a combined analysis of 22 studies. Am J Hum Genet 2003;72:1117-30.
2. Ferlay J, Parkin DM, Steliarova-Foucher E. Estimates of cancer incidence and mortality in Europe in 2008. Eur J Cancer 2010;46:765-81.
3. Howlader N, Noone A, Krapcho M, et al. SEER cancer statistics review, 1975-2012. Bethesda, MD: National Cancer Institute (updated 2015) (http://seer.cancer.gov/csr/1975_2012/).
4. McLaughlin JR, Rosen B, Moody J, et al. Long-term ovarian cancer survival associated with mutation in BRCA1 or BRCA2. J Natl Cancer Inst 2013;105:141-8.

DOI: 10.1056/NEJMc1602861

THE AUTHORS REPLY: Regarding the need for hysterectomy at the time of risk-reducing salpingo-oophorectomy, we agree with Karam that the risk of endometrial cancer in women with hereditary breast and ovarian cancer is not significantly elevated.[1] Nor did we intend to imply that the risk of endometrial cancer after treatment with tamoxifen would justify hysterectomy. In fact, in all the placebo-controlled trials in which tamoxifen was studied as a chemopreventive agent, only the National Surgical Adjuvant Breast and Bowel Project P-1 Study showed a statistically significant increase in endometrial cancer, and the absolute risk was 0.55% over 5 years.[2] We wish to highlight the point that tamoxifen remains an important option for the reduction of the risk of breast cancer in premenopausal women and in women who cannot take aromatase inhibitors because of low bone density or joint pain.

In women who do not have risk-reducing mastectomy, there remains a concern regarding the possible adverse effect on the risk of breast cancer associated with the use of a combination of estrogen and progesterone, especially among women who would use the agents for more than 10 years owing to the early age at which they undergo salpingo-oophorectomy. To our knowledge, there are no prospective data that address this specific question. Acknowledging the possible increase in the risk of breast cancer associated with combined treatment with estrogen and progesterone, the Society of Gynecologic Oncology suggests the use of a progestin-containing intrauterine device to accompany estrogen replacement and thus avoid the administration of systemic therapy with progestin.[3]

MacInnis and colleagues emphasized the use of data on the mortality associated with breast and ovarian cancer. In our article, we reviewed published data on both the incidence of and mortality from breast and ovarian cancer, since both end points inform decision making. Given the more lethal breast cancers that develop in *BRCA1* carriers, the use of SEER data to estimate the carriers' survival may not reflect the actual risks these women face. Given the space constraints in our article, we were not able to cover management issues for mutation carriers who have had a first breast cancer. Nevertheless, we appreciate these authors' reminder that for *BRCA1* carriers in particular who have an early first breast cancer, the risk of ovarian cancer and death from ovarian cancer remain major threats that justify the recommendation for salpingo-oophorectomy.[4]

Lynn C. Hartmann, M.D.
Mayo Clinic
Rochester, MN
hartmann.lynn@mayo.edu

Noralane M. Lindor, M.D.
Mayo Clinic
Scottsdale, AZ

Since publication of their article, the authors report no further potential conflict of interest.

1. Segev Y, Iqbal J, Lubinski J, et al. The incidence of endometrial cancer in women with BRCA1 and BRCA2 mutations: an international prospective cohort study. Gynecol Oncol 2013;130:127-31.
2. Hartmann LC, Degnim AC, Dupont WD. Atypical hyperplasia of the breast. N Engl J Med 2015;372:1271-2.
3. Walker JL, Powell CB, Chen LM, et al. Society of Gynecologic Oncology recommendations for the prevention of ovarian cancer. Cancer 2015;121:2108-20.
4. Metcalfe KA, Lynch HT, Ghadirian P, et al. The risk of ovarian cancer after breast cancer in BRCA1 and BRCA2 carriers. Gynecol Oncol 2005;96:222-6.

DOI: 10.1056/NEJMc1602861

Melanomas and Mechanical Stress Points on the Plantar Surface of the Foot

TO THE EDITOR: Sun exposure is widely recognized as the main causative factor in cutaneous melanoma. However, melanomas also emerge in areas of the skin (such as palmoplantar surfaces) that are not exposed to the sun. Genetic analyses indicate that melanomas in sun-exposed skin are frequently associated with oncogenic *BRAF* mutations that are largely absent from palmo-

plantar lesions.[1] These findings suggest that different pathogenic processes may be at work.[2] Here we report on a series of patients with melanomas that developed in areas of plantar surfaces that had the most mechanical stress.

We retrospectively collected data on 123 patients (54 men and 69 women) with melanomas of plantar volar skin who received treatment at Shinshu University Hospital between January 1990 and December 2014. The mean age of the patients was 73.5 years. The melanoma occurred on the left sole in 61 patients and on the right sole in 62 patients. The diagnosis was histopathologically confirmed in all the patients, and lesions that developed primarily in the subungual and periungual areas were excluded from the analysis. The study was approved by the institutional review board at the Shinshu University School of Medicine.

The Breslow thickness of the lesions was in situ in 28 patients, 1.00 mm or less in 12, 1.01 to 2.00 mm in 20, 2.01 to 4.00 mm in 28, and 4.01 mm or more in 33. Two patients had data that could not be evaluated.

We adjusted the width of the foot in each clinical image to 26 cm by means of digital magnification and then plotted the center of each lesion on grids divided into 0.25-cm^2 pixels (Fig. 1A). The distribution of lesions was as follows: 50 lesions (0.87 lesions per square centimeter) in the rear of the foot, 32 (0.71 per square centimeter) in the front of the foot, 14 (0.40 per square centimeter) in the midfoot, and 3 (0.07 per square centimeter) in the arch. The density of lesions on the entire plantar surface was 0.40 lesions per square centimeter.

In addition, the distribution pattern of the tumors was not associated with differences in the Breslow thickness. We also traced the lesion margins. Figure 1B shows the distribution according to the number of lesions in each pixel.

Although trauma and other factors increase the risk of melanoma in regions of the skin that are not exposed to the sun,[3] we found that the

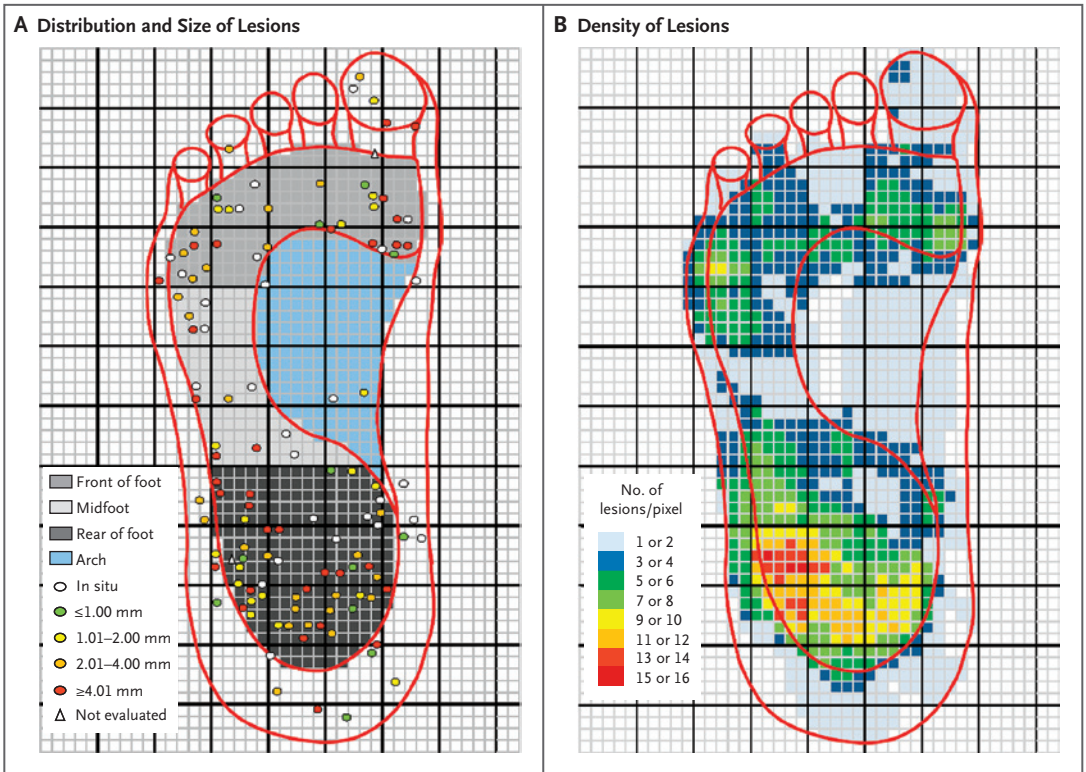

Figure 1. Distribution of Melanoma Lesions on the Plantar Surface.

In Panel A, the four areas of the sole are shown. The center of each lesion is plotted and color-coded according to its Breslow thickness. In Panel B, the number of lesion areas in each pixel is shown on a color scale. Each pixel measures 5 mm by 5 mm.

conditions of the rear of the foot and front of the foot were more conducive to the development of melanomas than other areas of the plantar surface. Mechanical stress such as plantar pressure and shear stress is higher in these two areas than in other areas of the foot,[4] and this stress is associated with the development of skin ulcers in persons with diabetes and with the development of calluses.[5] Taken together with these observations, our results suggest that mechanical stress also increases the formation of melanomas on the plantar surface. Studies to determine the pathogenesis of melanoma in plantar regions are lacking.

Akane Minagawa, M.D., Ph.D.
Toshikazu Omodaka, M.D.
Ryuhei Okuyama, M.D., Ph.D.

Shinshu University School of Medicine
Matsumoto, Japan
rokuyama@shinshu-u.ac.jp

Supported by a grant (15K19684) from the Grants-in-Aid for Scientific Research Program of the Japanese Society for the Promotion of Science.

Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

1. Curtin JA, Fridlyand J, Kageshita T, et al. Distinct sets of genetic alterations in melanoma. N Engl J Med 2005;353:2135-47.
2. Chang JW. Acral melanoma: a unique disease in Asia. JAMA Dermatol 2013;149:1272-3.
3. Green A, McCredie M, MacKie R, et al. A case-control study of melanomas of the soles and palms (Australia and Scotland). Cancer Causes Control 1999;10:21-5.
4. Stucke S, McFarland D, Goss L, et al. Spatial relationships between shearing stresses and pressure on the plantar skin surface during gait. J Biomech 2012;45:619-22.
5. Caputo GM, Cavanagh PR, Ulbrecht JS, Gibbons GW, Karchmer AW. Assessment and management of foot disease in patients with diabetes. N Engl J Med 1994;331:854-60.

DOI: 10.1056/NEJMc1512354

CORRECTION

Respiratory Syncytial Virus and Recurrent Wheeze in Healthy Preterm Infants (May 9, 2013;368:1791-9). In the final paragraph of the Primary and Secondary Outcomes subsection of Results (page 1794), the parenthetical at the end of the paragraph should have read, "(101 of 236 swabs [43%] vs. 63 of 197 swabs [32%], P=0.02)," rather than "(114 of 291 swabs [39%] vs. 70 of 233 swabs [30%], P=0.03)." These errors also occurred in Figure 1B, where the numbers in the "Swabs were taken" boxes should have been 236 (24%) in the second box from the left, with "101 (43%)" replacing "114 (39%)" in the box below, and 197 (22%) in the rightmost box, with "63 (32%)" replacing "70 (30%)" in the box below. The article is correct at NEJM.org.

NOTICES

Notices submitted for publication should contain a mailing address and telephone number of a contact person or department. We regret that we are unable to publish all notices received.

2ND INTERNATIONAL NEONATOLOGY ASSOCIATION CONFERENCE (INAC)

The conference will be held in Vienna, July 15–17.

Contact Janine Koeries, Paragon Group, 18 Avenue Louis-Casai, 1209 Geneva, Switzerland; or e-mail secretariat@worldneonatalogy.com; or see http://www.worldneonatalogy.com.

PRIMARY CARE FOCUS — 15TH ANNUAL SYMPOSIUM

The symposium will be held in Marco Island, FL, June 24–26.

Contact Baptist Health South Florida CME Department, 8900 North Kendall Dr., Miami, FL 33176-2197; or call (786) 596-2398; or e-mail CME@BaptistHealth.net; or see http://primarycarefocus.baptisthealth.net.

6TH INTERNATIONAL CONFERENCE ON TRANSCRANIAL BRAIN STIMULATION 2016

The conference will be held in Göttingen, Germany, Sept. 7–10.

Contact Conventus Congressmanagement & Marketing GmbH, Nadia Al-Hamadi/Sylvia Rudolph, Carl-Pulfrich-Strasse 1, 07745 Jena, Germany; or call (49) 3641 31 16-315/356; or e-mail tbs@conventus.de; or see http://www.tbs-conference.de.

AMERICAN COLLEGE OF CLINICAL PHARMACOLOGY

The 2016 Annual Meeting, entitled "Clinical Pharmacology: Discovery & Application in the Era of Precision Medicine," will be held in Bethesda, MD, Sept. 25–27.

Contact Krista Levy, ACCP, P.O. Box 1758, Ashburn, VA 20146-1758; or call (571) 291-3493; or e-mail KLevy@ACCP1.org; or see http://www.accp1.org.

CONNECTED HEALTH SYMPOSIUM 2016

The symposium, entitled "Digital Technology that Cares: Bringing the Human Element to Life," will be held in Boston, Oct. 20 and 21. It is presented by Partners HealthCare.

Contact the Center for Connected Health, 25 New Chardon St., Suite 300, Boston, MA 02114; or call (617) 724-3178; or see https://symposium.connectedhealth.org.

NEUROSCIENCE EDUCATION INSTITUTE

The "2016 NEI Psychopharmacology Congress" will be held in Colorado Springs, CO, Nov. 3–6. Deadline for submission of abstracts is Aug. 15.

Contact the Neuroscience Education Institute, 1930 Palomar Point Way, Suite 101, Carlsbad, CA 92008; or call (888) 535-5600; or e-mail customerservice@neiglobal.com; or see http://www.neiglobal.com/Congress/CNGOverview/tabid/147/Default.aspx.

THE *JOURNAL*'S WEB AND E-MAIL ADDRESSES

To submit a letter to the Editor: authors.NEJM.org

For information about the status of a submitted manuscript: authors.NEJM.org

To submit a meeting notice: meetingnotices@NEJM.org

The *Journal*'s web pages: NEJM.org