Redheads Carry Melanoma Risk Independent of Sun Exposure

Why are redheads more susceptible to melanoma?

People with red hair and fair skin are significantly more likely to develop melanoma than are people with darker skin. Sun exposure and ultraviolet (UV) radiation are proven risks for virtually all skin cancers, and researchers want to better understand why having red hair increases melanoma risks.

Among the deadliest cancers, melanoma can grow very aggressively and spread early if undetected. The number of cases is rising at a rate of 3 percent per year, especially among fair-skinned people. Unlike other forms of skin cancer, the elevated risk in fair-skinned people is not restricted to sun-exposed skin, which raised suspicion that UV radiation may not be the only risk factor for melanoma. Working with a mouse model of the redhead phenotype, Massachusetts General Hospital researchers discovered that, surprisingly, at least part of the increased risk is unrelated to any UV exposure. Rather, the pigment responsible for red hair causes oxidative damage in the skin, and that intrinsic damage promotes melanoma formation independent of UV radiation. The study, led by David E. Fisher, MD, PhD, appeared in the November 15, 2012, issue of Nature.

The laboratory of David E. Fisher, MD, PhD, genetically modified three types of mice with a BRAF mutation, the most common oncogenic mutation in melanoma. When the animals’ exposure to UV radiation was blocked, researchers found:

- Very, very low incidence of melanoma, and no pigment-induced oxidative damage
- High incidence (50 percent); red pigmentation causes DNA damage, leading to melanoma
- Low incidence of melanoma

Melanoma Genesis

The role of pigment production

Pigment production is controlled by the melanocortin 1 receptor (MC1R) in melanocytes, the melanin-
producing cells that become malignant in melanoma. In dark-haired animals, MC1R is activated by the binding of melanocyte stimulating hormone and produces the black/brown pigment eumelanin, which shields the skin’s DNA from UV waves. Redheads have an inactivated MC1R variant, causing melanocytes to produce the red/yellow pheomelanin pigment (which offers weak UV shielding), but no eumelanin.

Dr. Fisher developed a mouse model with the same inactivated MC1R variant that causes the redhead/fair-skin phenotype in humans and other animals, in order to investigate mechanisms leading to higher melanoma risks for redheads from UV radiation.

DECOPLING UV EXPOSURE FROM INHERENT MELANOMA RISK

For the 2012 study, Dr. Fisher conditionally expressed BRAFv600E, the most common melanoma oncprotein, in the melanocytes of the redhead mice. While singular expression of this oncprotein typically produces only benign moles, the combination of BRAFv600E plus the genetic red hair/fair skin background produced a high frequency of invasive melanoma tumors without UV exposure. While it was expected that the contribution of fair skin to melanoma formation involved UV-shielding, in this case it contributed without any UV exposure. Analysis of the mouse skin cells showed that pheomelanin (red pigment) produced reactive oxygen species that damaged the DNA in the melanocytes and induced carcinogenesis.

The researchers realized that this mouse model enabled them to decouple the effect of UV radiation exposure from any UV-independent risk factor for melanoma in redheads. To explore this pigment-induced carcinogenesis, they introduced an albino allele in one group of BRAF/redhead mice, which prevented the production of any pigments, including pheomelanin. The albinos exhibited much less oxidative damage in their skin and were dramatically protected from melanoma formation in the presence of BRAFv600E.

A third group of mice with the BRAF mutation had black hair, with a high ratio of eumelanin to pheomelanin. They had little oxidative damage and, despite the oncprotein, a low incidence of melanoma. “Although black-haired phenotypes produce some pheomelanin, the eumelanin appears to chemically ‘cage’ pheomelanin, neutralizing its oxidation-damaging effect,” explains Dr. Fisher.

EXPLORING PREVENTIVE STRATEGIES

The current study thus establishes that the red skin pigment itself produces reactive oxygen species that damage DNA in ways that lead to melanoma in mice even without sun exposure. The therapeutic impulse might be to deploy antioxidants to counter DNA-damaging oxidants, but, Dr. Fisher cautions, some antioxidants paradoxically act as pro-oxidants. His group is rigorously exploring this question in redhead mice.

While there is a UV-independent risk for developing melanoma in redheads, Dr. Fisher emphasizes that limiting sun and UV exposure remains an important preventive strategy. First, sunscreens prevent other forms of skin cancer, and they protect against sunburns and premature aging. Second, UV radiation may exacerbate the intrinsic mutational process in redheads’ melanocytes, and may be a larger contributor. Likewise, the pheomelanin-produced reactive oxygen species may contribute to the damage caused by certain UV wavelengths. The researchers are undertaking genome sequencing and biochemical studies to determine the relative contribution of environmental UV exposure and the inherent risk from red pigment.

AN AIM TO IMPROVE SUNSCREEN

This new research suggests that additional strategies are needed to prevent melanoma. Dr. Fisher and his colleagues are working to develop additional protective components for sunscreens, which may include both compounds that counter the oxidative damage inherent to redhead pigments and those that darken the melanocytes to better shield against UV light.

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A Landmark Study Compares Proton Beam Therapy with Standard Radiation Therapy

What is the value of proton beam therapy?

Massachusetts General Hospital, along with the University of Pennsylvania and several other proton centers, is leading a trial that may help settle a long-standing debate: Is proton beam therapy (PBT) more effective than intensity-modulated radiotherapy (IMRT) for prostate cancer?

The trial, Prostate Advanced Radiation Technologies Investigating Quality of Life (PARTIQoL), is the first large Phase III randomized clinical trial to directly compare PBT with IMRT in prostate cancer. The five-year multicenter study, which opened in July 2012, is sponsored by Mass General and the National Cancer Institute and is still accruing patients.

In recent years, the Agency for Healthcare Research and Quality, Institute of Medicine, Centers for Medicare & Medicaid Services, other federal agencies, policymakers, clinicians, researchers and the media have called for a rigorous comparative evaluation of these two treatments prior to PBT’s wider adoption. The study’s principal investigator, Jason A. Efstathiou, MD, DPhil, says that the results will help prostate cancer patients and their physicians make better informed decisions regarding the most effective therapy with the least burdensome quality-of-life (QOL) issues, while also contributing to the larger debate about the investment in and impact of innovative technologies.

TWO INNOVATIVE TECHNOLOGIES

Of the some 200,000 men who are diagnosed with prostate cancer annually, many will suffer lifelong morbidities resulting from treatment. PBT and IMRT are both targeted advanced radiation technologies that are capable of delivering higher doses of radiation more directly to the prostate than do older techniques, leading to higher cure rates. By sparing surrounding tissue and organs, these technologies are meant to decrease toxicity and perhaps reduce the rare risk of developing a second cancer.

Unlike IMRT, PBT delivers radiation by using a more focused beam to the targeted tumor, with less of a low-dose bath for the pelvis and no “exit” dose irradiating tissue beyond the tumor. Theoretically, PBT may thus cause fewer side effects than IMRT.

SCANT EVIDENCE OF PBT’S BENEFIT IN PROSTATE CANCER

The theoretical advantage of PBT seemed particularly relevant to the prostate, which lies close to the bowel, bladder and rectum, which all may be affected by scattered radiation. But it is also possible that protons are not as sharp at the depth of deep-seated tumors like the prostate, and there are other potential

Standard Radiotherapy vs. Proton Beam Therapy

For prostate cancer, intensity-modulated radiotherapy and proton beam therapy each have pros and cons.

**IMRT**

**PRO:** Targeting of the tumor is very accurate, and IMRT can be sculpted to the prostate to limit the exposure of high doses to neighboring organs such as the rectum.

**CON:** Lower-dose radiation is unavoidably deposited in normal tissues beyond the tumor because of the increased number of beam angles. This creates a low-dose radiation “bath” over a larger region of the pelvis.

**PBT**

**PRO:** Having no exit dose makes it potentially possible to deliver higher tumor doses with lower doses to surrounding normal tissues, especially tissues beyond the tumor.

**CONS:** With current delivery techniques, doses to the hips may be higher with PBT and the beam is a little less sharp with deep-seated tumors such as the prostate; the high-dose region to the rectum is likely similar to IMRT; it may cost up to twice as much as IMRT.

Costs: median Medicare reimbursement

- **IMRT**: $18,575
- **PBT**: $32,428
The few studies comparing PBT with IMRT in prostate cancer have been retrospective, uncontrolled and conflicting. A 2012 study in *JAMA*\(^3\) found that patients treated with IMRT had decreased bowel toxicity compared with those treated with PBT, while a 2012 study in the *Journal of the National Cancer Institute (JNCI)*\(^4\) found that patients treated with PBT had improved urinary function in the short term. However, both studies relied on data from physician billing codes rather than patient reports. In *Cancer* this year, Dr. Efstathiou and colleagues described patient-reported outcomes following PBT, IMRT or 3-D conformal radiotherapy. PBT initially caused fewer gastrointestinal and urinary problems, but after two years QOL outcomes were similar to IMRT.

### THE CONTROVERSY

According to the 2012 *JNCI* study, median Medicare reimbursement for PBT is $32,428, compared with $18,575 for IMRT. Despite the lack of well-designed prospective comparative studies to date and the higher cost, many men choose PBT over IMRT because of the assumption that it reduces long-term side effects. Prostate cancer has been a driving force behind the establishment of new proton beam facilities, which may double in three years and whose patient load in some cases may include up to 75 percent prostate patients.

### THE AIMS OF PARTIQoL

The PARTIQoL trial is looking at patient-reported QOL outcomes and other end points. The primary QOL end point is bowel function because it is the most specific long-term side effect. The study will also:

- Develop predictive models of the association between radiation dose distribution and patient-reported bowel, urinary and erectile functions
- Identify and evaluate biomarkers, including circulating tumor cells, for the response to PBT and IMRT to guide future personalized medicine decisionmaking
- Assess longer-term survival rates and late effects
- Compare cost-effectiveness at current and future pricing schemes

“Despite a clear benefit in some cancers, such as pediatric malignancies, the rapid adoption of PBT may be happening before its effectiveness and comparative value has been rigorously evaluated in all disease sites,” noted Dr. Efstathiou. He hopes PARTIQoL will serve as a model for evaluating costly yet promising medical technologies.

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The Meaningful Benefits of Early Palliative Care for Advanced Cancer

When should palliative care begin for cancer patients?

Palliative care focuses on a patient’s comfort and symptoms such as pain, shortness of breath and nausea, which are often substantial for people with cancer throughout their illness. But palliative care is usually delivered only in the last days or weeks of a patient’s life, and is usually provided on an inpatient basis. Research led by Jennifer S. Temel, MD, at Massachusetts General Hospital demonstrated in 2010 that for advanced lung cancer patients, offering early palliative care on an outpatient or ambulatory basis complemented standard oncology—and, unexpectedly, led to longer median survival time.

In a new study, published in the February 25, 2013, issue of *JAMA Internal Medicine,* Dr. Temel analyzed which features of the palliative care delivered during the 2010 trial provided these benefits. The results serve as a road map for delivering early palliative care.

**THE BENEFITS OF EARLY PALLIATIVE CARE**

In the 2010 clinical study, Dr. Temel’s group selected 151 newly diagnosed patients with advanced lung cancer and randomly assigned them to standard oncology alone or standard oncology with early palliative care. The study focused on lung cancer because patients generally have many complex symptoms and reduced quality of life.

The study, published in *The New England Journal of Medicine,* found that adding early palliative care to standard oncology care provided meaningful benefits to advanced lung cancer patients compared with standard care alone. Patients had better quality of life and suffered less depression. They also chose hospice or other end-of-life care at an earlier, more appropriate stage rather than opting for more intensive chemotherapy. Unexpectedly, the median survival time was longer (11.6 versus 8.9 months) for patients with early palliative care, despite their receiving less aggressive end-of-life care. (continued on page 6)

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Traditional vs. Early Palliative Care

Whereas traditional palliative care typically begins toward the end of life, the early approach begins right after diagnosis.

**TRADITIONAL**

Clinical turning point, such as growth of cancer on CT scans

Palliative care to manage symptoms and improve quality of life

**EARLY**

Relationship- and rapport-building

Throughout: Addressing symptoms, addressing coping, establishing illness understanding, engaging family members

End-of-life planning
Qualitative Analysis of Palliative Care Benefits

For the 2013 study, the researchers retrospectively analyzed what palliative care providers did in the 2010 study that led to the observed benefits. By reviewing medical records for each visit with a palliative care provider, they identified seven key elements of care that were different from standard oncology alone: relationship- and rapport-building, addressing symptoms, addressing coping, establishing illness understanding, discussing cancer treatments, end-of-life planning and engaging family members.

Timing the Key Elements of Palliative Care

The researchers also explored the timing of those elements, and compared the content of palliative care and oncology visits at clinical turning points. They found that the initial palliative care visits focused on building relationships; discussing cancer treatment and prognosis; and discussing preferences for receiving information.

Early visits did not include discussions of end-of-life and hospice care; these occurred at later, more appropriate stages. Many community oncologists hesitate to refer newly diagnosed patients to palliative care, for fear of upsetting them with end-of-life issues, Dr. Temel explained. She hopes that this finding alleviates oncologists’ concerns.

All visits focused on symptom management and the physical, psychosocial and spiritual well-being of the patient. Palliative care also focused on family and friends, who, Dr. Temel noted, also suffer from their loved ones’ diagnoses and provide much of the ongoing care.

Palliative Care Allows Oncologists to Focus on Oncology

The researchers also compared palliative care visits with oncologist visits at clinical turning points, such as when the disease progresses. Palliative care visits focused more on helping patients and their families cope, while oncology visits focused on medical management and treatment decisions.

Future Directions

Dr. Temel is now leading a larger clinical trial looking at early palliative care in patients with advanced lung and gastrointestinal cancer. The research team will explore the mediators of the outcomes prospectively, and whether the cost of early palliative care is offset by less intensive medical care at the end of life. They will also look for indicators that predict who will benefit the most from early palliative care. The trial is still accruing patients, and, uniquely, is also enrolling family members and friends.

Median Survival Time

Jennifer S. Temel, MD, was surprised to discover that patients who received early palliative care, despite undergoing less aggressive end-of-life care, tended to live longer.

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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.

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

BREAST CANCER
12-331
A multi-center, open-label, neoadjuvant, randomized study of weekly paclitaxel with or without LCL161 in patients with triple negative breast cancer
Phase II | Aditya Bardia, MD, MPH | 617-726-8478

GASTROINTESTINAL CANCERS
11-164
A clinical trial of LDE225 in combination with fluorouracil, leucovorin, oxaliplatin and irinotecan (FOLFIRINOX) in previously untreated locally advanced or metastatic pancreatic adenocarcinoma, with an expansion cohort at the recommended Phase II dose
Phase Ib | Eunice Kwak, MD, PhD | 617-726-9478

GENITOURINARY CANCERS
12-291
A randomized, double-blind, controlled study of cabozantinib (XL184) vs. prednisone in metastatic castration-resistant prostate cancer patients who have received prior docetaxel and prior abiraterone or MDV3100
Phase III | Matthew Smith, MD, PhD | 617-726-5257

HEAD AND NECK CANCERS
13-021
A randomized study of single agent GSK2118436 (BRAFi) versus combination regimen GSK2118436 (BRAFi) and GSK1120212 (MEKi) in patients with BRAF mutated thyroid carcinoma
Phase II | Leri Wirth, MD | 617-726-4000

LEUKEMIA
12-531
A study of the aurora A kinase inhibitor alisertib in combination with 7+3 induction chemotherapy in patients with acute myeloid leukemia
Phase I | Amir Fathi, MD | 617-726-1941

LYMPHOMA
11-462
Brentuximab vedotin plus AVD in non-bulky limited stage Hodgkin’s lymphoma
Phase II | Jeremy S. Abramson, MD | 617-726-8743

MELANOMA
12-088
A trial of lenalidomide in combination with vemurafenib in patients with V600 mutant metastatic melanoma
Phase I/II | Keith T. Flaherty, MD | 617-726-1941

MULTIPLE MYELOMA
12-325
A multicenter, randomized, double-blind, placebo-controlled study of tabalumab in combination with bortezomib and dexamethasone in patients with previously treated multiple myeloma
Phase II/III | Noopur Raje, MD | 617-726-4000

NEURO-Oncology
09-468
An open-label trial of orally administered PF-00299804 in adult patients with relapsed/recurrent glioblastoma
Phase II | Tracy Batchelor, MD, MPH | 617-643-5530

PEDIATRIC CANCERS
09-273
Reduced-duration Stanford V chemotherapy with or without low-dose tailored-field radiation therapy for favorable risk pediatric Hodgkin’s lymphoma
Phase II | Alison M. Friedmann, MD | 617-726-2737

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
12-290
A study of the evaluation of SAR260301, administered orally in monotherapy in patients with advanced solid tumors or lymphomas, and in combination with vemurafenib in patients with unresectable/metastatic BRAF mutated melanoma
Phase I/II | Keith T. Flaherty, MD | 617-726-1941

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 I/II | Lecia Sequist, MD, MPH | 617-726-4000

Introducing a new way to access targeted clinical trials: TargetedCancerCare.org

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.
New Physician Appointments

Massachusetts General Hospital is pleased to announce new physician appointments in the areas of Hematology/Oncology, Imaging, Neurology, Pathology, Radiation Oncology, Research, Surgical Oncology, and Urology. For more information about the Mass General Cancer Center or our new physicians, please visit massgeneral.org/cancer.

HEMATOLOGY/ONCOLOGY
Gastrointestinal
Lipika Goyal, MD
Hematologic Malignancies
Timothy Graubert, MD
Benign Hematology
Jonathan Carlson, MD, PhD
Mass General Hematology/Oncology Service at Exeter Hospital
Panos Fidias, MD
Mass General/North Shore Cancer Center—Genitourinary
Peter Yang, MD

IMAGING
Breast Imaging
Kathryn Humphrey, MD
Nuclear Medicine
Yingbing Wang, MD

NEUROLOGY
Neuro-Oncology
Isabel Arrillaga Romany, MD, PhD

PATHOLOGY
Clinical Pathology
Jason Baron, MD, PhD
Breast and Gastrointestinal
Kristina Braaten, MD
Molecular Pathology & Gastrointestinal Pathology
Valentina Nardi, MD

RADIATION ONCOLOGY
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Karen Bernstein, MD
Newton-Wellesley Hospital
Christine Olsen, MD

RESEARCH
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Ryan Corcoran, MD, PhD
Immunotherapy Research
Soldano Ferrone, MD, PhD
Gastrointestinal
David Ting, MD
Immune Regulation
Laurence Turka, MD
Surgical
Xinhui Wang, MD

SURGICAL ONCOLOGY
Melanoma and Sarcoma
Alex Haynes, MD, MPH

UROLOGY
Urologic Oncology
Matthew Wszolek, MD