Re: Carbonated Soft Drink Consumption and Risk of Esophageal Adenocarcinoma

In the recent study by Mayne et al. *(1)*, consumption of carbonated soft drinks (CSD) was positively associated with gastroesophageal reflux (GER) and inversely associated with adenocarcinoma of the esophagus. Likewise, in 1997, this study group had reported statistically significantly reduced risks for adenocarcinoma of the esophagus in wine drinkers (odds ratio [OR] = 0.6, 95% confidence interval [CI] = 0.5 to 0.8) and attributed this to sampling bias or residual confounding *(2)*. The reduced risks for adenocarcinoma of the esophagus in CSD drinkers could be attributed to similar reasons as discussed below.

First, the control subjects were younger than the case patients having adenocarcinoma of the esophagus *(2)*. There were 124 case patients and 357 control subjects aged 64 or less years and 169 case patients and 338 control subjects aged 65 or more years ($P = .009$) *(2)*. The Continuing Survey of Food Intakes by Individuals reported large differences in CSD by age *(3)*. Total CSD intakes in young (40–59 years) and old (60 years and older) White males were 374 g/day and 144 g/day, respectively *(3)*. Mayne et al. also found statistically significantly higher consumption of CSD in younger than in older control subjects *(1)*.

Second, the control subjects had statistically significantly higher income ($P_{trend} = .005$) than the case patients with adenocarcinoma of the esophagus *(2)*. The Continuing Survey of Food Intakes by Individuals reported large differences in CSD consumption by income *(4)*. For example, the daily diet-CSD intakes among men aged 40–59 years were 53 g/day, 80 g/day, and 139 g/day in subjects with incomes 131%, 131%–350%, and greater than 350% of the poverty line, respectively *(4)*. Mayne et al. found an increasing trend in total CSD consumption in the control subjects with higher income *(1)*. The consumption of diet CSD by income groups is not discussed.

Third, the duration of CSD consumption is missing from this study *(1)*. CSD consumption was ascertained for 3 to 5 years before the diagnosis of cancer *(1,2,5)*. It was hypothesized that CSD contribute to the development of adenocarcinoma of the esophagus by inducing GER for several decades *(6)*. The U.S. per capita trends show that rise in CSD consumption preceded the rise of adenocarcinoma of the esophagus by 20 years or more *(6)*. People with heartburn for 20 or more years have the highest risk for adenocarcinoma of the esophagus *(5,7)*. Stratification by GER symptoms cannot replace the duration of CSD intake in the decades prior to the diagnosis of cancer. This limitation is brought out in another publication of theirs *(5)*. Ever having used H2 blockers was not associated with esophageal adenocarcinoma risk (OR = 0.9, 95% CI = 0.5 to 1.5); the odds ratio was 1.3 (95% CI = 0.6 to 2.8) in long-term (4 or more years) users but increased to 2.1 (95% CI = 0.8 to 5.6) when used in the 5 years before the interview *(5)*.

The question of public health relevance is whether high school students and young adults can drink several cans of CSD everyday for many decades without increasing the lifetime risk of GER disease (GERD) and adenocarcinoma of the esophagus. More epidemiologic

studies are therefore needed to provide the answer. Maine et al. report more frequent self-reported reflux symptoms in participants who consumed more CSD (1). Therefore, CSD could be a new risk factor for GERD, the prevalence of which is rising rapidly.

MOHANDAS K. MALLATH

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NOTES

Correspondence to: Mohandas K. Mallath, MD, Department of Digestive Diseases and Clinical Nutrition, Tata Memorial Hospital, Parel, Mumbai 400012, India (e-mail: mohandaskm@vsnl.net).

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Mayne et al. *(1)* provided relevant information on the association between carbonated soft drinks (CSD) and esophageal cancer risk using data from a population-based case–control study conducted in the United States. CSD may increase gastric distension, and consequently gastroesophageal reflux disease and could hence have contributed to the increasing trend of esophageal adenocarcinoma *(2)*, which parallels the increase in CSD consumption. However, odds ratios (ORs) for the highest (≥1 drink/day) versus the lowest (<1 drink/month) quartiles of CSD consumption were 0.47 for esophageal adenocarcinoma (282 case patients), 0.74 for gastric cardia adenocarcinoma (255 case patients), 0.85 for esophageal squamous cell carcinoma (SCC, 206 case patients), and 0.65 for noncardia gastric adenocarcinoma (352 case patients), with a statistically significant inverse trend in risk for esophageal adenocarcinoma. To provide additional information to this issue, we analyzed data from a hospital-based case–control study conducted in northern Italy between 1992 and 1997 *(3)*.

Case patients were 304 individuals (275 men and 29 women, median age = 60 years, range = 39–77 years) with incident, histologically confirmed esophageal SCC. Control subjects were 743 patients (593 men and 150 women, median age = 60 years, range = 36–77 years) admitted to the same hospitals as case patients for a wide spectrum of acute, nonneoplastic conditions, not related to smoking, alcohol consumption, or long-term modification of diet. Control subjects were frequency matched with case patients by quinquennia of age, sex, year of interview, and area of residence. Case patients and control subjects were interviewed using a standard questionnaire that included questions pertaining to sociodemographic factors and lifestyle habits, such as tobacco smoking and alcohol consumption and anthropometric measures. Subjects' usual diet during the 2 years before cancer diagnosis or hospital admission was investigated using a validated 78-item food frequency questionnaire *(4,5)* that included a specific question on CSD consumption. Odds ratios for CSD consumption were estimated by using unconditional multiple logistic regression models *(6)*, including terms for age, sex, study center, education, tobacco smoking, alcohol drinking, body mass index (weight in kg/height in m^2), physical activity, and total energy intake.

Case patients and control subjects were grouped according to CSD consumption, overall and in strata of sex and age (Table 1). The overall odds ratio for

Table 1. Distribution of 304 squamous cell esophageal cancer case patients and corresponding 743 control subjects, according to consumption of carbonated soft drinks (CSDs), Italy, 1992–1997

	CSD nondrinkers* (<1 glass/mo)	CSD occasional drinkers (≥1 glass/mo and <1 glass/day)		CSD regular drinkers (≥1 glass/day)		All CSD drinkers (≥1 glass/mo)	
Characteristic	No. of case patients/no. of control subjects	No. of case patients/no. of control subjects	OR† (95% CI)	No. of case patients/no. of control subjects	OR† (95% CI)	No. of case patients/no. of control subjects	OR† (95% CI)
Total	202/475	57/148	0.86 (0.57 to 1.30)	45/120	0.80 (0.51 to 1.25)	102/268	0.86 (0.62 to 1.20)
Sex							
Men	183/373	51/122	0.85 (0.54 to 1.32)	41/98	0.80 (0.49 to 1.29)	92/220	0.82 (0.57 to 1.18)
Women	19/102	6/26	1.56 (0.44 to 5.58)	4/22	0.70 (0.15 to 3.19)	10/48	1.11 (0.38 to 3.27)
Age, y							
<60	80/207	34/74	1.23 (0.68 to 2.22)	27/63	0.94 (0.50 to 1.78)	61/137	1.09 (0.67 to 1.78)
≥60	122/268	23/74	0.58 (0.32 to 1.08)	18/57	0.86 (0.44 to 1.69)	41/131	0.69 (0.43 to 1.12)

*Referent category.

†OR = odds ratio; CI = confidence interval. Estimated by unconditional multiple logistic regression adjusted for age (<50, 50–54, 55–59, 60–64, 65–69, or ≥70 years), sex, study center (Pordenone, Milan, or Padua), education (<7, 7–11, or ≥12 years), tobacco smoking (never, ex-smoker, <15, 15–24, or ≥25 cigarettes per day), alcohol drinking (<2, 2–3, or ≥4 drinks per day), body mass index (kg/m^2; <24.2, 24.2–27.0, or ≥27.1), occupational physical activity at age 30–39 years (low, low–moderate, moderate, or high–very high), and total energy intake (<1782, 1782–2192, 2193–2583, 2584–3116, or ≥3117 kcal per day).

esophageal SCC incidence among those who drank one or more glasses of CSD per month was 0.86; it was 0.82 in men, 1.11 in women, 1.09 in subjects aged <60 years, and 0.69 in those aged ≥60 years. Corresponding estimates for regular CSD consumption (≥1 glass/day) were 0.80 overall, 0.80 in men, 0.70 in women, 0.94 in younger subjects, and 0.86 in older subjects. None of these estimates were statistically significant.

Our study, based on a large sample size of esophageal SCC, with a high participation rate (>95% for both case patients and control subjects), a satisfactory valid and reproducible *(4,5)* food frequency questionnaire (for CSD, Spearman r = .61), supports the findings of Mayne et al. *(1)* for esophageal SCC. The two studies suggest that CSD consumption does not increase the risk of esophageal cancer and that a moderate inverse association between CSD intake and esophageal SCC risk exists.

Silvano Gallus
Renato Talamini
Esteve Fernandez
Luigino Dal Maso
Silvia Franceschi
Carlo La Vecchia

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Affiliations of authors: Istituto di Ricerche Farmacologiche "Mario Negri," Milan, Italy (SG, CLV); Unità di Epidemiologia e Biostatistica, Centro di Riferimento Oncologico, Aviano (Pordenone), Italy (RT, LDM); Cancer Prevention and Control Unit, Institut Català d'Oncologia, L'Hospitalet, Spain (EF); Department of Experimental and Health Sciences, Universitat Pompeu Fabra, Barcelona, Spain (EF); International Agency for Research on Cancer, Lyon, France (SF); Istituto di Statistica Medica e Biometria, Università degli Studi di Milano, Milan, Italy (CLV).

Correspondence to: Silvano Gallus, ScD, Istituto di Ricerche Farmacologiche "Mario Negri," Via Eritrea, 62, 20157 Milan, Italy (e-mail: gallus@marionegri.it).

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RESPONSE

We appreciate the opportunity to address comments by Gallus et al. and by Mallath regarding our recent publication on carbonated soft drink (CSD) consumption and lack of increased esophageal adenocarcinoma risk. Gallus et al. analyzed data from a case–control study in Italy and reported a statistically non-significant inverse association between CSD consumption and risk of esophageal cancer. This was a study of esophageal squamous cell carcinoma rather than adenocarcinoma. Although these findings do not inform a possible link between CSDs and esophageal adenocarcinoma, the replication of our results for squamous cell carcinoma in a different population is reassuring.

Citing data from the Continuing Survey of Food Intakes by Individuals showing greater consumption of CSDs in younger and higher-income subjects, Mallath suggests that case–control differences in age and income might account for the lower consumption of CSDs by case patients than control subjects. We examined variables that could be associated with CSD consumption and, as shown in Table 1 of our manuscript, younger age and higher income were both related to higher CSD consumption among control subjects. Consequently, all of the risk estimates were adjusted for age, income, and education and several other potential confounders (shown in Table 2 of the manuscript). That the determinants of CSD consumption parallel those in the Continuing Survey of Food Intakes by Individuals suggests that the population control subjects in our study are representative of the general population.

Mallath also indicates that we had no data on duration of CSD consumption. We noted this potential limitation in our publication: "intake of CSDs 3–5 years prior to diagnosis might not reflect intake in the distant past." For this to explain our findings, however, case patients who reported consuming fewer CSDs 3–5 years before diagnosis would have had to consume substantially more CSDs in the distant past than control subjects. This seems unlikely unless case patients changed consumption habits to avoid exacerbation of reflux. However, the inverse association between CSD consumption and esophageal adenocarcinoma risk was found to persist among persons without reflux symptoms.

Mallath concludes that CSD may be a new risk factor for gastroesophageal reflux disease, which is consistent with our finding that control subjects who consumed more CSDs reported more frequent reflux symptoms than those who consumed less. An alternative explanation, however, is that CSDs may affect perception of reflux. Recent studies have shown that a majority of reflux episodes are asymptomatic *(1)*, with symptomatic episodes associated with pure gas reflux, acid exposure in the 75 minutes before the reflux episode, and greater refluxate acidity (pH <4), all of which may be related to CSD consumption. Because the determinants of self-reported reflux may simply reflect reflux perception, a causal relationship with esophageal adenocarcinoma risk cannot be assumed without supporting clinical and epidemiologic data.

Susan T. Mayne
Harvey A. Risch
Robert Dubrow
Wong-Ho Chow
Marilie D. Gammon
Thomas L. Vaughan
Joseph F. Fraumeni, Jr.

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Notes

Affiliation of authors: Yale University School of Medicine and Yale Cancer Center, New Haven, CT (STM, HAR, RD); National Cancer Institute, Division of Cancer Epidemiology and Genetics, Bethesda, MD (WHC, JFF); University of North Carolina, School of Public Health, Chapel Hill, NC (MDG); Fred Hutchinson Cancer Research Center and University of Washington School of Public Health and Community Medicine, Seattle, WA (TLV).

Correspondence to: Susan T. Mayne, PhD, Yale University School of Medicine, Department of Epidemiology and Public Health, 60 College Street, New Haven, CT 06520-8034 (e-mail: Susan.Mayne@yale.edu).

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