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WHOLE GRAIN FOOD INTAKE AND CANCER RISK

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The relationship between frequency of consumption of whole grain food and risk of selected neoplasms has been analysed using data from an integrated series of case-control studies conducted in northern Italy between 1983 and 1996. The overall dataset included the following incident, histologically confirmed neoplasms: oral cavity and pharynx 181, oesophagus 316, stomach 745, colon 828, rectum 498, liver 428, gallbladder 60, pancreas 362, larynx 242, breast 3,412, endometrium 750, ovary 971, prostate 127, bladder 431, kidney 190, thyroid 208, Hodgkin's disease 80, non-Hodgkin's lymphomas 200, multiple myelomas 120. Controls were 7,990 patients admitted to hospital for acute, non-neoplastic conditions, unrelated to long-term modifications in diet and not likely to have been caused by tobacco or alcohol use. Odds ratios (OR) for subsequent scores (never/occasional/frequent) of whole grain food consumption were derived after allowance for age, sex, education, smoking, alcohol intake and body mass index. High intake of whole grain foods consistently reduced risk of neoplasm at all sites, except thyroid. The ORs for the highest category of consumption were 0.2–0.3 for upper digestive and respiratory tract neoplasms, 0.5 for stomach, colon and gallbladder, 0.7 for rectum, 0.6 for liver, 0.8 for pancreas and prostate, 0.9 for breast and endometrium, 0.6 for ovary, 0.4 for bladder and kidney, 1.3 for thyroid and around 0.5 for lymphomas and myeloma. The tests for trend in risks were significant for all neoplasms, except pancreas, endometrium, Hodgkin's disease and multiple myeloma. No significant heterogeneity was found across strata of age at diagnosis, sex, education, smoking habit, alcohol intake and body mass index. Thus, even in the absence of a univocal and satisfactory biological interpretation, the consistency of the patterns observed indicate that, in this population, higher frequency of whole grain food intake is an indicator of reduced risk of several neoplasms. *Int. J. Cancer* 77:24–28, 1998.

Compared to refined grains, whole grains are much richer in insoluble fibers and several nutrients, such as antioxidants, indoles, phenolic compounds, including flavonoids, isothiocyanates and phytoestrogens, which are generally recommended as an important beneficial part of human diet (Steinmetz and Potter, 1991*a,b*). However, epidemiological information on the relationship between whole grain consumption and cancer risk remains unsatisfactory (Jacobs *et al.,* 1995).

Research has been focused mainly on the relationship between whole grain and gastrointestinal cancers, and generally showed some protection (Jacobs *et al.,* 1995). In some studies conducted in Europe (Trichopoulos *et al.,* 1985; La Vecchia *et al.,* 1987*b,* 1988; Boeing *et al.,* 1991*a,b;* Tuyns *et al.,* 1992; Hansson *et al.,* 1993) and one from North America (Wu-Williams *et al.,* 1990) the highest intake of whole grain foods was associated with a reduced risk of gastric cancer. With reference to colorectal cancer, a Belgian study (Tuyns *et al.,* 1988) and 2 American ones (Peters *et al.,* 1989; Slattery *et al.,* 1997) found a protection of whole grain foods. A review considering the relation between cereal fiber consumption and colorectal cancer risk (Hill, 1997), showed that 16 publications out of 19 (84%) reported a protective effect.

Scanty information is available on other neoplasms. Four studies showed a protective effect of whole grain intake on breast and endometrial cancer risk (La Vecchia *et al.,* 1986, 1987*a;* Franceschi *et al.,* 1996; Levi *et al.,* 1993) and 3 studies on pancreatic cancer (Gold *et al.,* 1985; Mack *et al.,* 1986; Olsen *et al.,* 1989).

Moreover, it is not clear whether this apparent protection is specifically linked to one or several nutrients, or whether a diet including whole grains represents a more general and non-specific indicator of a healthy diet or lifestyle. We have, therefore, systematically analysed the relationship between whole grain intake and risk of neoplasms at several sites, using data from a network of case-control studies conducted in northern Italy.

SUBJECTS AND METHODS

Data were obtained from a series of hospital-based case-control studies, whose general design has been previously described (Negri *et al.,* 1991; La Vecchia *et al.,* 1992). All studies followed the same scheme, the same criteria for inclusion of subjects and the same interview setting for cases and controls; *i.e.* during hospital admission. Trained interviewers identified and questioned patients. The collection of information for each study started between 1983 and 1985, and the present report is based on data collected before June 1996; for breast and colorectal cancer only cases collected until 1991 were included. The refusal rate of eligible patients (cases and controls) was below 3%.

The questionnaires comprised a basic structured section including education and other socio-demographic factors, anthropometric variables, medical history, general characteristics and habits, such as smoking and consumption of alcohol and coffee. Further, patients were asked to indicate the frequency of consumption per week of selected indicator foods including between 14 and 37 items, during the 2 years before diagnosis for cases or before interview for controls. All the questionnaires included a question on whole grain food (essentially bread or pasta, in this population) consumption, which consisted in a subjective score with 3 levels: 1 for no or rare consumption, 2 for a frequency of consumption of 1–3 days/week and 3 for a frequency of consumption of >3 days/week, thus making possible a combination of data from various studies in relation to this issue and major covariates of interest.

The cases included in the present analysis were patients below 75 years of age with incident (*i.e.,* diagnosed within one year before the interview), histologically confirmed cancers of the oral cavity and pharynx ($n = 181$), oesophagus ($n = 316$), stomach ($n = 745$),

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colon ($n = 828$), rectum ($n = 498$), liver ($n = 428$), gallbladder ($n = 60$), pancreas ($n = 362$), larynx ($n = 242$), breast ($n = 3,412$), endometrium ($n = 750$), ovary ($n = 971$), prostate ($n = 127$), bladder ($n = 431$), kidney ($n = 190$), thyroid ($n = 208$), Hodgkin's disease ($n = 80$), non-Hodgkin's lymphomas ($n = 200$) and multiple myelomas ($n = 120$). The patients were admitted to the National Cancer Institute, to several university clinics, or to the Ospedale Maggiore of Milan, which includes the 4 largest teaching and general hospitals in Milan.

The control group included 7,990 patients (3,220 men and 4,770 women) younger than 75 years, admitted to the same network of hospitals where cases had been identified for a wide spectrum of acute, non-neoplastic conditions. Thirty-two percent of controls were admitted for traumatic conditions, 17% had non-traumatic orthopaedic disorders, 29% had acute surgical conditions and 22% had other miscellaneous illnesses (such as ear, nose and throat, skin or dental disorders). For admission diagnoses, exclusions were made for any condition related to tobacco smoking, alcohol consumption, or any disorder which might have induced long-term modifications of diet.

The distribution of cases of various neoplasms and controls according to sex and age group is given in Table I.

Data analysis

Odds ratios (OR) of various neoplasms, and the corresponding 95% confidence intervals (CI), in relation to frequency of whole grain food consumption were derived from unconditional multiple logistic regression, fitted by the method of maximum likelihood (Breslow and Day, 1980). All regression equations included terms for age, sex, education, tobacco smoking, alcohol consumption and body mass index.

RESULTS

Table II shows the distribution of cases of various neoplasms and the comparison group according to scores of whole grain food intake, together with the corresponding multivariate ORs. There was a consistent pattern of protection of whole grain foods for all neoplasms considered, except thyroid. The OR for cancers of the upper aerodigestive tract (oral cavity/pharynx/oesophagus and larynx) was 0.2–0.3 for the highest *vs.* the lowest level of whole grain food intake. Corresponding values were 0.5 for stomach, colon and gallbladder, 0.7 for rectum, 0.6 for liver, 0.8 for pancreas, 0.9 for breast and endometrium, 0.6 for ovary, 0.4 for bladder and kidney, 0.8 for prostate and around 0.5 for lymphoreticular neoplasms. For thyroid cancer the OR for the highest level of intake compared to the lowest one was 1.3. The tests for trend in risks were significant for all neoplasms except pancreas, endometrium, prostate, Hodgkin's disease and multiple myeloma.

The relationship between whole grain food intake and the risk of various neoplasms in separate strata of selected covariates is shown in Table III. No appreciable heterogeneity or effect modification was found across strata of age at diagnosis, sex, education, smoking habit, alcohol intake and body mass index, although the association was apparently stronger for subjects in the category of higher body mass index, where the ORs tended to be lower.

DISCUSSION

Our results show a consistent pattern of inverse relationship between whole grain food intake and risk not only of gastrointestinal cancers, but also of most other neoplasms considered. The strength of the association varies among sites, but is consistent across strata of main covariates.

Compared to refined grains, whole grains are higher in their content of insoluble and soluble fibers, oat, zinc, magnesium, vitamin B_6, vitamin E, niacin, ferulic acid and lignans. Furthermore, they share with vegetables and fruit many nutrients and micronutrients, including antioxidants and phytoestrogens (Steinmetz and Potter, 1991*b;* Hill, 1997).

Different biological mechanisms have been proposed to explain the influence of whole grain foods on gastrointestinal carcinogenesis, possibly involving multiple and, in some cases, overlapping pathways (Slavin *et al.,* 1997). Insoluble fibers that reach the colon are fermented by intestinal microflora to short-chain fatty acids, which may increase fecal weight and colonic motility. These have been associated with reduced colorectal cancer risk (Glober *et al.,* 1977; Cummings *et al.,* 1992; Potter, 1992, 1995; Hill, 1997), possibly because of the shorter contact between carcinogens and the colonic mucosa. Antioxidants are considered protective against cancer risk at several sites (Steinmetz and Potter, 1991*b*), and particularly the oral cavity (Marshall and Boyle, 1996) and larynx (Riboli *et al.,* 1996). The strong protection observed for these neoplasms, however, may be partly explained in terms of an inverse relation between whole grain food intake and lower social class or a diet poor in several aspects, which are strongly related to the risk of

TABLE I – DISTRIBUTION OF CASES OF SELECTED NEOPLASMS AND CONTROLS ACCORDING TO SEX AND AGE (MILAN, ITALY 1983–1996)

	Men age group (years)				Women age group (years)				Total
	<45	45–54	55–64	65–74	<45	45–54	55–64	65–74	
Type of neoplasm									
Oral cavity and pharynx	9	53	64	26	2	7	15	5	181
Oesophagus	13	64	122	59	6	9	24	19	316
Stomach	37	103	165	151	29	56	104	100	745
Colon	34	74	152	163	41	78	143	143	828
Rectum	17	50	119	102	24	31	78	77	498
Liver	27	58	148	84	18	22	36	35	428
Gallbladder	3	4	12	8	2	7	8	16	60
Pancreas	16	62	87	64	8	22	49	54	362
Larynx	10	45	117	59	0	2	5	4	242
Breast	—	—	—	—	794	1,034	951	633	3,412
Endometrium	—	—	—	—	38	147	306	259	750
Ovary	—	—	—	—	200	305	312	154	971
Prostate	1	10	53	63	—	—	—	—	127
Bladder	7	43	159	152	4	6	25	35	431
Kidney	16	22	58	36	8	6	27	17	190
Thyroid	31	15	13	4	80	25	26	14	208
Hodgkin's disease	23	9	11	6	20	5	5	1	80
Non-Hodgkin's lymphomas	19	26	39	35	18	14	22	27	200
Multiple myelomas	3	12	21	25	5	12	10	32	120
Controls	683	859	996	682	1,089	1,173	1,403	1,105	7,990

TABLE II – DISTRIBUTION OF CASES OF SELECTED NEOPLASMS AND CONTROLS AND CORRESPONDING ODDS RATIOS (OR) WITH THEIR 95% CONFIDENCE INTERVALS (CI), ACCORDING TO SCORE OF INTAKE OF WHOLE GRAIN FOODS (MILAN, ITALY 1983–1996)

Intake (days/week)	Number of subjects score			OR (95% CI) score[1]		Chi-square trend
	Low[2]	Intermediate[2]	High[2]	Intermediate[2]	High[2]	
Type of neoplasm						
Oral cavity, pharynx and oesophagus	465	20	12	0.4 (0.2–0.6)	0.3 (0.2–0.5)	29.4[4]
Stomach	616	90	39	0.9 (0.7–1.1)	0.5 (0.4–0.7)	14.1[4]
Colon	662	119	47	0.9 (0.7–1.1)	0.5 (0.3–0.6)	21.1[4]
Rectum	404	57	37	0.8 (0.6–1.1)	0.7 (0.5–1.0)	6.1[3]
Liver	361	42	25	0.8 (0.5–1.1)	0.6 (0.4–0.9)	6.8[4]
Gallbladder	53	3	4	0.3 (0.1–1.0)	0.5 (0.2–1.4)	3.8[3]
Pancreas	289	44	29	0.9 (0.7–1.3)	0.8 (0.5–1.2)	0.9
Larynx	233	6	3	0.2 (0.1–0.5)	0.2 (0.0–0.5)	20.2[4]
Breast	2,332	603	477	0.9 (0.8–1.0)	0.9 (0.8–1.0)	4.6[3]
Endometrium	519	132	99	1.0 (0.8–1.2)	0.9 (0.7–1.1)	1.4
Ovary	696	179	96	0.9 (0.8–1.1)	0.6 (0.5–0.8)	11.6[4]
Prostate	106	13	8	0.9 (0.5–1.6)	0.8 (0.4–1.7)	0.4
Bladder	373	40	18	0.8 (0.5–1.1)	0.4 (0.3–0.7)	12.3[4]
Kidney	159	22	9	0.8 (0.5–1.2)	0.4 (0.2–0.8)	6.9[4]
Thyroid	121	58	29	1.9 (1.3–2.6)	1.3 (0.9–2.0)	6.1[3]
Hodgkin's disease	65	10	5	0.9 (0.4–1.7)	0.6 (0.2–1.5)	1.2
Non-Hodgkin's lymphomas	163	28	9	1.0 (0.6–1.5)	0.4 (0.2–0.8)	5.1[3]
Multiple myeloma	95	18	7	1.0 (0.6–1.7)	0.5 (0.2–1.1)	2.1
Controls	5,817	1,235	938			

[1]Derived from multiple logistic regression equations, including terms for age, sex, education, smoking habits, alcohol intake and body mass index. Reference category were subjects with low intake.–[2]Low: no or rare consumption; intermediate: 1–3 days/week; high: >3 days/week.–[3]$p \leq 0.05$.–[4]$p \leq 0.01$.

TABLE III – ODDS RATIOS[1] OF SELECTED NEOPLASMS IN RELATION TO WHOLE GRAIN FOOD INTAKE SCORE (≥1 TIMES/WEEK COMPARED TO <1 TIME/WEEK) IN STRATA OF SELECTED COVARIATES (MILAN, ITALY 1983–1996)

	Age (years)				Sex		Education (years)		Smoking habit		Alcohol intake		Body mass index (kg/m^2)	
	<45	45–54	55–64	65–74	Men	Women	<7	≥7	Never	Current	No	Yes	<25	≥25
Type of neoplasm														
Oral cavity, pharynx and oesophagus	0.3[3]	0.2[3]	0.3[3]	0.3[3]	0.3[3]	0.3[3]	0.3[3]	0.2[3]	0.1[3]	0.3[3]	0.3[3]	0.2[3]	0.3[3]	0.2[3]
Stomach	0.7	0.5[3]	0.6[3]	0.8	0.7[3]	0.6[3]	0.6[3]	0.8	0.6[3]	0.7[3]	0.6[3]	0.7[3]	0.8[3]	0.5[3]
Colon	0.8	0.8	0.8	0.6[3]	1.0	0.6[3]	0.7[3]	0.8[3]	0.7[3]	0.9	0.7[3]	0.8[3]	0.8	0.6[3]
Rectum	0.5	0.5[3]	0.8	0.8	0.8	0.7[3]	0.7[3]	0.7	0.6[3]	1.0	0.6[3]	0.8[3]	0.9	0.5[3]
Liver	0.3[3]	0.6	0.7	0.8	0.8	0.5[3]	0.6[3]	0.8	0.6	0.7[3]	0.6	0.6[3]	0.8	0.6[3]
Gallbladder	NE[2]	NE[2]	0.8	0.4	0.4	0.4[3]	0.3[3]	0.5	0.2[3]	0.5[2]	0.7[2]	0.3[3]	0.5	0.2[2]
Pancreas	0.9	0.9	0.8	0.8	0.9	0.8	0.7	1.0	1.0	0.9	0.7	0.9	0.9	0.8
Larynx	NE[2]	0.1	0.2[3]	0.2[3]	0.2[3]	0.2[2]	0.1[3]	0.3[3]	NE[2]	0.2[3]	NE	0.1[3]	0.2[3]	0.1[3]
Breast	0.8[3]	1.0	0.9[3]	1.0[3]	—	—	0.8[3]	0.9	0.9[3]	0.9	0.9[3]	0.9	1.0	0.8[3]
Endometrium	0.8	0.7	0.9	1.0	—	—	1.1	0.7	0.9	0.9	0.9	0.9	1.0	0.8
Ovary	1.0	0.7[3]	0.7[3]	0.9	—	—	0.7[3]	0.9	0.7	1.1	0.8[3]	0.8[3]	0.9	0.7[3]
Prostate	NE[2]	2.9[2]	1.0	0.6	—	—	0.5	1.1	0.8	1.3	1.7[2]	0.7	1.1	0.8
Bladder	0.3[2]	0.5	0.8	0.5[3]	0.7[3]	0.5[3]	0.7[3]	0.5[3]	0.53	0.7	0.3[3]	0.7[3]	0.7	0.5[3]
Kidney	1.1	0.6	0.7	0.5	0.8	0.5[3]	0.5[3]	0.8	0.5[3]	0.5	0.5[3]	0.7	0.7	0.6
Thyroid	1.9[3]	1.7	1.5	1.8[2]	1.7	1.8[3]	1.5	1.9[3]	2.2[3]	1.6	1.7[3]	1.8[3]	1.8[3]	1.7[3]
Hodgkin's disease	0.7	0.8[2]	0.5[2]	1.6[2]	1.1	0.5	0.8	0.7	0.9	0.4	0.1	1.2	0.9	0.3
Non-Hodgkin's lymphomas	0.5	0.7	0.9	0.7	0.8	0.7	0.6	0.8	0.6	0.8	0.8	0.7[3]	0.7	0.7
Multiple myelomas	0.4[2]	0.5	1.3	0.8	1.3	0.5[3]	0.8	0.9	0.6	0.8	0.6	0.9	0.8	0.8

[1]Derived from multiple logistic regression equations, including terms for age and sex. Reference category was subjects with low intake.–[2]Estimates based on less than 20 cases.–[3]$p \leq 0.05$.
NE = not estimated.

these neoplasms. Lignans, and more generally phytoestrogens, have a diphenolic structure similar to estrogenic compounds, and are related to sex hormone metabolism, behaving both as estrogenic or antiestrogenic compounds (Slavin *et al.,* 1997). Consequently, they may be associated to hormone-related neoplasms. Other possible mechanisms include the interaction with body mass and body fat composition, as well as changes in serum cholesterol and bile acid metabolism (Potter, 1992, 1995).

It is not clear, however, whether the apparent protection exerted by whole grains is specifically linked with any of those components and mechanisms, or whether other unknown substances or metabolites are involved. It is also possible that more frequent whole grain consumption simply implies a lower intake of refined grains, which have been associated with elevated risk of colorectal, breast and perhaps other cancer sites (Willett, 1989; Jacobs *et al.,* 1995; Franceschi *et al.,* 1996, 1997).

As for potential limitations of this study, in northern Italy whole grain foods (mainly bread) are consumed by a small proportion of the population; only about a quarter of controls reported some intake of whole grain foods, and the questionnaire did not include information on quantity and portion size. The potential confounding effect of several covariates (including education, alcohol, and tobacco) was allowed for in the analysis. Since consumption of vegetables and fruit is protective on most epithelial cancers (Negri

et al., 1991), the Spearman correlation coefficients between whole grain and vegetable or fruit intakes have been computed. These ranged for fruit intake between −0.01 for multiple myelomas to 0.20 for non-Hodgkin's lymphomas, and for vegetable intake between −0.07 for larynx to 0.18 for endometrium. Furthermore, no appreciable effect modification was observed when terms for fruit and vegetables were included in the regression analysis. Likewise, the results were not materially modified when allowance was made for estimates of beta-carotene (for all studies) or vitamin C (when available). Moreover, consistent protections were observed, across strata of major identified covariates.

With reference to possible selection bias, our study was not population-based, but cases were identified in the major teaching and general hospitals of the area under surveillance, and the participation was almost complete. We excluded from the control group patients admitted to hospital for chronic conditions and for any digestive tract diseases; thus, only acute conditions, unrelated to known or potential risk factors for the neoplasms considered, were included in the comparison group. No appreciable differences were found in the distribution of whole grain score for the three major groups of controls, and the similar interview setting provides further reassurance against potential information bias (D'Avanzo *et al.,* 1997). Further, indirect support for the existence of a real (though not necessarily causal) association with whole grain intake comes from the observation that such systematic inverse relationships were not observed with respect to several other foods.

In particular, elevated risk were observed with reference to refined bread, pasta or rice both for stomach (La Vecchia *et al.,* 1987*b*) and colorectal cancer (La Vecchia *et al.,* 1988; Franceschi *et al.,* 1997).

Still, some other correlates of whole grain food intake may partly or largely account for the protection observed. In Italy, whole grain intake is related to higher social class and to generally healthier lifestyle characteristics and habits, which may include complex aspects of quantity and quality of diet and physical activity. Although we were able to allow in the analysis for education, selected lifestyle and nutritional factors, and the multivariate OR were not appreciably different from the age and sex-adjusted ones, it is conceivable that a complex combination of favourable correlates of whole grain intake may contribute to the apparent protection. Although this may limit any causal inference, whole grain intake would in any case represent one of the most consistent indicators of a reduced risk for several cancer sites.

The finding that a higher consumption of whole grains confers some protection on risk of most neoplasms is particularly important in view of the potential inverse relationship between these foods and other chronic diseases, including cardiovascular diseases (Fraser *et al.,* 1992; Jacobs *et al.,* 1995).

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