cut-points for quintiles of the variables used in the present paper are shown in Appendix Table 2.

Analysis strategy

The approach used was to identify those risk models that best described the overall dataset, and then to investigate the extent to which the data from each individual study were consistent with those models. However, the most appropriate interpretation of the results from individual studies is, of course, that presented in the original papers referenced in Table 1. These original papers allow much more detailed presentation of individual study results, and can comment more meaningfully on study-specific conditions that may have affected these results.

Results

For all studies combined, there is a highly statistically significant, positive association with total energy intake for men, women, and both genders combined, with a pattern of generally increasing risk with increasing intake (Table 2).

The association with energy intake is confounded by the intakes of both cholesterol and fiber: adjustment for cholesterol decreases the strength of the association with energy, and adjustment for fiber increases the strength of that association as has been reported previously.[12] Thus, the results for energy intake shown in Table 2 are adjusted for cholesterol and fiber. However, there is no evidence of further confounding of the energy association by height, weight, BMI (wt/ht^2), nor was the estimate of the energy association altered by inclusion of any of the fat intake variables. The positive association with energy intake observed in the data emphasizes the necessity to adjust for this variable in interpreting any association with other nutrients as discussed above.

Table 3 shows ORs by quintile for height, weight, and BMI. A positive association with height is seen for men with a somewhat weaker and nonsignificant association for women. There appears to be no association with weight for men, but there is some evidence of an inverse association with this variable for women, although for the latter, the increase in risk appears restricted primarily to the two lowest quintiles. Height and weight are adjusted for each other in the results shown in Table 3. However, the results for height are essentially unaffected by adjustment for weight, and the results for weight are increased only slightly positively when not adjusted for height (data not shown). Adjusting height and weight for each other, therefore has little impact on the interpretation of the associations with these variables.

The associations with BMI – which are adjusted for height and potentially could confound this association – primarily reflect the effect of weight with little association for this index for men, and an inverse association for women (although this is primarily restricted to women in the lowest quintile). Adjustment for total energy intake and specific nutrients had very little effect on the strengths of the associations with height, weight, or BMI shown in Table 3.

Because of the positive association with total energy intake, all nutrients considered in the present paper, *i.e.*, total fat, fat sub-types, and cholesterol show positive associations in analyses that are not adjusted for total

Table 2. Case-control studies of diet and colorectal cancer; energy intake for combined studies[a]

Subjects	Odds ratios (95% confidence intervals) for quintile					
	1	2	3	4	5	*P* (trend)
Men	1.00	1.18 (0.96-1.44)	1.06 (0.86-1.30)	1.23 (0.99-1.52)	1.49 (1.16-1.90)	0.003
Women	1.00	1.10 (0.93-1.30)	1.13 (0.94-1.37)	1.25 (1.00-1.56)	1.94 (1.44-2.61)	0.0006
All[b]	1.00	1.15 (1.01-1.30)	1.12 (0.98-1.28)	1.27 (1.09-1.48)	1.63 (1.36-1.95)	< 0.0001

[a] All models adjusted for study and age group by stratification and for cholesterol and fiber intakes as continuous variables.
[b] Also adjusted for gender by stratification.

Table 3. Case-control studies of diet and colorectal cancer; height, weight, and body mass index (BMI) (wt/ht^2) for combined studies[a]

Factor	Subjects	Odds ratios (95% confidence intervals) for quintile					
		1	2	3	4	5	*P* (trend)
Height[b]	Men	1.00	1.08 (0.75-1.55)	1.06 (0.76-1.47)	1.25 (0.90-1.74)	1.31 (0.94-1.82)	0.006
	Women	1.00	0.99 (0.86-1.15)	1.12 (0.96-1.31)	0.94 (0.74-1.19)	1.31 (0.96-1.79)	0.19
	All	1.00	0.98 (0.86-1.12)	1.03 (0.90-1.18)	1.11 (0.96-1.30)	1.28 (1.08-1.50)	0.002
Weight[c]	Men	1.00	1.02 (0.81-1.30)	0.96 (0.75-1.22)	0.95 (0.75-1.22)	1.06 (0.82-1.36)	0.64
	Women	1.00	0.89 (0.77-1.04)	0.73 (0.61-0.87)	0.78 (0.64-0.95)	0.75 (0.60-0.93)	0.001
	All	1.00	0.91 (0.80-1.03)	0.79 (0.68-0.90)	0.81 (0.70-0.93)	0.87 (0.75-1.01)	0.047
BMI[c]	Men	1.00	1.04 (0.87-1.24)	0.85 (0.71-1.02)	1.04 (0.87-1.24)	1.16 (0.95-1.41)	0.14
	Women	1.00	0.72 (0.61-0.86)	0.77 (0.64-0.92)	0.71 (0.59-0.86)	0.68 (0.57-0.82)	0.0002
	All	1.00	0.86 (0.76-0.97)	0.78 (0.69-0.89)	0.86 (0.76-0.98)	0.88 (0.77-1.00)	0.13

[a] All models adjusted for study and age group by stratification.
[b] Also adjusted for weight as continuous variable.
[c] Also adjusted for height as continuous variable.

energy intake (data not shown). However, when total energy intake is included in such models, these associations are altered substantially for the combined data. Table 4 shows ORs by quintile for the nutrients in question when adjusted for total energy intake.

There is no evidence in Table 4 for any association with total fat intake for either men or women. Nor is any association seen with saturated fat intake for men. There is a suggestion of a positive association with saturated fat for women, but this association is weak, irregular and does not achieve conventional levels of statistical significance. The intake of monounsaturated fat is not associated with risk for either men or women. Although polyunsaturated fat shows no association for men, there is a suggestion of an inverse association for women; this association, however, is again weak and statistically non-significant. Finally, Table 4 shows ORs by quintile for cholesterol intake. There is evidence of a positive association for both men and women which seems unlikely to have arisen by chance ($P < 0.0001$ for both genders combined). However, the magnitudes of the ORs involved are not large, with an OR for the highest compared with the lowest quintile of cholesterol (residual) intake being approximately 1.3, again for both genders combined.

It has been suggested[16] that risk factors for colorectal cancer could vary by gender, age at diagnosis, and specific cancer site (right colon, left colon, or rectum). To examine this possibility, separate analyses were conducted for the risk factors considered in the present paper by gender, age, and cancer site. Age at diagnosis was dichotomized at 50 years to approximate any difference between pre- and postmenopausal women,[16] although, in practice, similar results to those reported are obtained by other dichotomies – *e.g.*, at age 55 years or 60 years. Formal tests of interaction between the risk factors and these potential modifying factors were conducted by including the appropriate interaction term in the model. Interaction tests across cancer sites were carried out by directly comparing the various subgroups of cancer cases.

Tables 5 and 6 present the results for the variables considered in Tables 2, 3, and 4, separately by gender, age at diagnosis, and cancer site.

For the site-specific analyses, data were restricted to the eight studies which had all three types of cases in order to ensure that these subgroups were comparable in terms of the studies from which the data had been obtained. For these analyses, the variables are treated as continuous variables in order to simplify the presentation.

For total energy intake, positive and statistically significant associations with similar estimates are seen for all subgroups. The formal test of interaction with gender yields a *P*-value of 0.04; given the similarity of the corresponding OR estimates, this nominally significant

Table 4. Case-control studies of diet and colorectal cancer; energy-adjusted total fat, fat components, and cholesterol intakes for combined studies[a]

Factor	Subjects	Odds ratios (95% confidence intervals) for quintile					
		1	2	3	4	5	*P* (trend)
Total fat[b]	Men	1.00	0.88 (0.72-1.08)	0.95 (0.77-1.18)	0.96 (0.77-1.19)	0.90 (0.72-1.13)	0.72
	Women	1.00	1.08 (0.84-1.38)	1.13 (0.87-1.48)	1.16 (0.88-1.53)	0.98 (0.73-1.32)	0.86
	All[c]	1.00	0.95 (0.82-1.11)	1.01 (0.86-1.19)	1.02 (0.86-1.22)	0.92 (0.77-1.10)	0.67
Saturated fat[b]	Men	1.00	1.11 (0.91-1.35)	1.04 (0.83-1.30)	1.17 (0.92-1.48)	0.97 (0.75-1.26)	0.88
	Women	1.00	1.04 (0.80-1.35)	1.13 (0.84-1.51)	1.31 (0.96-1.79)	1.23 (0.88-1.73)	0.087
	All[c]	1.00	1.08 (0.92-1.26)	1.06 (0.89-1.26)	1.21 (1.00-1.46)	1.06 (0.86-1.30)	0.39
Monounsaturated fat[b]	Men	1.00	0.91 (0.75-1.12)	0.92 (0.74-1.13)	0.93 (0.75-1.16)	0.89 (0.71-1.10)	0.42
	Women	1.00	1.03 (0.82-1.30)	1.29 (1.00-1.65)	1.24 (0.96-1.61)	0.95 (0.72-1.26)	0.94
	All[c]	1.00	0.95 (0.82-1.10)	1.06 (0.90-1.24)	1.05 (0.89-1.24)	0.91 (0.76-1.08)	0.54
Polyunsaturated fat[b]	Men	1.00	0.91 (0.76-1.08)	1.02 (0.85-1.22)	0.90 (0.74-1.09)	0.99 (0.83-1.19)	0.89
	Women	1.00	0.86 (0.71-1.04)	0.93 (0.76-1.14)	0.94 (0.76-1.17)	0.76 (0.61-0.94)	0.069
	All[c]	1.00	0.89 (0.78-1.01)	0.98 (0.86-1.12)	0.93 (0.81-1.07)	0.89 (0.77-1.02)	0.20
Cholesterol	Men	1.00	0.99 (0.82-1.19)	1.11 (0.92-1.35)	1.24 (1.03-1.49)	1.28 (1.07-1.53)	0.0005
	Women	1.00	1.18 (0.96-1.46)	1.41 (1.14-1.74)	1.33 (1.07-1.65)	1.42 (1.14-1.77)	0.002
	All[c]	1.00	1.07 (0.93-1.22)	1.24 (1.08-1.43)	1.27 (1.10-1.46)	1.34 (1.16-1.54)	< 0.0001

[a] All models adjusted for study and age group by stratification and for total energy and fiber intakes as continuous variables.
[b] Also adjusted for cholesterol intake as continuous variable.
[c] Also adjusted for gender by stratification.

result probably represents the effect of large numbers making a small difference statistically significant. Formal interaction tests with age and by site provided no evidence for any such interactions (all *P*-values > 0.5).

The difference in the strength of association seen for height between men and women shown in Table 3 is also reflected in the corresponding estimates based on continuous variables (Table 5). The difference has a *P*-value of 0.007. Although the estimates of the strength of the association with height appear to be somewhat different between the two age groups (Table 5), this difference could well have arisen by chance ($P = 0.4$). Again, although the positive association with height is somewhat irregular by cancer site, the observed differences easily could have arisen by chance (all *P*-values > 0.15).

There is evidence from Table 5 of a difference in the strength of the association with weight between men and women: women again show an inverse association and men show no association, as in Table 3. This difference in the strength of the association is statistically highly significant ($P < 0.0001$). There is little evidence of any systematic variation in the strength of the association with weight by age or cancer site (all interaction *P*-values > 0.2). The results for BMI in Table 5 again reflect those for weight with the difference between men and women being statistically significant ($P = 0.02$) and with no evidence of difference by age or site.

Table 6 presents the results for the nutrients by gender, age, and cancer site. Again, the nutrients are treated as continuous variables in order to simplify the presentation.

There is no evidence of any meaningful association with total fat or any of the fat components for men. For

Table 5. Case-control studies of diet and colorectal cancer; total energy intake, height, weight, and body mass index (BMI) (ht/wt^2), odds ratios (95% confidence intervals) by gender, age group, and cancer site for combined studies[a]

Subjects	Total Energy[b]	Height[c]	Weight[d]	BMI
Men[f]	1.80	1.44	1.18	1.16
	(1.44-2.23)	(1.14-1.80)	(0.97-1.44)	(0.96-1.40)
Women[f]	1.82	1.17	0.74	0.79
	(1.34-2.47)	(0.95-1.44)	(0.61-0.89)	(0.68-0.92)
Age < 50 years[g]	2.00	0.78	1.03	1.03
	(1.25-3.20)	(0.44-1.37)	(0.66-1.61)	(0.70-1.51)
Age 50+ years[g]	1.76	1.37	0.93	0.93
	(1.45-2.13)	(1.16-1.60)	(0.81-1.08)	(0.82-1.05)
Right colon cases and controls[f,g]	1.70	1.66	0.83	0.84
	(1.03-2.80)	(1.00-2.75)	(0.57-1.21)	(0.61-1.17)
Left colon cases and controls[f,g]	1.82	1.23	1.04	1.03
	(1.26-2.63)	(0.85-1.77)	(0.80-1.36)	(0.81-1.30)
Rectal cases and controls[f,g]	1.81	0.90	0.93	0.92
	(1.31-2.50)	(0.62-1.30)	(0.70-1.24)	(0.72-1.18)

[a] All models adjusted for study by stratification.
[b] Per 2,318 kcals/day; also adjusted for cholesterol and fiber intakes as continuous variables.
[c] Per 31.6 cm; also adjusted for weight as continuous variable.
[d] Per 37.4 kg; also adjusted for height as continuous variable.
[e] Per 11.9 kg/m^2; also adjusted for height as continuous variable.
[f] Also adjusted for age by stratification.
[g] Also adjusted for gender by stratification.

Table 6. Case-control studies of diet and colorectal cancer; energy-adjusted total fat, fat components, and cholesterol intakes; odds ratios (95% confidence intervals) by gender, age group, and cancer site for combined studies[a]

Subjects	Total fat[b,g]	Saturated fat[c,g]	Monounsaturated fat[d,g]	Polyunsaturated fat[e,g]	Cholesterol[f]
Men[h]	0.91	0.89	0.90	1.05	1.18
	(0.75-1.11)	(0.70-1.13)	(0.75-1.08)	(0.90-1.23)	(1.03-1.36)
Women[h]	1.00	1.29	1.07	0.80	1.30
	(0.75-1.34)	(0.92-1.81)	(0.82-1.38)	(0.66-0.98)	(1.07-1.57)
Age < 50 yrs[i]	1.07	1.62	1.15	0.70	1.13
	(0.72-1.61)	(0.93-2.81)	(0.79-1.67)	(0.48-1.02)	(0.84-1.53)
Age 50+ yrs[i]	0.91	0.94	0.92	0.99	1.24
	(0.77-1.09)	(0.76-1.15)	(0.78-1.08)	(0.87-1.13)	(1.10-1.40)
Right colon cases and controls[h,i]	1.06	1.11	1.13	1.07	1.33
	(0.68-1.64)	(0.63-1.96)	(0.75-1.72)	(0.66-1.72)	(0.98-1.80)
Left colon cases and controls[h,i]	1.26	1.32	1.32	1.18	1.15
	(0.91-1.74)	(0.86-2.02)	(0.97-1.79)	(0.83-1.67)	(0.92-1.45)
Rectal cases and controls[h,i]	1.03	1.39	1.00	0.73	1.53
	(0.79-1.36)	(0.96-1.99)	(0.78-1.30)	(0.53-1.00)	(1.26-1.87)

[a] All models adjusted for study by stratification and for total energy and fiber as continuous variables.
[b] Per 76.3 g/day.
[c] Per 44.6 g/day.
[d] Per 35.8 g/day.
[e] Per 21.3 g/day.
[f] Per 437 mg/day.
[g] Also adjusted for cholesterol intake as continuous variable.
[h] Also adjusted for age by stratification.
[I] Also adjusted for gender by stratification.

Table 7. Case-control studies of diet and colorectal cancer; total energy intake, height, weight, and body mass index (BMI) (ht/wt^2); odds ratios and 95% confidence intervals by individual study[a]

Study	Total energy intake[b]	Height[c]	Weight[d]	BMI[e]
Argentina	3.90	2.02	0.61	0.60
	(1.66-9.13)	(0.59-6.96)	(0.25-1.46)	(0.28-1.31)
Australia I	2.07	—	—	—
	(0.86-4.98)	—	—	—
Australia II	1.85	0.67	1.28	1.17
	(1.23-2.79)	(0.40-1.10)	(0.86-1.90)	(0.82-1.66)
Belgium	1.59	1.35	0.73	0.79
	(1.07-2.36)	(1.08-1.68)	(0.54-1.00)	(0.61-1.01)
Canada	1.72	1.61	0.71	0.74
	(1.11-2.65)	(0.95-2.75)	(0.49-1.01)	(0.54-1.01)
China	1.64	0.87	0.87	0.89
	(1.09-2.46)	(0.41-1.85)	(0.47-1.61)	(0.54-1.49)
France	0.66	1.13	0.76	0.78
	(0.24-1.80)	(0.52-2.48)	(0.44-1.32)	(0.49-1.24)
Greece	1.61	0.37	2.35	2.01
	(0.07-37.5)	(0.07-1.98)	(0.79-7.01)	(0.81-4.99)
North American Chinese	2.26	1.62	1.19	1.15
	(1.32-3.89)	(0.91-2.88)	(0.75-1.89)	(0.79-1.68)
Singapore	1.05	—	—	0.24
	(0.35-3.15)	—	—	—
Spain	2.93	5.68	0.20	0.24
	(1.19-7.24)	(1.88-17.2)	(0.08-0.50)	(0.11-0.55)
United States I	2.11	1.86	1.73	1.61
	(1.33-3.36)	(1.10-3.16)	(1.24-2.42)	(1.18-2.18)
United States II	2.56	1.40	0.63	0.68
	(1.03-6.34)	(0.61-3.22)	(0.37-1.08)	(0.42-1.10)
All studies combined	1.78	1.31	0.94	0.94
	(1.49-2.13)	(1.12-1.53)	(0.82-1.08)	(0.83-1.05)

[a] All models adjusted for gender and age group by stratification.
[b] Per 2,318 kcals/day; also adjusted for fiber intake as continuous variable.
[c] Per 31.6 cm; also adjusted for weight as continuous variable.
[d] Per 37.4 kg; also adjusted for height as continuous variable.
[e] Per 11.9 kg/m^2; also adjusted for height as continuous variable.
[f] Also adjusted for cholesterol intake as continuous variable.

women, there is a weak positive association with saturated fat intake, although this does not achieve conventional levels of statistical significance. However, for women, there is a significant inverse association with the intake of polyunsaturated fat. The positive association with cholesterol intake is again seen for both men and women. There is some evidence of a difference in the strength of the association between men and women for both saturated fat (interaction $P = 0.08$) and polyunsaturated fat (interaction $P = 0.06$), although not for total fat, monounsaturated fat, or cholesterol (all interaction P-values > 0.2).

For age at diagnosis, there is a suggestion of a positive association with saturated fat in younger subjects in contrast to older subjects, with the formal interaction test yielding a P-value of 0.08. An inverse association with polyunsaturated fat exists for younger but not older subjects (interaction P-value = 0.04). None of the other nutrients in Table 6 shows evidence of differences by age (all interaction P-values > 0.4).

With respect to cancer site, there is some variation in the magnitude of ORs observed for the various nutrients across these sites, but these differences, in general, are not large and the formal interaction tests do not provide any suggestion that these differences are other than those which might have arisen by chance (all interaction P-values > 0.09).

Results for energy intake, height, weight and BMI (wt/ht^2) by individual study are shown in Table 7.

Positive associations with energy intake are seen for 11 of the 13 studies, with ORs in excess of 1.5. Nine of these 11 positive associations are statistically significant. Of the 11 studies that have data for height, seven have ORs of 1.3 or greater, of which three are statistically significant. Results for weight for the same 11 studies are somewhat mixed: six have ORs of 0.8 or less, of which only one achieves conventional levels of statistical significance. The

Table 8. Case-control studies of diet and colorectal cancer; energy-adjusted total fat components and cholesterol intake; odds ratios (95% confidence intervals) by individual study[a]

Study	Total fat[b,g,h]	Saturated fat[c,g,h]	Monounsaturated fat[d,g,h]	Polyunsaturated fat[e,g,h]	Cholesterol[f,g,h]
Argentina	0.36	—	—	—	—
	(0.12, 1.10)	—	—	—	—
Australia I	0.87	0.97	0.88	0.91	1.03
	(0.38, 2.03)	(0.37, 2.53)	(0.36, 2.14)	(0.54, 1.54)	(0.57, 1.89)
Australia II	0.74	—	—	—	—
	(0.46, 1.19)	—	—	—	—
Belgium	0.51	0.75	0.50	0.94	1.13
	(0.34, 0.76)	(0.51, 1.09)	(0.35, 0.73)	(0.78, 1.14)	(0.86, 1.49)
Canada	1.06	1.31	1.01	0.93	1.29
	(0.71, 1.57)	(0.83, 2.09)	(0.67, 1.52)	(0.64, 1.35)	(0.95, 1.74)
China	0.90	0.95	0.94	0.71	1.28
	(0.66, 1.24)	(0.58, 1.53)	(0.69, 1.27)	(0.46, 1.08)	(1.00, 1.64)
France	0.24	0.76	0.28	1.02	—
	(0.09, 0.68)	(0.25, 2.27)	(0.14, 0.57)	(0.61, 1.69)	—
Greece	3.08	1.77	19.0	1.45	2.89
	(0.11, 87.7)	(0.09, 35.6)	(0.17-> 100)	(0.03, 64.2)	(0.63, 13.2)
North American Chinese	1.87	6.75	1.54	0.63	1.50
	(1.15, 3.02)	(3.16, 14.4)	(1.04, 2.31)	(0.35, 1.14)	(1.10, 2.06)
Singapore	2.34	1.26	2.67	6.49	1.09
	(0.59, 9.32)	(0.20, 8.06)	(0.56, 12.7)	(1.31, 32.1)	(0.59, 2.02)
Spain	0.55	0.96	0.61	0.73	1.95
	(0.27, 1.15)	(0.34, 2.72)	(0.38, 0.99)	(0.42, 1.26)	(1.07, 3.58)
United States I	1.02	0.73	1.18	1.10	0.94
	(0.62, 1.69)	(0.38, 1.43)	(0.66, 2.10)	(0.71, 1.69)	(0.72, 1.23)
United States II	0.83	0.24	1.38	2.72	1.19
	(0.31, 2.23)	(0.07, 0.85)	(0.44, 4.35)	(1.07, 6.92)	(0.74, 1.93)
All studies combined	0.94	1.00	0.95	0.96	1.22
	(0.80, 1.10)	(0.83, 1.21)	(0.82, 1.10)	(0.85, 1.08)	(1.09, 1.37)

[a] All models adjusted for gender and age group by stratification.
[b] Per 76.3 g/day.
[c] Per 44.6 g/day.
[d] Per 35.8 g/day.
[e] Per 21.3 g/day.
[f] Per 437 mg/day.
[g] Also adjusted for total energy and fiber intakes as continuous variables.
[h] Also adjusted for cholesterol intake as continuous variable (except Argentina, Australia II, and France).

results for BMI by study are very similar to those for weight.

Formal tests of interaction between the variables shown in Table 7 and the individual studies were computed. These are shown in Appendix Table 3. In general, there is significant heterogeneity in the strength of the association across studies, although this heterogeneity is reduced when tests are conducted separately for men and women. This suggests the possibility that part of the heterogeneity across studies for both genders combined could result from differing proportions of men and women in the various studies, but with somewhat different overall associations for men and women. Alternatively, this apparently reduced heterogeneity within gender simply may reflect the smaller number of study subjects in gender-specific analyses and, hence, a corresponding reduction in the power of the heterogeneity test.

Study-specific results for the intake of nutrients are shown in Table 8.

Of the 13 studies, only three show evidence of a positive association with total fat intake, namely those conducted in Greece, among the North American Chinese, and in Singapore; only the North American Chinese study achieves statistical significance. With respect to saturated fat, again both the Greek and North American Chinese studies show positive associations, with the latter being the only one that is statistically significant. The Singapore and Canadian studies show some indication of a weak positive effect although neither is statistically significant.

For monounsaturated fat, four of the 11 studies with data for this variable have positive associations, namely, the Greek, North American Chinese, Singapore, and

United States II studies – although again, only the OR for the North American Chinese study is statistically significant. Although the estimate for the Greek study is very large, the corresponding confidence interval is extremely wide. Three of the studies show statistically significant inverse relationships with the intake of monounsaturated fat. Two of the studies – namely, the Singapore and US II study – have positive and statistically significant associations with the intake of polyunsaturated fat, with the other nine studies either showing no association or weak inverse associations. Three of the studies have statistically significant positive associations with cholesterol, with another two having positive but statistically nonsignificant associations.

Formal interaction tests between the nutrient effects shown in Table 8 and the individual studies are given in Appendix Table 3. Again, there is evidence of heterogeneity across studies for most of the nutrients for men and women combined; however, in general, this heterogeneity is reduced, particularly for women, by gender-specific interaction tests. However, this again may reflect the reduced power of the heterogeneity tests when restricted to one gender.

Discussion

When interpreting the results of the present analysis, several *caveats* need to be borne in mind. First, case-control studies are potentially susceptible to several biases, of which the most important are likely to be recall bias (differential recall of risk factors by cases and controls) and selection bias (differential participation rates by cases and controls, with participation rates being correlated with risk factors). The possible existence of such biases in the present analysis cannot be addressed directly. However, a number of the studies included were conducted in populations in which knowledge of the postulated dietary associations with colorectal cancer are likely to have been little publicized, and a number of the studies had excellent response rates for both cases and controls. This should reduce the possibility of recall and selection biases in these studies.

A second limitation relates to the necessity of including, in most of the statistical models, a number of highly correlated variables to account for their potential confounding effects. This leads to large standard errors, and hence risk estimates with wide CIs (particularly when numbers are small), as for some of the individual studies. However, it has been shown by computer simulation that these types of models (*i.e.*, including several highly correlated dietary variables) produce unbiased OR estimates and correct confidence interval coverage even with small sample sizes;[46] hence, both point and interval estimates presented are statistically valid despite the highly correlated nature of the regression variables.

A third *caveat* relates to the issue of multiple comparisons. This applies particularly to analyses within subgroups of the data, for example, by gender and cancer site, and *P*-values for such subgroup analyses generally will underestimate the possible contribution of chance to such associations.

Fourth, a variety of dietary instruments have been used to collect data in the different studies. The ability of these instruments to collect valid dietary data will vary. Some of the dietary instruments have been subjected to validity or calibration studies as described in the original papers for which the references are provided in Table 1. However, the variation in the dietary instruments used in the different studies will have led to heterogeneity in OR estimates; this phenomenon certainly will have contributed to the significant heterogeneity across studies although other design and execution factors also will have contributed to such heterogeneity. To some extent inclusion of total energy intake may help to calibrate the dietary instruments with respect to nutrient analyses.[11]

An indication of true dietary heterogeneity and/or the precision of the dietary instruments is provided by the variance of individual (energy adjusted) nutrients across studies. In general, however, the study-specific variances for energy-adjusted total and saturated fat were not markedly dissimilar across studies and there was no suggestion that results for these variables across studies were correlated with study-specific variances (data not shown). The latter phenomenon might have been expected to occur if substantial and differential measurement error had led to differential attenuation of risk across studies.

The most consistent finding in the present analysis is the positive association with total energy intake. This inevitably leads to positive associations with those macronutrients contributing to energy intake (fat, protein, and carbohydrate) in analyses unadjusted for the effect of total energy. Thus, in order to distinguish between an energy effect and any specific (non-energy) nutrient effect, it is essential to adjust for total energy intake as in Tables 4, 6 and 8.[45]

Of particular interest in light of prior hypotheses are the possible energy-independent effects of total and saturated fats. In the overall data, there is essentially no evidence of any energy-independent effect for either of these variables (Tables 4 and 6). The study-specific results (Table 8) show that for only three of the studies is there evidence of an energy-independent positive association with total fat and only one has a *P*-value less than 0.05. For saturated fat, there are only two studies with ORs in excess of 1.5 for an energy-independent effect (Table 8); only one of these has a *P*-value less than 0.05.

There is some suggestion in the data of a positive

association with saturated fat for women and for cases diagnosed before age 50 (Table 6). However, neither of these associations is statistically significant and the associations are weak given that the unit in which the ORs are expressed is large.

For monounsaturated fat, the overall data do not provide evidence of any association for either men or women (Tables 4 and 6), nor within age-group or cancer site (Table 6). The study-specific results for monounsaturated fat (Table 8) show both positive and inverse associations, but no consistent pattern. For polyunsaturated fat, the combined data again do not demonstrate any meaningful associations. Although inverse associations are seen for women, for those aged under 50 years, and for rectal cancer (Table 6), they only achieve or come close to conventional levels of statistical significance. However, these associations are weak given the relatively large units in which ORs are expressed, and, again, there is the problem of multiple comparisons. The study-specific results for polyunsaturated fat (Table 8) do not show consistent patterns of either positive or inverse associations.

Overall, the combined data from the 13 case-control studies included in the present analysis provide substantive evidence of the lack of any meaningful or strong energy-independent association between the intake of total fat or any of the fat components and risk of colorectal cancer. This observation is in accord with the results of three recent cohort studies[7-9] which have both utilized adequate dietary instruments and adjusted appropriately for the effect of total energy intake. It is worth noting that two of the three studies were restricted to women. Although one of the studies[7] showed some evidence of a positive association, particularly with animal fat intake, the primary risk factor identified in that study was the intake of red meat compared with the intake of skinless chicken and fish. Empirically, therefore, there is little support from analytic epidemiologic studies of any meaningful energy-independent association with dietary fat intake. Although there exists a sensible biological rationale for the possible involvement of fat in colorectal carcinogenesis,[47] it appears that if fat is indeed involved in colorectal carcinogenesis, the mechanism must be more complex than that which would be implied by a simple empirical association with fat intake *per se*, *e.g.*, it could involve foods or some complex interaction amongst nutrients or other food components. Discussion of such potential biological mechanisms is beyond the scope of the present paper.

A positive association was observed in the combined data with cholesterol intake. The overall association appears unlikely to have arisen by chance (Tables 4 and 6), and shows some evidence of consistency among studies and by gender. The cholesterol association was unaffected by adjustment for saturated fat (with which it is highly correlated), although adjustment for cholesterol led to a small reduction in the OR for saturated fat, thus providing evidence that the cholesterol association is not indicative of a saturated fat association. None of the three cohort studies which have utilized adjustment for total energy[7-9] demonstrated any strong association with cholesterol intake but the weak positive association seen in the present data cannot be excluded by those cohort studies given the relatively wide corresponding CIs. The association seen in the present data is weak, which suggests the possibility that cholesterol *per se* may be a marker for some specific food or food group. In this context, the association with red meat intake reported from the US Nurses' Cohort Study[7] is of interest, although this association was not confirmed by the Iowa Cohort Study[8] or the Netherlands Cohort Study.[9] Steinmetz and Potter[48] have pointed out that analytic epidemiologic studies generally have found positive associations with egg consumption, another major source of dietary cholesterol. These studies include a number not used in the present analysis.

The most consistent finding in the present analysis is the positive association with energy intake, with an approximate 50 percent increase in risk for the highest, compared with the lowest quintile of intake, an association which is most unlikely to be due to chance ($P < 0.0001$). A positive association is seen for 11 of the 13 studies, and one of the studies where no association was observed, the Singapore study,[31] used a questionnaire not designed to ascertain complete energy intake. The positive association exists for both men and women and for cancers of the right- and left-sided colon, and rectum (Table 5). Two other indicators of metabolic status in addition to energy intake, namely height and weight, both show some evidence of associations in the combined data, albeit somewhat less consistently than for the energy association.

There are several possible interpretations of the pattern of associations with energy intake, height, and weight. The first possibility is recall bias, particularly for energy intake, which would occur if cases systematically over-reported consumption of all foods compared with controls. A second possible reporting bias could apply to self-reported height and weight. It has been noted that men tend to overestimate their height and women to underestimate their weight (J.M. Peters, USC School of Medicine, personal communication, 1996); however, such biased reporting would have to be differential between cases and controls to produce the associations seen. There is a tendency for cases to lose weight during diagnosis and treatment of their cancer, and this could influence reporting of weight prior to diagnosis. It is conceivable that the two reporting biases, *i.e.*, by women and cases, are not independent, thus leading to an apparent inverse

association with weight for women compared with men.

There was no evidence in the present analysis that the energy association was due to any energy independent effect of either protein or carbohydrate (data not shown). However, energy could be a marker for some other food component or specific food not available for the present analysis.

If the pattern of associations with energy, height, and weight are indeed indicative of causality, the interpretation remains somewhat ambiguous, given the absence of data on energy expenditure. The great majority of epidemiologic studies,[47] although not all,[8] suggests an inverse association between energy expenditure and risk of colorectal cancer. If this is so, the positive association with total energy intake seen in the present data would be anomalous – in that those with greater energy expenditure will have a greater energy intake when metabolic balance is maintained. While there appears to be a positive association with height, the latter is indicative of early rather than current nutritional status. Further, the available cohort studies,[7-9] in general, do not show evidence of a positive association with energy intake. However, it is worth noting that in an analysis of a case-control study completed too late for inclusion in the present analysis, Slattery *et al*[49] observed a complex interaction among energy intake, energy expenditure, and body mass. This suggests the possibility that if energy intake is associated causally with the risk of colorectal cancer, as consistently suggested by animal studies, the relationships involved are likely to be complex and not well-represented by simple relationships. Finally, even if there is a direct link between energy intake and risk, modification of total energy intake does not offer a meaningful sensible route to prevention.[11]

In summary, the present analysis has demonstrated a lack of any consistent energy-independent association with the intake of fat or any of the fat components. There is a weak positive association with cholesterol intake which could be indicative of the intake of specific foods such as meat or eggs. The most consistent association is with total energy intake and there is some evidence of a positive association with height and an inverse association with weight, although the latter appears limited to women. The energy association could be due to reporting bias or confounding but clearly does not offer any practical route to prevention. However, this phenomenon warrants further study utilizing data on both energy intake and expenditure and taking into consideration the possibility of complex interactions among the various metabolic factors.[49]

It should be noted that, despite the lack of an association with fat intake in the present analysis, this should not be construed as arguing against dietary recommendations to reduce fat intake and increase the consumption of fruits and vegetables,[50] since such recommendations are based on consideration of a number of chronic diseases and are not based on consideration of a single disease such as colorectal cancer.

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Appendix table 1. Case-control studies on diet and colorectal cancer; number of study subjects included in combined analyses

Subjects	Variables					
	Total energy		Total fat, saturated fat, monounsaturated fat, polyunsaturated fat, cholesterol		Height, weight, body mass index[a]	
	Cases	Controls	Cases	Controls	Cases	Controls
All	4,001	8,962	3,967	8,902	4,519	8,803
Men	2,155	4,736	2,146	4,714	2,413	4,625
Women	1,846	4,226	1,821	4,188	2,106	4,178
Age < 50 years	424	1,733	420	1,725	453	1,615
Age 50+ years	3,577	7,229	3,547	7,177	4,066	7,188
Right colon	362	4,507	360	4,480	462	5,032
Left colon	736	4,507	730	4,480	970	5,032
Rectum	739	4,507	732	4,480	1,005	5,032

[a] BMI = wt/ht^2.

Appendix table 2. Case-control studies of diet and colorectal cancer; cut-points for quintiles

Variables	Units	Cut-points			
Total energy	kcals/day	1,645	2,030	2,403	2,966
Height	cm	157	163	169	175
Weight	kg	55	63	70	78
Body mass index (wt/ht^2)	kg/m^2	20.8	22.8	24.8	27.3
Total fat residual[a]	g/day	75.5	92.8	103.5	115.3
Saturated fat residual[a]	g/day	23.3	31.9	38.3	46.8
Monounsaturated fat residual[a]	g/day	28.4	35.6	40.8	46.9
Polyunsaturated fat residual[a]	g/day	9.94	13.2	16.7	21.3
Cholesterol residual[a]	mg/day	241	314	378	460

[a] Adjusted to mean energy intake for all study subjects.

Appendix table 3. Case-control studies of diet and colorectal cancer; interaction *P*-values between variables and studies[a]

Variables	All subjects	Men	Women
Total energy	0.016	0.12	0.19
Height	0.022	0.079	0.21
Weight	< 0.0001	0.015	0.0002
Body mass index (wt/ht^2)	0.0001	0.0009	0.008
Total fat	0.002	0.005	0.46
Saturated fat	0.0007	0.0006	0.69
Monounsaturated fat	0.006	0.009	0.14
Polyunsaturated fat	0.29	0.19	0.97
Cholesterol	0.13	0.56	0.21

[a] Based on -2 log likelihood ratio test.