functional significance of the 2 SNPs to provide a molecular rationale and validity for their epidemiologic observations. However, many questions remain to be addressed. For example, did the different doses of anastrozole (1 mg/day or 10 mg/day) or letrozole (2.5 mg/day or 10 mg/day) in the neoadjuvant study affect the degree of suppression of the tumor aromatase activity post-AI therapy? Did body mass index or obesity affect the estrogen level in the follow-up study? What if the electrophoretic mobility shift and reporter gene assays were performed using the more relevant estrogen receptor–positive breast cancer cell lines or fibroblasts? Thus far, none of the coding SNPs of CYP19 have been shown to alter the inhibitory effect of the third-generation AIs. Is it possible that the non-coding SNPs of CYP19, such as the 2 SNPs identified in this study, that lead to an increase in aromatase production may overwhelm these agents? CYP19 is subjected to tissue-specific transcriptional regulation through the various untranslated exon 1s. How are these SNPs involved in this process in various normal and tumor tissues?

Unfortunately, the SNPs did not correlate with tumor response to AIs in this study by Wang and colleagues. One could attribute the finding to the small sample size of the study. However, it may not be too surprising, considering the absence of a demonstrated correlation between baseline aromatase expression and clinical response in the large phase III neoadjuvant trial of tamoxifen versus letrozole (P024 trial). What about long-term clinical outcome? In the P024 study, the presence of tumor aromatase expression at baseline was a favorable independent prognostic factor for both relapse-free survival and breast cancer–specific survival. Based on this observation, one would imagine that the variant alleles of the 2 SNPs would predict a favorable clinical outcome; however, how do we reconcile the finding by Wang and colleagues that these variants were actually associated with a higher post-AI estradiol level? Regardless, a larger study to validate their findings is needed, and the relationship of these 2 SNPs with the long-term outcomes of patients on these highly potent AIs remains to be seen. Furthermore, the considerable heterogeneity of estrogen receptor–positive breast cancer adds another layer of complexity to the problem.

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References

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**RADIATION THERAPY**

**Long-Term Results of Hypofractionated Radiation Therapy for Breast Cancer**

Whelan TJ, Pignol J-P, Levine MN, et al (McMaster Univ, Hamilton, Ontario, Canada; Odette Cancer Centre, Toronto, Ontario, Canada; et al)


**Background.**—The optimal fractionation schedule for whole-breast irradiation after breast-conserving surgery is unknown.

**Methods.**—We conducted a study to determine whether a hypofractionated 3-week schedule of whole-breast irradiation is as effective as a 5-week schedule. Women with invasive breast cancer who had undergone breast-conserving surgery and in whom resection margins were clear and axillary lymph nodes were negative were randomly assigned to receive whole-breast irradiation either at a standard dose of 50.0 Gy in 25 fractions over a period of 35 days (the control group) or at a dose of 42.5 Gy in 16 fractions over a period of 22 days (the hypofractionated-radiation group).

**Results.**—The risk of local recurrence at 10 years was 6.7% among the 612 women assigned to standard irradiation as compared with 6.2% among the 622 women assigned to the hypofractionated regimen (absolute difference,
0.5 percentage points; 95% confidence interval (CI), −2.5 to 3.5). At 10 years, 71.3% of women in the control group as compared with 69.8% of the women in the hypofractionated-radiation group had a good or excellent cosmetic outcome (absolute difference, 1.5 percentage points; 95% CI, −6.9 to 9.8).

Conclusions.—Ten years after treatment, accelerated, hypofractionated whole-breast irradiation was not inferior to standard radiation treatment in women who had undergone breast-conserving surgery for invasive breast cancer with clear surgical margins and negative axillary nodes. (ClinicalTrials.gov number, NCT00156052.)

This randomized trial of the Ontario Clinical Oncology Group, the results of which were recently published in the New England Journal of Medicine, is one of the largest randomized trials with long-term follow-up (10 years) and demonstrated equivalent long-term results with a modestly hypofractionated course of radiation therapy that can be delivered in 3 weeks as opposed to the standard 5-7 weeks of radiation therapy for early-stage invasive breast cancer. This landmark article by Whelan and colleagues is potentially practice changing, given its relatively large size and excellent long-term follow-up. The trial showed equivalent local control and cosmetic outcomes between the standard regimen and this hypofractionated regimen of 42.5 Gy in 16 fractions. While the results of this study clearly support the equivalence of this regimen to standard fractionation in terms of outcomes for selected patients, the trial raises several questions regarding its potential clinical implications. Since the patients in this trial had early-stage invasive cancers that were all node-negative and were treated without a boost to the tumor bed, and the majority did not receive chemotherapy, questions arise as to whether these results can be extrapolated to patients who have received current forms of chemotherapy, may benefit from a boost to the tumor bed, have ductal carcinoma in situ as opposed to invasive cancer, and, most importantly, have high-grade tumors, which were shown in this trial to have inferior local control.

Based on this study, given its excellent design, execution, and follow-up, most clinicians would agree that this hypofractionated regimen appears to be safe and effective in patients who met the eligibility criteria for the trial, are not going to receive a boost, are not receiving systemic chemotherapy, and who do not have high-grade tumors. For other patients, who either were not represented at all in this trial or who composed a minority of patients in the trial, these issues remain unsettled and clearly require additional data and follow-up. While some clinicians and patients might support either using a boost in the patients in this study population or using this regimen in patients who had received cytotoxic chemotherapy, others may not feel comfortable doing so. The issue of why patients with high-grade tumors had poorer local control, and whether this would be overcome with the use of a boost and/or systemic therapy, remains unresolved. These issues are discussed at length in an American Society of Therapeutic Radiation Oncology consensus panel document that is currently in press. However, this timely randomized trial from Canada clearly establishes hypofractionated whole-breast irradiation as an acceptable standard of care for selected patients with node-negative breast cancer. Hopefully, future studies will address some of the unanswered questions regarding the appropriateness of hypofractionated radiation therapy in a broader group of patients.

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Reference
