

A Decade of Breast Cancer Clinical Investigation: Results as Reported in the *Program/Proceedings of the American Society of Clinical Oncology*

By Rowan T. Chlebowski and Linda M. Lillington

Purpose: To test the hypothesis that clinical research results have driven changes in recent breast cancer management recommendations.

Methods: All breast cancer abstracts in the *Program/Proceedings of the American Society of Clinical Oncology* (ASCO) from 1984 to 1993 were prospectively reviewed in 31 areas and categorized by study type, study question, whether statistical significance was claimed, and whether the abstract was presented.

Results: Of 1,372 abstracts, 54% reported on prospective clinical trials (PCTs) and 17% on randomized clinical trials (RCTs). The total number of published abstracts progressively increased (from 87 in 1984 to 221 in 1993) and author citations nearly quadrupled (from 430 in 1984 to 1,642 in 1993, $P < .01$); however, RCTs have come to represent a smaller proportion of reports: 37% (33 of 89) in 1986 versus 10% (22 of 221) in 1993 ($P < .001$). The size of adjuvant-therapy RCTs has progressively increased (mean \pm SEM subjects/trial, 237 ± 43 in 1984 to 874 ± 374 in 1993), but has remained small in advanced-disease RCTs (mean \pm SEM subjects/

trial, 145 ± 25 in 1984 to 146 ± 34 in 1993). For adjuvant therapy, 14 of 90 RCTs (with 51,207 patients) reported a significant ($P < .05$) survival benefit for investigational therapies (16%). For advanced-disease therapy, only three of 141 RCTs (with 26,281 patients) reported a significant ($P < .05$) survival benefit for investigational therapies (2%). Randomization was rarely used in trials of dose-intensity with blood-product support (zero of 86 trials) or locally advanced disease.

Conclusion: For breast cancer ASCO abstracts in the past decade, we determined the following: (1) adjuvant trials have not infrequently supported study hypotheses; and (2) advanced-disease trials have consistently failed to identify new approaches with a significant impact on survival. These results suggest that a critical process evaluation of current policy and procedures involved in directing breast cancer research is warranted, especially for strategies in advanced disease.

J Clin Oncol 12:1789-1795. © 1994 by American Society of Clinical Oncology.

DESPITE THE recent, well-documented public and scientific interest in breast cancer,^{1,2} recommended management strategies for breast cancer patients with advanced disease have undergone little change in the past decade.³⁻⁵ In contrast, major change in patient management has occurred for patients treated with adjuvant treatment.^{3,6} Taken together, these observations suggest that changes in recommended clinical management for breast cancer patients over this period have been driven by corresponding changes in clinical research results. To test this hypothesis, a decade of clinical research activity in the area of breast cancer was prospectively evaluated for specific topic, study design, and reported outcome, accomplished by review of all abstracts published in the *Program/Proceedings of the American Society of Clinical Oncology* (ASCO) between 1984 and 1993 related to breast cancer.

The *Proceedings* were selected for review, because the Annual Meeting of ASCO has emerged in recent years as a major international forum for presentation of clinical oncology trial results. The abstracts submitted to this meeting and published in the *Proceedings* of ASCO are frequently referenced and represent a substantial influence on clinical practice. In addition, the ASCO *Proceedings* provide a cumulative summary of research activity both in the United States and around the world.

METHODS

Abstracts published during the most recent 10-year period, including 1984 through 1993, were reviewed for content in 31 prospectively determined categories by one investigator (R.T.C.). The categories for review were determined by concurrence of a three-person expert panel of medical oncologists; the information collected is listed in Table 1. Abstracts were categorized by study category (prospective clinical trial, analytic study, nonclinical), study question, whether statistical significance was claimed, and whether the abstract was selected for presentation.

The following definitions were used to categorize abstract reports: prospective clinical trials (PCTs) must have had a clearly defined prospective intervention not involving review of prior experience; randomized clinical trials (RCTs) must have additionally included the term randomization in the title or body of the abstract and must have incorporated two or more identifiable treatment arms. Analytic (cohort) studies involved either a prospective or a retrospective re-

From the Division of Medical Oncology, Harbor-University of California at Los Angeles Medical Center, Torrance, CA.

Submitted December 20, 1993; accepted April 21, 1994.

Address reprint requests to Rowan T. Chlebowski, MD, PhD, Professor of Medicine, University of California at Los Angeles School of Medicine, Associate Chief, Division of Medical Oncology, Harbor-University of California at Los Angeles Medical Center, 1000 W Carson St, Torrance, CA 90509.

© 1994 by American Society of Clinical Oncology.

0732-183X/94/1209-0009\$3.00/0

Table 1. Information Collected From ASCO Breast Cancer Reports

Year _____	Abstract ID _____	No. of authors _____
Institution: USA _____ Not USA-based _____		
No. of patients reported in abstract _____		
Study category		
I. Prospective clinical trial _____		
a) Multisite _____ Single-site _____		
b) Randomized _____ Not randomized _____		
c) Therapy category:		
Advanced disease _____ Adjuvant _____		
Locally advanced _____ Other _____		
II. Analytic (cohort) study _____		
a) Prospective _____ b) Retrospective _____		
III. Nonclinical _____		
Study question		
I. New drug _____		
a) Chemotherapy _____ b) Hormone therapy _____		
II. Chemotherapy dose-intensity _____		
a) With blood-product support (bone marrow/stem cell) _____		
b) Without blood-product support _____		
III. Prognostic factors _____		
IV. Compare regimens _____ v Other _____		
Statistical difference claimed in abstract _____		
I. On disease-free interval (in adjuvant trials) _____		
II. On response or disease-free interval _____		
III. On survival _____		
Selected for presentation _____		

view of a patient population, often used to identify prognostic factors, or reviews of institutional treatment experiences. Chemotherapy dose-intensity studies with blood-product support must have included reference to either bone marrow transplantation or prospective harvesting and subsequent infusion of stem cells. Studies in locally advanced disease must have included either that phrase or reference to therapy of stage IIIB disease.

All abstracts listed in the breast cancer section, as well as those indexed under the topic of breast cancer in the *ASCO Proceedings*, were reviewed and are the subject of this report, with additional attention given to those reporting on PCTs. For all parameters, descriptive summary information was determined (frequency, percentages, mean, and range). Comparisons between identified groups were determined by χ^2 analyses and paired *t* tests using the BMDP statistical software program.⁷

RESULTS

A total of 1,372 abstracts published in the *ASCO Proceedings* between 1984 and 1993 were identified as pertinent to breast cancer. The majority (54%) of abstracts were reports of PCTs, with RCTs accounting for 17% of all reports (Table 2). The worldwide scope of the *ASCO Proceedings* was reflected in the representation of both United States-based (in 54%) and non-United States-based (in 46%) investigative teams reporting breast cancer results as a relatively constant percentage throughout this period.

Table 2. ASCO Breast Cancer Reports (1984-1993) by Abstract Category

Abstract Category	Total Reports	
	No.	%
Breast cancer as topic	1,372	100
PCTs	741	54
RCTs (total)	236	17
RCTs in		
Advanced-disease therapy	141	10
Adjuvant therapy	93	7
Total no. of patients entered on randomized trials by category		
Adjuvant therapy	51,207	
Advanced-disease therapy	26,281	

The number of total abstracts, those reporting on PCTs, and those reporting on RCTs on an annual basis over the past 10 years are graphically depicted in Fig 1. The number of published breast cancer abstracts progressively increased throughout the decade of review, with major increases occurring in 1988 and 1992. The mean number of authors per abstract has almost steadily increased as well, from 5.32 ± 0.21 (mean \pm SEM) authors in 1984 to 7.43 ± 0.32 authors in 1993 ($P < .01$). Consequently, the number of authors of breast cancer reports in the *ASCO Proceedings* has nearly quadrupled from 430 in 1984 to 1,642 in 1993 ($P < .01$).

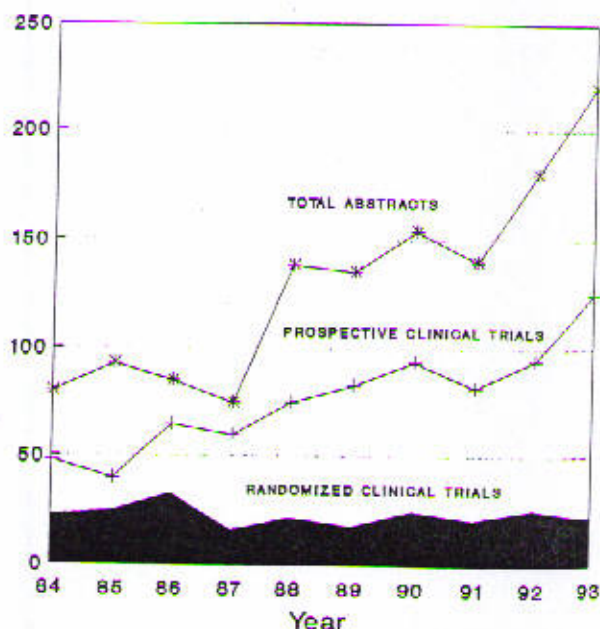


Fig 1. ASCO breast cancer reports by year and study type.

Table 3. Percentage of ASCO Breast Cancer Reports (1984-1993) Selected for Presentation by Abstract Category

Abstract Category	% Selected for Presentation
Breast cancer, total reports	26
United States-based reports	23
Non-United States-based reports	29
PCTs total	29
Nonrandomized	17
Randomized	54*
Randomized with significant difference between treatments	69*
Average no. of patients on PCT by abstract category	
Not selected for presentation	75 ± 24
Selected for presentation	272 ± 39†

*P < .05 v percent of total abstracts presented.

†P < .05 v abstracts not selected.

PCTs represented approximately half of all abstract reports. However, as the absolute number of abstracts reporting RCTs has remained constant, RCTs have become an increasingly smaller proportion of all ASCO breast cancer reports. RCTs represented 37% (33 of 89) of 1986 breast cancer abstracts, but only 10% (22 of 221) of 1993 breast cancer abstracts ($P < .001$). Single-institution reports of PCTs were consistently less likely to be randomized trials when compared with multisite reports throughout this period (18% v 84%, respectively; $P < .01$).

The number of breast cancer abstracts selected for presentation at the ASCO Annual Meeting also increased during this time from 24 in 1984 to 83 in 1993, which reflects mainly a recent increase in poster presentations. The percentage of abstracts selected for presentation by abstract category is listed in Table 3. Throughout this period, PCTs were more likely to be selected for presentation at ASCO if they reported on randomized compared with nonrandomized trials (54% v 17%, respectively; $P < .05$), and were especially likely to be selected if they reported a significant difference between treatments (69% presented). PCT reports selected for presentation were also nearly four times larger than those not presented (mean patient number, 272 ± 39 v 75 ± 24, respectively; $P < .05$).

The randomized trials reported in the ASCO *Proceedings*, segregated on the basis of study type (adjuvant therapy v therapy for advanced disease), as well as whether statistical significance was claimed for relapse-free survival (adjuvant), response frequency (advanced disease),

and/or overall survival (both adjuvant and advanced), are listed in Table 4. Duplicate abstracts (reports or updates of the same study) were unusual (with the exception of one community-based report on the same cohort of patients treated with a breast-sparing approach, which was reported in 7 separate years). Almost no randomized PCTs with negative results were represented by more than one abstract report. Table 4 has been adjusted to reflect the two adjuvant trials with significant differences between treatment groups that were reported in more than 1 year (resulting in a total of five abstract reports on the two trials in the 10-year period). The earliest reports^{8,9} that indicated a significant difference between treatment groups in these two trials are included in Table 4.

Of 90 RCTs reporting on adjuvant breast cancer therapy, a statistical difference in relapse-free survival was reported in 32 (36%). Fifteen abstracts reported a statistically significant survival benefit as well. The abstracts that reported significant survival differences were clustered in the most recent years (with only two such reports before 1989) and appeared to represent both larger adjuvant trial sample sizes and longer follow-up periods. When the individual studies that claimed a statistically significant survival benefit for adjuvant treatment are considered, the investigational arm was found to be superior to either no treatment (three trials) or standard treatment (12 trials) in 14 of 15 cases. Thus, in 16% (14 intervention arms better than standard therapy or no therapy/control arms in 90 total trials) of ASCO reports of RCT in adjuvant breast cancer, the proposed hypotheses was supported as manifested by a statistically significant influence on survival.

Table 4. ASCO Breast Cancer Reports (1984-1993) of RCTs by Category of Therapy and Trial Outcome

Year	Adjuvant Therapy			Advanced-Disease Therapy		
	No. of RCTs	No. of Reports With Significantly Improved		No. of RCTs	No. of Reports With Significantly Improved	
		Relapse-Free Survival	Overall Survival		Response Frequency	Overall Survival
1984	8	1	1	16	2	2
1985	10	4	1	15	1	0
1986	13	7	0	17	3	1
1987	7	3	0	10	2	2
1988	5	5	0	17	0	0
1989	7	1	1	10	2	1
1990	11	4	5	15	3	1
1991	11	3	0	10	1	1
1992	7	4	4	18	4	1
1993	9	0	3	13	0	0
Total	90	32	15*	141	18	9†

*Investigational therapy better than control standard therapy in 14 trials (of 90 total trials, 16%). Two adjuvant trials were reported more than once during this period and only the initial report is included.

†Investigational therapy better than standard therapy in 3 trials (of 141 total trials, 2%).

Table 5. ASCO Breast Cancer Reports (1984-1993): RCTs in Patients With Advanced Disease With Significant Difference in Survival Between Treatment Groups

Year	No. of Patients	Study Question	Summary Outcome	Study Results*			
				Response Frequency	P	Survival (months)	P
1984 ¹⁰	273	CMFP ± levamisole	Levamisole worse		NS	20 v 15	.01
1984† ¹⁹	291	FAC before, during, after tamoxifen	FAC after worse	68 v 56	NS	26 v 21	< .03
1986 ¹¹	48	A 70 mg/m ² v 35 mg/m ²	35 mg/m ² worse	54 v 28	.02	20 v 8	< .05
1987 ¹²	133	CMF high v low	Low worse	32 v 10	.01	16 v 12	.01
1987 ¹³	138	Tamoxifen v Megace	Megace worse	21 v 25	NS	32 v 26	.01
1989† ¹⁵	143	Megace (standard v high) 160 mg v 1,600 mg	High better	26 v 11	.02	18 v 11	.01
1990† ¹⁷	60	RT oophorectomy ± prednisolone	Prednisolone better	53 v 27	.03	Yes	.01
1991† ¹⁸	184	Tamoxifen v Provera	Provera better	34 v 15	< .05	32 v 24	< .05
1992 ¹⁴	173	FEC every 4 weeks (standard v every week)	Every-week schedule worse	47 v 29	.02	Yes	.02
1992 ¹⁶	368	Megace (standard v high) 160 mg v 800 mg v 1,600 mg	No difference		NS	28 v 24 v 27	NS

Abbreviations: A, doxorubicin; C, cyclophosphamide; E, epirubicin; M, methotrexate; F, fluorouracil; P, prednisone; RT, radiation therapy; NS, not significant; Megace, megestrol acetate (Bristol-Myers, Princeton, NJ).

*Comparative survival, in months with P value; comparative response as percent total response frequency with P value. Not all information provided in all abstract reports.

†See 1992 report that unsuccessfully attempted to confirm result.

‡Trials in which investigational therapy resulted in significant survival benefit compared with standard therapy.

The results reported in the ASCO *Proceedings* of randomized trials in advanced breast cancer provide a striking contrast to the adjuvant experience. Of 141 randomized prospective trials in patients with advanced breast cancer, a statistically significant influence on response frequency was reported in 18 instances (13%). More importantly, only nine reports identified statistically significant differences in survival between treatment arms. The advanced-disease trials that reported a significant difference in survival are listed in Table 5. The response frequency in the arm with decreased survival was less than 29% in all but one study. In five of nine reports, the standard-therapy rather than the investigational-therapy group was reported to have a significant increase in survival. For example, levamisole plus cyclophosphamide, methotrexate, fluorouracil, vincristine, and prednisone (CMFVP) was associated with shorter survival than was CMFVP alone (standard); megestrol acetate was worse than tamoxifen (standard); low-dose cyclophosphamide, methotrexate, and fluorouracil (CMF) was worse than full-dose CMF (standard), etc.¹⁰⁻¹⁴ Of the remaining four reports, one identified a survival benefit for high-dose compared with standard-dose megestrol acetate,¹⁵ a result that was not supported in a much larger trial that addressed the same question and was subsequently reported at ASCO in 1992.¹⁶ Thus, in only 2% (three of 141) of randomized trials in advanced breast cancer reported in

the ASCO *Proceedings* in the past decade has the proposed hypothesis been supported by a demonstration of a statistically significant influence on survival for the investigational treatment.

The three randomized studies in advanced breast cancer that reported a survival benefit for the investigational arm in the past 10 years in the ASCO *Proceedings* included the following: prednisolone addition to oophorectomy superior to oophorectomy alone in a 60-patient trial¹⁷; medroxyprogesterone acetate (Provera; The Upjohn Co, Kalamazoo, MI) superior to tamoxifen¹⁸; and tamoxifen plus concurrent fluorouracil, doxorubicin, and cyclophosphamide (FAC) superior to tamoxifen and delayed FAC chemotherapy.¹⁹ The latter represents the only report with a significant survival difference involving chemotherapy (of a total of 87 randomized chemotherapy trials) for patients with metastatic breast cancer.

Trends in the size of breast cancer clinical trials, as reflected by the average number of patients entered on randomized trials by year and study type (adjuvant v advanced), are outlined in Fig 2. The average sample size of trials of adjuvant therapy has progressively increased (from 237 ± 43 in 1984 to 874 ± 371 in 1993, mean ± SEM), while the average size of trials in advanced disease has not changed during this period (from 145 ± 25 in 1984 to 146 ± 34 in 1993, mean ± SEM). In terms of total number of patients on randomized trials reported a

A DECADE OF ASCO BREAST CANCER RESEARCH

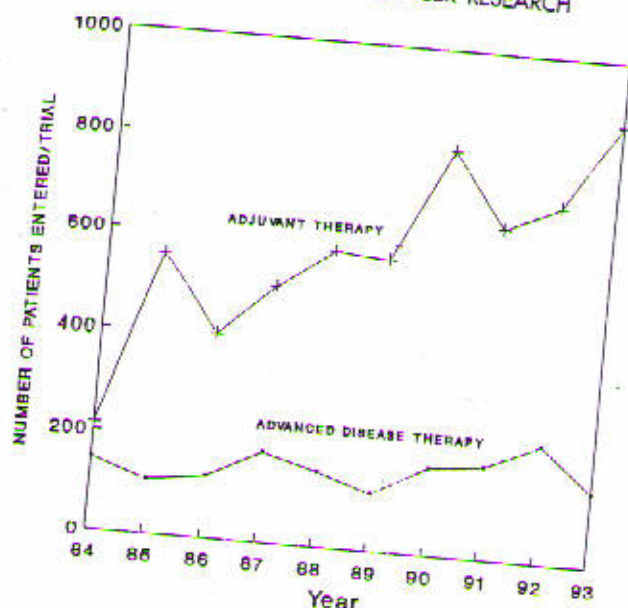


Fig 2. Average number of patients entered per randomized clinical trial by year and study type (adjuvant v advanced).

ASCO, in advanced disease trials 20% fewer patients were reported in 1993 compared with 1984 (trials included 2,304 patients in 1984 and included 1,885 patients in 1993, respectively), while in adjuvant trials a fourfold increase has occurred (adjuvant trials included 1,896 patients in 1984 and included 7,866 patients in 1993, respectively).

Trials of chemotherapy dose-intensity and those involving locally advanced breast cancer that were reported in the ASCO *Proceedings* rarely used randomized study designs. None of the 86 PCTs of dose-intensity that involved blood-product support (bone marrow transplantation or re-infusion of harvested stem cells) and were reported in the ASCO *Proceedings* in this interval were randomized. In the last 3 years alone, 64 separate abstracts have reported on 1,956 breast cancer patients who were treated with high-dose therapy with blood-product support in nonrandomized trials. For locally advanced disease in the same 3-year period, 33 abstracts have reported on PCTs involving 1,477 breast cancer patients, two of which were randomized and included a total of only 37 patients.

Finally, use of the described methodology to review the most recent 1994 ASCO *Proceedings* generates similar results: 232 breast cancer abstracts were published with significant survival benefit reported in no RCTs of advanced disease and only one RCT of adjuvant treatment.

DISCUSSION

The outcome of clinical investigations reported in the ASCO *Proceedings* has been favorable for investigational adjuvant breast cancer therapy. Not only have nearly 35% of trials reported relapse-free survival improvement, but more than 16% have reported a statistically significant impact on survival as well. Although apparently contradictory results raise some concerns,²⁰⁻²² taken in total, these results suggest a well-founded basis for hypothesis formulation in adjuvant breast cancer trials, with the size of patient populations entered on studies reasonably based on achievable therapeutic differences.⁶

For therapy of patients with advanced breast cancer, a different picture emerges. The 26,281 women reported in advanced breast cancer RCTs in the ASCO *Proceedings* in the past decade have provided surprisingly limited direction for clinical breast cancer management. In only three of 141 randomized PCTs in advanced breast cancer has the investigational arm demonstrated a statistically significant survival benefit compared with standard therapy.¹⁷⁻¹⁹ In two of these abstracts, which reported benefit for the new therapy, the standard therapy (of oophorectomy and tamoxifen, respectively) had surprisingly low response frequencies (27% and 15%, respectively), which suggests that chance rather than clinical efficacy may have dictated results.^{17,18} These results are disappointing, since, in many instances, similar hypotheses have been under evaluation in adjuvant and advanced breast cancer settings. Nonetheless, such negative results suggest that the experimental basis for bringing forward hypotheses to test in patients with advanced breast cancer may be inappropriate.^{1,23} It is more likely that the limited average number of patients entered on such trials has been too small to identify the type of differences in survival that can reasonably be anticipated²⁴ based on the extensive clinical experience available in this area.^{25,26} In any event, the decade of clinical investigation represented by publications in the ASCO *Proceedings* has failed to provide definitive information in support of new management approaches for breast cancer patients with advanced disease.

The recognized difficulty of demonstrating a survival benefit when any therapies are compared in patients with advanced breast cancer^{4,25,26} has focused attention on the use of new criteria for end-point evaluation, including the use of quality-of-life indices.^{24,27} However, to date, reliance on such end points to assess breast cancer trials has only rarely been reflected in ASCO reports.

For future advanced breast cancer trials, the sample size issue will most likely become more prominent as breast cancer patients who present today for advanced

breast cancer trials commonly have received adjuvant chemotherapy. Emerging data indicate that response rates to chemotherapy regimens for patients who fail to respond to adjuvant therapy are approximately half those seen in previously untreated patients.^{5,28,29} In addition, recent data suggest that prior adjuvant chemotherapy may lead to recurrence in harder-to-treat sites.³⁰ The expectation for reduced response frequencies for breast cancer patients who relapse following adjuvant treatment, and the corresponding need for larger study populations, has not been reflected in recently reported advanced breast cancer clinical trials in the ASCO *Proceedings*. In this context, the factors that influence the increasing reliance on nonrandomized study designs in contemporary breast cancer clinical investigation for advanced disease trials also warrant attention.

Two areas of increasing clinical interest in breast cancer patient management have been underrepresented by randomized trials in the ASCO *Proceedings* in the past decade: locally advanced breast cancer and dose-intensity with blood-product support. Over the last 3 years, despite experience with 1,954 breast cancer patients in 64 reports on trials of dose-intensity involving blood-product support, the absence of randomized trials precludes definitive comparison of high-dose to conventional treatment. Nonetheless, based on the published cost for transplantation during this interval of approximately \$100,000 per patient,³¹ these efforts have involved approximately \$200,000,000 in patient care/research expenditure. It should be noted that randomized trials of this question are now underway. However, the question of the most appropriate time to initiate phase III testing of new and expensive technology remains, especially given the reimbursement issues,³² associated with this area. A somewhat similar situation holds in the area of locally advanced breast cancer management, where the absence in recent years of large randomized trials continues to leave major questions unanswered.

In summary, prospective review of breast cancer abstracts published in the *Proceedings* of the ASCO for the

past decade indicates the following: (1) randomized trials have come to represent a decreasing proportion of ASCO abstract reports during this period; (2) trials of adjuvant breast cancer therapy have become progressively larger and not infrequently (in 16% of cases) support study hypothesis by demonstrating survival benefit for the investigational therapy under evaluation; and (3) trials of advanced breast cancer therapy have remained relatively small and have consistently failed to support study hypotheses or identify successful new management approaches as defined by a significant impact on patient survival.

Any recommendations based on these observations must recognize the complex nature of the clinical, scientific, and political issues surrounding breast cancer clinical investigation.³³ Nonetheless, the presented data suggest several questions. Is it prudent, or even ethical, to continue to conduct clinical trials in advanced breast cancer populations based on demonstrably unreasonable assumptions of the anticipated magnitude of benefit? What is the benefit to the clinical and scientific community of publishing an ever-increasing number of clinical breast cancer abstracts in the ASCO *Proceedings*? Could this policy and/or the recognized problems of clinical cancer researchers³³ be associated with some of the study design questions raised (such as encouraging small study populations)? Does current multisite clinical research policy apparently designed to maintain patient recruitment (which often results in new protocols being opened as soon as accrual to prior studies are completed) foster an environment that divorces clinical investigators from the results of their prior studies? Such questions and the need to conduct better breast cancer trials (larger in size and based on supportable hypotheses) lead to one recommendation: a critical process evaluation should be conducted of the policy and procedures associated with funding and conduct of breast cancer clinical investigation, especially in the advanced-disease area. As new agents are beginning to be evaluated in breast cancer clinical trials, lessons derived from the past could prove useful to define more effective evaluative strategies for the future.

REFERENCES

1. Editorial: Breast cancer: Have we lost our way? *Lancet* 341:343, 1993
2. Perkins T: The President's Special Commission on Breast Cancer to issue final report (News). *J Natl Cancer Inst* 85:1374, 1993
3. Henderson IC, Harris JR, Kinne DW, et al: Cancer of the breast, in DeVita VT, Hellman S, Rosenberg, SA (eds): *Cancer—Principles and Practice of Oncology* (ed 3) Philadelphia, PA, Lippincott, 1985, pp 1197-1258
4. Henderson IC, Harris JR: Principles in the management of metastatic disease, in Henderson IC, Hellman S, Harris JR, et al (eds): *Breast Diseases*. Philadelphia, PA, Lippincott, 1991, pp 547-559
5. Chlebowski RT: Treating the relapsed patient, in Henderson IC (ed): *Adjuvant Therapy of Breast Cancer*. Boston, MA, Kluwer Academic, 1992, pp 239-256
6. Early Breast Cancer Trialists Collaborative Group: Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy: 133 randomized trials involving 31,000 recurrences and 24,000 deaths among 75,000 women. *Lancet* 339:1-15, 71-85, 1992

7. BMDP: Statistical Software Manual. Berkeley, CA, University of California, 1990
8. Bonadonna G, Valagussa P, Rossi A, et al: CMF adjuvant program in operable breast cancer with positive axillary nodes: Ten-year experience. *Proc Am Soc Clin Oncol* 4:56, 1985 (abstr)
9. Rivkin SE, Glucksberg H, Foulkes M: Adjuvant chemotherapy for operable breast cancer with positive axillary nodes. *Proc Am Soc Clin Oncol* 3:125, 1984 (abstr)
10. Samal BA, Foulkes MA, McDonald B: Levamisole (L) probably shortens response and survival in CMF-maintained advanced breast cancer patients. *Proc Am Soc Clin Oncol* 3:126, 1984 (abstr)
11. Carmo-Pereira J, Costa FO, Henriques E, et al: Advanced breast carcinoma: A comparison of two dose levels of Adriamycin. *Proc Am Soc Clin Oncol* 5:56, 1986 (abstr)
12. Tannock IF, Boyd NF, Perrault DJ, et al: Randomized trial of two doses of CMF chemotherapy for metastatic breast cancer. *Proc Am Soc Clin Oncol* 6:50, 1987 (abstr)
13. Muss H, Paschold E, Black W, et al: Megestrol acetate vs tamoxifen in advanced breast cancer: A five year report. *Proc Am Soc Clin Oncol* 6:214, 1987 (abstr)
14. Blomqvist C, Elomaa I, Rissanen P, et al: The influence of treatment schedule on toxicity and efficacy of standard-dose FEC (cyclophosphamide-epirubicin-fluorouracil) in metastatic breast cancer—A randomized trial comparing weekly and four-weekly administration. *Proc Am Soc Clin Oncol* 11:74, 1992 (abstr)
15. Muss H, Case D, Cates-Wilkie S, et al: High (HiMEG) vs standard dose (S-MEG) oral progestin therapy (megestrol acetate, Megace[®]) for metastatic breast cancer (MBC): A phase III trial of the Piedmont Oncology Association (POA). *Proc Am Soc Clin Oncol* 8:22, 1989 (abstr)
16. Abraham JS, Cirincione C, Aisner J, et al: A phase III dose-response trial of megestrol acetate (MA) in metastatic breast cancer. *Proc Am Soc Clin Oncol* 11:56, 1992 (abstr)
17. da Luz RJ, Moore JW, Tong D, et al: A re-appraisal of ovarian ablation for metastatic breast cancer. *Proc Am Soc Clin Oncol* 9:28, 1990 (abstr)
18. Muss H, Case LD, Fussell R, et al: Tamoxifen (T) versus high dose oral medroxyprogesterone acetate (MPA) as first line endocrine therapy (RX) for metastatic breast cancer (MBC): A randomized trial of the Piedmont Oncology Association. *Proc Am Soc Clin Oncol* 10:41, 1991 (abstr)
19. Pouillart P, Jouve M, Palangie T, et al: Metastatic breast cancer. Controlled trial studying the optimal timing of hormone therapy combined with chemotherapy (preliminary report). *Proc Am Soc Clin Oncol* 3:129, 1984 (abstr)
20. Boccado F, Bruzzi P, Cappellini M, et al: Tamoxifen vs chemotherapy vs chemotherapy plus tamoxifen in stage II ER+ breast cancer patients. *Proc Am Soc Clin Oncol* 8:209, 1989 (abstr)
21. Fisher B, Redmond C, Poisson S, et al: Increased benefit from addition of adriamycin and cyclophosphamide (AC) to tamoxifen (T) for positive-node Tam-responsive postmenopausal breast cancer patients, results from NSABP B-16. *Proc Am Soc Clin Oncol* 9:72, 1990 (abstr)
22. Dornbrowsky P, Zedeler K, Hansen M, et al: Randomized trial of adjuvant CMF + radiotherapy, CMF alone vs CMF plus tamoxifen in pre- and menopausal stage II breast cancer. *Proc Am Soc Clin Oncol* 11:44, 1992 (abstr)
23. Bruverson AS: Chemotherapeutic failure: Resistance or insensitivity. *Ann Intern Med* 18:630-632, 1993
24. Freiman JA, Chalmers TC, Smith H, et al: The importance of beta, the type II error, and sample size in the design and interpretation of the randomized controlled trial. *N Engl J Med* 299:690-694, 1978
25. Chlehowski RT, Smalley RV, Weiner JM, et al: Combination versus sequential single agent chemotherapy in advanced breast cancer: Association with metastatic sites. *Br J Cancer* 63:1011-1042, 1989
26. Fraser SCA, Dobbs HJ, Ebbs SR, et al: Combination or mild single agent chemotherapy for advanced breast cancer? CMF vs epirubicin measuring quality of life. *Br J Cancer* 67:402-406, 1993
27. Coates AS, Gelski V, Signori D, et al: Prognostic value of quality of life scores during chemotherapy for advanced breast cancer. *J Clin Oncol* 10:1833-1838, 1992
28. Houston SJ, Richards MA, Bentley AE, et al: The influence of adjuvant chemotherapy on outcome after relapse in patients with breast cancer. *Proc Am Soc Clin Oncol* 11:108, 1992 (abstr)
29. Louvet C, de Gramont A, Demuyneck B, et al: Folinic acid, 5-fluorouracil bolus and infusion and mitoxantrone with or without cyclophosphamide in metastatic breast cancer. *Eur J Cancer* 29:1835-1838, 1993
30. Goldhirsch A, Gelber RD, Price KN, et al: Effect of systemic adjuvant treatment on first sites of breast cancer relapse. *Lancet* 343:377-381, 1994
31. Smith TJ, Buonaiuto DA, Hillner BE, et al: The learning curve for cost of autologous bone marrow transplantation (ABMT) for breast cancer. *Proc Am Soc Clin Oncol* 12:54, 1993 (abstr)
32. Peters WP, Rogers MC: Variations in approval by insurance companies of coverage for autologous bone marrow transplantation for breast cancer. *N Engl J Med* 330:473-477, 1994
33. Frei E III, Freireich FJ: The clinical cancer researcher—Still an embattled species. *J Clin Oncol* 11:1639-1651, 1993