

Guidelines for International Breast Health and Cancer Control–Implementation

Supplement to Cancer

Effective but Cost-Prohibitive Drugs in Breast Cancer Treatment

A Clinician's Perspective

Jose Bines, MD¹
Alexandru Eniu, MD²

¹ Instituto Nacional de Cancer, Rio de Janeiro, Brazil.

² Department of Breast Tumors, Cancer Institute "Ion Chiricuta," Cluj-Napoca, Romania.

The views expressed in this article are the results of independent work and do not represent the views of the authors' institutions.

Dr. Bines has received honoraria from Astra-Zeneca and has acted as either a consultant or in an advisory role for Bristol Myers-Squibb and Astra-Zeneca.

Complete financial disclosures are presented at the end of this article.

We express our gratitude to Gabriel N. Hortobágyi, MD and Robert W. Carlson, MD for their review of earlier drafts.

Address for reprints: Jose Bines, MD, Instituto Nacional de Cancer-Brasil, Rua Visconde de Santa Isabel 274, Rio de Janeiro, Brasil; Fax: (011) 55-21-2577-6941; E-mail: jose_bines@yahoo.com

Received June 10, 2008; accepted June 24, 2008.

New pharmacologic treatments for early-stage breast cancer have been proven effective, but many of them are cost prohibitive in low economic settings. Differences in breast cancer mortality rates between developed and developing countries may be because of differences in screening and treatment options, some of which may be unavailable or limited by cost constraints in countries with limited resources. It is well recognized that treatment choices have to be made within budgetary constraints, and treatment guidelines that address the need to stratify treatment options by available resources have been published by the Breast Health Global Initiative. Practical treatment choices need to be made based on the best available cost-effective information. This article reviews new and emerging medical strategies that may improve the cost-effectiveness equation. *Cancer* 2008;113(8 suppl):2353–8. © 2008 American Cancer Society.

KEYWORDS: breast cancer, treatment, cost, drugs.

Breast cancer mortality in developed countries has been decreasing since the 1990s.¹ At the same time, breast cancer mortality trends have continued to increase in Brazil and other less developed countries.² This discrepancy is associated with increasing breast cancer incidence, later stage disease at presentation (associated with incomplete implementation of effective screening strategies, such as mammography), and lack of adequate adjuvant, systemic treatment in developing countries.³ New pharmacologic treatments have been proven effective in the management of early-stage breast cancer: hormone agents (the selective aromatase inhibitors [AIs]⁴ in postmenopausal women), chemotherapy (the taxanes paclitaxel⁵ and docetaxel^{6,7}), and human epidermal growth factor receptor 2 (HER-2)-targeted therapies (trastuzumab).^{8–10} Compared with earlier standard pharmacologic regimens, it has been demonstrated that these new agents independently decrease the relative risk of breast cancer mortality on the order of 30%, which translates into an absolute benefit in breast cancer mortality of approximately 3%.^{4–10} It should be noted that these advantages are proportional to the initial risk; the higher the risk, the greater the benefit.

These new agents, as well as many of the more established effective medications, remain unaffordable in low- and middle-

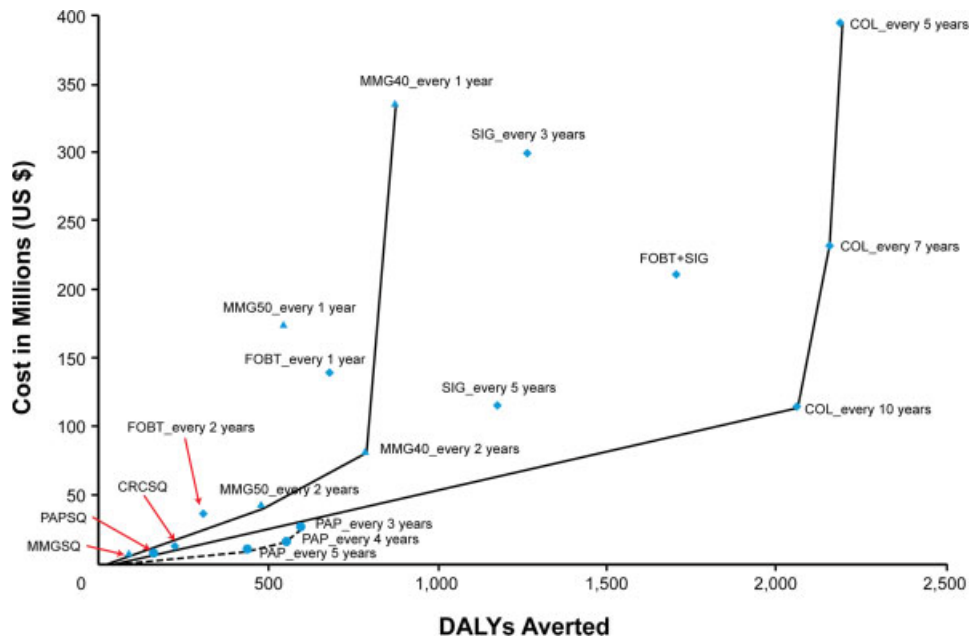


FIGURE 1. Expansion path for the most cost-effective set of cancer screening strategies according to average and incremental cost effectiveness. DALY indicates disability-adjusted life-year; PAP, Papanicolaou (Pap) smear testing; MMG, mammography screening; FOBT, fecal occult blood testing; SIG, sigmoidoscopy screening; FOBT + SIG, annual fecal occult blood testing plus sigmoidoscopy screening every 5 years; COL, colonoscopy screening; SQ, status quo; CRC, colorectal cancer. PAP_every 3 years, Pap smear screening every 3 years at 100% coverage; MMG40_every 2 years, mammography screening every 2 years for those ages 40 to 74 years at 100% coverage; MMG50_every 2 years, mammography screening every 2 years for those ages 50 to 74 years at 100% coverage, and so on.¹³ Reprinted with permission from Woo PPS, Kim JJ, Leung GM. What is the most cost-effective population based cancer screening package for Chinese women? *J Clin Oncol.* 2007;25:617-624.

income countries. In the public sector, although treatments often are provided free of charge, the reality of budgetary considerations can make high-cost drugs unavailable.¹¹ Whereas these drugs may be available in the private sector or in clinical trials, only a minority of patients will have access to high-cost drugs. Our greatest challenge in the next decade is to broaden the access to new pharmacologic treatments both for underserved groups in developed countries and for the general population in less affluent nations.

Broadening the Concept of Cost-effectiveness

Cost-effectiveness analyses are important strategies that can be used to measure the value attributed to an intervention. However, most cost-effectiveness studies consider only a single intervention compared with either no intervention or some representation of usual practice.¹² Other methods to consider include that used by Woo et al¹³ to evaluate mammography. Those authors set out lists of the most effective combinations of women's cancer screening activities that can be encompassed within current and hypotheti-

cally increased spending levels. In their example (see Fig. 1), a sharp increase in cost can be anticipated if screening mammography is performed annually after age 40 years compared with every 2 years. A yearly screening strategy did not add much benefit when measured in disability-adjusted life-years (DALYs) (Fig. 1). Those results originated from local cancer epidemiologic data, and the budgets were derived from local expenditure patterns. This overall approach to decision-making based on a limited budget, as observed in the example of mammography, can be generalized; analogous conclusions likely could be applied to other situations such as the breast cancer treatments.

We need to set limits for the interventions that are planned, and evaluating the 10-year survival benefit is 1 strategy. For example, Telli et al¹⁴ used the remaining risk of death after 10 years for women with early-stage breast cancer who underwent surgery and received adjuvant chemotherapy to identify low-risk, intermediate-risk, and high-risk groups, with an associated distant recurrence-free survival (DRFS) of 80%, 60%, and 40%, respectively (Table 1). Assuming that tumors have HER-2 gene amplifica-

TABLE 1
Projected 10-year Survival Benefits by the Addition of Trastuzumab and Associated Costs for Women With a Projected 10-year Low, Intermediate, and High Risk of Death From Breast Cancer After Adjuvant Chemotherapy: From National Surgical Adjuvant Breast and Bowel Project Trial B-31 and North Central Cancer Treatment Group Trial N-9831*

Risk Group	Projected 10-year Survival After Chemotherapy		Projected 10-year Survival Benefit of Trastuzumab			Cost
	%	RB, %	AB, %	NNT		
Low risk	80	33	7	15	\$\$\$	
Intermediate risk	60	33	13	7.5	\$\$	
High risk	40	33	20	5	\$	

RB indicates relative benefit; AB, absolute benefit; NNT, number needed to treat.
 *Modified from Telli ML, Hunt SA, Carlson RW, Guardino AE. Trastuzumab-related cardiotoxicity: calling into question the concept of reversibility. *J Clin Oncol.* 2007;25:3525-3533.¹⁵

tion (or protein overexpression), the addition of trastuzumab decreases mortality risk by 33%. Without taking into consideration data on long-term treatment toxicity (currently unavailable), the analysis of the projected 10-year DRFS translates into an absolute benefit of 7%, 13%, and 20% for the low-risk, intermediate-risk, and high-risk groups, respectively. The corresponding numbers needed to treat are 15 patients, 7.5 patients, and 5 patients, respectively. With limited resources and multiple treatment options, a 10-year survival benefit analysis can help inform treatment decisions.

Exploring Changes in Treatment Duration

Reduced treatment duration

One way to reduce costs is to decrease the length of treatment. The HER-2 gene is amplified in approximately 20% of breast cancers.¹⁵ Large, adjuvant, anti-HER-2-targeted therapy trials with trastuzumab that enrolled thousands of women worldwide consistently showed an improvement in disease-free and overall survival in the order of 50% and 30%, respectively.⁹⁻¹¹ Those studies compared chemotherapy alone with chemotherapy and trastuzumab treatment for a total duration of 1 year. Although studies comparing 1 year of treatment versus 2 years of treatment are ongoing, other trials are looking at shorter administration periods. An encouraging trial of 9 weeks of trastuzumab treatment has been reported.¹⁶ Despite a much smaller sample size, the magnitude of the benefits of 9 weeks of trastuzumab are remarkably similar to those observed in larger trials using 52 weeks of trastuzumab. Another trial is comparing 6

months versus 1 year of trastuzumab treatment.¹⁷ Along with diminishing treatment expenses, effective shortened treatment regimens also may have an added benefit of increased patient compliance.

Intermittent versus continuous treatment

New strategies are being studied as we develop a better understanding of the mechanisms of action and resistance to hormone agents. Clinical trials are ongoing based on the theoretical principle that AI withdrawal may permit estrogenic stimulation and increase the susceptibility of the residual resistant cells to AI reintroduction. One such study is comparing continuous versus intermittent letrozole for 5 years after prior tamoxifen and/or AI treatment.¹⁸ Intermittent versus continuous AI treatment would result in reduced treatment costs.

Exploring Drug Bioavailability

The increase in the number of oral compounds available for breast cancer treatment provides an opportunity for drug interactions with either food or other drugs that may increase bioavailability, reducing the dose needed to treat, and hence lowering the overall cost of treatment. For example, lapatinib is an oral epidermal growth factor receptor and HER-2 tyrosine kinase inhibitor that recently was approved for advanced HER-2-overexpressing/amplified breast cancer after trastuzumab failure. Ratain and Cohen¹⁹ recently published pharmacokinetics data showing that lapatinib plasma concentrations increase when taken with food, particularly fat (although the label use advises it should be taken on an empty stomach). In addition, inhibitors of the enzyme CYP3A (such as grapefruit juice) may raise lapatinib bioavailability further. Therefore, it may be speculated that just by taking advantage of these simple food interactions, the overall treatment costs can be decreased significantly. Although these results are provocative, we need to await prospective clinical data to validate this concept.

Exploring Targeted Treatment

The first and most important advance in targeted therapy for breast cancer is the ability to target the estrogen receptor. After the subsequent advances in HER-2-targeted therapies, we are now on the verge of the release of a multitude of new targeted drugs.²⁰ The emerging contributions of genomics, proteomics, and pharmacogenetics may increase the effectiveness of treatment and decrease unnecessary toxicity as well as cost by selecting the appropriate treatment-patient-tumor match.²¹

Multigene panels

Multigene panels such as Oncotype DX represent such an effort. This panel of 21 genes (including 5 reference genes) is reported in the form of a recurrence score that classifies tumors into low risk, intermediate risk, and high risk. Oncotype DX was validated retrospectively on biopsy material from the National Surgical Adjuvant Breast and Bowel Project Trial B-20,²² which reported no significant difference in the distant disease-free survival rate with the addition of combined chemotherapy (cyclophosphamide, methotrexate, and fluorouracil [CMF]) to tamoxifen in the low-risk recurrence group (Table 2). At the same time, in the high-risk group, the addition of chemotherapy led to a remarkable benefit. Multigene arrays can identify a large number of patients who do not need adjuvant chemotherapy in addition to tamoxifen and can turn regimens such as CMF chemotherapy into targeted treatment. Although multigene arrays may decrease the costs associated with chemotherapy administration, to date, the test itself is costly enough to limit its usefulness in countries of limited resources.

Pharmacogenetics and enzyme metabolites

Pharmacogenetics also can provide a more individualized treatment choice based on a patient's enzyme levels. There is genetic variation and inhibition of the enzyme system CYP2D6, a key enzyme in many drug metabolic pathways, including tamoxifen. Patients can be classified as decreased, intermediate, or extensive metabolizers, according to their enzyme variants. On the basis of adjuvant tamoxifen trials in postmenopausal women, Goetz et al²³ demonstrated that patients with decreased metabolism had a significantly shorter time to recurrence and worse recurrence-free survival compared with the intermediate and extensive metabolizers. Once this strategy is validated prospectively, it may be of value in determining the most cost-effective adjuvant hormone therapy.

New roles for old drugs

Older drugs that previously were discarded or were considered minimally active in breast cancer are being reevaluated from a targeted perspective. The platinum drugs, such as cisplatin, resurfaced as active treatment for breast cancer after preclinical models suggested their synergism with trastuzumab as HER-2-targeted treatment.²⁴ There is growing evidence for their role as effective therapy in the breast cancer triple-negative subgroup.²⁵ Small and continuous daily doses of cyclophosphamide and methotrexate, known as 1 of the metronomic chemo-

TABLE 2
Ten-year Distant Recurrence-free Survival From National Surgical Adjuvant Breast and Bowel Project Trial B-20 (Lymph Node-negative, Estrogen Receptor-positive Tumors) According to the Recurrence Score in the Low-risk and High-risk Groups

Recurrence Score	Tamoxifen, %	Tamoxifen and CMF, %
Low (<18)	97	96
High (≥31)	60	88

CMF indicates combined cyclophosphamide, methotrexate, and 5-fluorouracil.

*Modified from Paik S, Tang G, Shak S, et al. Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. *J Clin Oncol*. 2006;24:3726-3734.²²

therapy regimens, may have antiangiogenic properties as 1 of its mechanisms of action and is active against metastatic disease.^{26,27} Adjuvant studies are ongoing that randomize patients with receptor-negative disease, after the completion of adjuvant chemotherapy, to observation versus 1 year of metronomic chemotherapy with cyclophosphamide and methotrexate.²⁸ In the same venue, drugs that are off patent, such as megestrol acetate²⁹ and estradiol,³⁰ may find their way back in the unfolding sequences of hormone agents in breast cancer treatment. Finding an active role for older and off-patent drugs may represent an enormous advantage in the cost-benefit ratio.

DISCUSSION

Treatment options are limited by available resources.¹² Choices have to be based on cost and the effectiveness of the different management strategies. There is a need to broaden the concept of cost-effectiveness and include multiple interventions as opposed to a single intervention. The information provided by each intervention strategy has to be combined to provide better integrated care planning. Quantifying 10-year survival benefit data also may help inform decisions, because there is a direct correlation between the level of risk, the benefit from treatment, and decreasing costs, as shown in Table 1.

A straightforward and pragmatic view of improving the cost-effectiveness equation is to decrease costs or to increase effectiveness. Decreasing costs is complex and involves many factors and players, including patients and society as a whole, the payers (the individual, government, or third-party payers), the medical providers, and the healthcare system.³¹ From a medical perspective, studies of effective shortened treatment duration and intermittent administration are needed. Strategies to improve on existing therapies may be able to take advantage of drug

interactions with food and other drugs that increase their bioavailability.

The emerging contributions of genomics, proteomics, and pharmacogenetics may increase the effectiveness of treatment and decrease unnecessary toxicity as well as cost by selecting the appropriate treatment-patient-tumor match. We are moving rapidly into the targeted drug era for breast cancer treatment in which the goal is to optimize customized treatment. Through the use of multigene arrays and pharmacogenetics, treatment may be selected for the patients who most likely will benefit from it, avoiding unnecessary toxicity and cost. At the same time, older drugs (with lower costs compared with newer treatments) may find their way back and have the potential to assume new roles as they are selected for the right target patient population. The implementation of new pharmacologic treatments into practice likely will decrease breast cancer mortality rates further. The 'work in progress' is determining how to provide these treatments worldwide to this growing population in need.

FINANCIAL DISCLOSURES

Funding for the International Breast Health and Cancer Control-Implementation (BHGI) 2007 Global Summit on International Breast Health-Implementation and *Guidelines for International Breast Health and Cancer Control-Implementation* publication came from partnering organizations who share a commitment to medically underserved women. We thank and gratefully acknowledge these organizations and agencies for grants and conference support: Fred Hutchinson Cancer Research Center; Susan G. Komen for the Cure; American Society of Clinical Oncology (ASCO); US National Cancer Institute, Office of International Affairs (OIA); American Cancer Society; Lance Armstrong Foundation; US Agency for Healthcare Research and Quality (AHRQ) (*Grant 1 R13 HS017218-01); US Centers for Disease Control and Prevention, Division of Cancer Prevention and Control, National Center for Chronic Disease Prevention and Health Promotion; American Society of Breast Disease; Oncology Nursing Society; US National Cancer Institute, Office of Women's Health (OWH); and US National Institutes of Health, Office of Research on Women's Health (ORWH).

*Funding for the 2007 *Global Summit on International Breast Health—Implementation* was made possible (in part) by Grant No. 1 R13 HS017218-01 from the Agency for Healthcare Research and Quality (AHRQ). The views expressed in written conference materials or publications and by speakers and moderators do not necessarily reflect the official policies of the Department of Health and Human Services; nor does mention of trade names, commercial practices, or organizations suggest endorsement by the US Government.

We thank and gratefully acknowledge the generous support of our corporate partners through unrestricted educational grants: Pfizer Inc.; AstraZeneca; Bristol-Myers Squibb Company; Ethicon Endo Surgery, Inc.; GE Healthcare; F. Hoffmann-La Roche AG; and Novartis Oncology.

BHGI is a global health alliance of organizations and individuals. We are grateful to our collaborators throughout the

world who share the BHGI mission and vision. Thank you for your important contributions to this endeavor for medically underserved women.

REFERENCES

1. Peto R, Boreham J, Clarke M, Davies C, Beral V. UK and USA breast cancer deaths down 25% in year 2000 at ages 20–69 years [letter]. *Lancet*. 2000;355:1822.
2. Ministry of Health of Brazil. National Cancer Institute Annual Report. Rio de Janeiro, Brazil: Ministry of Health of Brazil; 2002.
3. Berry DA, Cronin KA, Plevritis SK, et al. Effect of screening and adjuvant therapy on mortality from breast cancer. *N Engl J Med*. 2005;353:1784-1792.
4. Kaufmann M, Jonat W, Hilfrich J, et al. Improved overall survival in postmenopausal women with early breast cancer after anastrozole initiated after treatment with tamoxifen compared with continued tamoxifen: the ARNO 95 study. *J Clin Oncol*. 2007;25:2664-2670.
5. Henderson IC, Berry DA, Demetri GD, et al. Improved outcomes from adding sequential paclitaxel but not from escalating doxorubicin dose in an adjuvant chemotherapy regimen for patients with node-positive primary breast cancer. *J Clin Oncol*. 2003;21:976-983.
6. Roche H, Fumoleau P, Spielmann M, et al. Sequential adjuvant epirubicin-based and docetaxel chemotherapy for node-positive breast cancer patients: the FNCLCC PACS 01 trial. *J Clin Oncol*. 2006;24:5664-5671.
7. Martin M, Pienkowski T, Mackey J, et al. Adjuvant docetaxel for node-positive breast cancer. *N Engl J Med*. 2005;352:2302-2313.
8. Smith I, Procter M, Gelber RD, et al. 2-Year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: a randomised controlled trial. *Lancet*. 2007;369:29-36.
9. Perez EA, Romond EH, Suman VJ, et al. Updated results of the combined analysis of NCCTG N9831 and NSABP B-31 adjuvant chemotherapy with/without trastuzumab in patients with HER2-positive breast cancer [abstract]. ASCO Annual Meeting Proceedings. *J Clin Oncol*. 2007;25:18S. Abstract 512.
10. Robert NJ, Eiermann W, Pienkowski T, et al. BCIRG 006: docetaxel and trastuzumab-based regimens improve DFS and OS over AC-T in node positive and high risk node negative HER2 positive early breast cancer patients: quality of life (QOL) at 36 months follow-up [abstract]. ASCO Annual Meeting Proceedings. *J Clin Oncol*. 2007;25:18S. Abstract 19647.
11. Steinbrook R. Closing the affordability gap for drugs in low-income countries. *N Engl J Med*. 2007;357:1996-1999.
12. Schechter CB. Cost effectiveness in context. *J Clin Oncol*. 2007;25:609-610.
13. Woo PPS, Kim JJ, Leung GM. What is the most cost-effective population based cancer screening package for Chinese women? *J Clin Oncol*. 2007;25:617-624.
14. Telli ML, Hunt SA, Carlson RW, Guardino AE. Trastuzumab-related cardiotoxicity: calling into question the concept of reversibility. *J Clin Oncol*. 2007;25:3525-3533.
15. Slamon DJ, Clark GM, Wong SG, Levin W, Ullrich A, McGuire W. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/*neu* oncogene. *Science*. 1987;235:177-182.
16. Joensuu H, Kellokumpu-Lehtinen PL, Bono P, et al. Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer. *N Engl J Med*. 2006;354:809-820.

17. National Institutes of Health. Trastuzumab for 6 months or 1 year in treating women with nonmetastatic breast cancer that can be removed by surgery. Clinical trials no. NCT00381901. Bethesda, Md: National Institutes of Health; 2007. Available at:<http://clinicaltrials.gov/show/NCT00381901>. Accessed on March 13, 2008.
18. Colleoni M, Maibach R. BIG 1-07/1BCSG 35-07 SOLE Ready for Activation. *Breast International Group Newsletter*. 2007;9:22.
19. Ratain M, Cohen EE. The value meal: how to save \$1700 per month or more on lapatinib. *J Clin Oncol*. 2007;25:3397-3398.
20. Pegram MD, Pietras R, Bajamonde A, et al. Targeted therapy: wave of the future. *J Clin Oncol*. 2005;23:1776-1781.
21. Sledge GW Jr. What is targeted therapy? *J Clin Oncol*. 2005;23:1614-15.
22. Paik S, Tang G, Shak S, et al. Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. *J Clin Oncol*. 2006;24:3726-3734.
23. Goetz MP, Knox SK, Suman VJ, et al. The impact of cytochrome P450 2D6 metabolism in women receiving adjuvant tamoxifen. *Breast Cancer Res Treat*. 2007;101:113-121.
24. Pegram M, Hsu S, Lewis G, et al. Inhibitory effects of combinations of HER-2/neu antibody and chemotherapeutic agents used for treatment of human breast cancers. *Oncogene*. 1999;13:2241-2251.
25. Garber JE, Richardson A, Harris LN, et al. Neo-adjuvant cisplatin (CDDP) in "triple-negative" breast cancer (BC). Presented at the 29th Annual San Antonio Breast Cancer Symposium, San Antonio, Texas, December 14-17, 2006. Abstract 3074.
26. Colleoni M, Rocca A, Sandri MT, et al. Low-dose oral methotrexate and cyclophosphamide in metastatic breast cancer: antitumor activity and correlation with vascular endothelial growth factor levels. *Ann Oncol*. 2002;13:73-80.
27. Burstein HJ, Spigel D, Kindsvogel K, et al. Metronomic chemotherapy with and without bevacizumab for advanced breast cancer: a randomized phase II study. Presented at the 28th Annual San Antonio Breast Cancer Symposium, San Antonio, Texas, December 8-11, 2005. Abstract 4.
28. National Institutes of Health. Combination chemotherapy after surgery in treating patients with stage I, stage II, or stage III breast cancer. Clinical trials no. NCT00022516. Bethesda, Md: National Institutes of Health; 2007. Available at: <http://clinicaltrials.gov/ct2/show/NCT00022516?term=ibcsg+22&rank=1>. Accessed on March 13, 2008.
29. Branco LP, Dienstmann R, Bines J. Megestrol acetate after aromatase inhibitor failure in metastatic breast cancer [abstract]. ASCO Annual Meeting Proceedings. *J Clin Oncol*. 2006;24. Abstract 10572.
30. Lewis JS, Meeke K, Osipo C. Intrinsic mechanism of estradiol-induced apoptosis in breast cancer cells resistant to estrogen deprivation. *J Natl Cancer Inst*. 2005;23:1746-1759.
31. Blackman DJ, Masi CM. Racial and ethnic disparities in breast cancer mortality: are we doing enough to address the root causes? *J Clin Oncol*. 2006;24:2170-2178.