‘Confounding’ Our Future

Margaret R. Spitz

With substantive input from colleagues in the Division of Cancer Epidemiology and Genetics at the National Cancer Institute, I outline three emerging scientific challenges that are likely to engage cancer epidemiologists in the future. An abbreviated version of these topics was presented to the "Big/Provocative Questions" think tank led by Dr. Harold Varmus, Director of the National Cancer Institute in October 2010:

Challenge 1: How do we discover the hereditary component of cancer and characterize the biological basis of cancer susceptibility? How can epidemiologists capitalize on large-scale investments in somatic characterization studies, such as The Cancer Genome Atlas Project?

Genome-wide association studies (GWAS) have identified novel genetic loci contributing to cancer risk, but these explain only a fraction of inherited contribution. Lower-frequency alleles are not adequately represented on commercial arrays, and effect sizes of common risk alleles are small. Most regions discovered point toward regulatory mechanisms, not coding changes, and tagging functional variants requires follow-up mapping. Risk prediction has not been sufficiently robust to integrate discovered single-nucleotide polymorphisms into disease prediction, and power is low to detect gene-environment interactions (hence the value of large consortia, meta-analyses and novel statistical approaches).

We need quality exposure assessment, and studies of ethnic groups with wider ranges of exposures. With new technologies and dropping costs, it is possible to scan/sequence larger data sets, with improved power to detect more, and a wider spectrum of, risk variants. We must consider functional pathway analyses and robust methods for statistical and laboratory validation. Future studies should target resequencing of regions identified by GWAS, whole-exome, and whole-genome sequencing in high-risk populations (based on family history or well-defined exposures) as well as deploying other "OMIC" platforms.

These goals are furthering our knowledge of the genetic architecture of cancer and generating more precise risk prediction to improve clinical utility of risk models.

Challenge 2: What mechanisms link energy balance and obesity to cancer? Is the association reversible if obesity is treated?

Obesity, excessive caloric intake, physical inactivity, or combinations thereof increase risk of colon, postmenopausal breast, endometrial, esophageal adenocarcinoma, and kidney cancers, and are implicated in poor survival. Obesity and physical inactivity are a worldwide problem, yet underlying causal mechanisms for tumorigenesis remain unclear. Attributable risks vary by population and cancer site (estimated 14% for colon cancer and over 50% for endometrial cancer). Calorie restriction suppresses carcinogenesis in animal models, and recent longitudinal studies of bariatric surgical patients provide suggestive evidence that weight loss is associated with reduction in cancer risk. The role of metformin the antidiabetic drug, in reducing both hyperinsulinemia and cancer risk is intriguing, as is adaptive thermogenesis in brown adipose fat (BAT), now accurately assessed in adults using noninvasive scanning.

Much research has focused on attempts to disentangle intertwined pathways (e.g., inflammation, sex hormones, insulin, insulin growth factors, Akt/mTOR, adipokines, etc.,),
and sirtuins). Epidemiologic studies, however, are unli-
kely to accelerate mechanistic understanding.

We need well-designed prospective studies with "next generation" measures of diet; physical activity; body fat and type distribution; and extensive biospec-
imens for high-throughput multiplex measurements of metabolic hormones and inflammatory markers. Com-
parative studies in populations with wider and differ-
ent ranges of body fat distribution and diets and long-
term follow-up of bariatric surgery patients for sus-
tained weight loss and cancer risk reduction are recom-
mended. Preclinical models mimicking Western diet
exposures to examine pathway perturbations (systems
 genetics) and nutri-epigenomics could contribute to
mechanistic understanding. We can screen chemical
libraries for dominant regulators of BAT determination
to develop novel antiobesity therapies targeting cellular
energy expenditure.

Better characterization of the neuronal, genetic, meta-
bolic, inflammatory, and behavioral determinants of obe-
sity phenotypes could result in more successful weight
loss interventions. Demonstrating reversibility of cancer
risk with weight reduction is potentially a powerful
behavioral incentive.

Challenge 3: What are the relationships among the
human microbiome, cancer, and obesity? Does the
microbiome partly explain susceptibility to adverse
environmental exposures? Does the microbiome deter-
mine capability to metabolize pharmaceuticals or other
ingested exposures?

Complex interactions between microbiota systems and
between the microbiota and the human host have ren-
dered the one pathogen–one disease model outmoded. It
is unknown why people vary in their microbiome or how
individual microbiota changes over time. The micro-
bio is affected by host and microorganism genetics,
vegetarian diets, probiotic foods, supplements, pharma-
ceuticals (antibiotics, proton pump inhibitors), additives,
and climate. Microbiota are implicated in inflammatory
bowel disease and may alter cancer risk by direct action
(e.g., Helicobacter pylori colonization and gastric cancer;
lack of H. pylori increasing esophageal cancer risk) or
indirectly (e.g., exposure to bacterially produced N-
nitroso compounds), chronic immune stimulation and
tolerance, and changes in metabolism of endogenous and
exogenous hormones. Animal models of disease and
their interpretation may be confounded by their different
microbiomes. Differences in the colon microbiome are
also linked with increased body fat in germ-free mice and
therefore with obesity.

We need well-characterized cohorts, comprehensive
biospecimens (e.g., fecal) for biomarker studies, and
multidisciplinary teams for molecular and functional
classification of microbiota at multiple organ sites. Extant
studies are limited by small size and lack of epidemi-
ologic rigor. While most focus has been on gastrointestinal
malignancies, a systemic effect on cancer risk must be
explored.

Characterization of the complete microbiome in gut
compartments by speciation or full metagenomic char-
acterization may help us to improve our understanding
of the dynamic relationships among the intestinal eco-
system, human physiology, metabolism, and health out-
comes, and also help to generate new approaches to
nutrition research.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Received February 16, 2011; accepted February 16, 2011;
published online March 31, 2011.
'Confounding' Our Future

Margaret R. Spitz


Updated version
Access the most recent version of this article at:
http://cebp.aacrjournals.org/content/20/4/578

Supplementary Material
Access the most recent supplemental material at:
http://cebp.aacrjournals.org/content/suppl/2011/03/24/20.4.578.DC1

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.