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Session: Whole cereal grains, fibre and human cancer
Wholegrain cereals and cancer in Italy

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The relationship between frequency of consumption of whole-grain foods and cancer risk has been analysed using data from an updated series of case–control studies conducted in Northern Italy between 1983 and 1997. The overall dataset included the following incident histologically-confirmed neoplasms: oral cavity and pharynx 524, oesophagus 410, stomach 745, colon 955, rectum 625, liver 435, gallbladder 65, pancreas 402, larynx 388, soft tissue sarcomas 217, breast 3412, endometrium 750, ovary 971, prostate 127, bladder 431, kidney 190, thyroid 428, Hodgkin's disease 201, non-Hodgkin's lymphomas 529, multiple myelomas 185. Controls were 10 058 patients admitted to hospital for acute non-neoplastic conditions unrelated to long-term modifications in diet, tobacco or alcohol use. The multivariate odds ratios for the highest category of wholegrain cereal consumption were 0·3–0·5 for upper digestive tract and respiratory neoplasms and colon, 0·6 for rectum and liver, 0·4 for gallbladder, 0·8 for pancreas, 0·2 for soft tissue sarcomas, 0·9 for breast and endometrium, 0·7 for ovary, 0·7 for prostate, 0·4 for bladder and kidney, 1·1 for thyroid and about 0·5 for lymphomas and 0·6 for myelomas. In this population whole-grain food consumption is an indicator of reduced risk of several neoplasms.

Wholegrain cereal consumption: Cancer risk: Case–control studies: Diet: Epidemiology: Fibre

Whole grains are rich in insoluble fibres and several nutrients, such as antioxidants, indoles, phenolic compounds, including flavonoids, isothiocyanates and phyto-oestrogens, which are potential favourable aspects of diet.

Wholegrain cereals, moreover, have lower rates of digestion than refined cereals, and have consequently a lower glycaemic index and related increase in plasma insulin concentration and insulin-like growth factor 1, a possible promoter of human carcinogenesis (Giovannucci, 1995; Yu & Rohan, 2000). Glycaemic index and glycaemic load have been inversely related to the risk of breast (Augustin *et al*. 2001) and colo-rectal (Franceschi *et al*. 2001) cancer in large multicentre case–control studies from Italy.

In studies conducted in Europe and North America high intake of whole-grain foods was associated with a reduced risk of gastric cancer (Trichopoulos *et al*. 1985; La Vecchia *et al*. 1987), and a few other neoplasms (Jacobs *et al*. 1995, 1998). With reference to colo-rectal cancer, a Belgian study (Tuyns *et al*. 1988) and two US studies (Peters *et al*. 1989; Slattery *et al*. 1997) reported protective effects of whole-grain foods. A Swiss study (Levi *et al*. 2000) found an inverse relationship between wholegrain cereals and risk of oral, oesophageal and laryngeal cancers, whereas refined cereals were directly related to risk. A review considering the relationship between cereal fibre consumption and colo-rectal cancer risk showed that sixteen of nineteen (84 %) papers reported a protective effect (Hill, 1997).

It is not clear, however, whether this apparent protection is specifically linked to one or several nutrients, or whether a diet including whole grains represents a more general non-specific indicator of healthy diet or lifestyle (La Vecchia & Chatenoud, 1998; Chatenoud *et al*. 1999). The relationship between frequency of consumption of whole-grain foods and cancer risk has therefore been analysed using information from an updated series of case–control studies conducted in Italy between 1983 and 1997.

Subjects and methods

Data were obtained from a series of hospital-based case–control studies, conducted in the Greater Milan area and the province of Pordenone, Northern Italy, between 1983 and

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1997. For breast and colo-rectal cancers, only data collected until 1991 were included. An analysis of part of this dataset has been published previously (Chatenoud *et al*. 1998). All studies had the same design, the same criteria for inclusion and the same interview setting for cases and controls, during hospital admission. The overall dataset included the following incident histologically-confirmed neoplasms: oral cavity and pharynx 524, oesophagus 410, stomach 745, colon 955, rectum 625, liver 435, gallbladder 65, pancreas 402, larynx 388, soft tissue sarcomas 217, breast 3412, endometrium 750, ovary 971, prostate 127, bladder 431, kidney 190, thyroid 428, Hodgkin's disease 201, non-Hodgkin's lymphomas 529, multiple myelomas 185. Controls were 10 058 patients admitted to hospital for acute non-neoplastic conditions unrelated to long-term modifications in diet and unlikely to have been related to tobacco or alcohol use. Of the control group, 30 % were admitted for traumas, 16 % for non-traumatic orthopaedic conditions, 29 % for acute surgical diseases and 25 % for other miscellaneous conditions. The refusal rate of eligible patients (cases and controls) was < 5 %.

All the questionnaires included information on whole-grain food (bread or pasta) consumption, based on a three-level score: low, no or rare consumption; intermediate, a frequency of consumption of 1–3 d/week; high, a frequency of consumption of > 3 d/week.

Odds ratios of various neoplasms, and the corresponding 95 % CI, in relation to whole-grain food consumption were derived from unconditional multiple logistic regression, fitted by the method of maximum likelihood (Breslow & Day, 1980). All regression equations included terms for age and area of residence, gender, education, tobacco smoking, alcohol consumption and BMI.

Results

Table 1 gives the distribution of cases and controls according to type of neoplasm, gender and age.

The main findings with reference to whole-grain food consumption are given in Table 2 and Fig. 1. High intake of whole-grain foods was inversely related to the risk of neoplasm at all sites, except thyroid. The odds ratios for the highest category of consumption were 0·3–0·5 for upper digestive tract and respiratory neoplasms and colon, 0·6 for rectum and liver, 0·4 for gallbladder, 0·8 for pancreas, 0·2 for soft tissue sarcomas, 0·7 for prostate, 0·9 for breast and endometrium, 0·7 for ovary, 0·4 for bladder and kidney, 1·1 for thyroid, 0·5 for lymphomas and 0·6 for myelomas.

Table 3 considers the relationship between whole-grain foods and the risk of various cancers across strata of selected covariates. No appreciable heterogeneity or effect modification was found across strata of age at diagnosis, gender, education, smoking habits and alcohol consumption.

Discussion

The present results show a consistent pattern of inverse relationships between whole-grain food intake and risk of not only gastrointestinal cancers, but also of several other neoplasms. The strength of the association varied among sites, but was consistent across strata of main covariates.

Compared with refined grains, whole grains are richer in insoluble and soluble fibres, Zn, Mg, vitamin B_6, vitamin E, niacin, phenolic acid and lignans (Truswell, 2002). Furthermore, they share many nutrients and micronutrients with vegetables and fruit, including antioxidants and phyto-

Table 1. Distribution of cases of selected neoplasms and controls (no. of subjects) according to gender and age in data from case–control studies in Milan, Italy 1983–97

	Men				Women				
Age-group (years)	< 45	45–54	55–64	65–74	< 45	45–54	55–64	65–74	Total
Type of neoplasm									
Oral cavity and pharynx	43	131	168	105	8	20	36	13	524
Oesophagus	15	83	156	89	6	10	27	24	410
Stomach	37	103	165	151	29	56	104	100	745
Colon	44	90	179	185	51	91	158	157	955
Rectum	21	63	153	137	25	40	91	95	625
Liver	27	58	148	90	18	22	37	35	435
Gallbladder	3	4	12	10	2	7	8	19	65
Pancreas	19	70	95	74	8	25	52	59	402
Larynx	17	65	188	99	1	4	6	8	388
Soft tissue sarcomas	41	25	29	18	26	28	26	24	217
Breast	–	–	–	–	794	1034	951	633	3412
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	53	27	30	6	163	62	59	28	428
Hodgkin's disease	59	27	21	12	49	11	12	10	201
Non-Hodgkin's lymphomas	56	61	56	65	50	44	58	81	529
Multiple myelomas	5	20	26	40	7	16	16	55	185
Controls	990	1179	1346	918	1354	1342	1611	1318	10 058

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Table 2. Distribution of cases of selected neoplasms and controls (no. of subjects) and corresponding odds ratios (OR)† according to score of intake of whole-grain foods in data from case–control studies in Milan, Italy 1983–97 (odds ratios and 95 % confidence intervals)

	Intake score			Intake score				
				Intermediate		High		
	Low	Intermediate	High	OR	95 % CI	OR	95 % CI	χ^2 for trend
Type of neoplasm								
Oral cavity and pharynx	494	13	17	0·3	0·1, 0·4	0·5	0·3, 0·8	23·0**
Oesophagus	372	23	15	0·4	0·3, 0·7	0·4	0·2, 0·7	18·5**
Stomach	616	90	39	0·8	0·7, 1·1	0·5	0·3, 0·7	18·5**
Colon	771	127	57	0·9	0·7, 1·0	0·5	0·4, 0·6	26·0**
Rectum	519	64	42	0·7	0·6, 1·0	0·6	0·4, 0·8	13·5**
Liver	367	42	26	0·7	0·5, 1·0	0·6	0·4, 0·9	8·2**
Gallbladder	58	3	4	0·3	0·1, 0·8	0·4	0·2, 1·2	5·3*
Pancreas	318	49	35	0·9	0·7, 1·3	0·8	0·6, 1·2	1·2
Larynx	363	16	9	0·4	0·2, 0·6	0·3	0·2, 0·6	20·5**
Soft tissue sarcomas	178	33	6	1·1	0·7, 1·6	0·2	0·1, 0·6	8·0**
Breast	2332	603	477	0·9	0·8, 1·1	0·9	0·8, 1·1	0·7
Endometrium	519	132	99	1·0	0·8, 1·3	0·9	0·8, 1·4	0·2
Ovary	696	179	96	0·9	0·8, 1·2	0·7	0·5, 0·9	6·3**
Prostate	106	13	8	0·9	0·5, 1·6	0·7	0·3, 1·5	1·1
Bladder	373	40	18	0·7	0·5, 1·0	0·4	0·3, 0·7	14·1**
Kidney	159	22	9	0·8	0·5, 1·2	0·4	0·2, 0·8	6·9**
Thyroid	284	92	52	1·6	1·2, 2·0	1·1	0·8, 1·6	3·9*
Hodgkin's disease	170	20	11	0·7	0·5, 1·2	0·5	0·3, 1·0	4·7*
Non-Hodgkin's lymphomas	441	58	30	0·8	0·6, 1·1	0·5	0·3, 0·7	13·5**
Multiple myelomas	148	24	13	1·0	0·6, 1·6	0·6	0·3, 1·0	2·9
Controls	7456	1468	1134					

Low, no or rare consumption; intermediate, 1–3 d/week; high, > 3 d/week.
*$P \leq 0{\cdot}05$, **$P \leq 0{\cdot}01$.
†Derived from multiple logistic regression equations, including terms for age, area of residence, education, smoking habits, alcohol intake and when required, gender. Reference category was subjects with low intake.

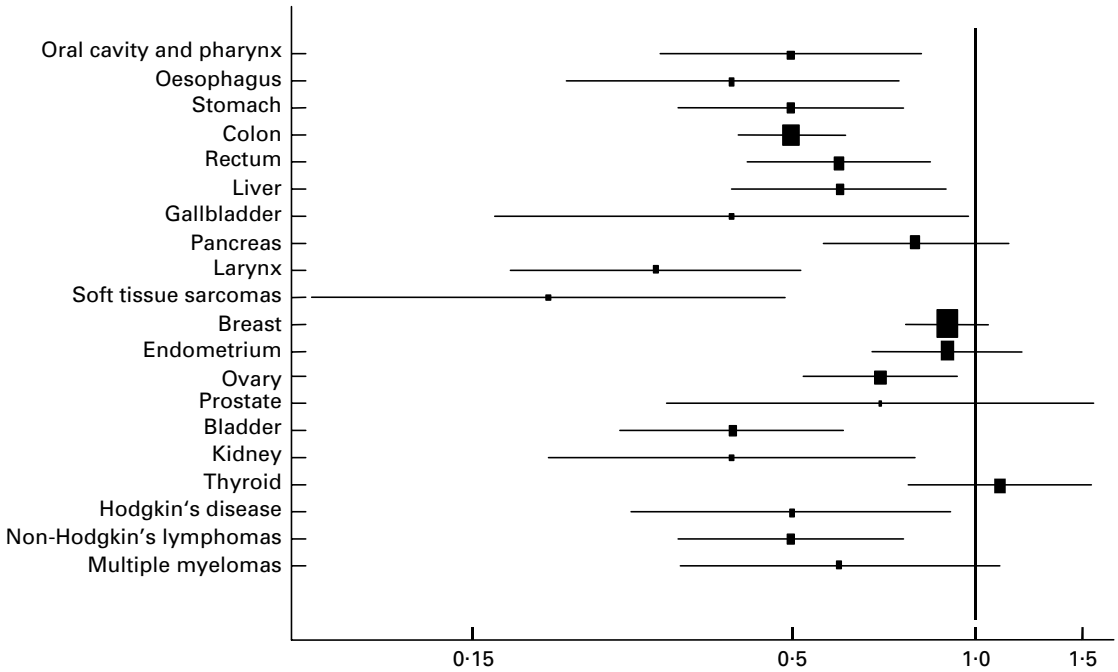

Fig. 1. Odds ratios for high score of intake of whole-grain foods in data from case–control studies in Milan, Italy 1983–97. Points are odds ratios with 95 % confidence intervals represented by horizontal bars.

oestrogens. Antioxidants have been shown to be protective against cancer risk at several sites, including those of the oral cavity, oesophagus and larynx (La Vecchia *et al*. 1990; Franceschi *et al*. 2000; Negri *et al*. 2000; Gallus *et al*. 2001). The protection observed for these neoplasms, however, may be partly explained in terms of an inverse relationship

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Table 3. Odds ratios† of selected neoplasms in relation to whole-grain food intake score (≥ 1 times/week compared with < 1 time/week) in strata of selected covariates in data from case–control studies in Milan, Italy 1983–97

	Age (years)				Gender		Education (years)		Smoking habit		Alcohol intake	
	< 45	45–54	55–64	65–74	Men	Women	< 7	≥ 7	Never	Current	No	Yes
Type of neoplasm												
Oral cavity and pharynx	0·7	0·1*	0·2*	0·3*	0·2*	0·3*	0·3*	0·3*	0·4*	0·2*	0·2*	0·3*
Oesophagus	0·2‡	0·3*	0·5*	0·4*	0·5*	0·2*	0·5*	0·3*	0·2*	0·5*	0·5	0·4*
Stomach	0·7	0·6*	0·6*	0·8	0·7*	0·6*	0·6*	0·8	0·6*	0·8	0·6*	0·7*
Colon	0·8	0·7	0·8	0·6*	0·9	0·6*	0·7*	0·8*	0·6*	0·9	0·7*	0·7*
Rectum	0·6	0·4*	0·8	0·7*	0·7*	0·6*	0·6*	0·7*	0·6*	0·9	0·6*	0·7*
Liver	0·3*	0·6	0·8	0·8	0·8	0·5*	0·6*	0·8	0·7*	0·7	0·7	0·7*
Gallbladder	NE‡	NE‡	0·8	0·3	0·3	0·3*	0·3*	0·4	0·2*	0·4‡	0·7‡	0·3*
Pancreas	1·0	0·9	0·8	0·9	1·0	0·8	0·7	1·0	1·0	1·0	0·7	0·9
Larynx	0·3‡	0·1*	0·3*	0·4*	0·3*	0·1‡	0·3*	0·3*	0·5‡	0·3*	0·2	0·3*
Soft tissue sarcomas	0·7	0·5	0·6	1·0	0·6	0·7	0·4*	0·9	0·5*	0·8	0·7	0·7
Breast	0·8*	1·0	0·9	0·9	–	–	0·9*	0·9	0·8*	1·0	0·8	0·9
Endometrium	0·8	0·7	0·9	1·0	–	–	1·1	0·7	0·9	0·9	1·0	0·9
Ovary	1·0	0·7*	0·7*	0·8	–	–	0·7*	0·9	0·7	1·1	0·8	0·8*
Prostate	NE‡	2·9‡	1·0	0·6	–	–	0·5	1·1	0·8	1·1	1·7‡	0·8
Bladder	0·3‡	0·5	0·8	0·5*	0·7*	0·4*	0·7*	0·5*	0·5	0·7	0·3*	0·7*
Kidney	1·2	0·6	0·7	0·5	0·8	0·5*	0·5*	0·8	0·5*	0·5	0·5	0·8
Thyroid	1·3*	1·2	1·1	1·3	1·8*	1·2	1·1	1·4*	1·4*	1·3	1·2	1·3*
Hodgkin's disease	0·6	0·5‡	0·4‡	1·0	0·8	0·4*	0·5	0·6*	0·6	0·5	0·1*	0·8
Non-Hodgkin's lymphomas	0·4*	0·6	0·6	0·8	0·8	0·5*	0·5*	0·8	0·5*	0·6	0·6	0·6*
Multiple myelomas	0·6‡	0·6	1·2	0·7	1·4	0·4*	0·8	0·8	0·5*	0·7	0·5	0·8

NE, not estimated.
*$P \leq 0{\cdot}05$.
†Derived from multiple logistic regression equations, including terms for age and gender. Reference category was subjects with low intake.
‡Estimates based on less than twenty cases.

between whole-grain food intake and lower social class or a diet poor in several aspects, although the correlation between social class and upper digestive tract neoplasms has been changing in Italy over the last few years (Bosetti *et al*. 2001).

Nevertheless, some other correlations for whole-grain food may partly or largely account for the protection observed. In Italy wholegrain intake is generally related to healthier lifestyle and habits, which may include complex aspects of diet, as well as physical activity (La Vecchia, 2001).

Lignans and, more generally phyto-oestrogens, have a diphenolic structure similar to that of oestrogenic compounds, and they may be related to sex hormone metabolism, behaving as oestrogenic or anti-oestrogenic compounds (Slavin *et al*. 1999). Consequently, they may be favourably related to hormone-related neoplasms.

Insoluble fibres that reach the colon are fermented by intestinal microflora to short-chain fatty acids, which may increase faecal weight and colonic motility. These factors have been associated with reduced colo-rectal cancer risk (Negri *et al*. 1998).

Frequent wholegrain consumption may, however, simply imply a lower intake of refined grains, which has been associated with an elevated risk of colo-rectal (Franceschi *et al*. 2001), breast (Augustin *et al*. 2001) and perhaps other cancer sites (Chatenoud *et al*. 1999; Fig. 2). Whole-grain cereals, in fact, have a lower rate of digestion than refined grains, and are therefore inversely related to glycaemic overload and compensatory increases in plasma concentration of insulin-like growth factor I, which is a mutagen and a stimulant of tumour cell growth *in vitro* (Giovannucci, 1995; Yu & Rohan, 2000).

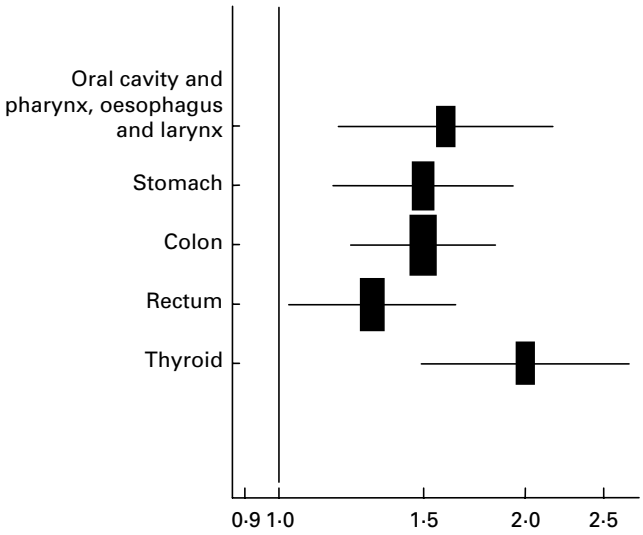

Fig. 2. Odds ratios for highest *v*. lowest tertile of intake of refined cereals in data from case–control studies in Milan, Italy 1983–97. Points are odds ratios with 95 % confidence intervals represented by horizontal bars.

Since consumption of vegetables and fruit is protective for most epithelial cancers (Potter & Steinmetz, 1996; La Vecchia *et al*. 1999), the Spearman correlation coefficients between wholegrain and vegetable or fruit intakes were computed. These values ranged for fruit intake between

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–0·01 for multiple myelomas and 0·20 for non-Hodgkin's lymphomas, and for vegetable intake between –0·07 for larynx and 0·18 for endometrium. Likewise, no appreciable effect modification was observed when allowance was made for fruit and vegetables in the analysis, and the results were not materially modified when allowance was made for estimates of β-carotene or vitamin C.

Even in the absence of a simple biological interpretation, the consistency of the patterns observed indicate that, in this population, higher frequency of whole-grain food consumption is an indicator of reduced risk of several neoplasms. The finding that a higher consumption of whole grains confers some protection on the risk of several common neoplasms is particularly important in view of the accumulating evidence of an unfavourable effect of refined cereals (Chatenoud *et al*. 1999), as well as the potential favourable influence of whole-grain foods on other chronic conditions, including diabetes and cardiovascular diseases (Liu *et al*. 1999; Hu *et al*. 2000; Truswell, 2002).

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