

# Tea Consumption and Mortality After Acute Myocardial Infarction

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**Background**—Some studies have suggested that tea consumption may be associated with lower mortality among individuals with cardiovascular disease, but the effects of tea consumption on mortality after acute myocardial infarction are unknown.

**Methods and Results**—As part of the Determinants of Myocardial Infarction Onset Study, we performed a prospective cohort study of 1900 patients hospitalized with a confirmed acute myocardial infarction between 1989 and 1994, with a median follow-up of 3.8 years. Trained interviewers assessed self-reported usual weekly caffeinated tea consumption during the year before infarction with a standardized questionnaire. We compared long-term mortality according to tea consumption using Cox proportional hazards regression. Of the 1900 patients, 1019 consumed no tea (nondrinkers), 615 consumed <14 cups per week (moderate tea drinkers), and 266 consumed 14 or more cups per week (heavy tea drinkers). Compared with nondrinkers, age- and sex-adjusted mortality was lower among moderate tea drinkers (hazard ratio, 0.69; 95% CI, 0.53 to 0.89) and heavy tea drinkers (hazard ratio, 0.61; 95% CI, 0.42 to 0.86). Additional adjustment for clinical and sociodemographic characteristics did not appreciably alter this association (hazard ratio, 0.72; 95% CI, 0.55 to 0.94 for moderate tea drinkers; hazard ratio, 0.56; 95% CI, 0.37 to 0.84 for heavy tea drinkers). The association of tea and mortality was similar for total and cardiovascular mortality.

**Conclusions**—Self-reported tea consumption in the year before acute myocardial infarction is associated with lower mortality after infarction. (*Circulation*. 2002;105:2476-2481.)

**Key Words:** mortality ■ myocardial infarction ■ nutrition

The effects of tea on health have been widely studied, in part because tea contains flavonoids and other antioxidant components.<sup>1</sup> Flavonoids are a ubiquitous class of antioxidants found naturally in various foods derived from plants, especially black and green tea, and are hypothesized to prevent cardiovascular disease. For example, by inhibiting the oxidation of low-density lipoprotein cholesterol,<sup>2</sup> flavonoids could lower its atherogenicity.<sup>3</sup> Epidemiological evidence linking tea or flavonoid consumption with coronary heart disease or total mortality among healthy adults is conflicting,<sup>4–12</sup> but tea consumption may have its strongest effect among patients with cardiovascular disease.<sup>13</sup> For example, one study of men with prevalent cardiovascular disease found that flavonoid intake was associated with 37% lower coronary mortality,<sup>6</sup> but this finding had limited precision and was not statistically significant. A recent randomized crossover trial showed that short- and long-term black tea consumption could reverse endothelial dysfunction in patients with documented coronary heart disease,<sup>13</sup> providing a

plausible mechanism for an effect of tea in patients with cardiovascular disease. However, we know of no studies that have examined the association of tea consumption with mortality among early survivors of acute myocardial infarction, who might be expected to benefit from tea consumption.

To test the hypothesis that tea consumers have better long-term survival after acute myocardial infarction, we studied patients enrolled in the Determinants of Myocardial Infarction Onset Study (Onset Study).<sup>14</sup> This prospective, multicenter, cohort study included chart reviews and face-to-face interviews with hospitalized patients with confirmed acute myocardial infarction.

## Methods

### Onset Study Enrollment and Data Collection

The Onset Study was conducted in 45 community hospitals and tertiary care medical centers in the United States. Between August 1989 and September 1994, 1935 patients (601 women and 1334 men) were interviewed a median of 4 days after sustaining a

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myocardial infarction. Trained research interviewers identified eligible patients by reviewing coronary care unit admission logs and patient charts. For inclusion, patients were required to have a creatine kinase level above the upper limit of normal for each center, positive MB isoenzymes, an identifiable onset of symptoms of infarction, and the ability to complete a structured interview. For these analyses, we excluded patients with missing information about usual tea consumption ( $n=35$ ), leaving 1900 eligible patients. The institutional review board of each center approved this protocol, and each patient gave informed consent.

Interviewers used a structured data abstraction and questionnaire form. Participants were asked their usual frequency of consumption of caffeinated tea over the last year. Based on the distribution of tea consumption within the Onset Study population, we categorized usual tea consumption as none,  $<14$  cups per week (moderate use), or  $\geq 14$  cups per week (heavy use). We did not determine the consumption of decaffeinated tea.

Other information collected from each interview and chart review included demographics, medical history, and medication use (both prescription and nonprescription). During the chart review, interviewers recorded complications of congestive heart failure and ventricular tachycardia based on diagnoses recorded in the medical record. Interviewers also recorded all creatine kinase values available at the time of the interview.

We defined present aspirin use as the reported use of any aspirin or aspirin-containing product in the 4 days before the index myocardial infarction, based on previous Onset Study analyses and the duration of its physiological effect.<sup>15</sup> We defined initial hypotension as a presenting systolic blood pressure  $<90$  mm Hg. We used 1990 United States census data to derive median household income from United States Postal Service zip codes.<sup>16</sup> We derived body mass index as the weight (in kilograms) divided by the square of the height (in meters). We defined noncardiac comorbidity as a previous history of stroke, respiratory disease, renal disease, or cancer. We determined weekly non-tea caffeine consumption from reported caffeinated cola and coffee consumption, based on estimates of caffeine content derived from United States Department of Agriculture sources.<sup>17</sup>

We searched the National Death Index for deaths of Onset Study subjects through December 31, 1995 and requested death certificates from state offices of vital records for all probable matches, using a previously validated algorithm.<sup>18</sup> Three physicians blinded to each participant's tea consumption independently verified the determination of each death. Two physicians categorized each death as attributable to cardiovascular or noncardiovascular causes. Disagreements among raters were resolved by discussion.

## Statistical Analysis

We analyzed continuous and binary variables using ANOVA and Fisher's exact tests, respectively. We used Cox proportional-hazards models to examine the association of tea intake with survival after adjustment for potentially confounding factors. The covariates we included were age, sex, previous myocardial infarction, diabetes mellitus, hypertension, noncardiac comorbidity, medication use (aspirin,  $\beta$ -adrenergic antagonists, calcium-channel blockers, digoxin, diuretics, lipid-lowering agents, and ACE inhibitors), present smoking, previous smoking, body mass index, use of thrombolytic therapy, usual frequency of exertion (in 3 categories), usual alcohol consumption (in 3 categories), household income (in quartiles), educational attainment (in 3 categories), and complications of congestive heart failure or ventricular tachycardia during hospitalization. As previously described,<sup>19</sup> we also included an interaction term between age and sex in all models. Models that incorporated covariates on the basis of stepwise selection procedures yielded identical results and are not shown here. We assigned indicator variables for subjects with missing information on education ( $n=58$ ) and income ( $n=60$ ). For all other covariates, subjects with missing information were deleted from multivariate models ( $n=77$ ). Models that assigned these subjects mean levels of continuous covariates and modal levels of binary covariates yielded nearly identical results and are not shown here. We tested the assumption of proportional

hazards using time-varying covariates and found no violations. For all analyses, we present 95% CIs and probability values from 2-sided statistical tests using SAS software (Release 8; SAS Institute).

To assess the robustness of our findings, we also tested tea consumption using propensity analysis.<sup>14,20</sup> Each patient's score represents that individual's probability of consuming a given amount of tea, relative to abstinence from tea. To calculate propensity scores, we used logistic regression models in which the dependent variable was moderate to heavy tea consumption (compared with abstinence), using all covariates noted above (except thrombolytic therapy and complications during hospitalization), as well as usual coffee consumption (in 3 categories), multivitamin supplement use, previous angina, previous congestive heart failure, quadratic terms for age and body mass index, and interactions of sex with age and race. We then used the actual propensity score in Cox models along with age, sex, and measures of infarct treatment and severity (receipt of thrombolytic therapy, complications during hospitalization, peak creatine kinase level, and initial hypotension). We tested moderate and heavy tea consumption in separate propensity models.

## Results

The characteristics of the Onset Study participants have been previously reported.<sup>14</sup> Table 1 shows patient characteristics according to usual tea consumption. Median tea consumption was 2 cups weekly among patients consuming  $<14$  cups weekly (moderate tea drinkers) and 19 cups weekly among patients consuming  $\geq 14$  cups weekly (heavy tea drinkers). Heavy tea drinkers were more likely to be older and female and had lower mean body mass index, but they had a similar prevalence of hypertension and smoking and similar levels of education and household income. Ventricular tachycardia during hospitalization, abstinence from alcohol, and a sedentary lifestyle were somewhat less frequent among intermediate tea drinkers but not heavy tea drinkers. Coffee and tea consumption were inversely correlated (Spearman rank correlation coefficient,  $-0.09$ ;  $P<0.001$ ).

Of the 1900 eligible patients, 313 (16%) died during a median (and mean) follow-up of 3.8 years. Approximately 75% of the deaths were from cardiovascular causes. Table 2 shows the relation of tea consumption to total mortality. In age- and sex-adjusted analyses, we found a graded inverse relationship between tea consumption and mortality. Additional control for sociodemographic and clinical characteristics attenuated the inverse association among intermediate tea drinkers but actually strengthened it among heavier tea drinkers. Table 2 also shows that tea consumption was inversely associated with cardiovascular mortality, with a pattern similar to that for overall mortality, as expected from the predominance of cardiovascular deaths.

To evaluate the robustness of our findings, we performed several sensitivity analyses. When we controlled for coffee consumption in addition to the covariates in the full model, the hazard ratios were 0.77 (95% CI, 0.59 to 1.01) among intermediate tea drinkers and 0.60 (95% CI, 0.40 to 0.90) among heavier tea drinkers. Propensity analysis produced similar estimates, with hazard ratios for total mortality of 0.76 (95% CI, 0.58 to 0.99) for moderate tea drinkers and 0.62 (95% CI, 0.41 to 0.93) for heavy tea drinkers. Exclusion of the 44 participants who died within 30 days of hospitalization did not affect our findings (data not shown). In selected patient subgroups, we found generally similar inverse associations of tea consumption with mortality regardless of age,

**TABLE 1. Characteristics of 1900 Onset Study Participants According to Usual Weekly Tea Consumption**

	Usual Weekly Tea Consumption			<i>P</i> *
	None	<14 Cups	≥14 Cups	
Number	1019	615	266	...
Age, y†	61±12	61±13	63±13	0.06
Female, %	29	31	41	<0.001
White, %	92	89	90	0.11
BMI, kg/m <sup>2</sup> ‡	27.5±5.3	27.2±5.0	26.4±5.0	0.02
Present smoker, %	35	32	32	0.42
Former smoker, %	43	40	39	0.29
Hypertension, %	44	44	45	0.87
Diabetes, %	22	20	17	0.14
Previous myocardial infarction, %	30	27	25	0.31
Noncardiac comorbidity, %‡	13	17	17	0.08
Regular use of				
Aspirin, %	33	33	35	0.78
β-Blockers, %	22	18	19	0.16
Ca <sup>2+</sup> -blockers, %§	26	22	23	0.12
ACE inhibitors, %	12	13	9	0.20
Digoxin, %	8	7	8	0.52
Hypolipidemics, %	8	8	6	0.79
Diuretics, %	20	19	21	0.77
Thrombolytic use, %	34	39	38	0.12
Complications during admission, %				
CHF	15	14	15	0.81
VT¶	15	9	11	0.002
Income, \$†#	38 322±13 169	38 822±13 282	37 699±12 671	0.50
Exertion ≥6 MET (episodes/week), %				
<1	83	78	83	0.03
1–4	9	13	8	
≥5	8	10	10	
Education, %				
Less than high school	25	22	26	0.35
High school	40	42	44	
Some college	35	35	30	
Alcohol intake (servings/week), %				
None	51	41	47	0.002
<7	33	42	37	
≥7	16	17	16	
Caffeinated coffee intake (cups/week), †	18±27	16±19	12±28	<0.001
None, %	27	18	40	<0.001
≤14, %	39	51	38	
>14, %	34	31	23	

\**P* values for binary and continuous variables derive from exact tests and ANOVA, respectively.

†Mean values with SD are shown for continuous variables.

‡Noncardiac comorbidity included a previous history of stroke, cancer, renal disease, or respiratory disease.

§Ca<sup>2+</sup>-blockers indicates calcium-channel blockers.

||CHF indicates congestive heart failure during the index hospitalization.

¶VT indicates ventricular tachycardia during the index hospitalization.

#Household income was derived from zip codes according to 1990 United States Census Bureau data.

**TABLE 2. Hazard Ratios for All-Cause and Cardiovascular Mortality After Acute Myocardial Infarction According to Usual Weekly Tea Consumption Among Onset Study Participants**

	Usual Weekly Tea Consumption			<i>P</i> (trend)
	None	<14 Cups	≥14 Cups	
Number	1019	615	266	
Deaths (%)	191 (19)	86 (14)	37 (14)	
Cardiovascular deaths (%)	141 (14)	67 (11)	26 (10)	
Person-years	3747	2278	981	
Age- and sex-adjusted (95% CI)	1.00	0.69 (0.53–0.89)	0.61 (0.42–0.86)	<0.001
Full model* (95% CI)	1.00	0.72 (0.55–0.94)	0.56 (0.37–0.84)	<0.001
CV mortality† (95% CI)	1.00	0.79 (0.58–1.08)	0.54 (0.33–0.87)	0.005

\*The full model adjusted for age, sex, previous myocardial infarction, noncardiac comorbidity, hypertension, diabetes, body mass index, present smoking, former smoking, educational attainment, race, household income, usual frequency of exertion, usual alcohol consumption, use of thrombolytic therapy, use of cardiac medications (aspirin,  $\beta$ -blockers, calcium-channel blockers, digoxin, diuretics, lipid-lowering agents, or ACE inhibitors), and congestive heart failure or ventricular tachycardia during hospitalization.

†These models show hazard ratios for death from cardiovascular causes, adjusted for the same covariates as the full model.

sex, smoking status, obesity, hypertension, diabetes, or previous infarction (data not shown).

In another stratified analysis, we found an interaction of borderline significance ( $P=0.08$ ) between alcohol consumption and tea consumption. Among 1061 patients who consumed <1 alcoholic drink per month, the hazard ratios for total mortality were 0.63 (95% CI, 0.45 to 0.88) for moderate tea drinkers and 0.44 (95% CI, 0.27 to 0.73) for heavy tea drinkers after adjustment for all other covariates other than alcohol use. Among 787 patients who drank alcohol at least monthly (median, 5 servings per week), the corresponding hazard ratios were 0.83 (95% CI, 0.52 to 1.32) and 0.79 (95% CI, 0.41 to 1.53).

To evaluate whether caffeine intake per se was responsible for the inverse association of tea consumption and mortality, we assessed non-tea caffeine intake and mortality in similar fashion. Non-tea caffeine intake was not associated with mortality (adjusted hazard ratio per 1000 mg of caffeine intake per week, 1.01; 95% CI, 0.97 to 1.06).

## Discussion

In this multicenter, prospective study of early survivors of acute myocardial infarction, we found that self-reported tea consumption during the year before infarction was associated with lower subsequent mortality after infarction. This association was graded, unchanged by adjustment for sociodemographic and clinical characteristics after controlling for age and sex, and extended to both total and cardiovascular mortality.

We know of no previous studies that have specifically examined the effect of tea consumption after acute myocardial infarction. In a secondary analysis of the Health Professionals Follow-Up Study, Rimm et al<sup>6</sup> found that higher flavonoid intake was associated with a lower risk of coronary mortality only among men with prevalent cardiovascular disease. Although only 105 men died during follow-up and

the findings did not reach statistical significance, their results agree well with ours (relative risk, 0.63; 95% CI, 0.33 to 1.20). Klatsky et al<sup>11</sup> found a weak but statistically significant effect of tea consumption on mortality only among individuals with baseline morbidity (relative risk per cup per day, 0.98;  $P=0.04$ ), although this group included subjects with a diverse set of diagnoses. The Zutphen Elderly Study reported that a history of previous myocardial infarction did not statistically significantly modify the inverse association of flavonoid consumption with coronary mortality among men ( $P=0.58$ ).<sup>7</sup> However, only 112 men had sustained a previous infarction, of whom only 23 died, and the authors did not report the effect of flavonoid consumption in this small subgroup. All of these studies were limited to prevalent cases of cardiovascular disease, raising the possibility of survivorship bias.

Several possible mechanisms could explain an association between tea consumption and survival among patients with acute myocardial infarction. A recent randomized trial found that acute and chronic black tea consumption improved endothelial function in patients with coronary heart disease in an additive fashion.<sup>13</sup> This provides a suggestive mechanism for a beneficial impact of tea intake on survivors of acute myocardial infarction, given the adverse prognosis associated with coronary endothelial dysfunction in patients with coronary heart disease.<sup>21</sup> Flavonoids also inhibit LDL oxidation, perhaps by reducing macrophage superoxide production.<sup>2</sup> Oxidized LDL may promote atheroma formation by increasing macrophage uptake,<sup>22</sup> monocyte recruitment,<sup>23</sup> and direct endothelial cell damage,<sup>24</sup> and antioxidant use may prevent myocardial infarction, at least in some patients.<sup>25</sup>

Another hypothesized mechanism for a beneficial effect of tea on cardiovascular disease is an antithrombotic effect of flavonoids.<sup>26</sup> Flavonoids inhibit platelet aggregation in vitro, perhaps via suppression of phosphodiesterase or cyclooxygenase activity,<sup>27</sup> although whether this activity occurs in

vivo remains unclear.<sup>28</sup> Because alcohol consumption also has antithrombotic activity,<sup>29</sup> our finding that tea consumption seems most protective among alcohol abstainers supports this as a possible mechanism.

Whether the observed association between tea consumption and postinfarction survival reflects these physiological effects of tea or confounding by other factors associated with tea intake can only be answered in a large-scale, long-term randomized trial, although such a trial is unlikely to be performed in the near future.

We asked participants to report their usual tea consumption over the year before the infarction that resulted in their hospitalization. By measuring these variables prospectively, we minimized the possibility of differential misclassification during the follow-up period. For example, if sicker patients tend to give up tea consumption more often than healthier patients do after their infarctions, studies that assess postinfarction tea consumption may be biased in favor of tea consumption. The design of our study argues against that possibility. Interestingly, Cleophas et al<sup>30</sup> found that tea consumption was essentially identical when considered 1 year before, during, or 1 year after an acute myocardial infarction. The inception cohort design of our study also minimizes the possibility that tea has different associations with intermediate- and long-term mortality after acute myocardial infarction, causing a survivorship bias.<sup>14</sup>

### Study Limitations

In this study, we asked patients to report their usual consumption of caffeinated tea, which includes black and green teas, and we cannot determine whether black tea differs from green tea in this study. We also may have misclassified patients who predominately drank decaffeinated tea as nondrinkers, although caffeinated black tea represents the bulk of tea consumed in the United States during the years of this study. Although we relied on self-reported tea intake, this method has proven valid among both women<sup>31</sup> and men.<sup>32</sup>

As with any observational study, the associations we observed could be accounted for, at least in part, by differences between tea drinkers and nondrinkers. For example, we did not have detailed dietary information available for these patients, and we cannot exclude the possibility that dietary differences account for some of the association between tea and survival. In this regard, results from the Zutphen Elderly Study are instructive; controlling for age and diet in that population actually strengthened the association between flavonoid consumption and lower coronary mortality.<sup>7</sup> Similarly, in our study, adjustment for a wide variety of differences between tea drinkers and nondrinkers strengthened the association of tea and mortality among heavier tea drinkers once we controlled for age and sex. To account fully for our results, any remaining uncontrolled confounder would need to be strongly associated with both tea consumption and long-term mortality and generally unrelated to the sociodemographic and clinical characteristics for which we already controlled.

Our power to define mortality differences between levels of tea consumption was limited. Although we found a consistent, graded, inverse association between tea intake and

mortality, consumption of large amounts of tea was uncommon among Onset Study participants. A similar study with a larger number of tea drinkers could define the dose-response relationship between tea and mortality more precisely.

If tea drinkers had a higher case-fatality rate during acute myocardial infarction than nondrinkers, then the surviving population of tea drinkers in this study may have been enriched with healthier patients more likely to survive over several years. However, some previous studies have reported that flavonoid consumption has a stronger inverse association with coronary mortality than incident myocardial infarction, implying that tea drinkers could actually have a lower case-fatality rate from acute myocardial infarction.<sup>6,7</sup> Differential mortality before enrollment is less likely to affect our study than previous ones that relied on patients with prevalent cases of cardiovascular disease.

In summary, we found that tea consumption is associated with greater survival after acute myocardial infarction among Onset Study participants. This finding was consistent for total and cardiovascular mortality and did not change with additional adjustment after we controlled for age and sex. Although our findings support the hypothesis that tea consumption may improve survival among patients after acute myocardial infarction, confirmation of this relation from other observational studies or, better yet, controlled clinical trials is needed.

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