The Big Fat Question: What Is the Role of Excess Weight in Cancer Risk, Mortality?

In 1981, British researchers Richard Doll and Richard Peto took on the task of estimating the percentage of cancer deaths in the United States that could be avoided by changing one’s lifestyle. In a 119-page article in the Journal of the National Cancer Institute that has since been cited thousands of times, they estimated that tobacco use and poor diet each accounted for about one-third of cancer deaths in the United States. When combined with alcohol consumption, certain infectious conditions, and environmental and occupational carcinogens, Doll and Peto estimated that about 75%–80% of cancer deaths could, in principle, be prevented.

Whereas Doll and Peto linked their conclusions about smoking to a large body of existing evidence, they had much less information on which to base their estimates about diet and nutrition, other than epidemiologic comparisons across countries or studies of immigrants who moved from one country to another. Still, Doll and Peto estimated that “diet,” which they defined not as caloric input but more as nutrition, could be responsible for up to 35% of cancer deaths—at least as much as tobacco use.

Decades later, and with much more evidence available from large studies, there are still some doubts about which factors under the umbrella term “diet” actually do or do not affect cancer risk. For example, two recent studies from large prospective cohorts found no association between consumption of fruit and vegetables and cancer incidence (see News, Vol. 97, No. 7, p. 474). Doll himself said in a recent BBC interview that, “We know a lot about diet in relation to heart disease, but in relation to cancer, it’s still very confused. I feel I know less about it now than I did 20 years ago.”

One dietary factor that has biologic plausibility and some backing in epidemiologic data is the contribution of excess body weight to cancer development and death. With decades more data than Doll and Peto had, the International Agency for Research on Cancer estimated in a 2002 report that overweight and obesity may be responsible for about 10% of breast cancer and colorectal cancer cases and between 25% and 40% of kidney, esophageal, and endometrial cancers.

But even with obesity, there are still many unanswered questions: the magnitude to which obesity may contribute to the risk of cancer and other adverse health effects, whether a few extra pounds constitutes a cancer risk, and the appropriate way to measure all of these effects.

Zeroing In on Obesity

The first evidence that body weight played a role in cancer death came in 1978 in the first American Cancer Society (ACS) cohort study, when researchers found a “J” shaped relationship between underweight and overweight Americans and an increased risk of death from cancer. “For quite a while, the dangers of excessive leanness received more attention than dangers of excessive obesity,” said Michael Thun, M.D., head of epidemiologic research for the ACS and an author on many of the later ACS research findings. “The analysis at the time was not paying attention to the fact that both smoking and being sick distorts the relationship between leanness and health.”

Several large cohort studies were launched both before and after Doll and Peto’s study that have followed thousands of people over decades. Many of these studies have found more evidence of a connection between weight and cancer, the details of which were laid out in a 2003 Institute of Medicine report, Fulfilling the Potential of Cancer Prevention and Early Detection. According to the report, obesity is more strongly associated with both cancer mortality and cancer development than any other lifestyle factor apart from smoking. Regular physical exercise also lowers the risk of cancers of the colon and breast, the report concluded.

“The big picture now is weight management,” said one of the report’s authors, Graham Colditz, M.D., Dr.P.H., an epidemiologist at the Harvard School of Public Health in Boston and the principal investigator of the Nurses’ Health Study I. “What used to be allocated under diet now includes lack of physical activity and obesity as two of the key markers of increased risk of developing cancers.”

Cancer Deaths From Body Fat

In April 2003, researchers quantified the risk of cancer death associated with excess weight using data from the 900,000 Americans in the Cancer Prevention Study II. The authors of the study, which was published in the New England Journal of Medicine, said that overweight and obesity accounts for up to 20% of all cancer deaths in U.S. women and 14% in U.S. men. Cancer death rates were 52% higher in obese men than in normal-weight men, and for obese women, their death rate was 62% higher than their normal-weight counterparts. The
researchers concluded that 90,000 cancer deaths could be prevented if Americans maintained a healthy weight.

At the same time that researchers are attempting to measure the impact of excess weight on cancer, the Centers for Disease Control and Prevention (CDC) is trying to quantify the effect of obesity as a matter of public health—a discussion that has turned into a debate over methodology. In 2004, CDC researchers put the total number of annual deaths due to excess weight at about 400,000. Several months later, citing faulty computer-related calculations, they lowered that number to 365,000.

But a report issued this April in the *Journal of the American Medical Association* estimated that the total number of deaths due to obesity is actually much smaller than that. Using data from the National Health and Nutrition Examination Survey (NHANES) I, II, and III, the researchers found that, in 2000, obesity (a body mass index [BMI] of 30 or greater) was associated with about 112,000 excess deaths and, of these deaths, more than 82,000 occurred in people with a BMI of 35 or higher. But the researchers also found that being overweight (a BMI of 25 to less than 30) was actually associated with a reduction in mortality—86,000 fewer deaths—relative to the normal weight category (BMI from 18.5 to less than 25).

However, some researchers argue that this latest study was also flawed. It may have substantially underestimated the number of deaths caused by obesity because, critics maintain, people who are lean are often the ones who are sick, so deaths in the obese category looked to be comparatively fewer.

“It was based on a much smaller study than the ACS or Harvard cohorts and was less able to eliminate biases from tobacco smoking and concurrent illness, both of which distort the relationship between leanness and health,” Thun said.

Walter Willett, M.D., Dr.P.H., who is principal investigator of the Nurses Health Study II and the Health Professionals study at Harvard Medical School in Boston, put the issue as a “problem of reverse causation. People lose weight because of being ill, not the other way around.”

But Mitchell Gail, M.D., Ph.D., and Barry Graubard, Ph.D., two of the authors of the JAMA study from the National Cancer Institute’s Division of Cancer Epidemiology and Genetics, said that they achieved similar results when they excluded smokers from the analysis, when they excluded the first 5 years of follow-up during which sick subjects are expected to die, and when they restricted the analysis to subjects who maintained their weights for 10 years.

Gail further points out that the NHANES cohorts are randomly selected to represent the entire U.S. population, whereas the other large cohort studies all use self-selected volunteers and that conclusions about obesity and weight are often made using subsets of those cohorts. “It would be useful to see if similar trends are observed in other cohorts as in our study,” added Graubard.

The controversy about the latest CDC study rose to such a level that CDC director Julie Gerberding, M.D., called a press conference June 2 to try to address the confusion. She apologized for the inconsistencies, saying, “This risk estimation process is in its infancy, and we have a lot to learn about the best kinds of study designs.”

**No Need for Precise Numbers**

Meanwhile, if the latest estimate of 112,000 total deaths associated with obesity and the 2003 estimate of 90,000 cancer deaths associated with obesity are both correct, then cancer deaths would be the primary factor in total deaths associated with excess weight. And many say that just doesn’t add up.

One point that researchers do agree on is that, smoking aside, it is very difficult to pin a person’s actual risk of
cancer on the way he or she lives. Medical practice and health behavior constantly change, as do the food industry and people’s own habits—weight, physical activity, and food consumption may be in constant flux when seen over time.

Indeed, the estimates given for each of the influences of diet, exercise, and body weight to cancer risk “are all pretty rough; not at all precise,” said Rachel Ballard-Barbash, M.D., NCI’s associate director for the Applied Research Program. “People are just citing an old reference.”

That may be because mortality studies that link obesity to cancer death rely on imprecise methodology, Gerberding said. “We can’t get accurate estimates of the association because obesity is not listed on death records, so we have to use methods that rely on extrapolations. The studies that have been done have used different methods and different sources of information, and they’ve come to some different conclusions—so what we’ve needed to do is to get the scientists in the room and straighten this out.”

Compounding the problem is the new recognition that excess weight, at certain times during a person’s life, may be protective. For example, Willett and his group have found that the risk of developing postmenopausal breast cancer is related to weight gain in a woman after age 20, but higher BMI at the age of 18 years was associated with lower breast cancer incidence both before and after menopause. “There is no simple answer to this because the dose–response relation varies by cancer,” Willett said. “Different factors act in different time frames. We don’t have precise estimates because the answers, in part, depend on specific populations, age, and the magnitude of the obesity. Accounting for all of this is now rough.”

But Ballard-Barbash, as well as Thun, Gerberding, and others, believe that enough of a connection exists between cancer risk and these factors that research is needed into ways to modulate that risk. “Do I think it is terribly important that we know the exact percent? No. Do I think it’s substantive? Yes,” Ballard-Barbash said. Willett agrees, saying “hyperprecision is not necessary to know that obesity is a huge problem.”

For those reasons, the NCI has launched an “energy balance” initiative, led by Ballard-Barbash, which is part of a broader obesity research program undertaken by the National Institutes of Health.

The NCI program will specifically look at the intersection of diet, obesity, and physical activity as it relates to cancer risk. “Given that we all live in a world where these factors have to interact, it is important that we look at it that way,” she said.

“To wait until we fully understand everything, one can go down that road for a very long time,” Ballard-Barbash said. “We have sufficient evidence now that these factors influence a number of cancers as well as many chronic diseases.”

—Renee Twombly