

# Mediterranean Epidemiological Evidence on Tomatoes and the Prevention of Digestive-Tract Cancers

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**Abstract.** Tomatoes have been estimated as the second most important source of vitamin C, after oranges, in an Italian population. We have therefore considered the relationship between tomato intake and the risk of digestive tract cancers using data from a series of case-control studies conducted in Italy between 1983 and 1992, and including 317 histologically confirmed, incident cases of cancer of the oral cavity and pharynx, 85 of the esophagus, 723 of the stomach, 955 of the colon, and 629 of the rectum, and a total of 2879 controls admitted for acute, non-neoplastic conditions, unrelated to long-term modifications of diet. Multivariate odds ratios (OR) and 95% confidence intervals (CI) for subsequent quartiles of intake of tomatoes were derived, after allowance for age, sex, study center, education, smoking, alcohol drinking, and total calorie intake. There was a consistent pattern of protection for all sites. The ORs for the highest consumption quartile were 0.65 (95% CI 0.4–1.0) for oral cavity, pharynx, and esophagus, 0.43 (95% CI 0.3–0.6) for stomach, 0.39 (95% CI 0.3–0.5) for colon, and 0.42 (95% CI 0.3–0.6) for rectum.

Another study of colorectal cancer, based on 1,953 cases and 4,154 controls, conducted between 1992 and 1996 and using a more detailed food frequency questionnaire, confirmed that tomato intake was significantly protective on colorectal cancer risk, even after allowance for several potential confounding factors, including measures of body mass index, calorie intake, and physical activity. The ORs for the highest consumption quintile were 0.79 (95% CI 0.6–0.9) for colon, and 0.71 (95% CI 0.5–0.9) for rectal cancer. The beneficial effect of tomatoes observed in these epidemiological studies may be due to the fact that they constitute one of the most specific features of the Mediterranean diet. This has both a scientific and a public health relevance.

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A beneficial effect of the Mediterranean diet was first suggested on the basis of the low mortality from cardiovascular diseases in these countries. Mortality from several important cancer sites, including intestines, pancreas, breast, and prostate, is also low in Mediterranean countries (1).

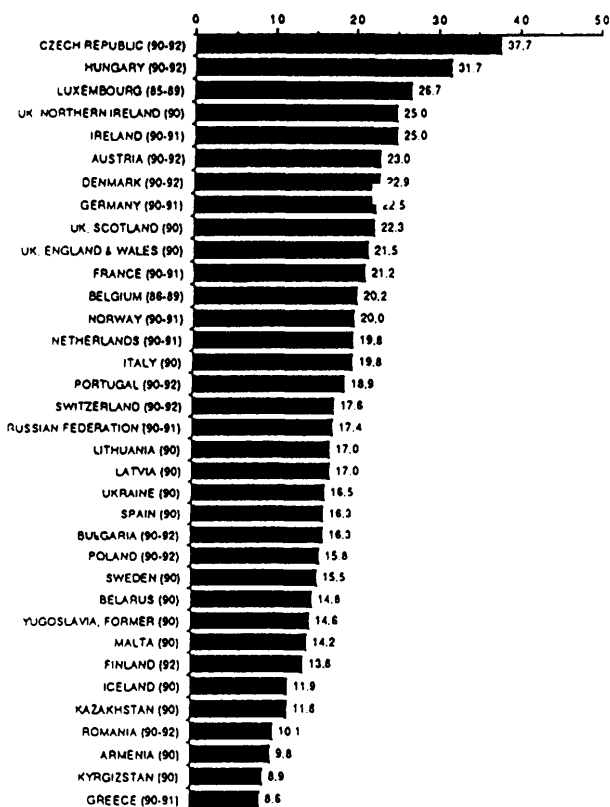
In the 1950s a substantial heterogeneity was present in colorectal cancer mortality, since Britain and central European countries had elevated rates, whereas southern and eastern Europe had consistently lower mortality. A systematic tendency toward leveling of rates, over more recent calendar periods, around higher values (i.e., between 18 and 25/100,000 males, and between 13 and 20/100,000 females, world standard) was observed (Figure 1, (2, 3)). In particular, appreciable rises in intestinal cancer mortality were observed in Italy, Spain, Portugal, and Greece (4, 5). Rates were, however, still somewhat lower in Italy, Spain, and mostly Greece, though persisting upward trends in these countries suggested that they may reach levels comparable to those of other European areas in the near future.

Since diet plays an important role in the aetiology of large bowel cancer (6, 7), and hence in its geographical

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INTESTINES, MALES (ICD-9 : 152-4)



INTESTINES, FEMALES (ICD-9 : 152-4)

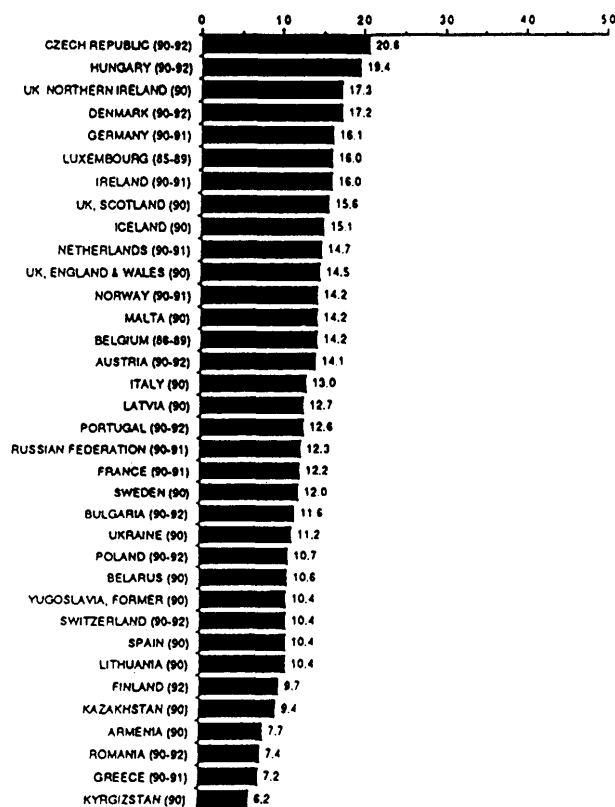


Figure 1. Age-standardized (world population) death certification rates for males from cancer of the intestines (mainly colon and rectum) in various European countries. (Used with permission from Reference 3)

distribution worldwide (5), this pattern of trends probably reflects the tendency toward more uniform dietary habits throughout Europe.

Likewise, European mortality data for pancreatic cancer indicate a substantial advantage for Mediterranean countries, with appreciably lower rates in all these areas. Oral, esophageal, and stomach cancer rates are also comparatively low in southern Italy and Greece (8, 3). This favorable picture has been attributed, at least in part, to a beneficial impact of Mediterranean dietary habits.

It is important, nonetheless, to focus epidemiological research toward understanding and quantifying the role of each specific component of the Mediterranean diet on cancer risk, in order to open perspectives for information and education on a public health scale, intervene for the food industry, and define priorities for cancer prevention.

Consumption of tomatoes is particularly high in Italy, as they are part of the typical Mediterranean diet. Tomatoes, for instance, besides being the first source of lycopene, have been estimated as the second most important source of vitamin C, after oranges, in Italy. Still, tomato intake shows wide variability across different segments of the Italian population.

## The Epidemiological Data

Several epidemiological studies have shown that high consumption of vegetables and fruits is consistently associated with a reduced risk of cancer. The association is especially marked for epithelial cancers of the digestive tract (9). Analysis of the association between cancer and individual vegetables retains considerable importance. In fact, because the translation of foods into nutrients is incomplete, many potentially relevant nutrients are still inadequately quantified or little studied (10).

We have therefore considered the relationship between tomato intake and the risk of digestive tract cancers using data from a series of case-control studies conducted in Italy between 1985 and 1991 (11). We included 317 histologically confirmed, incident cases of cancer of the oral cavity and pharynx, 85 of the esophagus, 723 of the stomach, 955 of the colon, and 629 of the rectum, and a total of 2879 controls admitted for acute, non-neoplastic conditions, unrelated to long-term modifications of diet.

Frequency of consumption of raw tomatoes was divided into four levels (i.e.,  $\leq 2$ , 3–4, 5–6, and  $\geq 7$  servings per week) including, as far as possible, comparable numbers of control subjects (approximate quartiles).

Multivariate odds ratios (OR) and the corresponding 95% confidence intervals (CI) for subsequent quartiles of tomato intake were derived, after allowance for age, sex, study center, education, smoking, alcohol drinking, and total calorie intake (12, 13). There was a consistent pattern of protection for all sites. The ORs for the highest consumption quartile were 0.65 (95% CI 0.4–1.0) for oral cavity, pharynx, and esophagus, 0.43 (95% CI 0.3–0.6) for stomach, 0.39 (95% CI 0.3–0.5) for colon, and 0.42 (95% CI 0.3–0.6) for rectum (Table I).

Adjustment for dietary and nondietary potentially confounding factors slightly weakened the association between low tomato intake and risk of cancer of the oral cavity, pharynx, and esophagus, since the consumption of tomatoes, as well as of most vegetables and fruits, was inversely associated with tobacco and alcohol consumption. Conversely, the apparent protection of tomato consumption against cancer of the stomach, colon, and rectum was somewhat strengthened by adjustment for education, consumption of alcohol and tobacco, and total calorie intake.

A significant inverse trend in risk for tomatoes (OR = 1.0, 0.7, 0.7,  $P < 0.001$ ) was seen in the another Italian case-control study of gastric cancer (14). Likewise, Modan *et al.* (15) in Israel noted a significant inverse association of tomatoes with a combination of gastrointestinal cancers. Furthermore, Colditz *et al.* (16) reported a 50% reduced mortality from cancers of all sites among elderly Americans reporting high tomato intake.

Another large, multicenter study of colorectal cancer, based on 1953 cases and 4154 controls, conducted between 1992 and 1996 and using a more detailed and validated food frequency questionnaire (17, 10), confirmed that tomatoes were significantly protective against colorectal cancer.

Table II gives the distribution of cases of colon cancer, of rectal cancer, and the comparison group according to approximate quintile of tomato intake. After allowance for several potential confounding factors, including measures of body mass index, calorie intake, and physical activity, the

**Table II.** Distribution of 1953 cases of colorectal cancer and 4154 controls according to tomato consumption (portions per week). Italy, 1992–1996.

Tomatoes, portions per week	Colon cancer		Rectal cancer		Controls	
	No.	%	No.	%	No.	%
<1	223	18.2	133	18.3	656	15.8
1 < 1.5	184	15.0	116	15.9	581	14.0
1.5 < 2	229	18.7	133	18.3	640	15.4
2 < 3.5	290	23.7	200	27.5	1153	27.8
≥3.5	299	24.4	146	20.1	1124	27.1
Total	1225	100.0	728	100.0	4154	100.0

ORs for the highest consumption quintile were 0.79 (95% CI 0.6–0.9) for colon cancer and 0.71 (95% CI 0.5–0.9) for rectal cancer. The continuous OR for the difference between the upper cutoff of the fourth versus the first quintile were 0.93 (95% CI 0.88–0.97) for colon cancer, 0.92 (95% CI 0.87–0.98) for rectal cancer, and 0.92 (95% CI 0.89–0.96) for total colorectal cancer (Table III).

Olive oil, another typical feature of the Mediterranean diet, has been shown to be protective against breast and colorectal cancer (18, 19). Intake of olive oil is positively correlated with tomato consumption. Although these are difficulties in disentangling the separate effect of various foods and nutrients, and hence in any epidemiological inference on highly collinear foods, when stratified and multivariate analyses were performed, the protection by tomatoes was stronger and more consistent as compared to that given by olive oil.

## Conclusions

The beneficial effect of tomatoes observed in these epidemiological studies is consistent across studies and types of digestive tract neoplasms, and is comparable or in some case greater than that afforded by other fruits and vegetables. This may be due to the fact that tomatoes constitute

**Table I.** Relative risk (and 95% confidence interval)<sup>a</sup> of selected digestive tract neoplasms according to tomato intake. Italy, 1985–91

Type of cancer	Tomato intake, quartile			
	1 (low) <sup>b</sup>	2	3	4 (high)
Oral cavity, pharynx, and oesophagus ( <i>n</i> = 402)	1	0.66 (0.5–1.0)	0.78 (0.6–1.1)	0.65 (0.4–1.0)
Stomach ( <i>n</i> = 723)	1	0.59 (0.5–0.8)	0.45 (0.3–0.6)	0.43 (0.3–0.6)
Colon ( <i>n</i> = 955)	1	0.80 (0.7–1.0)	0.62 (0.5–0.8)	0.39 (0.3–0.5)
Rectum ( <i>n</i> = 629)	1	0.67 (0.5–0.9)	0.67 (0.5–0.8)	0.42 (0.3–0.6)

<sup>a</sup> Estimates from multiple logistic regression equations including terms for age, sex, study center, education, tobacco, alcohol, and total calorie consumption. From Franceschi *et al.*, 1994 (11), modified.

<sup>b</sup> Reference category

**Table III.** Odds ratio (and 95% confidence interval)<sup>a</sup> of colorectal cancer according to quintile of intake of tomatoes. Italy, 1992–1996

Type of cancer	Intake of tomatoes, quintile:					$\chi^2$ (trend)	OR continuous
	1 <sup>a</sup>	2	3	4	5		
Colorectal	1 <sup>b</sup>	0.96 (0.8–1.2)	1.08 (0.9–1.3)	0.80 (0.7–0.9)	0.76 (0.6–0.9)	13.93 <sup>c</sup>	0.92 (0.89–0.96)
Colon	1 <sup>b</sup>	0.95 (0.8–1.2)	1.15 (0.5–1.6)	0.76 (0.6–0.9)	0.79 (0.6–0.9)	9.42 <sup>c</sup>	0.93 (0.88–0.97)
Rectal	1 <sup>b</sup>	0.97 (0.7–1.3)	1.02 (0.8–1.3)	0.87 (0.7–1.1)	0.71 (0.5–0.9)	6.90 <sup>c</sup>	0.92 (0.87–0.98)

<sup>a</sup> Derived from multiple logistic regression equations including terms for age, sex, body mass index, total calories, and physical exercise.

<sup>b</sup> Reference category

<sup>c</sup>  $p < 0.01$

one of the most highly consumed features of the Mediterranean diet. This has both a scientific and a public health relevance for cancer prevention, as indicated by the most recent issue of the European Code against Cancer (20). Tomatoes, moreover, are not difficult to grow or transport, especially with the advent of molecular engineering, and they are easy to prepare. Therefore, they may serve as a simple focal point and tool for gastrointestinal cancer prevention campaigns.

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