Collaboration Is Key to Treating Uncommon Cancers

Scientists and patients champion research in these rare diseases


Dr. Hammer reviews an x-ray from a patient with adrenal cancer.

When, as a freshman in college, Josh Sommer was diagnosed with a rare malignant bone cancer called chordoma, there was no drug known to be effective in fighting the disease, and survival statistics were grim.

But Sommer, aided by his mother, a physician, was not ready to give up. Instead, he and his mother founded the Chordoma Foundation in 2007 to gather input from experts worldwide to rapidly develop effective treatments for the disease. At the same time, Sommer began working in the laboratory of 1 of those experts, Michael Kelley, MD, of Duke University in Durham, North Carolina, to help discover genes that may play a role in chordoma.

"Rare diseases need a champion, usually a doctor or a patient," says Gary Hammer, MD, PhD, an endocrinologist and the Millie Schembechler Professor of adrenal cancer at the University of Michigan Comprehensive Cancer Center in Ann Arbor, Michigan. He is a champion of research into the rare and very deadly adrenocortical carcinoma. Such champions—whether they are a patient or scientist—work to create public awareness of the disease, support and educate patients, recruit patients for clinical trials, gather experts in the field, and raise research funds.

Key Points

- Research on rare cancers faces unique challenges, including obtaining enough specimens for studies and getting government and pharmaceutical companies to do research.
- One challenge is agreeing on a definition of what constitutes a rare cancer.
- A first-of-its-kind NIH workshop recently explored ideas for advancing research into rare cancers, including developing centers of excellence and international collaborations and providing incentives to the pharmaceutical industry.
- The Kennedy-Hutchison Cancer Bill, which includes a section on ultra-rare cancers, was stalled by healthcare reform and was still waiting to be reintroduced into the Senate at press time.

Experts Gather to Tackle Rare Disease

Both Sommer and Dr. Hammer participated in a National Institutes of Health (NIH)–sponsored workshop in December 2009 that was the first of its kind to address the challenges of research into the prevention and treatment of rare cancers.

Sponsored jointly by the NIH Office of Rare Diseases Research and the Division of Cancer Prevention at the National Cancer Institute (NCI), the workshop brought together experts from across the country to discuss ways of facilitating scientific collaborations and building new research programs in this emerging field. Approximately 200 participants—including scientists, clinicians, representatives from industry and government, and patient advocates—gathered for the day-and-a-half workshop.

The late US Senator Edward M. Kennedy (D-Massachusetts) had drafted language proposing that the NCI Early Detection Research Network consider a subcommittee for rare cancers, but the legislation was delayed by healthcare reform efforts, according to Sudhir Srivastava, PhD, MPH, chief of the cancer biomarker research group in the Division of Cancer Prevention at NCI, who helped organize the December workshop. "So we asked what we could do to accelerate research," he says, adding that the NIH meeting was the result. Participants hope it will be the first of several meetings that will help chart a course for improving research into rare cancers. According to physicians who deal with rare cancers, the challenges are many, including:

- Lack of necessary specimens to conduct research;

- Lack of incentives for the government and pharmaceutical industry to invest in research because, with small patient populations, there does not appear to be much return on investment;
- Few available research results to build on and develop future studies;
- An inability to obtain grant funding for research because many NIH/NCI peer-review teams do not have an expert in rare cancers; and
- Lack of incentives for researchers to study a rare cancer because little funding is available and research is often centered in 1 location.

Deadly Cancers Need Attention, Too

Although rare cancers certainly need attention, so do the biggest cancer killers, some of which are fairly common, say several advocacy organizations. "In 1971, the overall survival rate for all cancers together was 50%, and a number of cancers still haven't reached that benchmark," says Megan Gordon Don, director of government affairs for the Pancreatic Cancer Action Network and chair of the Deadly Cancer Coalition.

Don testified before the US House Subcommittee on Health about the importance of supporting research for these cancers, which together caused nearly half of the 562,340 estimated cancer deaths in 2009. These cancers and their survival rates include: ovary (45.5%), brain (35%), myeloma (34.9%), stomach (24.7%), esophagus (15.2%), liver (11.7%), and pancreas (5.1%).

Because the number of pancreatic cancer cases has surpassed 40,000 annually, the disease is not considered rare, and yet it is clearly deadly, with few treatment options, Don notes. In addition, the deadliest cancers are expected to increase dramatically in the next 20 years, she adds, citing the following projections published in the *Journal of Clinical Oncology*: lung cancer is expected to increase by 52%, pancreatic cancer by 55%, liver cancer by 59%, and stomach cancer by 67%.[1] "All of these deadly cancers are underfunded, and there are few early detection tests or treatments. For many, we don't even have agents that we're testing," Don says.

Deadly cancers face some of the same hurdles as rare cancers in terms of obtaining research funding, according to Don. Pancreatic cancer, for example, receives less than 2% of the NCI's nearly $5 billion budget, whereas less than 18% of the NCI's 2008 research budget was dedicated to the 8 deadly cancers, she notes. In Don's testimony to Congress and in a request to the NCI, the Deadly Cancer Coalition called for the creation of a targeted cancers program focused on deadly cancers, a strategic plan for deadly cancer research, a dedicated grant program, and expert review of grants for these cancers.

Reference

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NIH participants addressed the importance of developing rare cancer "centers of excellence" that span the entire spectrum of basic science discovery, translational research, and clinical care. The University of Michigan's adrenal cancer program, which has advanced research in the disease, has been cited as an example of such a center. Approximately 600 people in the United States are diagnosed annually with adrenal cancer, and Michigan's center is 1 of only 4 multidisciplinary clinics nationwide that treat these patients, seeing approximately 25% to 50% of US patients, as well as patients from Europe and Hong Kong.

The growth of the Internet has helped adrenal cancer patients from across the country find centers such as that at the University of Michigan. And because of the numbers they see (10 to 15 patients per week), Dr. Hammer and colleagues have developed an expertise in treating the disease. In addition to their clinical work, they focus on understanding the molecular genetics of adrenal cancer in an effort to develop targeted therapy. For example, they currently are studying adrenal stem cells based on the hypothesis that defects in stem cells are what lead to cancer formation. (Currently, the only approved treatment for adrenal cancer is mitotane, a derivative of the pesticide DDT, which was approved in 1959.)

In addition, the University of Michigan's adrenal cancer program and other centers specializing in the disease began holding international adrenal cancer meetings in 2003, creating an international consortium of researchers and physicians that has led to the first clinical trials in adrenal cancer in 50 years. Such international collaborations are essential because they play a vital role in collecting biosamples, pooling scientific expertise, training new investigators, linking to advocacy groups, and sharing new ideas and discoveries, according to Dr. Srivastava.

For example, adrenal cancer researchers at the University of Michigan and elsewhere are investigating the role of the insulin-like growth factor 2 (*Igf2*) gene, which is mutated in adrenal cancer. They are using a monoclonal antibody to target a receptor in *Igf2*, essentially blocking the receptor's ability to activate the cancer cell. Adrenal cancer is 1 of only a few malignancies that appear to be driven by the *Igf2* genetic mutation, according to Dr. Hammer.

Champions of Research for Rare Cancer

Not every rare cancer has a champion or a significant funding source, however. That is 1 reason why Senator Kennedy supported the portion of the Kennedy-Hutchison Cancer Bill that supported the advancement of ultra-rare cancer research. Although tabled until healthcare reform was completed, at press time the bill was expected to be reintroduced in the Senate and introduced for the first time in the House of Representatives by Lois Capps (D-California). In the Senate, Chris Dodd (D-Connecticut) will take Senator Kennedy's place in cosponsoring the legislation along with Kay Bailey Hutchison (R-Texas).

"Senator Kennedy was 1 of the biggest champions of the disenfranchised, and rare cancer patients are truly orphans without any voice or any good therapy," says Dr. Hammer, who was consulted as an expert for the ultra-rare cancers section of the bill. "To him, it was the most important part of the bill."

What Qualifies a Cancer as Rare?

Even the definition of what constitutes a rare cancer is tricky because under the Rare Diseases Act of 2002 and the US Orphan Drug Act, a rare disease or condition is defined as affecting fewer than 200,000 people per year, which would include approximately 95% of all cancers. Conversely, the American Cancer Society defines rare cancers as affecting 40,000 or fewer people per year. Adding to the confusion, the term "rare cancer" has never been legislatively defined. "We need to come to terms on rare cancers and decide the incidence number that defines them," says Dr. Srivastava.

However, that subject was tabled at the NIH workshop in favor of discussions on what can be done in the areas of etiology/biology of rare cancers, how to accelerate clinical trials, and how to develop an infrastructure of research support.

Meanwhile, supporters of the ultra-rare cancer section of the Kennedy-Hutchison bill chose to focus on cancers that affect fewer than 1 in 100,000 people per year. In 2009, that number would be approximately fewer than 3000 new cases per year. However, a number of other types of cancers fall within the proposed definition, including variants of commonly occurring cancers that are characterized by a specific genetic abnormality or a specific biologic behavior that is different from the typical biological behavior of that common cancer, or variants of commonly occurring cancers that are confined to a specific demographic, ethnic group, or etiology. The goal of the bill is to "level the playing field" for people with extremely rare cancers, Dr. Hammer notes. Among its original provisions were:

- Funding and designating ultra-rare cancer centers of excellence that can coordinate collaborative research nationally and internationally, sponsor symposia, implement training programs in clinical care and research, and make available specimens for research;
- Enabling access to such centers of excellence for patients with ultra-rare cancers, and requiring insurance companies to cover their care;
- Providing incentives for clinical trial enrollment by reserving a percentage of enrollment slots for patients with ultra-rare cancers;
- Providing incentives to the pharmaceutical industry to research and market drugs for ultra-rare cancers;
- Developing an ultra-rare cancer registry and national tumor bank, to be maintained by 1 or more rare cancer centers of excellence; and
- Creating NCI scientific review groups with expertise in ultra-rare cancers to review research proposals in the field.

Although those in the rare cancer community have a unique set of challenges, Dr. Hammer remains optimistic about the progress they are making. "I'm incredibly hopeful," he says. "I wouldn't be in this business where 95% of patients die within 5 years if I didn't have hope that we'll find effective treatments. I believe we're on that road now."

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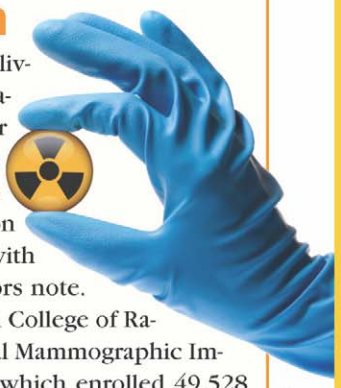
Study Finds That Digital Mammography Delivers Less Radiation



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The overall radiation dose delivered by digital mammography is an average of 22% lower than that of conventional film mammography, according to a recent study.[1] The reduction could be lower in women with larger, denser breasts, the authors note. The data are from the American College of Radiology Imaging Network Digital Mammographic Imaging Screening Trial (DMIST), which enrolled 49,528 women and was published in 2005. The original study concluded that digital mammography detected up to 28% more cancers than film mammography in women aged younger than 50 years and in women with dense breasts.

The current DMIST study included an evaluation of 5102 participants and demonstrated that the radiation dose received by women who had undergone digital mammography was significantly lower than that received by the same women with standard film mammography. The average breast radiation dose per view was 2.37 milligrays (mGy) for film mammography versus 1.86 mGy for digital mammography, according to R. Edward Hendrick, PhD, lead author of the study.

Although the radiation doses from both screening methods are low, this is another advantage to digital mammography, which is continuing to become more widely available, Dr. Hendrick notes, adding that greater than 60% of breast imaging facilities in the United States now offer the screening technology.

Reference

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