that it will be adopted is also very high,” Conti said.

**Diffusion Rates Uneven in the Population**

Still, the uptake even of new drugs for lethal cancers with limited therapeutic options may not distribute equally across the population. For instance, in the new docetaxel study diffusion rates were lower among blacks, older patients, and patients living in lower socioeconomic settings than among younger, more affluent patients with advanced prostate cancer. Why that’s so isn’t well understood. But the finding is consistent with other studies showing that some patient groups have less access to new therapies than others. For example, Robin Yabroff, Ph.D., an epidemiologist in NCI’s Division of Cancer Control and Population Sciences, and colleagues found that older, less educated patients with renal cell cancer were less likely to be treated with newer systemic therapies. Similarly, the researchers found that older, unmarried patients were less likely to receive adjuvant and concurrent temozolomide treatment with radiotherapy after surgery for glioblastoma, after randomized clinical trials published in 2005 showed that the drug improved overall survival.

Yabroff said that limitations in existing data can constrain efforts to understand diffusion rates in the population. Investigators rely by necessity on longitudinal medical claims data or medical encounter data that, she said, are “geared more for reimbursement purposes than research.” Far more is known about diffusion in the Medicare population—which can be studied using resources such as the SEER–Medicare linked database—than in younger patients, especially in patients who lack insurance. Without medical claims data, the timing and receipt of cancer care among uninsured patients can be challenging to assess, Yabroff said. Groups such as NCI’s Cancer Research Network, a consortium of research groups affiliated with nonprofit health care delivery systems, are evaluating the diffusion of new treatments more comprehensively.

Of particular interest in diffusion research is how expert bodies such as the National Comprehensive Cancer Network affect diffusion of new treatments, especially in off-label settings. Hershman acknowledged that recommendations issued by these groups in their published compendia are needed because requiring a separate FDA indication for every new use of a drug would overwhelm available resources.

“Even when FDA hasn’t approved an indication, most payers will reimburse on the basis of compendia recommendations,” said Gary Lyman, M.D., an oncologist at Seattle’s Fred Hutchinson Cancer Research Center. “And that’s a way to deal with the resource problem—it’s a newer trend, building during the last 5 years or so.”

Yet according to Hershman, the resources savings afforded by compendia may also impose a cost in terms of quality review. Investigations have shown that some compendia lack transparency or cite limited evidence in their recommendations, which is troubling considering that benefits from treatment are not a foregone conclusion and that off-label uses can carry a high sticker price. Conti’s research reveals that nearly half of the $6 billion–$7 billion spent on just 10 chemotherapy regimens in the United States goes toward paying for off-label uses.

“We’ve got a reimbursement system that allows doctors to experiment on patients when there is some evidence to support the application of a new therapy, but not randomized-control evidence,” she said. “And it is entirely possible that by using drugs in an off-label setting, some patients will benefit and the scientific community will learn from their experience. But when these drugs are priced high relative to benefit, some people will get nervous and upset.”

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**New Evidence for Link Between Coffee and Risk for Endometrial Cancer**

By Sue Rochman

Applying a technique used to link genes to disease risk, a new study associated coffee consumption with decreased risk of endometrial cancer. The finding adds to the evidence that coffee contains compounds that may reduce risk for several diseases, including cancer.

The February 2015 study in Cancer Epidemiology, Biomarkers, and Prevention (doi:10.1158/1055-9965.EPI-14-0970) first used a “nutrient-wide association” approach to look for relationships between cancer risk and 84 foods/nutrients in data collected from 301,107 women in the European Prospective Investigation into Cancer and Nutrition (EPIC) study.

“Our study was different from previous research because we didn’t set out to specifically investigate the association between coffee consumption and endometrial cancer risk,” said Melissa A. Merritt, Ph.D., research fellow in cancer epidemiology at Imperial College London. “Instead, we used the nutrient-wide association study method to evaluate an extensive list of dietary factors.”

The analysis linked consumption of 10 items to endometrial cancer risk. Butter, yogurt, potatoes, and carbohydrates were associated with increased risk; cheese, coffee, cream desserts, total fat, monounsaturated fat, and phosphorus were associated with decreased risk.

To confirm these findings, the researchers then looked for a relationship...
between nine of those items (excluding cream desserts) and endometrial cancer risk in data collected from 155,406 women in the Nurses’ Health Studies (NHS). This nutrient-wide association study confirmed that higher coffee consumption was associated with lower risk for endometrial cancer. No other associations were confirmed.

A total of 2,834 women reported an endometrial cancer diagnosis in the EPIC and NHS studies. Women in the EPIC cohort who drank about three cups of coffee per day had a 19% lower risk for endometrial cancer than those who drank less than one cup. In the NHS cohorts, women who drank about four cups of coffee per day had an 18% lower risk than those who never drank coffee.

“This study confirmed observations from many—but not all—previous studies that found having a high versus low intake of coffee may be associated with a lower risk for endometrial cancer,” Merritt said.

The nutrient-wide association approach used in the study has its roots in methods developed for genomewide association studies, which look for genetic variation that may increase a person’s risk of developing certain diseases. In these genetic studies, researchers study single-nucleotide polymorphisms. In a nutrient-wide association study, each food or nutrient is akin to a single-nucleotide polymorphism in a genomewide association study.

“The approach is useful for foods and nutrients because it allows us to test an extensive list of foods and nutrients while controlling for multiple comparisons, and by testing the significant findings in independent cohorts this provides additional confidence in the study results,” Merritt said.

Susanna C. Larsson, Ph.D., associate professor at the Institute of Environmental Medicine at Stockholm’s Karolinska Institutet, said she believes a nutrient-wide association study “provides a higher level of confidence in the observed findings.” She also said she expects to see it used more in future studies.

But Walter Willett, M.D., Dr.P.H., professor of epidemiology and nutrition and chair of the department of nutrition at the Harvard School of Public Health in Boston, said he doesn’t see this approach as “a major step forward.”

A nutrient-wide association study “has some of the strengths and some of the major weaknesses of the kind of analysis done in genomewide association studies,” said Willett, principal investigator of the second NHS. “It may be useful in some specific applications, but it really is not that different than a lot of routine exploratory analyses that have been done before” and then replicated in another data set. Also, connecting disease to a food item is more complicated than connecting a disease to genetics. “There is very little confounding by other factors in genetic studies,” Willett said, but it is inherent in studies of diet and disease risk.

“The approach is useful for foods and nutrients because it allows us to test an extensive list of foods and nutrients while controlling for multiple comparisons, and by testing the significant findings in independent cohorts this provides additional confidence in the study results.”

Endometrial cancer is the fourth most common cancer in U.S. women, accounting for about 7% of all female cancer diagnoses. The American Cancer Society estimates that 54,870 women will be diagnosed with, and 10,170 will die of, this cancer in 2015. Risk factors for endometrial cancer include obesity; diabetes; and use of menopausal hormones, birth control pills, tamoxifen, or intrauterine contraception. According to the society, overweight or obese women have a risk up to 3.5 times greater of being diagnosed with endometrial cancer than that of women who have a healthy weight. Studies have also associated higher levels of physical activity with lower endometrial cancer risk.

Many researchers, including Larsson, have studied the relationship between coffee consumption and disease risk. Overall, “coffee consumption does not seem to reduce the risk of other cancers and total cancer mortality,” she said. Yet “coffee in moderate amounts has not only been shown to be inversely associated with risk of endometrial and liver cancer but also with risk of type 2 diabetes and cardiovascular disease.”

Willett said he believes the evidence is now strong enough to support a modest association between coffee and decreased endometrial cancer risk. He also noted that conducting—let alone getting funding for—the type of randomized study that might move the association from correlation to causation would be difficult.

“This is a cancer that, while moderately common, has very low mortality, and coffee is likely to have only a modest protective benefit,” Willett said. “If we are deciding where to put resources, then it is more important to study the relationship between coffee and diabetes and cardiovascular disease, which affect a bigger population. That research also may help us learn more about whether coffee reduces endometrial cancer risk, but we already know that whatever effect coffee has on reducing that risk, it’s minor compared to the increased risk of being overweight or obese.”

Even so, Merritt said, her research group intends to investigate molecular mechanisms that may link coffee with lower risk of endometrial cancer. They also are using the nutrient-wide association approach to identify links between diet and other cancers in the EPIC study.