Effects of ovarian ablation or suppression on breast cancer recurrence and survival: patient-level meta-analysis of 15 000 women in 23 randomised trials

*Early Breast Cancer Trialists' Collaborative Group (EBCTCG)**

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Summary

Background For premenopausal women with oestrogen receptor (ER)-positive early breast cancer, the additional protective effect of ovarian function suppression (OFS, by ablation or drugs) may depend on menopausal status after any chemotherapy, and tamoxifen usage. We assess the effects of OFS on breast cancer outcomes among premenopausal women and how they vary by patient or tumour characteristics and receipt of other treatments.

Methods We conducted a meta-analysis of individual participant data from the randomised trials comparing OFS versus no OFS, in women with ER-positive or ER-unknown early breast cancer who were premenopausal at randomisation and younger than 55 years. Trials were categorised by whether premenopausal status was or was not confirmed after chemotherapy (if given), and by allocation to tamoxifen. Primary outcomes were invasive breast cancer recurrence, breast cancer mortality, other mortality, and all-cause mortality. ER-weighted log-rank methods estimated event rate ratios (RRs) for ER-positive disease.

Findings Datasets were provided for 23 of 25 identified eligible trials, comprising 18 851 (98·9%) of 19 053 randomly assigned women. Among 15 075 premenopausal women with ER-positive or ER-unknown tumours, allocation to OFS significantly reduced recurrence rates (RR 0·82, 95% CI 0·77–0·87; p<0·00001), with larger reductions in women who were confirmed premenopausal after chemotherapy (or who did not receive chemotherapy) than in those with unconfirmed premenopausal status after chemotherapy; heterogeneity p=0·0004. Among confirmed premenopausal women, recurrence reductions were larger in older trials without tamoxifen (RR 0·61, 0·52–0·71; p<0·0001) than in more recent trials of OFS plus tamoxifen versus tamoxifen (RR 0·79, 0·70–0·91; p=0·0008). In these more recent trials, the additional recurrence reduction with OFS appeared larger in women younger than 45 years than in women aged 45–54 years (RR 0·73, 0·63–0·86 *vs* RR 0·95, 0·75–1·21; p=0·072); in those younger than 45 years, breast cancer mortality was similarly improved (RR 0·74, 0·58–0·94; p=0·012). There was no increase in deaths without recurrence. Findings did not differ significantly by OFS method or other recorded patient or tumour characteristics.

Interpretation For premenopausal women with ER-positive early breast cancer, even if chemotherapy or tamoxifen are given, OFS significantly reduces the 15-year risk of recurrence and death.

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Introduction

In women with oestrogen receptor (ER)-positive early breast cancer, following surgery and, where indicated, radiotherapy and chemotherapy, adjuvant endocrine therapy can substantially improve survival.[1] In postmenopausal women, suppression of oestrogen production with aromatase inhibitors is more effective than treatment with the selective oestrogen receptor modulator tamoxifen.[2] In premenopausal women, however, ovarian oestrogen production means that although tamoxifen is effective, aromatase inhibitors alone are not effective. Some uncertainty remains about the effect of circulating oestrogens on recurrence risk in premenopausal women, particularly those taking tamoxifen, and about the extent to which suppression of ovarian function might or might not further reduce this risk.

Early trials examined the effect of irreversible ovarian ablation (with surgery or ovarian irradiation), whereas more recent trials have generally used a gonadotrophin-releasing hormone agonist (GnRHa) to achieve potentially reversible pharmacological suppression of ovarian oestrogen production.[3–7] Previous meta-analyses by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) of individual participant data, which were restricted to older trials, reported fewer breast cancer recurrences and deaths with ovarian ablation or suppression, but only in the absence of other systemic

Research in context

Evidence before this study

A previous Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis showed that, for women with early breast cancer, ablation of ovarian function significantly reduces breast cancer recurrence and death in the absence of other systemic treatments. Subsequent trials and systematic reviews on the effects of pharmacological ovarian suppression using a gonadotrophin-releasing hormone agonist, and of ablation by irradiation, reported no clear benefit, so questions remain as to whether ovarian function suppression (OFS) by ablation or drugs can materially improve long-term outcomes beyond the effects of tamoxifen or chemotherapy. The EBCTCG's ongoing systematic searches of bibliographic databases, including MEDLINE, Embase, the Cochrane Library, and meeting abstracts, up to Sept 1, 2025, sought all randomised trials of OFS versus no OFS, with other treatments the same in both arms.

Added value of this study

This collaborative meta-analysis collated, checked, and analysed individual patient-level data from 15 075 premenopausal women with oestrogen receptor (ER)-positive or ER-unknown disease in 23 trials. Long-term follow-up of all the available randomised evidence provides unbiased estimates of the risks and benefits of OFS among premenopausal women, including those who remained premenopausal after any chemotherapy. For women with confirmed premenopausal status, the results show that OFS greatly reduces the 15-year risk of breast cancer recurrence and death among women who were not scheduled to receive any other endocrine therapy. Among women who were allocated tamoxifen (for about 4 years), the improvements were still definite, and for women younger than 45 years they were substantial, with recurrence, distant recurrence, breast cancer mortality and all-cause mortality rates during the first decade all reduced by about a quarter. There were few deaths from causes other than breast cancer, and no increase with OFS. Numbers were insufficient for reliable subgroup analyses, but there was no evidence that the proportional risk reductions differed by prognostic factors or method of OFS.

Implications of all the available evidence

For premenopausal women with early-stage, ER-positive breast cancer, including those who are still premenopausal after any chemotherapy, the additional long-term benefits of OFS over and above the established benefits of tamoxifen and of chemotherapy can reliably inform clinical guidelines as well as individual clinician and patient discussions.

treatments.[1,8] More recent reviews that focused on the separate effects of ovarian suppression by GnRHa[7,9] and by ovarian irradiation[10] reported unclear benefit.

Hence, questions remain about the comparative effectiveness of ovarian ablation and pharmacological ovarian suppression, and about whether long-term benefits outweigh any potential adverse effects on quality of life[11,12] and non-cancer mortality.[13] The effect of ovarian ablation and suppression (hereafter ovarian function suppression, or OFS) when added to chemotherapy and tamoxifen is also uncertain.[14] This report addresses these questions, providing updated and extended meta-analyses of the effects of OFS, whether by surgery, radiotherapy, or drug therapy, for premenopausal women with ER-positive breast cancer or tumours with unknown ER status.

Methods

Study design and participants

This meta-analysis was conducted in accordance with the Preferred Reporting Items for a Systematic Review and Meta-analysis of Individual Participant Data statement,[15] with additional information available on the EBCTCG website. Trial identification procedures have been described previously[1,16–19] and include extensive searching of bibliographic databases, journals and conference proceedings, and communications with breast cancer researchers to identify and include published and unpublished trials. The current paper uses data that were collected up to Nov 1, 2024, with no additional trials identified by a further search done on Sept 1, 2025. For the main analyses presented here, information was sought on all women with early breast cancer who entered a randomised trial of OFS versus no OFS that started recruitment before Jan 1, 2010, and had recurrence or mortality as a main outcome. Trials were not eligible if they included additional therapies (other than prednisone) in one group but not the other (eg, trials that compared OFS *vs* chemotherapy)[20] or if they had only non-oncological outcomes (eg, trials testing short-term ovarian suppression during chemotherapy to try to prevent chemotherapy-induced menopause).[21] In some eligible trials of OFS versus no OFS, no other adjuvant therapy was to be given, whereas in others all participants were to be offered the same additional therapy, usually chemotherapy or 2–5 years of tamoxifen, or both.

For more on **EBCTCG** see https://www.ctsu.ox.ac.uk/research/ebctcg

Information was requested from study investigators about each woman in all eligible trials, including individual patient data on randomisation date, allocated treatment, age, tumour diameter, grade, histology, axillary-lymph-node involvement, ER, progesterone receptor, and HER2 status, follow-up duration, dates of any breast cancer recurrence (locoregional, contralateral, or distant), dates and sites of any other second primary cancer; and dates and causes of death. The most recent follow-up data request was supplemented for one UK trial[6] by mortality information from National Health Service Digital and its predecessors. Datasets were

checked for consistency, with queries resolved, if possible, through correspondence with investigators.

Protocol-specified primary outcomes were recurrence of invasive breast cancer (locoregional, distant, or new contralateral), breast cancer mortality, other mortality, and all-cause mortality. Deaths without recorded recurrence from an unknown cause were ascribed to breast cancer, as other causes are uncommon at these ages.

Statistical analysis

Statistical methods have been described in earlier EBCTCG reports[1,16–19] and the Statistical Analysis Plan (appendix pp 38–45). Forest plots and Kaplan–Meier graphs describe the separate trials and their combined results, and subgroup analyses help explore whether the proportional risk reductions produced by treatment depend strongly on patient or tumour characteristics. Time-to-first-event analyses, stratified by age, nodal status, year of follow-up, and trial, give the log-rank observed minus expected (O−E) statistic and its variance (V). These statistics yield the significance test and the first-event rate ratio, RR, and its CI (using the one-step estimate $\log_e RR=[O-E]/V$ with variance 1/V). The contribution of tumours with unknown ER status to each of these (O−E) values is multiplied by 0·75 (yielding ER-weighted RRs that assume the effect of OFS in ER-unknown disease is only 75% of that in ER-positive disease).[18] For overall results, 95% CIs are given. Results for subgroups and individual trials are given with 99% CIs. χ^2 tests for heterogeneity or, where appropriate, trend compare RRs in different subgroups. Median (IQR) follow-up duration (among women who would have been survivors) was from Kaplan–Meier graphs of time to follow-up cessation. All p values are two-sided. In-house FORTRAN programs were used for analyses.

Breast cancer mortality RRs are estimated by subtracting the log-rank statistics (O−E and V) for mortality without recurrence from those for overall mortality (log-rank subtraction).[20] This avoids having to determine which deaths after recurrence were from breast cancer without inappropriately assuming all were.

The main analyses include only women younger than 55 years who were premenopausal at randomisation and had ER-positive or ER-unknown tumours. Where individual information on menopausal status was unavailable, we assumed women were premenopausal if trial eligibility required this criterion, and only included those younger than 50 years if trials did not restrict eligibility by premenopausal status. One trial had a three-way randomisation phase;[22] for balance, the 78 control patients in this phase are counted twice in totals (but not in calculation of log-rank statistics). Women who were premenopausal at randomisation but then received chemotherapy might have developed chemotherapy-induced menopause before commencing OFS.[23,24] Premenopausal status was not confirmed after chemotherapy in some trials so the main analyses therefore divided trials into four categories: by whether premenopausal status was certain because no chemotherapy was given or premenopausal status was assessed after chemotherapy (confirmed premenopausal) or uncertain when not assessed after chemotherapy (unconfirmed premenopausal), and also by whether or not tamoxifen was given.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

See **Online** for appendix

Results

We identified 27 unconfounded trials of OFS versus not that recruited women between 1948 and 2014: trial designs and patient characteristics are shown online (appendix pp 3–4). Individual patient datasets were provided from 25 of them, comprising 19 235 (99·0%) of 19 439 women randomly assigned. Two of the 25 trials that provided data (n=384) were ineligible as they included only postmenopausal women. Women who were aged 55 years or older, postmenopausal, or had ER-negative disease were excluded. Analyses presented here focus on the remaining 23 trials and the 15 075 women who were considered to be premenopausal at the time of randomisation and had ER-positive or unknown ER status tumours (figure 1). Sensitivity analyses on the groups excluded from the main analyses found no benefit from OFS (appendix pp 6–8).

15 of the trials included women who were confirmed premenopausal prior to allocation to OFS or not, 12 (n=4012) because participants did not receive any chemotherapy after randomisation, and three (n=3430) because premenopausal status was confirmed following chemotherapy by measurement of serum oestradiol[25] or

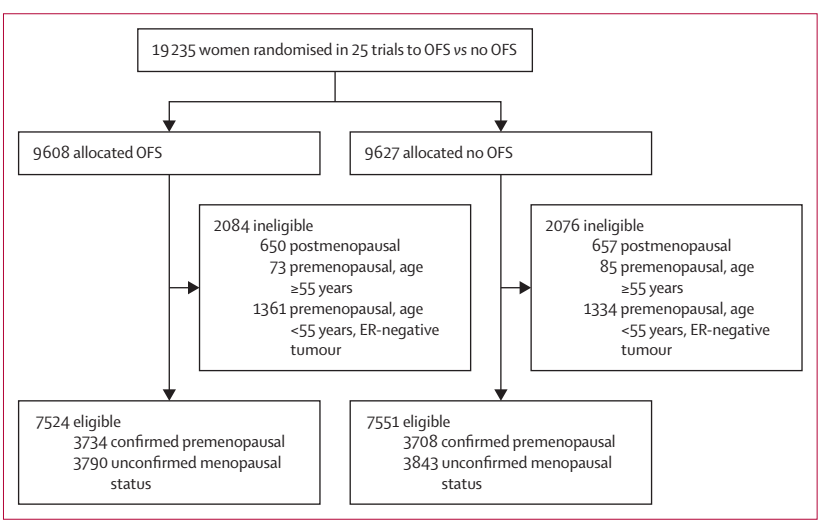
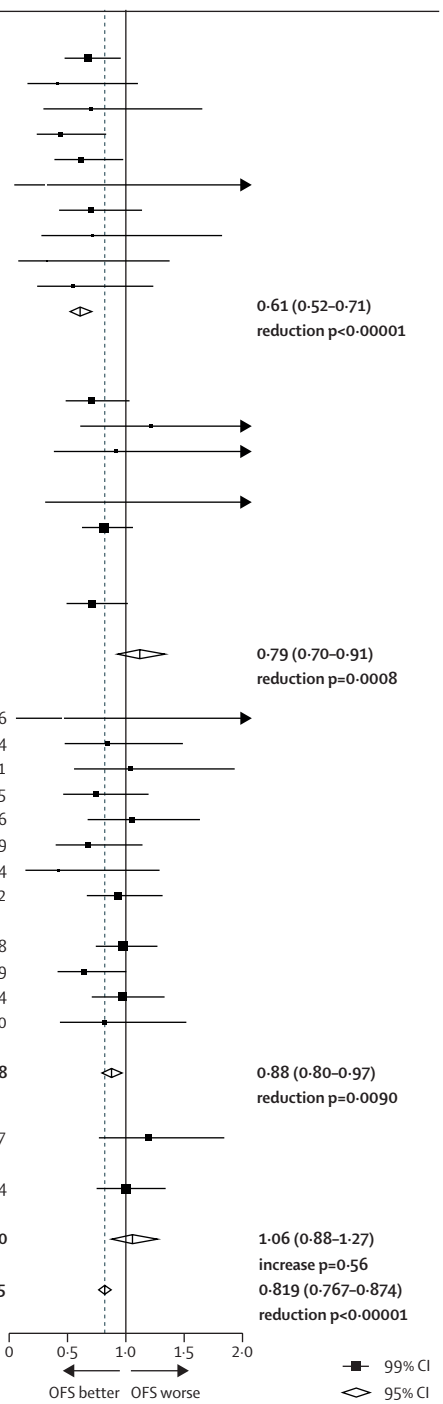


Figure 1: **Flow chart for the trials of OFS versus no OFS in early breast cancer**
OFS=ovarian function suppression. To make all comparisons evenly (1:1) balanced, 78 controls in the only three-way comparison are counted twice.

measurement of follicle stimulating hormone levels and assessment of vaginal bleeding history.[26,27] Median follow-up was 11·0 years (IQR 8·2–14·9) and median age was 42 years (IQR 38–46). 13 trials (n=7633) recruited women whose premenopausal status was not reconfirmed following post-randomisation chemotherapy

	Treatment	Events/women		OFS events		Ratio of annual event rate (95% CI or 99% CI)
		Allocated OFS	Allocated control	Log-rank O – E*	Variance of O – E*	OFS *vs* control
A **No chemotherapy or premenopausal status confirmed after chemotherapy; no tamoxifen**						
1948 Christie A	± ovarian irradiation	239/352	252/356	−21·4	54·3	
1957 Norwegian RH	± ovarian irradiation	17/76	35/93	−6·1	7·0	
1961 NSABP B–03	± oophorectomy	62/129	30/55	−3·2	8·9	
1964 Saskatchewan CF	± oophorectomy	67/169	81/144	−13·7	16·8	
1965 PMH Toronto†	±(ovarian irradiation [± prednisone])	126/239	135/218	−15·1	31·1	
1974 Bradford RI	± oophorectomy	7/25	11/25	−2·0	1·7	
1987 ZIPP	± goserelin 2+ years	60/176	81/187	−9·9	27·8	
1990 IBCSG VIII	± goserelin 2 years	16/42	17/35	−2·5	7·5	
1991 CAMS China	± ovarian ablation	6/60	14/59	−3·6	3·2	
1992 ICCG C/9/91 UK	8FECq3w; ± GnRHa 3 years	22/63	33/90	−6·0	9·9	
Subtotal		**622/1331 (46·7%)**	**689/1262 (54·6%)**	**−83·5**	**168·2**	**0·61 (0·52–0·71) reduction p<0·00001**
B **No chemotherapy or premenopausal status confirmed after chemotherapy; tamoxifen**						
1987 ZIPP	Tamoxifen 2 years ± goserelin 2+ years	98/406	133/435	−16·1	46·5	
1992 ICR–CTSU/NCRI BCSG	Tamoxifen 5 years ± ovarian ablation	45/176	45/182	2·7	13·9	
1994 EST3193/INT0142	Tamoxifen 5 years ± goserelin/leuprorelin/ oophorectomy/ovarian irradiation	18/170	18/165	−0·7	8·7	
1994 JATBCZ ZXBC–1002	Tamoxifen 2 years ± goserelin 2 years	6/20	2/18	1·4	1·6	
2003 SOFT/IBCSG 24–02	± chemotherapy; tamoxifen 5 years ± triptorelin 5 years/oophorectomy/ovarian irradiation	181/997	212/1000	−19·4	94·3	
2008 Zhejiang China	Tamoxifen 5 years ± goserelin 1·5 years	(110 patients)		(no data)		
2009 ASTRRA Korea	Neoadjuvant/adjuvant chemotherapy + tamoxifen 5 years ± goserelin 2+ years	86/634	121/646	−17·4	50·4	
Subtotal with data‡		**434/2403 (18·1%)**	**531/2446 (21·7%)**	**−49·5**	**215·4**	**0·79 (0·70–0·91) reduction p=0·0008**
C **Premenopausal status not confirmed after chemotherapy; no tamoxifen**						
1974 Bradford RI	MTt ± oophorectomy	5/23	8/19	−1·2	1·6	
1978 Toronto-Edmonton	CMF ± BCG ± (ovarian ablation + prednisone)	55/95	60/98	−3·5	20·4	
1978 BCCA Vancouver	6CMFq3w ± (ovarian irradiation + prednisone)	46/63	37/58	0·6	17·1	
1978 IBCSG/Ludwig II	(± oophorectomy); (CMFq4w + prednisone) 1 year	86/123	99/129	−8·7	29·5	
1979 SWOG 7827 B	(± oophorectomy); (CMFV + prednisone) 1 year	81/150	68/134	1·6	33·6	
1987 ZIPP	(6CMFq4w) ± goserelin 2+ years	66/144	83/145	−9·4	23·9	
1987 Pretoria RSA	6CMFq4w ± buserelin 5 years	18/60	24/65	−4·6	5·4	
1989 FNCLCC France	6FA/ECq3w or q4w; ± triptorelin 3 years/ ovarian irradiation/oophorectomy	147/377	147/371	−3·8	57·2	
1989 ECOG EST5188	6CAFq4w; ± goserelin 5 years	198/436	199/443	−2·7	91·8	
1990 IBCSG VIII	6CMFq4w; ± goserelin 18 months	56/271	85/281	−14·9	33·9	
1991 CAMS China	CMF ± ovarian ablation	172/989	195/1060	−2·0	66·4	
1993 GABG 4 Germany	(±4ECq3w; 3CMFq4w); ± goserelin 2 years	36/163	39/146	−3·5	17·0	
Unk IT Naples	4Eq3w; 4CMFq4w; ± goserelin 2 years	(92 patients)		(no data)		
Subtotal with data‡		**966/2894 (33·4%)**	**1044/2949 (35·4%)**	**−52·1**	**397·8**	**0·88 (0·80–0·97) reduction p=0·0090**
D **Premenopausal status not confirmed after chemotherapy; tamoxifen**						
1987 ZIPP	(6CMF + tamoxifen 2 years) ± goserelin 2+ years	103/203	92/200	6·1	34·7	
1992 ICR–CTSU/NCRI BCSG	(Chemotherapy [73% CMF] + tamoxifen 5 years) ± ovarian irradiation/suppression	233/693	241/694	0·2	78·4	
Subtotal		**336/896 (37·5%)**	**333/894 (37·2%)**	**6·2**	**113·0**	**1·06 (0·88–1·27) increase p=0·56**
Total (A + B + C + D)		**2358/7524 (31·3%)**	**2597/7551 (34·4%)**	**−178·8**	**894·5**	**0·819 (0·767–0·874) reduction p<0·00001**



Heterogeneity between four subtotals: χ^2_3=24·2; p=0·00002
Heterogeneity within subtotals: χ^2_{26}=25·6; p=0·49
Two-way heterogeneity tests: (A) versus (B) χ^2_1=7·0, p=0·0080;
(C) versus (D) χ^2_1=2·8, p=0·10; **(A + B) versus (C + D)** χ^2_1=12·4, p=0·00042

(unconfirmed premenopausal). Most women were treated with cyclophosphamide, methotrexate, and fluorouracil, and a substantial proportion would have become postmenopausal following such chemotherapy.[23] Median follow-up for these comparisons was 11·2 years (IQR 8·5–14·3) and median age was 43 years (IQR 39–47). Five trials contributed women to both categories.

For the 23 eligible trials that provided data, results for any first invasive breast cancer recurrence (distant, locoregional or new contralateral disease) are shown in figure 2. Trials are categorised by confirmed (either no chemotherapy administered or premenopausal status assessed after chemotherapy) or unconfirmed (not assessed after chemotherapy) premenopausal status at the start of OFS and by the presence or absence of tamoxifen in both comparator arms. For each trial, the information includes the year recruitment started, trial name, method of OFS, use of chemotherapy, log-rank statistics, and the ratio of event rates. Similar plots for distant recurrence at any time, locoregional, and contralateral recurrence as first event, breast cancer mortality, death without recurrence (in the first year and overall), and all-cause mortality are shown in the appendix (pp 10–16). Across all trials, women assigned to OFS had an 18% lower rate of breast cancer recurrence (RR 0·82, 95% CI 0·77–0·87; p<0·00001) than did women assigned to control; the 15-year absolute risks were 36·5% versus 41·9% (appendix p 17). The rate of breast cancer death was reduced by 14% (RR 0·86, 0·80–0·93; p=0·0009), with 15-year absolute risk of 31·3% versus 34·4% (appendix pp 13, 17).

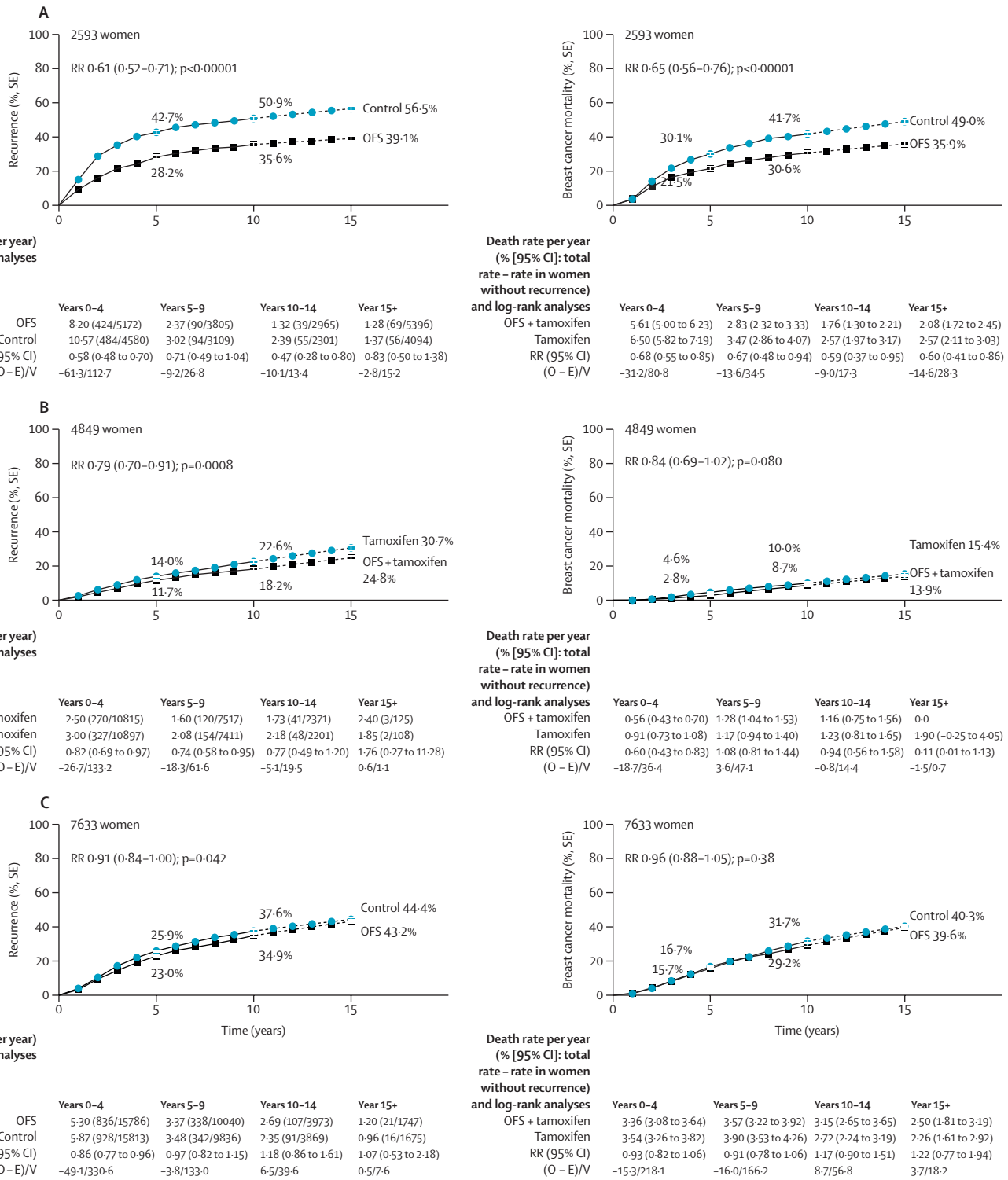
As anticipated, there was significant heterogeneity (χ^2_3=22·2, p<0·0001) in the recurrence and breast cancer mortality reductions between the four categories of trial comparisons. Allowing for the different lengths of follow-up in the trials, heterogeneity tests restricted to years 0–14 of follow-up showed a significant difference (χ^2_1=12·4; p=0·0004) between trials where premenopausal status was confirmed after chemotherapy (or no chemotherapy was administered) and those in which it was not, and, within women with confirmed premenopausal status, between those allocated, and not allocated tamoxifen (χ^2_1=7·0; p=0·0080). In women with unconfirmed premenopausal status after chemotherapy there was no heterogeneity by tamoxifen or not (χ^2_1=9·8; p=0·098). Consequently, further analyses combine all women with unconfirmed premenopausal status.

Where premenopausal status was confirmed at the start of OFS and women were not allocated tamoxifen, recurrence rates were 39% lower with OFS compared with control (RR 0·61, 95% CI 0·52–0·71; p<0·0001), with a 15-year recurrence risk of 39·1% versus 56·5% (figure 2A, 3A). Breast cancer mortality was similarly reduced (RR 0·65, 95% CI 0·56–0·76; p<0·0001; 15-year breast cancer mortality of 35·9% *vs* 49·0%; figure 3A). In the second category, where confirmed premenopausal women received tamoxifen and were randomised to the addition of OFS or not, there was a 21% lower recurrence rate with than without OFS (RR 0·79, 95% CI 0·70–0·91; p=0·0008) and an absolute 5·9% lower 15-year recurrence risk (24·8% *vs* 30·7%, figure 2B, 3B). Rates of breast cancer mortality were 16% (RR 0·84, 95% CI 0·69–1·02; p=0·080) lower but this did not reach statistical significance; figure 3B. In trials in which premenopausal status was not confirmed after chemotherapy, OFS reduced the risk of recurrence (RR 0·91, 95% CI 0·84–1·00, p=0·042) but there was little apparent effect on breast cancer mortality (RR 0·96, 95% CI 0·88–1·05, p=0·38; figure 3C).

Figure 4 shows the effect of OFS (with or without tamoxifen) on recurrence risk in confirmed premenopausal women by age at randomisation. In those aged under 45 years, in the absence of tamoxifen, there was a 42% recurrence reduction (RR 0·58, 95% CI 0·47–0·70; p<0·0001) and in those aged 45–54 years a 35% reduction (RR 0·65, 95% CI 0·52–0·82, p=0·0003). In the presence of tamoxifen, the reduction again appeared larger in women aged under 45 years than those aged 45–54 years; RR 0·73 (95% CI 0·63–0·86; p=0·0002) versus RR 0·95 (0·75–1·21; p=0·67), although a test for interaction by age did not reach significance (χ^2_1=3·2; p=0·072).

In current practice, as in the more recent trials included in these meta-analyses, premenopausal women are more likely to be offered tamoxifen with consideration given to the addition of OFS or not. Figure 5 shows subgroup analyses, for the trials of OFS versus not in confirmed premenopausal women who received tamoxifen, by site of recurrence, period of follow-up, age, ER and PR status, use of previous chemotherapy, method of ovarian suppression (surgery or irradiation, or pharmacological suppression), nodal status, T-stage, tumour grade and HER2 status, with similar plots for trials in the absence of tamoxifen given in the appendix (p 25). Distant, locoregional and contralateral recurrences were all reduced by OFS (figure 5A; appendix p 19). Statistically and clinically significant reductions in recurrence were seen in years 0–4, and these persisted undiminished through to years 5–9, and 10–14, with little follow-up after year 15 (figure 5B). Proportional reductions did not differ significantly by nodal status, tumour size or grade

Figure 2: **Trial-specific recurrence rate ratios by allocation to OFS versus no OFS in ER-positive or ER-unknown early breast cancer, estimated from ER-weighted analyses of four types of randomised comparison**
Recurrence rate ratios (local, distant, or new contralateral invasive disease) are for ER-positive disease*. A=doxorubicin. BCG=Bacillus Calmette–Guèrin. C=cyclophosphamide. E=epirubicin. F=fluorouracil. GnRHa=gonadotrophin-releasing hormone agonist. M=methotrexate. O–E=observed minus expected. OFS=ovarian function suppression. Tt=Triethylenephosphoramide. q4w=4-weekly. q3w=3-weekly. V=vincristine. Unk=unknown. *ER weighting: the contribution to each O–E value from ER-unknown disease is 0·75 of what the unweighted contribution would have been. †To make all comparisons evenly (1:1) balanced, the 78 controls in the three-way phase of this one trial are counted twice. ‡The two trials with no data do not contribute to the subtotals or total.



Event rate (% per year) and log-rank analyses

	Years 0–4	Years 5–9	Years 10–14	Year 15+
OFS	8·20 (424/5172)	2·37 (90/3805)	1·32 (39/2965)	1·28 (69/5396)
Control	10·57 (484/4580)	3·02 (94/3109)	2·39 (55/2301)	1·37 (56/4094)
RR (95% CI)	0·58 (0·48 to 0·70)	0·71 (0·49 to 1·04)	0·47 (0·28 to 0·80)	0·83 (0·50 to 1·38)
(O – E)/V	–61·3/112·7	–9·2/26·8	–10·1/13·4	–2·8/15·2

Death rate per year (% [95% CI]: total rate – rate in women without recurrence) and log-rank analyses

	Years 0–4	Years 5–9	Years 10–14	Year 15+
OFS + tamoxifen	5·61 (5·00 to 6·23)	2·83 (2·32 to 3·33)	1·76 (1·30 to 2·21)	2·08 (1·72 to 2·45)
Tamoxifen	6·50 (5·82 to 7·19)	3·47 (2·86 to 4·07)	2·57 (1·97 to 3·17)	2·57 (2·11 to 3·03)
RR (95% CI)	0·68 (0·55 to 0·85)	0·67 (0·48 to 0·94)	0·59 (0·37 to 0·95)	0·60 (0·41 to 0·86)
(O – E)/V	–31·2/80·8	–13·6/34·5	–9·0/17·3	–14·6/28·3

Event rate (% per year) and log-rank analyses

	Years 0–4	Years 5–9	Years 10–14	Year 15+
OFS + tamoxifen	2·50 (270/10815)	1·60 (120/7517)	1·73 (41/2371)	2·40 (3/125)
Tamoxifen	3·00 (327/10897)	2·08 (154/7411)	2·18 (48/2201)	1·85 (2/108)
RR (95% CI)	0·82 (0·69 to 0·97)	0·74 (0·58 to 0·95)	0·77 (0·49 to 1·20)	1·76 (0·27 to 11·28)
(O – E)/V	–26·7/133·2	–18·3/61·6	–5·1/19·5	0·6/1·1

Death rate per year (% [95% CI]: total rate – rate in women without recurrence) and log-rank analyses

	Years 0–4	Years 5–9	Years 10–14	Year 15+
OFS + tamoxifen	0·56 (0·43 to 0·70)	1·28 (1·04 to 1·53)	1·16 (0·75 to 1·56)	0·0
Tamoxifen	0·91 (0·73 to 1·08)	1·17 (0·94 to 1·40)	1·23 (0·81 to 1·65)	1·90 (–0·25 to 4·05)
RR (95% CI)	0·60 (0·43 to 0·83)	1·08 (0·81 to 1·44)	0·94 (0·56 to 1·58)	0·11 (0·01 to 1·13)
(O – E)/V	–18·7/36·4	3·6/47·1	–0·8/14·4	–1·5/0·7

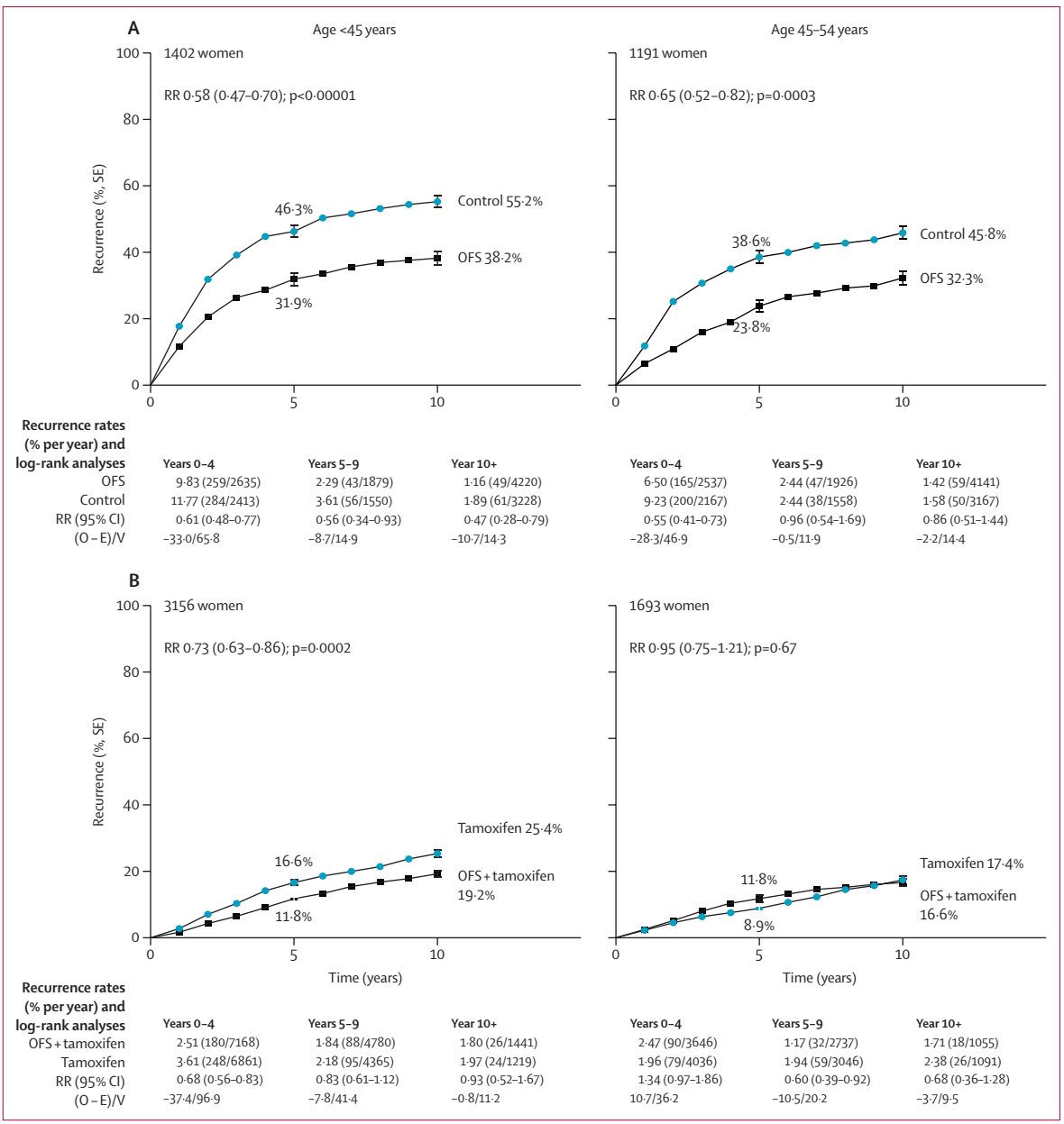
Event rate (% per year) and log-rank analyses

	Years 0–4	Years 5–9	Years 10–14	Year 15+
OFS	5·30 (836/15786)	3·37 (338/10040)	2·69 (107/3973)	1·20 (21/1747)
Control	5·87 (928/15813)	3·48 (342/9836)	2·35 (91/3869)	0·96 (16/1675)
RR (95% CI)	0·86 (0·77 to 0·96)	0·97 (0·82 to 1·15)	1·18 (0·86 to 1·61)	1·07 (0·53 to 2·18)
(O – E)/V	–49·1/330·6	–3·8/133·0	6·5/39·6	0·5/7·6

Death rate per year (% [95% CI]: total rate – rate in women without recurrence) and log-rank analyses

	Years 0–4	Years 5–9	Years 10–14	Year 15+
OFS + tamoxifen	3·36 (3·08 to 3·64)	3·57 (3·22 to 3·92)	3·15 (2·65 to 3·65)	2·50 (1·81 to 3·19)
Tamoxifen	3·54 (3·26 to 3·82)	3·90 (3·53 to 4·26)	2·72 (2·24 to 3·19)	2·26 (1·61 to 2·92)
RR (95% CI)	0·93 (0·82 to 1·06)	0·91 (0·78 to 1·06)	1·17 (0·90 to 1·51)	1·22 (0·77 to 1·94)
(O – E)/V	–15·3/218·1	–16·0/166·2	8·7/56·8	3·7/18·2

***Figure 3*: Outcome by allocation to OFS versus no OFS in women with ER-positive or ER-unknown early breast cancer, for each of three types of randomised comparison**
(A) No chemotherapy (or still premenopausal after chemotherapy) and tamoxifen not given. (B) No chemotherapy (or still premenopausal after chemotherapy), but tamoxifen given (mean 4 years). (C) chemotherapy, with unknown premenopausal status after. Plots are smoothed beyond year 10. RRs are from ER-weighted estimates of effect of OFS in women with ER-positive disease. O – E=observed minus expected. ER=oestrogen receptor. OFS=ovarian function suppression. RR=rate ratio. V=variance.



Recurrence rates (% per year) and log-rank analyses	Years 0–4	Years 5–9	Year 10+	Years 0–4	Years 5–9	Year 10+
OFS	9·83 (259/2635)	2·29 (43/1879)	1·16 (49/4220)	6·50 (165/2537)	2·44 (47/1926)	1·42 (59/4141)
Control	11·77 (284/2413)	3·61 (56/1550)	1·89 (61/3228)	9·23 (200/2167)	2·44 (38/1558)	1·58 (50/3167)
RR (95% CI)	0·61 (0·48–0·77)	0·56 (0·34–0·93)	0·47 (0·28–0·79)	0·55 (0·41–0·73)	0·96 (0·54–1·69)	0·86 (0·51–1·44)
(O – E)/V	–33·0/65·8	–8·7/14·9	–10·7/14·3	–28·3/46·9	–0·5/11·9	–2·2/14·4

Recurrence rates (% per year) and log-rank analyses	Years 0–4	Years 5–9	Year 10+	Years 0–4	Years 5–9	Year 10+
OFS + tamoxifen	2·51 (180/7168)	1·84 (88/4780)	1·80 (26/1441)	2·47 (90/3646)	1·17 (32/2737)	1·71 (18/1055)
Tamoxifen	3·61 (248/6861)	2·18 (95/4365)	1·97 (24/1219)	1·96 (79/4036)	1·94 (59/3046)	2·38 (26/1091)
RR (95% CI)	0·68 (0·56–0·83)	0·83 (0·61–1·12)	0·93 (0·52–1·67)	1·34 (0·97–1·86)	0·60 (0·39–0·92)	0·68 (0·36–1·28)
(O – E)/V	–37·4/96·9	–7·8/41·4	–0·8/11·2	10·7/36·2	–10·5/20·2	–3·7/9·5

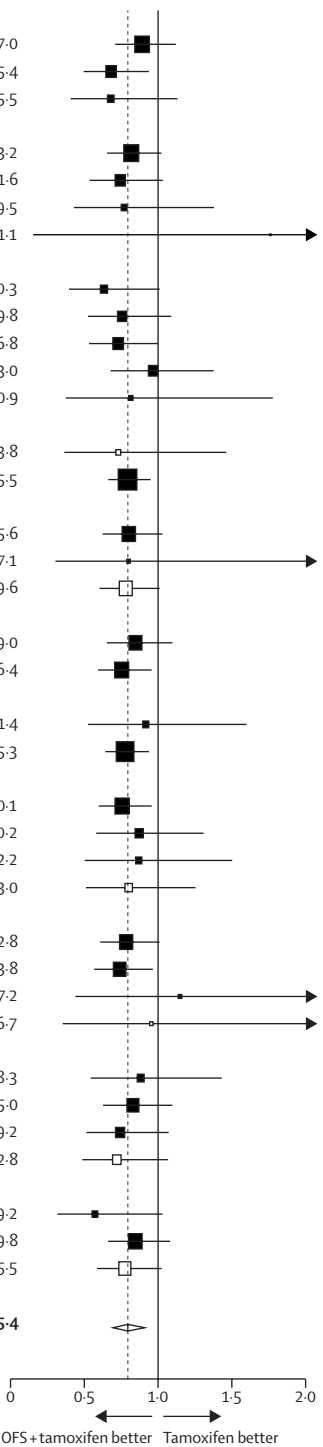
Figure 4: **Recurrence by allocation to OFS versus not OFS in confirmed premenopausal women with ER-positive or ER-unknown early breast cancer, estimated by age and by tamoxifen use**

(A) No chemotherapy (or still premenopausal after chemotherapy) and tamoxifen not given. (B) No chemotherapy (or still premenopausal after chemotherapy), but tamoxifen given (mean 4 years). RRs are from ER-weighted estimates of effect of OFS in women with ER-positive disease. ER=oestrogen receptor. O – E=observed minus expected. OFS=ovarian function suppression. RR=rate ratio. V=variance.

(figure 5H–J). Few women had HER2 status measured, and trials were mostly conducted before the availability of trastuzumab, but benefits appeared at least as large in HER2-positive as in HER2-negative disease. In this subgroup analysis there was limited power to assess the relative benefits of ovarian ablation versus suppression, or duration of pharmacological OFS as most of the trials administered 2 to 5 years of GnRHa to suppress ovarian oestrogen production.

For confirmed premenopausal women aged under 45 years, figure 6 shows that adding OFS to tamoxifen compared with tamoxifen alone leads to a one quarter reduction in distant recurrence (RR 0·77, 95% CI 0·64–0·93; p=0·0067) and breast cancer mortality (RR 0·74, 95% CI 0·58–0·94; p=0·012; figure 6A, B). Rates of death from other causes were less than 0·1% per year, and not significantly affected by OFS (figure 6C), leading to an overall survival benefit in these women

	Events/woman-years (% per year)		OFS + tamoxifen events		Ratio of annual event rate (95% CI or 99% CI)
	Allocated OFS + tamoxifen	Allocated tamoxifen	Log-rank O–E*	Variance of O–E*	OFS + tamoxifen *vs* tamoxifen
A Site of first recurrence (χ^2_2=3·8; p=0·15)					
Distant	269/20784 (1·3%)	302/20577 (1·5%)	−14·6	127·0	0·89 (0·71–1·12)
Isolated local	120/20781 (0·6%)	166/20576 (0·8%)	−25·1	65·4	0·68 (0·50–0·94)
Contralateral	45/20781 (0·2%)	63/20562 (0·3%)	−9·9	25·5	0·68 (0·41–1·13)
B Follow-up period, years (trend χ^2_1=0·1; p=0·79)					
0–4	270/10765 (2·5%)	327/10846 (3·0%)	−26·7	133·2	0·82 (0·65–1·02)
5–9	120/7489 (1·6%)	154/7376 (2·1%)	−18·3	61·6	0·74 (0·54–1·03)
10–14	41/2343 (1·7%)	48/2173 (2·2%)	−5·1	19·5	
15+	3/116 (2·6%)	2/96 (2·1%)	0·6	1·1	
C Age at entry, years (trend χ^2_1=2·7; p=0·10†)					
Age <35	62/2040 (3·0%)	77/1714 (4·5%)	−13·8	30·3	0·63 (0·40–1·01)
Age 35–39	99/3664 (2·7%)	127/3807 (3·3%)	−13·9	49·8	0·76 (0·53–1·09)
Age 40–44	133/7642 (1·7%)	163/6874 (2·4%)	−21·1	66·8	0·73 (0·53–1·00)
Age 45–49	114/5908 (1·9%)	127/6336 (2·0%)	−1·8	53·0	
Age 50–54	26/1509 (1·7%)	37/1811 (2·0%)	−2·2	10·9	
D ER status (χ^2_1=0·1; p=0·77)					
ER-unknown	49/1561 (3·1%)	60/1586 (3·8%)	−4·3	13·8	
ER-positive	385/19247 (2·0%)	471/19009 (2·5%)	−47·6	205·5	0·79 (0·66–0·95)
E PR status (χ^2_1=0·1; p=0·98)					
PR-positive	201/11804 (1·7%)	240/11664 (2·1%)	−23·4	105·6	0·80 (0·62–1·03)
PR-negative	16/653 (2·5%)	20/607 (3·3%)	−1·6	7·1	
PR-unknown	217/8320 (2·6%)	271/8291 (3·3%)	−24·6	99·6	0·78 (0·60–1·01)
F Previous chemotherapy use (χ^2_1=0·7; p=0·39)					
Absence	220/11274 (2·0%)	260/11399 (2·3%)	−16·5	99·0	0·85 (0·65–1·10)
Presence	214/9510 (2·3%)	271/9178 (3·0%)	−33·0	116·4	0·75 (0·59–0·96)
G Ablation or suppression (χ^2_1=0·5; p=0·47)					
Ablation	56/2273 (2·5%)	66/2227 (3·0%)	−1·9	21·4	
Suppression	360/17051 (2·1%)	447/16907 (2·6%)	−46·9	185·3	0·78 (0·64–0·94)
H Nodal status (trend χ^2_1=0·7; p=0·41)					
N0	239/14562 (1·6%)	300/14312 (2·1%)	−33·5	120·1	0·76 (0·60–0·96)
N1–3	85/2920 (2·9%)	97/2964 (3·3%)	−5·5	40·2	0·87 (0·58–1·31)
N4+	49/880 (5·6%)	58/812 (7·1%)	−3·1	22·2	0·87 (0·50–1·50)
N unknown	61/2422 (2·5%)	76/2489 (3·1%)	−7·3	33·0	0·80 (0·51–1·25)
I Tumour diameter (trend χ^2_1=0·1; p=0·85)					
1–20 mm (T1)	203/13407 (1·5%)	256/13587 (1·9%)	−25·1	102·8	0·78 (0·61–1·01)
21–50 mm (T2)	187/6598 (2·8%)	237/6185 (3·8%)	−28·3	93·8	0·74 (0·57–0·97)
>50 mm (T3–T4)	24/348 (6·9%)	18/354 (5·1%)	1·0	7·2	
Other or unknown	20/421 (4·8%)	20/430 (4·7%)	−0·3	6·7	
J Tumour grade (trend χ^2_1=0·6; p=0·44)					
Well differentiated	60/4214 (1·4%)	67/4164 (1·6%)	−3·5	28·3	0·88 (0·55–1·43)
Moderately	173/8698 (2·0%)	206/8584 (2·4%)	−15·9	85·0	0·83 (0·63–1·10)
Poorly	100/3215 (3·1%)	130/3207 (4·1%)	−14·6	49·2	0·74 (0·51–1·07)
Unknown	101/4610 (2·2%)	128/4572 (2·8%)	−14·0	42·8	0·72 (0·49–1·07)
K HER2 status (χ^2_1=2·5; p=0·11)					
Positive	34/1918 (1·8%)	49/1597 (3·1%)	−10·7	19·2	0·57 (0·32–1·03)
Negative	211/11170 (1·9%)	245/11189 (2·2%)	−18·4	109·8	0·85 (0·66–1·08)
Unknown	189/7685 (2·5%)	237/7783 (3·0%)	−21·8	85·5	0·77 (0·59–1·02)
Total	**434/20784 (2·1%)**	**531/20577(2·6%)**	**−49·5**	**215·4**	**0·795 (0·695–0·908) p=0·0008**

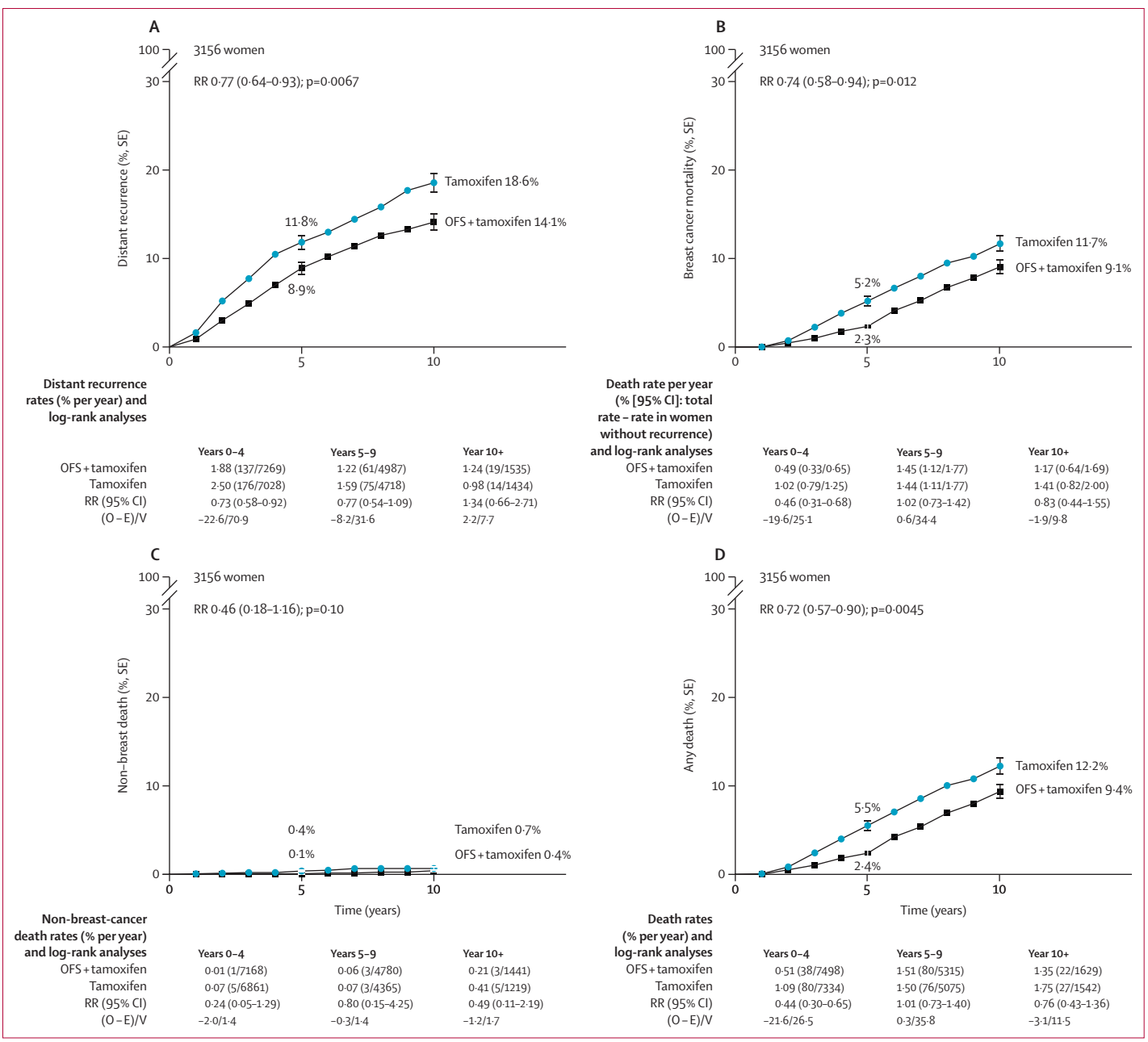


99% CI 95% CI Other or unknown

Figure 5: **Subgroup analyses of recurrence by allocation to OFS plus tamoxifen versus tamoxifen in confirmed premenopausal women with ER-positive or ER-unknown early breast cancer**
RRs are from ER-weighted estimates of effect of OFS in women with ER-positive disease. EST3193 did not provide individual patient data for method used for ovarian suppression so has been excluded from (G): 55% had oophorectomy or radiation, and 36% had GnRHa. ER=oestrogen receptor. GnRHa=gonadotrophin-releasing hormone agonist. O – E=observed minus expected. OFS=ovarian function suppression. PR=progesterone receptor. RR=rate ratio. *ER weighting: the contribution to each O – E value from ER-unknown disease is 0·75 of what the unweighted contribution would have been. †Heterogeneity between participants younger than 45 years and those aged 45 years and older, χ^2_1=3·2; p=0·072.

(RR 0·72, 95% CI 0·57–0·90; p=0·0045), and 10-year mortality of 9·4% versus 12·2%.

Across all trials there was no evidence that OFS caused any increase or decrease in non-breast second primary cancers, or deaths from known causes other than breast cancer (appendix pp 15, 28–30). There were comparatively few non-breast cancer deaths recorded among these women, who were all aged under 55 years at randomisation, with an RR of non-breast cancer death rates of 1·10 (0·86–1·41; p=0·45). Analyses of deaths without recorded recurrence showed no relationship between nodal status and mortality in the 426 (42·9%) of 993 women with a specified cause of death, indicating that only a few of these are likely to be misclassified breast cancer deaths (appendix p 31). However, the 567 (57·1%) of 993 deaths without recorded recurrence that were reported as being from an unknown cause occurred at twice the rate in women with node-positive disease than



Distant recurrence rates (% per year) and log-rank analyses

	Years 0–4	Years 5–9	Year 10+
OFS + tamoxifen	1·88 (137/7269)	1·22 (61/4987)	1·24 (19/1535)
Tamoxifen	2·50 (176/7028)	1·59 (75/4718)	0·98 (14/1434)
RR (95% CI)	0·73 (0·58–0·92)	0·77 (0·54–1·09)	1·34 (0·66–2·71)
(O – E)/V	–22·6/70·9	–8·2/31·6	2·2/7·7

Death rate per year (% [95% CI]: total rate – rate in women without recurrence) and log-rank analyses

	Years 0–4	Years 5–9	Year 10+
OFS + tamoxifen	0·49 (0·33/0·65)	1·45 (1·12/1·77)	1·17 (0·64/1·69)
Tamoxifen	1·02 (0·79/1·25)	1·44 (1·11/1·77)	1·41 (0·82/2·00)
RR (95% CI)	0·46 (0·31–0·68)	1·02 (0·73–1·42)	0·83 (0·44–1·55)
(O – E)/V	–19·6/25·1	0·6/34·4	–1·9/9·8

Non-breast-cancer death rates (% per year) and log-rank analyses

	Years 0–4	Years 5–9	Year 10+
OFS + tamoxifen	0·01 (1/7168)	0·06 (3/4780)	0·21 (3/1441)
Tamoxifen	0·07 (5/6861)	0·07 (3/4365)	0·41 (5/1219)
RR (95% CI)	0·24 (0·05–1·29)	0·80 (0·15–4·25)	0·49 (0·11–2·19)
(O – E)/V	–2·0/1·4	–0·3/1·4	–1·2/1·7

Death rates (% per year) and log-rank analyses

	Years 0–4	Years 5–9	Year 10+
OFS + tamoxifen	0·51 (38/7498)	1·51 (80/5315)	1·35 (22/1629)
Tamoxifen	1·09 (80/7334)	1·50 (76/5075)	1·75 (27/1542)
RR (95% CI)	0·44 (0·30–0·65)	1·01 (0·73–1·40)	0·76 (0·43–1·36)
(O – E)/V	–21·6/26·5	0·3/35·8	–3·1/11·5

Figure 6: **Main outcomes by allocation to OFS plus tamoxifen versus tamoxifen for confirmed premenopausal women younger than 45 years with ER-positive or ER-unknown early breast cancer**

(A) Distant recurrence at any time. (B) Breast cancer mortality. (C) Non-breast cancer mortality. (D) All-cause mortality. RRs are from ER-weighted estimates of effect of OFS in women with ER-positive disease. ER=oestrogen receptor. O – E=observed minus expected. OFS=ovarian function suppression. RR=rate ratio. V=variance.

in node-negative disease, indicating that, in a young population with few other expected causes of death, most of these deaths were from breast cancer. Sensitivity analyses which counted deaths from unknown causes without recurrence as non-breast cancer deaths, gave very similar results (RR 0·86 *vs* 0·85 for breast cancer mortality; 1·10 *vs* 1·00 for non-breast cancer mortality; appendix pp 32–33).

Recording of toxicity varied considerably between trials, so patient-level data on non-fatal toxicity were not sought. Instead, toxicities reported in trial publications are summarised in the appendix (pp 34–37). Toxicity was more consistently reported from the more recent trials of OFS plus tamoxifen versus tamoxifen. While adverse event reporting varied between trials, the addition of OFS was consistently associated with more higher grade hot flushes. For other adverse events, for example, weight gain, musculoskeletal symptoms, fatigue, insomnia, and neuropsychiatric toxicity, there was no consistent increase with OFS versus control. Two trials reported more glucose intolerance and more grade 3 hypertension with the addition of OFS but it is unclear whether this represents selective reporting. Of the 23 trials, only four studies (SOFT, ZIPP, EST3193, and ICR-CTSU) collected data on quality of life (QOL) measurements and these are best reviewed in the individual publications.

Discussion

Ablation or suppression of premenopausal ovarian function is one of the earliest forms of endocrine therapy for breast cancer, first used in the 19th century.[3,4] It was the first cancer treatment assessed in a randomised trial,[5] initiated at the Christie Hospital in 1948. Further trials of radiotherapy or surgery to ablate ovarian function were undertaken over the next half-century. More recently, these irreversible procedures have often been replaced by pharmacological suppression of ovarian function, which leaves open the possibility that, for some women, ovarian oestrogen production might resume after the scheduled end of suppression.

This updated meta-analysis summarises all available unconfounded randomised evidence on OFS for premenopausal women with early breast cancer. The ER-weighted analyses confirm that, for women with ER-positive disease who are confirmed to be premenopausal (after any other treatments), OFS substantially reduces the risk of recurrence and death from breast cancer, with the breast cancer death rate reduced considerably not only during the first decade but also during the second decade. This is clinically relevant, as the risk of recurrence of ER-positive disease remains appreciable for at least 20 years.[28]

Results are consistent with, but more definite than, those in previous meta-analyses.[7,8] The proportional reduction in breast cancer recurrence and death is greater in the earlier trials where women in both groups did not receive tamoxifen. Nonetheless, even in more recent trials of OFS plus tamoxifen versus tamoxifen alone (tamoxifen allocated for a mean of about 4 years) a significant benefit was observed, particularly among women younger than 45 years. It is unclear if the smaller effect in these trials can be at least partially explained by adherence to therapy (either pharmacological OFS or tamoxifen) because adherence data were not routinely collected. For premenopausal women who received chemotherapy (and most chemotherapy in these trials involved cyclophosphamide, methotrexate, and fluorouracil, which often causes menopause),[23] if menopausal status was uncertain after chemotherapy, there appeared to be little benefit from OFS.

Nowadays, many premenopausal women with ER-positive disease are prescribed tamoxifen, and this meta-analysis reliably confirms that the use of OFS offers further benefit. In the presence of OFS, however, aromatase inhibitors are more effective than tamoxifen in such women,[19] indicating that, depending on their absolute risk of recurrence and tolerability, the optimal endocrine treatment for premenopausal women might be a combination of aromatase inhibitors and either ovarian ablation or long-term adherence to ovarian suppression. The optimal duration of endocrine treatment in these circumstances is not known, but in postmenopausal women 10 years of an aromatase inhibitor appears somewhat more effective than just 5 years.[29] Additionally, if a premenopausal woman cannot adhere long term to tamoxifen or an aromatase inhibitor, this meta-analysis confirms a substantial oncological benefit from OFS as the sole endocrine treatment, but OFS alone can also be associated with intrusive endocrine symptoms.

Previous chemotherapy did not appear to affect the benefits of OFS for women who remained premenopausal and with modern chemotherapy recovery of ovarian function is common, particularly for younger women.[30] Despite the introduction of targeted agents, and increasing use of genomic assays to help inform chemotherapy treatment decisions, it is probable that OFS remains relevant to premenopausal women with a current diagnosis of early breast cancer.[31,32] For these women, further research is needed to fully evaluate the safety and efficacy of adding newer therapies such as selective ER degraders or CDK 4/6 inhibitors, with or without previous chemotherapy, to OFS. Concerns about the risk of thrombosis[33] or cardiac events[34] with tamoxifen and some CDK 4/6 inhibitors will limit consideration of this combination, but most premenopausal women receiving adjuvant CDK 4/6 inhibitors will be at sufficient risk of recurrence to be recommended OFS with an aromatase inhibitor.

Many trials did not report side-effects or QOL, although OFS can cause more menopausal symptoms.[12] There are limited data on late toxicities, making reliable assessment of any long-term harms of OFS difficult. However, after

pharmacological OFS ends, QOL symptom scores can recover.[35] While OFS is known to cause osteoporosis,[14,36] bone mineral density was not routinely measured; but this risk can be ameliorated with bisphosphonates and monitoring of bone health. There was no evidence of adverse effects on non-breast-cancer mortality, or cancer incidence.

A limitation is that many trials took place before the 1980s, when ER status was not routinely available, diagnosis of recurrence was less sensitive, and adjuvant therapy was not routinely used. However, even comparing OFS plus tamoxifen versus tamoxifen alone, this meta-analysis shows that the addition of OFS reduces breast cancer recurrence and mortality rates by about a quarter among premenopausal women younger than 45 years. Interestingly this benefit was seen in the trials where most premenopausal women receiving OFS plus tamoxifen had pharmacological OFS rather than ovarian ablation, many receiving only about 2 years of such therapy, but the benefits appeared to be persistent. Further research is needed to assess the optimal duration of pharmacological OFS.

Proportional risk reductions appeared similar for women regardless of their individual or tumour characteristics, so the absolute benefits, unlike any harms, are likely to increase with increasing recurrence risk. Since these studies were conducted, there has been a steady improvement in breast cancer outcomes[37] (and corresponding decreases in population-wide breast cancer mortality rates in middle age) which complicates prediction of the additional absolute benefit from OFS for women diagnosed today. Nevertheless, this meta-analysis of trials in ER-positive early breast cancer of OFS, together with those trials of OFS with 5 years of tamoxifen or of an aromatase inhibitor, demonstrate large reductions in distant recurrence or breast cancer mortality rates throughout the first decade and, at least for OFS and tamoxifen (and perhaps for aromatase inhibitors),[29] into the second decade. Collectively, these results remain relevant to contemporary practice and emphasise the importance of effective long-term prevention of ER stimulation by oestrogen from the ovaries or from the aromatase enzymes, while minimising side-effects from ER blockade or oestrogen deprivation.

Contributors

RB, JBr, RG, and RKH designed and carried out the analyses, with all members of the writing committee providing input to the analysis plan. RB, RG and RKH accessed and verified the data. RB, JBr, RG, RKH and RP drafted the report and all other writing committee members contributed to revising it. Interim analyses were presented and discussed at steering committee meetings. The EBCTCG secretariat (G Beake, R Berry, C Boddington, R Bradley, J Braybrooke, M Clarke, C Davies, L Davies, D Dodwell, F Duane, V Evans, J Gay, L Gettins, J Godwin, R Gray, R K Hills, F Holt, S James, A Kerr, H Liu, Z Liu, E MacKinnon, G Mannu, P McGale, T McHugh, P Morris, M Nakahara, H Pan, R Peto, S Read, E Straiton, C Taylor, H Taylor) was responsible for maintaining collaboration, identifying trials, and obtaining and checking datasets. All authors of the writing committee had responsibility for the decision to submit for publication.

Declaration of interests

JBr reports financial interest by being clinical advisor for National Institute for Health and Care Excellence and for Genesis Care. JBe reports research grants from Amgen, AstraZeneca, Bayer, Merck, Pfizer, Roche, and Sanofi-Aventis to Karolinska Institutet or University Hospital for molecular marker studies or clinical studies; payment or honoraria from Roche, AstraZeneca, Novartis, and Stratipath; stocks in Stratipath; and financial interests from UpToDate. JBl reports grants from AstraZeneca, Merck Sharp & Dohme, Puma Biotecnology, Pfizer, Janssen-Cilag, Novartis, Eli Lilly, Breast Cancer Now, Breast International Group, Glaxo Smith Kline, Kortuc, National Institute for Health and Care Research, and Verastem; and participation on a Data Safety Monitoring Board for ATNEC (University of Warwick) and POSNOC (University of Nottingham). MMR reports support from Breast Cancer Research Foundation; grants from Pfizer, TerSera Therapeutics, Ispen, DebioPharm, and AstraZeneca; consulting fees from TerSera Therapeutics, Tolmar Pahrmaceuticals, and AstraZeneca; and payments or honoraria from Bristol-Myers Squibb, St Gallen Oncology Conferences and McGill University funded by Merck; participation on a Data Safety Monitoring Board for ABCSG; and leadership or fiduciary role for ETOP IBCSG Partners Foundation. PAF reports honorarium from Eli Lilly. SMS reports consulting fees from TERSERA and Molecular Templates; payment or honoraria from Chugai Pharmaceuticals, Merck and AstraZeneca; support for attending meetings from Roche, Chugai, SEAGEN, IMMUNOME, and NAPO; participation on Data Safety Monitoring Board for Napo Pharmaceuticals Scientific Advisory board, Merck Advisory board, and AstraZeneca Advisory board; leadership or fiduciary role for SEAGEN BOD (November, 2022, to December, 2023), Immunome BOD (April, 2024, to present), and NSABP BOD (unpaid); stock or stock options in SEAGEN and Immunome; and medical writing third party with AstraZeneca.

Data sharing

All datasets provided to the EBCTCG remain the property of the trial groups sending them, to whom data sharing requests should be made. The EBCTCG data sharing policy is available at https://www.ctsu.ox.ac.uk/research/the-early-breast-cancer-trialists-collaborative-groupebctcg/data-policy-for-the-early-breast-cancer-trialists2019-collaborativegroup-ebctc.

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