Therefore, as suggested in our article, further detailed study is warranted to understand this risk and the methods to reduce the risk. Because the outcome is rare, a nested case-control study within a large cohort, such as the Childhood Cancer Survivor Study, is needed to evaluate an ample number of cases to determine the site and source of strokes and potential modifying risk factors. Knowledge regarding additional factors that increase risk, including comorbidities and genetic determinants, could lead to better defining a population where the risk is sufficiently high that the cost-benefit for an appropriate form of screening would be justified. Second, a well-designed and adequately powered multicenter study of asymptomatic young adult Hodgkin's survivors and a population-based comparison group is needed to determine the prevalence of clinically significant carotid artery disease and to assess the measurement metrics (false-positive/negative rates, positive/negative predictive value rates) of carotid artery duplex ultrasound. Without this information, we cannot recommend universal screening in this population at the present time.

Daniel C. Bowers
Department of Pediatrics, University of Texas Southwestern Medical School, Dallas, TX

Kevin C. Oeffinger
Departments of Pediatrics and Internal Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY

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The authors indicated no potential conflicts of interest.

Progesterone Receptor and Human Epidermal Growth Factor Receptor 2 Status: An Independent Influence on the Efficacy of Endocrine Therapy in Breast Cancer?

To the Editor: The paper by Dowsett et al[1] adds convincing evidence on the relevance of progesterone receptor status in influencing the clinical outcome of early-stage breast cancer patients who undergo hormonal treatment. The authors also hypothesized that the greater benefit of anastrozole over tamoxifen in estrogen receptor–positive (ER+)/progesterone receptor–negative (PgR−) tumors might be explained, at least in part, by a greater expression of type1 growth factor receptors in this group, as recently suggested by others.[2] In order to investigate this specific issue, we examined our institutional series of 972 breast cancer patients who received the following adjuvant hormonal treatments: tamoxifen (n = 725), tamoxifen with luteinizing hormone releasing hormone analogs (n = 127), and aromatase inhibitors (n = 120). Immunohistochemistry was used to assess hormone receptor status (staining of > 1% of cells was considered as positive) and HER-2 status (human epidermal growth factor receptor 2; staining of 0% to 5% was coded as 0, 6% to 15% as 1+, 16% to 39% as 2+, and 40% to 100% as 3+).

We found that ER+/PgR− versus ER+/PgR+ tumors were characterized by larger size (diameter ≥ 2 cm: 57.1% *v* 42.6%; $P = .003$), nodal involvement (≥ 1 positive node: 51.8% *v* 45.0%; $P = .1$), higher tumor grade (grade 2-3: 88.2% *v* 79.0%; $P = .008$), higher Ki-67 expression (≥ 20%: 42.9% *v* 28.7%; $P = .001$), and lower ER expression (mean percentage of cell stained: 54.9% *v* 70.3%; $P = .000$). ER+/PgR− tumors were also more likely to overexpress HER-2 than ER+/PgR + tumors (2-3+: 36.5% *v* 17.9%; $P = .000$; mean percentage of stained cells: 21.5% *v* 9.2%; $P = .000$).

At the univariate analysis of survival, lack of PgR expression (hazard ratio [HR], 1.9; 95% CI, 1.0 to 3.6; $P = .03$) and HER-2 overexpression (HR, 2.2; 95% CI, 1.1 to 4.1; $P = .01$), as well as nodal status (HR, 2.9; 95% CI, 1.5 to 5.4; $P = .001$), tumor diameter (HR, 2.7; 95% CI, 1.4 to 4.9; $P = .001$), and tumor grading (HR, 5.0; 95% CI, 1.1 to 20.9; $P = .02$) showed a significant association with shorter disease-free survival (DFS), even after controlling for continuous levels of ER expression. In the multivariate Cox model including all variables, lack of PgR expression (HR, 4.0; 95% CI, 1.6 to 10.0; $P = .003$), tumor diameter (HR, 5.2; 95% CI, 1.1 to 23.1; $P = .003$), and nodal status (HR, 4.4; 95% CI, 1.2 to 15.3; $P = .01$), but not HER-2 overexpression ($P = .7$), retained their prognostic significance. We then conducted a subset analysis to evaluate the prognostic value of HER-2 overexpression in the subgroups of ER+/PgR+ and ER+/PgR− tumors, but we could not find any significant association with DFS even in this subset of patients.

Our study confirms that the lack of PgR expression in ER+ breast cancer is associated with aggressive tumor features and with HER-2 overexpression. Nevertheless, in our series of patients receiving 5 years of tamoxifen as the prevalent adjuvant treatment, only PgR status and not HER-2 status was an independent predictor of the risk of recurrence. Due to the small number of patients treated with anastrozole, we could not ascertain whether PgR and/or HER-2 status provide different information between patients who receive anastrozole versus tamoxifen. Nonetheless, the predictive value of PgR expression in the whole series was stronger and not dependent on HER-2 expression; therefore, we suggest that the difference in the relative efficacy of anastrozole and tamoxifen according to PgR status in the study by Dowsett at al is unlikely due to its segregation with HER-2 status.

Riccardo Ponzone, Furio Maggiorotto, Claudio Robba, Luca Fuso, and Piero Sismondi
Academic Department of Gynecological Oncology, Institute for Cancer Research and Treatment (IRCC) of Candiolo, University of Turin Medical School, Turin, Italy

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Authors	Employment	Leadership	Consultant	Stock	Honoraria	Research Funds	Testimony	Other
Riccardo Ponzone					AstraZeneca (A)			AstraZeneca (A); Novartis (A)
Piero Sismondi					AstraZeneca (A); Novartis (A)			AstraZeneca (A); Novartis (A)

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In Reply: We read with interest the data and comments of Ponzone et al regarding our hypothesis-generating article[1] on the possible differential sensitivity of anastrozole and tamoxifen to breast cancer based on progesterone receptor (PgR) status. Their focus is on the possible explanation of our results by human epidermal growth factor receptor 2 (HER-2) status being higher in PgR− tumors and HER-2–positive tumors being possibly more sensitive to aromatase inhibitors than to tamoxifen. Although the HER-2 positivity rates in their ER+ patients are higher than we generally find, we concur with their view that it is unlikely that this correlation with HER-2 fully explains our data. In a separate series of 617 ER+ patients, we found 19.5% of the PgR− tumors were HER-2+ compared with just 7.3% in the PgR+ group.[2] It seems implausible that an effect in only about one fifth of the PgR− patients could explain the profound effects on the outcome seen. We are currently collecting the archival tumors blocks from the Anastrozole or Tamoxifen Alone or in Combination (ATAC) trial to allow systematic centralized analysis of these key parameters. However, we would like to take this opportunity to emphasize that the data that we presented were an unplanned retrospective subgroup analysis and that the extent to which the observations are generalizable depends on their reproducibility in independent studies.

Mitch Dowsett
Royal Marsden NHS Foundation Trust, London, United Kingdom

Jack Cuzick and Chris Wale
Wolfson Institute of Preventive Medicine, Barts and The London Queen Mary's School of Medicine and Dentistry, London, United Kingdom

Tony Howell
Christie Hospital NHS Trust, Manchester, United Kingdom

Joan Houghton and Michael Baum
University College London Hospitals NHS Trust, London, United Kingdom

Aman Buzdar
The University of Texas M.D. Anderson Cancer Center, Houston, TX

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Authors	Employment	Leadership	Consultant	Stock	Honoraria	Research Funds	Testimony	Other
Mitch Dowsett			AstraZeneca (A); Novartis (B)		AstraZeneca (A); Novartis (A); Pfizer (A)	AstraZeneca (C); Novartis (C)		
Jack Cuzick			AstraZeneca (B); Eli Lilly (A); Novartis (A)					
Tony Howell					AstraZeneca (B); Eli Lilly (A); Novartis (A)			AstraZeneca (B); Novartis (A); Pfizer (A)
Joan Houghton						AstraZeneca (C)		AstraZeneca (B)
Michael Baum			AstraZeneca (B)		AstraZeneca (B)			
Aman Buzdar					AstraZeneca (A); Pfizer (A); Genentech (A)	AstraZeneca (C); Pfizer (C); Genentech (C)		

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