Task Force has already recommended that women be screened only after age 50 years, and then every other year until age 74 years. Yet the American Cancer Society rejects that change, in favor of a more conservative, earlier protocol that recommends yearly screening for women aged 40 years and older. Some experts say that breast screening could mimic screening protocols used for prostate cancer, with "watchful waiting" recommended for lesions that don't seem to pose near-term risks.

Yet apart from the potential medical concerns Jochelson raised, legal issues are also a worry. Nancy Davidson, MD, an oncologist and director of the University of Pittsburgh Cancer Institute, said that failure to diagnose cancer ranks among the largest source of U.S. medical malpractice claims.

"That's the elephant in the room," she said.

Ultimately, new evidence will be necessary before diagnostic thresholds in mammography can be changed with confidence. Welch suggests that a prospective trial that randomizes women either to current screening protocols or to a higher-threshold approach that ignores small (and probably harmless, he said) findings could investigate differences in mortality between the two groups over time. But he concedes that the resources and expense of conducting such a trial are likely to be prohibitive, a view that Kramer and Davidson share.

The alternative, Kramer said, is to study the natural history of smaller lesions, meaning their propensity to become aggressive or not on the basis of their underlying biology. According to Kramer, two NCI research programs are now focused on the natural history of breast lesions: the Early Detection Research Network, through which dozens of organizations are investigating ways to assess newly diagnosed lesions, and a newly approved network that will compare the natural history of newly screened lesions with that of symptomatic tumors. Similarly, clinicians might increasingly rely on tools such as Oncotype DX to estimate a lesion's prognosis on the basis of its gene expression profile.

"Everyone agrees that mammography is an imperfect technology," Kramer said, "because it gives anatomic information when what we really need is more dynamic knowledge of tumor behavior."

Meanwhile, Davidson acknowledges that women can feel jerked around by growing disputes over mammography. A point to consider, Welch added, is that the decision to screen should rest with the patient rather than with an infrastructure that imposes it from above. But most women won't feel personally qualified to make that choice, so a doctor's guidance will remain crucial, Davidson said.

"It's difficult for a patient to get a mammogram without talking to a practitioner, but it's easy not to get one without that discussion," she said. "This shouldn't be a unilateral decision."

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Cancer Risk: The Fat Tissue–BMI–Obesity Connection

By Anna Azvolinsky

Just as with tobacco, policy and legislation could dramatically affect the U.S. obesity problem, according to Rachel Ballard-Barbash, MD, associate director of the Applied Research Program at the National Cancer Institute's Division of Cancer Control and Population Science.

"Research is growing on policies and environment changes related to diet, weight, and physical activity that can be used to understand the types of policies that would enable people to be physically active, to achieve weight control, and to eat healthy" Ballard-Barbash said. Released in February, the International Agency for Research on Cancer's *World Cancer Report 2014* predicted that in the next 20 years, new cancer cases will increase by about 57% each year, from 14 million to 22 million. The report predicts that cancer deaths will increase by about 59%, from 8.2 million in 2012 to 13 million in 2032.

Many of these cancers are linked to lifestyle choices, such as tobacco and alcohol use, eating processed foods, and low levels of physical activity, the report said. It also concludes that the risk of being diagnosed with esophageal, colon, pancreatic, endometrial, kidney, and postmenopausal breast cancers is higher in people with excess body fat.

Obesity-Related Cancers: It's Official

"Obesity-related cancer is now an official definition used by both the American Cancer Society and the National Cancer Institute," said Niyati Parekh, PhD, assistant professor of public health and nutrition at New York University. "But this does not mean that other cancers are not related to obesity, only that there is currently not enough evidence because the cancer is either not well-studied or rare." Only lung cancer has so far not been linked to obesity, probably because of its strong association with smoking and air quality status.

A study using Surveillance, Epidemiology, and End Results (SEER) data estimated that in 2007, 84,500 newly diagnosed cancers in US adults were due to obesity (*Cancer Detect. Prev.* 2008;32:190–9). By 2013, the authors estimated, 500,000

new cancer cases would occur if current obesity trends continued.

The latest data from the National Health and Nutrition Examination Survey (NHANES) in 2010 show that more than one-third (35.7%) of adults in the US are obese, meaning that their body mass index (BMI) is at least 30 kg/m^2 of body surface area. Almost 17% of children and teens are obese. Being overweight or obese increases risk of type II diabetes, heart disease, stroke, and some cancers.

"There is growing and strong evidence that obesity, and adult weight gain, is associated with an increased risk of several types of cancer," said Susan Gapstur, PhD, MPH, a cancer epidemiologist at the American Cancer Society.

Ties That Bind

But although oncologists, researchers, and epidemiologists have found evidence of a link between extra fat deposits and risk of cancer diagnosis, the ways that obesity contributes to cancer risk are only now emerging.

"Cancer is a multifactorial, complex disease, and obesity is one factor that contributes to the disease risk," Parekh said.

To add to the complexity, there are several potential obesity-related mechanisms that influence cancer risk and these are likely to be different for what are now termed obesity-related cancers, said Lorelei Mucci, PhD, associate professor of epidemiology at the Harvard School of Public Health.

Parekh found that consistent exposure to perturbations in glucose levels for 10 or more years increased the relative risk of a cancer diagnosis by 44% after adjustment of data for age and other variables (*Cancer Epidemiol. Biomarkers Prev.* 2013;22:1825–36). Those who had elevated blood sugar levels for 20 or more years had a 57% increased risk. The prospective study of 4,615 individuals monitored glucose and insulin levels and recorded self-reported lifestyle information. These analyses was part of the Framingham Heart Study which collected data over an almost 40 year period and originally designed to identify factors related to cardiovascular disease.

"The study explicitly recognized that metabolic disturbances over a significantly long time period may be important," Parekh said.

The common factor among diabetes, heart disease, and cancer is metabolic deregulation The findings of this study and others indicate that there may be shared risk factors for diseases such as diabetes, heart disease, and cancer. Still, more studies are needed to clarify the risk factors for these multifaceted diseases.

"But teasing out causes and links is complicated because age and genes also play a role, and there are many metabolic pathways that may be involved," said Parekh. Parekh is now working on a longitudinal study to understand how sugars and carbohydrates affect insulin levels and cancer risk.

"Research is growing on policies and environment changes related to diet, weight, and physical activity that can be used to understand the types of policies that would enable people to be physically active, to achieve weight control, and to eat healthy"

Some evidence indicates that diabetes contributes to increased risk of cancers such as endometrial, colon, and breast, potentially through insulin levels, which have been linked to cancer since the 1960s.

Several studies have established higher BMI as a risk factor for postmenopausal breast cancer, but identifying the biology of how extra weight can increase risk is still the subject of many research studies. An American Cancer Society study suggesting that low levels of adiponectin (a cytokine secreted by fat cells) and high levels of C-reactive protein and insulin-like growth factor 1—all obesity-related blood biomarkers—are associated with increased breast cancer risk (*Int. J. Mol. Epidemiol. Genet.* 2013;4:156–66). The study hints that breast tumor formation is influenced by a high-insulin state that is a symptom of type II diabetes.

Location of fat deposits may matter for cancer risk. A National Institute on Aging (NIA) study reported that men aged 70–79 years, even those with a normal BMI, who have visceral abdominal fat deposits have a higher risk of obesity-related cancers. For older women, overall BMI conferred risk of cancer diagnosis.

Rachel Ballard-Barbash, MD

"It's not just a healthy BMI but also a risk of carrying fatty tissue in specific depots that seems to be important, according to our study," said lead author Rachel A. Murphy, PhD, of NIA's Laboratory of Epidemiology and Population Sciences.. She and her colleagues are now studying how fat cells may influence tumorigenesis, including whether inflammation in this tissue type can confer cancer risk.

Such studies suggest that for risk of cancer or other chronic disease, it's not as simple as saying that being overweight is bad and having a normal weight is good. Normal-weight adults can develop type II diabetes, for example, if they are metabolically obese as characterized by triglycerides and insulin levels (*JAMA* 2012;308:581–90).

"There is such a thing as 'metabolically healthy obese' and 'metabolically unhealthy obese,'" said Ballard-Barbash. Researchers are only beginning to define the metabolic characteristics of these subgroups and explore the relation to cancer risk.

These studies suggest that BMI is only an initial measurement and that including more detailed fat deposit information and metabolic biomarkers will yield more information on a population and individual level.

"BMI is a convenient measurement for large epidemiology studies that rely on self-reported information. But smaller studies that are examining mechanisms by which obesity may influence cancer risk are using other measures, such as leptin

or adiponectin in the blood that are associated with fat mass, and measures of fat such as computed tomography. However, these more expensive technologies are not feasible for use in large population studies," Ballard-Barbash said.

A Tangled Web

Besides discouraging tobacco use, recent American Cancer Society guidelines recommend maintaining a healthful weight, staying physically active, and eating a healthy diet—all of which are thought to reduce lifetime risk of developing or dying from cancer.

Over the last 20 years research and exploded on how physical activity influences cancer risk and prognosis, said Ballard-Barbash, to think that researchers can fully untangle the effects of healthy behaviors such as weight control, diet, and exercise is naïve. "Both diet and physical activity are key components of weight control; the two cannot be truly separated."

Chronic diseases, including cancer, can take 20–50 years to develop through multiple insults over a lifetime. Body weight during adolescence or childhood may affect cancer later in life. But a large gap, which remains to be filled is how obesity and nutritional risk factors that have complex and changing pattern of exposure over the course of one's life affects cancer risk, according to Parekh.

"If you are obese for a major portion of your adult life, does this stay with you, or is your risk of cancer reduced if you lose weight and keep it off?" said Gapstur. Little research on this question exists, and on the potential benefits of weight loss, she said, partly because of the difficulty of sustaining weight loss.

That's precisely the question Murphy now wants to study: how changes in fat tissue and fluctuations in weight affect cancer risk.

"This type of study would partly address how cumulative effects of lifelong obesity and changes in weight are linked with cancer risk," Murphy said.

"Randomized, controlled trials suggest that there are some benefits of modest weight loss of about 10 pounds when it comes to heart disease, diabetes, and hypertension but how long the benefit lasts if weight is regained is not clear," said Ballard-Barbash. "For cancer risk, we think it may be beneficial to maintain a healthy body weight, but whether a few episodes of small weight loss reduce risk is not known because there is no clinical trial evidence of whether weight loss will reduce risk or improve prognosis."

Informally observing the interaction of clinicians and patients (both cancer survivors and noncancer patients) in clinics and offices, Parekh said that obesity and unhealthy food habits by healthcare professionals may prevent them from bring up obesity and recommending changing diet and exercise habits to their patients.

"We need individual, targeted counseling for patients. Despite a lot of work to understand obesity trends and general policy and messaging efforts we haven't seen many changes—yet."

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Nuts May Lower Cancer Risk

By Mike Fillon

During the last decade, studies have sporadically linked nut consumption with a decreased risk of, and as potential therapies for, many diseases. Several new studies, including one in the November 13, 2013 issue of The *New England Journal of Medicine (NEJM)*, have found that people who ate a daily handful of nuts were significantly less likely to die from any cause than those who never ate nuts. The researchers found that of the 521,763 study subjects that reported they never ate nuts, versus the 164,042 who ate nuts five of more times per week, that over a 30-year-period, there were 5,203 deaths among those who never at nuts versus 1746 deaths from those who ate nuts daily.

The biggest gain was for cardiovascular deaths; the study found 1,355 deaths for the non-nut eaters, versus 457 deaths from those who ate nuts daily. For cancer, the results were also pronounced; there were 1,883 reported deaths for the non-nut eaters versus 632 for those who ate nuts daily.

Lead author of the *NEJM* study, Ying Bao, MD, associate epidemiologist at Brigham and Women's Hospital and Harvard Medical School, said that earlier observational and intervention studies of nut consumption uncovered reductions in many chronic disease triggers, including oxidative stress, inflammation, visceral adiposity, hyperglycemia, insulin resistance, and endothelial dysfunction. Also, prospective cohort studies associated increased nut intake with reduced risks of type 2 diabetes mellitus, metabolic syndrome, colon cancer, hypertension, gallstone disease, diverticulitis, and death from inflammatory diseases.

"Despite these inverse associations between nut intake and several major chronic diseases," said Bao, "few studies have investigated nut consumption in relation to total mortality."

She added that investigations have often been limited by small samples, single assessment of diet and other covariates, or inadequate adjustment for important confounding factors. To overcome these limitations, Bao and colleagues examined nut consumption in relation to total and cause-specific mortality in two large, independent cohort studies of nurses and other health professionals. The Nurses' Health Study supplied data on 76,464 women between 1980 and 2010, and the Health Professionals' Follow-up Study yielded data on 42,498 men from 1986 to 2010. Study participants filled out detailed food