

1. Wright RO, Tsaih SW, Schwartz J, Wright RJ, Hu H. Association between iron deficiency and blood lead level in a longitudinal analysis of children followed in an urban primary care clinic. *J Pediatr* 2003;142:9-14.
2. Osman K, Schütz A, Åkesson B, Maciag A, Vahter M. Interactions between essential and toxic elements in lead exposed children in Katowice, Poland. *Clin Biochem* 1998;31:657-65.
3. Ballew C, Bowman B. Recommending calcium to reduce lead toxicity in children: a critical review. *Nutr Rev* 2001;59:71-9.

Obesity and Cancer

TO THE EDITOR: In the abstract of their article on overweight, obesity, and mortality from cancer, Calle et al. (April 24 issue)¹ conclude, "Increased body weight was associated with increased death rates for all cancers combined and for cancers at multiple specific sites." However, if one looks at the data for men (alas, this does not hold true for women), one sees that the relative risk of cancer among men who were "grade 1 overweight" (body-mass index [the weight in kilograms divided by the square of the height in meters], 25.0 to 29.9), as compared with men in the "normal range" (body-mass index, 18.5 to 24.9) is 0.97. Since 29,227 of the men studied fell into these two categories of body-mass index, whereas only 3076 had a higher body-mass index, this conclusion is diametrically opposed to what the data show to be true for more than 90 percent of this population of men — and presumably for any similarly stratified population of men. Thus, the advice implied in the conclusion of the abstract is exactly contrary to what the data suggest would be good advice.

Marshall E. Deutsch, Ph.D.

41 Concord Rd.
Sudbury, MA 01776-2328
med41@aol.com

1. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. *N Engl J Med* 2003;348:1625-38.

TO THE EDITOR: Calle et al. attempt to estimate the fraction of deaths due to cancer in the U.S. population that are attributable to overweight and obesity by using multivariate-adjusted relative risks and the distribution of body-mass index in the subgroup of the current population that is 50 to 69 years old. The formula they cite for the calculation of the population attributable fraction is appropriate for unadjusted relative risks¹; the use of adjusted relative risks in this formula is incorrect and can result in biased estimates.^{2,3} With adjusted relative risks, the population attributable fraction should be calculated on the basis of the distribution of body-mass index among persons who have died of cancer. Both

the distribution of body-mass index and the rate of death due to cancer vary according to age, race, smoking status, and other confounding factors. When there is confounding, the expected distribution of body-mass index among persons who have died of cancer cannot be calculated directly from the distribution of body-mass index in the general population, because the distribution of confounding factors will also affect the distribution of body-mass index among persons who died of cancer. Estimates of the population attributable fraction that are calculated on the basis of adjusted relative risks and the distribution of body-mass index in the general population without taking into account the distribution of confounding factors may be biased.

Katherine M. Flegal, Ph.D.

Centers for Disease Control and Prevention
Hyattsville, MD 20782
kflegal@cdc.gov

David F. Williamson, Ph.D.

Centers for Disease Control and Prevention
Atlanta, GA 30341

Barry I. Graubard, Ph.D.

National Cancer Institute
Bethesda, MD 20892

1. Kleinbaum DG, Kupper LL, Morgenstern H. *Epidemiologic research: principles and quantitative methods*. Belmont, Calif.: Lifetime Learning, 1982.
2. Rockhill B, Newman B, Weinberg C. Use and misuse of population attributable fractions. *Am J Pub Health* 1998;88:15-9.
3. Benichou J. A review of adjusted estimators of attributable risk. *Stat Methods Med Res* 2001;10:195-216.

TO THE EDITOR: Calle et al. report that obesity is a risk factor for cancer-related death, but although they adjusted their analyses for multiple potential confounders, they did not address two important statistical issues: the sensitivity of relative risk to proportional hazards and the potential for artifacts in evaluations of cancer-specific risk among adults who may have other diseases. Since the authors did not give readers access to their raw data or present a summary of the data that is adequate for an evaluation of these phenomena, a simulation must suffice to demonstrate these points. Suppose

there were equal frequencies of death due to cancer and death from causes other than cancer (e.g., cardiovascular disease) among nonobese adults, with a common median survival of 80 years. In the group of obese adults, suppose there was a shift toward an earlier age at death due to cardiovascular disease and a higher frequency of death due to cardiovascular disease, with a corresponding reduction in the rate of cancer-related death. Figure 1 shows the anomalous effect of a decrease in cancer-specific survival among obese adults, which is further overstated by the use of the relative risk.¹ Without full consideration of competing risks,²⁻⁴ the authors' conclusion is debatable, even though the overall danger of obesity is not.

Paul H. Frankel, Ph.D.

City of Hope National Medical Center
Duarte, CA 91010-3000
pfrankel@coh.org

1. Frankel P, Longmate J. Parametric models for accelerated and long-term survival: a comment on proportional hazards. *Stat Med* 2002;21:3279-89.
2. Gooley TA, Leisenring W, Crowley J, Storer BE. Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. *Stat Med* 1999;18:695-706.
3. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 1999;94:496-509.
4. Tsiatis A. A nonidentifiability aspect of the problem of competing risks. *Proc Natl Acad Sci U S A* 1975;72:20-2.

TO THE EDITOR: Calle et al. may have exaggerated the risk of death due to cancer associated with a body-mass index of 25.0 or higher. Mortality from all types of cancer was actually lowest among overweight men. Furthermore, the authors' assertion that "more than 90,000 deaths per year from cancer might be avoided if everyone in the adult population could maintain a body-mass index under 25.0 throughout life" is questionable. Most adults in the United States gain weight as they age. Over a 16-year period, the average U.S. adult's body-mass index might be expected to increase by 1 to 2 units.¹ Approximately 10 percent of adults have an increase in body-mass index of at least 5 units over a period of just 10 years.² Thus, it is probable that a number of persons who were in the apparently low-risk body-mass-index range in 1982 could have been in the overweight range 16 years later. It is also worth noting that data from the American Cancer Society Cancer Prevention Study I revealed that in virtually all subgroups analyzed, intentional weight loss was not associated with a lower rate of death due to cancer, nor was unintentional weight gain

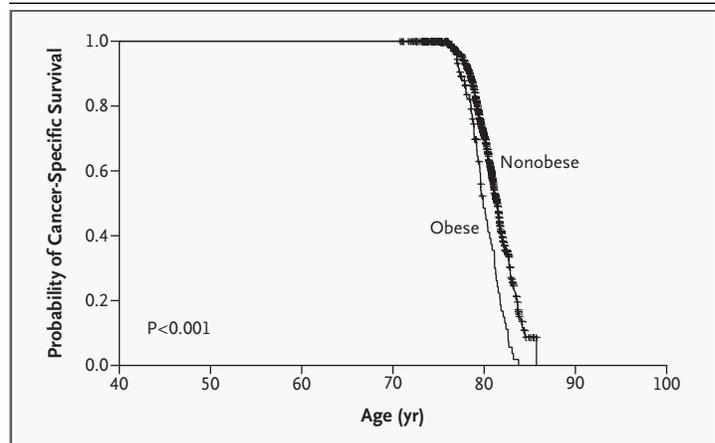


Figure 1. Obesity and the Risk of Death Due to Cancer.

The analysis is based on the following assumptions: of 800 nonobese adults, 50 percent die from cancer (median [\pm SD] survival, 80 ± 5 years) and 50 percent die from other causes (median survival, 80 ± 5 years); of 200 obese adults, 30 percent die from cancer (median survival, 80 ± 5 years) and 70 percent die from other causes (median survival, 75 ± 5 years). Results for all groups were modeled with a normal distribution. When data on adults who died from causes other than cancer were censored in a Cox regression analysis, the relative risk of cancer among obese adults in this typical simulation was more than twice that among nonobese adults (2.03). The time-dependent test for the violation of proportional hazards was not statistically significant in this simulation.

associated with an increased rate of death due to cancer.^{3,4}

Glenn A. Gaesser, Ph.D.

University of Virginia
Charlottesville, VA 22904
gag2q@virginia.edu

1. Williamson DF, Kahn HS, Remington PL, Anda RF. The 10-year incidence of overweight and major weight gain in US adults. *Arch Intern Med* 1990;150:665-72.
2. Williamson DF. Descriptive epidemiology of body weight and weight change in U.S. adults. *Ann Intern Med* 1993;119:646-9.
3. Williamson DF, Pamuk E, Thun M, Flanders D, Byers T, Heath C. Prospective study of intentional weight loss and mortality in never-smoking overweight US white women aged 40-64 years. *Am J Epidemiol* 1995;141:1128-41. [Erratum, *Am J Epidemiol* 1995;142:369.]
4. Idem. Prospective study of intentional weight loss and mortality in overweight white men aged 40-64 years. *Am J Epidemiol* 1999;149:491-503.

TO THE EDITOR: Calle et al. report that a body-mass index of 35.0 or higher was associated with higher rates of mortality from cancer. However, this connection does not prove that obesity causes or contributes to cancer directly. Although the statistical model was adjusted for a number of potential con-

founders, there was no discussion of the effect of these variables, apart from that of smoking status. Furthermore, there may be differences within populations of overweight adults. For example, differences between subgroups of persons who follow different diets with similar caloric intake could be examined through the comparison of typical Western diets with Mediterranean diets. Although the accompanying Perspective article by Adami and Trichopoulos¹ highlights the finding that caloric restriction in laboratory animals reduces the incidence of cancer and, presumably, obesity, these animals are usually fed ad libitum and confined. Therefore, these models cannot necessarily be extrapolated to humans. The effect of potential lifestyle-related and behavioral factors on the risk of cancer, as well as differences within overweight populations, should be examined. The identification of a causal factor in the cancer epidemic that is linked to obesity may provide the evidence necessary to induce overweight people and other people at increased risk to adopt healthier lifestyles and eating habits.

John A. Smith, Ph.D.

803 Reading Ct.
West Chester, PA 19380
jasphdfacsm@aol.com

1. Adami H-O, Trichopoulos D. Obesity and mortality from cancer. *N Engl J Med* 2003;348:1623-4.

THE AUTHORS REPLY: The comments of Flegal et al. regarding the formula we used to estimate the population attributable fraction are technically correct. Moreover, we were aware that, within a given population, the population attributable fraction may be more accurately estimated with the use of a formula based on the distribution of the prevalence of exposure among persons who died of cancer if the relative risks are adjusted for confounders.¹ In fact, within our cohort, we calculated the population attributable fraction using both the formula cited in the footnote to Table 4, which relies on the prevalence of exposure among all subjects in the Cancer Prevention Study II according to the number of person-years at risk, and the formula suggested by Flegal et al., which relies on the prevalence of exposure among subjects in the study who died of cancer. The results were identical. However, with the use of either formula, these results estimated the propor-

tion of deaths due to cancer among the subjects in the study that could be attributed to obesity.

The public health effect of obesity in this country cannot be measured by calculating the population attributable fraction in a relatively lean population. Far more important to the magnitude of the population attributable fraction than the potential bias that Flegal et al. point out is the absolute prevalence of overweight and obesity in the population under consideration.

Our desire was to estimate the proportion of deaths that may be attributable to obesity in a population with a prevalence of overweight and obesity similar to that in the United States at the present time. To derive such an estimate, we assumed that the relative risks found in our study represented valid estimates that were reasonably generalizable to the U.S. population. The absolute levels of overweight and obesity in the study cohort are not generalizable to the U.S. population, and this is why we chose not to use a formula for the population attributable fraction that was based on the prevalence of exposure in our cohort.

Dr. Deutsch questions whether overweight men (with a body-mass index between 25.0 and 29.9) are actually at lower risk for death from cancer than normal-weight men because the relative risk for this group was 0.97. In the subgroup of men in this body-mass-index group who had never smoked, the relative risk was 1.11, which we believe to be the more valid estimate of risk, as previously discussed.

We do not agree with Dr. Frankel's suggestion that our results represent an anomalous effect of competing risks. Dr. Gaesser suggests that our study would have been stronger if we had obtained measurements of weight continuously throughout the follow-up period, and he is correct. He also correctly notes that our study does not address the issues of weight gain and weight loss.

Eugenia E. Calle, Ph.D.

Carmen Rodriguez, M.D., M.P.H.

Michael J. Thun, M.D., M.P.H.

American Cancer Society
Atlanta, GA 30329-4251
jcalleg@cancer.org

1. Rockhill B, Newman B, Weinberg C. Use and misuse of population attributable fractions. *Am J Public Health* 1998;88:15-9.