Tomatoes, Lycopene Intake, and Digestive Tract and Female Hormone-Related Neoplasms

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Tomato consumption showed a consistent inverse relation with the risk of digestive tract neoplasms in Italy in an integrated series of studies conducted in the 1980s. Another series of case-control studies was conducted between 1992 and 1999 in different areas of Italy. Cases were patients below age 80 with incident, histologically confirmed cancer of the oral cavity and pharynx (n = 754), esophagus (n = 304), colorectum (n = 1953), breast (n = 2529), and ovary (n = 1031). The comparison group involved, overall, over 5000 patients below age 80 with acute, non-neoplastic, nonhormone-related diseases, unrelated to long-term diet modifications and admitted to the same network of hospitals. Information was collected in hospital by trained interviewers using a validated food frequency questionnaire, including 78 foods or groups of foods, various alcoholic beverage, and fat-intake pattern. The multivariate relative risk (RR) of oral, pharyngeal, and esophageal cancer decreased across subsequent levels of lycopene intake to reach 0.7 (95% confidence interval [CI] 0.4–1.0) for oral and pharyngeal, and 0.7 (95% CI 0.4-1.1) for esophageal cancer in the highest quintile of intake. Both trends in risk were of borderline statistical significance. With reference to colorectal, breast, and ovarian cancer, although no consistent association was observed for lycopene (RR = 1.0 for colorectal, 1.2 for breast, and 1.1 for ovary in the highest quintile), tomato intake was inversely and significantly related with colorectal cancer (RR = 0.8). The inverse relation between lycopene and upper digestive tract neoplasms was not explained by alcohol or tobacco, sociodemographic factors, or total energy intake. The interpretation of such an inverse relation, however, remains open to discussion because it may be related to an effect of lycopene due to its antioxidant effect and/or a potential role of lycopene in decreasing insulin growth factor I, which is a promoter in the process of carcinogenesis.
Exp Biol Med 227:860–863, 2002

Key words: vegetables; fruit; micronutrients; neoplasms; human

The inverse relation between vegetable and fruit intake and the risk of several common epithelial cancers has been one of the most frequently reported and consistent factors in the dietary epidemiology of cancer (1). In an integrated series of case-control studies conducted in northern Italy and including over 10,000 cases and 10,000 controls, the relative risks (RR) of most common epithelial cancers ranged between 0.2 and 0.7 for the highest versus the lowest tertile of vegetable intake (2, 3).

Tomatoes and Digestive Tract Neoplasms

Tomatoes are of specific interest because they are a typical aspect of Italian and, in general, of Mediterranean diet, they are relatively cheap and easy to store and maintain, and also because they are the main source of lycopene, a carotenoid with strong antioxidant properties that is not converted to vitamin A.

Separate analysis of tomatoes and digestive tract neoplasms in Italy showed consistent inverse relations with the risk of major digestive tract neoplasms (4, 5). Data were analyzed from an integrated series of case-control studies conducted between 1985 and 1991 in northern Italy, where tomato consumption is high and also variable. The dataset included 314 cases of cancers of the oral cavity and pharynx, 85 of the esophagus, 723 of the stomach, 955 of the colon, 629 of the rectum, and 2879 controls admitted to hospital for acute, nonneoplastic conditions.

There were significant inverse trends in risk between reported frequency of tomato consumption and various digestive tract neoplasms considered. The multivariate RR for the highest versus the lowest quartile of intake were 0.7 (95% confidence interval [CI] 0.4–1.0) for cancers of the oral cavity, pharynx, and esophagus, 0.4 (95% CI 0.3–0.6) for stomach, 0.4 (95% CI 0.3–0.5) for colon, and 0.4 (95% CI 0.3–0.6) for rectum.

A subsequent series of case-control studies based on a more comprehensive and validated food frequency questionnaire was conducted between 1992 and 1999 in different areas of northern, central, and southern Italy, and its main results with reference to lycopene are given below.

Lycopene and Cancer Risk In Italy

Lycopene has been inversely related to the risk of prostate cancer in studies conducted in North America (6), as well as to several other cancer sites in a number of studies from North America, Europe, China, and Japan (7).

Therefore, we decided to systematically consider the relation between tomatoes, lycopene, and selected cancers

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1535-3702//-0860$15.00

of the digestive tract, breast, and ovary in a series of large and multicentric case-control studies conducted during the 1990s in Italy.

Briefly, cases were patients below the age of 80 with incident, histologically confirmed cancer of the oral cavity and pharynx (n = 754) (8), esophagus (n = 304) (9), colorectum (n = 1953) (10), breast (n = 2529) (11), and ovary (n = 1031) (12) admitted to a network of teaching and general hospitals in the areas under surveillance in northern, central, and southern Italy. The comparison group involved, overall, over 5000 patients below the age of 80 with acute, nonneoplastic, nonhormone-related diseases, unrelated to long-term diet modifications, and admitted to the same network of hospitals. Of these, about 25% were admitted for traumas, 25% for nontraumatic orthopedic diseases, 20% for acute surgical conditions, and 30% for miscellaneous other illnesses, including eye, skin, nose, and throat, and dental conditions.

Information was collected in hospital by trained interviewers using a validated food-frequency questionnaire (13), including 78 foods or groups of foods, various alcoholic beverages, and fat-intake pattern. To compute nutrient intake, Italian food-composition databases were used, integrated by information from manufacturers (14). Information was also collected on sociodemographic characteristics, smoking, alcohol and coffee consumption, physical activity, anthropometric measures at various ages, and a problem-oriented personal and family medical history. Allowance for these factors, as well as for a measure of total energy intake, was made using multiple logistic regression.

Table I gives the relation between lycopene and, for comparative purposes, carotene, and oral and pharyngeal and esophageal cancer. The RRs decreased across subsequent levels of lycopene intake to reach 0.7 (95% CI 0.4–1.0) for oral and pharyngeal cancer and 0.7 (95% CI 0.4–1.1) for esophageal cancer in the highest quintile of intake. Both trends in risk were of borderline statistical significance. The associations were in the same direction and, if anything, stronger for carotene with reference to both cancer sites.

Table II considers similar data for colorectal, breast, and ovarian cancer. No consistent association was observed for lycopene (RR = 1.0 for colorectal, 1.2 for breast, and 1.1 for ovary in the highest quintile).

However, in the same dataset, the frequency of tomato consumption was inversely related to the risk of colorectal cancer (Table III) (5). The multivariate RRs for the highest quintile of consumption, after allowance for energy intake and physical exercise, were 0.8 for colon, 0.7 for rectum, and 0.8 for colorectal cancer combined, the trends in risk were significant, and the continuous RR were around 0.9 for all intestinal subsites.

Discussion

The data from this integrated network of studies confirm that tomato consumption is a favorable indicator of the risk of digestive tract neoplasms, and they indicate that lycopene, as well as several other carotenoids, is inversely related to the risks of upper digestive tract neoplasms, confirming a large amount of data on the issue (7). The association with lycopene, however, was less consistent for breast and colorectal neoplasms, although the frequency of tomato consumption was inversely related to colorectal cancer after allowance for total energy intake, physical activity, and other potentially relevant covariates.

Lycopene was inversely related to breast cancer risks in a study conducted in French-speaking Switzerland, with a significant RR of 0.4 in the highest consumption tertile (15), and with lung cancer in two perspective U.S. cohorts (16), though not with breast cancer in a recent analysis of the Nurses Health Study, based on 2697 cases (17), nor with colon cancer in a case-control study including 2410 cases from California and Utah (18) and in another study of 223 cases from Switzerland (19).

In the present study, the inverse relation between lycopene and upper digestive tract neoplasms was not explained

Table I. Multivariate OR and Corresponding 95% CI of Oral and Pharyngeal and Esophageal Cancer According to Lycopene and Carotene Intake.[a] Italy, 1992–1999

Type of cancer (number of cases: number of controls)	Intake quintile, OR (95% CI)					χ^2, Trend	OR, Continous[c]
	1	2	3	4	5		
Oral cavity and pharynx (754:1775)							
Lycopene	1[b]	0.8 (0.6–1.2)	0.7 (0.5–1.1)	0.8 (0.5–1.1)	0.7 (0.4–1.0)	3.24 (n = 0.07)	0.9 (0.8–1.0)
Carotene	1[b]	0.7 (0.5–1.0)	0.6 (0.4–0.8)	0.4 (0.2–0.5)	0.4 (0.2–0.3)	23.32 (P < 0.001)	0.6 (0.5–0.7)
Esophagus (304:743)							
Lycopene	1[b]	1.0 (0.6–1.6)	0.8 (0.5–1.3)	0.6 (0.4–1.0)	0.7 (0.4–1.1)	4.10 (P < 0.05)	0.8 (0.7–1.0)
Carotene	1[b]	0.4 (0.3–0.7)	0.5 (0.3–0.8)	0.3 (0.2–0.6)	0.3 (0.2–0.6)	16.92 (P < 0.001)	0.6 (0.5–0.8)

[a] Modified from Negri *et al.*, 2000 (8) and Franceschi *et al.*, 2000 (9).
[b] Reference category.
[c] ns means nonsignificant.

Table II. Multivariate OR and Corresponding 95% CI of Colorectal, Breast, and Ovarian Cancer According to Lycopene and Carotene Intake.[a] Italy, 1992–1999

Type of cancer (number of cases:number of controls)	Intake quintile, OR (95% CI)					χ^2, Trend
	1	2	3	4	5	
Colorectum (1954:4154)						
Lycopene	1[b]	1.1 (0.9–1.3)	1.0 (0.8–1.2)	1.0 (0.8–1.2)	1.0 (0.8–1.2)	0.01 (*ns*)[c]
Breast (2569:2588)						
Lycopene	1[b]	1.0 (0.8–1.2)	1.0 (0.9–1.3)	1.0 (0.9–1.2)	1.2 (1.0–1.4)	0.64 (*ns*)[c]
Ovary (1031:2411)						
Lycopene	1[b]	1.0 (0.7–1.3)	1.0 (0.7–1.3)	1.1 (0.8–1.4)	1.1 (0.9–1.5)	1.48 (*ns*)[c]

[a] Modified from La Vecchia et al., 1997, 1999 (10, 11)
[b] Reference category.
[c] Nonsignificant.

Table III. OR (and 95% CI)[a] of Colorectal Cancer According to Quintile of Intake of Tomatoes. Italy, 1992–1996

Type of cancer (number of cases)	Intake of tomatoes, quintile, OR (95% CI)				*P*, trend
	2	3	4	5	
Colorectum (1553)	1.0 (0.8–1.2)	1.1 (0.9–1.3)	0.8 (0.7–0.9)	0.8 (0.6–0.9)	<0.01
Colon (1225)	1.0 (0.8–1.2)	1.2 (0.5–1.6)	0.8 (0.6–0.9)	0.8 (0.6–0.9)	<0.01
Rectum (728)	1.0 (0.7–1.3)	1.0 (0.8–1.3)	0.9 (0.7–1.1)	0.7 (0.5–0.9)	<0.01

[a] Derived from multiple logistic regression equations including terms for age, sex, body mass index, total calories, and physical exercise. Modified from La Vecchia, 1998 (5).
[b] Reference category: lowest quintile.

by alcohol or tobacco, sociodemographic factors, or total energy intake. The interpretation of such an inverse relation, however, remains open to discussion because it may be related to a direct effect of lycopene due to its antioxidant effect and/or a potential role of lycopene in decreasing insulin growth factor I (IGF-I), which is a promoter in the process of carcinogenesis at various sites (20–24). Furthermore, carotenoids and sterols may affect wall membrane structure and integrity (1).

Alternatively, the apparent protection of lycopene may be due to other micronutrients included in its main source, tomatoes, because consumption of tomatoes, and of several other fruits and vegetables, has been shown to be protective on digestive tract neoplasms, as well as several other epithelial cancers (3, 4), and a number of other potentially beneficial compounds are present in tomatoes. Complex interactions between multiple nutrients may thus contribute to the anticancer properties of tomatoes (7).

Furthermore, the effect of lycopene may be partly or largely due to the fact that it constitutes one of the most specific indicators of the Mediterranean diet in Italy. "Mediterranean diet" is a generic term, varying from one country to another (25, 26), but it is characterized by a few common factors. Several of these factors, including a low intake of saturated fat, a high intake of olive oil (27–30), and a high intake of fruit and vegetables (2), specifically, tomatoes, eggplant, or peppers, can contribute to a reduced risk of several cancer sites. In particular, measures of olive oil intake were strongly and inversely related to the risk of cancers of the oral cavity, pharynx, and esophagus, with RRs of the order of 0.3–0.4 for the highest level of intake (30, 31).

Still, if tomatoes protect against cancer of the upper digestive tract, this may have relevant implications for both scientific and practical viewpoints, in consideration of heat resistance and widespread availability of tomatoes and tomato derivatives in several areas of the world (4, 5, 7).

This work was partially supported by the Italian Association for Cancer Research, Milan. We thank Ms. Ivana Garimoldi for her editorial assistance.

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