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Using an Ocean of Data, Researchers Model Real-Life Benefits of Cancer Screening

Randomized clinical trials are widely acknowledged as the best way to determine whether a cancer screening test saves lives. But even when trial results indicate that a particular screening method has a clear benefit, the findings may not be easily translated into recommendations for the public. The results of a screening trial may apply only to certain people, and the findings can change as the study period lengthens—all of which means that the results may not apply to the general population.

CISNET runs enormous amounts of data through computer models to identify the best way to implement screening for different types of cancer.

For example, the National Lung Screening Trial (NLST) showed that screening of current or former heavy smokers with three annual low-dose spiral CT scans can reduce their risk of dying from lung cancer. But NLST enrolled only people aged 55 to 74 who had smoked for 30 pack years and had quit less than 15 years previously.

“Would a similar screening regimen also benefit younger or older smokers? Would lighter smokers benefit equally? And when should they start and stop screening?” asked Dr. Eric “Rocky” Feuer, scientific coordinator of NCI’s Cancer Intervention and Surveillance Modeling Network (CISNET). Patients and doctors alike will almost certainly ask these questions.

CISNET’s five research teams use modeling to try to answer these types of questions for several different cancer types. Using the results of screening trials, the teams are trying to estimate the true benefit of screening in the general population and to identify the optimal way to implement screening within the health care system.

The teams’ extremely complex computer programs, which for some cancer types (such as breast and colorectal) have been used and constantly refined for over a decade, incorporate a wide variety

of information. This information includes not only trial data but observational data, epidemiologic data, and information on the natural history of each cancer type.

One of CISNET's original mandates was to tease out the role that screening has played in the observed decline in deaths from some cancer types over the last few decades. In a landmark 2005 paper in the *New England Journal of Medicine*, CISNET researchers determined that screening mammography likely accounted for half of the 24 percent decrease in breast cancer mortality that was observed between 1989 and 2000.

From there, the teams moved to providing data that inform screening guidelines, said Dr. Feuer. In 2008, the United States Preventive Services Task Force (USPSTF) used a CISNET modeling study as part of the evidence behind the update of its screening recommendations for colorectal cancer. In 2009 a similar modeling study was used to update the USPSTF mammography screening recommendations. Now, CISNET teams are trying to help resolve some of the questions emerging from screening trials in lung, prostate, and esophageal cancer.

Matching the Population Experience

A major goal of the CISNET lung cancer team is to "integrate the NLST results into general practice," said Dr. Pamela McMahon of Massachusetts General Hospital, the principal investigator of the lung cancer team, which also includes researchers from five other universities. "We have to extrapolate from the limited scenario of the NLST, because that [trial] doesn't match the population experience." (See "After Landmark Study, Exploring Questions about Lung Cancer Screening.")

"We're looking at every permutation you can think of: ages to start screening, ages to stop screening, how many pack years [smoked], how many years since quitting, how frequently to do the screens," said Dr. McMahon.

The team is aided by access to data on every single patient enrolled in NLST as well as every patient in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO), also funded by NCI.

Once the results are complete, the researchers hope to use them to create an interactive projection tool that will let policy makers see how implementations of different lung cancer screening programs in their community would alter lung cancer mortality, similar to the mortality projection tool produced by the CISNET colorectal cancer team.

Two Enormous Trials, Two Different Results

The three research groups in the CISNET prostate cancer team are tackling an equally ambitious, although entirely different problem. Two large randomized clinical trials of prostate cancer screening—one in the United States and one in Europe—have generated long-term data on how screening may affect prostate cancer mortality. And the two trials had different results.

In the European Randomized Study of Screening for Prostate Cancer (ERSPC), men who were screened for prostate cancer were less likely to die from prostate cancer than men who were not screened. That was not the case in the PLCO trial, which found that men who were screened did not have a lower risk of dying from prostate cancer than unscreened men. The trials were conducted very differently, and each had limitations, including a large number of unscheduled screenings (referred to as "contamination") in the control group of the PLCO trial and a lack of standardized cancer treatment in ERSPC.

“So the question that we’re trying to answer is whether there is a range of screening benefits that is consistent with the results of both trials,” said Dr. Ruth Etzioni of the Fred Hutchinson Cancer Research Center, principal investigator of the CISNET prostate team. Researchers from both trials have allowed the CISNET team access to all of their data, down to the level of each individual patient, to resolve whether screening reduces prostate cancer deaths.

The CISNET team has spent years modeling the natural history of prostate cancer. “We can’t see when a person’s cancer begins…but we can see how disease is diagnosed in the population, at what ages people get diagnosed, and at what stages they get diagnosed. All of that informs us about what’s happening at a somewhat-below-the-surface level,” explained Dr. Etzioni.

The prostate modeling groups will use their knowledge of the natural history of prostate cancer and overall health and life histories of men in the United States “to ‘replicate’ what happened in ERSPC and PLCO on top of those life histories and disease histories,” Dr. Etzioni elaborated. “And when we replicate the two trials we’ll see if there is a range of true benefit, where we get something reasonably close to what was observed in both trials.”

The team is also beginning to look at how immediate versus delayed treatment may change the benefit/harm ratio of prostate cancer screening and at how the prevention of endpoints other than mortality—such as metastatic disease—may also alter that ratio. (See "Benefits and Harms of Prostate Cancer Screening.")

Modeling Targeted Screening

For the first 10 years of the program, CISNET focused on four of the most common cancers in the United States: breast, prostate, lung, and colorectal. In 2010, it added a less common cancer—esophageal—which presents a different set of issues: determining how to screen for a cancer in a subpopulation of people with well-known risk factors for the disease.

“Esophageal cancer is not common enough to do population-based screening, but [doctors do] targeted screening based on individual risk,” explained Dr. Chin Hur of Massachusetts General Hospital, principal investigator of the esophageal cancer team.

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—Dr. Chin Hur

“We chose a less common cancer [to include in CISNET] because the effort that we go through to find a relatively few esophageal cancers is incredibly inefficient,” commented Dr. Feuer. Although gastroesophageal reflux disease and a related condition called Barrett esophagus are known risk factors for esophageal cancer, relatively few people with either problem will develop the disease.

But doctors do not yet know how to identify which people with these conditions are most likely to develop esophageal cancer and may, therefore, benefit from targeted screening. “There’s huge potential to do things better,” said Dr. Feuer. The goal for the CISNET team is “to come up with cost-effective strategies to diminish the morbidity and mortality from esophageal cancer,” added Dr. Hur.

The esophageal team is developing three models using existing clinical trial data and is collaborating with modelers working at the molecular level of cancer. This so-called “multiscale modeling” will let the team build a more accurate representation of the natural history of esophageal cancer into their models. Once the models have been finalized, the researchers will use them to virtually “re-run” and analyze trials not only of endoscopic monitoring and radiofrequency ablation in people with Barrett esophagus but also other emerging strategies for preventing the progression of esophageal cancer.

Although endoscopic screening and radiofrequency ablation of Barrett esophagus have been tested in many smaller clinical studies, these trials have nowhere near the numbers of patients—or, therefore, the statistical power or general applicability—that large screening trials for breast, prostate, lung, and colorectal cancer have.

This poses a paradox for the modelers and for the esophageal cancer research community in general: “Where there is less clinical trial data available, there’s more uncertainty about the projections. At the same time, there is less data around to inform both clinical decision making and policy, so our results are more important. So, although there’s more uncertainty about [modeling], there’s also more need for it,” summarized Dr. Hur.

“We need to be very open and transparent about the limitations, explore those fully, and be careful about the conclusions of our analyses,” he said. “But [modeling] is better than someone just taking a best guess. It’s a systematic approach, with intense peer review and multiple modeling groups, that tries to distill the evidence that is out there.”

—*Sharon Reynolds*