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In 2002, another IARC working group associated five cancers—colon cancer, breast cancer, endometrial cancer, esophageal adenocarcinoma, and renal cell carcinoma—with being overweight or obese. The new report adds stomach, liver, gallbladder, pancreas, ovary, and thyroid cancers to the list, as well as multiple myeloma and meningioma (N Engl J Med 2016;375:794–8).

After reviewing more than 1,000 epidemiologic studies on cancer risk and excess body fat, the group concluded that the risks were similar for men and women and consistent across different geographic regions. They noted a particularly pronounced association between obesity and esophageal adenocarcinoma: The risk was nearly five times greater for adults with a BMI of 40 or higher, compared with those of normal weight.

Graham Colditz, MD, DrPH, the group's chair and a cancer prevention expert at Washington University School of Medicine in St. Louis, MO, explains that obesity promotes chronic inflammation and various metabolic and endocrine abnormalities, including the overproduction of estrogen and testosterone, as well as altered insulin signaling, all of which influence carcinogenesis.

"We'd like to find potentially modifiable risk factors—for instance, druggable pathways—to benefit people who may not be able to easily change other lifestyle-related factors for various reasons," he says.

Nonetheless, intentional weight loss is important and beneficial, Colditz emphasizes. Data from follow-up observations of women who underwent bariatric, or stomach size-reducing, surgery suggest that losing weight significantly lowers the risk of endometrial and breast cancers. "It's a signal," he says. "Still, because most people who lose weight don't keep it off, accurately measuring the long-term beneficial effects has been difficult. We'd really like to gather more evidence from larger studies of sustained weight loss."

To that end, Colditz hopes a recently launched clinical trial at Dana-Farber Cancer Institute in Boston, MA, will be fruitful. Oncologist Jennifer Ligibel, MD, has partnered with Fitbit to recruit approximately 3,200 overweight or obese women with early-stage breast cancer through oncology practices across the United States and Canada. Participants will receive fitness-tracking devices and phone counseling to assist in meeting their weight-loss goals; they'll also be followed to assess whether losing weight prevents disease recurrence.

Overall, Colditz sees similarities between documenting the roles of excess body fat and smoking, respectively, in cancer risk. "It took a while for us to understand that smoking is associated with multiple cancers, not just lung, due to the accumulation of toxins over a lifetime," he observes. "I think the same will be true as we learn more about the molecular mechanisms affected by being overweight or obese."
–Alissa Poh ■

Unfurling the Genetic Map of Sarcomas

An international team led by the Garvan Institute of Medical Research in New South Wales, Australia, has uncovered multiple new germline mutations that may influence the development of sarcomas. Their findings suggest "a large, clinically significant, and under-recognized burden of genetic risk" in these connective-tissue cancers (Lancet Oncol 2016;17:1261–71).

The researchers obtained blood or saliva samples from 1,162 patients with 32 sarcoma subtypes, and carried out targeted exon sequencing of 72 genes selected for potential associations with cancer risk. They discovered that 55% of patients carried known or likely pathogenic germline mutations in at least one gene. However, only 155 (13.3%) patients fulfilled criteria for a family history of known cancer-predisposing disorders such as Li-Fraumeni syndrome, which is driven by germline *TP53* mutations and characterized by early-onset soft-tissue sarcomas, among other cancers.

"This suggests that sarcomas are more hereditary than previously thought, but familial patterns alone may be insufficient to determine risk," says senior author David Thomas, MD, PhD.

Germline variants in several DNA damage sensing and repair genes, including *BRCA2*, *ATM*, *ATR*, and *ERCC2*, contributed greatly to sarcoma risk, the researchers reported. Among patients given radiation for their primary cancer, which results in treatment-induced DNA damage, the high probability of developing a secondary sarcoma is well established. Therefore, "in retrospect, our finding makes sense," Thomas says. "These genes were not previously linked with sarcomas, however, other than anecdotally in the case of *BRCA2*. And *ERCC2* was a total surprise; until now it's only been associated with risk for skin cancers."

The team also found that approximately one fifth of study patients carried germline variants in multiple genes—two to six, on average. These individuals received their first cancer diagnosis at a median age of 25 years, compared with 32 years for those with mutant *TP53*, "the strongest known sarcoma gene," Thomas says. "This suggests a polygenic contribution to sarcoma risk, and more variants in a given individual appear to be associated with earlier onset of cancer."

To Gary Schwartz, MD, deputy director of the Herbert Irving Comprehensive Cancer Center at Columbia University in New York, NY, "this study shows the absolute importance of conducting not only somatic, but also germline mutation analyses, in patients with sarcoma."

Schwartz notes that many of the implicated genes are already druggable: PARP inhibitors may be effective against *BRCA2* variants, for instance, whereas *ATM* and *ATR* variants may benefit from drugs targeting cell-cycle checkpoints such as WEE1 or CHK1. Mutations in *ERCC2* render cells more sensitive to cisplatin, he adds, so this drug—not commonly used to treat sarcomas—may be another therapeutic option.

"Germline mutations are still greatly underappreciated as a source of biomarkers for targeted therapy," Thomas agrees.

The next steps for Thomas's team include evaluating still more patients with different sarcomas to better parse the genetic signals specific to each subtype. Acknowledging that targeted exon sequencing is inherently biased, he says they'll use a whole-genome approach instead, which could reveal

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many more pathogenic germline variants. *–Alissa Poh* ■

Group Aims to Make 1,000 Cancer Cell Lines

An international group announced its intent to create 1,000 new cancer cell lines, nearly doubling the number currently available. They aim to address challenges with current cancer cell lines, such as the lack of data on the tumors of origin and cancer subtypes that are missing or poorly represented.

The Human Cancer Models Initiative (HCMI) is a joint effort of the NCI, Cancer Research UK and the Wellcome Trust Sanger Institute in the UK, and Hubrecht Organoid Technology (HUB) in the Netherlands. The collaborators aim to meet their goal in the 3-year pilot phase of the project. If they're successful, the organizers might continue and increase their output to about 10,000 lines total, which they estimate would be enough to represent the diversity of human cancer types. The NCI has issued a call for applications to host one of three U.S. cell-line development centers; HUB and Sanger Institute will also be generating new cell lines.

"It's becoming painfully obvious that for many genetic subtypes of cancer, we sometimes don't have any models, or only one or a handful of models, to work with," says Louis Staudt, MD, PhD, director of the NCI's Center for Cancer Genomics. Even for the cell lines available, scientists often have no way of knowing if they mutated in culture over time, or how much they differ from the original tumor.

"Many existing lines bear little resemblance to the tumor types they were derived from," says Adi Gazdar, MD, a professor of pathology at The University of Texas Southwestern Medical Center in Dallas. Crucial data, such as patient responses to particular treatments, are often unavailable on the tumors from which the cell lines were derived. The new lines will be linked to both genome sequences of the original tumors and clinical outcomes.

Advances in cell-line production methods over the past few years have made the initiative seem feasible. Two techniques in particular, Staudt says, are likely to be employed: Organoid technology, developed by Hans Clevers, MD, PhD, of HUB, uses the Wnt activator R-spondin and 3-dimensional scaffolds to generate cell lines. Separately, conditional reprogramming relies on a Rho kinase inhibitor and a feeder layer of irradiated mouse fibroblasts.

Although the main goal is to assess the practicability of making so many new lines, diversity of the panel is a priority for the HCMI organizers as well. They want cell lines from rare and pediatric tumors, both of which are lacking in the current spectrum of lines available to scientists. Staudt also hopes to collect tumors from people of various ethnicities, many of which are also poorly represented among the cancer cell lines available now. To promote diversity, the NCI, in its call for applications, has stated these tumor types are a priority.

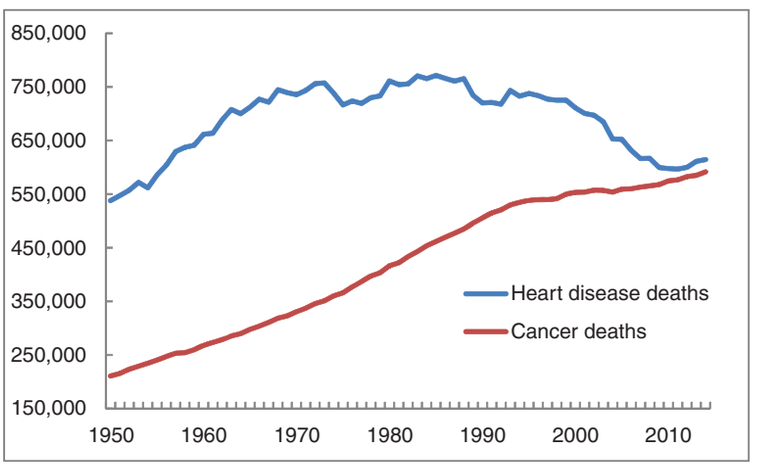
Making the project an international collaboration, rather than an effort spearheaded by a single institution, should speed up the generation of cell lines, says Mathew Garnett, PhD, a group leader at the Sanger Institute. "It really draws on the different strengths of the organizations: the expertise of HUB in developing organoid technology, the large-scale biology approach of the Sanger Institute, the clinical network of Cancer Research UK, and the wide strategic view of the National Cancer Institute," he says. Representatives from each organization will meet regularly to share what they've learned.

"They are very ambitious," says Gazdar. "It would be a great, enormous scientific help if they can achieve their aims."

The project will make the cell lines available to researchers as soon as possible, says Staudt, who predicts that the first ones will be ready in early 2017. *–Amber Dance* ■

BY THE NUMBERS

Mortality Burden of Heart Disease and Cancer, 1950–2014



National Center for Health Statistics

In the United States, heart disease has been the leading cause of death overall for decades, with cancer second. The total number of deaths from each has increased since 1950, largely due to the nation's aging population, but the gap between the two has narrowed greatly.

Although heart disease still ranks first overall, cancer became the leading cause of death in 22 states in 2014. In 2000, it killed more people in just two states—Alaska and Minnesota. The 20 states added to that once-short list are Arizona, California, Colorado, Delaware, Idaho, Kansas, Kentucky, Maine, Massachusetts, Montana, Nebraska, New Hampshire, New Mexico, North Carolina, Oregon, Vermont, Virginia, Washington, West Virginia, and Wisconsin.

Complete data are available through the National Center for Health Statistics at the Centers for Disease Control and Prevention, www.cdc.gov/nchs/products/databriefs/db254.htm.

AACR American Association for Cancer Research

CANCER DISCOVERY

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