

Long-Running Study Shows 15-Years Survival Gains in Early Breast Cancer

by David W. Sharp

More than 20 years ago, lead investigators in randomized trials in early breast cancer agreed that every five years the data from individual patients would be pooled and reanalyzed in a series of "overviews." That this agreement, known as the Early Breast Cancer Trialists' Collaborative Group (EBCTCG), has had a profound effect on clinical practice and on patients is suggested both by the appearance of authoritative guidelines that draw heavily on EBCTCG findings and by a total of more than 10,000 citations to the various reports. The fourth of these overviews has reached a citation pinnacle (#1). This paper looks at adjuvant chemotherapy and hormonal therapy (mainly tamoxifen). A companion article, focusing on local treatment—i.e., the surgical and radiotherapeutic aspects of the management of patients with this cancer—appeared seven months later (EBCTCG, *Lancet*, 366 [9503]: 2087-106, 2005; 21 citations this bimonthly period, with

WHAT'S HOT IN MEDICINE

Rank	Paper	Citations This Period (Mar-Apr 07)	Rank Last Period (Jan-Feb 07)
1	Early Breast Cancer Trialists' Collaborative Group (EBCTCG), "Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials," <i>Lancet</i> , 365(9472): 1687-1717, 14 May 2005. [c. 150 institutions worldwide] *925VV	58	3
2	J.A. Lieberman, et al., "Effectiveness of antipsychotic drugs in patients with chronic schizophrenia," <i>New Engl. J. Med.</i> , 353(12): 1209-23, 22 September 2005. [8 U. S. institutions] *966DS	49	1
3	F.A. Shepherd, et al., "Erlotinib in previously treated non-small-cell lung cancer," <i>New Engl. J. Med.</i> , 353(2): 123-32, 14 July 2005. [15 institutions worldwide] *944OP	48	5

116 total to date, compared with paper #1's 400+ citations as of mid-summer 2007).

This long-standing collaboration, which currently has access to data on 350,000 women randomized in 400 clinical trials, provides statistically powerful evidence on the benefits and risks, at around the 15-year mark, of treatments being looked at from the 1980s. Typically the systemic (as opposed to local) treatments were six months or so of treatment with triple drug combinations of fluorouracil and cyclophosphamide plus either doxorubicin (Adriamycin) or epirubicin and longer-term tamoxifen. As the EBCTCG concedes, "there is ample room for better drugs... and for better use of existing drugs." This is despite the evidence that the longer-established regimens can halve the annual death rate of estrogen-receptor positive breast cancers, the most important, but far from the only, result of this multidimensional study. The halving of breast cancer mortality in countries such as the U.S.A and the U.K. since the 1980s has come about through a succession of modest improvements reliably recognized by large-scale randomized evidence. The mortality benefits of polychemotherapy have widened with time, being twice as good at the 15-year mark

4	I. Iakovou, <i>et al.</i> , "Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents," <i>JAMA</i> , 293(17): 2126-30, 4 May 2005. [5 Italian and German institutions] *922AO	41	†
5	C.L. Ogden, <i>et al.</i> , "Prevalence of overweight and obesity in the United States, 1999-2004," <i>JAMA</i> , 295 (13): 1549-55, 5 April 2006. [Ctrs. for Disease Control, Atlanta, GA] *028RG	41	†
6	M.J. Piccart-Gebhart, <i>et al.</i> , "Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer," <i>New Engl. J. Med.</i> , 353(16): 1659-72, 20 October 2005. [26 institutions worldwide] *9751C	38	†
7	E.H. Romond, <i>et al.</i> , "Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer," <i>New Engl. J. Med.</i> , 353 (16): 1673-84, 20 October 2005. [19 U.S. institutions] *9751C	35	†
8	R.J. Klein, <i>et al.</i> , "Complement factor H polymorphism in age-related macular degeneration," <i>Science</i> , 308(5720): 385-9, 15 April 2005. [6 U.S. institutions] *917TL	33	4

as they had been at five years; for tamoxifen the differential is even greater.

Clinicians today are also interested in looking at different treatments such as taxanes, selective estrogen-receptor inhibitors, aromatase inhibitors, and trastuzumab, which were not available when these trials began. Also, the notion that cancer treatments should be tailored to the molecular and genetic make-up of the patient and her tumor is attracting attention. Are reliable answers to important clinical questions about the newer drugs and about more molecularly sensitive approaches going to take another 15 to 20 years? "Where next for EBCTCG?" seemed an appropriate question, so *Science Watch* posed it and Prof. Richard Peto, one of the founders of EBCTCB, kindly replied. "There are at least as many opportunities now for the EBCTCG as there have been in the past," he told *Science Watch*, "and at least as much prospect of further survival improvement for women with breast cancer." Topics that the Group is currently addressing, he noted, include the effect of very intensive chemotherapy and ways of minimizing the fatal side-effects of radiotherapy. "Trials of newer drugs will also soon be sufficiently mature for consideration within the EBCTCG framework," added Dr. Sarah Darby, another member of the EBCTCG Secretariat in Oxford, U.K. ■

9	C. Baigent, <i>et al.</i> (Cholesterol Treatment Trialists' [CTT] Collaborators), " Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90 056 participants in 14 randomised trials of statins ," <i>Lancet</i> , 366 (9493): 1267-78, 8 October 2005. [Correspond. addresses: Clin. Trial Serv. Unit and Epidem. Stud. Unit, Oxford, U.K.; Natl. Hlth. & Med. Res. Council Clin. Trials Ctr., Sydney, Australia] *971st	33	†
10	J.A. Dormandy, <i>et al.</i> , " Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial ," <i>Lancet</i> , 366(9493): 1279-89, 8 October 2005. [13 U.S. and European institutions] *971ST	31	†
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