Tomato and Lycopene Consumption Is Inversely Associated with Total and Cause-Specific Mortality: A Population-based Cohort Study, on behalf of the International Lipid Expert Panel (ILEP)

Mohsen Mazidi*¹, Niki Katsiki², Elena S George³, Maciej Banach⁴⁻⁶

¹-Department of Biology and Biological Engineering, Food and Nutrition Science, Chalmers University of Technology, SE-412 96 Gothenburg, Sweden; ². Second Propedeutic Department of Internal Medicine, Medical School, Aristotle University of Thessaloniki, Hippokration Hospital, Thessaloniki, Greece; ³. Institute for Physical Activity and Nutrition, School of Exercise and Nutrition Sciences, Deakin University, Geelong, Australia; ⁴. Department of Hypertension, Chair of Nephrology and Hypertension, Medical University of Lodz, Poland; ⁵. Polish Mother’s Memorial Hospital Research Institute (PMMHRI), Lodz, Poland; ⁶. Cardiovascular Research Centre, University of Zielona Gora, Zielona Gora, Poland.

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*Corresponding author:* Mohsen Mazidi, PhD, Department of Biology and Biological Engineering, Food and Nutrition Science, Chalmers University of Technology, SE-412 96 Gothenburg, Sweden. Email: mazidi@chalmers.se, Tel:+8613167518660

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ABSTRACT:

No data exist on the associations of dietary tomato and lycopene consumption with total and cause-specific mortality. Using the National Health and Nutrition Examination Surveys (NHANES) 1999-2010, we evaluated the long-term impact of tomato and lycopene intake on total and cause-specific (coronary heart disease [CHD] and cerebrovascular disease) mortality. We also assessed the changes in cardio-metabolic risk factors according to tomato and lycopene intake. Vital status through December 31, 2011 was ascertained. Cox proportional hazard regression models (followed by propensity score-matching) were used to investigate the link between tomato and lycopene consumption total, CHD and cerebrovascular mortality. Among the 23,935 participants included (mean age = 47.6 years, 48.8% men), 3403 deaths occurred during 76.4 months of follow-up. Tomato intake was inversely associated with total (risk ratio (RR):0.86, 95% confidence interval (CI):0.81-0.92), CHD (0.76, 95%CI: 0.70-0.85) and cerebrovascular (0.70, 95%CI: 0.62-0.81) mortality. Similar inverse associations were found between lycopene consumption, total (0.76, 95%CI: 0.72-0.81), CHD (0.73, 95%CI: 0.65-0.83) and cerebrovascular (0.71, 95%CI: 0.65-0.78) mortality; these associations were independent of anthropometric, clinical and nutritional parameters. Age and obesity did not affect the associations of tomato and lycopene consumption with total, CHD and cerebrovascular mortality. C-reactive protein significantly moderated the link between lycopene and tomato intake with total, CHD and cerebrovascular mortality. Analysis of co-variance showed that
participants with a higher tomato and lycopene consumption had a more cardio-protective profile compared with those with a lower intake. Our results highlighted the favorable effect of tomato and lycopene intake on total and cause-specific mortality as well as to cardio-metabolic risk factors. These findings should be taken into consideration for public health strategies.

**Keywords:** Mortality, Tomato, Lycopene, Coronary Heart Disease, Cardio-metabolic, Cerebrovascular Disease

**Introduction**

Globally, behavioral parameters including a range of dietary risk factors, e.g. low intakes of fruit and vegetables, can impair human health and promote disease such as cardiovascular disease (CVD) and stroke (1). A variety of epidemiological evidence indicates that, particularly, cardiovascular health is strongly affected by a healthy diet; fruit and vegetables are considered an important element of a cardioprotective diet (2-4). Fruit and vegetables consumption in the range commonly recommended (e.g. >5 servings) are associated with 21 to 26% reductions in the risk of stroke (5), and with 17 to 25% reductions in the risk of coronary heart disease (CHD)(6).

Tomatoes represent one of the most frequently consumed vegetables, just below the consumption of potatoes, lettuce and vegetable salads and onions (7). Tomatoes are fruits that are rich in lycopene, an antioxidant with immunostimulatory properties, and contain moderate amounts of a- and b-carotene and vitamin C (7, 8). A systematic review reported that tomato or lycopene supplementation significantly improved CVD risk factors including low density lipoprotein (LDL) -cholesterol, interleukin-6, flow mediated dilation (FMD), and systolic blood pressure (SBP) (7). A previous study (n=5,135) reported that a higher intake of tomato products was significantly associated with a reduced incidence of CVD (9). No significant link was observed between the risk of stroke and tomato consumption (hazard ratio [HR]: 0.99, 95%CI: 0.90, 1.10) (9). In contrast, another study including 38,445 participants found that tomato product consumption was not significantly related to the risk of CVD and myocardial infarction(10)(10) (10); however, tomato intake decreased the risk of stroke (10). A meta-analysis by Song et al. showed that dietary lycopene intake was significantly linked to the risk of CHD (risk ratio [RR]: 0.87; 95% Cl: 0.76–0.98) and stroke (RR: 0.83; 95% CI: 0.69–0.96) (11). The authors concluded that further research is needed to evaluate the potential pathways between
lycopene/tomato consumption and CVD outcomes, focusing on whether lycopene has independent effects on the risk of CVD (11). The above-mentioned findings triggered an interest on the effects of lycopene and tomato intake on health outcomes.

To the best of our knowledge, there is currently no study evaluating the associations between tomato consumption and mortality (total or cause-specific). In this context, we prospectively examined the relationship of tomato and lycopene intake with total and cause-specific (CHD and stroke) mortality. As a secondary objective, we evaluated the changes in cardiometabolic risk factors according to the tomato and lycopene consumption levels; we implemented these by applying on a nationally representative sample of US adults. We hypothesized that a higher consumption of tomato and lycopene is associated with a lower risk of total and cause-specific mortality; furthermore, those individuals would have a more favorable cardiometabolic profile.

METHODS

Population:

This was a prospective cohort study using data from the US National Health and Nutrition Examination Survey (NHANES). The National Center for Health Statistics (NCHS) Research Ethics Review Board approved the underlying protocol and written informed consent was obtained from all participants. The current study is based on the analysis of data from 2-year NHANES survey cycles (between 1999 and 2010), restricted to participants aged ≥20 years. Details on the NHANES Laboratory/Medical Technologists Procedures and Anthropometry Procedures are described elsewhere (12, 13).

Dietary intake was assessed via 24h recalls obtained by a trained interviewer, with the use of a computer-assisted dietary interview system with standardized probes, i.e. the US Department of Agriculture (USDA) Automated Multiple-Pass Method (AMPM) (14, 15). Briefly, the type and quantity of all beverages and foods consumed in a single 24h period before the interview (from midnight to midnight) were collected by performing AMPM. AMPM can enhance accurate and complete data collection while reducing respondent burden (15, 16). The USDA food and nutrient database for dietary studies were used to determine the nutrient content of foods.

Cardiometabolic risk factors:
A blood specimen was drawn from an antecubital vein. Fasting blood glucose (FBG) was measured by a hexokinase method using a Roche/Hitachi 911 Analyzer and Roche Modular P Chemistry Analyzer (NJ, USA). Levels of triglyceride (TG) were measured enzymatically. Insulin was measured using an ELISA immunoassay (Mercodia, Uppsala, Sweden) (17). Serum C-reactive protein (CRP) concentrations were measured by latex enhanced nephelometry (Seattle, USA) (18, 19). Other laboratory-test details are available in the NHANES Laboratory/Medical Technologists Procedures Manual (20). The anthropometrically predicted visceral adipose tissue (apVAT) was predicted with gender-specific validated equations that included age, body mass index (BMI), waist (WC) circumference (WC) and thigh circumference (21). The equation for men was: \(6 \times WC - 4.41 \times \text{proximal thigh circumference} + 1.19 \times \text{age} - 213.65\), and the equation for women was: \(2.15 \times WC - 3.63 \times \text{proximal thigh} + 1.46 \times \text{age} + 6.22 \times \text{BMI} - 92.713\) (21). Diabetes mellitus (DM) was diagnosed as a self-reported history of diabetes or fasting plasma glucose \(\geq 126\, \text{mg/dl}\). Hypertension (HTN) was diagnosed in individuals with systolic blood pressure \(\geq 140\, \text{mmHg}\) and/or diastolic blood pressure \(\geq 90\, \text{mmHg}\), as well as in those taking antihypertensive drugs (22).

A digital scale was used to measure weight to the nearest 100 g and a fixed stadiometer to measure height to the nearest mm. BMI was calculated as weight in kg divided by the square of height in m. WC was measured at the iliac crest to the nearest mm, using a steel tape (18).

**Mortality**

The de-identified and anonymized data of the NHANES 1999-2010 participants were linked to longitudinal Medicare and mortality data using the NHANES assigned sequence number. Mortality follow-up data are available from the date of survey participation until December 31, 2011. We examined all-cause mortality, as well as mortality due to CHD (I00-I09, I11, I13, I20-I51), and cerebrovascular disease (I60-I69). Cause of death was determined using the 10th revision of the International Classification of Diseases (ICD-10).

**Statistical analysis**

Since the present study is of an observational design, it is vulnerable to selection bias (23) to identify a more robust measure of the association between tomato consumption and mortality. Therefore, propensity score matching (PSM) was applied. Analyses were conducted according to the guidelines set by the Centers for Disease Control and Prevention for analysis of
the NHANES dataset, accounting for the masked variance and using their suggested weighting methodology (24, 25). Continuous and categorical demographic variables were compared across tertiles of tomato and lycopene consumption using the analysis of variance (ANOVA) and Chi-square tests, respectively. Adjusted (for age, gender, race, education, marital status, poverty to income ratio, total energy intake, physical activity, smoking, alcohol consumption, intake of fiber, fat and meat) means of cardiometabolic factors across tomato and lycopene consumption tertiles were calculated using the analysis of co-variance (ANCOVA).

Multivariable Cox proportional hazards were performed to determine the hazard ratios (HRs) and 95% confidence intervals (CIs) of mortality for each quartile of tomato and lycopene intake, with the lowest quartile (Q1) always used as reference. To derive the HR and 95%CI, we used 2 different models, **Model 1**: Adjusted for age, gender, race, education, marital status, poverty to income ratio, total energy intake, physical activity, smoking and alcohol consumption; **Model 2**: Adjusted for age, gender, race, education, marital status, poverty to income ratio, total energy intake, physical activity, smoking, alcohol consumption, dietary intake of fat, fiber, meat and carbohydrates, BMI, CRP, HTN and DM. A two-sided p <0.05 was used to characterise significant results. Data were analysed using the SPSS® complex sample module version 22.0 (IBM Corp, Armonk, NY).

Furthermore, we performed sensitivity analyses to evaluate the HRs for all-cause mortality in participants being in the first quartile (Q1) of tomato intake compared with those in the fourth quartile (Q4) using PSM Cox proportional analyses. PSM was applied to control for confounding factors. PSM was first proposed by Rosenbaum and Rubin in 1983 (26). This statistical method is based on a counterfactual concept and can help reinforce causal arguments in observational studies by reducing selection bias (26). Firstly, tomato intake [first quartile (Q1): 0; fourth quartile (Q4): 1] was the dependent variable, whereas the confounding factors (age, gender, race, education, marital status, poverty to income ratio, total energy intake, physical activity, smoking, alcohol consumption, BMI, dietary intake of fat, fiber, meat and carbohydrates, CRP, BMI, hypertension and DM) were used as covariates. This model yielded a C-index of 0.593 (95%CI 0.528–0.611; p<0.001), indicating an appropriate ability to differentiate between subjects with lowest and highest tomato intake. For the prediction model, calibration was assessed using the Hosmer-Lemeshow goodness-of-fit test, which showed good calibration (p = 0.312). Secondly, treatment case [first quartile (Q1) of tomato intake] was matched with
control case [fourth quartile (Q4) of tomato intake] by using 1:1 nearest-neighborhood matching.

We also quantified the impact of CRP on the link between lycopene consumption, total, CHD and stroke mortality by applying the moderation model using the SPSS Macro developed by Preacher and Hayes (27). By applying this Macro, we could simultaneously test the moderator impact of the variable of interest, CRP, adjusting for the confounding factors. Furthermore, this approach permitted the visualisation of the impact of each SD change in the potential moderators on the relationship between independent and dependent variables. We tested for the presence of an effect of CRP in the adjusted (for age, gender, race, education, marital status, poverty to income ratio, total energy intake, physical activity, smoking, alcohol consumption, dietary intake of fat, fiber, meat and carbohydrates, BMI, hypertension and DM) model.

RESULTS

General information:

Overall, 23,935 participants were included, with a mean age of 47.6 years, comprising 48.8% men. The demographic characteristics of the participants according to tomato and lycopene consumption are shown in Table 1. Individuals with a higher tomato intake (1.8 cups/day) were significantly younger compared with those with the lowest tomato consumption (0.02 cups/day) (43.3 vs. 49.2 years, respectively, p<0.001, Table 1). Men consisted the majority in the highest compared with the lowest tomato consumption group (53.0 vs. 47.0%, respectively, p<0.001), whereas women had the highest percentage in the lowest category (53.6 vs. 46.4%, respectively, p<0.001, Table 1). With regard to race/ethnicity, in the highest tomato intake group, the distribution was as follows: Non-Hispanic White (52.4%), Non-Hispanic Black (23.3%) and Mexican-American (12.2%) (p<0.001, Table 1). The majority of individuals with “more than high school” education (49.3%) were in the higher tomato consumption group, while most of those with “less than high school” education (30.1%) were in the lowest category (Table 1). Similar results were obtained for the lycopene intake groups (Table 1).
**Associations of Cardiovascular Risk Factors with Tomato and Lycopene intake:**

The adjusted means of cardiovascular risk factors across the tertiles of tomato and lycopene consumption are presented in Table 2. With increasing tomato intake, participants had more favorable levels of systolic blood pressure (SBP), HDL-C, FBG, insulin and CRP (p<0.001 for all comparisons, Table 2). For example, HDL-C and SBP were 51.6 mg/dl and 124.1 mmHg for subjects in the lowest tomato consumption group, increasing to 53.6 mg/dl and 120.6 mmHg for those in the highest tomato intake group. In contrast, no significant changes were found for BMI, WC, apVAT, DBP and TG across tomato consumption groups (Table 2).

Furthermore, as the consumption of lycopene increased, subjects had also a more protective profile of cardiometabolic factors, including SBP, DBP, TG, HDL-C, FBG and CRP (p<0.001 for all comparisons, Table 2). For example, both SBP and DBP decreased from 125.1 and 125.1 mmHg in the lowest lycopene intake group, to 121.2 and 68.1 mmHg, respectively, in the highest lycopene consumption group (both p<0.001, Table 2). No significant modifications were observed for the anthropometrical parameters (i.e. BMI, WC and apVAT) and insulin levels in relation to lycopene intake (Table 2).

**Associations of Total, CHD and Stroke mortality with Tomato and Lycopene consumption:**

A negative link between tomato consumption and total mortality was found both in Model 1 (HR: 0.79, 95%CI: 0.74-0.82) and Model 2 (RR: 0.86, 95%CI: 0.81-0.92, Table 3). Similarly, a reverse association was observed between tomato intake, CHD and stroke mortality in both Model 1 and Model 2 (Table 3). Interestingly, after adjustments for more confounders (in Model 2), this link became greater for stroke mortality (Model 1: 0.76, 95%CI: 0.69–0.82, Model 2: 0.70, 95%CI: 0.62–0.81), whereas for CHD death, it remained significant but to a lesser extent (Model 1: 0.53, 95%CI: 0.37–0.73, Model 2: 0.76, 95%CI: 0.70–0.85) (Table 3).

Lycopene intake was also negatively associated with total, CHD and cerebrovascular mortality in both models (Table 3). All associations, however, were slightly weakened after adjusting for more confounders in Model 2, as shown in Table 3.)
**Sensitivity Analysis:**

After matching, no significant difference was observed between subjects at the lowest (Q1) and the highest quartile (Q4) of tomato intake in relation to our confounders. After performing PSM Cox regression, we found that subjects in the highest quartile (Q4) of tomato consumption had a 17% increased risk of total mortality (RR: 0.83, 95%CI: 0.79-0.91).

In the adjusted model, no difference was found between non-obese and obese (BMI>30 kg/m²) subjects with regard to the link between both tomato and lycopene consumption with total, CHD and stroke mortality (data not shown). Furthermore, the reverse association between lycopene intake, total, CHD and stroke mortality was more pronounced in non-smokers compared with smokers (p<0.001 for all comparisons) (data not shown). This was not observed for tomato intake, thus implying a detrimental role of smoking in the link between lycopene and mortality. No difference was found between older (age >50 years) and younger adults in relation to the associations of both tomato and lycopene consumption with total, CHD and stroke mortality (data not shown).

CRP significantly moderated the relationship between total, CHD and stroke mortality with lycopene intake (p<0.001 for all comparisons). For example, for the same level of lycopene consumption, subjects with higher CRP levels had a greater risk of mortality. In this context, in the adjusted model for CHD mortality, when lycopene intake increased from low (154 mcq/g, mean-SD) to high (224 mcq/g, mean+SD), the risk of CHD mortality among subjects with low CRP levels (0.37 mg/dl, mean-SD) changed from 0.96 to 0.72 (a decrease of 0.24). However, among those at high CRP concentrations (0.47 mg/dl, mean+SD), CHD mortality risk was reduced from 0.97 to 0.92 (a decrease of 0.5). These findings suggest that CRP may strongly modulate the impact of lycopene consumption on CHD mortality, since subjects at higher CRP levels seem to benefit less from lycopene intake compared with those with lower CRP concentrations.

**DISCUSSION**

By applying on a nationally representative sample of US adults, we evaluated the impact of tomato and lycopene consumption on total and cause-specific mortality. Furthermore, we investigated the changes in cardiometabolic risk factors across the tomato and lycopene intake groups. We found that there was the association between total, CHD and stroke mortality with tomato and lycopene intake (i.e. a higher intake of tomato and lycopene consumption was...
linked to a lower risk of all-cause and cause-specific mortality). These associations were robust even after further adjustments for clinical, dietary and anthropometrical confounders. Furthermore, individuals with a higher tomato and lycopene intake had a more favorable profile of cardiometabolic risk factors; these relationships were independent of demographic, lifestyle and dietary factors. The beneficial impact of lycopene consumption on total, CHD and stroke mortality was more pronounced in non-smokers; this was not observed for tomato intake. Finally, CRP was found to significantly mediate the link between lycopene consumption, total, CHD and stroke mortality (i.e. subjects with similar levels of lycopene intake had a greater risk of mortality when they also had higher than lower CRP levels.

Lycopene is one of the most potent antioxidants and a predominant carotenoid in human plasma (28). It is also assumed to be one of the active compounds responsible for the health benefits of tomato (29). Our results highlight the beneficial impact of both lycopene and tomato consumption on total and cause-specific mortality. A recent meta-analysis of prospective studies was in agreement with the findings from the present study, indicating that dietary intake and/or blood carotenoids which included lycopene were inversely associated with CHD, stroke, CVD, cancer and/or all-cause mortality (30). Epidemiological evidence indicates an inconsistent association between tomato products and/or lycopene and lower CVD incidence (9, 10). However, to the best of our knowledge, no study has examined the link between tomato or lycopene consumption and death. Furthermore, the majority of the previous original studies has important limitations, including a small sample size and short follow-up (31). Participants selection, lycopene metabolism, characteristics of lycopene consumption (time, type, quantity etc.), interaction with other antioxidants and conventional CVD risk factors should be taken into account when conducting and interpreting such studies (31). In this context, a previous meta-analysis demonstrated that dietary lycopene intake was related to a significant reduction in the risk of both CHD and stroke (11). The pooled RR was similar for circulating lycopene levels but the only significant association was for stroke (11). No significance was found in relation to the link between circulating lycopene concentrations and CHD incidence, with a high heterogeneity ($I^2 = 61.5\%$), which may be partly due to the small sample size in the CHD subgroup (11). A previous systematic review, including human intervention trials in relation to the cardioprotective effects of lycopene, demonstrated mixed results (28). Our findings on the association of lycopene and tomato intake with cardiometabolic factors, are in agreement with earlier reports such as a meta-analysis of 21 studies showing that lycopene supplementation
from different sources significantly reduced the lipid profile (7). Other meta-analyses also found that lycopene supplementation significantly improved lipids (31) and BP (31-33). The BP-lowering properties of lycopene and tomato have been attributed to the stimulation of nitric oxide production in the endothelium (32). In this context, several studies demonstrated that at least four weeks of daily oral supplementation with tomato extract or tomato juice significantly decreased BP (33-37), while others showed no association (38, 39). In contrast, Paterson et al. found that lycopene intake (4.5 mg/day, for 4 weeks) could elevate BP (40).

In the present study, subjects with a higher tomato and lycopene intake had lower CRP levels. Similarly, 3 RCTs reported beneficial effects of tomato supplementation on CRP concentrations (41-43), whereas only in 1 study tomato intake increased CRP levels (45). However, in a meta-analysis of 21 studies by Chen et al. (7), tomato and lycopene supplementation did not affect CRP concentrations. In relation to lycopene supplementation, results are also controversial; only 1 study reported improvements in CRP levels after lycopene supplementation (35), whereas 2 studies found increases in CRP concentrations following lycopene consumption (35, 43). No significant changes in CRP levels were reported in another 2 studies subsequent to lycopene supplementation (42, 44). Furthermore, evidence for the effects of lycopene supplementation on oxidative stress is scarce (45).

A number of potential mechanisms are responsible for our findings. Tomatoes are the primary source of lycopene, the most powerful antioxidant, and are therefore likely to lower oxidative stress (induced by reactive oxygen species, inflammation and platelet aggregation), decrease lipid peroxidation and reduce LDL-C (46). Lycopene, the major carotenoid in tomatoes, might be more important than other carotenoids in preventing atherosclerosis and CVD (28). However, tomatoes contain also other compounds (e.g. antioxidants, such as vitamin C) possessing lipid-lowering properties (47, 48). Potential biological mechanisms by which lycopene could protect against CVD have been suggested, including cholesterol reduction, modulation of inflammatory markers, inhibition of oxidation processes, enhanced intercellular communication, induction of apoptosis and anti-angiogenic effects (31, 49). In this context, it has been widely accepted that lycopene played an important role in the reduction of intracellular cholesterol levels through inhibition of cholesterol synthesis, modulation of LDL receptor and acylcoenzyme A: cholesterol acyltransferase activity (50).
Implications for health and future research

Our results showed a significant improvement in cardiometabolic risk factors as well as total and cause-specific mortality across tomato and lycopene intake groups in a nationally representative US population. These findings may have important implications in the primary and secondary prevention of atherosclerosis, CVD morbidity and mortality. In this context, the 7th report of the Joint National Committee (JNC) on BP estimated that a SBP reduction of at least 5 mmHg (similar to the observed decline in SBP after lycopene supplementation) could decrease the risk of stroke death by 13-14% (51) and CVD mortality by 9% (51). Results from the Global Burden of Disease (GBD) Collaboration (52), indicate that cardiometabolic risk factors such as hypertension (1st) and hypercholesterolemia (7th), as well as behavioral risk factors including low fruit (13th) and vegetable (20th) consumption, are among the top 30 leading causes of death and disability.

Strengths and limitations

The misclassification of exposure to tomato and lycopene is unavoidable in dietary assessments. Although we included major possible confounders of lifestyle and dietary factors in the present multivariable analysis, residual or unmeasured confounding might still exist. Furthermore, since this is an observational study, we cannot establish causality between tomato/lycopene consumption and the outcomes. In clinical trials, maintaining high adherence to a dietary intervention for a long time is typically difficult, in part because of dietary changes contradicting participants’ long-term dietary references. Hence, poor adherence may dilute the true effect of an intervention. Lycopene content and bioavailability can be influenced by climate, soil, tomato varieties, geography and processing (53). Furthermore, the preparation method including cooking, which is known to enhance lycopene bioavailability, is also relevant for the association between tomato consumption and risk of mortality. Roasted and fried tomatoes are carriers of salt and fats; acrylamide formation may be an additional problem in tomatoes cooked at temperatures above 120°C (54). However, information on the way of preparation was not available in the present analysis, thus representing a limitation; prospective studies focusing on this issue are needed. Since data collection in the NHANES was performed on all weekdays, throughout the year, the potential for day-specific information bias is very low (55, 56). It would be nice for the future studies to perform the analysis based on the source of the tomato. Finally, total carotenoid intake was not available in the data set used and thus could not be adjusted for in the analysis.
To the best of our knowledge, this is the first cohort study evaluating the long-term impact of tomato and lycopene consumption on total and cause-specific mortality. The strengths of this study include the consistency of findings across the cross-sectional data and prospective findings, which reflect the validity of our findings. Furthermore, the validity of the results is strengthened by the evaluation of both tomato and lycopene intake. Circulating levels of tomato and lycopene were not measured in the NHANES, which could provide more valid results. However, it has been reported that lycopene consumption has been associated with higher plasma lycopene concentrations, thus dietary intake could represent a marker of circulating lycopene levels (57).

Conclusions

In a large, nationally representative sample of US adult population, lycopene and tomato intake were associated with lower risks of total, CHD and stroke mortality as well as with a more favorable cardiometabolic profile. Smoking could moderate the beneficial impact of lycopene consumption on mortalities. Furthermore, CRP was shown to strongly modulate the link between lycopene intake, total, CHD and cerebrovascular mortality. The present findings provide reasonable and consistent evidence supporting the important role of tomato products and lycopene as a part of a healthy cardioprotective diet. These results are useful for policy makers, contributing to increased public awareness about the role of the diet on health and the controversy regarding lycopene and tomato consumption.

REFERENCES:


26. Rosenbaum PR, Rubin DB.
40. Paterson E, Gordon MH, Niwat C, George TW, Parr L, Waroonphan S, et al. Supplementation with fruit and vegetable soups and beverages increases plasma carotenoid


Table 1. Characteristics of the study participants according to tomato and lycopene consumption.

<table>
<thead>
<tr>
<th>Tomato Consumption (cups consumed/day)</th>
<th>Lycopene Consumption (mcg) 50\textsuperscript{th} (25\textsuperscript{th} - 75\textsuperscript{th})</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.02 (cups consumed/day) (n=7869)</td>
<td>485 (265-796) (n=8025)</td>
<td>0.02</td>
</tr>
<tr>
<td>0.3 (cups consumed/day) (n=7991)</td>
<td>1605 (1029-2685) (n=7962)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1.8 (cups consumed/day) (n=8075)</td>
<td>9365 (5934-12463) (n=7948)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age years</td>
<td>49.2±0.2</td>
<td>50±0.1</td>
</tr>
<tr>
<td>Gender</td>
<td>46.4</td>
<td>46.4</td>
</tr>
<tr>
<td>Race/Ethnicity</td>
<td>Mexican-American (%)</td>
<td>19.3</td>
</tr>
<tr>
<td></td>
<td>Non-Hispanic White (%)</td>
<td>46.2</td>
</tr>
<tr>
<td></td>
<td>Non-Hispanic Black (%)</td>
<td>19.6</td>
</tr>
<tr>
<td>Marital Status</td>
<td>Married (%)</td>
<td>51.3</td>
</tr>
<tr>
<td></td>
<td>Divorced (%)</td>
<td>10.8</td>
</tr>
<tr>
<td></td>
<td>Never married (%)</td>
<td>17.5</td>
</tr>
<tr>
<td>Education Status</td>
<td>Less than high school (%)</td>
<td>30.1</td>
</tr>
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<thead>
<tr>
<th>Mortality status</th>
<th>Completed high school (%)</th>
<th>More than high school (%)</th>
<th>Total mortality</th>
<th>Coronary heart disease mortality</th>
<th>Cerebrovascular disease mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>24.2</td>
<td>23.9</td>
<td>24.2</td>
<td>25.8</td>
<td>23.2</td>
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<tr>
<td></td>
<td>46.3</td>
<td>47.1</td>
<td>49.3</td>
<td>47.6</td>
<td>45.2</td>
</tr>
<tr>
<td>Total mortality</td>
<td>1095</td>
<td>1082</td>
<td>1226</td>
<td>&lt;0.001</td>
<td>1234</td>
</tr>
<tr>
<td>Coronary heart disease mortality</td>
<td>268</td>
<td>209</td>
<td>235</td>
<td>&lt;0.001</td>
<td>301</td>
</tr>
<tr>
<td>Cerebrovascular disease mortality</td>
<td>73</td>
<td>69</td>
<td>89</td>
<td>&lt;0.001</td>
<td>80</td>
</tr>
</tbody>
</table>

Groups were compared by either chi-square or analysis of variance. Values expressed as standard error of mean or %.
Table 2. Clinical characteristics of the study participants by tomato and lycopene consumption adjusted for age, gender, race, education, marital status, poverty to income ratio, total energy intake, physical activity, smoking, alcohol consumption and intake of fiber, carbohydrate, fat and meat.

<table>
<thead>
<tr>
<th></th>
<th>Tomato Consumption</th>
<th>Lycopene Consumption</th>
<th>p</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T1</td>
<td>T2</td>
<td>T3</td>
<td>T1</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>27.9±0.1</td>
<td>28.4±0.1</td>
<td>28.3±0.1</td>
<td>0.283</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>96.9±0.3</td>
<td>97.5±0.2</td>
<td>97.4±0.3</td>
<td>0.276</td>
</tr>
<tr>
<td>apVAT</td>
<td>180.1±2.9</td>
<td>181.7±2.7</td>
<td>179.3±2.2</td>
<td>0.144</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>124.1±0.2</td>
<td>122.9±0.2</td>
<td>120.6±0.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>69.2±0.3</td>
<td>68.2±0.7</td>
<td>68.4±0.2</td>
<td>0.142</td>
</tr>
<tr>
<td>TG (mg/dl)</td>
<td>157.3±2.6</td>
<td>154.6±3.1</td>
<td>155.0±2.9</td>
<td>0.235</td>
</tr>
<tr>
<td>HDL-C (mg/dl)</td>
<td>51.6±0.2</td>
<td>52.1±0.3</td>
<td>53.6±0.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FBG (mg/dl)</td>
<td>100.2±0.4</td>
<td>99.8±0.3</td>
<td>98.3±0.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Insulin (mU/ml)</td>
<td>14.4±0.2</td>
<td>13.8±0.2</td>
<td>13.2±0.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CRP (mg/dl)</td>
<td>0.41±0.01</td>
<td>0.38±0.01</td>
<td>0.36±0.01</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Adjusted means were compared by analysis of co-variance (ANCOVA).

apVAT, anthropometrically predicted visceral adipose tissue; TG, Triglyceride; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; CRP, C-reactive protein.
Table 3. Multivariable-adjusted hazard ratios (95% confidence intervals) for mortality risk according to tomato and lycopene consumption.

<table>
<thead>
<tr>
<th></th>
<th>Tomato Consumption</th>
<th></th>
<th>Lycopene Consumption</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T1</td>
<td>T2</td>
<td>T3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 (Reference)</td>
<td>0.86(0.81–0.92)</td>
<td>0.79(0.74–0.82)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>p</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Mortality Model 1</td>
<td>1 (Reference)</td>
<td>0.89(0.83–0.94)</td>
<td>0.86(0.81–0.92)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Model 2</td>
<td>1 (Reference)</td>
<td>0.78(0.70–0.86)</td>
<td>0.76(0.70–0.85)</td>
</tr>
<tr>
<td></td>
<td>p</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
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<td>1 (Reference)</td>
<td>0.78(0.70–0.86)</td>
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</tr>
<tr>
<td></td>
<td>p</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Coronary Heart Disease</td>
<td>1 (Reference)</td>
<td>0.60(0.40–0.81)</td>
<td>0.53 (0.37–0.73)</td>
<td></td>
</tr>
<tr>
<td>Mortality Model 1</td>
<td>1 (Reference)</td>
<td>0.79(0.68–0.88)</td>
<td>0.76(0.69–0.82)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Model 2</td>
<td>1 (Reference)</td>
<td>0.85(0.61–1.17)</td>
<td>0.70(0.62–0.81)</td>
</tr>
<tr>
<td></td>
<td>p</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Coronary Heart Disease</td>
<td>1 (Reference)</td>
<td>0.75(0.66–0.88)</td>
<td>0.67(0.48–0.93)</td>
<td></td>
</tr>
<tr>
<td>Mortality Model 2</td>
<td>1 (Reference)</td>
<td>0.76(0.55–1.09)</td>
<td>0.71(0.65–0.78)</td>
<td></td>
</tr>
<tr>
<td>Cerebrovascular Disease</td>
<td>1 (Reference)</td>
<td>0.79(0.68–0.88)</td>
<td>0.76(0.69–0.82)</td>
<td></td>
</tr>
<tr>
<td>Mortality Model 1</td>
<td>1 (Reference)</td>
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</tr>
</tbody>
</table>

Model 1: Adjusted for age, gender, race, education, marital status, poverty to income ratio, total energy intake, dietary intake of fat, fiber and meat, physical activity, smoking and alcohol consumption

Model 2: Adjusted for age, gender, race, education, marital status, poverty to income ratio, total energy intake, dietary intake of fat, fiber, meat and carbohydrates, physical activity, smoking, alcohol consumption, body mass index, C-reactive protein, hypertension and diabetes.