

## CORRESPONDENCE



## Polygenes, Risk Prediction, and Targeted Prevention of Breast Cancer

**TO THE EDITOR:** In their discussion of polygenics and breast cancer, Pharoah et al. (June 26 issue)<sup>1</sup> do not mention cost-effectiveness. If we take 3% for the reduction in total disease burden estimated by Pharoah et al. and apply it to the calculated 0.6-year increase in life expectancy if all breast cancers were eliminated,<sup>2</sup> current polygenic tests would increase life expectancy by just 1 week for the whole female population.

Although the gain is modest, the relatively low cost of implementing the polygenic approach makes it attractive when one considers the estimated additional quality-adjusted life years (QALYs). Even a comprehensive genomewide scan incorporating 500,000 markers now costs only \$1,000,<sup>3</sup> so using the figures for health-adjusted life expectancy,<sup>2</sup> one arrives at a cost of \$67,000 per additional QALY. This compares favorably with other approaches to improving survival among patients with breast cancer<sup>4</sup> and is certain to become more favorable as the cost of genome scanning plummets, more risk genes are documented, and many medical professionals use genome scans.

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**TO THE EDITOR:** Pharoah et al. concluded “that genetic risk profiles would improve population-based programs of intervention for breast cancer.” They assumed that there are two copies of each locus in the genome and that the risk conferred by seven breast-cancer susceptibility alleles is allele-dose-dependent. They also estimated the relative risk of breast cancer using a multiplicative model for interaction among seven common susceptibility alleles. However, they did not take into account the effect of copy-number variations. Moreover, three of seven alleles are located in regions of copy-number variations (<http://projects.tcag.ca/variation/>); for two of them, losses of copy in HapMap controls have been identified. Therefore, the number of possible combinations is higher than estimated, and the relative risk should be reassessed. Copy-number variations have been shown to be associated with common disorders<sup>1</sup> and to be responsible for variation in gene expression.<sup>2</sup> We would like to emphasize the difficulty of stratifying people according to genetic risk and the complexity of integrating different types of genetic variations in a statistical model at present.

### THIS WEEK'S LETTERS

- 1406 Polygenes, Risk Prediction, and Targeted Prevention of Breast Cancer
- 1407 Graves' Disease
- 1410 Retraction: Barlogie et al. Duration of Survival in Patients with Myeloma Treated with Thalidomide. *N Engl J Med* 2008;359:210-2.
- 1410 Zoledronic Acid Infusion and Orbital Inflammatory Disease

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**TO THE EDITOR:** Pharoah et al. report on seven polymorphic markers for breast-cancer risk replicated in genomewide-association studies. Although it is well known that cases of premenopausal and postmenopausal breast cancer have different risk factors, these cases were analyzed as one group. Polymorphisms may alter gene expression, but expression is also regulated by environmental factors, which may lead to epigenetic changes.<sup>1</sup> The magnitude of risk modification may be miscalculated when premenopausal and postmenopausal patients are combined and no questionnaire data on relevant environmental risk factors are considered. For example, the protective effect of caf-

feinated coffee on hereditary and sporadic breast cancer appears to be substantial but limited to women with the CYP1A2\*1F C allele.<sup>2,3</sup> CYP1A2 is a key enzyme in caffeine and estrogen metabolism.<sup>4</sup> It is biologically plausible that various combinations of genetic and nongenetic factors (e.g., coffee) that regulate CYP1A2 expression<sup>5</sup> affect risk differently. Combining data from questionnaires and genomewide-association studies in which premenopausal and postmenopausal patients are stratified may yield better risk estimates for the selection of women for screening.

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## Graves' Disease

**TO THE EDITOR:** In his Clinical Practice article on Graves' disease, Brent (June 12 issue)<sup>1</sup> comments on the combined use of antithyroid drugs and radioiodine and refers to the results of our trial,<sup>2</sup> showing no effects of antithyroid drugs on radioiodine therapy after a 3-day-withdrawal. However, in a subsequent meta-analysis,<sup>3</sup> we found that antithyroid drugs significantly reduced the success of radioiodine therapy, even when the drugs were discontinued for a week. This conclusion contradicted those of most of the included trials (including our own), which were most likely underpowered to detect significant differences. We now discontinue antithyroid drugs for more than a week before radioiodine therapy, if clinically feasible. Adequately powered trials are needed to better inform this issue.

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**TO THE EDITOR:** As noted by Brent and others,<sup>1</sup> thyroid volume, circulating titers of thyrotropin-receptor antibodies, sex, and age are predictors