Refined-cereal intake and risk of selected cancers in Italy[1–3]

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ABSTRACT

Background: Although consumption of whole-grain foods seems to reduce the risk of several types of neoplasms, the potential influence of a diet rich in starches and refined grains is less clear.

Objective: We studied the relation between the frequency of consumption of refined cereals (bread, pasta, or rice) and the risk of selected neoplasms.

Design: This was an integrated series of case-control studies conducted in northern Italy between 1983 and 1993. The subjects were patients admitted to the major teaching and general hospitals in Milan and Pordenone with incident, histologically confirmed cancers: 343 with cancer of the oral cavity and pharynx, 94 with cancer of the esophagus, 146 with cancer of the larynx, 745 with cancer of the stomach, 955 with cancer of the colon, 625 with cancer of the rectum, and 428 with cancer of the thyroid. The control subjects were 3526 patients admitted to the same network of hospitals for acute nonneoplastic conditions unrelated to long-term modification of diet. Odds ratios (ORs) for consecutive tertiles of refined-cereal consumption were computed after allowance for sociodemographic variables, education, smoking status, alcohol consumption, body mass index, and consumption of fruit, vegetables, and whole-grain foods.

Results: The ORs for the highest tertile of refined-cereal intake were 1.6 for cancer of the oral cavity, pharynx, esophagus, or larynx; 1.5 for stomach cancer; 1.5 for colon cancer; 1.3 for cancer of the rectum; and 2.0 for thyroid cancer. The trends in risk were significant for all neoplasms considered.

Conclusion: Consumption of refined cereals was associated with an increased risk of cancers of the large bowel, the stomach, and other selected digestive and nondigestive sites. *Am J Clin Nutr* 1999;70:1107–10.

KEY WORDS Cancer, humans, Italy, diet, epidemiology, insulin, starches, whole grains, refined cereals, oral cavity, pharynx, esophagus, larynx, stomach, colon, rectum, thyroid

INTRODUCTION

In a combined analysis of a series of case-control studies conducted in northern Italy on cancers of various sites, we showed previously a systematic inverse relation between consumption of whole-grain food and the risk of most neoplasms studied, with odds ratios (ORs) between 0.2 and 0.7 for digestive sites and <1 for breast, endometrial, ovary, prostate, urinary tract, and lymphoid neoplasms (1). This was consistent with the results of several other studies that showed a general protective effect of whole-grain foods on cancer risk (2–4). However, several studies showed that diets rich in starches and refined cereals are associated with an increased risk of cancers of the upper digestive and respiratory tract (5, 6), stomach (7–11), colorectum (12–16), lung (17), breast (18), and endometrium (19). In particular, 2 large case-control studies from northern Italy (20–23) showed ORs in the highest quintile of consumption of refined bread, pasta, or rice of 1.3 for breast cancer and 1.7 for colorectal cancer, with significant trends in risk. We systematically reanalyzed the relation between refined-grain intake and the risk of several cancers by using a combined data set from a network of case-control studies conducted in Italy.

SUBJECTS AND METHODS

Data were obtained from a series of hospital-based case-control studies conducted in northern Italy, the general design of which was described previously (1, 24, 25). All studies had the same scheme, the same criteria for inclusion of subjects, and the same interview setting for both case and control subjects (ie, during hospital admission). Data collection for each study started between 1983 and 1985. This report is based on data collected before December 1993; for colorectal cancer only, the study ended in 1991. The refusal rate of eligible patients (case and control subjects) was <3%. The study protocol was approved by the ethical committees of the participating hospitals. Before completing the questionnaire, subjects provided oral consent to their participation in the study.

The questionnaires were tested for reproducibility (26) and contained a basic structured section that covered education and other sociodemographic factors, anthropometric variables,

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TABLE 1
Distribution of Italian case and control subjects by sex and age, 1983–1993

	Men				Women				
	<45 y	45–54 y	55–64 y	65–74 y	<45 y	45–54 y	55–64 y	65–74 y	Total
Case subjects (according to site of neoplasm)									
Oral cavity and pharynx	34	78	104	79	6	13	21	8	343
Esophagus	2	19	34	30	0	1	3	5	94
Larynx	7	20	71	40	1	2	1	4	146
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
Thyroid	53	27	30	6	163	62	59	28	428
Control subjects	504	586	604	375	380	315	428	334	3526

medical history, and general characteristics or habits (eg, smoking status, alcohol use, and coffee drinking). Patients were asked to indicate their frequency of consumption per week of selected indicator foods (30–37 items) during the 2 y before their cancer was diagnosed (case subjects) or before the interview (control subjects). All questionnaires included questions on the weekly frequency of consumption of fruit, vegetables, meats, dairy products, and most common refined-cereal foods (bread, pasta, and rice), allowing a combination of data from various studies. About 50% of refined-grain intake was accounted for by bread, 35% by pasta, and 16% by rice (27). The rate of consumption of whole-grain foods was reported by using a simple score (low, intermediate, or high) rather than being reported as a number of times per week (1).

The case subjects were patients younger than 75 y (to improve reliability and validity of information) with incident (ie, diagnosed within 1 y of the interview), histologically confirmed cancers of the oral cavity and pharynx (n = 343), the esophagus (n = 94), the larynx (n = 146), the stomach (n = 745), the colon (n = 955), the rectum (n = 625), and the thyroid (n = 428). The patients were admitted to the National Cancer Institute of Milan; several university clinics; the Ospedale Maggiore of Milan, which includes the 4 largest teaching and general hospitals in Milan; or (until 1991) the Cancer Institute and General Hospital in Pordenone.

The control group comprised 3526 patients (2069 men and 1457 women) younger than 75 y with a wide spectrum of acute nonneoplastic conditions who were admitted to the same network of hospitals at which case subjects had been identified. Thirty percent of control subjects were admitted for trauma, 16% for nontraumatic orthopedic disorders, 29% for acute surgical conditions, and 25% for other miscellaneous illnesses (otolaryngeal, skin, or dental disorders). Subjects admitted for any condition related to tobacco smoking or alcohol consumption or with any disorder that might have induced long-term modifications of diet were excluded from the control group. The distribution of case and control subjects by sex and age group is shown in **Table 1**.

Data analysis

ORs of various neoplasms and the corresponding 95% CIs, in relation to approximate tertiles of frequency of refined-cereal intake, were derived from unconditional multiple logistic regression fitted by the method of maximum likelihood (28). All regression equations included terms for the study center, calendar period at interview, age, sex, education, tobacco smoking, alcohol consumption, body mass index (BMI), and vegetable, fruit, and whole-grain-food consumption. These categories of food consumption were introduced to accommodate confounding by the corresponding food groups and to control for possible systematic, across-the-board overreporting by case subjects. The ORs and corresponding 95% CIs for each type of neoplasm in relation to the major covariates studied are shown in **Table 2**.

The frequency of intake of refined cereals was also introduced as a continuous variable. In these models, the unit of measurement was set at 7 portions per week. Hence, these models give an estimate of the OR relative to an increase of one serving per day.

RESULTS

The distribution of case and control subjects according to approximate tertiles of frequency of consumption of refined cereals (bread, pasta, and rice) is shown in **Table 3** together with

TABLE 2
Association between selected covariates and the risk of various neoplasms, Italy, 1983–1993[1]

Site of neoplasm	Education	Smoking	Alcohol consumption	BMI	Fruit consumption	Vegetable consumption	Whole-grain consumption
Oral cavity and pharynx, esophagus, and larynx	0.2 (0.1–0.3)[2]	8.7 (6.0–12.4)[2]	11.4 (5.8–22.4)[2]	0.5 (0.4–0.6)[2]	0.5 (0.4–0.6)[2]	0.5 (0.3–0.7)[2]	0.5 (0.3–0.7)[2]
Stomach	0.7 (0.5–0.9)[2]	1.1 (0.9–1.4)	0.8 (0.7–1.0)	0.3 (0.2–0.4)[2]	0.5 (0.4–0.6)[2]	0.3 (0.2–0.3)[2]	0.5 (0.4–0.7)[2]
Colon	1.7 (1.4–2.1)[2]	0.7 (0.5–0.8)	1.0 (0.8–1.2)	0.6 (0.5–1.0)	0.8 (0.6–0.9)[2]	0.4 (0.3–0.5)[2]	0.6 (0.4–0.7)[2]
Rectum	0.7 (0.4–1.2)[2]	0.7 (0.6–0.9)	0.9 (0.7–1.1)	0.6 (0.5–0.9)	0.9 (0.8–1.1)	0.4 (0.3–0.7)[2]	0.6 (0.4–0.9)[2]
Thyroid	1.2 (0.9–1.6)[2]	0.7 (0.5–0.9)	1.7 (1.3–2.3)	1.2 (0.9–1.5)	1.5 (1.1–1.9)	0.7 (0.6–0.9)[2]	1.3 (0.9–1.8)

[1] Odds ratios with 95% CIs in parentheses for the highest versus the lowest categories. Values are estimates from multiple logistic regression equations, adjusted for age and sex.

[2] P for trend < 0.05.

TABLE 3
Distribution and corresponding OR with 95% CI of case and control subjects according to intake of refined cereals, Italy, 1983–1993[1]

	Intake category					
	No. of subjects			OR (95% CI)		
	0–14 portions/wk	15–21 portions/wk	≥22 portions/wk	15–21 portions/wk	≥22 portions/wk	OR continuous (95% CI)[2]
Case subjects (according to site of neoplasm)						
Oral cavity and pharynx, esophagus, and larynx	92	175	316	1.24 (0.9, 1.7)	1.59 (1.2, 2.2)	1.10 (1.0, 1.2)
Stomach	219	264	262	1.24 (1.0, 1.5)	1.54 (1.2, 2.0)	1.15 (1.1, 1.2)
Colon	291	360	304	1.33 (1.1, 1.6)	1.46 (1.2, 1.8)	1.12 (1.1, 1.2)
Rectum	207	197	221	0.95 (0.8, 1.2)	1.27 (1.0, 1.6)	1.10 (1.0, 1.2)
Thyroid	125	165	138	1.68 (1.3, 2.2)	2.02 (1.5, 2.7)	1.23 (1.1, 1.3)
Control subjects	1136	1224	1166	—	—	—

[1] Odds ratios (ORs) derived from multiple logistic regression equations that included terms for center, age, sex, education, smoking habits, alcohol intake, BMI, and intake of fruit, vegetables, and whole grains. Reference-category subjects consumed ≤14 portions/wk.
[2] OR relative to an increase of one serving per day.

the corresponding multivariate ORs. There was a consistent pattern of increasing risk with increasing intake of refined cereals; the ORs were 1.6 for cancer of the oral cavity and pharynx, esophagus, or larynx; 1.5 for stomach cancer; 1.5 for colon cancer; 1.3 for cancer of the rectum; and 2.0 for thyroid cancer for the highest tertile of refined-cereal intake. The trends in risk were of borderline significance for rectal cancer and clearly significant for all other types of neoplasms. Multivariate ORs for increments of one serving per day ranged between 1.10 and 1.23. When the relation between subsequent refined-cereal intake and the risk of various neoplasms was considered in separate strata of age, sex, education, and BMI, most ORs for the highest tertile of consumption were >1.

No significant effect modification (as observed by comparing the increase in the −2 log likelihood between the models with and without interaction terms with the chi-square distribution, with degrees of freedom given by the number of interaction terms) was evident for age, education, or BMI. The association tended to be stronger in women than in men for cancers of the stomach, colon, or rectum ($P < 0.05$). No appreciable differences were found in the frequency of refined-cereal intake among the 4 types of control subjects (ie, admitted for trauma, orthopedic disorders, surgical conditions, or other miscellaneous illnesses).

DISCUSSION

This systematic analysis of an integrated series of case-control studies showed a consistent pattern of direct association between frequent intake of refined cereals (mainly bread and pasta, but also rice) and the risk of several common neoplasms, including those of the major digestive tract sites, the larynx, and the thyroid, in this Italian sample. These findings agree with those of several other studies that showed that refined cereals have an unfavorable effect on carcinogenesis of the large bowel, the stomach, the upper digestive tract, and selected other sites; these studies include 2 large case-control studies of breast cancer (20) and colorectal cancer (22, 23) conducted at several Italian study sites and based on a more detailed food-frequency questionnaire.

Similar associations were observed with sugar (29–31), which, from a nutritional viewpoint, confirms the metabolic similarities between sugars and refined cereals. It is known that refined cereals and sugars have a higher rate of digestion than do whole-grain cereals and other components of diet, causing glycemic overload and compensatory increases in plasma insulin concentration and insulin-like growth factor I, an important mitogenic stimulant of tumor cell growth in vitro (32).

Other interpretations have to be considered, however. First, pasta, bread, and other refined cereals may simply be indicators of a poor diet and other unfavorable lifestyle characteristics in this Italian sample. Thus, a diet rich in refined cereals may be not only poor in whole grains and fibers (1) but also relatively poor in fruit and vegetables and various micronutrients, which have been shown to protect against the risk of several types of cancer (24, 33, 34). Allowance for the confounding factors did not account for the association between consumption of refined cereals and various types of cancer considered, and several ORs were indeed higher after allowance for consumption of vegetables, fruit, and whole-grain foods (which may also serve as a proxy for total dietary intake). Still, it is conceivable that a complex combination of unfavorable nutritional and lifestyle correlates of a diet rich in refined cereals may contribute to the associations we observed. For instance, the association with thyroid cancer may have been due to the relatively low iodine content of such a diet (25).

This study was not population based, but case subjects were identified in the major teaching and general hospitals of the areas in which the study was conducted, and the participation of case and control subjects was almost complete. Patients admitted to the hospital for chronic conditions, neoplastic diseases, or any disease related to known or likely risk factors for the neoplasms under study were excluded from the control group. No appreciable differences were found in the frequency of refined-cereal intake among control subjects with traumatic conditions, those with orthopedic disorders, those with surgical conditions, and those with other miscellaneous illnesses, and the fact that a similar interview setting was used for both case and control subjects provides further reassurance against potential information bias (26). The association was consistent across strata of age, BMI, and education and was stronger in women. This may be due to the greater reliability of food-

intake information from women. Furthermore, indirect support for the existence of a real (but not necessarily causal) association between consumption of refined cereals and some cancers comes from the observation that such a relation was not observed for several other foods (1, 24).

Whatever the potential limitations of the study design, our findings appear to have relevant implications for public health and prevention. The Italian diet is characterized by a high intake of pasta and bread, which are the top 2 sources of energy (27, 35). In this southern European population, consequently, a further increase in refined-cereal intake should not be assumed to result in a diet that reduces the risk of cancer, even if the refined cereals replace meat, fats, or any other nutrient that may have been related to increased risk of particular neoplasms (36).

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