Smokers’ Perceptions of Lung Cancer Risks

Does lung screening promote smoking cessation?

More than 220,000 new cases of lung cancer are diagnosed each year, usually at a late stage. Cigarette smoking is responsible for 87 percent of lung cancer deaths in men and 70 percent in women. The U.S. Preventive Services Task Force Guidelines recently recommended annual lung cancer screening for current and former heavy smokers in an effort to detect lung cancers at an earlier, more treatable stage. Many health experts believe it is also important to understand smokers’ attitudes regarding their smoking behavior and whether the screening changes their attitudes.

Researchers at Massachusetts General Hospital Cancer Center, led by psychologist Elyse R. Park, PhD, MPH, undertook a series of studies to examine the effect of lung screening on attitudes and smoking behavior in a subset of participants in the National Lung Screening Trial (NLST) that ran from 2002 to 2004. “An important question, given the high cost of screening, is whether screening motivates smoking cessation and reinforces quitting among former smokers,” says Dr. Park.

LUNG SCREENING
The NLST enrolled 53,545 participants who were current and former heavy smokers 55 years old...

Scientists have long wrestled with the question of whether smokers’ perceptions of their personal risk of lung cancer are accurate. A study led by Dr. Park suggested that lung screening did not change participants’ perceived risk or promote smoking cessation, regardless of screening results.

Though few smokers quit, many began engaging in healthier activities. Most current smokers believed that they would not succeed at smoking cessation, whereas most former smokers believed they would never relapse.

Smokers’ Perceptions of Lung Cancer Risks

Key findings from studies by Elyse R. Park, PhD, MPH, reveal differences in current and former smokers’ risk perceptions.

- Only a third of current and former smokers understood that a pack-a-day smoker’s risk of getting lung cancer was 10 times that of a nonsmoker.
- Current smokers overestimated their personal risk, but underestimated their comparative risk for lung cancer and smoking-related diseases.
- Lung screening did not change participants’ perceived risk or promote smoking cessation, regardless of screening results.
- Most current smokers believed that they would not succeed at smoking cessation, whereas most former smokers believed they would never relapse.

Smokers’ Perceptions of Lung Cancer Risks

The high level of confidence among the majority of former smokers did not entice them to resume smoking.

...yet the high level of confidence among the majority of former smokers did not entice them to resume smoking.

The most common oncogene.

Researchers focus on a combination therapy for the most common oncogene.

CIRCULATING TUMOR CELLS
Could the transition status of these cells predict the aggressiveness of human cancers?

OPEN TRIALS
A selection of clinical trials currently enrolling new cancer patients.

massgeneral.org/cancer
screening may provide an opportunity to change an individual’s perception of the risk involved in smoking, and thus motivate current smokers to quit and former smokers to avoid relapse. But not much was known about how current and former smokers perceive their risk, or how screening affects those perceptions.

### DETERMINING WHAT SMOKERS ACTUALLY THINK AND DO

Prior to the first baseline screening, 630 NLST participants completed a risk perception questionnaire created by Dr. Park. Previous studies of risk perception had focused primarily on an individual’s perception of his/her personal risk (based on objective knowledge of the dangers of smoking) and focused only on lung cancer. This study, published in the June 2009 *Annals of Behavioral Medicine*, also considered other smoking-related diseases (SRDs) and the perception of comparative risk (an individual’s risk compared to the average person, others of the same age and sex, and other former/current smokers). \(^1\)

The following year, 430 of those participants completed a follow-up questionnaire prior to their second screening to see whether their risk perceptions for lung cancer and SRDs had changed, and whether those changes had affected smoking behavior. The results were reported in the April 2013 issue of *Cancer*. \(^2\)

In a second follow-up qualitative study, reported in the Sept. 2, 2013 issue of *Nicotine & Tobacco Research*, \(^3\) the researchers conducted structured, in-depth phone interviews of 35 randomly selected participants from the 2009 study one to two years after the initial screening. This study sought to determine if screening was a cue for behavioral change; elucidate risk perceptions and underlying behavior change determinants for lung cancer and smoking-related diseases; and explore post-screening intentions and changes.

The results were consistent across the three studies. Despite the fact that many participants understood that

### A Call for Screening High-Risk Current and Former Smokers

The United States Preventive Services Task Force (USPSTF) recommends annual low-dose CT screening for current and former smokers at high risk for lung cancer. High risk is defined as:

- individuals age 55-80
- cumulative smoking history of at least 30 pack-years
- must have smoked within the last 15 years
- asymptomatic

All persons undergoing screening should also receive smoking cessation counseling, and they must not have already-diagnosed lung cancer. The Mass General Cancer Center, in collaboration with Thoracic Imaging, Pulmonary Medicine and Thoracic Surgery, offer a multidisciplinary approach to the detection and treatment of lung cancer.

### FOR PATIENTS:

If you think you may be eligible for lung screening, contact your primary care physician to discuss it. Screening CTs should be ordered by your primary physician.

### FOR PROVIDERS:

To schedule a low dose CT scan, access the Radiology Order Entry system at http://mghoe (within the Partners network) or http://www.mghro.com/ (outside the Partners network), or call 617-724-9729.

For pulmonary nodule management, patients can be referred to the Lung Screening and Pulmonary Nodule Clinic by sending an email to LungScreeningClinic@partners.org.
Circulating Tumor Cells 
Transition From State to State

Can epithelial-mesenchymal transition status predict the aggressiveness of human cancers?

Cancer cells reinstate many processes observed mainly in embryonic cells and adult stem cells, including undergoing an epithelial-mesenchymal transition (EMT). In EMT, stationary epithelial cells become mesenchymal, gaining motility, invasiveness and resistance to cell death. In laboratory studies, cancer cells that undergo EMT are more resistant to drug treatment, more invasive and more likely to metastasize than cancers with an epithelial phenotype.

The correlation between EMT and cancer aggressiveness has been well studied in both ex vivo tumors and mice, particularly in breast cancer, which is an epithelial cancer. To investigate EMT in human cancers, Shyamala Maheswaran, PhD, scientific director of the Center for Cancer Risk Assessment at Massachusetts General Hospital Cancer Center, and Daniel A. Haber, MD, PhD, director of the Cancer Center, developed a new method to reliably identify the epithelial and mesenchymal phenotypes in breast cancers. They applied this method to the analysis of circulating tumor cells (CTCs), which may provide a window into the EMT process.1 (continued on page 4)

Contributor

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CTCs from a Breast Cancer Patient

This index patient underwent one round of treatment with P13K + MEK inhibition, relapsed, underwent a second round of treatment with chemotherapy, and relapsed again, over the course of 12 months. Shown below is the plot of the epithelial (E) and mesenchymal (M) circulating tumor cells (CTCs) isolated from the patient at different points in time. Predominantly epithelial states characterize periods of treatment response (R), while predominantly mesenchymal states characterize periods of disease progression (P).
The team confirmed that EMT occurs in patients with breast cancer and correlates with cancer aggressiveness, and they discovered two unpredicted twists: EMT is reversible and dynamic, and mesenchymal CTCs can travel in clusters. The study appeared in the Feb. 1, 2013 issue of Science.²

MIXED PHENOTYPES

To differentiate the epithelial (E) and mesenchymal (M) states in primary breast tumors, the researchers used RNA transcripts to highlight multiple markers instead of the traditional one marker for each state. The tumors did not just have an either/or phenotype, but also exhibited both E+ and M+ markers to varying degrees. The more invasive breast cancer subtype, triple negative breast cancer, had more M+ markers than did hormone positive or HER2 positive breast cancers, but altogether, mesenchymal cells were very rare in primary breast tumors.

The team used a microfluidic device developed by Mehmet Toner, PhD, director of the Center for Bioengineering in Medicine and BioMEMS laboratory at Mass General, to capture CTCs in patients’ bloodstreams. The CTCs had a much higher percentage of mixed and M+ phenotypes than cells in the primary tumors. These findings are consistent with the theory that CTCs carry the more motile cells that are the seeds for metastasis.

Surprisingly, some of the mesenchymal CTCs formed clusters ranging from 4 to more than 50 cells. The researchers had not predicted the cluster phenomenon because the prevailing theory holds that mesenchymal cells are solitary. The Haber Lab is investigating whether CTCs break off from the tumor as clusters or whether mesenchymal CTCs form clusters in the bloodstream, in interaction with platelets.

EMT DYNAMICS AND REVERSIBILITY

In other experiments, the researchers analyzed CTCs in 10 breast cancer patients before and after targeted therapy. The mesenchymal phenotype decreased in patients who responded to therapy but increased in patients whose disease progressed during therapy. Thus cancer cells that had acquired mesenchymal features disappeared as effective drugs were administered, but they tended to reappear along with emerging drug resistance.

In a follow-up, the researchers analyzed seven serial samples from one breast cancer patient. The M+ phenotype in CTCs decreased when the patient was responding to therapy, increased when the patient relapsed, decreased again under a new therapy and increased when the patient relapsed again.

BROAD IMPLICATIONS

The researchers are now analyzing RNA in CTCs to determine how gene activity changes with EMT dynamics.

“The better our new drugs become, the more we need to know what they do to the cancer, and how cancers adapt and become resistant,” Dr. Haber says. “This technique gives us a whole new window for drug testing.”

The technology enabling this recent study still requires scale-up, standardization and commercialization. Still, the researchers predict that analyzing the EMT in CTCs will become an important tool for managing cancer.
Can a new approach to drug combination therapy eradicate KRAS-mutant cancers?

A major challenge in cancer involves the most commonly mutated oncogene, KRAS, which produces a small protein that activates other proteins that drive cancer. Some 90 percent of pancreatic cancers, 40 percent of colorectal cancers and 20 percent of cancers overall have mutations in KRAS. Yet KRAS has proven difficult to target with small molecule drugs. The most effective candidates inhibit MEK, a signaling pathway activated by KRAS mutations. Although MEK inhibition can slow the growth of KRAS cancers, it does not kill them. Researchers have undertaken genetic screens to find additional genes whose disruption is specifically toxic to KRAS-mutant cancers.

Jeffrey Engelman, MD, PhD, director of the Center for Thoracic Cancers at Massachusetts General Hospital Cancer Center, undertook an alternate strategy. He hypothesized that another gene works in conjunction with MEK, one that on its own may not drive cancer and thus would not be identified in traditional genetic screens. His team performed an unbiased screen that identified a novel target, BCL-XL. The team is now ushering a combination of MEK and BCL-XL inhibition to clinical trial. The study appeared in the January 14, 2013 issue of Cancer Cell.¹

**MEK ELUDES CELL DEATH SIGNALS FOLLOWING INHIBITION**

Dr. Engelman’s team used a large library of RNA molecules, each of which may disrupt a different gene in a different cell. They tested the RNAs in cancer cells with and without the KRAS mutation. Half of each type was grown in the presence of a MEK inhibitor (selumetinib). Any KRAS cell that died when bathed in a MEK inhibitor had a deactivated gene that normally operates with MEK to evade cell death. By searching for the cell in which the disrupted gene had the most potent effect in combination with the MEK inhibitor, the researchers identified that “co-conspirator” gene as BCL-XL.

MEK inhibition initially upregulates the protein BIM, which primes the KRAS cancer cells... (continued on page 6)
SYNERGETIC INHIBITION

Dr. Engelman’s team tested a combination of selumetinib with an investigational BCL-XL inhibitor (navitoclax, or ABT-263). In both cell cultures and mice, the combined inhibition caused a dramatic increase in tumor cell death, and was much more lethal to KRAS cells than inhibiting just one or the other. In genetically engineered mouse models of human KRAS-mutant cancer, the combined therapy caused significant tumor regression.

However, the experiments showed a differential effect among cells that had epithelial versus mesenchymal phenotypes. Cells in the epithelial state demonstrated a more robust response than those in the mesenchymal state. Given the large body of research finding that cells transitioning from an epithelial to a mesenchymal state (EMT) are evolving to become more invasive and drug resistant, this result suggests that mesenchymal status may predict patient prognosis and drug response. (For more on Mass General Cancer Center’s investigation of EMT, see page 3.)

Dr. Engelman has received approval to test the combination in a clinical trial, which should begin this year. Researchers will collect data on patients’ epithelial-mesenchymal status to study whether it correlates with patient response.

TAKING THE BCL-XL FINDING FURTHER

A study by Dr. Engelman’s team in the January 2014 issue of Cancer Discovery found a similar lethal combination by inhibiting both BCL-XL and mTOR, a master regulator of numerous cell growth signals. Here, the team screened more than 600 colorectal cancer cell lines with 130 drugs to determine which ones made the cells more sensitive to BCL-XL inhibition with navitoclax. The researchers found that an inhibitor of mTOR, AZD8055, worked synergistically with BCL-XL inhibition in colorectal cancers driven by KRAS or BRAF, an oncogene driving 5 percent to 15 percent of colorectal cancers. However, the combination was not effective in non-small-cell lung cancers with KRAS mutations.

Each of the two approaches—using RNA and drug screens—has advantages and limitations. The first strategy casts a wide net to find novel targets. However, some of those hits may be difficult to target with drugs because they lack an accessible binding site. The second approach restricts the number of targets being explored, but because it uses existing or investigational drugs, it may accelerate the translation from bench to patient bedside. Together, the strategies may provide the synergy needed to treat KRAS-mutant cancers. “There hasn’t been a single agent that is effective against KRAS,” says Dr. Engelman. “These combinations are the next best approach.”

Combined Drug Treatment

Lung tumors in mice treated with a combination of a MEK inhibitor and a BCL-XL inhibitor led to a dramatic increase in tumor cell death after one week of treatment.

Pre-Treatment

ABT + AZD (week 1)


Contributor

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Selected Open Clinical Trials

The Massachusetts General Hospital Cancer Center conducts nearly 400 clinical trials in collaboration with the Dana-Farber/Harvard Cancer Center. Selected Mass General Cancer Center clinical trials currently enrolling new cancer patients are listed here. For a complete list, go to massgeneral.org/cancer/trials. To receive a monthly email about select open clinical trials at the Cancer Center, please send your contact information to MGHAdvancesinCancer@partners.org.

**BONE MARROW TRANSPLANT**

2012P001355

Combined haploidentical reduced-intensity bone marrow and kidney transplantation for patients with chronic kidney disease and advanced hematological disorders

Pilot  |  Yi-Bin Chen, MD  |  617-726-1124

**HEMATOLOGY**

2012P002559

Tissue repository for the study of idiopathic/immune thrombocytopenic purpura and autoimmune hemolytic anemia

David Kuter, MD, DPhil  |  617-726-8743

**LEUKEMIA**

13-371

A multicenter, open-label, dose-escalation, safety, pharmacokinetic, pharmacodynamic and clinical activity study of orally administered AG-221 in subjects with advanced hematologic malignancies with an IDH2 mutation

Phase I  |  Amir Fathi, MD  |  617-726-6799

**LYMPHOMA**

13-348

A study of CPI-0610, a small-molecule inhibitor of BET proteins, in patients with progressive lymphoma

Phase I  |  Jeremy S. Abramson, MD  |  617-726-8743

**PEDIATRIC CANCERS**

09-361

A study of proton beam radiotherapy for medulloblastoma and pineoblastoma: an assessment of acute toxicity and long-term neurocognitive, neuroendocrine and ototoxicity outcomes

Phase II  |  Torunn Yock, MD  |  617-726-6876

**SARCOMA**

13-115

A study of olaparib and temozolomide in adult patients with recurrent/metastatic Ewing’s sarcoma following failure of prior chemotherapy

Phase I  |  Edwin Choy, MD  |  617-643-0230

**TARGETED THERAPIES**

13-121

An open-label, multicenter study of the combination of BYL719 plus AMG 479 (ganitumab in adult patients with selected advanced solid tumors)

Phase I/II  |  Dejan Juric, MD  |  617-671-5392

**THORACIC CANCERS**

12-098

An open-label, safety, pharmacokinetic and preliminary efficacy study of oral CO-1686 in patients with previously treated mutant EGFR non-small-cell lung cancer

Phase II  |  Lecia Sequist, MD, MPH  |  617-724-4000

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**BREAST CANCER**

13-283

A trial of LEE011 in combination with everolimus (RAD001) and exemestane in the treatment of postmenopausal women with estrogen receptor positive locally advanced or metastatic breast cancer

Phase Ib/II  |  Aditya Bardia, MD, MPH  |  617-723-2208

**GASTROINTESTINAL CANCERS**

12-477

A randomized placebo-controlled study of GDC-0068, an inhibitor to AKT, in combination with fluoropyrimidine plus oxaliplatin in patients with locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma

Phase II  |  Eunice Kwak, MD, PhD  |  617-726-8478

**GENITOURINARY CANCERS**

13-068

A multicenter, randomized, double-blind, placebo-controlled study of ARN-509 in men with non-metastatic (M0) castration-resistant prostate cancer

Phase III  |  Matthew Smith, MD, PhD  |  617-724-5257

**HEAD AND NECK CANCERS**

13-409

An open-label study of the safety and pharmacokinetics of MEHD7945A in combination with either cisplatin and 5-FU or paclitaxel and carboplatin in patients with recurrent/metastatic squamous cell carcinoma of the head and neck

Phase Ib  |  Lori Wirth, MD  |  617-724-4000

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2012P002559

Tissue repository for the study of idiopathic/immune thrombocytopenic purpura and autoimmune hemolytic anemia

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**MELANOMA**

13-010

A dose-escalation, safety, pharmacokinetics and pharmacodynamic study of BVD-523 in patients with advanced malignancies

Phase I  |  Keith T. Flaherty, MD  |  617-726-1941

**MULTIPLE MYELOMA**

12-014

A dose-escalation study of PXK-410, a multi-peptide cancer vaccine, in patients with smoldering multiple myeloma

Phase I/IIa  |  Noopur Raje, MD  |  617-724-4000

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**NEURO-ONCOLOGY**

12-440

CALGB 51101: A randomized trial of myeloablative versus non-myeloablative consolidation chemotherapy for newly diagnosed primary CNS B-cell lymphoma

Phase II  |  Tracy Batchelor, MD, MPH  |  617-643-5530

**PEDIATRIC CANCERS**

09-361

A study of proton beam radiotherapy for medulloblastoma and pineoblastoma: an assessment of acute toxicity and long-term neurocognitive, neuroendocrine and ototoxicity outcomes

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At the Mass General Cancer Center, we are closing the gap between groundbreaking gene-based cancer research and life-changing treatments. We recently developed and launched an industry-leading website, TargetedCancerCare.org, that connects users with the Cancer Center’s innovative clinical research in the field of targeted cancer therapies.

TargetedCancerCare.org features:

- The latest information related to tumor-specific genetic and molecular biomarkers
- An interactive tool that enables users to search for targeted cancer therapy clinical trials. Users can input as much information as they have available, searching by disease type, cancer gene or specific mutation
- Customized search results
- A user-friendly format designed to guide physicians through what can be an increasingly complex field with unique opportunities