The U.S. Food and Drug Administration's Evidence-Based Review for Qualified Health Claims: Tomatoes, Lycopene, and Cancer

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Several studies have reported an inverse association between tomato and/or lycopene intake and the risk of some types of cancer. In 2004, the U.S. Food and Drug Administration (FDA) received two petitions for qualified health claims regarding tomatoes, lycopene, and the risk reduction for some forms of cancer. Health claims that characterize the relationship between a food or food component and a disease or health-related condition require premarket approval by FDA to be included on the labels of conventional foods and dietary supplements. Here we describe FDA's review of the scientific data for tomato and/or lycopene intake with respect to risk reduction for certain forms of cancer. The FDA found no credible evidence to support an association between lycopene intake and a reduced risk of prostate, lung, colorectal, gastric, breast, ovarian, endometrial, or pancreatic cancer. The FDA also found no credible evidence for an assocaition between tomato consumption and a reduced risk of lung, colorectal, breast, cervical, or endometrial cancer. The FDA found very limited evidence to support an association between tomato consumption and reduced risks of prostate, ovarian, gastric, and pancreatic cancers.

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Health claims that characterize the relationship between a substance (e.g., a food or food component) and a disease (e.g., cancer or cardiovascular disease) or health-related condition (e.g., hypertension) require premarket approval by the U.S. Food and Drug Administration (FDA) to be included on the labels of conventional foods and dietary supplements. Before 1990, health claims about disease were not allowed on food labels. However, in the late 1980s, emerging evidence about relationships between diet and health generated interest among consumers and the food industry about conveying this information on the food label. Health claims were first authorized by FDA after the enactment of the Nutrition Labeling and Education Act of 1990 (1). Initially, the only health claims that were allowed were authorized health claims, i.e., those that met FDA's standard of "significant scientific agreement." FDA's determination of significant scientific agreement represents the agency's best judgment as to whether qualified experts would likely agree that the scientific evidence supports the substance–disease relationship that is the subject of a proposed health claim. The significant scientific agreement standard is intended to be a strong standard that provides a high level of confidence about the validity of a substance–disease relationship.

Qualified health claims are based on less scientific evidence than authorized health claims and must be accompanied by a disclaimer or otherwise qualified in their wording. Qualified health claims were first issued for the labeling of dietary supplements after several court decisions regarding First Amendment issues and were later expanded to conventional foods as the result of a major FDA initiative in 2003 (2). For example, in the case of Pearson v. Shalala (3), the court concluded that First Amendment protection of commercial speech does not permit FDA to reject health claims that it determines are potentially misleading (4). As a result of this ruling, FDA began to allow commercial speech about health claims rather than impose an outright ban on such claims, but it could require disqualifying statements. In the case of Whitaker v. Thompson (5), the court ruling stated that when there is "credible evidence" to support a health claim, the health claim cannot be absolutely prohibited. However, the court outlined two situations in which a complete ban on health claims would be appropriate: when there was no evidence to support a health claim or when the evidence in support of the claim was qualitatively weaker than the evidence against the claim and when the government could demonstrate that disqualifying statements would "bewilder" consumers.

Both authorized health claims and qualified health claims require extensive scientific review. In July 2003, FDA released a guidance document that outlined an interim evidence-based review system for qualified health claims (6). The evidence-based review system allows a systematic evaluation of the strength of the scientific evidence for a proposed health claim. Here we describe how the FDA used this system to evaluate the scientific evidence for proposed qualified health claims for tomatoes and lycopene with respect to the risks of different types of cancer.

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Background

Much attention has been focused on the relationship between tomatoes and/or lycopene and cancer risk reduction (i.e., cancer prevention) (7,8). Lycopene is thought to be the active component in tomatoes that is responsible for various types of cancer risk reduction (7). Lycopene, a carotenoid with 11 conjugated double bonds and two unconjugated double bonds (9), can function as an antioxidant (10). It has been suggested that antioxidants, because they reduce oxidative damage, may thereby prevent chronic diseases such as cancer and cardiovascular disease (10). Other potential mechanisms of action for lycopene that have been proposed include regulation of gene function, communication via gap junctions, modulation of hormone and immune activity, and metabolism of carcinogens (10).

In 2004, FDA received two petitions for qualified health claims regarding tomatoes and/or lycopene and cancer risk reduction from The Lycopene Health Claim Coalition (consisting of H. J. Heinz Company, LycoRed Natural Products Industries, Ltd, The Morningstar Company, and The Prostate Cancer Foundation) and American Longevity, Inc. Both petitioners requested that FDA evaluate the relationship between tomato and/or lycopene consumption and prostate cancer risk. One petitioner also requested that FDA review the relationship between tomato and/or lycopene consumption and the risks of other forms of cancer, including lung, colorectal, gastric, breast, cervical, ovarian, endometrial, and pancreatic cancers. In response to these petitions, FDA evaluated evidence for associations between lycopene (a food component) and tomatoes (a food) separately and each form of cancer.

The Qualified Health Claim Petition Process

Qualified health claim petitions submitted to FDA must follow specific requirements outlined in the Code of Federal Regulations (11). These requirements include definitions of the substance(s), diseases, or health-related conditions; a summary of the scientific data both positive and negative (e.g., research articles); copies of all computerized literature searches performed by the petitioner and of all information relied on by the petitioner to support the proposed health claim; and any data regarding adverse consequences. FDA acknowledges receipt of the petition within 15 days and files it within 45 days of receipt, thereby making its contents public. At the time of filing, FDA posts the petition on the Center for Food Safety and Applied Nutrition Web site (http://www.cfsan.fda.gov/~dms/lab-qhc.html) for 60 days to allow public comment. During this time, written comments may be submitted to FDA. On or before 270 days after receipt of the petition, FDA sends the petitioner a final decision about whether it intends to exercise enforcement discretion with respect to a qualified health claim or deny the petition. The decision letter (i.e., letter of enforcement discretion) is posted on the Center for Food Safety and Applied Nutrition Web site and in the public docket. Issuance of a letter of enforcement discretion indicates that FDA does not intend to object to the use of the claim specified in the letter, provided that the products that bear the claim are consistent with the stated criteria in the letter such as disqualifying nutrient levels (e.g., foods may not have high levels of fat, sodium, or cholesterol) and 10% minimum nutrient requirements (foods contain at least 10% of the Daily Value for vitamin A, vitamin C, iron, calcium, protein, or dietary fiber per reference amount customarily consumed). Extensions of time for the final decision beyond 270 days may be granted upon mutual agreement between the petitioner and FDA.

Evidence-Based Review System

The evidence-based review system used by FDA to evaluate the scientific evidence to support qualified health claims (6) is built on the Institute for Clinical Systems Improvement model (12) but includes modifications specific to FDA. FDA uses this system to systematically review, rate, and rank the scientific evidence for a given substance–disease relationship (i.e., health claim). Among the evidence that FDA reviews are studies that were included in petitions seeking health claims. FDA also performs its own literature search to identify additional studies that may be relevant to the petitioned health claims. FDA focuses its literature review on intervention and observational studies in humans but also considers other sources of data and information, such as meta-analyses, review articles, and animal and in vitro studies. FDA may use data and information from these other sources to assist its understanding of scientific issues concerning the substance and/or the disease or health-related condition; however, that material, by itself, is not used by FDA to support a health claim.

FDA evaluates all human studies in the literature that assess the substance–disease relationship. Because health claims are directed toward reducing the risk of a disease in people who do not already have the disease or health-related condition that is the subject of the claim, FDA will consider evidence from studies that include individuals who have been diagnosed with the disease that is the subject of the health claim only if extrapolation of the study's findings to individuals who do not have the disease is scientifically appropriate. For example, the mechanism by which calcium lowers blood pressure in hypertensive and normotensive subjects was determined to be similar (13). Therefore, FDA used studies that included hypertensive subjects to evaluate the relationship between calcium and a reduced risk of hypertension.

In the scientific review process, FDA uses surrogate markers or endpoints in the evaluation for disease risk only when they have been appropriately validated and recognized by the National Institutes of Health and the FDA Center for Drug Evaluation and Research. FDA considers only two surrogate markers or clinical endpoints to be valid for use in identifying risk reduction for purposes of a health claim evaluation involving cancer: incident cases of the particular cancer being studied (all cancers) and recurrent colon or rectal polyps (colorectal cancer).

FDA then evaluates the individual reports of human studies to determine whether any scientific conclusions can be drawn from each study. Studies that lack critical factors (e.g., a control group or statistical analysis) cannot be used by FDA to draw scientific conclusions (14); such studies are excluded from further review because they cannot support the health claim relationship. Next, FDA rates the methodologic quality of the remaining human intervention and observational studies for which scientific conclusions could be drawn. This quality rating is based on several criteria related to study design (e.g., use of a placebo control versus a nonplacebo control group), data collection (e.g., the method of

dietary assessment), the quality of the statistical analysis, the type of outcome measured (e.g., disease incidence versus a validated surrogate endpoint), and the characteristics of the study population (e.g., whether there was selection bias or whether important information about the study subjects, such as age and smoking status, was gathered and reported). For example, if the scientific study adequately addressed all or most of the criteria, it would receive a high methodologic quality rating. The study would be rated as being of moderate or low quality based on the extent of the deficiencies or uncertainties in the quality criteria. Studies that are so deficient that scientific conclusions cannot be drawn from them cannot be used to support the health claim relationship, and FDA eliminates these from further review.

FDA evaluates the results of the remaining human studies and then ranks the strength of the total body of publicly available evidence by considering the study type (e.g., intervention, prospective cohort, case–control, or cross-sectional observational study), the methodologic quality rating previously assigned, the quantity of evidence (i.e., the number of the various types of studies and sample sizes), whether the body of scientific evidence supports a health claim relationship for the US population or a target subgroup, whether study results supporting the proposed claim have been replicated (15), and the overall consistency of the total body of evidence (16). On the basis of the totality of the scientific evidence, FDA determines whether such evidence is credible to support the substance–disease relationship and, if so, ranks the scientific evidence (e.g., level of scientific support) that reflects the level of comfort among qualified scientists that such a relationship is scientifically valid.

Lycopene and Cancer Risk Reduction

Among the studies of lycopene intake and cancer risk reduction that were identified by the FDA literature review and by the two petitioners, none was an interventional study of lycopene intake in subjects who had not been diagnosed with cancer. Eighty-one observational studies examined the relationship between lycopene intake and the risk of prostate, lung, colorectal, gastric, breast, cervical, ovarian, endometrial, or pancreatic cancer, all of which FDA excluded from consideration (Table 1). These studies fall into three groups: 1) observational studies that estimated lycopene intake from dietary sources and assessed the risk of cancer associated with dietary lycopene intake (n = 43), 2) observational studies that measured serum lycopene concentration in subjects without cancer and examined the relationship between serum lycopene concentration and the risk of subsequent cancer (n = 23); and 3) studies that measured serum lycopene levels in subjects who were diagnosed with cancer (n = 15).

FDA concluded that scientific conclusions could not be drawn from the 43 observational studies (17–59) that evaluated the relationship between lycopene intake and cancer risk from food-frequency questionnaires for the following reasons (Table 1). First, in these studies, dietary lycopene intake had been estimated by using lycopene concentration values for individual food product categories that were derived from a nutrient database, such as the United States Department of Agriculture National Nutrient Database for Standard Reference (98), with intake determined by recall. However, observational studies that use dietary recall data have a limited ability to ascertain the actual intake of a food or nutrient for the population studied. Second, the lycopene content of foods can vary substantially depending on the type of food, its stage of ripening, the procedures used to process or cook it, and the duration and temperature of storage (7,99–101), which makes it difficult to ascertain an accurate amount of the lycopene consumed based on reports of dietary intake of foods. Third, lycopene-containing foods contain other nutrients that may be associated with the metabolism of lycopene or the etiology of certain cancers, making it difficult to study lycopene in isolation (102). Consequently, for studies that were based on recorded dietary intake of such foods, it was not possible to accurately determine whether any of the associations between lycopene and cancer risk were due to: 1) lycopene alone; 2) interactions between lycopene and other nutrients; 3) other nutrients acting alone or together; or 4) decreased consumption of other nutrients or substances contained in foods that may have been displaced from the diet by an increased intake of lycopene-rich foods. Furthermore, the observational studies that calculated lycopene intake from estimated dietary intake did not specify whether the reported intakes of tomatoes and tomato-based foods were derived from red tomatoes. Of the three varieties of tomatoes (red, green, and yellow), only red tomatoes contain lycopene according to the United States Department of Agriculture Nutrient Database (98).

FDA concluded for several reasons that conclusions could not be drawn from the 23 studies that used a single measure of serum lycopene and cancer risk in subjects who did not have cancer (Table 1). First, dietary lycopene intake is poorly correlated with serum lycopene levels (correlation coefficients range from 0.11 to 0.45) (103–106). Second, many factors can affect the serum lycopene levels, including age, basal metabolic index, smoking status, serum cholesterol levels, and time of the year (105–107). Therefore, a single measure of serum lycopene may not accurately reflect a subject's usual lycopene intake over time.

Fifteen studies (64–67,75–81,94–97) compared serum lycopene levels in subjects with and without cancer (Table 1). These studies were ultimately excluded from FDA's review because of the poor correlation of serum lycopene level with dietary intake and because they used subjects who were diagnosed with cancer. That is, because health claims are meant for healthy people and the data from subjects diagnosed with cancer cannot be extrapolated to healthy people.

On the basis of the three reasons discussed above, FDA concluded that there was no credible evidence supporting a relationship between lycopene consumption, either as a food ingredient, a component of food, or as a dietary supplement, and any of the cancers evaluated in the studies.

Tomatoes and Cancer Risk Reduction

Among the studies identified by the two petitioners and the FDA literature review on tomato consumption and cancer risk reduction, none was an interventional study that evaluated tomato consumption in subjects who had not been diagnosed with cancer. A total of 64 observational studies of the association between tomato or tomato product consumption and cancer risk were identified.

Table 1. Studies that were excluded from FDA's review of lycopene and cancer risk reduction*

	Cancer							
Type of study	**Prostate cancer**	**Lung cancer**	**Breast cancer**	**Colorectal cancer**	**Gastric cancer**	**Ovarian cancer**	**Endometrial cancer**	**Cervical cancer**
Studies that estimated lycopene intake from food-frequency questionnaires or 24-h recalls	Jian, 2005 (17); Giovannucci, 2002 (18); Schuurman, 2002 (19); Norrish, 2000 (20); Cohen, 2000 (21); Deneo-Pellegrini, 1999 (22); Hayes, 1999 (23); Key, 1997 (24); Meyer, 1997 (25)	Wright, 2003 (26); Hollick, 2002 (27); Rohan, 2002 (28); Michaud, 2000 (29); Voorrips, 2000 (30); De Stefani, 1999 (31); Garcia-Closas, 1998 (32); Candelora, 1992 (33); Ziegler, 1999 (34); Le Marchand, 1993 (35); Kneckt, 1991 (36)	Terry, 2002 (37); La Vecchia, 2002 (38); Levi, 2001 (39); Ronco, 1999 (40); Zhang, 1999 (41); Jarvinen, 1997 (42); Freudenheim, 1996 (43)	Malila, 2002 (44); Levi, 2000 (45); Slattery, 2000 (46); Le Marchand, 1997 (47); La Vecchia, 1997 (48); Enger, 1996 (49)	De Stefani, 2000 (50); Botterweck, 2000 (51); Garcia-Closas, 1999 (52)	La Vechhia, 2002 (38); Cramer, 2001 (53)	Jain, 2000 (54); McCann, 2000 (55); Goodman, 1997 (56)	Sedjo, 2002 (57); Kanetsky, 1998 (58); VanEenwyk, 1991 (59)
Studies that evaluated serum lycopene levels	Huang, 2003 (60); Gann, 1999 (61); Nomura, 1997 (62);Hsing, 1990 (63); Vogt, 2002† (64); Lu, 2001† (65); Rao, 1999† (66); Clinton, 1996† (67)	Ito, 2003 (68); Yan, 2001 (69); Comstock, 1997 (70)	Sato, 2002 (71); Hulten, 2001 (72); Tonilo, 2001 (73); Dorgan, 1998 (74); Ching, 2002† (75); Simon, 2000† (76); Ito, 1999† (77); Zhang, 1997† (78); London, 1992† (79); Potischman, 1992† (80); Potischman, 1990† (81)		Nagao, 2000 (82); Tsubono, 1999 (83); Nomura, 1997 (84); Tsugane, 1992 (85)	Helzlsouer, 1996 (86)	Burney, 1989 (87)	Schiff, 2001 (88); Nagata, 1999 (89); Goodman, 1998 (90); Giuliano, 1997 (91); Palan, 1996 (92); Batieha, 1993 (93); Peng, 1998† (94); Palan, 1998† (95); Potischman, 1994† (96); Potischman, 1991† (97)

* Studies are listed by first author, year of publication (reference).

† Studies that included subjects who were diagnosed with cancer.

Table 2. Studies excluded from FDA's review of tomatoes and cancer risk reduction, by reason for exclusion*

Republication or reanalysis	Nonvalidated endpoint of cancer	No information on the validation of the food-frequency questionnaire	No statistical analysis	No calculation of risk
Norrish, 2000 (20); Tzonou, 1999 (108); Garcia-Closase, 1998(32); Giovannucci, 1995 (109); La Vecchia, 1987 (110)	Mucci, 2001 (111); de Vet, 1991 (112)	Seow, 2002 (113); Brennan, 2000 (114); Norrish, 2000 (20); Cohen, 2000 (21); Mayne, 1994 (115); Franceschi, 1994 (116); Levi, 1993 (117); Ramon, 1993 (118); Fraser, 1991 (119); Hu, 1991 (120); Bond, 1987 (121); Tuyns, 1988 (122); Tajima, 1985 (123); Kvale, 1983 (124); Haenszel, 1972 (125)	Boeing, 1991 (126)	Baghurst, 1991 (127); Graham, 1991 (128); Marshall, 1983 (129)

* Studies are listed by first author, year of publication (reference).

Of these, 25 (20,21,48,108–129) were not reviewed further because they were a republication or reanalysis of data that were already used to evaluate the health claim and/or because they had scientific deficiencies that prevented FDA from drawing scientific conclusions from the study (Table 2). For example, studies that measured biomarkers that had not been previously validated for the specific cancer under study [e.g., serum level of insulin-like growth factor (111) and cervical dysplasia (112)] were excluded because they did not provide reliable evidence for risk reduction, and therefore, no scientific conclusions could be drawn from them for the evaluation of a qualified health claim about cancer. Studies for which no information was provided about the validation of the food-frequency questionnaire used were also excluded because failure to validate a food-frequency questionnaire may lead to false conclusions about associations between dietary factors and disease risk (130,131). Studies without a validated food-frequency questionnaire were considered to provide no information on the accuracy of measuring tomato intake, and hence, no scientific conclusions could be drawn from them for the evaluation of a qualified health claim. One study (126) was excluded because it lacked a statistical analysis of the data, which prevented FDA from determining if there was a difference in cancer risk between subjects who did and did not consume tomatoes. Finally, three studies (127–129) were excluded because they did not calculate a risk ratio, which made it impossible to determine if tomato intake reduced the risks of the cancers under study.

In the following sections, we present the results of FDA's review of the remaining 39 observational studies for a qualified health claim for tomatoes and tomato products by cancer type.

Prostate Cancer

FDA identified 18 observational studies (18,20,21,23,24,108,109,111,132–141) on tomato and/or tomato-based food consumption and risk of prostate cancer, of which three (18,109,132) were prospective cohort studies, one (133) was a case–cohort study, 13 (20,21,23,24,108,109,111,134–139) were case–control studies, and two (140,141) were ecologic studies. Five of the 18 studies (20,21,108,109,111) were eliminated from further review (Table 2).

FDA evaluated the remaining 13 observational studies for the relationship between tomatoes and/or tomato-based foods and the risk of prostate cancer (Table 3). All 13 studies received high to moderate methodologic quality ratings based on FDA's scientific evidence–based review system. Two large cohort studies conducted in the United States evaluated tomato and/or tomato sauce intake and prostate cancer risk (18,132). Giovannucci et al. (18) followed 47 365 men in the Health Professionals Follow-Up Study cohort for approximately 12 years, during which time, 2481 cases of prostate cancer were identified. Tomato sauce intake was evaluated with the use of three food-frequency questionnaires that were administered at the beginning of the study and at 4-year intervals thereafter. In that study, consuming one or more than one serving of tomato sauce per week was associated with a statistically significant decreased incidence of prostate cancer (relative risk [RR] = 0.80, 95% confidence interval [CI] = 0.70 to 0.91 and 0.77, 95% CI = 0.66 to 0.90, respectively). Mills et al. (132) followed a cohort of 14 000 male Seventh-Day Adventists for 6 years, during which time, 180 cases of prostate cancer were identified. In that study, consuming tomatoes one to four times per week or more than five times per week was associated with a statistically significant decreased incidence of prostate cancer (RR = 0.62, 95% CI = 0.40 to 0.96, and RR = 0.60, 95% CI = 0.37 to 0.97, respectively).

One case–cohort study (133) evaluated the association between tomato consumption and prostate cancer risk in 642 case subjects with prostate cancer and 1668 randomly chosen healthy control subjects from a cohort in The Netherlands. In that study, neither tomato intake (per 25 g of tomatoes; RR = 1.05, 95% CI = 0.90 to 1.22) nor tomato juice intake (per 25 g; RR = 1.12, 95% CI = 0.96 to 1.29) was associated with prostate cancer incidence.

Of the eight case–control studies (23–24,134–139) that evaluated tomato intake and prostate cancer risk, three found an association (Table 3). Jain et al. (136) reported that consuming more than 109 g of tomatoes per day was associated with a reduced risk of prostate cancer (odds ratio [OR] = 0.64 [95% CI = 0.45 to 0.91]). This case–control study was conducted in Canada and included 617 prostate cancer case patients and 636 control subjects. Bosetti et al. (138) conducted a case–control study in Greece that included 320 prostate cancer case patients and 246 control subjects. They reported that intake of cooked tomatoes was inversely associated with prostate cancer risk (OR for the highest tertile of intake versus the lowest tertile of intake = 1.91, 95% CI = 1.20 to 3.04). However, they found no association between intake of raw tomatoes and prostate cancer risk. Jian et al. (137) conducted a case–control

Table 3. Prospective and retrospective observational studies reviewed for the qualified health claim for tomatoes and tomato products and a reduced risk of prostate cancer*

First author, year of publication (reference)	Study type	Study location	No. of case patients/No. of control subjects	Exposure	Dose, results
Giovannucci, 2002 (18)	Cohort	United States	2481/47 365	Tomato sauce	>2 servings per wk, adjusted RR = 0.77 (95% CI = 0.66 to 0.90)
Mills, 1989 (132)	Cohort	United States	180/14 000	Tomatoes	>5 servings per wk, adjusted RR = 0.60 (95% CI = 0.37 to 0.97)
Schuumaan, 1998 (133)	Case–cohort	The Netherlands	642/1699	Tomatoes	Per 25g, adjusted RR = 1.05 (95% CI = 0.90 to 1.22)
				Tomato juice	Per 25g, adjusted RR = 1.12 (95% CI = 0.96 to 1.29)
Villeneuve, 1999 (134)	Case–control	Canada	1623/1623	Tomatoes or tomato juice	>7 servings per wk, adjusted OR = 1.0 (95% CI = 0.70 to 1.3)
Key, 1997 (23)	Case–control	England	328/328	Raw tomatoes	>5 servings per wk, adjusted OR = 1.06 (95% CI = 0.55 to 1.62)
				Cooked tomatoes	>2 servings per wk, adjusted OR = 0.92 (95% CI = 0.59 to 1.42)
Hayes, 1999 (24)	Case–control	United States	932/1201	Raw tomatoes	>5 servings per wk, adjusted OR = 0.8†
				Cooked tomatoes/ sauce	>5 servings per wk, adjusted OR = 1.3†
				Tomato juice	>5 servings per wk, adjusted OR = 1.5†
Kolonel, 2000 (135)	Case–control	United States, Canada	1619/1618	Tomatoes	Highest quintile, adjusted OR = 1.07 (95% CI = 0.83 to 1.38)
				Cooked tomatoes	Highest quintile, adjusted OR = 0.94 (95% CI = 0.58 to 1.52)
Jain, 1999 (136)	Case–control	Canada	617/636	Tomatoes	>109.6 g/day, adjusted OR = 0.64 (95% CI = 0.45 to 0.91)
Jian, 2005 (137)	Case–control	China	130/274	Tomatoes	>35.62 g/day, adjusted OR = 0.16 (95% CI = 0.11 to 0.49)
Bosetti, 2000 (138)	Case–control	Greece	320/246	Raw tomatoes	Tertiles (highest tertile of intake vs lowest tertile of intake), adjusted OR = 1.55 (95% CI = 1.0 to 2.52)
				Cooked tomatoes	Tertiles (highest tertile of intake vs lowest tertile of intake), adjusted OR = 1.91 (95% CI = 1.20 to 3.04)
Le Marchand, 1991 (139)	Case–control	United States	452/899	Tomatoes	No dose or risk ratio provided; however, paper states that data are not statistically significant

* RR = relative risk; CI = confidence interval; OR = odds ratio.

† No 95% confidence interval was reported; however, the odds ratio was described as being non–statistically significant.

study that included 130 prostate cancer case patients and 274 control subjects from China and found that tomato intake was associated with a reduced risk of prostate cancer (OR = 0.16, 95% CI = 0.11 to 0.49).

Five of the eight case–control studies found no association between tomato consumption and prostate cancer risk (23,24, 134,135,139). One of these studies (134), which was conducted in Canada and included 1623 case patients and 1623 control subjects, found no association between tomato or tomato juice consumption and prostate cancer risk (OR = 1.0, 95% CI = 0.7 to 1.3). Another case–control study (24), conducted in England, included 328 case patients and 328 control subjects; it found no association between raw or cooked tomato intake and prostate cancer risk (OR = 1.06 [95% CI = 0.55 to 1.62] and 0.92 [95% CI = 0.59 to 1.42], respectively). Hayes et al. (23) conducted a case–control study in the United States with 932 case patients and 1201 control subjects. Tomato juice and raw or cooked tomato intakes were not associated with prostate cancer risk. Kolonel et al. (135) conducted a multiethnic case–control study of 1619 case patients and 1618 control subjects from the United States and Canada. They found no association between raw or cooked tomato consumption and prostate cancer risk. Le Marchand et al. (139) conducted a case–control study in Hawaii that included 452 case patients and 899 control subjects. Tomato consumption was not associated with prostate cancer risk in that study.

FDA also reviewed two ecologic studies (140,141) that evaluated the association between tomato consumption and prostate cancer risk. In one study, Grant (140) compared prostate cancer mortality data from 41 countries with the tomato supply for each country (28 of the 41 countries consumed at least 5 kcal of tomatoes per person daily). Among the 28 countries that reported consumption of more than 5 kcal per day from tomatoes, there was an inverse correlation between tomato intake and prostate cancer mortality. In the other study, Ganmaa et al. (141) evaluated prostate cancer incidence rates and tomato consumption (based on the

average intake) for 44 countries. They found no correlation between tomato consumption and prostate cancer risk.

After reviewing the evidence summarized above, FDA found that there was limited credible evidence for a qualified health claim about tomato consumption and a reduced risk of prostate cancer. The strongest evidence for an association between tomatoes and prostate cancer risk came from the two large prospective cohort studies (18,132) that reported statistically significant inverse associations between tomato consumption and risk. The eight case–control, one case–cohort, and two ecologic studies reported mixed results on the association. FDA therefore concluded that there was a very low level of comfort that a relationship exists between the consumption of tomatoes and/or tomato sauce and prostate cancer risk.

Lung Cancer

FDA identified 18 observational studies on tomato and/or tomato-based food intake and the risk of lung cancer, including three prospective cohort studies (119,124,142), two nested case–control studies (121,143), one case–cohort study (144), and 12 case–control studies (32,114,115,145–153). Six studies (32,114,115,119,121,124) were not reviewed further (Table 2).

Of the 12 remaining studies, two studies (145,146) included subjects who were not relevant to the general US population (i.e., tin miners from China). Indeed, the authors of these studies pointed out that these subjects had unique environmental exposures (i.e., arsenic and severe pollution) that increased the incidence of lung cancer, and thus, their findings were not generalizable to a general population of the United States (145).

Further evaluation of the 10 remaining studies revealed that seven case–control studies (147–153) included a greater proportion of smokers among the case patients than among the control subjects and reported results that were not stratified by smoking status. Because smoking causes lung cancer (154,155) and can lead to many dietary changes, including decreased weight and appetite (156), which may affect food intake and could have biased the results of these studies, it was not possible to determine whether differences in the consumption of tomatoes and/or tomato-based foods contributed independently to the results in the lung cancer case patients. Therefore, FDA concluded that scientific conclusions about the relationship between tomatoes and tomato-based food consumption and lung cancer risk could not be drawn from these seven studies.

The remaining three studies (142–144) were observational studies that evaluated the relationship between tomato consumption and lung cancer risk and had a high to moderate methodologic quality rating. Speizer et al. (142) followed a cohort of 89 284 nurses for approximately 16 years and identified 593 cases of lung cancer. They found that eating one or more servings of tomatoes per day was not associated with lung cancer incidence. Steinmetz et al. (143) analyzed a case–cohort of 2814 female control subjects and 138 female case patients from Iowa to evaluate tomato intake and lung cancer risk. They found that tomato intake was not associated with lung cancer risk. Voorrips et al. (144) conducted a nested case–control study that included a case–cohort study with 2953 control subjects and 1010 case patients from The Netherlands. They observed no association between raw tomato consumption (25 g/day) and lung cancer risk. On the basis of its evaluation of these three reports, FDA concluded that there was no credible evidence supporting an association between tomato or tomato-based food consumption and lung cancer risk.

Breast Cancer

FDA identified four case–control studies (116,128,157,158) that examined the association between tomato intake and the risk of breast cancer. Two of these studies (116,128) were not considered for further review because they had scientific deficiencies (Table 2). The two remaining case–control studies were rated as having high (157) or moderate (158) methodologic quality. Ewertz and Gill (157) evaluated tomato intake and breast cancer risk in 1486 case patients and 1336 control subjects from Denmark. They found that tomato consumption was not associated with breast cancer risk (OR = 1.04, 95% CI = 0.79 to 1.34). Ronco et al. (158) conducted a case–control study in Uruguay among 400 case patients and 405 control subjects. They also found no association between tomato consumption and breast cancer risk (OR = 0.62, 95% CI = 0.36 to 1.06). On the basis of these two studies, FDA concluded that there was no credible evidence supporting an association between tomato or tomato-based food consumption and breast cancer risk.

Colorectal Cancer

FDA identified seven case–control studies (47,113,116,120,122,123, 159) that examined the association between tomato or tomato-based food intake and the risk of colorectal cancer. None of the studies evaluated colorectal polyp recurrence. Five studies (113,116,120,122,123) were not further reviewed because of scientific deficiencies (Table 2). The two remaining studies were rated as having high (47) or moderate (159) methodologic quality. Le Marchand et al. (47) evaluated the association between tomato intake and colorectal cancer risk among 1192 case patients and 1192 control subjects from the United States. They reported that consumption of tomato-based foods was not associated with the risk of colorectal cancer in males (OR = 0.8, 95% CI = 0.5 to 1.2) or in females (OR = 0.9, 95% CI = 0.5 to 1.4). Franceschi et al. (159) evaluated the association between pizza consumption and the risk of colon cancer among 1225 case patients and 4154 control subjects and found no statistically significant association (OR = 0.8, 95% CI = 0.7 to 1.0). On the basis of these two studies, FDA concluded that there was no credible evidence supporting an association between tomato or tomato-based food consumption and the risk of colorectal cancer.

Gastric Cancer

FDA identified 13 case–control studies (110,116,118,123,125,126, 160–166) that evaluated associations among tomatoes, tomato-based foods, and the risk of gastric cancer. Six studies (110,116,118, 123,125,126) were not used to evaluate the relationship between tomato intake and gastric cancer risk reduction because they had scientific deficiencies (Table 2). Each of the remaining seven studies (160–166) was rated as having moderate methodologic quality. Three studies reported conflicting results in subgroup analyses that could not easily be explained. Graham et al. (160) conducted a study in 293 case patients and 293 control subjects from upstate

New York and found that tomato intake was associated with a reduced risk of gastric cancer in males but not in females. Correa et al. (161) conducted a case–control study in Louisiana among 391 case patients and 391 control subjects. They found that tomato consumption was associated with a decreased risk of gastric cancer in blacks (OR = 0.56, 95% CI = 0.34 to 0.9) but not in whites (OR = 0.82, 95% CI = 0.53 to 1.28). Hansson et al. (162) conducted a case–control study in Sweden among 456 case patients and 669 control subjects. They found that tomato intake during adolescence (at 15–18 years of age) was associated with a decreased risk of gastric cancer (OR = 0.36, 95% CI = 0.23 to 0.58) but tomato intake during adulthood was not (OR = 0.72, 95% CI = 0.47 to 1.11). Consistency of findings among similar and different study designs is important for evaluating the strength of the scientific evidence; these studies did not provide consistent findings among different groups of subjects in the studies.

FDA found that the remaining four studies (163–166) did not report an association between tomato consumption and gastric cancer risk. Gonzalez et al. (163) carried out a case–control study in Spain that included 354 case patients and 354 control subjects. They found that tomato intake was not associated with the risk of gastric cancer. A case–control study (164) from Sweden that included 258 case patients and 815 control subjects found that consuming 4–12 servings of tomatoes per week was not associated with gastric cancer incidence. A case–control study (165) from Belgium that included 449 case patients and 3524 control subjects found no association between tomato intake and the risk of gastric cancer. Finally, Ramon et al. (166) found that tomato intake was not associated with gastric cancer risk reduction in a study that included 117 case patients and 234 control subjects from Spain.

To summarize the data, all of the studies that evaluated the tomato and gastric cancer relationship had a retrospective study design. Prospectively designed studies provide stronger evidence for an association than case–control studies because they are subject to fewer biases. Moreover, the findings in Graham et al. (160), Correa et al. (161), and Hansson et al. (162) were not consistent within each study. Based on FDA's review of the strength of the total body of publicly available scientific evidence for the consumption of tomatoes or tomato-based food and reduced risk of gastric cancer, the agency found that there was very limited credible evidence for a qualified health claim about tomatoes and gastric cancer and, because none of the studies evaluated tomato-based foods, no credible evidence for a qualified health claim about tomato-based foods and gastric cancer. FDA ranked the evidence for tomatoes and gastric cancer as the lowest level for a qualified health claim. FDA concluded that it is unlikely that tomatoes reduce the risk of gastric cancer.

Ovarian Cancer

FDA identified a single case–control study (53) that evaluated the association between tomato and tomato-based food intakes and the risk of ovarian cancer among 549 case patients and 516 control subjects from the United States; this study received a high methodologic quality rating. This study found no association between intake of tomato or tomato juice and the risk of ovarian cancer (OR = 0.88 [95% CI = 0.50 to 1.54] and 0.65 [95% CI = 0.34 to 1.22], respectively) but did find that those who ate tomato sauce two or more times per week had a statistically significantly lower risk of ovarian cancer (OR = 0.60, 95% CI = 0.37 to 0.99). Because these findings have not been replicated and are subject to biases because of the retrospective study design, FDA determined that there was very limited credible evidence for a qualified health claim about tomato sauce consumption and reduced risk of ovarian cancer. Based on FDA's review of the strength of the total body of publicly available scientific evidence, FDA ranked this evidence as the lowest level for a qualified health claim about tomato sauce and ovarian cancer. FDA concluded that it is unlikely that tomatoes reduce the risk of ovarian cancer.

Endometrial Cancer

FDA identified no studies that evaluated the association between tomato or tomato-based food intake and the risk of endometrial cancer. Therefore, there was no credible evidence available to support this relationship.

Cervical Cancer

FDA identified two case–control studies (112,129) that evaluated the association between tomato intake and the risk of cervical cancer. Both studies were eliminated from further review because of scientific deficiencies (Table 2). Consequently, FDA concluded that there was no credible evidence to support a relationship between the consumption of tomatoes or tomato-based foods and cervical cancer risk.

Pancreatic Cancer

FDA identified three observational studies—one cohort study (167) and two case–control studies (127,168)—that evaluated the association between tomato and/or tomato-based food intake and the risk of pancreatic cancer. One case–control study (127) was not reviewed further because of scientific deficiency (Table 2). The remaining studies both received moderate methodologic quality ratings. Mills et al. (167) followed a cohort of 34000 Seventh-Day Adventists from California for 7 years, during which time, there were 162 pancreatic cancer deaths. They found that tomato consumption was not associated with the risk of death from pancreatic cancer. The case–control study (168) included 164 case patients and 480 control subjects from The Netherlands. It found that among all subjects who completed a food-frequency questionnaire, raw tomato intake was not associated with the risk of pancreatic cancer. However, among a subset of the subjects (n = 421) who were interviewed individually by a dietician, raw tomato intake was statistically significantly and inversely associated with the risk of pancreatic cancer. On the basis of these two studies, FDA found that there was very limited credible evidence for a qualified health claim about tomatoes and a reduced risk of pancreatic cancer and no credible evidence for a qualified health claim about tomato-based foods and pancreatic cancer because none of the studies evaluated tomato-based foods. FDA ranked this evidence as the lowest level for a qualified health claim about tomatoes and pancreatic cancer and concluded that it was highly unlikely that the consumption of tomatoes reduces the risk of pancreatic cancer.

Summary and Claims

Based on FDA's consideration of the scientific evidence discussed above, the agency concluded that there was no credible evidence to

support qualified health claims for tomatoes or tomato-based foods and a reduced risk for lung, colorectal, breast, cervical, or endometrial cancer. FDA further concluded that there was no credible evidence to support qualified health claims for lycopene, as a food ingredient, component of food, or as a dietary supplement, and a reduced risk of any of these cancers. Thus, FDA denied these claims. FDA concluded that there was very limited credible evidence for qualified health claims for tomatoes and/or tomato sauce and a reduced risk for prostate, gastric, ovarian, and pancreatic cancers provided that the qualified health claims were appropriately worded so as to not mislead consumers.

On November 8, 2005, FDA issued letters of enforcement discretion for four qualified health claims. The qualified health claim for prostate cancer was "Very limited and preliminary scientific research suggests that eating one-half to one cup of tomatoes and/or tomato sauce a week may reduce the risk of prostate cancer. FDA concludes that there is little scientific evidence supporting this claim." The qualified health claim for gastric cancer was "Four studies did not show that tomato intake reduces the risk of gastric cancer, but three studies suggest that tomato intake may reduce this risk. Based on these studies, FDA concludes that it is unlikely that tomatoes reduce the risk of gastric cancer." The qualified health claim for ovarian cancer was "One study suggests that consumption of tomato sauce two times per week may reduce the risk of ovarian cancer; while this same study shows that consumption of tomatoes or tomato juice had no effect on ovarian cancer risk. FDA concludes that it is highly uncertain that tomato sauce reduces the risk of ovarian cancer." The qualified health claim for pancreatic cancer was "One study suggests that consuming tomatoes does not reduce the risk of pancreatic cancer, but one weaker, more limited study suggests that consuming tomatoes may reduce this risk. Based on these studies, FDA concludes that it is highly unlikely that tomatoes reduce the risk of pancreatic cancer."

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Note

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