Webappendix: Supplementary figures and tables for "Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100 000 women in 123 randomised trials"

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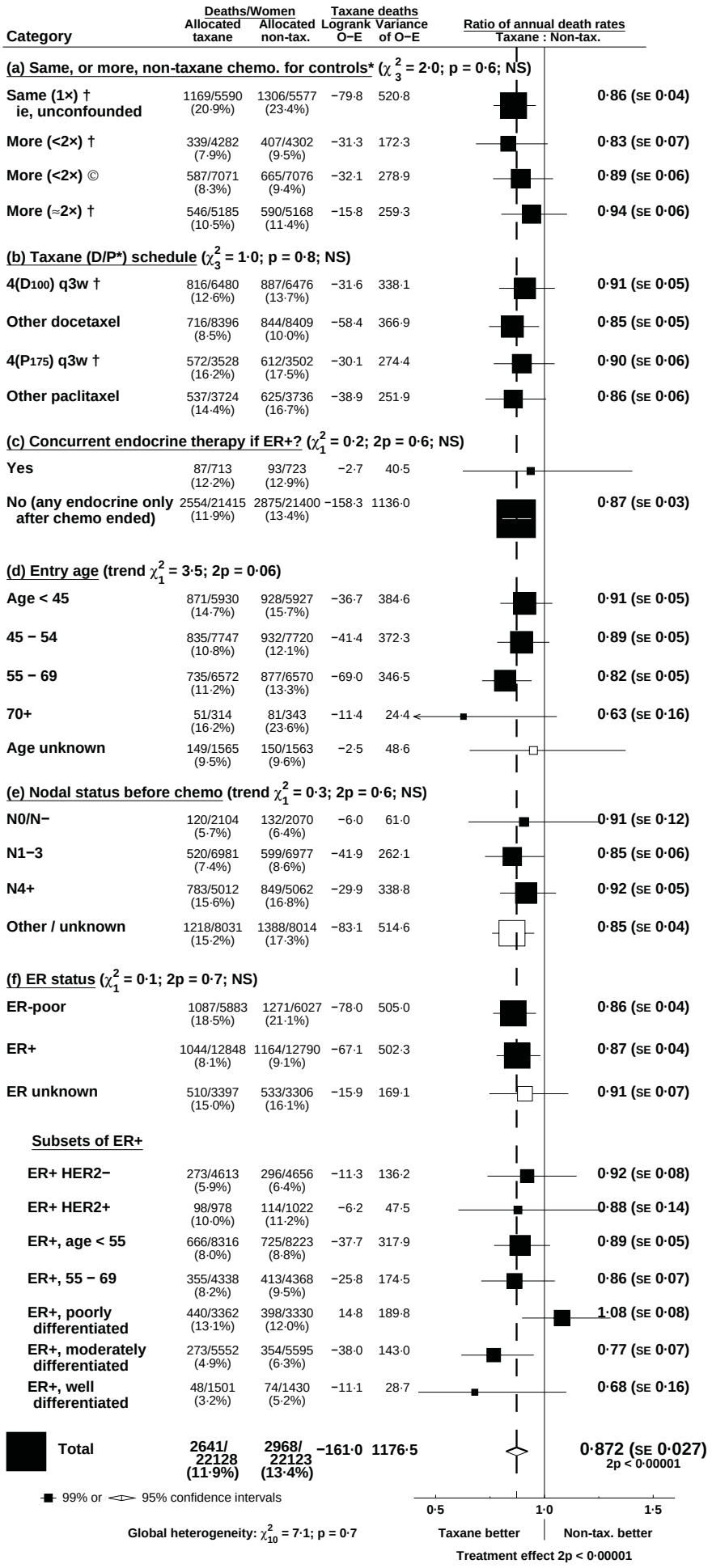
(***Download powerpoint presentation from EBCTCG website***)

Notes on statistical methods: Annual breast cancer mortality rates are by subtraction of mortality rates among women without recurrence from those among all women. Likewise, breast cancer mortality rate ratios (RR±1SE, newer treatment *vs* control) derive from logrank subtraction (ie, subtraction of logrank analyses of mortality without recurrence from logrank analyses of overall mortality).

Forest plots of recurrence (or of mortality without recurrence) give woman-years before first recurrence, those of overall mortality give woman-years before death and those of mortality without recurrence give numbers randomised. Numbers of women randomised, woman-years and first events generally double-count controls in 2:1 comparisons (and triple-count those in 3:1 comparisons), but calculations of the logrank statistic (O-E) and its variance V are unaffected by this, and do not double- or triple-count controls. If a logrank statistic (O−E) has variance V, then, defining $z=(O-E)/\sqrt{V}$ and $b=(O-E)/V$, RR=exp(b) is the event rate ratio, and is taken to have SE=(RR−1)/z and 95% CI $\exp(b\pm1.96/\sqrt{V})$. P-values (all of which are two-sided) are obtained by comparing z with a standard normal distribution (so z=1.96 yields 2p=0.05). In calculating p-values for side-effects (before recurrence), a continuity correction of 0.5 is applied to (O-E).

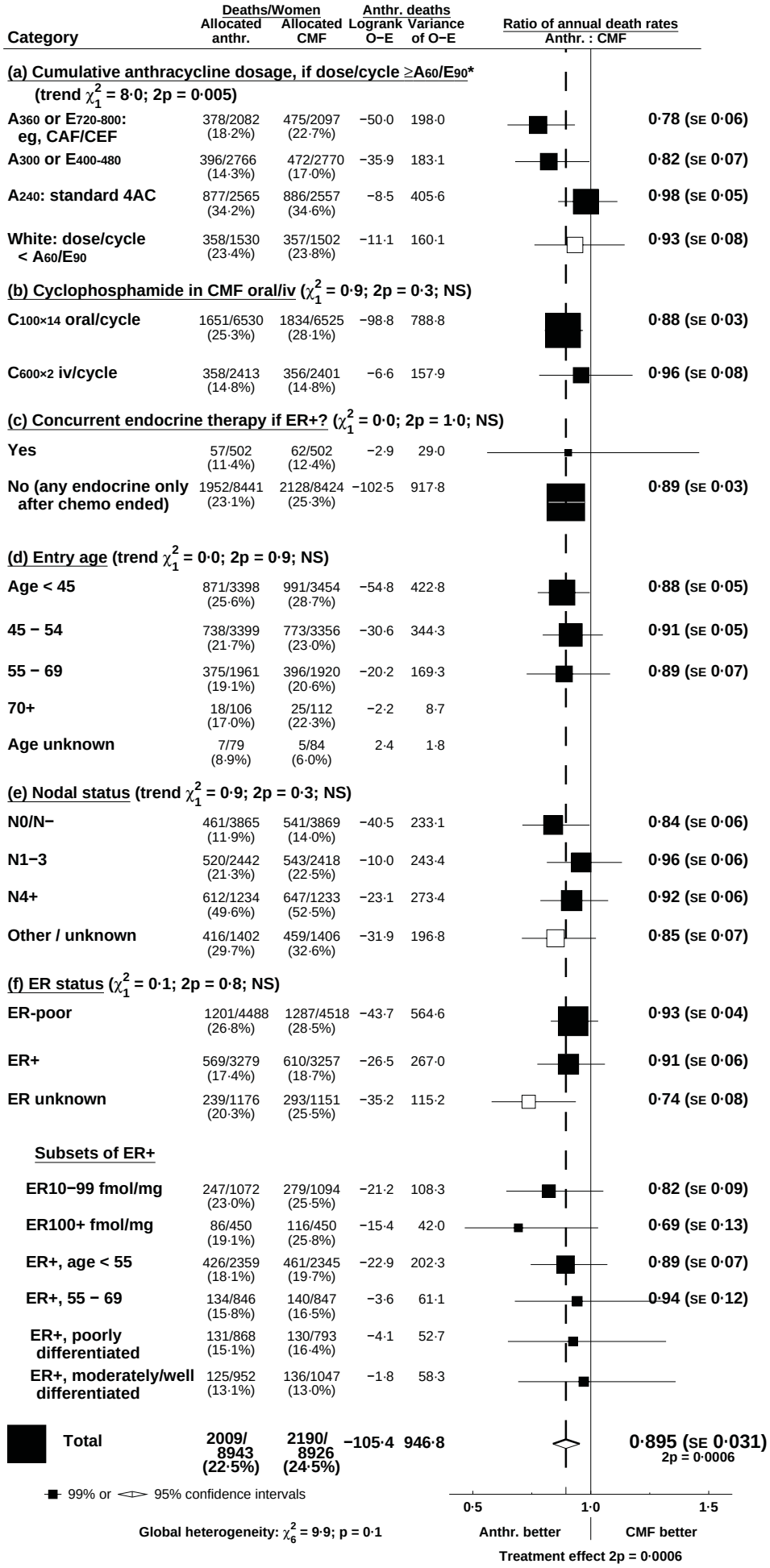
P 2: Subgroup analyses of BREAST CANCER MORTALITY (mortality with recurrence, by logrank subtraction), taxane-plus-anthracycline-based regimen vs SAME, or MORE (< doubled or ~doubled) non-taxane cytotoxic chemotherapy NB First four subgroups are as in forest plots*.



* Forest plots (webappendix pp 21-26) give details of each trial's cytotoxic regimens
D = docetaxel; **P** = paclitaxel; 4(**D**100) q3w means 4 doses of docetaxel 100 mg/m² at intervals of 3 weeks
† Taxane courses do not overlap other chemotherapy courses
© Taxane given concurrently with anthracycline

P 3: Subgroup analyses of BREAST CANCER MORTALITY (mortality with recurrence, by logrank subtraction), any anthracycline-based regimen vs. standard CMF (or near-standard CMF).

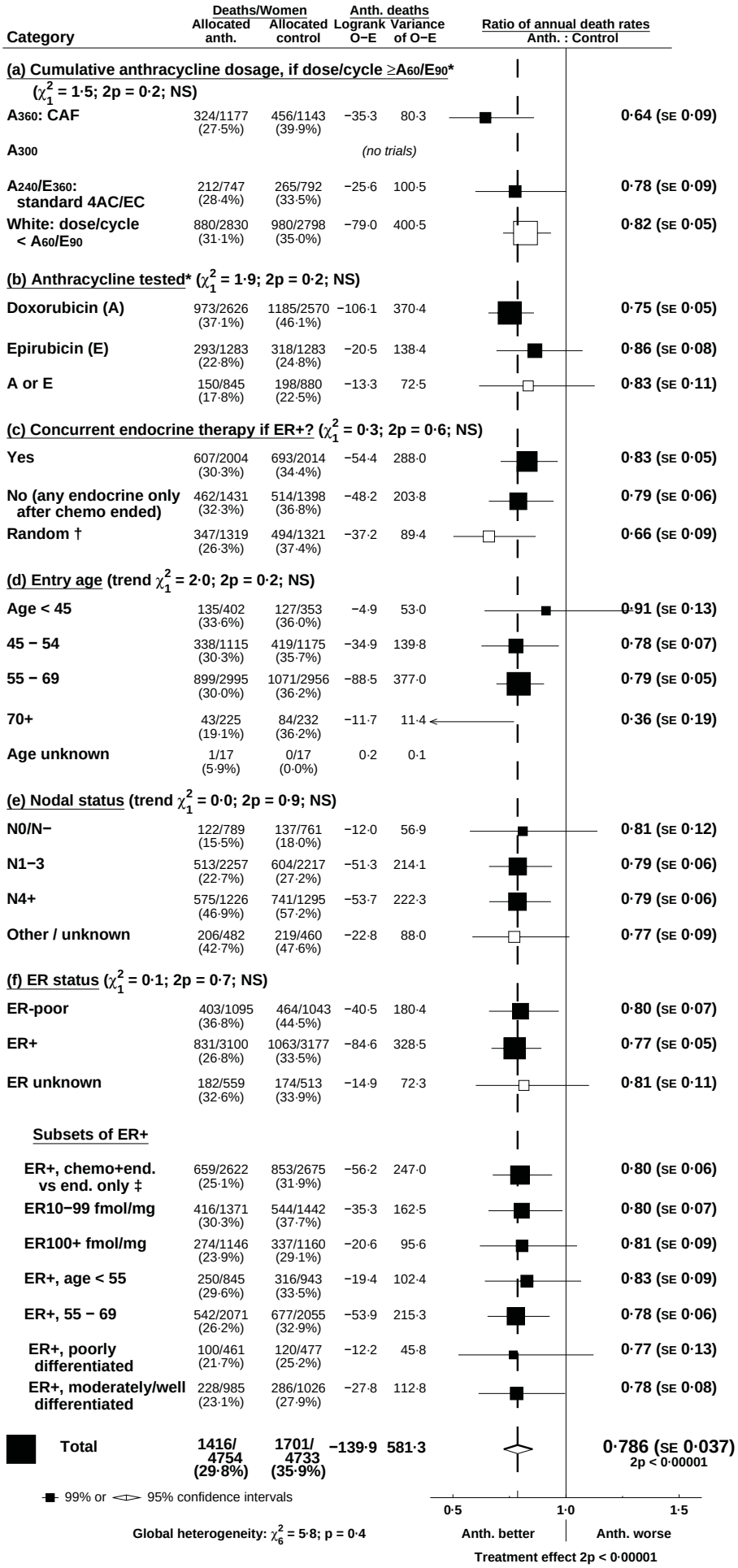
NB First four subgroups are as in forest plots*.



* Forest plots (webappendix pp 27-32) give details of each trial's cytotoxic regimens
Anthracyclines: **A** = doxorubicin (Adriamycin), **E** = epirubicin. Other cytotoxics: **C** = cyclophosphamide, **M** = methotrexate, **F** = fluorouracil
Dose/cycle (and cumulative dosage) is given after the drug name in mg/m²; **A60/E90** means 60 mg/m² of doxorubicin or 90 mg/m² of epirubicin

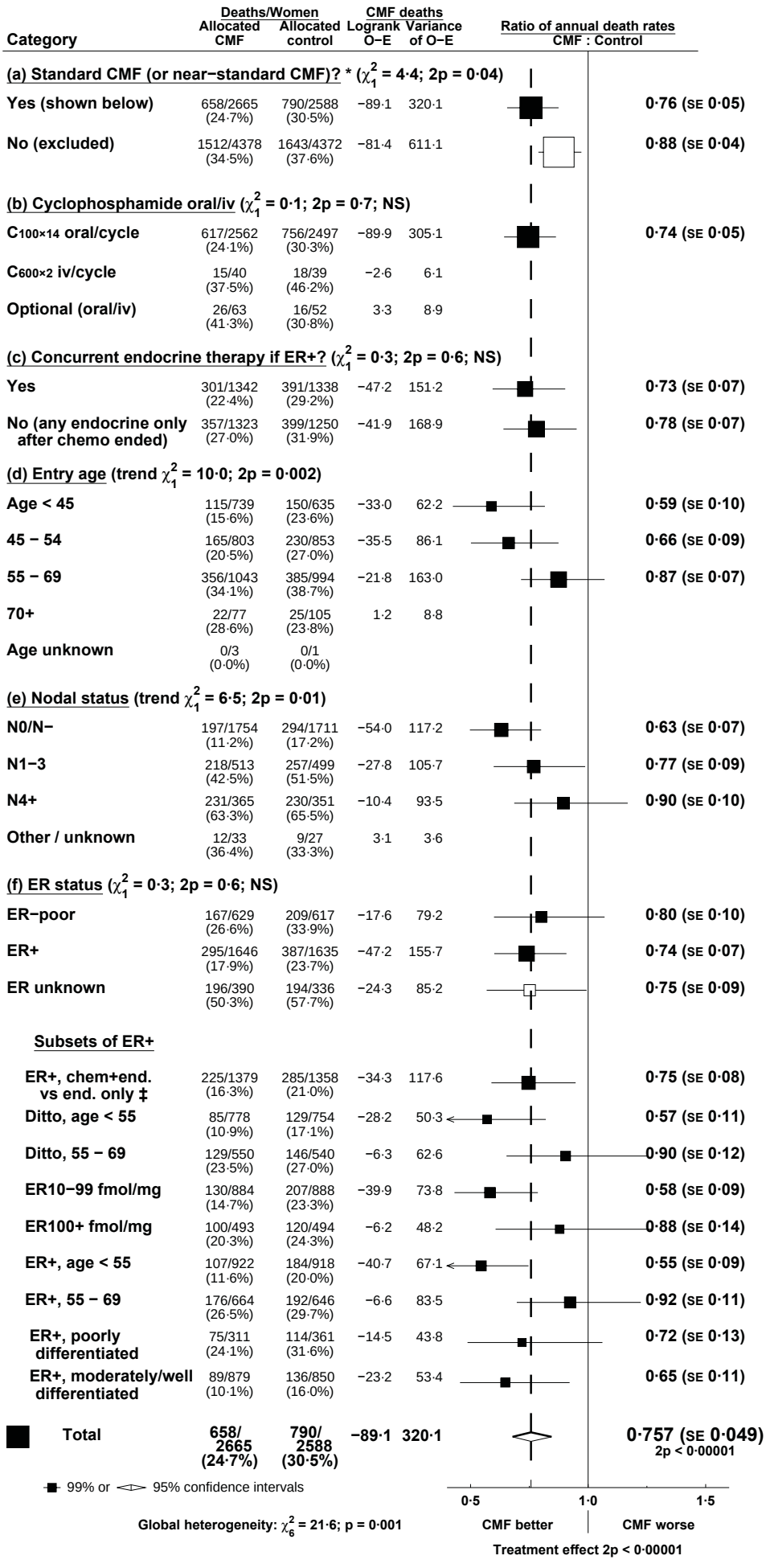
P 4: Subgroup analyses of BREAST CANCER MORTALITY (mortality with recurrence, by logrank subtraction), any anthracycline-based regimen vs No chemotherapy

NB First four subgroups are as in forest plots*.



* Forest plots (webappendix pp 33-38) give details of each trial's cytotoxic regimens
Anthracyclines: **A** = doxorubicin (Adriamycin), **E** = epirubicin. Other cytotoxics: **C** = cyclophosphamide, **M** = methotrexate, **F** = fluorouracil
Dose/cycle (and cumulative dosage) is given after the drug name in mg/m²; **A**60/**E**90 means 60 mg/m² of doxorubicin or 90 mg/m² of epirubicin
† In the SWOG 8814 trial of CAF in postmenopausal ER+ disease, tamoxifen started randomly with or after the chemotherapy.
‡ chem+end. = chemo-endocrine therapy

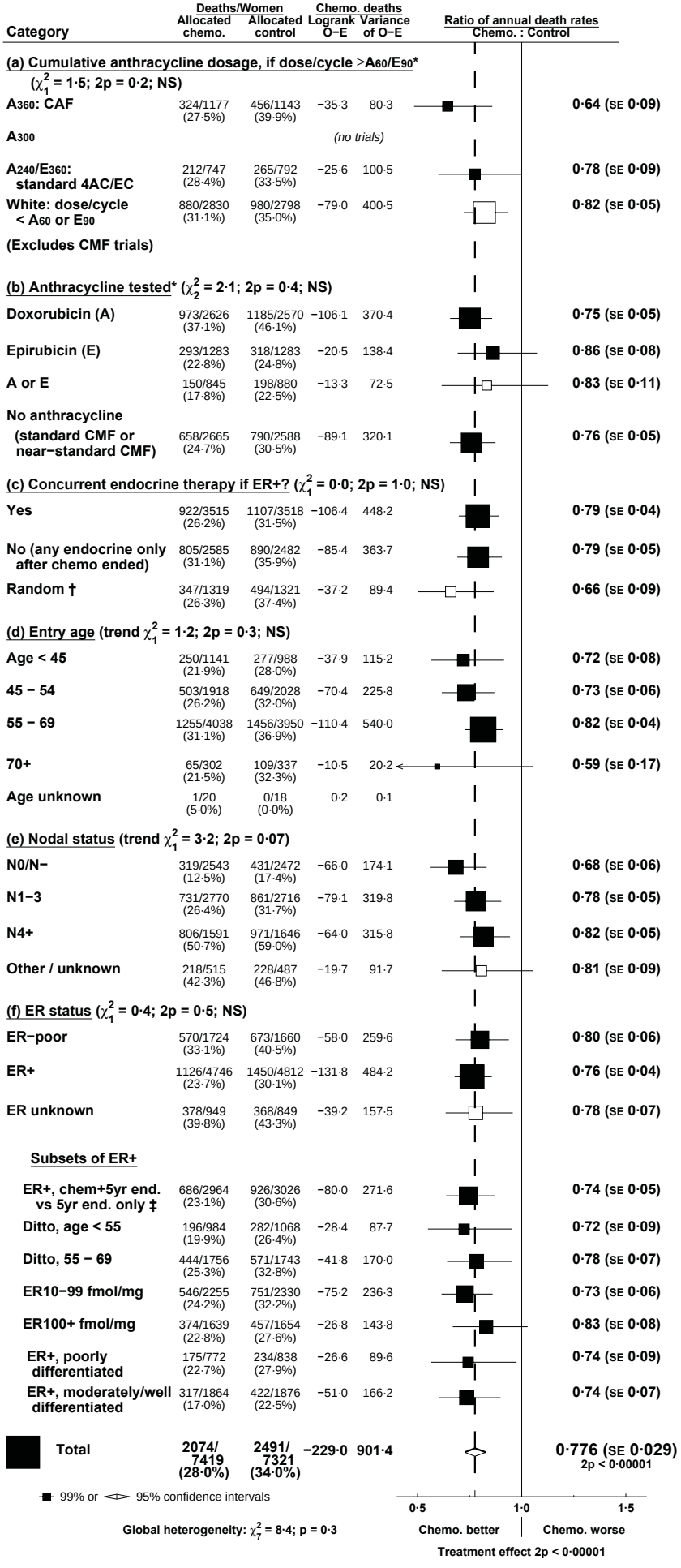
P 5: Subgroup analyses of BREAST CANCER MORTALITY (mortality with recurrence), standard CMF (or near-standard CMF)* vs. No chemotherapy



* See forest plots (webappendix pp 51−56) for details of regimens tested. Except in the first section, all analyses are of standard CMF (or near standard CMF). Trials of other CMF regimens (all with lower dose/cycle of at least one drug) are shown only in the first section (as a white square), and are then excluded.

‡ chem+end. = chemo−endocrine therapy

P 6: Subgroup analyses of BREAST CANCER MORTALITY (mortality with recurrence), anthracycline-based regimen (eg, standard 4AC) or standard CMF (or near-standard CMF) vs. No chemotherapy

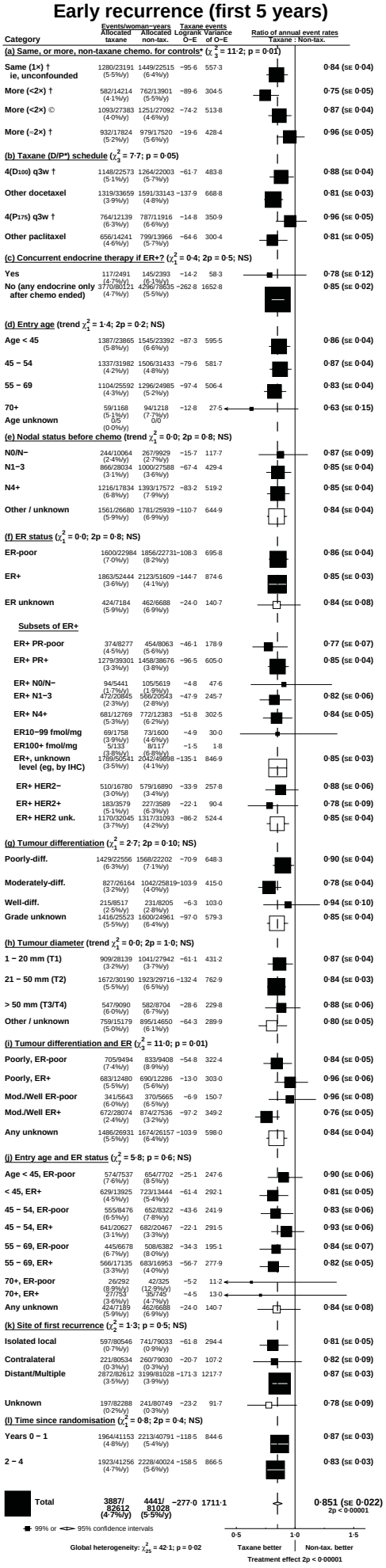


* Forest plots (webappendix pp 39−44) give details of each trial's cytotoxic regimens
Anthracyclines: **A** = doxorubicin (Adriamycin), **E** = epirubicin. Other cytotoxics: **C** = cyclophosphamide, **M** = methotrexate, **F** = fluorouracil
Dose/cycle (and cumulative dosage) is given after the drug name in mg/m²; **A60/E90** means 60 mg/m² of doxorubicin or 90 mg/m² of epirubicin
† In the SWOG 8814 trial of CAF in postmenopausal ER+ disease, tamoxifen started randomly with or after the chemotherapy.
‡ chem+end. = chemo−endocrine therapy; 5yr end. = 5 years of tamoxifen (or, in part of one trial, toremifine)

P 7: Subgroup analyses of RECURRENCE, taxane-plus-anthracycline-based regimen vs SAME, or MORE (< doubled or ~doubled) non-taxane cytotoxic chemotherapy

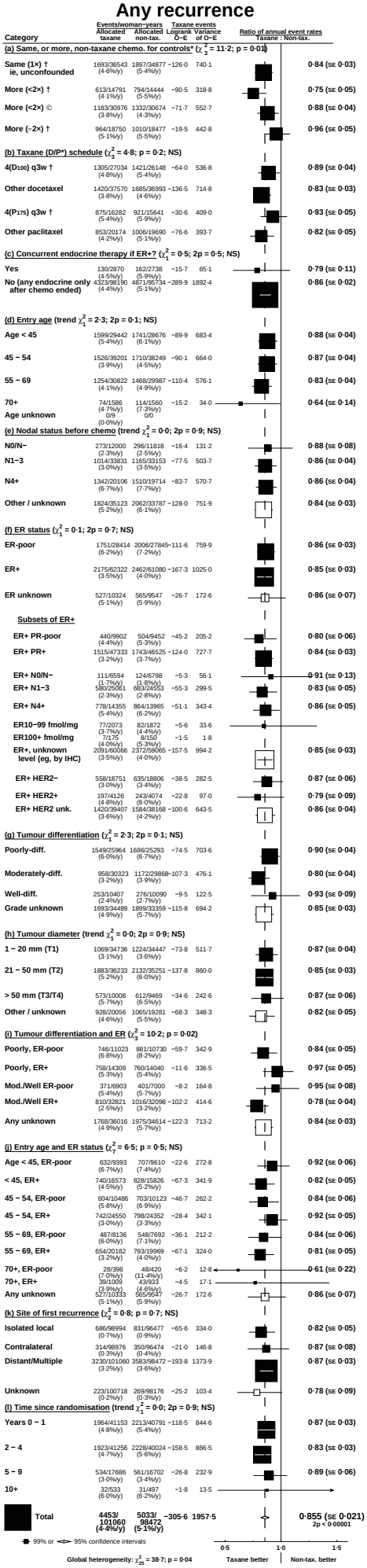
NB First four subgroups are as in forest plots*.

Early recurrence (first 5 years)



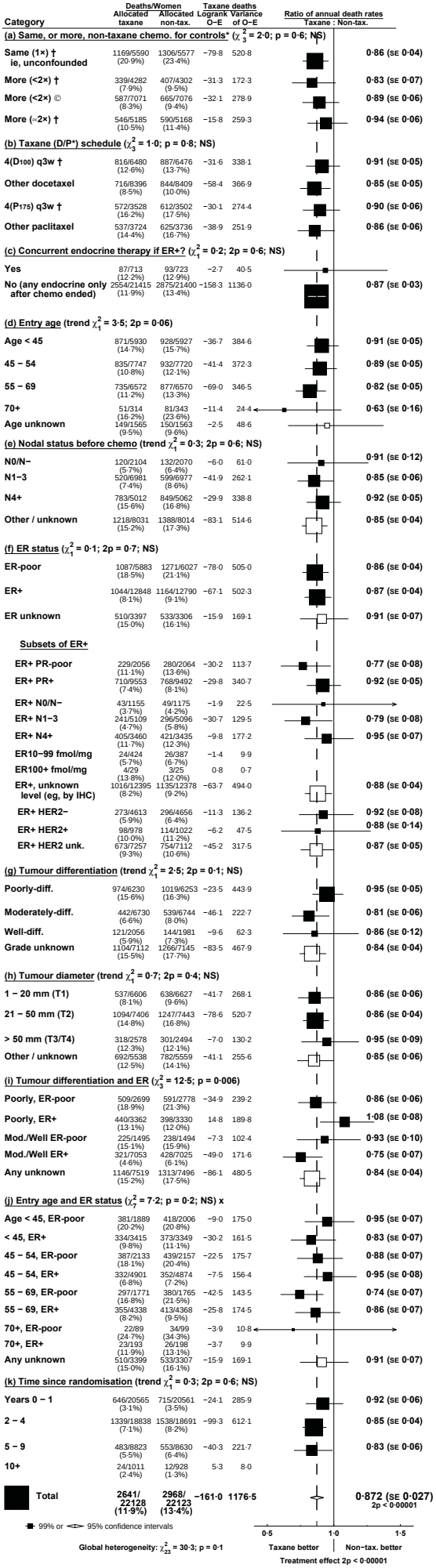
* Forest plots (webappendix pp 21-26) give details of each trial's cytotoxic regimens
D = docetaxel; P = paclitaxel; 4(D100) q3w means 4 doses of docetaxel 100 mg/m² at intervals of 3 weeks
† Taxane courses do not overlap other chemotherapy courses
© Taxane given concurrently with anthracycline

Any recurrence



* Forest plots (webappendix pp 21-26) give details of each trial's cytotoxic regimens
D = docetaxel; P = paclitaxel; 4(D100) q3w means 4 doses of docetaxel 100 mg/m² at intervals of 3 weeks
† Taxane courses do not overlap other chemotherapy courses
© Taxane given concurrently with anthracycline

P 8: Subgroup analyses of BREAST CANCER MORTALITY (mortality with recurrence, by logrank subtraction), taxane-plus-anthracycline-based regimen vs SAME, or MORE (< doubled or ~doubled) non-taxane cytotoxic chemotherapy NB First four subgroups are as in forest plots*.



* Forest plots (webappendix pp 21-26) give details of each trial's cytotoxic regimens
D = docetaxel; **P** = paclitaxel; 4(**D**100) q3w means 4 doses of docetaxel 100 mg/m² at intervals of 3 weeks
† Taxane courses do not overlap other chemotherapy courses
© Taxane given concurrently with anthracycline

P 9: Subgroup analyses of RECURRENCE, any anthracycline-based regimen vs. standard CMF (or near-standard CMF). NB First four subgroups are as in forest plots*.

Early recurrence (first 5 years)

Category	Events/woman-years Allocated anthr.	Allocated CMF	Anthr. events Logrank O−E	Variance of O−E	Ratio of annual event rates Anthr. : CMF
(a) Cumulative anthracycline dosage, if dose/cycle ≥A60/E90* (trend χ^2_1 = 6·7; 2p = 0·01)					
A360 or E720–800: eg, CAF/CEF	381/9229 (4·1%/y)	473/9038 (5·2%/y)	−50·9	194·3	0·77 (SE 0·06)
A300 or E400–480	608/10194 (6·0%/y)	669/9997 (6·7%/y)	−24·0	262·7	0·91 (SE 0·06)
A240: standard 4AC	820/10274 (8·0%/y)	830/10090 (8·2%/y)	−8·7	355·5	0·98 (SE 0·05)
White: dose/cycle < A60/E90	398/6194 (6·4%/y)	389/6021 (6·5%/y)	−10·0	170·9	0·94 (SE 0·07)
(b) Cyclophosphamide in CMF oral/iv (χ^2_1 = 1·2; 2p = 0·3; NS)					
C100×14 oral	1708/26046 (6·6%/y)	1859/25377 (7·3%/y)	−87·1	768·7	0·89 (SE 0·03)
C600×2 iv	499/9845 (5·1%/y)	502/9769 (5·1%/y)	−6·5	214·8	0·97 (SE 0·07)
(c) Concurrent endocrine therapy if ER+? (χ^2_1 = 0·8; 2p = 0·4; NS)					
Yes	73/2251 (3·2%/y)	70/2231 (3·1%/y)	1·9	34·2	
No (any endocrine only after chemo ended)	2134/33730 (6·3%/y)	2291/32915 (7·0%/y)	−95·5	949·3	0·90 (SE 0·03)
(d) Entry age (trend χ^2_1 = 0·1; 2p = 0·8; NS)					
Age < 45	963/13406 (7·2%/y)	1067/13306 (8·0%/y)	−43·7	433·2	0·90 (SE 0·05)
45 – 54	802/13866 (5·8%/y)	824/13475 (6·1%/y)	−25·9	357·6	0·93 (SE 0·05)
55 – 69	406/8013 (5·1%/y)	430/7708 (5·6%/y)	−26·2	178·9	0·86 (SE 0·07)
70+	20/427 (4·7%/y)	23/426 (5·4%/y)	−0·1	8·2	
Age unknown	16/179 (8·9%/y)	17/231 (7·4%/y)	2·3	5·5	
(e) Nodal status (trend χ^2_1 = 0·3; 2p = 0·6; NS)					
N0/N−	558/16757 (3·3%/y)	593/16587 (3·6%/y)	−16·0	265·3	0·94 (SE 0·06)
N1−3	583/9794 (6·0%/y)	603/9587 (6·3%/y)	−13·5	259·9	0·95 (SE 0·06)
N4+	613/3996 (15·3%/y)	663/3798 (17·5%/y)	−27·2	253·4	0·90 (SE 0·06)
Other / unknown	453/5344 (8·5%/y)	502/5174 (9·7%/y)	−36·9	204·9	0·84 (SE 0·06)
(f) ER status (χ^2_1 = 0·0; 2p = 0·9; NS)					
ER−poor	1241/18040 (6·9%/y)	1304/17790 (7·3%/y)	−34·7	547·2	0·94 (SE 0·04)
ER+	688/13372 (5·1%/y)	712/13152 (5·4%/y)	−17·3	305·3	0·95 (SE 0·06)
ER unknown	278/4479 (6·2%/y)	345/4204 (8·2%/y)	−41·6	131·0	0·73 (SE 0·07)
Subsets of ER+					
ER+ PR−poor	124/1805 (6·9%/y)	119/1570 (7·6%/y)	−4·0	48·4	
ER+ PR+	404/8942 (4·5%/y)	451/8074 (5·0%/y)	−20·1	189·8	0·90 (SE 0·07)
ER+ N0/N−	170/5561 (3·1%/y)	187/5459 (3·4%/y)	−12·1	81·1	0·86 (SE 0·10)
ER+ N1−3	181/4184 (4·3%/y)	181/4197 (4·3%/y)	1·7	77·9	
ER+ N4+	135/1168 (11·6%/y)	138/1061 (13·0%/y)	−4·0	56·3	
ER10−99 fmol/mg	246/4549 (5·4%/y)	269/4532 (5·9%/y)	−17·5	103·2	0·84 (SE 0·09)
ER100+ fmol/mg	85/1973 (4·3%/y)	119/1876 (6·3%/y)	−16·6	42·1	0·67 (SE 0·13)
ER+, unknown level (eg, by IHC)	357/6752 (5·3%/y)	324/6649 (4·9%/y)	17·0	147·0	
(g) Tumour differentiation (χ^2_1 = 2·7; 2p = 0·10; NS)					
Poorly−diff.	523/9730 (5·4%/y)	593/9461 (6·3%/y)	−29·1	231·7	0·88 (SE 0·06)
Moderately/Well	352/7555 (4·7%/y)	334/7521 (4·4%/y)	7·0	150·5	1·05 (SE 0·08)
Grade unknown	1332/18564 (7·2%/y)	1434/18133 (7·9%/y)	−70·1	607·8	0·89 (SE 0·04)
(h) Tumour diameter (trend χ^2_1 = 0·3; 2p = 0·6; NS)					
1 – 20 mm (T1)	579/13819 (4·2%/y)	622/13741 (4·5%/y)	−13·8	269·4	0·95 (SE 0·06)
21 – 50 mm (T2)	964/13436 (7·2%/y)	1019/13296 (7·7%/y)	−32·1	425·1	0·93 (SE 0·05)
> 50 mm (T3/T4)	123/1055 (11·7%/y)	133/939 (14·2%/y)	−6·7	42·7	0·86 (SE 0·14)
Other / unknown	541/7551 (7·2%/y)	587/7142 (8·2%/y)	−44·8	246·3	0·83 (SE 0·06)
(i) Tumour differentiation and ER (χ^2_3 = 2·1; p = 0·6; NS)					
Poorly, ER−poor	252/5157 (4·9%/y)	269/5235 (5·1%/y)	−1·1	112·0	0·99 (SE 0·09)
Poorly, ER+	183/3343 (5·5%/y)	193/2970 (6·5%/y)	−10·5	73·9	0·87 (SE 0·11)
Mod./Well ER−poor	120/2679 (4·5%/y)	110/2328 (4·7%/y)	−2·5	50·2	
Mod./Well ER+	172/3768 (4·6%/y)	171/4160 (4·1%/y)	6·9	77·4	
Any unknown	1480/20902 (7·1%/y)	1618/20422 (7·9%/y)	−84·9	676·4	0·88 (SE 0·04)
(j) Entry age and ER status (χ^2_7 = 1·8; p = 1·0; NS)					
Age < 45, ER−poor	579/7496 (7·7%/y)	633/7620 (8·3%/y)	−10·2	259·5	0·96 (SE 0·06)
< 45, ER+	269/4310 (6·2%/y)	280/4315 (6·5%/y)	−7·2	118·4	0·94 (SE 0·09)
45 – 54, ER−poor	460/6754 (6·8%/y)	444/6477 (6·9%/y)	−7·7	197·5	0·96 (SE 0·07)
45 – 54, ER+	248/5302 (4·7%/y)	260/5145 (5·1%/y)	−7·3	112·6	0·94 (SE 0·09)
55 – 69, ER−poor	190/3535 (5·4%/y)	205/3382 (6·1%/y)	−15·1	83·9	0·84 (SE 0·10)
55 – 69, ER+	157/3503 (4·5%/y)	161/3470 (4·6%/y)	−3·7	69·3	0·95 (SE 0·12)
70+, ER−poor	8/219 (3·7%/y)	17/265 (6·4%/y)	−1·5	4·9	
70+, ER+	9/171 (5·3%/y)	5/119 (4·2%/y)	0·5	2·8	
Any unknown	287/4601 (6·2%/y)	356/4353 (8·2%/y)	−41·4	134·7	0·74 (SE 0·07)
(k) Site of first recurrence (χ^2_2 = 3·4; p = 0·2; NS)					
Isolated local	279/25593 (1·1%/y)	286/25046 (1·1%/y)	−8·3	130·8	0·94 (SE 0·08)
Contralateral	172/35881 (0·5%/y)	160/35142 (0·5%/y)	6·3	78·5	
Distant/Multiple	1637/35891 (4·6%/y)	1800/35146 (5·1%/y)	−93·5	717·8	0·88 (SE 0·03)
Unknown	119/35866 (0·3%/y)	115/35124 (0·3%/y)	1·9	56·3	
(l) Time since randomisation (χ^2_1 = 9·2; 2p = 0·002)					
Years 0 – 1	1064/16586 (6·4%/y)	1257/16378 (7·7%/y)	−94·4	490·8	0·83 (SE 0·04)
2 – 4	1143/19183 (6·0%/y)	1104/18621 (5·9%/y)	0·8	492·6	1·00 (SE 0·05)
Total	**2207/35891 (6·1%/y)**	**2361/35146 (6·7%/y)**	**−93·6**	**983·5**	**0·909 (SE 0·030) 2p = 0·003**

99% or 95% confidence intervals

Global heterogeneity: χ^2_{21} = 28·6; p = 0·1

Ratio of annual event rates: 0·5 | 1·0 | 1·5 — Anthr. better | CMF better

Treatment effect 2p = 0·003

* Forest plots (webappendix pp 27–32) give details of each trial's cytotoxic regimens

Anthracyclines: **A** = doxorubicin (Adriamycin), **E** = epirubicin. Other cytotoxics: **C** = cyclophosphamide, **M** = methotrexate, **F** = fluorouracil

Dose/cycle (and cumulative dosage) is given after the drug name in mg/m²; A60/E90 means 60 mg/m² of doxorubicin or 90 mg/m² of epirubicin

Any recurrence

Category	Events/woman-years Allocated anthr.	Allocated CMF	Anthr. events Logrank O−E	Variance of O−E	Ratio of annual event rates Anthr. : CMF
(a) Cumulative anthracycline dosage, if dose/cycle ≥A60/E90* (trend χ^2_1 = 4·8; 2p = 0·03)					
A360 or E720–800: eg, CAF/CEF	585/20175 (2·9%/y)	670/19703 (3·4%/y)	−51·5	288·0	0·84 (SE 0·05)
A300 or E400–480	707/12972 (5·5%/y)	767/12810 (6·0%/y)	−20·5	302·3	0·93 (SE 0·06)
A240: standard 4AC	1114/21307 (5·2%/y)	1105/20804 (5·3%/y)	−6·8	489·9	0·99 (SE 0·04)
White: dose/cycle < A60/E90	525/10219 (5·1%/y)	522/9961 (5·2%/y)	−13·3	227·6	0·94 (SE 0·06)
(b) Cyclophosphamide in CMF oral/iv (χ^2_1 = 1·1; 2p = 0·3; NS)					
C100×14 oral	2293/50195 (4·6%/y)	2430/48833 (5·0%/y)	−87·9	1032·7	0·92 (SE 0·03)
C600×2 iv	638/14478 (4·4%/y)	634/14445 (4·4%/y)	−4·2	275·2	0·99 (SE 0·06)
(c) Concurrent endocrine therapy if ER+? (χ^2_1 = 2·7; 2p = 0·1; NS)					
Yes	101/4053 (2·5%/y)	87/4067 (2·1%/y)	7·6	45·2	
No (any endocrine only after chemo ended)	2830/64673 (4·4%/y)	2977/59211 (5·0%/y)	−99·7	1262·7	0·92 (SE 0·03)
(d) Entry age (trend χ^2_1 = 0·2; 2p = 0·6; NS)					
Age < 45	1267/25005 (5·1%/y)	1367/24995 (5·5%/y)	−42·7	572·4	0·93 (SE 0·04)
45 – 54	1092/24816 (4·4%/y)	1091/23939 (4·6%/y)	−20·2	484·7	0·96 (SE 0·04)
55 – 69	526/13869 (3·8%/y)	558/13275 (4·2%/y)	−32·2	233·4	0·87 (SE 0·06)
70+	28/789 (3·5%/y)	31/808 (3·8%/y)	−0·2	11·3	
Age unknown	18/194 (9·3%/y)	17/261 (6·5%/y)	3·3	6·0	
(e) Nodal status (trend χ^2_1 = 0·9; 2p = 0·3; NS)					
N0/N−	804/31296 (2·6%/y)	819/30996 (2·6%/y)	−8·5	375·8	0·98 (SE 0·05)
N1−3	798/17484 (4·6%/y)	815/17250 (4·7%/y)	−12·8	358·3	0·96 (SE 0·05)
N4+	745/7090 (10·5%/y)	795/6512 (12·2%/y)	−30·6	310·0	0·91 (SE 0·05)
Other / unknown	584/8803 (6·6%/y)	635/8520 (7·5%/y)	−40·1	263·9	0·86 (SE 0·06)
(f) ER status (χ^2_1 = 0·1; 2p = 0·8; NS)					
ER−poor	1619/35068 (4·6%/y)	1669/34555 (4·8%/y)	−30·1	721·0	0·96 (SE 0·04)
ER+	931/22500 (4·1%/y)	967/22322 (4·3%/y)	−24·8	418·1	0·94 (SE 0·05)
ER unknown	381/7105 (5·4%/y)	428/6401 (6·7%/y)	−37·1	168·7	0·80 (SE 0·07)
Subsets of ER+					
ER+ PR−poor	167/3412 (4·9%/y)	144/3053 (4·7%/y)	1·0	62·8	
ER+ PR+	581/15853 (3·7%/y)	641/16096 (4·0%/y)	−26·8	276·7	0·91 (SE 0·06)
ER+ N0/N−	271/10580 (2·6%/y)	285/10464 (2·7%/y)	−12·0	127·4	0·91 (SE 0·08)
ER+ N1−3	236/6118 (3·9%/y)	236/6093 (3·9%/y)	−0·3	102·2	1·00 (SE 0·10)
ER+ N4+	166/1776 (9·3%/y)	160/1615 (9·9%/y)	−0·3	67·7	
ER10−99 fmol/mg	372/9657 (3·9%/y)	393/9697 (3·9%/y)	−12·6	152·5	0·92 (SE 0·08)
ER100+ fmol/mg	147/4067 (3·6%/y)	172/3792 (4·5%/y)	−16·9	66·4	0·78 (SE 0·11)
ER+, unknown level (eg, by IHC)	412/8710 (4·7%/y)	412/8755 (4·7%/y)	3·8	177·8	1·02 (SE 0·08)
(g) Tumour differentiation (χ^2_1 = 2·2; 2p = 0·1; NS)					
Poorly−diff.	623/13923 (4·5%/y)	677/13701 (4·9%/y)	−22·9	270·6	0·92 (SE 0·06)
Moderately/Well	465/11687 (4·0%/y)	445/11639 (3·8%/y)	10·6	196·1	1·06 (SE 0·07)
Grade unknown	1843/39038 (4·7%/y)	1942/37924 (5·1%/y)	−78·9	846·9	0·91 (SE 0·03)
(h) Tumour diameter (trend χ^2_1 = 0·4; 2p = 0·5; NS)					
1 – 20 mm (T1)	842/25557 (3·3%/y)	890/25285 (3·5%/y)	−13·6	392·2	0·97 (SE 0·05)
21 – 50 mm (T2)	1227/24532 (5·0%/y)	1282/24601 (5·2%/y)	−33·8	542·2	0·94 (SE 0·04)
> 50 mm (T3/T4)	146/1942 (7·5%/y)	152/1712 (8·9%/y)	−6·3	50·5	0·88 (SE 0·13)
Other / unknown	716/12612 (5·7%/y)	740/11660 (6·3%/y)	−42·2	320·9	0·88 (SE 0·05)
(i) Tumour differentiation and ER (χ^2_3 = 2·5; p = 0·5; NS)					
Poorly, ER−poor	303/7951 (3·8%/y)	310/8207 (3·8%/y)	4·8	132·8	1·04 (SE 0·09)
Poorly, ER+	218/4358 (5·0%/y)	224/3890 (5·8%/y)	−10·5	86·7	0·89 (SE 0·10)
Mod./Well ER−poor	159/4540 (3·5%/y)	140/3922 (3·6%/y)	−0·8	65·1	
Mod./Well ER+	227/5514 (4·1%/y)	231/6223 (3·7%/y)	10·5	101·5	
Any unknown	2024/42285 (4·8%/y)	2159/41022 (5·3%/y)	−95·2	927·6	0·90 (SE 0·03)
(j) Entry age and ER status (χ^2_7 = 6·0; p = 0·5; NS)					
Age < 45, ER−poor	764/14966 (5·1%/y)	815/15437 (5·3%/y)	−3·3	347·1	0·99 (SE 0·05)
< 45, ER+	352/7380 (4·8%/y)	380/7374 (5·2%/y)	−18·0	158·9	0·89 (SE 0·08)
45 – 54, ER−poor	597/13157 (4·5%/y)	576/12364 (4·7%/y)	−13·0	259·1	0·95 (SE 0·06)
45 – 54, ER+	359/8860 (4·1%/y)	347/8780 (4·0%/y)	5·9	158·7	1·04 (SE 0·08)
55 – 69, ER−poor	241/6522 (3·7%/y)	255/6186 (4·1%/y)	−14·8	107·0	0·87 (SE 0·09)
55 – 69, ER+	202/5820 (3·5%/y)	223/5840 (3·8%/y)	−11·1	93·6	0·89 (SE 0·10)
70+, ER−poor	13/382 (3·4%/y)	18/522 (3·4%/y)	1·3	6·3	
70+, ER+	11/347 (3·2%/y)	11/208 (5·3%/y)	−3·0	4·3	
Any unknown	392/7239 (5·4%/y)	439/6587 (6·7%/y)	−35·9	172·9	0·81 (SE 0·07)
(k) Site of first recurrence (χ^2_2 = 13·2; p = 0·001)					
Isolated local	343/43329 (0·8%/y)	344/42463 (0·8%/y)	−8·6	159·6	0·95 (SE 0·08)
Contralateral	339/64648 (0·5%/y)	271/63274 (0·4%/y)	28·6	144·1	
Distant/Multiple	2021/64673 (3·1%/y)	2227/63278 (3·5%/y)	−113·5	896·7	0·88 (SE 0·03)
Unknown	228/64618 (0·4%/y)	222/63244 (0·4%/y)	1·7	107·9	1·02 (SE 0·10)
(l) Time since randomisation (trend χ^2_1 = 10·4; 2p = 0·001)					
Years 0 – 1	1064/16586 (6·4%/y)	1257/16378 (7·7%/y)	−94·4	490·8	0·83 (SE 0·04)
2 – 4	1143/19183 (6·0%/y)	1104/18621 (5·9%/y)	0·8	492·6	1·00 (SE 0·05)
5 – 9	535/19578 (2·7%/y)	552/19106 (2·9%/y)	−12·7	247·6	0·95 (SE 0·06)
10+	189/8935 (2·1%/y)	151/8766 (1·7%/y)	14·2	76·8	
Total	**2931/64673 (4·5%/y)**	**3064/63278 (4·8%/y)**	**−92·0**	**1307·9**	**0·932 (SE 0·027) 2p = 0·01**

99% or 95% confidence intervals

Global heterogeneity: χ^2_{21} = 44·5; p = 0·002

Ratio of annual event rates: 0·5 | 1·0 | 1·5 — Anthr. better | CMF better

Treatment effect 2p = 0·01

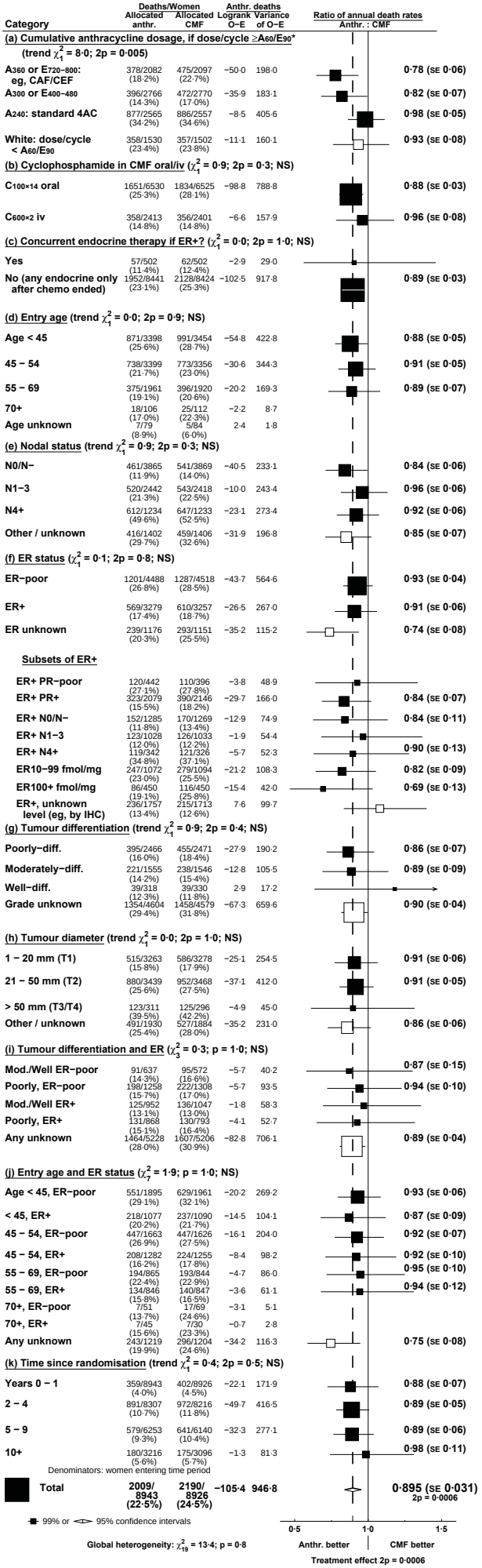
* Forest plots (webappendix pp 27–32) give details of each trial's cytotoxic regimens

Anthracyclines: **A** = doxorubicin (Adriamycin), **E** = epirubicin. Other cytotoxics: **C** = cyclophosphamide, **M** = methotrexate, **F** = fluorouracil

Dose/cycle (and cumulative dosage) is given after the drug name in mg/m²; A60/E90 means 60 mg/m² of doxorubicin or 90 mg/m² of epirubicin

P 10: Subgroup analyses of BREAST CANCER MORTALITY (mortality with recurrence, by logrank subtraction), any anthracycline-based regimen vs. standard CMF (or near-standard CMF).

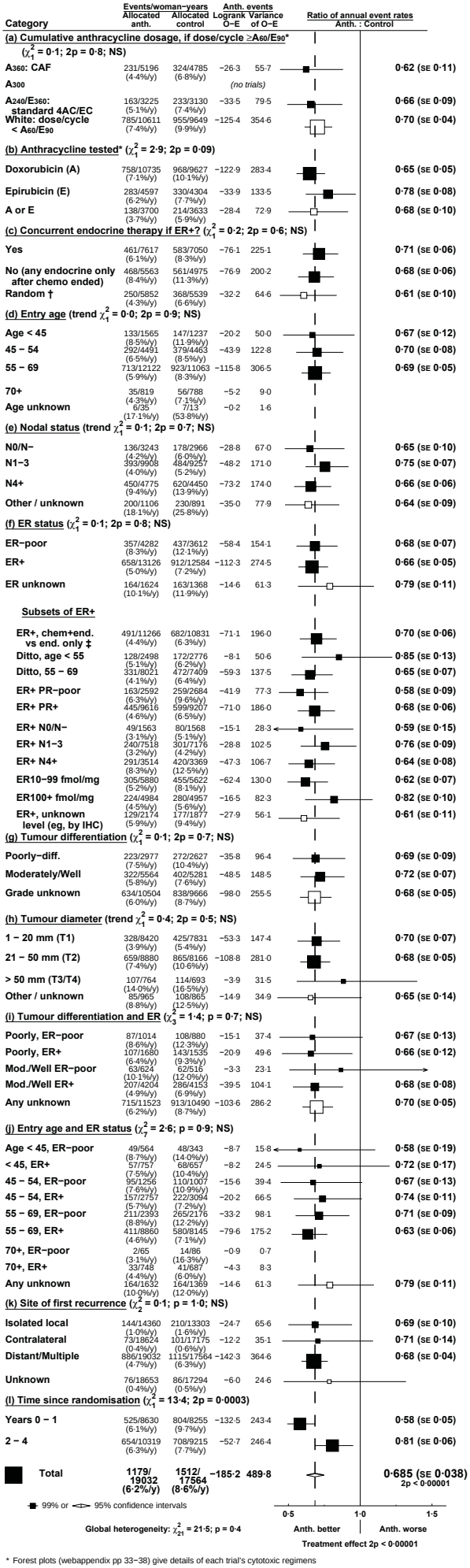
NB First four subgroups are as in forest plots*.



* Forest plots (webappendix pp 27−32) give details of each trial's cytotoxic regimens
Anthracyclines: **A** = doxorubicin (Adriamycin), **E** = epirubicin. Other cytotoxics: **C** = cyclophosphamide, **M** = methotrexate, **F** = fluorouracil
Dose/cycle (and cumulative dosage) is given after the drug name in mg/m²; **A60/E90** means 60 mg/m² of doxorubicin or 90 mg/m² of epirubicin

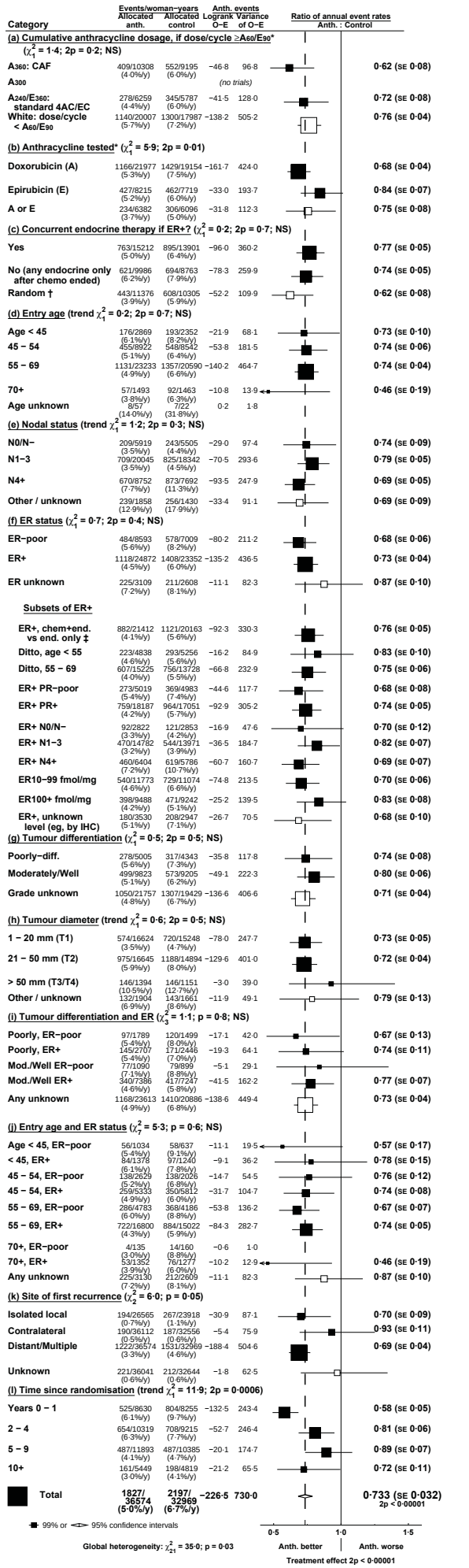
P 11: RECURRENCE in trials of any anthracycline-based regimen (eg, standard 4AC) vs. No chemotherapy

Early recurrence (first 5 years)



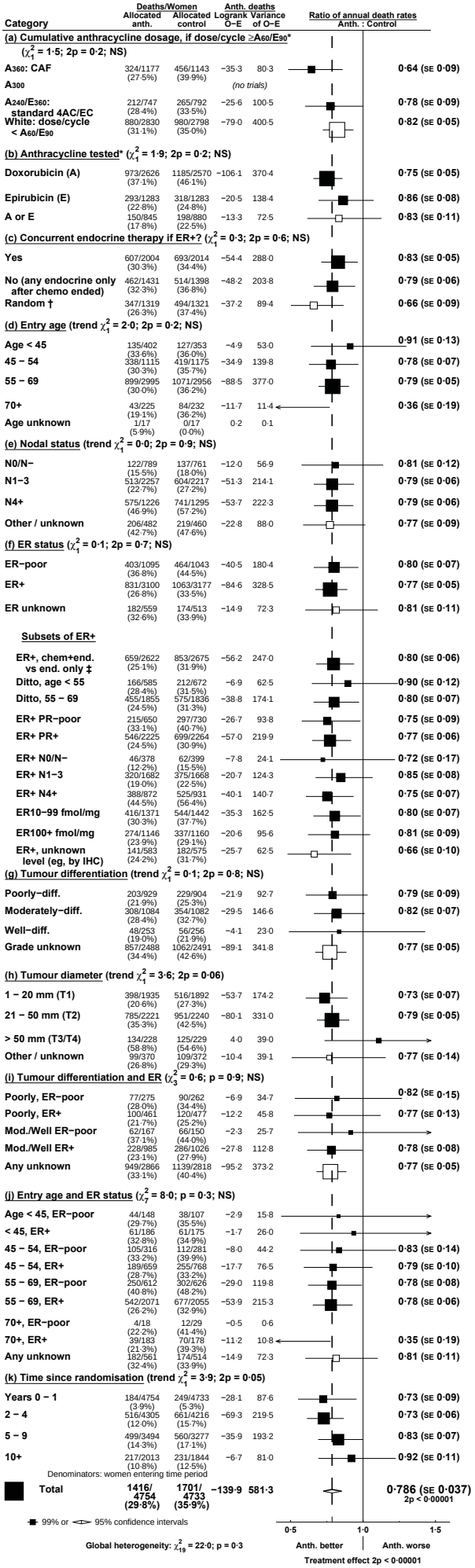
* Forest plots (webappendix pp 33−38) give details of each trial's cytotoxic regimens
Anthracyclines: **A** = doxorubicin (Adriamycin), **E** = epirubicin. Other cytotoxics: **C** = cyclophosphamide, **M** = methotrexate, **F** = fluorouracil
Dose/cycle (and cumulative dosage) is given after the drug name in mg/m²; **A60/E90** means 60 mg/m² of doxorubicin or 90 mg/m² of epirubicin
† In the SWOG 8814 trial of CAF in postmenopausal ER+ disease, tamoxifen started randomly with or after the chemotherapy.
‡ chem+end. = chemo−endocrine therapy

Any recurrence



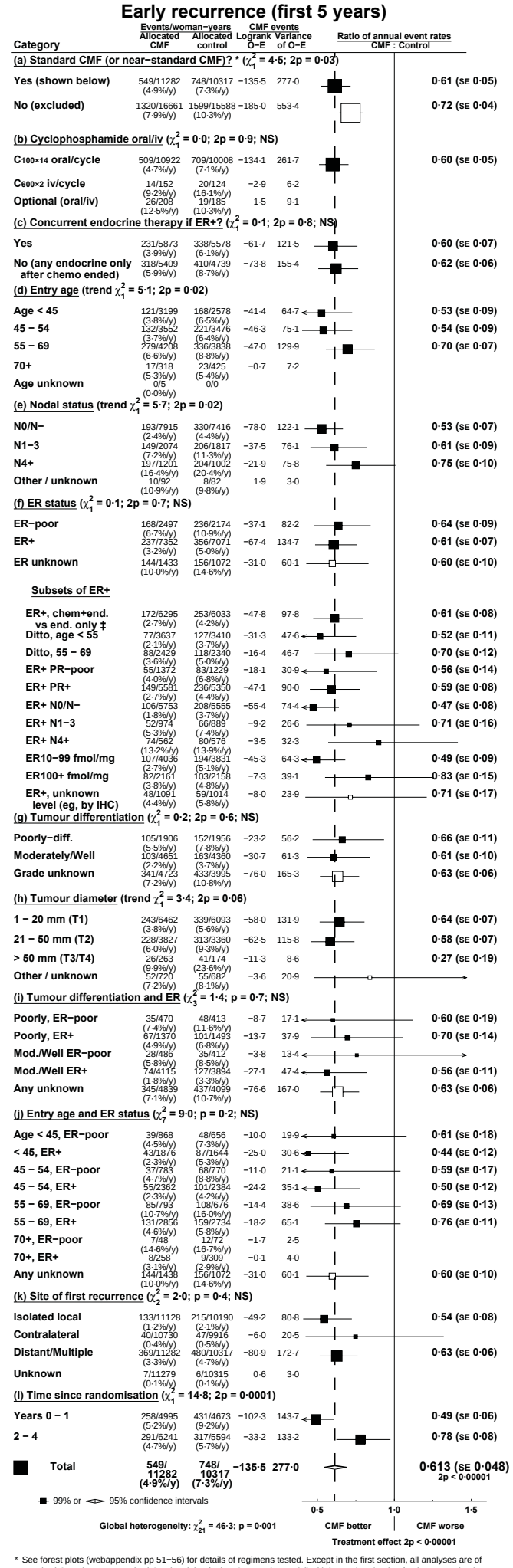
* Forest plots (webappendix pp 33−38) give details of each trial's cytotoxic regimens
Anthracyclines: **A** = doxorubicin (Adriamycin), **E** = epirubicin. Other cytotoxics: **C** = cyclophosphamide, **M** = methotrexate, **F** = fluorouracil
Dose/cycle (and cumulative dosage) is given after the drug name in mg/m²; **A60/E90** means 60 mg/m² of doxorubicin or 90 mg/m² of epirubicin
† In the SWOG 8814 trial of CAF in postmenopausal ER+ disease, tamoxifen started randomly with or after the chemotherapy.
‡ chem+end. = chemo−endocrine therapy

P 12: BREAST CANCER MORTALITY (MORTALITY WITH RECURRENCE) in trials of any anthracycline-based regimen (eg, standard 4AC) vs. No chemotherapy



* Forest plots (webappendix pp 33−38) give details of each trial's cytotoxic regimens
Anthracyclines: **A** = doxorubicin (Adriamycin), **E** = epirubicin. Other cytotoxics: **C** = cyclophosphamide, **M** = methotrexate, **F** = fluorouracil
Dose/cycle (and cumulative dosage) is given after the drug name in mg/m²; **A60/E90** means 60 mg/m² of doxorubicin or 90 mg/m² of epirubicin
† In the SWOG 8814 trial of CAF in postmenopausal ER+ disease, tamoxifen started randomly with or after the chemotherapy.
‡ chem+end. = chemo−endocrine therapy

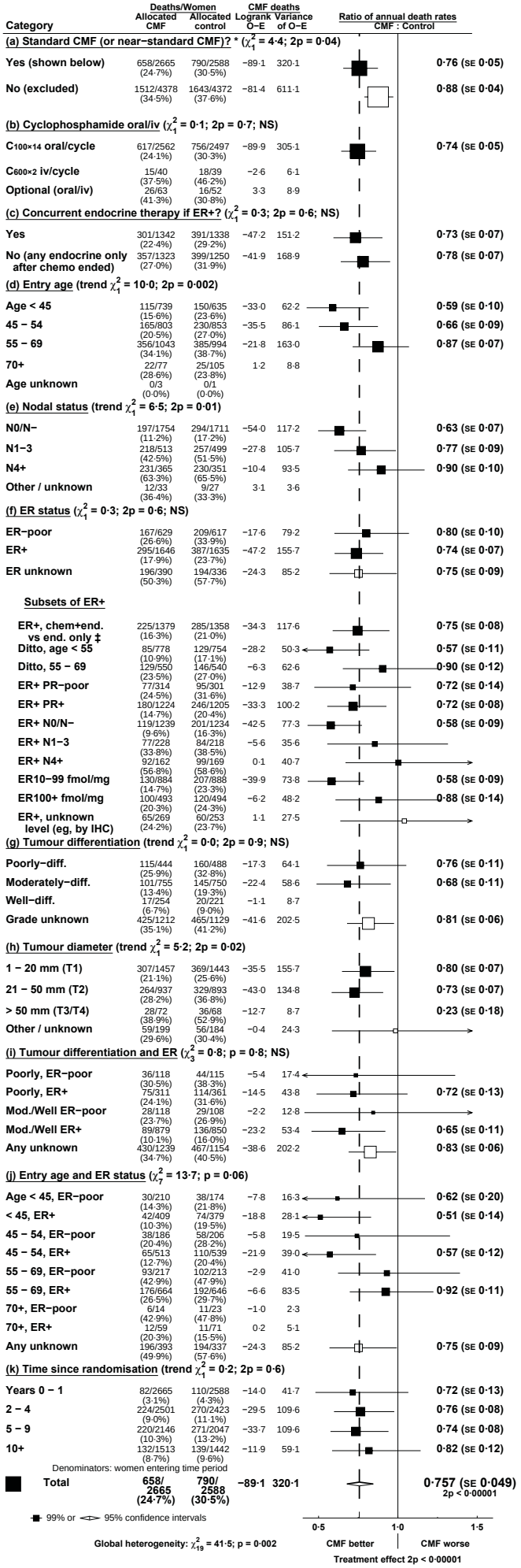
P 13: RECURRENCE in trials of standard CMF (or near-standard CMF)* vs. No chemotherapy



* See forest plots (webappendix pp 51−56) for details of regimens tested. Except in the first section, all analyses are of standard CMF (or near standard CMF). Trials of other CMF regimens (all with lower dose/cycle of at least one drug) are shown only in the first section (as a white square), and are then excluded.

‡ chem+end. = chemo−endocrine therapy

P 14: BREAST CANCER MORTALITY (MORTALITY WITH RECURRENCE) in trials of standard CMF (or near-standard CMF)* vs. No chemotherapy



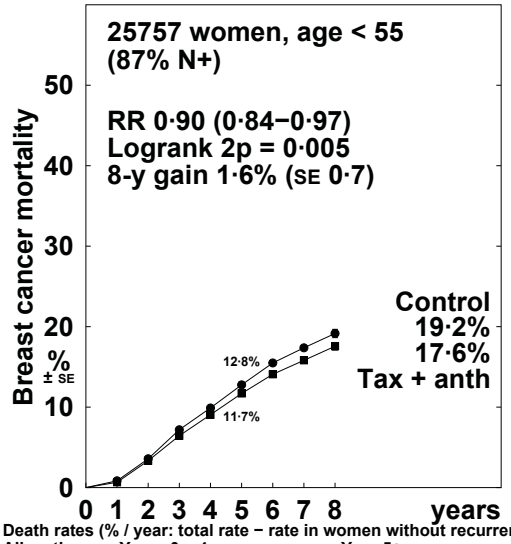
* See forest plots (webappendix pp 51−56) for details of regimens tested. Except in the first section, all analyses are of standard CMF (or near standard CMF). Trials of other CMF regimens (all with lower dose/cycle of at least one drug) are shown only in the first section (as a white square), and are then excluded.

‡ chem+end. = chemo−endocrine therapy

P 15: Any taxane-plus-anthracycline-based regimen vs control with the SAME or MORE non-taxane chemotherapy (all trials combined): subgroup analyses of 8-year breast cancer mortality

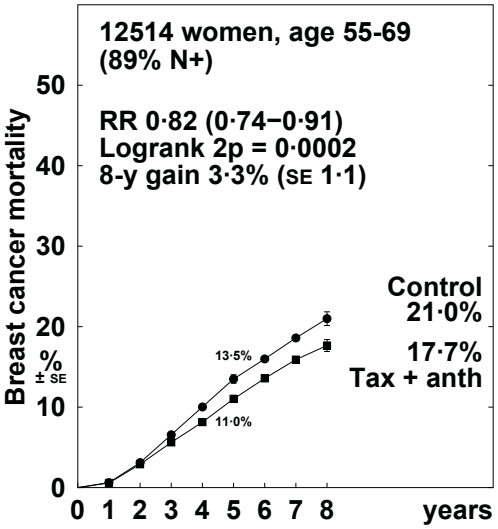
RR (and its 95% CI): event rate ratio, from summed logrank statistics for all time periods. Gain (and its SE): absolute difference between ends of graphs.

Entry age<55 or 55-69 years



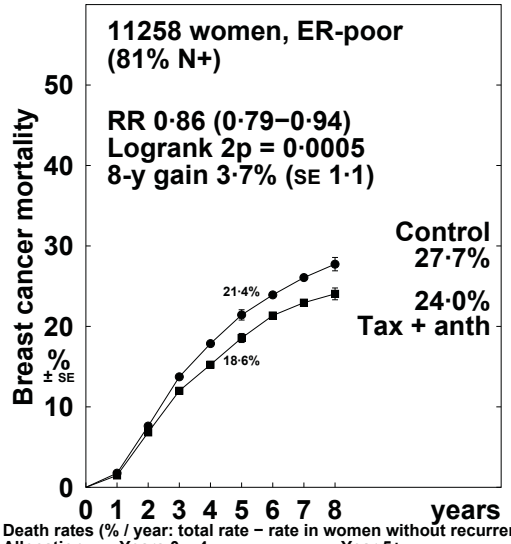
Death rates (% / year: total rate − rate in women without recurrence) and logrank analyses

Allocation	Years 0 − 4	Year 5+
Tax + anth	2·42 SE 0·07	2·36 SE 0·13
Control	2·62 SE 0·07	2·63 SE 0·15
Rate ratio	0·91 SE 0·04	0·88 SE 0·08
(O−E) / V	−58·4 / 604·0	−19·6 / 152·8



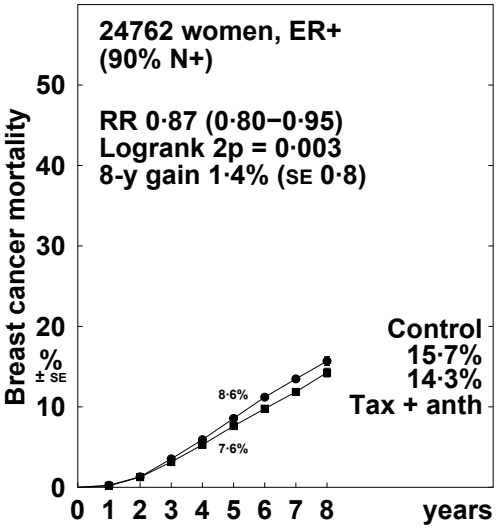
Years 0 − 4	Year 5+
2·21 SE 0·09	2·64 SE 0·21
2·69 SE 0·11	3·14 SE 0·25
0·81 SE 0·05	0·85 SE 0·11
−57·7 / 275·4	−11·4 / 71·0

ER status, mainly by immunohistochemistry



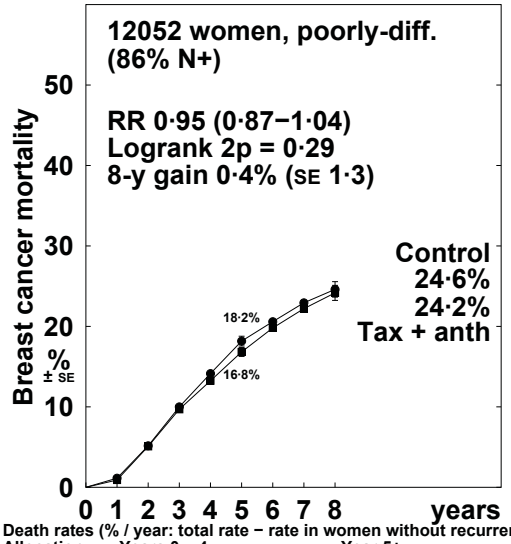
Death rates (% / year: total rate − rate in women without recurrence) and logrank analyses

Allocation	Years 0 − 4	Year 5+
Tax + anth	4·00 SE 0·13	2·44 SE 0·20
Control	4·86 SE 0·15	2·67 SE 0·23
Rate ratio	0·85 SE 0·04	0·91 SE 0·12
(O−E) / V	−71·7 / 438·8	−6·2 / 66·1



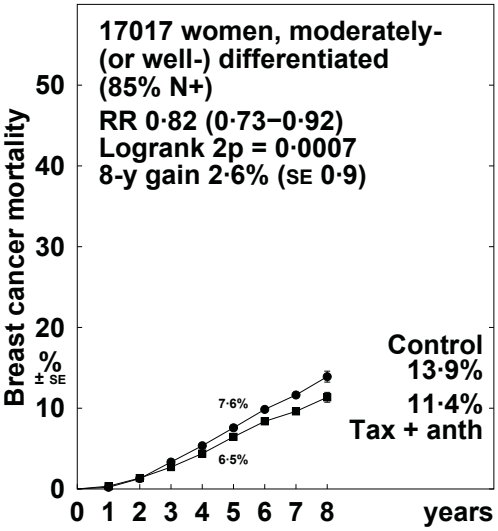
Years 0 − 4	Year 5+
1·45 SE 0·05	2·51 SE 0·15
1·62 SE 0·06	2·87 SE 0·16
0·89 SE 0·05	0·85 SE 0·08
−44·3 / 365·5	−22·8 / 136·8

Tumour grade (few were well-differentiated)



Death rates (% / year: total rate − rate in women without recurrence) and logrank analyses

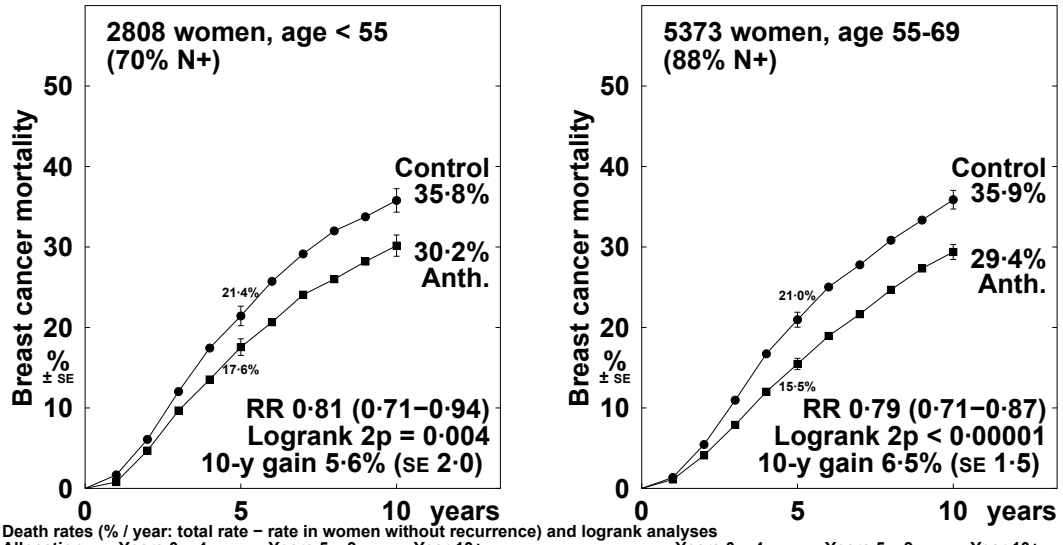
Allocation	Years 0 − 4	Year 5+
Tax + anth	3·53 SE 0·12	3·07 SE 0·28
Control	3·79 SE 0·13	2·69 SE 0·28
Rate ratio	0·93 SE 0·05	1·16 SE 0·15
(O−E) / V	−29·3 / 390·0	7·3 / 49·1



Years 0 − 4	Year 5+
1·22 SE 0·06	1·85 SE 0·17
1·45 SE 0·07	2·37 SE 0·19
0·84 SE 0·06	0·75 SE 0·11
−37·5 / 216·0	−19·0 / 64·9

P 16: At least 4 cycles of any anthracycline-based regimen (eg, standard 4AC) vs no adjuvant chemotherapy: subgroup analyses of 10-year breast cancer mortality by age, ER status and tumour grade RR (and its 95% CI): event rate ratio, from summed logrank statistics for all time periods. Gain (and its SE): absolute difference between ends of graphs.

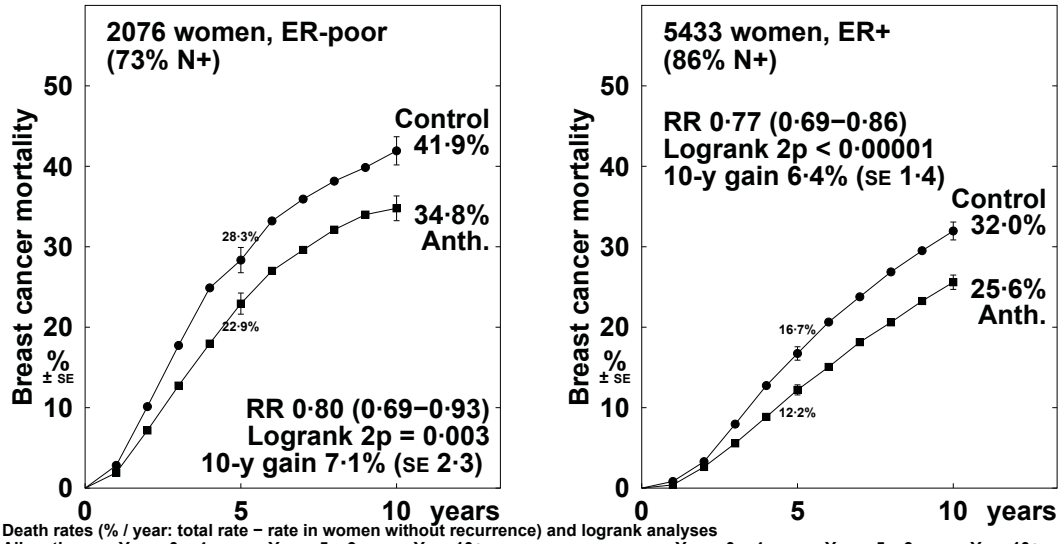
Entry age<55 or 55-69 years



Death rates (% / year: total rate − rate in women without recurrence) and logrank analyses

Allocation	Years 0 − 4	Years 5 − 9	Year 10+	Years 0 − 4	Years 5 − 9	Year 10+
Anth.	3·81 SE 0·24	3·53 SE 0·28	1·85 SE 0·25	3·26 SE 0·16	3·63 SE 0·20	3·43 SE 0·28
Control	4·77 SE 0·29	4·11 SE 0·34	2·01 SE 0·28	4·79 SE 0·22	4·40 SE 0·27	3·65 SE 0·33
Rate ratio	0·79 SE 0·09	0·81 SE 0·11	0·96 SE 0·21	0·71 SE 0·06	0·86 SE 0·08	0·94 SE 0·13
(O−E) / V	−25·5 / 108·4	−13·5 / 63·4	−0·9 / 21·0	−65·9 / 193·2	−19·2 / 125·4	−3·5 / 58·3

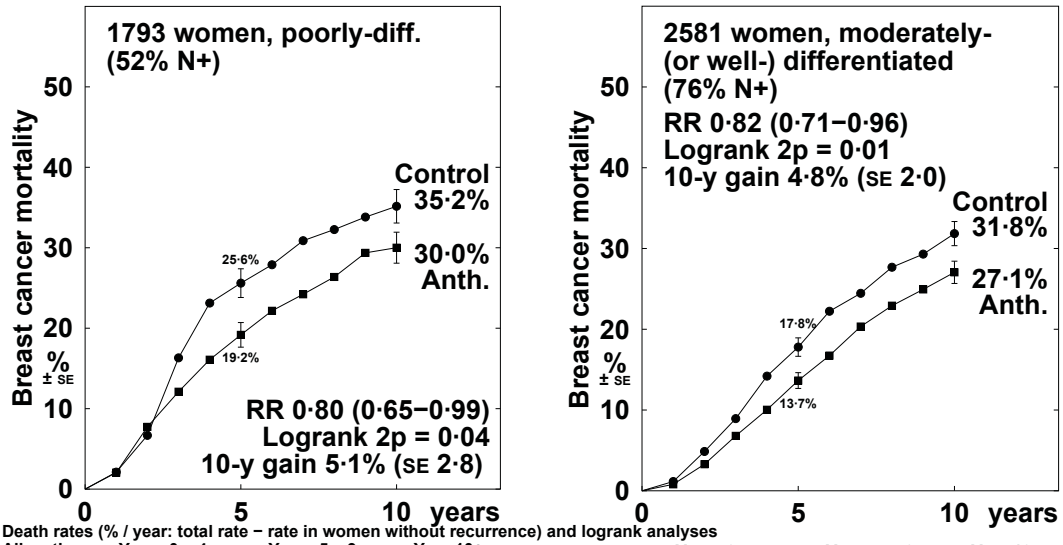
ER status



Death rates (% / year: total rate − rate in women without recurrence) and logrank analyses

Allocation	Years 0 − 4	Years 5 − 9	Year 10+	Years 0 − 4	Years 5 − 9	Year 10+
Anth.	4·96 SE 0·32	3·50 SE 0·33	2·64 SE 0·36	2·60 SE 0·14	3·40 SE 0·19	3·09 SE 0·26
Control	6·84 SE 0·41	4·47 SE 0·42	2·92 SE 0·41	3·63 SE 0·19	4·17 SE 0·25	3·14 SE 0·30
Rate ratio	0·76 SE 0·08	0·80 SE 0·13	0·98 SE 0·20	0·71 SE 0·07	0·81 SE 0·08	0·92 SE 0·14
(O−E) / V	−29·2 / 107·7	−10·8 / 48·7	−0·5 / 24·1	−54·3 / 156·2	−26·4 / 123·3	−4·0 / 48·9

Tumour grade (few were well-differentiated)



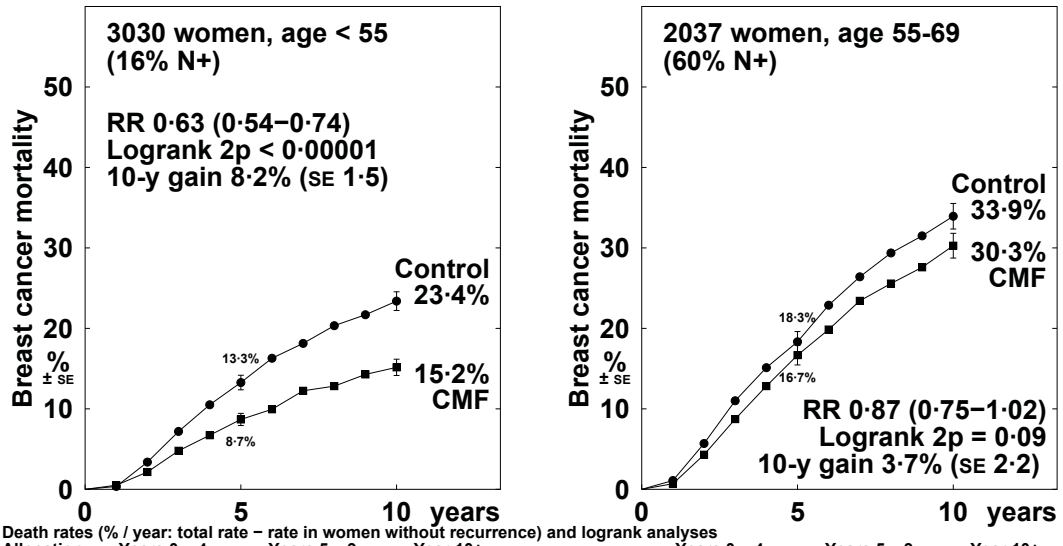
Death rates (% / year: total rate − rate in women without recurrence) and logrank analyses

Allocation	Years 0 − 4	Years 5 − 9	Year 10+	Years 0 − 4	Years 5 − 9	Year 10+
Anth.	4·31 SE 0·36	2·98 SE 0·40	0·76 SE 0·31	2·85 SE 0·22	3·45 SE 0·30	2·51 SE 0·36
Control	5·73 SE 0·44	2·88 SE 0·43	0·58 SE 0·29	3·89 SE 0·26	3·91 SE 0·34	2·67 SE 0·40
Rate ratio	0·73 SE 0·11	1·05 SE 0·22	1·07 SE 0·78	0·74 SE 0·09	0·89 SE 0·12	1·02 SE 0·23
(O−E) / V	−20·6 / 65·5	1·0 / 22·1	0·1 / 1·7	−25·7 / 86·4	−6·5 / 58·5	0·4 / 20·1

P 17: Standard CMF (or near-standard CMF) vs no adjuvant chemotherapy: subgroup analyses of 10-year breast cancer mortality by age, ER status and tumour grade

RR (and its 95% CI): event rate ratio, from summed logrank statistics for all time periods. Gain (and its SE): absolute difference between ends of graphs.

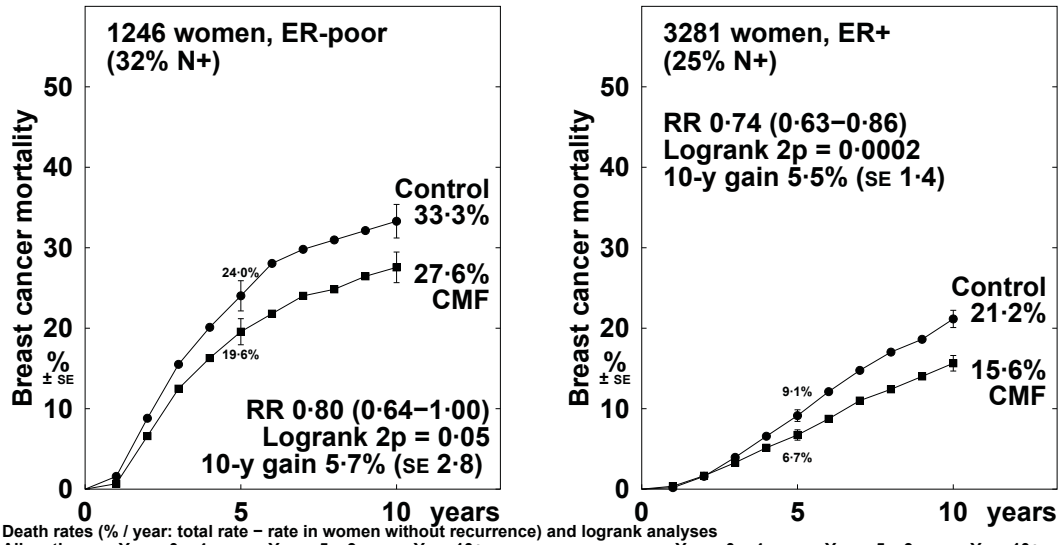
Entry age<55 or 55-69 years



Death rates (% / year: total rate − rate in women without recurrence) and logrank analyses

Allocation	Years 0 − 4	Years 5 − 9	Year 10+	Years 0 − 4	Years 5 − 9	Year 10+
CMF	1·85 SE 0·16	1·62 SE 0·17	1·38 SE 0·18	3·59 SE 0·28	3·60 SE 0·33	2·32 SE 0·28
Control	2·75 SE 0·20	2·43 SE 0·22	1·89 SE 0·23	3·97 SE 0·30	4·33 SE 0·36	2·54 SE 0·31
Rate ratio	0·64 SE 0·10	0·60 SE 0·11	0·66 SE 0·15	0·89 SE 0·11	0·83 SE 0·12	0·93 SE 0·18
(O−E) / V	−32·1 / 71·9	−24·3 / 47·5	−11·9 / 28·9	−8·9 / 75·9	−11·0 / 58·5	−1·9 / 28·5

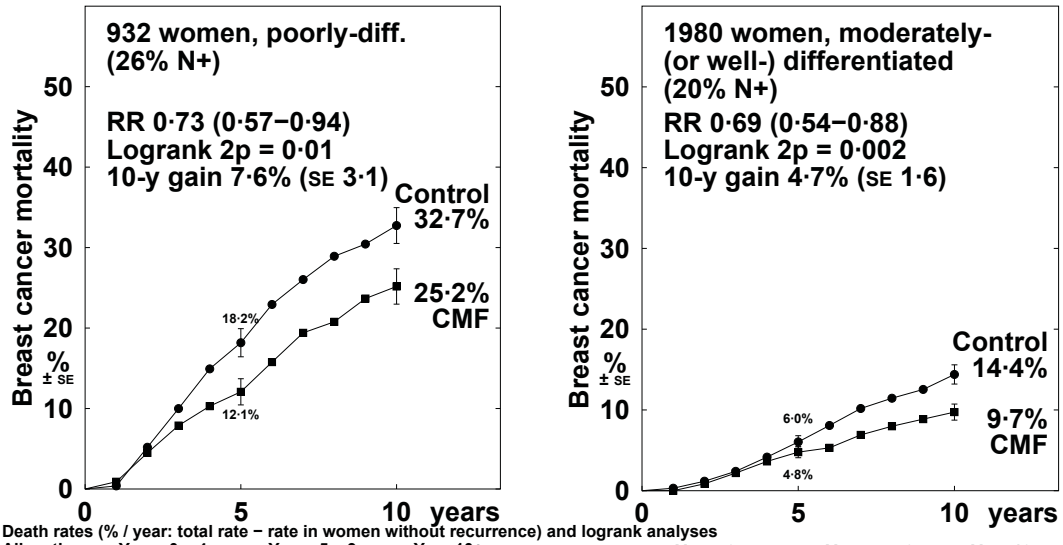
ER status



Death rates (% / year: total rate − rate in women without recurrence) and logrank analyses

Allocation	Years 0 − 4	Years 5 − 9	Year 10+	Years 0 − 4	Years 5 − 9	Year 10+
CMF	4·08 SE 0·39	2·20 SE 0·34	0·77 SE 0·21	1·42 SE 0·14	2·02 SE 0·18	1·58 SE 0·20
Control	5·67 SE 0·47	2·71 SE 0·39	0·96 SE 0·25	1·84 SE 0·15	2·87 SE 0·22	1·85 SE 0·22
Rate ratio	0·78 SE 0·12	0·79 SE 0·20	1·05 SE 0·43	0·73 SE 0·11	0·71 SE 0·10	0·83 SE 0·17
(O−E) / V	−13·4 / 54·1	−4·5 / 19·2	0·3 / 5·8	−18·4 / 58·9	−23·2 / 67·5	−5·6 / 29·3

Tumour grade (few were well-differentiated)



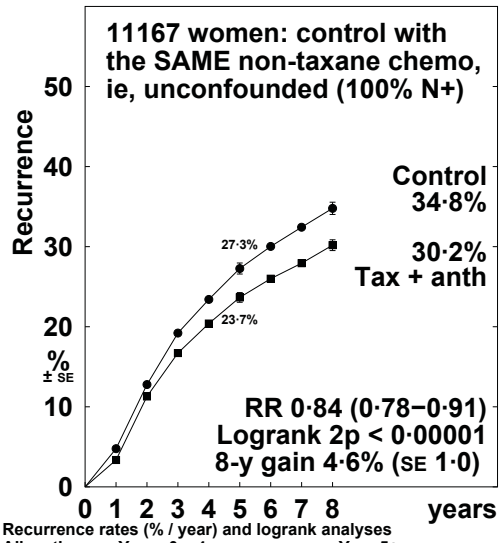
Death rates (% / year: total rate − rate in women without recurrence) and logrank analyses

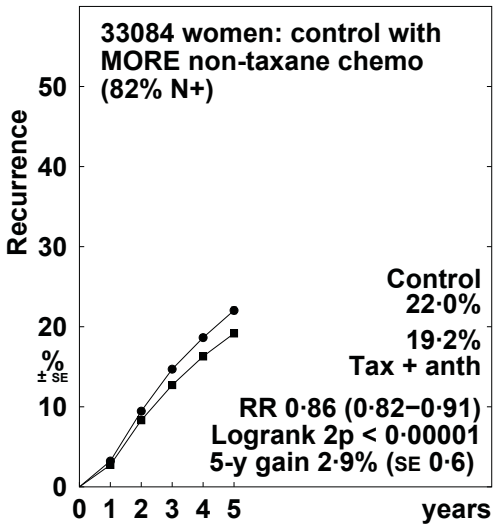
Allocation	Years 0 − 4	Years 5 − 9	Year 10+	Years 0 − 4	Years 5 − 9	Year 10+
CMF	2·71 SE 0·36	3·26 SE 0·46	1·01 SE 0·36	0·99 SE 0·14	1·06 SE 0·16	1·29 SE 0·24
Control	3·76 SE 0·41	4·09 SE 0·51	1·40 SE 0·42	1·21 SE 0·16	1·89 SE 0·22	1·69 SE 0·28
Rate ratio	0·65 SE 0·15	0·82 SE 0·18	0·85 SE 0·43	0·78 SE 0·18	0·58 SE 0·15	0·77 SE 0·23
(O−E) / V	−13·5 / 31·4	−5·3 / 26·5	−0·7 / 4·6	−5·9 / 24·1	−15·0 / 27·2	−3·9 / 15·1

P 18: Taxane-plus-anthracycline-based regimen vs control with Left: the SAME, or Right: MORE, non-taxane chemotherapy

Time to recurrence, breast cancer mortality and overall mortality. Trials vs the SAME non-taxane chemotherapy (usually 4AC) just added 4 extra taxane-only cycles. RR (and its 95% CI): event rate ratio, from summed logrank statistics for all time periods. Gain (and its SE): absolute difference between ends of graphs.

Recurrence

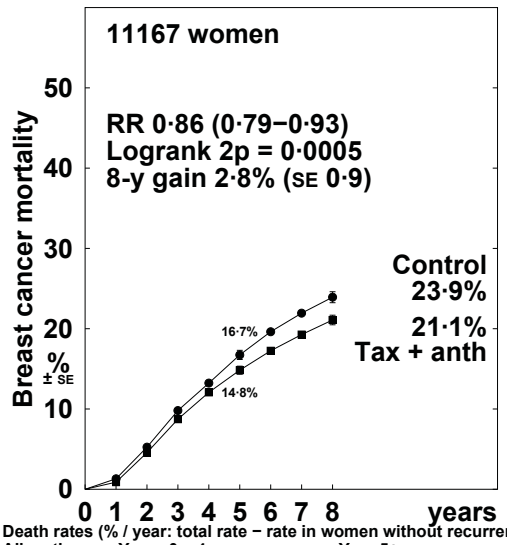


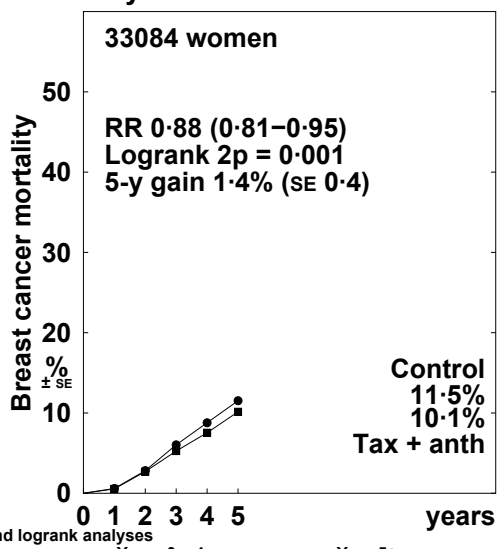


Recurrence rates (% / year) and logrank analyses

Allocation	Years 0 − 4	Year 5+	Years 0 − 4	Year 5+
Tax + anth	5·51 (1280 / 23249)	3·10 (413 / 13343)	4·37 (2607 / 59665)	3·01 (153 / 5082)
Control	6·43 (1239 / 19259)	3·62 (381 / 10534)	5·02 (2586 / 51508)	2·69 (127 / 4727)
Rate ratio	0·84 SE 0·04	0·85 SE 0·07	0·85 SE 0·03	1·03 SE 0·13
(O−E) / V	−95·5 / 557·3	−30·5 / 182·8	−181·4 / 1153·8	1·9 / 63·6

Breast cancer mortality

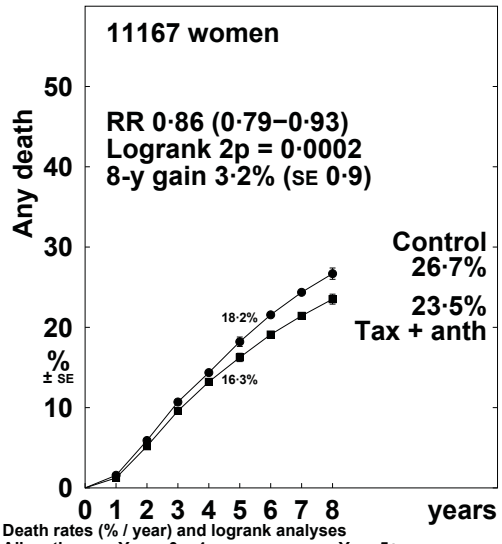


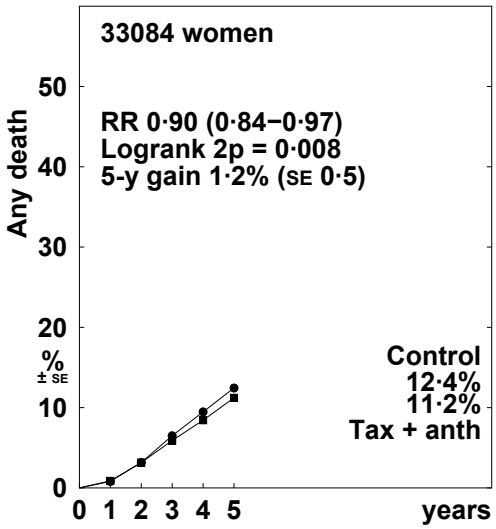


Death rates (% / year: total rate − rate in women without recurrence) and logrank analyses

Allocation	Years 0 − 4	Year 5+	Years 0 − 4	Year 5+
Tax + anth	3·21 SE 0·11	2·48 SE 0·13	2·01 SE 0·06	2·37 SE 0·20
Control	3·58 SE 0·13	3·06 SE 0·16	2·30 SE 0·07	2·26 SE 0·21
Rate ratio	0·88 SE 0·05	0·82 SE 0·07	0·87 SE 0·04	0·97 SE 0·13
(O−E) / V	−46·4 / 348·5	−33·3 / 172·3	−77·0 / 549·5	−1·7 / 57·4

Overall mortality





Death rates (% / year) and logrank analyses

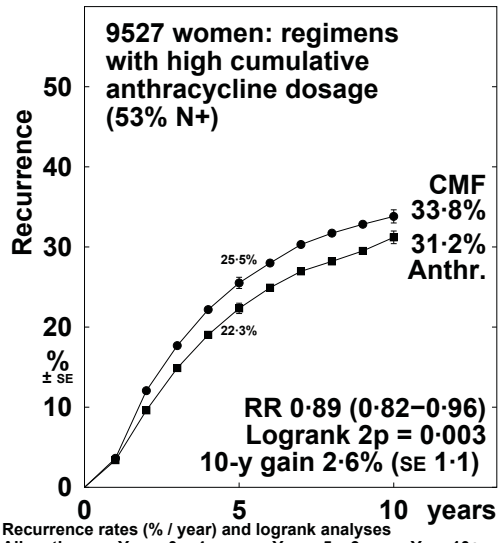
Allocation	Years 0 − 4	Year 5+	Years 0 − 4	Year 5+
Tax + anth	3·55 (881 / 24821)	3·09 (465 / 15061)	2·24 (1326 / 59104)	2·85 (161 / 5658)
Control	3·93 (819 / 20850)	3·76 (458 / 12178)	2·51 (1326 / 52888)	2·84 (152 / 5358)
Rate ratio	0·88 SE 0·05	0·82 SE 0·06	0·90 SE 0·04	0·96 SE 0·12
(O−E) / V	−48·6 / 386·0	−41·3 / 213·4	−66·3 / 608·4	−3·1 / 70·9

P 19: Selected anthracycline-based regimens vs standard CMF (or near-standard CMF)
Left: regimens with cumulative dosage > 240 mg/m^2 doxorubicin or 360 mg/m^2 epirubicin (eg, CAF or CEF), Right: standard 4AC (cumulative dosage 240 mg/m^2 doxorubicin)

(All graphs exclude regimens with < 60 mg/m^2 doxorubicin or 90 mg/m^2 epirubicin per cycle)

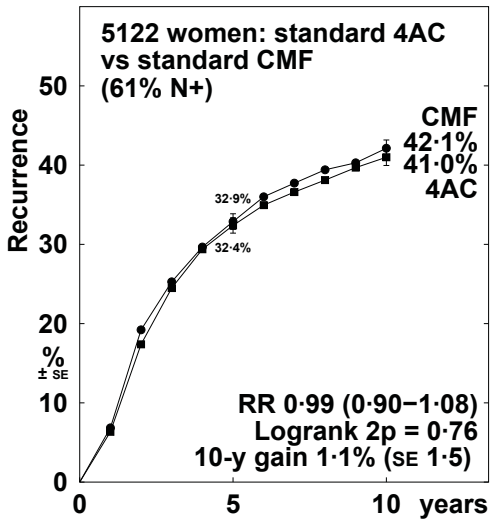
Time to recurrence, breast cancer mortality and overall mortality. RR (and its 95% CI): event rate ratio, from summed logrank statistics for all time periods. Gain (and its SE): absolute difference between ends of graphs.

Recurrence



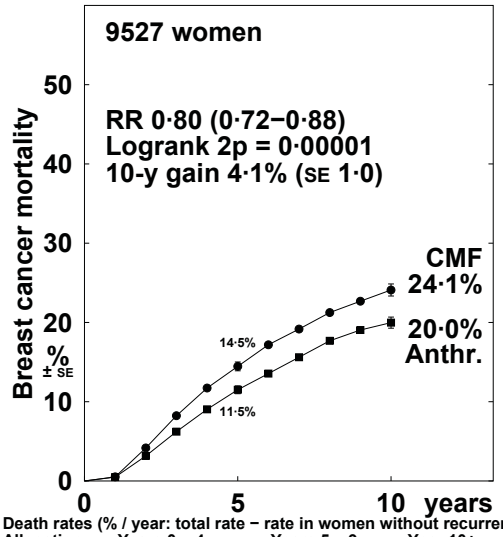
Recurrence rates (% / year) and logrank analyses

Allocation	Years 0 − 4	Years 5 − 9	Year 10+
Anthr.	5·05 (989 / 19575)	2·45 (238 / 9723)	1·64 (65 / 3973)
CMF	6·01 (1104 / 18377)	2·57 (237 / 9236)	1·35 (54 / 4007)
Rate ratio	0·85 SE 0·04	1·00 SE 0·10	1·12 SE 0·21
(O−E) / V	−74·9 / 457·0	0·1 / 106·9	2·9 / 26·4



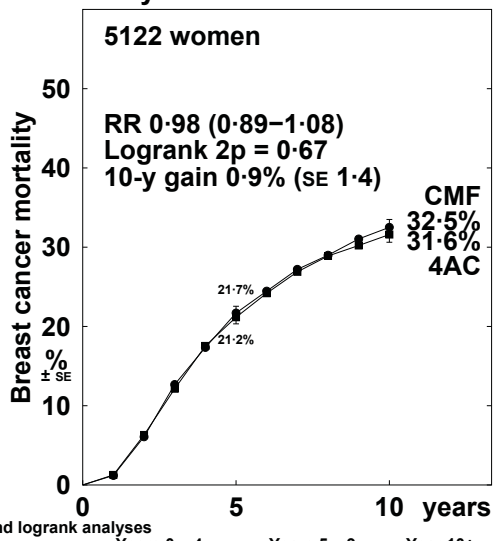
Years 0 − 4	Years 5 − 9	Year 10+
7·97 (820 / 10292)	2·86 (194 / 6795)	2·36 (100 / 4237)
8·21 (830 / 10108)	2·99 (199 / 6658)	1·87 (76 / 4054)
0·98 SE 0·05	0·91 SE 0·10	1·28 SE 0·17
−8·7 / 355·5	−8·5 / 92·1	10·4 / 42·3

Breast cancer mortality



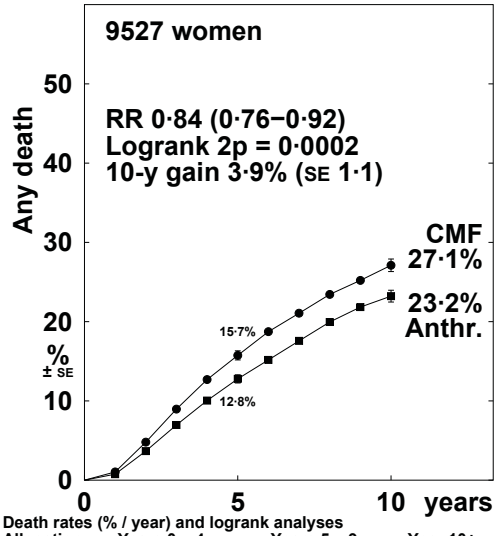
Death rates (% / year: total rate − rate in women without recurrence) and logrank analyses

Allocation	Years 0 − 4	Years 5 − 9	Year 10+
Anthr.	2·39 SE 0·11	2·08 SE 0·14	0·91 SE 0·14
CMF	3·06 SE 0·12	2·50 SE 0·15	1·11 SE 0·16
Rate ratio	0·78 SE 0·06	0·84 SE 0·09	0·84 SE 0·20
(O−E) / V	−62·9 / 248·9	−19·3 / 111·5	−3·5 / 20·8



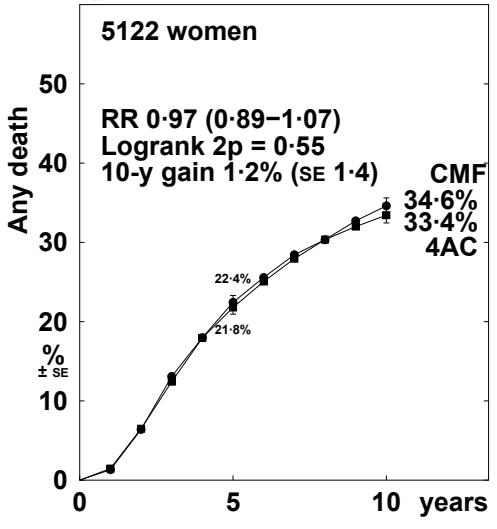
Years 0 − 4	Years 5 − 9	Year 10+
4·65 SE 0·20	2·94 SE 0·19	2·06 SE 0·20
4·81 SE 0·21	3·04 SE 0·20	1·96 SE 0·20
0·97 SE 0·06	0·97 SE 0·09	1·03 SE 0·15
−6·3 / 245·2	−3·7 / 111·6	1·5 / 48·9

Overall mortality



Death rates (% / year) and logrank analyses

Allocation	Years 0 − 4	Years 5 − 9	Year 10+
Anthr.	2·67 (561 / 20977)	2·60 (290 / 11151)	1·99 (90 / 4528)
CMF	3·36 (669 / 19894)	2·99 (319 / 10661)	1·92 (87 / 4523)
Rate ratio	0·79 SE 0·05	0·88 SE 0·08	1·06 SE 0·16
(O−E) / V	−65·0 / 277·4	−17·8 / 137·2	2·5 / 40·9

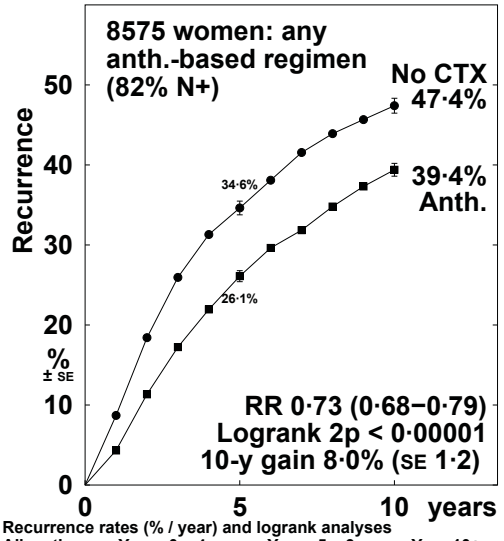


Years 0 − 4	Years 5 − 9	Year 10+
4·81 (551 / 11458)	3·33 (266 / 7994)	2·67 (141 / 5281)
5·00 (567 / 11351)	3·48 (274 / 7883)	2·57 (131 / 5106)
0·97 SE 0·06	0·96 SE 0·09	1·01 SE 0·13
−8·1 / 254·9	−5·3 / 127·6	0·8 / 64·2

P 20: Chemotherapy vs no adjuvant chemotherapy (no CTX)
Left: ≥4 cycles of any anthracycline-based regimen, eg standard 4AC,
Right: standard CMF (or near-standard CMF)

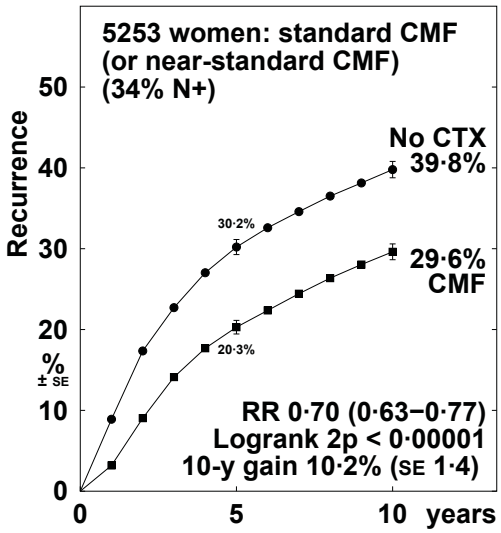
Time to recurrence, breast cancer mortality and overall mortality. RR (and its 95% CI): event rate ratio, from summed logrank statistics for all time periods. Gain (and its SE): absolute difference between ends of graphs.

Recurrence



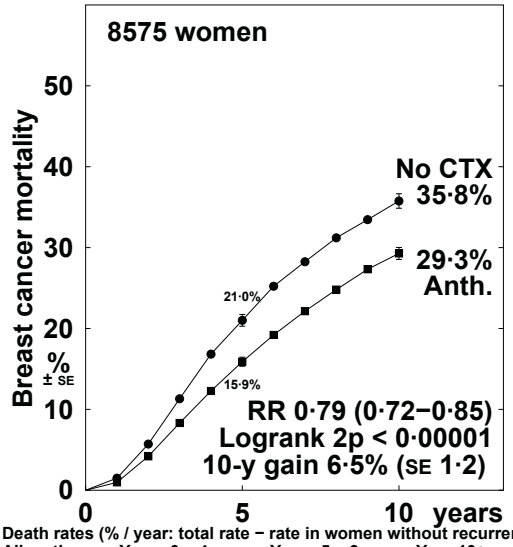
Recurrence rates (% / year) and logrank analyses

Allocation	Years 0 − 4	Years 5 − 9	Year 10+
Anth.	6·14 (1179 / 19190)	4·06 (487 / 11981)	2·91 (161 / 5530)
No CTX	9·06 (1259 / 13899)	4·56 (365 / 8011)	3·87 (159 / 4104)
Rate ratio	0·69 SE 0·04	0·89 SE 0·07	0·72 SE 0·11
(O−E) / V	−185·2 / 489·8	−20·0 / 174·7	−21·2 / 65·5



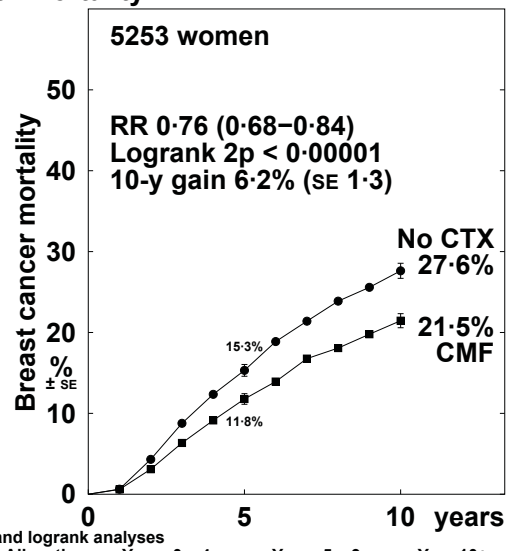
Allocation	Years 0 − 4	Years 5 − 9	Year 10+
CMF	4·83 (549 / 11357)	2·58 (207 / 8038)	1·88 (116 / 6155)
No CTX	7·20 (748 / 10385)	2·93 (210 / 7158)	1·90 (100 / 5260)
Rate ratio	0·61 SE 0·05	0·84 SE 0·09	0·99 SE 0·14
(O−E) / V	−135·5 / 277·0	−16·9 / 95·9	−0·7 / 48·7

Breast cancer mortality



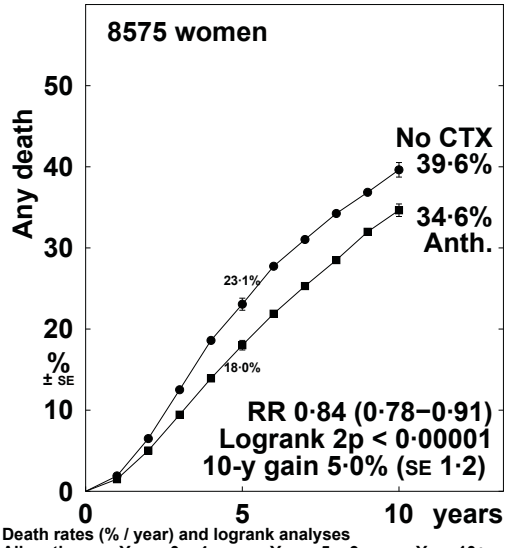
Death rates (% / year: total rate − rate in women without recurrence) and logrank analyses

Allocation	Years 0 − 4	Years 5 − 9	Year 10+
Anth.	3·38 SE 0·13	3·57 SE 0·16	2·83 SE 0·19
No CTX	4·77 SE 0·17	4·31 SE 0·21	2·98 SE 0·22
Rate ratio	0·73 SE 0·05	0·83 SE 0·07	0·92 SE 0·11
(O−E) / V	−97·5 / 307·0	−35·9 / 193·2	−6·7 / 81·0



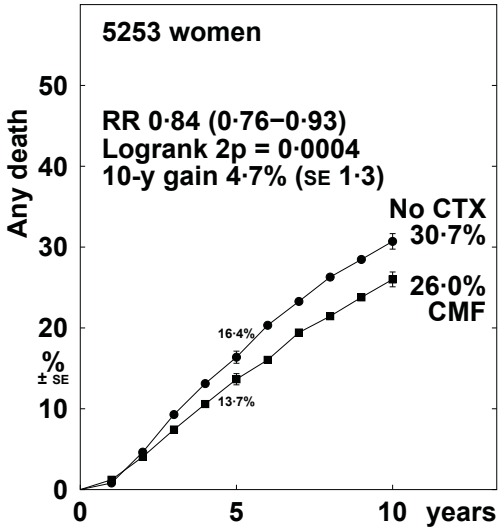
Allocation	Years 0 − 4	Years 5 − 9	Year 10+
CMF	2·51 SE 0·14	2·42 SE 0·16	1·80 SE 0·16
No CTX	3·23 SE 0·17	3·14 SE 0·19	2·10 SE 0·18
Rate ratio	0·75 SE 0·07	0·74 SE 0·08	0·82 SE 0·12
(O−E) / V	−43·5 / 151·3	−33·7 / 109·6	−11·9 / 59·1

Overall mortality



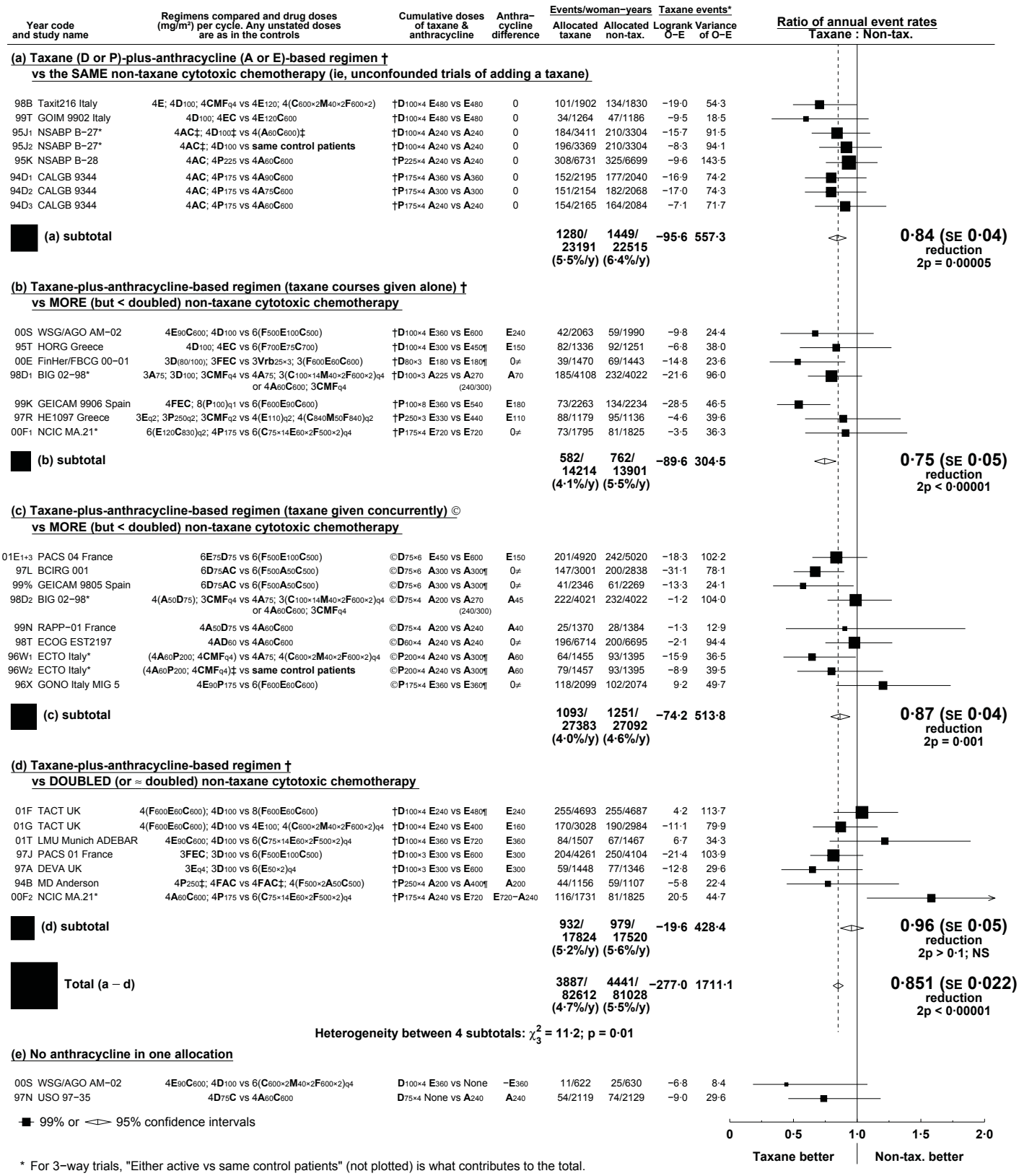
Death rates (% / year) and logrank analyses

Allocation	Years 0 − 4	Years 5 − 9	Year 10+
Anth.	3·91 (811 / 20718)	4·62 (645 / 13969)	4·39 (337 / 7680)
No CTX	5·25 (834 / 15889)	4·93 (492 / 9975)	4·34 (259 / 5969)
Rate ratio	0·75 SE 0·05	0·92 SE 0·06	1·00 SE 0·09
(O−E) / V	−99·0 / 346·4	−19·1 / 234·6	−0·1 / 120·2



Allocation	Years 0 − 4	Years 5 − 9	Year 10+
CMF	2·93 (357 / 12167)	3·15 (286 / 9091)	3·14 (230 / 7318)
No CTX	3·49 (410 / 11756)	3·78 (326 / 8617)	3·39 (224 / 6612)
Rate ratio	0·82 SE 0·07	0·81 SE 0·08	0·91 SE 0·10
(O−E) / V	−33·6 / 170·7	−28·5 / 137·2	−8·8 / 96·2

P 21: EARLY RECURRENCE (first 5 years) in trials of taxane-plus-anthracycline-based regimen vs SAME, or MORE (< doubled or ~doubled) non-taxane cytotoxic chemotherapy



* For 3−way trials, "Either active vs same control patients" (not plotted) is what contributes to the total.
For 95J NSABP B−27, this (O−E) is −16·5 with variance V = 120·8; 96W ECTO Italy (O−E) = −16·1, V = 48·4;
98D BIG 02−98 (O−E) = −15·0, V = 131·9; 00F MA.21 (O−E) = 11·2; V = 56·3

† Taxane courses do not overlap with any other chemotherapy courses; hence, total chemotherapy duration is increased

‡ Pre−operative chemotherapy: all patients in these trials were analysed as unknown nodal status

© Concurrent treatment with taxane and anthracycline; total chemotherapy duration and number of courses not increased

≠ Same cumulative anthracycline dose, but differences in other drugs

¶ Control anthracycline dose less than **E**90 or **A**60 per cycle

Taxanes: **D** = docetaxel; **P** = paclitaxel. Anthracyclines: **A** = doxorubicin (Adriamycin); **E** = Epirubicin
Other agents: **C** = cyclophosphamide; **F** = fluorouracil; **M** = methotrexate; **V** = vincristine; **Vrb** = vinorelbine
(Not shown: G−CSF, erythropoietin, trastuzumab, antibiotic, hormonal, local or steroid therapies)

All regimens q3week (unless specified as q1, q2 or q4). Semicolon [;] indicates treatment sequence.
×14 means d1−14 po; ×2 (×3) means d1, d8 (d15) iv (except that in trial 94B, **F**500×2 was d1, d4 iv and in trial 01F, **C**600×2 could be **C**100×14).

P 22: RECURRENCE in trials of taxane-plus-anthracycline-based regimen vs SAME, or MORE (< doubled or ~doubled) non-taxane cytotoxic chemotherapy

Year code and study name	Regimens compared and drug doses (mg/m²) per cycle. Any unstated doses are as in the controls	Cumulative doses of taxane & anthracycline	Anthra-cycline difference	Events/woman-years: Allocated taxane	Events/woman-years: Allocated non-tax.	Taxane events*: Logrank O−E	Taxane events*: Variance of O−E
(a) Taxane (D or P)-plus-anthracycline (A or E)-based regimen † vs the SAME non-taxane cytotoxic chemotherapy (ie, unconfounded trials of adding a taxane)							
98B Taxit216 Italy	4**E**; 4D_{100}; 4**CMF**$_{q4}$ vs 4E_{120}; 4($C_{600\times2}M_{40\times2}F_{600\times2}$)	†$D_{100\times4}$ E_{480} vs E_{480}	0	112/2089	139/2007	−16·8	58·0
99T GOIM 9902 Italy	4D_{100}; 4**EC** vs 4$E_{120}C_{600}$	†$D_{100\times4}$ E_{480} vs E_{480}	0	38/1369	52/1280	−9·7	20·5
95J$_1$ NSABP B−27*	4**AC**‡; 4D_{100}‡ vs 4($A_{60}C_{600}$)‡	†$D_{100\times4}$ A_{240} vs A_{240}	0	252/5361	277/5127	−17·8	124·1
95J$_2$ NSABP B−27*	4**AC**‡; 4D_{100} vs **same control patients**	†$D_{100\times4}$ A_{240} vs A_{240}	0	257/5318	277/5127	−12·7	124·7
95K NSABP B−28	4**AC**; 4P_{225} vs 4$A_{60}C_{600}$	†$P_{225\times4}$ A_{240} vs A_{240}	0	476/12066	507/11744	−22·4	225·9
94D$_1$ CALGB 9344	4**AC**; 4P_{175} vs 4$A_{90}C_{600}$	†$P_{175\times4}$ A_{360} vs A_{360}	0	184/3462	208/3190	−18·4	89·2
94D$_2$ CALGB 9344	4**AC**; 4P_{175} vs 4$A_{75}C_{600}$	†$P_{175\times4}$ A_{300} vs A_{300}	0	182/3437	223/3188	−23·5	91·5
94D$_3$ CALGB 9344	4**AC**; 4P_{175} vs 4$A_{60}C_{600}$	†$P_{175\times4}$ A_{240} vs A_{240}	0	192/3441	214/3214	−14·7	92·9
(a) subtotal				**1693/ 36543 (4·6%/y)**	**1897/ 34877 (5·4%/y)**	**−126·0**	**740·1**
(b) Taxane-plus-anthracycline-based regimen (taxane courses given alone) † vs MORE (but < doubled) non-taxane cytotoxic chemotherapy							
00S WSG/AGO AM−02	4$E_{90}C_{600}$; 4D_{100} vs 6($F_{500}E_{100}C_{500}$)	†$D_{100\times4}$ E_{360} vs E_{600}	E_{240}	42/2063	59/1990	−9·8	24·4
95T HORG Greece	4D_{100}; 4**EC** vs 6($F_{700}E_{75}C_{700}$)	†$D_{100\times4}$ E_{300} vs E_{450}¶	E_{150}	92/1548	105/1423	−8·5	43·2
00E FinHer/FBCG 00−01	3$D_{(80/100)}$; 3**FEC** vs 3**Vrb**$_{25\times3}$; 3($F_{600}E_{60}C_{600}$)	†$D_{80\times3}$ E_{180} vs E_{180}¶	0≠	39/1470	69/1443	−14·8	23·6
98D$_1$ BIG 02−98*	3A_{75}; 3D_{100}; 3**CMF**$_{q4}$ vs 4A_{75}; 3($C_{100\times14}M_{40\times2}F_{600\times2}$)$_{q4}$ or 4$A_{60}C_{600}$; 3**CMF**$_{q4}$	†$D_{100\times3}$ A_{225} vs A_{270} (240/300)	A_{70}	197/4376	245/4290	−22·0	102·0
99K GEICAM 9906 Spain	4**FEC**; 8(P_{100})$_{q1}$ vs 6($F_{600}E_{90}C_{600}$)	†$P_{100\times8}$ E_{360} vs E_{540}	E_{180}	73/2265	134/2236	−28·5	46·5
97R HE1097 Greece	3E_{q2}; 3P_{250q2}; 3**CMF**$_{q2}$ vs 4(E_{110})$_{q2}$; 4($C_{840}M_{50}F_{840}$)$_{q2}$	†$P_{250\times3}$ E_{330} vs E_{440}	E_{110}	96/1271	100/1233	−3·5	42·3
00F$_1$ NCIC MA.21*	6($E_{120}C_{830}$)$_{q2}$; 4P_{175} vs 6($C_{75\times14}E_{60\times2}F_{500\times2}$)$_{q4}$	†$P_{175\times4}$ E_{720} vs E_{720}	0≠	74/1798	82/1829	−3·5	36·8
(b) subtotal				**613/ 14791 (4·1%/y)**	**794/ 14444 (5·5%/y)**	**−90·5**	**318·8**
(c) Taxane-plus-anthracycline-based regimen (taxane given concurrently) © vs MORE (but < doubled) non-taxane cytotoxic chemotherapy							
01E$_{1+3}$ PACS 04 France	6$E_{75}D_{75}$ vs 6($F_{500}E_{100}C_{500}$)	©$D_{75\times6}$ E_{450} vs E_{600}	E_{150}	202/4952	243/5046	−18·2	102·7
97L BCIRG 001	6D_{75}**AC** vs 6($F_{500}A_{50}C_{500}$)	©$D_{75\times6}$ A_{300} vs A_{300}¶	0≠	151/3042	202/2880	−30·3	79·5
99% GEICAM 9805 Spain	6D_{75}**AC** vs 6($F_{500}A_{50}C_{500}$)	©$D_{75\times6}$ A_{300} vs A_{300}¶	0≠	44/2608	63/2504	−13·3	25·2
98D$_2$ BIG 02−98*	4($A_{50}D_{75}$); 3**CMF**$_{q4}$ vs 4A_{75}; 3($C_{100\times14}M_{40\times2}F_{600\times2}$)$_{q4}$ or 4$A_{60}C_{600}$; 3**CMF**$_{q4}$	©$D_{75\times4}$ A_{200} vs A_{270} (240/300)	A_{45}	236/4270	245/4290	−1·2	110·2
99N RAPP−01 France	4$A_{50}D_{75}$ vs 4$A_{60}C_{600}$	©$D_{75\times4}$ A_{200} vs A_{240}	A_{40}	26/1430	31/1440	−2·4	13·9
98T ECOG EST2197	4AD_{60} vs 4$A_{60}C_{600}$	©$D_{60\times4}$ A_{240} vs A_{240}	0≠	245/9235	244/9209	−0·4	116·4
96W$_1$ ECTO Italy*	(4$A_{60}P_{200}$; 4**CMF**$_{q4}$) vs 4A_{75}; 4($C_{600\times2}M_{40\times2}F_{600\times2}$)$_{q4}$	©$P_{200\times4}$ A_{240} vs A_{300}¶	A_{60}	66/1517	96/1457	−16·5	37·6
96W$_2$ ECTO Italy*	(4$A_{60}P_{200}$; 4**CMF**$_{q4}$)‡ vs **same control patients**	©$P_{200\times4}$ A_{240} vs A_{300}¶	A_{60}	86/1510	96/1457	−6·9	41·6
96X GONO Italy MIG 5	4$E_{90}P_{175}$ vs 6($F_{600}E_{60}C_{600}$)	©$P_{175\times4}$ E_{360} vs E_{360}¶	0≠	127/2412	112/2391	9·0	54·0
(c) subtotal				**1183/ 30976 (3·8%/y)**	**1332/ 30674 (4·3%/y)**	**−71·7**	**552·7**
(d) Taxane-plus-anthracycline-based regimen † vs DOUBLED (or ≈ doubled) non-taxane cytotoxic chemotherapy							
01F TACT UK	4($F_{600}E_{60}C_{600}$); 4D_{100} vs 8($F_{600}E_{60}C_{600}$)	†$D_{100\times4}$ E_{240} vs E_{480}¶	E_{240}	255/4731	255/4721	4·2	113·7
01G TACT UK	4($F_{600}E_{60}C_{600}$); 4D_{100} vs 4E_{100}; 4($C_{600\times2}M_{40\times2}F_{600\times2}$)$_{q4}$	†$D_{100\times4}$ E_{240} vs E_{400}	E_{160}	173/3048	190/3006	−9·7	80·6
01T LMU Munich ADEBAR	4$E_{90}C_{600}$; 4D_{100} vs 6($C_{75\times14}E_{60\times2}F_{500\times2}$)$_{q4}$	†$D_{100\times4}$ E_{360} vs E_{720}	E_{360}	84/1507	67/1467	6·7	34·3
97J PACS 01 France	3**FEC**; 3D_{100} vs 6($F_{500}E_{100}C_{500}$)	†$D_{100\times3}$ E_{300} vs E_{600}	E_{300}	215/4525	261/4347	−21·8	109·2
97A DEVA UK	3E_{q4}; 3D_{100} vs 6($E_{50\times2}$)$_{q4}$	†$D_{100\times3}$ E_{300} vs E_{600}	E_{300}	65/1662	82/1544	−12·2	32·1
94B MD Anderson	4P_{250}‡; 4**FAC** vs 4**FAC**‡; 4($F_{500\times2}A_{50}C_{500}$)	†$P_{250\times4}$ A_{200} vs A_{400}¶	A_{200}	56/1545	73/1563	−7·2	28·3
00F$_2$ NCIC MA.21*	4$A_{60}C_{600}$; 4P_{175} vs 6($C_{75\times14}E_{60\times2}F_{500\times2}$)$_{q4}$	†$P_{175\times4}$ A_{240} vs E_{720}	$E_{720}-A_{240}$	116/1732	82/1829	20·5	44·7
(d) subtotal				**964/ 18750 (5·1%/y)**	**1010/ 18477 (5·5%/y)**	**−19·5**	**442·8**
Total (a − d)				**4453/ 101060 (4·4%/y)**	**5033/ 98472 (5·1%/y)**	**−305·6**	**1957·5**
Heterogeneity between 4 subtotals: χ^2_3 = 11·2; p = 0·01							
(e) No anthracycline in one allocation							
00S WSG/AGO AM−02	4$E_{90}C_{600}$; 4D_{100} vs 6($C_{600\times2}M_{40\times2}F_{600\times2}$)$_{q4}$	$D_{100\times4}$ E_{360} vs None	$-E_{360}$	12/655	25/663	−6·3	8·6
97N USO 97−35	4D_{75}**C** vs 4$A_{60}C_{600}$	$D_{75\times4}$ None vs A_{240}	A_{240}	63/2433	82/2427	−8·7	33·8

Ratio of annual event rates Taxane : Non-tax.

(a) subtotal: 0·84 (SE 0·03) reduction 2p < 0·00001

(b) subtotal: 0·75 (SE 0·05) reduction 2p < 0·00001

(c) subtotal: 0·88 (SE 0·04) reduction 2p = 0·002

(d) subtotal: 0·96 (SE 0·05) reduction 2p > 0·1; NS

Total (a − d): 0·855 (SE 0·021) reduction 2p < 0·00001

99% or 95% confidence intervals

0 0·5 1·0 1·5 2·0

Taxane better | Non-tax. better

* For 3−way trials, "Either active vs same control patients" (not plotted) is what contributes to the total.
For 95J NSABP B−27, this (O−E) is −20·6 with variance V = 162·1; 96W ECTO Italy (O−E) = −15·0, V = 50·8;
98D BIG 02−98 (O−E) = −15·2, V = 140·0; 00F MA.21 (O−E) = 11·2; V = 56·7

† Taxane courses do not overlap with any other chemotherapy courses; hence, total chemotherapy duration is increased

‡ Pre−operative chemotherapy: all patients in these trials were analysed as unknown nodal status

© Concurrent treatment with taxane and anthracycline; total chemotherapy duration and number of courses not increased

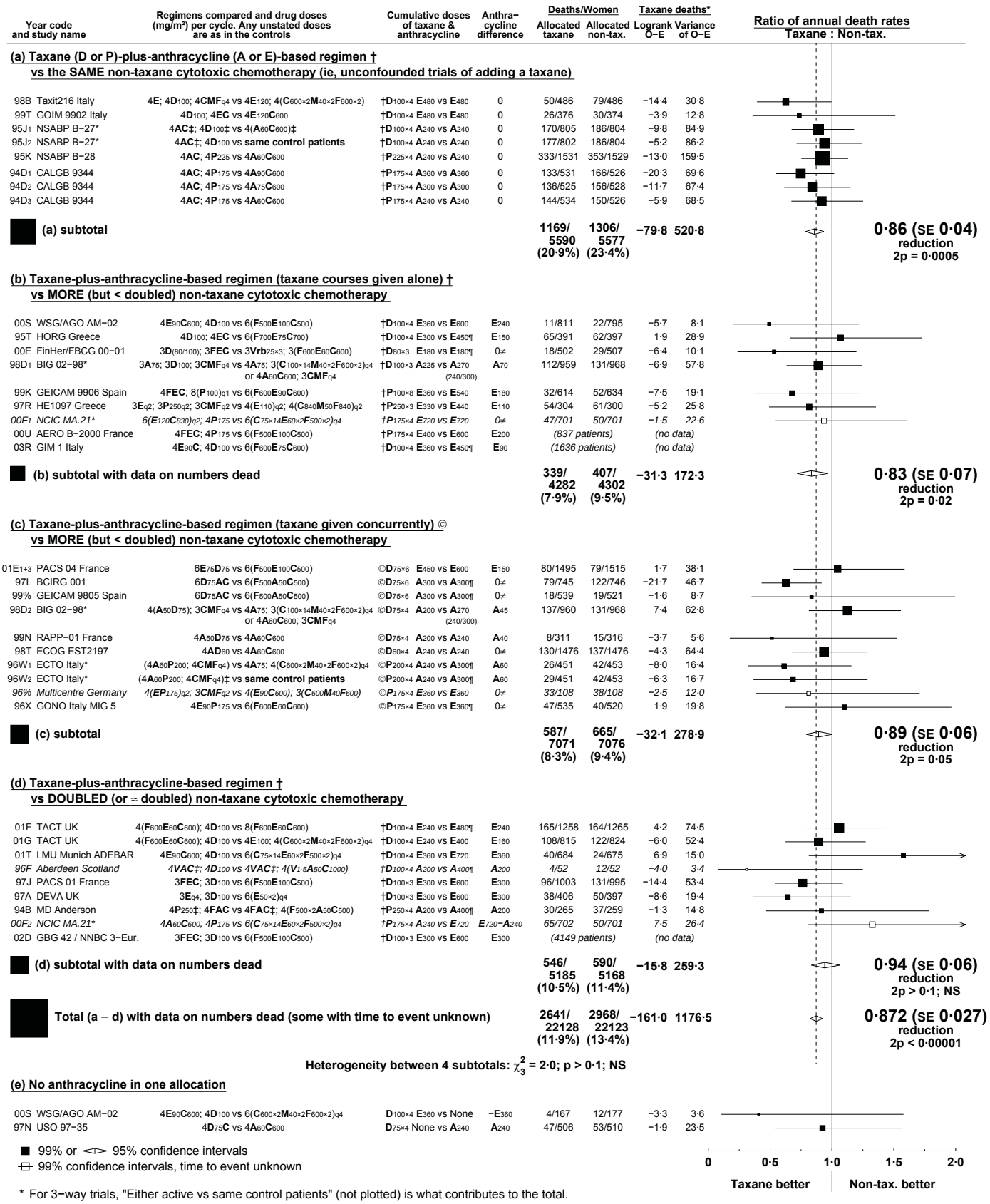
≠ Same cumulative anthracycline dose, but differences in other drugs

¶ Control anthracycline dose less than E_{90} or A_{60} per cycle

Taxanes: **D** = docetaxel; **P** = paclitaxel. Anthracyclines: **A** = doxorubicin (Adriamycin); **E** = Epirubicin
Other agents: **C** = cyclophosphamide; **F** = fluorouracil; **M** = methotrexate; **V** = vincristine; **Vrb** = vinorelbine
(Not shown: G−CSF, erythropoietin, trastuzumab, antibiotic, hormonal, local or steroid therapies)

All regimens q3week (unless specified as q1, q2 or q4). Semicolon [;] indicates treatment sequence.
×14 means d1−14 po; ×2 (×3) means d1, d8 (d15) iv (except that in trial 94B, $F_{500\times2}$ was d1, d4 iv and in trial 01F, $C_{600\times2}$ could be $C_{100\times14}$).

P 23: Breast cancer mortality (mortality with recurrence, by logrank subtraction), any taxane-plus-anthracycline-based regimen vs control with the SAME, or MORE (<doubled or ~doubled) non-taxane cytotoxic chemotherapy



* For 3−way trials, "Either active vs same control patients" (not plotted) is what contributes to the total.
For 95J NSABP B−27, this (O−E) is −10·5 with variance V = 112·2; 96W ECTO Italy (O−E) = −9·3, V = 20·8;
98D BIG 02−98 (O−E) = 0·4, V = 81·5; 00F MA.21 (O−E) = 4·0; V = 33·2

† Taxane courses do not overlap with any other chemotherapy courses; hence, total chemotherapy duration is increased

‡ Pre−operative chemotherapy: all patients in these trials were analysed as unknown nodal status

© Concurrent treatment with taxane and anthracycline; total chemotherapy duration and number of courses not increased

≠ Same cumulative anthracycline dose, but differences in other drugs

¶ Control anthracycline dose less than **E**90 or **A**60 per cycle

Taxanes: **D** = docetaxel; **P** = paclitaxel. Anthracyclines: **A** = doxorubicin (Adriamycin); **E** = Epirubicin
Other agents: **C** = cyclophosphamide; **F** = fluorouracil; **M** = methotrexate; **V** = vincristine; **Vrb** = vinorelbine
(Not shown: G−CSF, erythropoietin, trastuzumab, antibiotic, hormonal, local or steroid therapies)

All regimens q3week (unless specified as q1, q2 or q4). Semicolon [;] indicates treatment sequence.
×14 means d1−14 po; ×2 (×3) means d1, d8 (d15) iv (except that in trial 94B, **F**500×2 was d1, d4 iv and in trial 01F, **C**600×2 could be **C**100×14).

P 24: MORTALITY WITHOUT RECURRENCE IN FIRST YEAR in trials of taxane-plus-anthracycline-based regimen vs SAME, or MORE (< doubled or ~doubled) non-taxane cytotoxic chemotherapy

Year code and study name	Regimens compared and drug doses (mg/m^2) per cycle. Any unstated doses are as in the controls	Cumulative doses of taxane & anthracycline	Anthra-cycline difference	Deaths/woman-years: Allocated taxane	Deaths/woman-years: Allocated non-tax.	Taxane deaths*: Logrank O−E	Taxane deaths*: Variance of O−E
(a) Taxane (D or P)-plus-anthracycline (A or E)-based regimen † vs the SAME non-taxane cytotoxic chemotherapy (ie, unconfounded trials of adding a taxane)							
98B Taxit216 Italy	**4E**; 4$\mathbf{D}_{100}$; 4**CMF**$_{q4}$ vs 4$\mathbf{E}_{120}$; 4(**C**$_{600\times2}$**M**$_{40\times2}$**F**$_{600\times2}$)	†$\mathbf{D}_{100\times4}$ $\mathbf{E}_{480}$ vs $\mathbf{E}_{480}$	0	1/458	1/458	0·0	0·5
99T GOIM 9902 Italy	4$\mathbf{D}_{100}$; 4**EC** vs 4$\mathbf{E}_{120}$**C**$_{600}$	†$\mathbf{D}_{100\times4}$ $\mathbf{E}_{480}$ vs $\mathbf{E}_{480}$	0	0/350	0/339		
95J$_1$ NSABP B−27*	4**AC**‡; 4$\mathbf{D}_{100}$‡ vs 4(**A**$_{60}$**C**$_{600}$)‡	†$\mathbf{D}_{100\times4}$ $\mathbf{A}_{240}$ vs $\mathbf{A}_{240}$	0	5/789	1/783	2·0	1·5
95J$_2$ NSABP B−27*	4**AC**‡; 4$\mathbf{D}_{100}$ vs **same control patients**	†$\mathbf{D}_{100\times4}$ $\mathbf{A}_{240}$ vs $\mathbf{A}_{240}$	0	5/779	1/783	2·0	1·5
95K NSABP B−28	4**AC**; 4$\mathbf{P}_{225}$ vs 4$\mathbf{A}_{60}$**C**$_{600}$	†$\mathbf{P}_{225\times4}$ $\mathbf{A}_{240}$ vs $\mathbf{A}_{240}$	0	5/1500	4/1499	0·4	2·2
94D$_1$ CALGB 9344	4**AC**; 4$\mathbf{P}_{175}$ vs 4$\mathbf{A}_{90}$**C**$_{600}$	†$\mathbf{P}_{175\times4}$ $\mathbf{A}_{360}$ vs $\mathbf{A}_{360}$	0	2/513	4/508	−0·9	1·5
94D$_2$ CALGB 9344	4**AC**; 4$\mathbf{P}_{175}$ vs 4$\mathbf{A}_{75}$**C**$_{600}$	†$\mathbf{P}_{175\times4}$ $\mathbf{A}_{300}$ vs $\mathbf{A}_{300}$	0	1/510	1/504	0·0	0·5
94D$_3$ CALGB 9344	4**AC**; 4$\mathbf{P}_{175}$ vs 4$\mathbf{A}_{60}$**C**$_{600}$	†$\mathbf{P}_{175\times4}$ $\mathbf{A}_{240}$ vs $\mathbf{A}_{240}$	0	1/518	1/506	0·0	0·5
▪ **(a) subtotal**				**20/ 5417 (0·4%/y)**	**13/ 5380 (0·2%/y)**	**2·2**	**7·6**
(b) Taxane-plus-anthracycline-based regimen (taxane courses given alone) † vs MORE (but < doubled) non-taxane cytotoxic chemotherapy							
00S WSG/AGO AM−02	4$\mathbf{E}_{90}$**C**$_{600}$; 4$\mathbf{D}_{100}$ vs 6(**F**$_{500}$**E**$_{100}$**C**$_{500}$)	†$\mathbf{D}_{100\times4}$ $\mathbf{E}_{360}$ vs $\mathbf{E}_{600}$	$\mathbf{E}_{240}$	2/769	2/752	0·1	1·0
95T HORG Greece	4$\mathbf{D}_{100}$; 4**EC** vs 6(**F**$_{700}$**E**$_{75}$**C**$_{700}$)	†$\mathbf{D}_{100\times4}$ $\mathbf{E}_{300}$ vs $\mathbf{E}_{450}$¶	$\mathbf{E}_{150}$	0/356	3/356	−1·2	0·7
00E FinHer/FBCG 00−01	3$\mathbf{D}_{(80/100)}$; 3**FEC** vs 3**Vrb**$_{25\times3}$; 3(**F**$_{600}$**E**$_{60}$**C**$_{600}$)	†$\mathbf{D}_{80\times3}$ $\mathbf{E}_{180}$ vs $\mathbf{E}_{180}$¶	0≠	2/449	0/452	1·0	0·5
98D$_1$ BIG 02−98*	3$\mathbf{A}_{75}$; 3$\mathbf{D}_{100}$; 3**CMF**$_{q4}$ vs 4$\mathbf{A}_{75}$; 3(**C**$_{100\times14}$**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$ or 4$\mathbf{A}_{60}$**C**$_{600}$; 3**CMF**$_{q4}$	†$\mathbf{D}_{100\times3}$ $\mathbf{A}_{225}$ vs $\mathbf{A}_{270}$ (240/300)	$\mathbf{A}_{70}$	1/928	1/936	0·1	0·5
99K GEICAM 9906 Spain	4**FEC**; 8($\mathbf{P}_{100}$)$_{q1}$ vs 6(**F**$_{600}$**E**$_{90}$**C**$_{600}$)	†$\mathbf{P}_{100\times8}$ $\mathbf{E}_{360}$ vs $\mathbf{E}_{540}$	$\mathbf{E}_{180}$	4/579	1/602	1·6	1·2
97R HE1097 Greece	3$\mathbf{E}_{q2}$; 3$\mathbf{P}_{250q2}$; 3**CMF**$_{q2}$ vs 4(**E**$_{110}$)$_{q2}$; 4(**C**$_{840}$**M**$_{50}$**F**$_{840}$)$_{q2}$	†$\mathbf{P}_{250\times3}$ $\mathbf{E}_{330}$ vs $\mathbf{E}_{440}$	$\mathbf{E}_{110}$	1/276	0/275	0·5	0·2
▪ **(b) subtotal**				**10/ 3357 (0·3%/y)**	**7/ 3373 (0·2%/y)**	**2·0**	**4·1**
(c) Taxane-plus-−anthracycline-based regimen (taxane given concurrently) © vs MORE (but < doubled) non-taxane cytotoxic chemotherapy							
01E$_{1+3}$ PACS 04 France	6$\mathbf{E}_{75}$**D**$_{75}$ vs 6(**F**$_{500}$**E**$_{100}$**C**$_{500}$)	©$\mathbf{D}_{75\times6}$ $\mathbf{E}_{450}$ vs $\mathbf{E}_{600}$	$\mathbf{E}_{150}$	5/1451	2/1479	1·6	1·8
97L BCIRG 001	6$\mathbf{D}_{75}$**AC** vs 6(**F**$_{500}$**A**$_{50}$**C**$_{500}$)	©$\mathbf{D}_{75\times6}$ $\mathbf{A}_{300}$ vs $\mathbf{A}_{300}$¶	0≠	4/720	5/716	−0·5	2·2
99% GEICAM 9805 Spain	6$\mathbf{D}_{75}$**AC** vs 6(**F**$_{500}$**A**$_{50}$**C**$_{500}$)	©$\mathbf{D}_{75\times6}$ $\mathbf{A}_{300}$ vs $\mathbf{A}_{300}$¶	0≠	0/516	0/503		
98D$_2$ BIG 02−98*	4(**A**$_{50}$**D**$_{75}$); 3**CMF**$_{q4}$ vs 4$\mathbf{A}_{75}$; 3(**C**$_{100\times14}$**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$ or 4$\mathbf{A}_{60}$**C**$_{600}$; 3**CMF**$_{q4}$	©$\mathbf{D}_{75\times4}$ $\mathbf{A}_{200}$ vs $\mathbf{A}_{270}$ (240/300)	$\mathbf{A}_{45}$	2/931	1/936	0·5	0·8
99N RAPP−01 France	4$\mathbf{A}_{50}$**D**$_{75}$ vs 4$\mathbf{A}_{60}$**C**$_{600}$	©$\mathbf{D}_{75\times4}$ $\mathbf{A}_{200}$ vs $\mathbf{A}_{240}$	$\mathbf{A}_{40}$	2/298	0/302	1·0	0·5
98T ECOG EST2197	4**AD**$_{60}$ vs 4$\mathbf{A}_{60}$**C**$_{600}$	©$\mathbf{D}_{60\times4}$ $\mathbf{A}_{240}$ vs $\mathbf{A}_{240}$	0≠	6/1440	2/1445	2·0	2·0
96W$_1$ ECTO Italy*	(4$\mathbf{A}_{60}$**P**$_{200}$; 4**CMF**$_{q4}$) vs 4$\mathbf{A}_{75}$; 4(**C**$_{600\times2}$**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$	©$\mathbf{P}_{200\times4}$ $\mathbf{A}_{240}$ vs $\mathbf{A}_{300}$¶	$\mathbf{A}_{60}$	2/434	1/430	0·5	0·7
96W$_2$ ECTO Italy*	(4$\mathbf{A}_{60}$**P**$_{200}$; 4**CMF**$_{q4}$)‡ vs **same control patients**	©$\mathbf{P}_{200\times4}$ $\mathbf{A}_{240}$ vs $\mathbf{A}_{300}$¶	$\mathbf{A}_{60}$	1/437	1/430	−0·1	0·5
96X GONO Italy MIG 5	4$\mathbf{E}_{90}$**P**$_{175}$ vs 6(**F**$_{600}$**E**$_{60}$**C**$_{600}$)	©$\mathbf{P}_{175\times4}$ $\mathbf{E}_{360}$ vs $\mathbf{E}_{360}$¶	0≠	0/507	3/488	−1·5	0·8
▪ **(c) subtotal**				**22/ 6734 (0·3%/y)**	**15/ 6729 (0·2%/y)**	**3·6**	**8·8**
(d) Taxane-plus-anthracycline-based regimen † vs DOUBLED (or ≈ doubled) non-taxane cytotoxic chemotherapy							
01F TACT UK	4(**F**$_{600}$**E**$_{60}$**C**$_{600}$); 4$\mathbf{D}_{100}$ vs 8(**F**$_{600}$**E**$_{60}$**C**$_{600}$)	†$\mathbf{D}_{100\times4}$ $\mathbf{E}_{240}$ vs $\mathbf{E}_{480}$¶	$\mathbf{E}_{240}$	5/1220	1/1227	2·2	1·5
01G TACT UK	4(**F**$_{600}$**E**$_{60}$**C**$_{600}$); 4$\mathbf{D}_{100}$ vs 4$\mathbf{E}_{100}$; 4(**C**$_{600\times2}$**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$	†$\mathbf{D}_{100\times4}$ $\mathbf{E}_{240}$ vs $\mathbf{E}_{400}$	$\mathbf{E}_{160}$	4/783	1/786	1·5	1·2
01T LMU Munich ADEBAR	4$\mathbf{E}_{90}$**C**$_{600}$; 4$\mathbf{D}_{100}$ vs 6(**C**$_{75\times14}$**E**$_{60\times2}$**F**$_{500\times2}$)$_{q4}$	†$\mathbf{D}_{100\times4}$ $\mathbf{E}_{360}$ vs $\mathbf{E}_{720}$	$\mathbf{E}_{360}$	4/605	5/582	−0·1	2·2
97J PACS 01 France	3**FEC**; 3$\mathbf{D}_{100}$ vs 6(**F**$_{500}$**E**$_{100}$**C**$_{500}$)	†$\mathbf{D}_{100\times3}$ $\mathbf{E}_{300}$ vs $\mathbf{E}_{600}$	$\mathbf{E}_{300}$	0/984	0/975		
97A DEVA UK	3$\mathbf{E}_{q4}$; 3$\mathbf{D}_{100}$ vs 6(**E**$_{50\times2}$)$_{q4}$	†$\mathbf{D}_{100\times3}$ $\mathbf{E}_{300}$ vs $\mathbf{E}_{600}$	$\mathbf{E}_{300}$	1/379	4/368	−1·4	1·2
94B MD Anderson	4$\mathbf{P}_{250}$‡; 4**FAC** vs 4**FAC**‡; 4(**F**$_{500\times2}$**A**$_{50}$**C**$_{500}$)	†$\mathbf{P}_{250\times4}$ $\mathbf{A}_{200}$ vs $\mathbf{A}_{400}$¶	$\mathbf{A}_{200}$	0/242	0/230		
▪ **(d) subtotal**				**14/ 4213 (0·3%/y)**	**11/ 4168 (0·3%/y)**	**2·2**	**6·1**
■ **Total (a − d)**				**66/ 19721 (0·3%/y)**	**46/ 19650 (0·2%/y)**	**9·8**	**26·3**
Heterogeneity between 4 subtotals: χ^2_3 = 0·1; p > 0·1; NS							
(e) No anthracycline in one allocation							
00S WSG/AGO AM−02	4$\mathbf{E}_{90}$**C**$_{600}$; 4$\mathbf{D}_{100}$ vs 6(**C**$_{600\times2}$**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$	$\mathbf{D}_{100\times4}$ $\mathbf{E}_{360}$ vs None	−$\mathbf{E}_{360}$	0/154	0/164		
97N USO 97−35	4$\mathbf{D}_{75}$**C** vs 4$\mathbf{A}_{60}$**C**$_{600}$	$\mathbf{D}_{75\times4}$ None vs $\mathbf{A}_{240}$	$\mathbf{A}_{240}$	3/482	1/487	0·9	1·0

Ratio of annual death rates Taxane : Non-tax.

(a) subtotal: **1·34 (SE 0·42)** increase 2p > 0·1; NS

(b) subtotal: **1·64 (SE 0·64)** increase 2p > 0·1; NS

(c) subtotal: **1·50 (SE 0·42)** increase 2p > 0·1; NS

(d) subtotal: **1·44 (SE 0·49)** increase 2p > 0·1; NS

Total (a − d): **1·452 (SE 0·236)** increase 2p = 0·06

■ 99% or ◁▷ 95% confidence intervals

0 0·5 1·0 1·5 2·0

Taxane better | Non-tax. better

* For 3−way trials, "Either active vs same control patients" (not plotted) is what contributes to the total.
For 95J NSABP B−27, this (O−E) is 2·7 with variance V = 2·4; 96W ECTO Italy (O−E) = 0·3, V = 0·9;
98D BIG 02−98 (O−E) = 0·4, V = 0·9; 00F MA.21 (O−E) = 0·0; V = 0·0

† Taxane courses do not overlap with any other chemotherapy courses; hence, total chemotherapy duration is increased

‡ Pre−operative chemotherapy: all patients in these trials were analysed as unknown nodal status

© Concurrent treatment with taxane and anthracycline; total chemotherapy duration and number of courses not increased

≠ Same cumulative anthracycline dose, but differences in other drugs

¶ Control anthracycline dose less than $\mathbf{E}_{90}$ or $\mathbf{A}_{60}$ per cycle

Taxanes: **D** = docetaxel; **P** = paclitaxel. Anthracyclines: **A** = doxorubicin (Adriamycin); **E** = Epirubicin

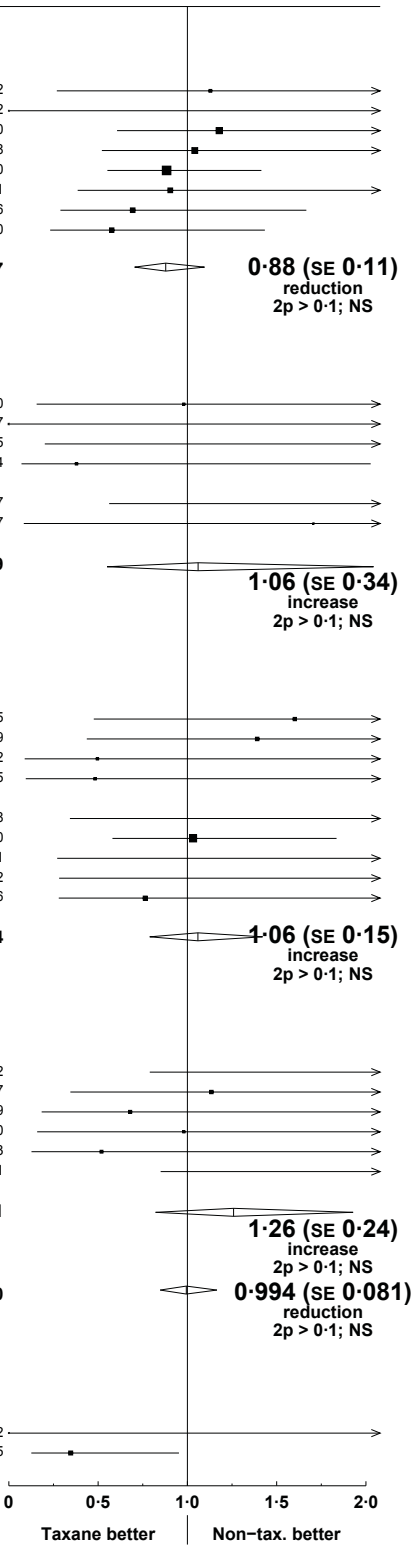
Other agents: **C** = cyclophosphamide; **F** = fluorouracil; **M** = methotrexate; **V** = vincristine; **Vrb** = vinorelbine
(Not shown: G−CSF, erythropoietin, trastuzumab, antibiotic, hormonal, local or steroid therapies)

All regimens q3week (unless specified as q1, q2 or q4). Semicolon [;] indicates treatment sequence.

×14 means d1−14 po; ×2 (×3) means d1, d8 (d15) iv (except that in trial 94B, $\mathbf{F}_{500\times2}$ was d1, d4 iv and in trial 01F, $\mathbf{C}_{600\times2}$ could be $\mathbf{C}_{100\times14}$).

P 25: MORTALITY WITHOUT RECURRENCE in trials of taxane-plus-anthracycline-based regimen vs SAME, or MORE (< doubled or ~doubled) non-taxane cytotoxic chemotherapy

Year code and study name	Regimens compared and drug doses (mg/m²) per cycle. Any unstated doses are as in the controls	Cumulative doses of taxane & anthracycline	Anthra-cycline difference	Deaths/woman-years: Allocated taxane	Deaths/woman-years: Allocated non-tax.	Taxane deaths*: Logrank O−E	Taxane deaths*: Variance of O−E
(a) Taxane (D or P)-plus-anthracycline (A or E)-based regimen † vs the SAME non-taxane cytotoxic chemotherapy (ie, unconfounded trials of adding a taxane)							
98B Taxit216 Italy	4**E**; 4D_{100}; 4**CMF**$_{q4}$ vs 4E_{120}; 4(**C**$_{600\times2}$**M**$_{40\times2}$**F**$_{600\times2}$)	†**D**$_{100\times4}$ **E**$_{480}$ vs **E**$_{480}$	0	7/2089	6/2007	0·4	3·2
99T GOIM 9902 Italy	4D_{100}; 4**EC** vs 4E_{120}**C**$_{600}$	†**D**$_{100\times4}$ **E**$_{480}$ vs **E**$_{480}$	0	0/1369	1/1280	−0·5	0·2
95J$_1$ NSABP B−27*	4**AC**‡; 4D_{100}‡ vs 4(**A**$_{60}$**C**$_{600}$)‡	†**D**$_{100\times4}$ **A**$_{240}$ vs **A**$_{240}$	0	34/5361	27/5127	2·5	15·0
95J$_2$ NSABP B−27*	4**AC**‡; 4D_{100} vs **same control patients**	†**D**$_{100\times4}$ **A**$_{240}$ vs **A**$_{240}$	0	29/5318	27/5127	0·6	13·8
95K NSABP B−28	4**AC**; 4P_{225} vs 4**A**$_{60}$**C**$_{600}$	†**P**$_{225\times4}$ **A**$_{240}$ vs **A**$_{240}$	0	59/12066	64/11744	−3·7	30·0
94D$_1$ CALGB 9344	4**AC**; 4P_{175} vs 4**A**$_{90}$**C**$_{600}$	†**P**$_{175\times4}$ **A**$_{360}$ vs **A**$_{360}$	0	19/3462	19/3190	−0·9	9·1
94D$_2$ CALGB 9344	4**AC**; 4P_{175} vs 4**A**$_{75}$**C**$_{600}$	†**P**$_{175\times4}$ **A**$_{300}$ vs **A**$_{300}$	0	15/3437	20/3188	−3·2	8·6
94D$_3$ CALGB 9344	4**AC**; 4P_{175} vs 4**A**$_{60}$**C**$_{600}$	†**P**$_{175\times4}$ **A**$_{240}$ vs **A**$_{240}$	0	14/3441	20/3214	−4·4	8·0
■ **(a) subtotal**				**177/ 36543 (0·5%/y)**	**184/ 34877 (0·5%/y)**	**−10·2**	**78·7**
(b) Taxane-plus-anthracycline-based regimen (taxane courses given alone) † vs MORE (but < doubled) non-taxane cytotoxic chemotherapy							
00S WSG/AGO AM−02	4**E**$_{90}$**C**$_{600}$; 4D_{100} vs 6(**F**$_{500}$**E**$_{100}$**C**$_{500}$)	†**D**$_{100\times4}$ **E**$_{360}$ vs **E**$_{600}$	**E**$_{240}$	4/2063	4/1990	0·0	2·0
95T HORG Greece	4D_{100}; 4**EC** vs 6(**F**$_{700}$**E**$_{75}$**C**$_{700}$)	†**D**$_{100\times4}$ **E**$_{300}$ vs **E**$_{450}$¶	**E**$_{150}$	0/1548	3/1423	−1·2	0·7
00E FinHer/FBCG 00−01	3$D_{(80/100)}$; 3**FEC** vs 3**Vrb**$_{25\times3}$; 3(**F**$_{600}$**E**$_{60}$**C**$_{600}$)	†**D**$_{80\times3}$ **E**$_{180}$ vs **E**$_{180}$¶	0≠	2/1470	1/1442	1·0	0·5
98D$_1$ BIG 02−98*	3**A**$_{75}$; 3D_{100}; 3**CMF**$_{q4}$ vs 4**A**$_{75}$; 3(**C**$_{100\times14}$**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$ or 4**A**$_{60}$**C**$_{600}$; 3**CMF**$_{q4}$	†**D**$_{100\times3}$ **A**$_{225}$ vs **A**$_{270}$ (240/300)	**A**$_{70}$	3/4375	7/4289	−2·3	2·4
99K GEICAM 9906 Spain	4**FEC**; 8(**P**$_{100}$)$_{q1}$ vs 6(**F**$_{600}$**E**$_{90}$**C**$_{600}$)	†**P**$_{100\times8}$ **E**$_{360}$ vs **E**$_{540}$	**E**$_{180}$	8/2265	3/2236	2·7	2·7
97R HE1097 Greece	3**E**$_{q2}$; 3**P**$_{250q2}$; 3**CMF**$_{q2}$ vs 4(**E**$_{110}$)$_{q2}$; 4(**C**$_{840}$**M**$_{50}$**F**$_{840}$)$_{q2}$	†**P**$_{250\times3}$ **E**$_{330}$ vs **E**$_{440}$	**E**$_{110}$	2/1271	1/1232	0·4	0·7
▪ **(b) subtotal**				**19/ 12992 (0·1%/y)**	**19/ 12612 (0·2%/y)**	**0·5**	**8·9**
(c) Taxane−plus−anthracycline−based regimen (taxane given concurrently) © vs MORE (but < doubled) non−taxane cytotoxic chemotherapy							
01E$_{1+3}$ PACS 04 France	6**E**$_{75}$**D**$_{75}$ vs 6(**F**$_{500}$**E**$_{100}$**C**$_{500}$)	©**D**$_{75\times6}$ **E**$_{450}$ vs **E**$_{600}$	**E**$_{150}$	11/4952	7/5046	2·1	4·5
97L BCIRG 001	6**D**$_{75}$**AC** vs 6(**F**$_{500}$**A**$_{50}$**C**$_{500}$)	©**D**$_{75\times6}$ **A**$_{300}$ vs **A**$_{300}$¶	0≠	12/3042	8/2880	1·6	4·9
99% GEICAM 9805 Spain	6**D**$_{75}$**AC** vs 6(**F**$_{500}$**A**$_{50}$**C**$_{500}$)	©**D**$_{75\times6}$ **A**$_{300}$ vs **A**$_{300}$¶	0≠	3/2608	8/2504	−1·6	2·2
98D$_2$ BIG 02−98*	4(**A**$_{50}$**D**$_{75}$); 3**CMF**$_{q4}$ vs 4**A**$_{75}$; 3(**C**$_{100\times14}$**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$ or 4**A**$_{60}$**C**$_{600}$; 3**CMF**$_{q4}$	©**D**$_{75\times4}$ **A**$_{200}$ vs **A**$_{270}$ (240/300)	**A**$_{45}$	3/4270	7/4289	−1·8	2·5
99N RAPP−01 France	4**A**$_{50}$**D**$_{75}$ vs 4**A**$_{60}$**C**$_{600}$	©**D**$_{75\times4}$ **A**$_{200}$ vs **A**$_{240}$	**A**$_{40}$	5/1430	2/1440	1·5	1·8
98T ECOG EST2197	4**AD**$_{60}$ vs 4**A**$_{60}$**C**$_{600}$	©**D**$_{60\times4}$ **A**$_{240}$ vs **A**$_{240}$	0≠	41/9235	40/9209	0·6	20·0
96W$_1$ ECTO Italy*	(4**A**$_{60}$**P**$_{200}$; 4**CMF**$_{q4}$) vs 4**A**$_{75}$; 4(**C**$_{600\times2}$**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$	©**P**$_{200\times4}$ **A**$_{240}$ vs **A**$_{300}$¶	**A**$_{60}$	4/1518	1/1457	1·3	1·1
96W$_2$ ECTO Italy*	(4**A**$_{60}$**P**$_{200}$; 4**CMF**$_{q4}$)‡ vs **same control patients**	©**P**$_{200\times4}$ **A**$_{240}$ vs **A**$_{300}$¶	**A**$_{60}$	4/1510	1/1457	1·3	1·2
96X GONO Italy MIG 5	4**E**$_{90}$**P**$_{175}$ vs 6(**F**$_{600}$**E**$_{60}$**C**$_{600}$)	©**P**$_{175\times4}$ **E**$_{360}$ vs **E**$_{360}$¶	0≠	13/2411	15/2390	−1·8	6·6
■ **(c) subtotal**				**96/ 30976 (0·3%/y)**	**89/ 30672 (0·3%/y)**	**2·5**	**44·4**
(d) Taxane−plus−anthracycline−based regimen † vs DOUBLED (or ≈ doubled) non−taxane cytotoxic chemotherapy							
01F TACT UK	4(**F**$_{600}$**E**$_{60}$**C**$_{600}$); 4D_{100} vs 8(**F**$_{600}$**E**$_{60}$**C**$_{600}$)	†**D**$_{100\times4}$ **E**$_{240}$ vs **E**$_{480}$¶	**E**$_{240}$	15/4731	6/4721	4·6	5·2
01G TACT UK	4(**F**$_{600}$**E**$_{60}$**C**$_{600}$); 4D_{100} vs 4**E**$_{100}$; 4(**C**$_{600\times2}$**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$	†**D**$_{100\times4}$ **E**$_{240}$ vs **E**$_{400}$	**E**$_{160}$	10/3048	9/3006	0·6	4·7
01T LMU Munich ADEBAR	4**E**$_{90}$**C**$_{600}$; 4D_{100} vs 6(**C**$_{75\times14}$**E**$_{60\times2}$**F**$_{500\times2}$)$_{q4}$	†**D**$_{100\times4}$ **E**$_{360}$ vs **E**$_{720}$	**E**$_{360}$	6/1508	10/1467	−1·5	3·9
97J PACS 01 France	3**FEC**; 3D_{100} vs 6(**F**$_{500}$**E**$_{100}$**C**$_{500}$)	†**D**$_{100\times3}$ **E**$_{300}$ vs **E**$_{600}$	**E**$_{300}$	4/4525	4/4347	0·0	2·0
97A DEVA UK	3**E**$_{q4}$; 3D_{100} vs 6(**E**$_{50\times2}$)$_{q4}$	†**D**$_{100\times3}$ **E**$_{300}$ vs **E**$_{600}$	**E**$_{300}$	6/1660	9/1543	−2·2	3·3
94B MD Anderson	4**P**$_{250}$‡; 4**FAC** vs 4**FAC**‡; 4(**F**$_{500\times2}$**A**$_{50}$**C**$_{500}$)	†**P**$_{250\times4}$ **A**$_{200}$ vs **A**$_{400}$¶	**A**$_{200}$	8/1544	1/1562	3·4	2·1
■ **(d) subtotal**				**49/ 17016 (0·3%/y)**	**39/ 16646 (0·2%/y)**	**4·9**	**21·1**
■ **Total (a − d)**				**341/ 97527 (0·3%/y)**	**331/ 94807 (0·3%/y)**	**−0·9**	**151·0**
Heterogeneity between 4 subtotals: χ^2_3 = 2·6; p > 0·1; NS							
(e) No anthracycline in one allocation							
00S WSG/AGO AM−02	4**E**$_{90}$**C**$_{600}$; 4D_{100} vs 6(**C**$_{600\times2}$**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$	**D**$_{100\times4}$ **E**$_{360}$ vs None	−**E**$_{360}$	0/655	1/663	−0·5	0·2
97N USO 97−35	4**D**$_{75}$**C** vs 4**A**$_{60}$**C**$_{600}$	**D**$_{75\times4}$ None vs **A**$_{240}$	**A**$_{240}$	8/2433	20/2427	−6·9	6·5



■ 99% or ◁▷ 95% confidence intervals

* For 3−way trials, "Either active vs same control patients" (not plotted) is what contributes to the total.
For 95J NSABP B−27, this (O−E) is 2·1 with variance V = 19·5; 96W ECTO Italy (O−E) = 1·8, V = 1·9;
98D BIG 02−98 (O−E) = −2·8, V = 2·8; 00F MA.21 (O−E) = 0·0; V = 0·0

† Taxane courses do not overlap with any other chemotherapy courses; hence, total chemotherapy duration is increased

‡ Pre−operative chemotherapy: all patients in these trials were analysed as unknown nodal status

© Concurrent treatment with taxane and anthracycline; total chemotherapy duration and number of courses not increased

≠ Same cumulative anthracycline dose, but differences in other drugs

¶ Control anthracycline dose less than **E**$_{90}$ or **A**$_{60}$ per cycle

Taxanes: **D** = docetaxel; **P** = paclitaxel. Anthracyclines: **A** = doxorubicin (Adriamycin); **E** = Epirubicin
Other agents: **C** = cyclophosphamide; **F** = fluorouracil; **M** = methotrexate; **V** = vincristine; **Vrb** = vinorelbine
(Not shown: G−CSF, erythropoietin, trastuzumab, antibiotic, hormonal, local or steroid therapies)

All regimens q3week (unless specified as q1, q2 or q4). Semicolon [;] indicates treatment sequence.
×14 means d1−14 po; ×2 (×3) means d1, d8 (d15) iv (except that in trial 94B, **F**$_{500\times2}$ was d1, d4 iv and in trial 01F, **C**$_{600\times2}$ could be **C**$_{100\times14}$).

P 26: OVERALL MORTALITY in trials of taxane-plus-anthracycline-based regimen vs SAME, or MORE (< doubled or ~doubled) non-taxane cytotoxic chemotherapy

Year code and study name	Regimens compared and drug doses (mg/m²) per cycle. Any unstated doses are as in the controls	Cumulative doses of taxane & anthracycline	Anthra−cycline difference	Deaths/Women: Allocated taxane	Deaths/Women: Allocated non−tax.	Taxane deaths*: Logrank O−E	Taxane deaths*: Variance of O−E
(a) Taxane (D or P)−plus−anthracycline (A or E)−based regimen † vs the SAME non−taxane cytotoxic chemotherapy (ie, unconfounded trials of adding a taxane)							
98B Taxit216 Italy	**4E**; 4**D**$_{100}$; 4**CMF**$_{q4}$ vs 4**E**$_{120}$; 4(**C**$_{600\times2}$**M**$_{40\times2}$**F**$_{600\times2}$)	†**D**$_{100\times4}$ **E**$_{480}$ vs **E**$_{480}$	0	57/486	85/486	−14·0	34·0
99T GOIM 9902 Italy	4**D**$_{100}$; 4**EC** vs 4**E**$_{120}$**C**$_{600}$	†**D**$_{100\times4}$ **E**$_{480}$ vs **E**$_{480}$	0	26/376	31/374	−4·4	13·0
95J$_1$ NSABP B−27*	4**AC**‡; 4**D**$_{100}$‡ vs 4(**A**$_{60}$**C**$_{600}$)‡	†**D**$_{100\times4}$ **A**$_{240}$ vs **A**$_{240}$	0	204/805	213/804	−7·3	99·9
95J$_2$ NSABP B−27*	4**AC**‡; 4**D**$_{100}$ vs **same control patients**	†**D**$_{100\times4}$ **A**$_{240}$ vs **A**$_{240}$	0	206/802	213/804	−4·7	100·0
95K NSABP B−28	4**AC**; 4**P**$_{225}$ vs 4**A**$_{60}$**C**$_{600}$	†**P**$_{225\times4}$ **A**$_{240}$ vs **A**$_{240}$	0	392/1531	417/1529	−16·7	189·4
94D$_1$ CALGB 9344	4**AC**; 4**P**$_{175}$ vs 4**A**$_{90}$**C**$_{600}$	†**P**$_{175\times4}$ **A**$_{360}$ vs **A**$_{360}$	0	152/531	185/526	−21·2	78·8
94D$_2$ CALGB 9344	4**AC**; 4**P**$_{175}$ vs 4**A**$_{75}$**C**$_{600}$	†**P**$_{175\times4}$ **A**$_{300}$ vs **A**$_{300}$	0	151/525	176/528	−14·9	76·0
94D$_3$ CALGB 9344	4**AC**; 4**P**$_{175}$ vs 4**A**$_{60}$**C**$_{600}$	†**P**$_{175\times4}$ **A**$_{240}$ vs **A**$_{240}$	0	158/534	170/526	−10·3	76·5
(a) subtotal				**1346/ 5590 (24·1%)**	**1490/ 5577 (26·7%)**	**−89·9**	**599·3**
(b) Taxane−plus−anthracycline−based regimen (taxane courses given alone) † vs MORE (but < doubled) non−taxane cytotoxic chemotherapy							
00S WSG/AGO AM−02	4**E**$_{90}$**C**$_{600}$; 4**D**$_{100}$ vs 6(**F**$_{500}$**E**$_{100}$**C**$_{500}$)	†**D**$_{100\times4}$ **E**$_{360}$ vs **E**$_{600}$	**E**$_{240}$	15/811	26/795	−5·8	10·0
95T HORG Greece	4**D**$_{100}$; 4**EC** vs 6(**F**$_{700}$**E**$_{75}$**C**$_{700}$)	†**D**$_{100\times4}$ **E**$_{300}$ vs **E**$_{450}$¶	**E**$_{150}$	65/391	65/397	0·7	29·6
00E FinHer/FBCG 00−01	3**D**$_{(80/100)}$; 3**FEC** vs 3**Vrb**$_{25\times3}$; 3(**F**$_{600}$**E**$_{60}$**C**$_{600}$)	†**D**$_{80\times3}$ **E**$_{180}$ vs **E**$_{180}$¶	0≠	20/502	30/507	−5·3	10·6
98D$_1$ BIG 02−98*	3**A**$_{75}$; 3**D**$_{100}$; 3**CMF**$_{q4}$ vs 4**A**$_{75}$; 3(**C**$_{100\times14}$**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$ or 4**A**$_{60}$**C**$_{600}$; 3**CMF**$_{q4}$	†**D**$_{100\times3}$ **A**$_{225}$ vs **A**$_{270}$ (240/300)	**A**$_{70}$	115/959	138/968	−9·2	60·1
99K GEICAM 9906 Spain	4**FEC**; 8(**P**$_{100}$)$_{q1}$ vs 6(**F**$_{600}$**E**$_{90}$**C**$_{600}$)	†**P**$_{100\times8}$ **E**$_{360}$ vs **E**$_{540}$	**E**$_{180}$	40/614	55/634	−4·8	21·8
97R HE1097 Greece	3**E**$_{q2}$; 3**P**$_{250q2}$; 3**CMF**$_{q2}$ vs 4(**E**$_{110}$)$_{q2}$; 4(**C**$_{840}$**M**$_{50}$**F**$_{840}$)$_{q2}$	†**P**$_{250\times3}$ **E**$_{330}$ vs **E**$_{440}$	**E**$_{110}$	56/304	62/300	−4·9	26·5
*00F$_1$ NCIC MA.21**	*6(**E**$_{120}$**C**$_{830}$)$_{q2}$; 4**P**$_{175}$ vs 6(**C**$_{75\times14}$**E**$_{60\times2}$**F**$_{500\times2}$)$_{q4}$*	*†**P**$_{175\times4}$ **E**$_{720}$ vs **E**$_{720}$*	*0≠*	*47/701*	*50/701*	*−1·5*	*22·6*
00U AERO B−2000 France	4**FEC**; 4**P**$_{175}$ vs 6(**F**$_{500}$**E**$_{100}$**C**$_{500}$)	†**P**$_{175\times4}$ **E**$_{400}$ vs **E**$_{600}$	**E**$_{200}$	*(837 patients)*		*(no data)*	
03R GIM 1 Italy	4**E**$_{90}$**C**; 4**D**$_{100}$ vs 6(**F**$_{600}$**E**$_{75}$**C**$_{600}$)	†**D**$_{100\times4}$ **E**$_{360}$ vs **E**$_{450}$¶	**E**$_{90}$	*(1636 patients)*		*(no data)*	
(b) subtotal with data on numbers dead				**358/ 4282 (8·4%)**	**426/ 4302 (9·9%)**	**−30·8**	**181·2**
(c) Taxane−plus−anthracycline−based regimen (taxane given concurrently) © vs MORE (but < doubled) non−taxane cytotoxic chemotherapy							
01E$_{1+3}$ PACS 04 France	6**E**$_{75}$**D**$_{75}$ vs 6(**F**$_{500}$**E**$_{100}$**C**$_{500}$)	©**D**$_{75\times6}$ **E**$_{450}$ vs **E**$_{600}$	**E**$_{150}$	91/1495	86/1515	3·8	42·5
97L BCIRG 001	6**D**$_{75}$**AC** vs 6(**F**$_{500}$**A**$_{50}$**C**$_{500}$)	©**D**$_{75\times6}$ **A**$_{300}$ vs **A**$_{300}$¶	0≠	91/745	130/746	−20·0	51·6
99% GEICAM 9805 Spain	6**D**$_{75}$**AC** vs 6(**F**$_{500}$**A**$_{50}$**C**$_{500}$)	©**D**$_{75\times6}$ **A**$_{300}$ vs **A**$_{300}$¶	0≠	21/539	27/521	−3·1	11·0
98D$_2$ BIG 02−98*	4(**A**$_{50}$**D**$_{75}$); 3**CMF**$_{q4}$ vs 4**A**$_{75}$; 3(**C**$_{100\times14}$**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$ or 4**A**$_{60}$**C**$_{600}$; 3**CMF**$_{q4}$	©**D**$_{75\times4}$ **A**$_{200}$ vs **A**$_{270}$ (240/300)	**A**$_{45}$	140/960	138/968	5·6	65·3
99N RAPP−01 France	4**A**$_{50}$**D**$_{75}$ vs 4**A**$_{60}$**C**$_{600}$	©**D**$_{75\times4}$ **A**$_{200}$ vs **A**$_{240}$	**A**$_{40}$	13/311	17/316	−2·2	7·4
98T ECOG EST2197	4**AD**$_{60}$ vs 4**A**$_{60}$**C**$_{600}$	©**D**$_{60\times4}$ **A**$_{240}$ vs **A**$_{240}$	0≠	171/1476	177/1476	−3·6	84·4
96W$_1$ ECTO Italy*	(4**A**$_{60}$**P**$_{200}$; 4**CMF**$_{q4}$) vs 4**A**$_{75}$; 4(**C**$_{600\times2}$**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$	©**P**$_{200\times4}$ **A**$_{240}$ vs **A**$_{300}$¶	**A**$_{60}$	30/451	43/453	−6·8	17·5
96W$_2$ ECTO Italy*	(4**A**$_{60}$**P**$_{200}$; 4**CMF**$_{q4}$)‡ vs **same control patients**	©**P**$_{200\times4}$ **A**$_{240}$ vs **A**$_{300}$¶	**A**$_{60}$	33/451	43/453	−5·0	18·0
96% Multicentre Germany	*4(**EP**$_{175}$)$_{q2}$; 3**CMF**$_{q2}$ vs 4(**F**$_{90}$**C**$_{600}$); 3(**C**$_{600}$**M**$_{40}$**F**$_{600}$)*	*©**P**$_{175\times4}$ **E**$_{360}$ vs **E**$_{360}$*	*0≠*	*33/108*	*38/108*	*−2·5*	*12·0*
96X GONO Italy MIG 5	4**E**$_{90}$**P**$_{175}$ vs 6(**F**$_{600}$**E**$_{60}$**C**$_{600}$)	©**P**$_{175\times4}$ **E**$_{360}$ vs **E**$_{360}$¶	0≠	60/535	55/520	0·2	26·4
(c) subtotal				**683/ 7071 (9·7%)**	**754/ 7076 (10·7%)**	**−29·5**	**323·2**
(d) Taxane−plus−anthracycline−based regimen † vs DOUBLED (or ≈ doubled) non−taxane cytotoxic chemotherapy							
01F TACT UK	4(**F**$_{600}$**E**$_{60}$**C**$_{600}$); 4**D**$_{100}$ vs 8(**F**$_{600}$**E**$_{60}$**C**$_{600}$)	†**D**$_{100\times4}$ **E**$_{240}$ vs **E**$_{480}$¶	**E**$_{240}$	180/1258	170/1265	8·8	79·6
01G TACT UK	4(**F**$_{600}$**E**$_{60}$**C**$_{600}$); 4**D**$_{100}$ vs 4**E**$_{100}$; 4(**C**$_{600\times2}$**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$	†**D**$_{100\times4}$ **E**$_{240}$ vs **E**$_{400}$	**E**$_{160}$	118/815	131/824	−5·4	57·1
01T LMU Munich ADEBAR	4**E**$_{90}$**C**$_{600}$; 4**D**$_{100}$ vs 6(**C**$_{75\times14}$**E**$_{60\times2}$**F**$_{500\times2}$)$_{q4}$	†**D**$_{100\times4}$ **E**$_{360}$ vs **E**$_{720}$	**E**$_{360}$	46/684	34/675	5·4	18·9
96F Aberdeen Scotland	*4**VAC**‡; 4**D**$_{100}$ vs 4**VAC**‡; 4(**V**$_{1\cdot5}$**A**$_{50}$**C**$_{1000}$)*	*†**D**$_{100\times4}$ **A**$_{200}$ vs **A**$_{400}$¶*	***A**$_{200}$*	*4/52*	*12/52*	*−4·0*	*3·4*
97J PACS 01 France	3**FEC**; 3**D**$_{100}$ vs 6(**F**$_{500}$**E**$_{100}$**C**$_{500}$)	†**D**$_{100\times3}$ **E**$_{300}$ vs **E**$_{600}$	**E**$_{300}$	100/1003	135/995	−14·4	55·4
97A DEVA UK	3**E**$_{q4}$; 3**D**$_{100}$ vs 6(**E**$_{50\times2}$)$_{q4}$	†**D**$_{100\times3}$ **E**$_{300}$ vs **E**$_{600}$	**E**$_{300}$	44/406	59/397	−10·8	22·7
94B MD Anderson	4**P**$_{250}$‡; 4**FAC** vs 4**FAC**‡; 4(**F**$_{500\times2}$**A**$_{50}$**C**$_{500}$)	†**P**$_{250\times4}$ **A**$_{200}$ vs **A**$_{400}$¶	**A**$_{200}$	38/265	38/259	2·0	16·8
*00F$_2$ NCIC MA.21**	*4**A**$_{60}$**C**$_{600}$; 4**P**$_{175}$ vs 6(**C**$_{75\times14}$**E**$_{60\times2}$**F**$_{500\times2}$)$_{q4}$*	*†**P**$_{175\times4}$ **A**$_{240}$ vs **E**$_{720}$*	***E**$_{720}$−**A**$_{240}$*	*65/702*	*50/701*	*7·5*	*26·4*
02D GBG 42 / NNBC 3−Eur.	3**FEC**; 3**D**$_{100}$ vs 6(**F**$_{500}$**E**$_{100}$**C**$_{500}$)	†**D**$_{100\times3}$ **E**$_{300}$ vs **E**$_{600}$	**E**$_{300}$	*(4149 patients)*		*(no data)*	
(d) subtotal with data on numbers dead				**595/ 5185 (11·5%)**	**629/ 5168 (12·2%)**	**−10·9**	**280·4**
Total (a − d) with data on numbers dead (some with time to event unknown)				**2982/ 22128 (13·5%)**	**3299/ 22123 (14·9%)**	**−161·9**	**1327·3**
(e) No anthracycline in one allocation							
00S WSG/AGO AM−02	4**E**$_{90}$**C**$_{600}$; 4**D**$_{100}$ vs 6(**C**$_{600\times2}$**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$	**D**$_{100\times4}$ **E**$_{360}$ vs None	−**E**$_{360}$	4/167	13/177	−3·8	3·9
97N USO 97−35	4**D**$_{75}$**C** vs 4**A**$_{60}$**C**$_{600}$	**D**$_{75\times4}$ None vs **A**$_{240}$	**A**$_{240}$	55/506	73/510	−8·7	30·0

Heterogeneity between 4 subtotals: χ^2_3 = 3·1; p > 0·1; NS

Ratio of annual death rates
Taxane : Non−tax.

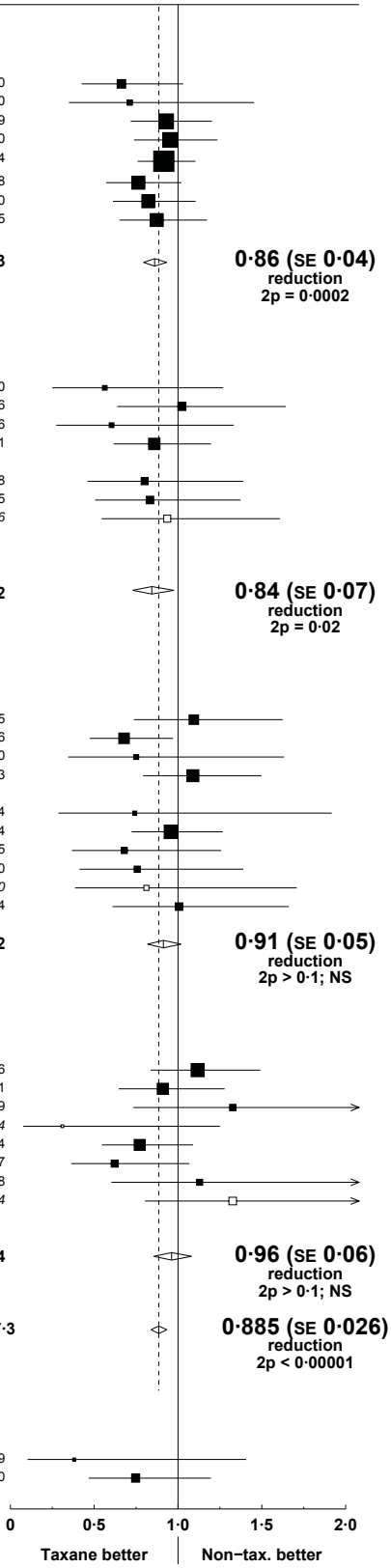
0·86 (SE 0·04) reduction 2p = 0·0002

0·84 (SE 0·07) reduction 2p = 0·02

0·91 (SE 0·05) reduction 2p > 0·1; NS

0·96 (SE 0·06) reduction 2p > 0·1; NS

0·885 (SE 0·026) reduction 2p < 0·00001



■ 99% or ◇ 95% confidence intervals
⊟ 99% confidence intervals, time to event unknown

* For 3−way trials, "Either active vs same control patients" (not plotted) is what contributes to the total.
For 95J NSABP B−27, this (O−E) is −8·4 with variance V = 131·6; 96W ECTO Italy (O−E) = −7·5, V = 22·7;
98D BIG 02−98 (O−E) = −2·3, V = 84·2; 00F MA.21 (O−E) = 4·0; V = 33·2

† Taxane courses do not overlap with any other chemotherapy courses; hence, total chemotherapy duration is increased

‡ Pre−operative chemotherapy: all patients in these trials were analysed as unknown nodal status

© Concurrent treatment with taxane and anthracycline; total chemotherapy duration and number of courses not increased

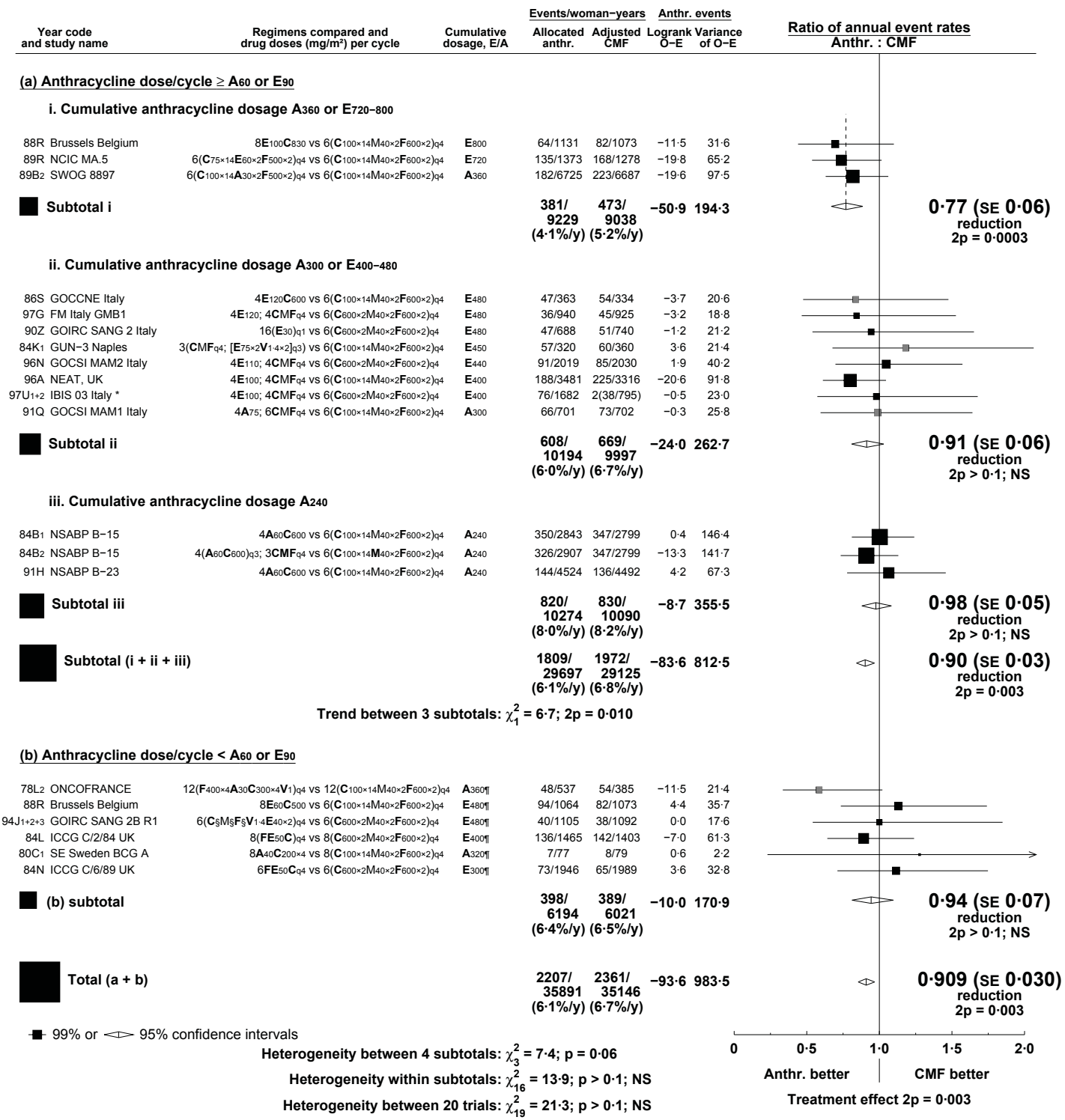
≠ Same cumulative anthracycline dose, but differences in other drugs

¶ Control anthracycline dose less than **E**$_{90}$ or **A**$_{60}$ per cycle

Taxanes: **D** = docetaxel; **P** = paclitaxel. Anthracyclines: **A** = doxorubicin (Adriamycin); **E** = Epirubicin
Other agents: **C** = cyclophosphamide; **F** = fluorouracil; **M** = methotrexate; **V** = vincristine; **Vrb** = vinorelbine
(Not shown: G−CSF, erythropoietin, trastuzumab, antibiotic, hormonal, local or steroid therapies)

All regimens q3week (unless specified as q1, q2 or q4). Semicolon [;] indicates treatment sequence.
×14 means d1−14 po; ×2 (×3) means d1, d8 (d15) iv (except that in trial 94B, **F**$_{500\times2}$ was d1, d4 iv and in trial 01F, **C**$_{600\times2}$ could be **C**$_{100\times14}$).

P 27: EARLY RECURRENCE (first 5 years) in trials of any anthracycline-based regimen vs. standard CMF (or near-standard CMF)



* 97U was (4**E**; 4**CMF**) vs (4**CMF**; 4**E**) vs (6**CMF**), and its controls count twice in subtotal and in total of events/woman−years; the study included women with highly proliferative disease, and slightly updated results from it have recently been published (webappendix p66)

Anthracyclines: **A** = doxorubicin (Adriamycin); **E** = Epirubicin

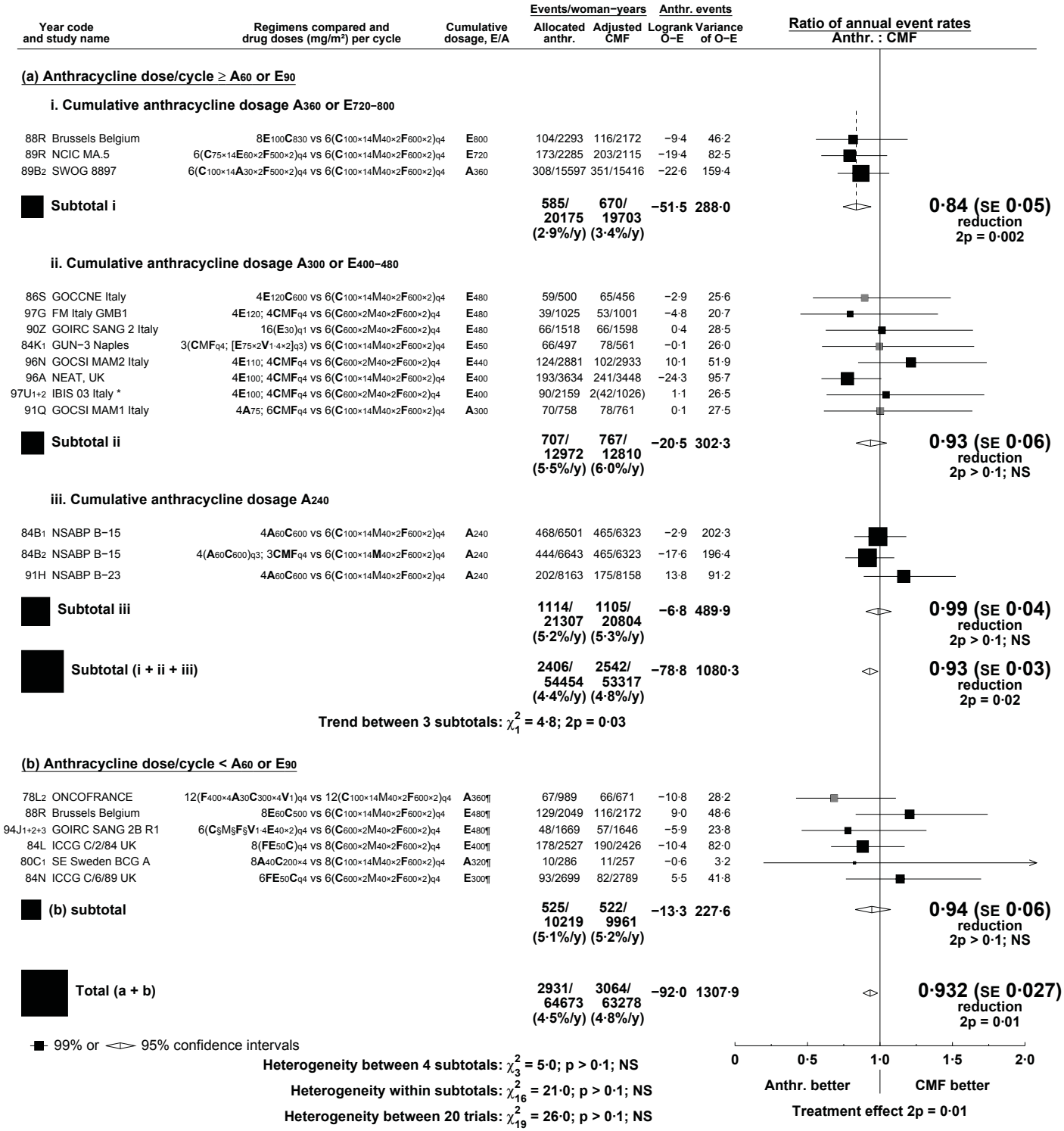
Other agents: **C** = cyclophosphamide; **F** = fluorouracil; **M** = methotrexate; **V** = vincristine
(Not shown: antibiotic, hormonal, local or steroid therapies)

All regimens q3week (unless specified as q4). Semicolon [;] indicates treatment sequence
×2 means d1,8 iv; ×4 means d3−6 iv

¶ Dose less than **E**90 or **A**60 per cycle of anthracycline

§ 94J interwoven drug schedule: anthracycline group omitted **C**, **M** or **F** respectively on cycles (3, 2 or 1) and (6, 5 or 4)

P 28: RECURRENCE in trials of any anthracycline-based regimen vs. standard CMF (or near-standard CMF)



* 97U was (4**E**; 4**CMF**) vs (4**CMF**; 4**E**) vs (6**CMF**), and its controls count twice in subtotal and in total of events/woman−years; the study included women with highly proliferative disease, and slightly updated results from it have recently been published (webappendix p66)

Anthracyclines: **A** = doxorubicin (Adriamycin); **E** = Epirubicin

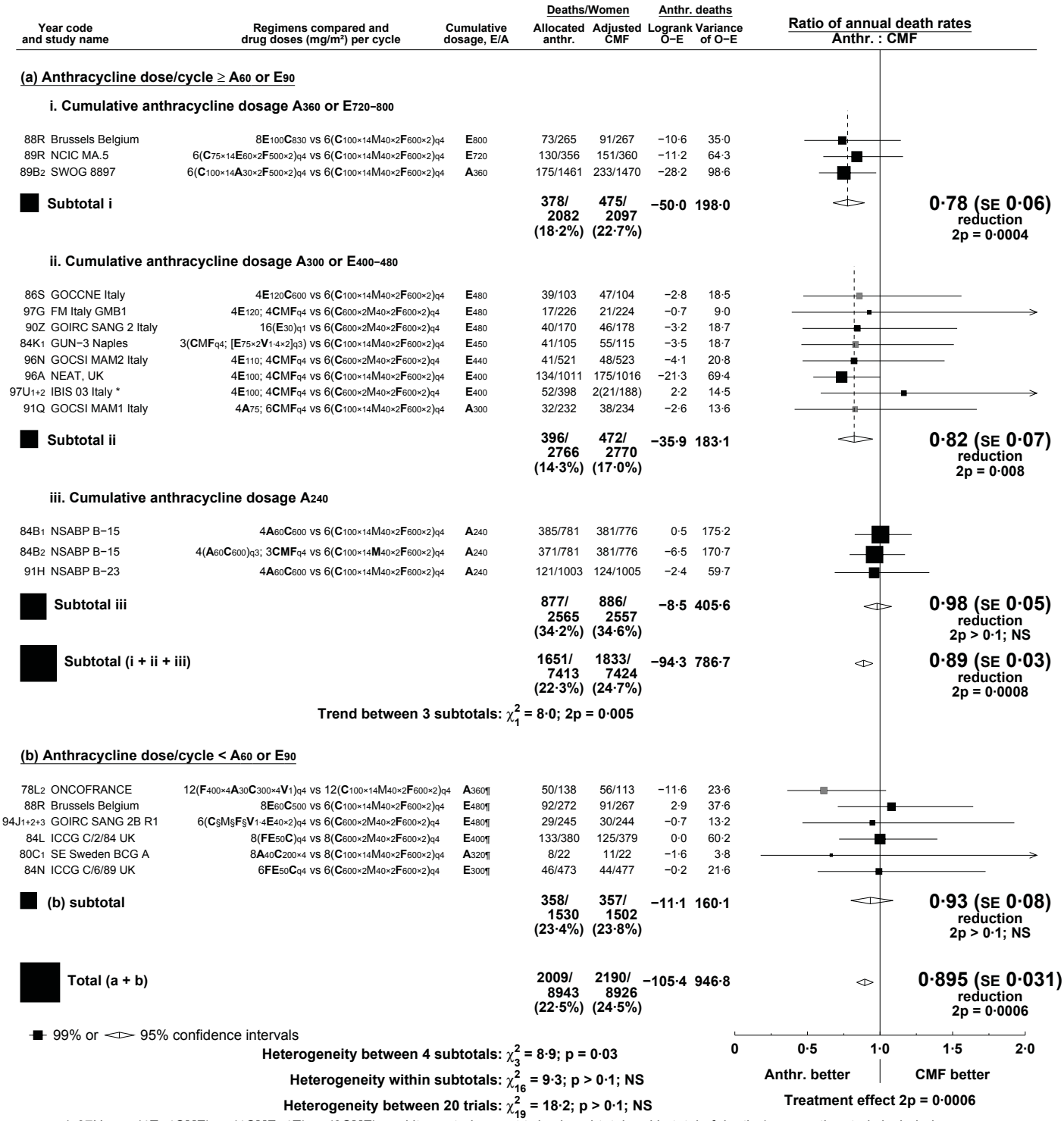
Other agents: **C** = cyclophosphamide; **F** = fluorouracil; **M** = methotrexate; **V** = vincristine
(Not shown: antibiotic, hormonal, local or steroid therapies)

All regimens q3week (unless specified as q4). Semicolon [;] indicates treatment sequence
×2 means d1,8 iv; ×4 means d3−6 iv

¶ Dose less than **E**90 or **A**60 per cycle of anthracycline

§ 94J interwoven drug schedule: anthracycline group omitted **C**, **M** or **F** respectively on cycles (3, 2 or 1) and (6, 5 or 4)

P 29: BREAST CANCER MORTALITY (MORTALITY WITH RECURRENCE) in trials of any anthracycline-based regimen vs. standard CMF (or near-standard CMF)



* 97U was (4**E**; 4**CMF**) vs (4**CMF**; 4**E**) vs (6**CMF**), and its controls count twice in subtotal and in total of deaths/women; the study included women with highly proliferative disease, and slightly updated results from it have recently been published (webappendix p66)

Anthracyclines: **A** = doxorubicin (Adriamycin); **E** = Epirubicin

Other agents: **C** = cyclophosphamide; **F** = fluorouracil; **M** = methotrexate; **V** = vincristine
(Not shown: antibiotic, hormonal, local or steroid therapies)

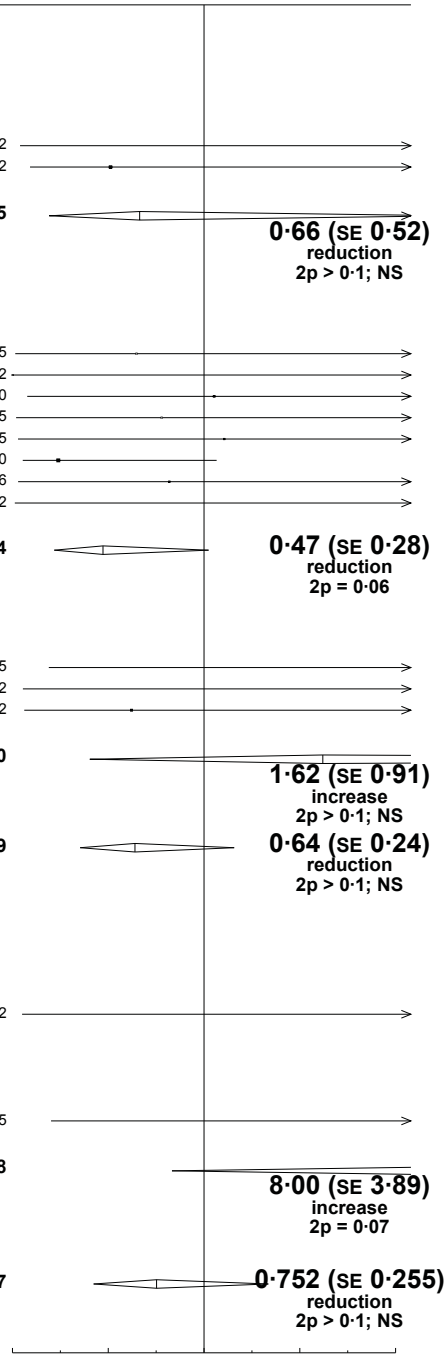
All regimens q3week (unless specified as q4). Semicolon [;] indicates treatment sequence
×2 means d1,8 iv; ×4 means d3−6 iv

¶ Dose less than **E**90 or **A**60 per cycle of anthracycline

§ 94J interwoven drug schedule: anthracycline group omitted **C**, **M** or **F** respectively on cycles (3, 2 or 1) and (6, 5 or 4)

P 30: MORTALITY WITHOUT RECURRENCE IN FIRST YEAR in trials of any anthracycline-based regimen vs. standard CMF (or near-standard CMF)

Year code and study name	Regimens compared and drug doses (mg/m²) per cycle	Cumulative dosage, E/A	Deaths/woman−years: Allocated anthr.	Deaths/woman−years: Adjusted CMF	Anthr. deaths: Logrank O−E	Anthr. deaths: Variance of O−E
(a) Anthracycline dose/cycle ≥ A60 or E90						
i. Cumulative anthracycline dosage A360 or E720−800						
88R Brussels Belgium	8**E**100**C**830 vs 6(**C**100×14M40×2**F**600×2)q4	**E**800	0/230	0/229		
89R NCIC MA.5	6(**C**75×14**E**60×2**F**500×2)q4 vs 6(**C**100×14M40×2**F**600×2)q4	**E**720	1/340	0/341	0·5	0·2
89B2 SWOG 8897	6(**C**100×14**A**30×2**F**500×2)q4 vs 6(**C**100×14M40×2**F**600×2)q4	**A**360	3/1432	6/1438	−1·5	2·2
. **Subtotal i**			**4/ 2002 (0·2%/y)**	**6/ 2008 (0·3%/y)**	**−1·0**	**2·5**
ii. Cumulative anthracycline dosage A300 or E400−480						
86S GOCCNE Italy	4**E**120**C**600 vs 6(**C**100×14M40×2**F**600×2)q4	**E**480	1/93	1/91	−0·2	0·5
97G FM Italy GMB1	4**E**120; 4**CMF**q4 vs 6(**C**600×2M40×2**F**600×2)q4	**E**480	0/215	1/214	−0·5	0·2
90Z GOIRC SANG 2 Italy	16(**E**30)q1 vs 6(**C**600×2M40×2**F**600×2)q4	**E**480	2/145	2/156	0·0	1·0
84K1 GUN−3 Naples	3(**CMF**q4; [**E**75×2**V**1·4×2]q3) vs 6(**C**100×14M40×2**F**600×2)q4	**E**450	1/87	1/92	−0·1	0·5
96N GOCSI MAM2 Italy	4**E**110; 4**CMF**q4 vs 6(**C**600×2M40×2**F**600×2)q4	**E**440	1/448	1/445	0·1	0·5
96A NEAT, UK	4**E**100; 4**CMF**q4 vs 6(**C**100×14M40×2**F**600×2)q4	**E**400	2/965	10/965	−4·2	3·0
97U1+2 IBIS 03 Italy *	4**E**100; 4**CMF**q4 vs 6(**C**600×2M40×2**F**600×2)q4	**E**400	2/361	2(1/173)	−0·1	0·6
91Q GOCSI MAM1 Italy	4**A**75; 6**CMF**q4 vs 6(**C**100×14M40×2**F**600×2)q4	**A**300	1/171	0/178	0·3	0·2
▪ **Subtotal ii**			**10/ 2485 (0·4%/y)**	**18/ 2487 (0·7%/y)**	**−4·8**	**6·4**
iii. Cumulative anthracycline dosage A240						
84B1 NSABP B−15	4**A**60**C**600 vs 6(**C**100×14M40×2**F**600×2)q4	**A**240	2/746	0/740	1·0	0·5
84B2 NSABP B−15	4(**A**60**C**600)q3; 3**CMF**q4 vs 6(**C**100×14M40×2**F**600×2)q4	**A**240	1/741	0/740	0·6	0·2
91H NSABP B−23	4**A**60**C**600 vs 6(**C**100×14M40×2**F**600×2)q4	**A**240	2/982	3/978	−0·6	1·2
. **Subtotal iii**			**5/ 2469 (0·2%/y)**	**3/ 2458 (0·1%/y)**	**1·0**	**2·0**
▪ **Subtotal (i + ii + iii)**			**19/ 6956 (0·3%/y)**	**27/ 6953 (0·4%/y)**	**−4·9**	**10·9**
(b) Anthracycline dose/cycle < A60 or E90						
78L2 ONCOFRANCE	12(**F**400×4**A**30**C**300×4**V**1)q4 vs 12(**C**100×14M40×2**F**600×2)q4	**A**360¶	1/131	0/103	0·5	0·2
88R Brussels Belgium	8**E**60**C**500 vs 6(**C**100×14M40×2**F**600×2)q4	**E**480¶	0/236	0/229		
94J1+2+3 GOIRC SANG 2B R1	6(**C**§M§**F**§**V**1·4**E**40×2)q4 vs 6(**C**600×2M40×2**F**600×2)q4	**E**480¶	0/219	0/214		
84L ICCG C/2/84 UK	8(**FE**50**C**)q4 vs 8(**C**600×2M40×2**F**600×2)q4	**E**400¶	1/360	0/355		
80C1 SE Sweden BCG A	8**A**40**C**200×4 vs 8(**C**100×14M40×2**F**600×2)q4	**A**320¶	0/11	0/10		
84N ICCG C/6/89 UK	6**FE**50**C**q4 vs 6(**C**600×2M40×2**F**600×2)q4	**E**300¶	2/445	0/457	1·0	0·5
. **(b) subtotal**			**4/ 1402 (0·3%/y)**	**0/ 1368 (0·0%/y)**	**1·6**	**0·8**
▪ **Total (a + b)**			**23/ 8358 (0·3%/y)**	**27/ 8321 (0·3%/y)**	**−3·3**	**11·7**



■ 99% or ◁▷ 95% confidence intervals

Trend between 3 subtotals: χ^2_1 **= 0·7; 2p > 0·1; NS**

Heterogeneity between 4 subtotals: χ^2_3 **= 6·8; p = 0·08**

Heterogeneity within subtotals: χ^2_{11} **= 8·5; p > 0·1; NS**

Heterogeneity between 15 trials: χ^2_{14} **= 15·3; p > 0·1; NS**

* 97U was (4**E**; 4**CMF**) vs (4**CMF**; 4**E**) vs (6**CMF**), and its controls count twice in subtotal and in total of deaths/woman−years; the study included women with highly proliferative disease, and slightly updated results from it have recently been published (webappendix p66)

Anthracyclines: **A** = doxorubicin (Adriamycin); **E** = Epirubicin

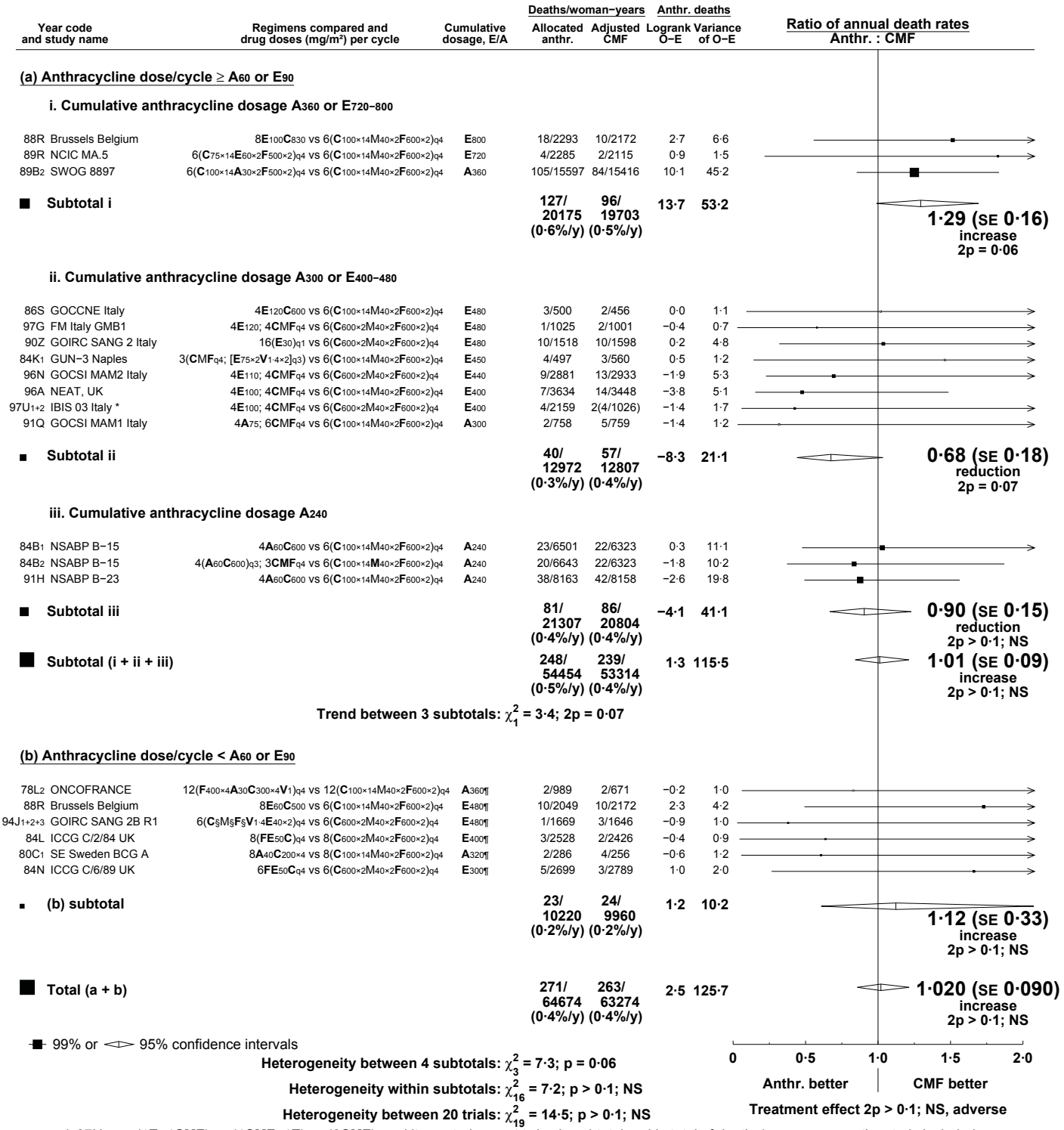
Other agents: **C** = cyclophosphamide; **F** = fluorouracil; **M** = methotrexate; **V** = vincristine
(Not shown: antibiotic, hormonal, local or steroid therapies)

All regimens q3week (unless specified as q4). Semicolon [;] indicates treatment sequence
×2 means d1,8 iv; ×4 means d3−6 iv

¶ Dose less than **E**90 or **A**60 per cycle of anthracycline

§ 94J interwoven drug schedule: anthracycline group omitted **C**, **M** or **F** respectively on cycles (3, 2 or 1) and (6, 5 or 4)

P 31: MORTALITY WITHOUT RECURRENCE in trials of any anthracycline-based regimen vs. standard CMF (or near-standard CMF)



* 97U was (4**E**; 4**CMF**) vs (4**CMF**; 4**E**) vs (6**CMF**), and its controls count twice in subtotal and in total of deaths/woman−years; the study included women with highly proliferative disease, and slightly updated results from it have recently been published (webappendix p66)

Anthracyclines: **A** = doxorubicin (Adriamycin); **E** = Epirubicin

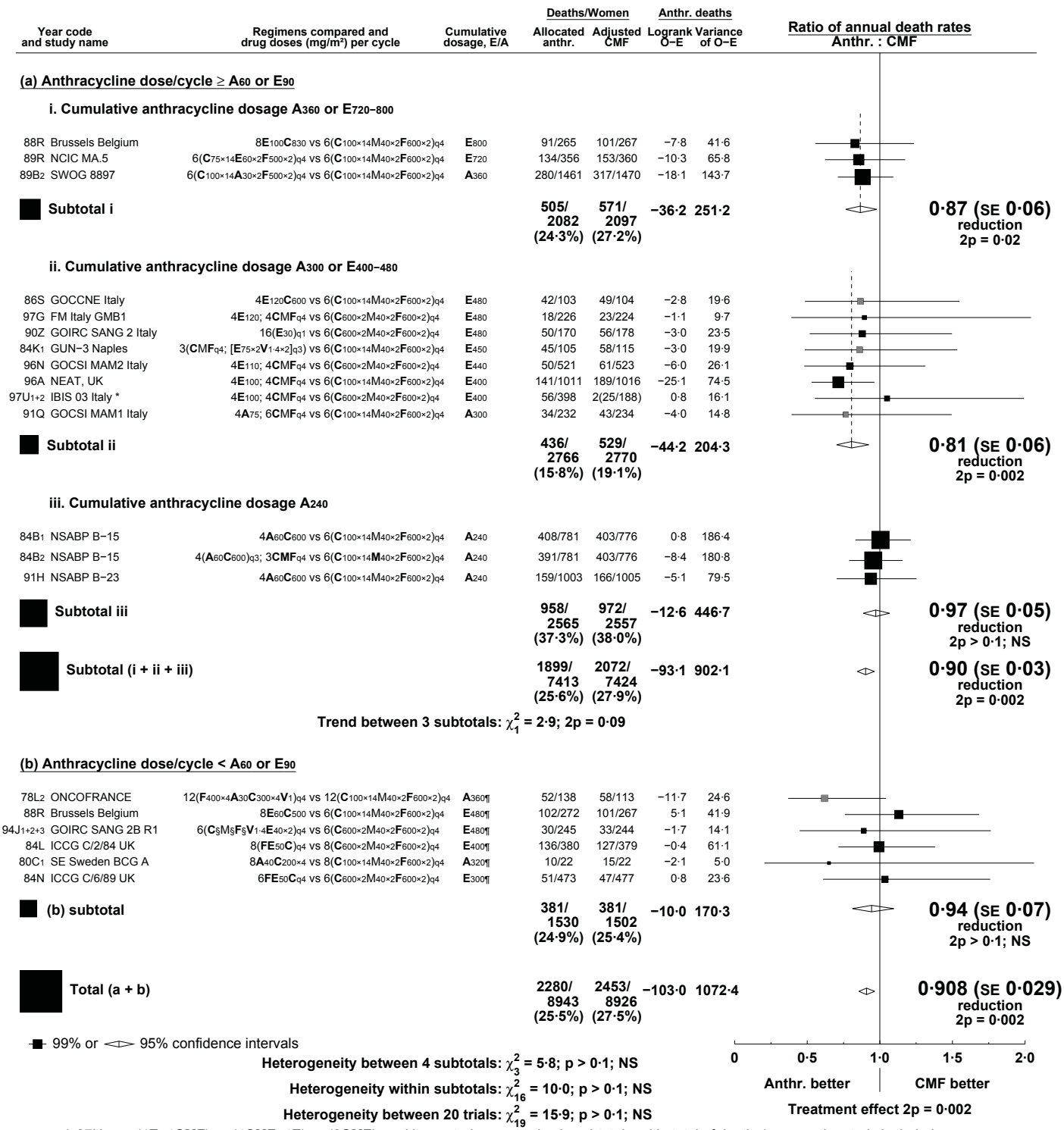
Other agents: **C** = cyclophosphamide; **F** = fluorouracil; **M** = methotrexate; **V** = vincristine
(Not shown: antibiotic, hormonal, local or steroid therapies)

All regimens q3week (unless specified as q4). Semicolon [;] indicates treatment sequence
×2 means d1,8 iv; ×4 means d3−6 iv

¶ Dose less than **E**90 or **A**60 per cycle of anthracycline

§ 94J interwoven drug schedule: anthracycline group omitted **C**, **M** or **F** respectively on cycles (3, 2 or 1) and (6, 5 or 4)

P 32: OVERALL MORTALITY in trials of any anthracycline-based regimen vs. standard CMF (or near-standard CMF)



* 97U was (4**E**; 4**CMF**) vs (4**CMF**; 4**E**) vs (6**CMF**), and its controls count twice in subtotal and in total of deaths/women; the study included women with highly proliferative disease, and slightly updated results from it have recently been published (webappendix p66)

Anthracyclines: **A** = doxorubicin (Adriamycin); **E** = Epirubicin

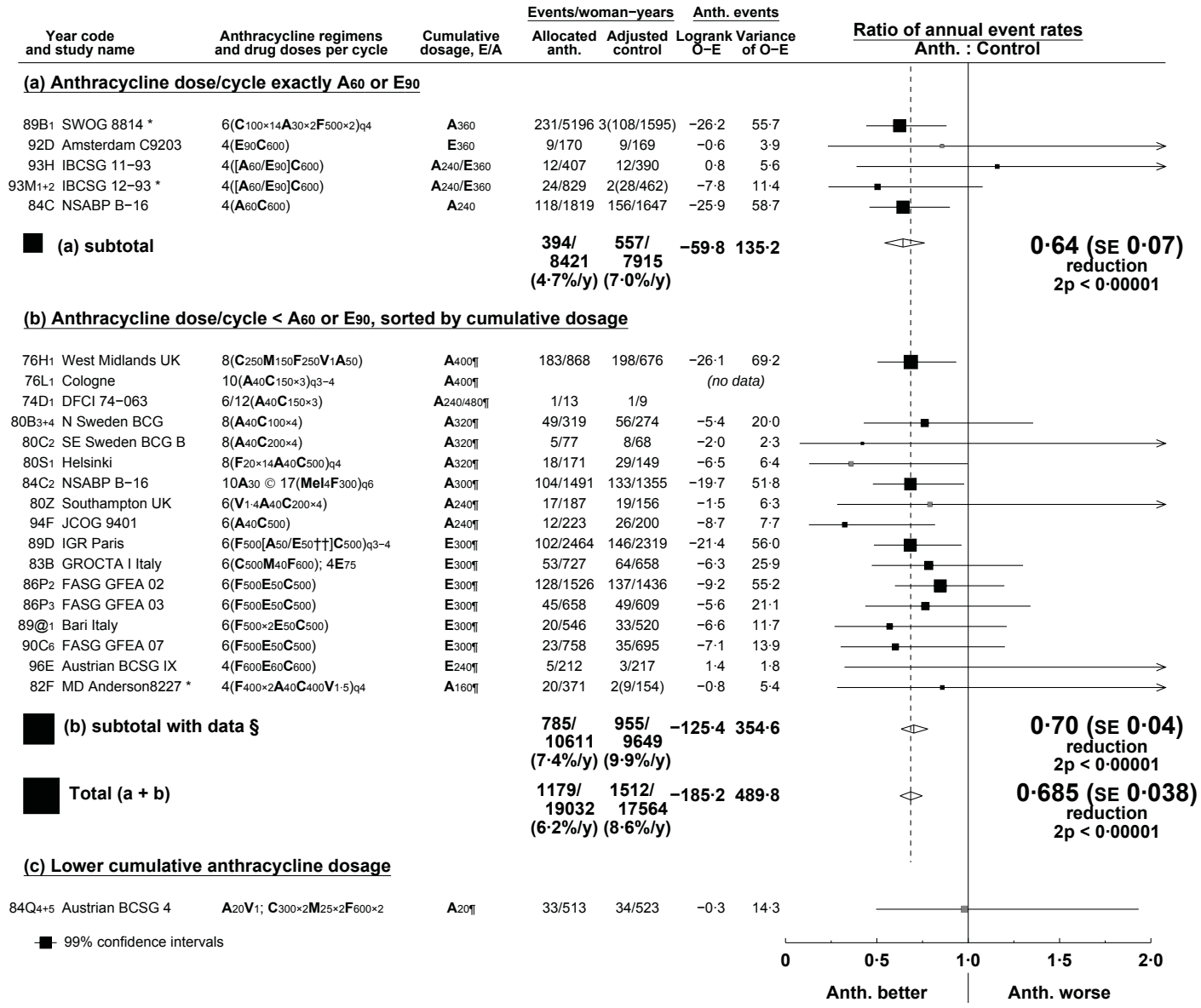
Other agents: **C** = cyclophosphamide; **F** = fluorouracil; **M** = methotrexate; **V** = vincristine
(Not shown: antibiotic, hormonal, local or steroid therapies)

All regimens q3week (unless specified as q4). Semicolon [;] indicates treatment sequence
×2 means d1,8 iv; ×4 means d3−6 iv

¶ Dose less than **E**90 or **A**60 per cycle of anthracycline

§ 94J interwoven drug schedule: anthracycline group omitted **C**, **M** or **F** respectively on cycles (3, 2 or 1) and (6, 5 or 4)

P 33: EARLY RECURRENCE (first 5 years) in trials of any anthracycline-based regimen vs. No chemotherapy



§ 1 trial with no data does not contribute to subtotals or to the overall total.

* For balance, subtotals and totals count control patients 2 or 3 times in trials with 2 or 3 times as many allocated chemotherapy; logrank statistics are unaffected.

Anthracyclines: **A** = doxorubicin (Adriamycin); **E** = Epirubicin

Other agents: **C** = cyclophosphamide; **F** = fluorouracil; **M** = methotrexate; **Mel** = Melphalan; **V** = vincristine
(Not shown: antibiotic, hormonal, local or steroid therapies)

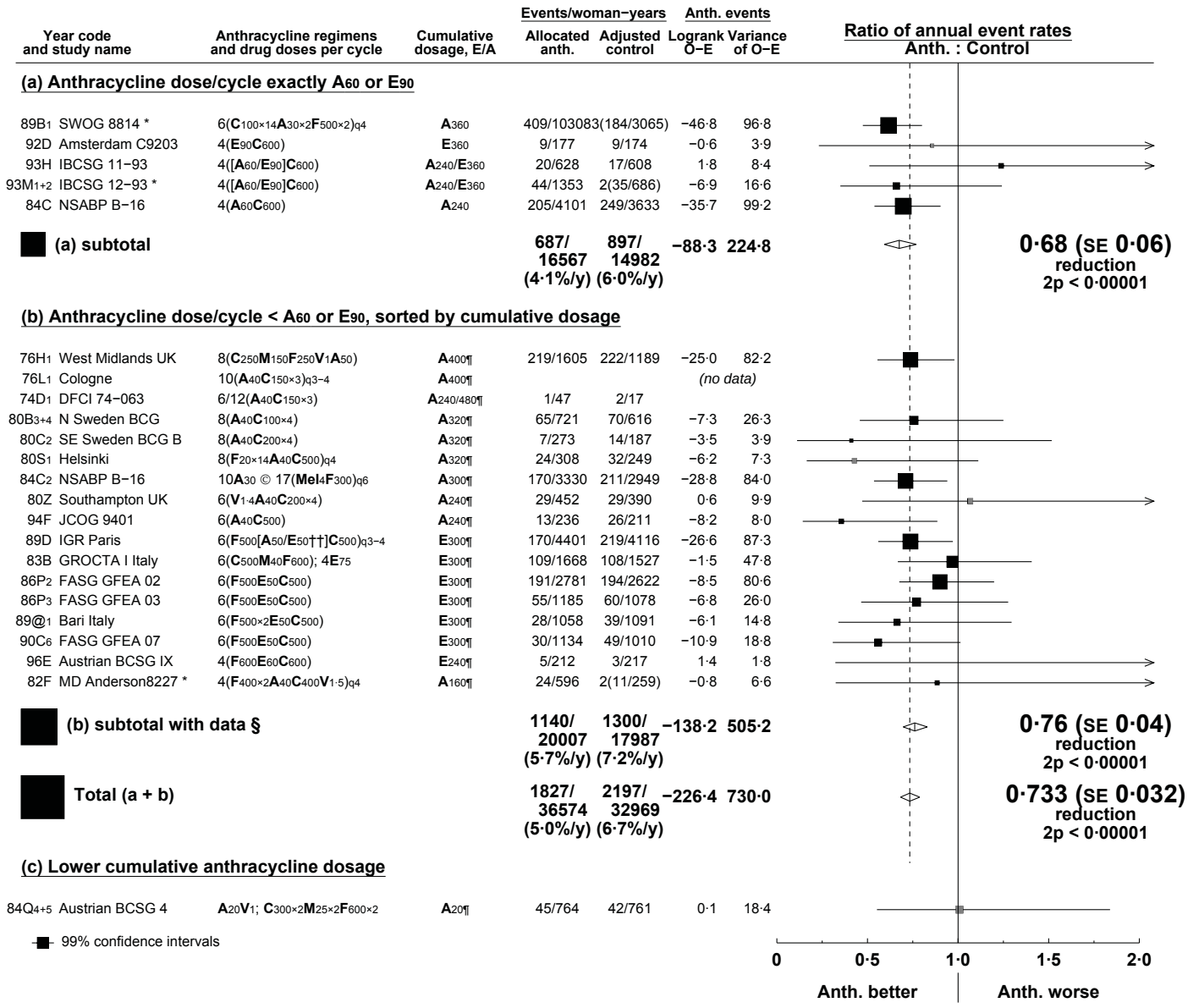
All regimens q3week (unless specified as q4). Semicolon [;] indicates treatment sequence, © indicates concurrent regimens

×2 means d1,8 iv; ×4 means d3−6 iv

¶ Dose less than **A**60 or **E**90 per cycle

††91% given **E**, 9% given **A**

P 34: RECURRENCE in trials of any anthracycline-based regimen vs. No chemotherapy



§ 1 trial with no data does not contribute to subtotals or to the overall total.

* For balance, subtotals and totals count control patients 2 or 3 times in trials with 2 or 3 times as many allocated chemotherapy; logrank statistics are unaffected.

Anthracyclines: **A** = doxorubicin (Adriamycin); **E** = Epirubicin

Other agents: **C** = cyclophosphamide; **F** = fluorouracil; **M** = methotrexate; **Mel** = Melphalan; **V** = vincristine
(Not shown: antibiotic, hormonal, local or steroid therapies)

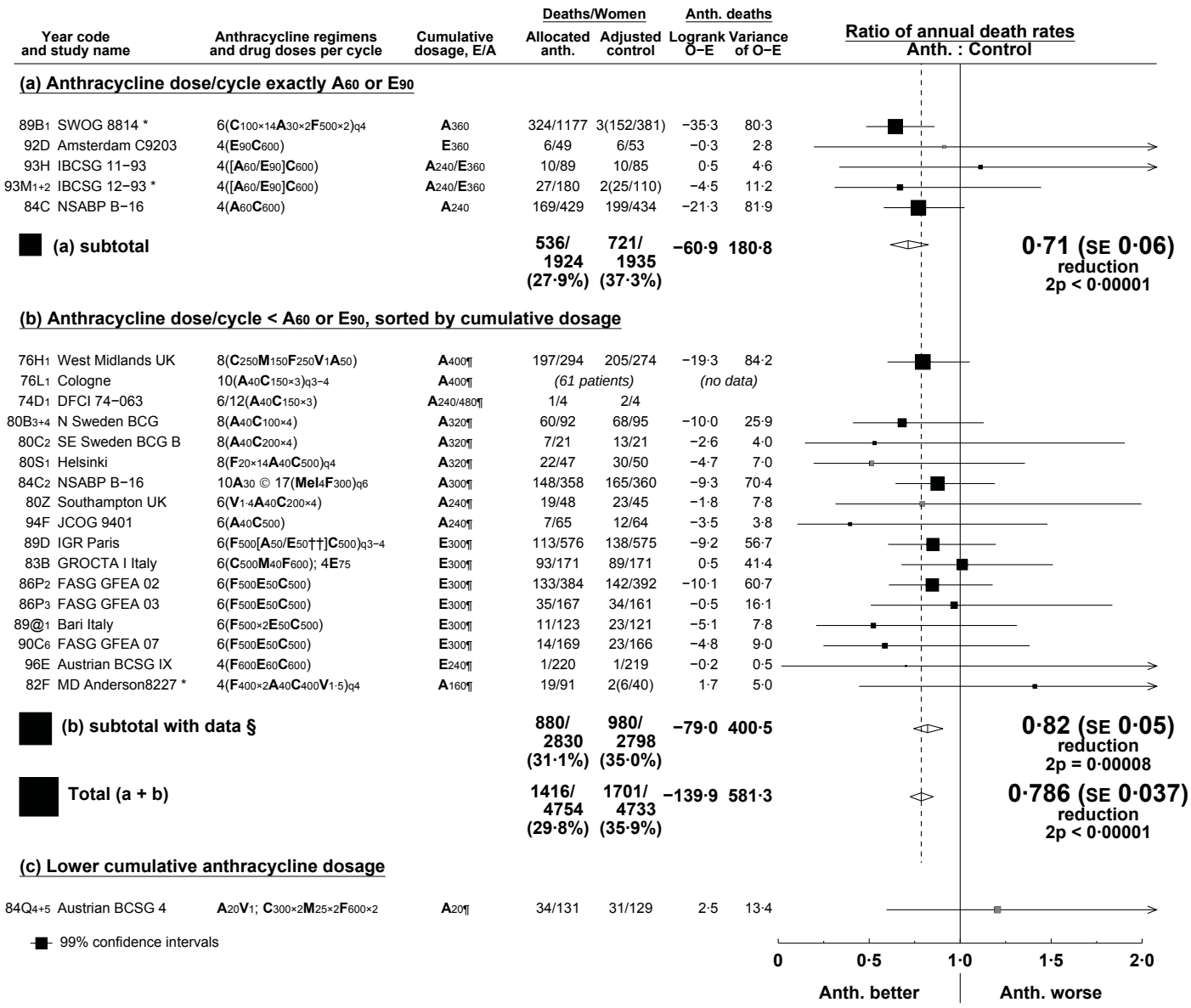
All regimens q3week (unless specified as q4). Semicolon [;] indicates treatment sequence, © indicates concurrent regimens

×2 means d1,8 iv; ×4 means d3−6 iv

¶ Dose less than **A**60 or **E**90 per cycle

††91% given **E**, 9% given **A**

P 35: BREAST CANCER MORTALITY (MORTALITY WITH RECURRENCE) in trials of any anthracycline-based regimen vs. No chemotherapy



§ 1 trial with no data does not contribute to subtotals or to the overall total.

* For balance, subtotals and totals count control patients 2 or 3 times in trials with 2 or 3 times as many allocated chemotherapy; logrank statistics are unaffected.

Anthracyclines: **A** = doxorubicin (Adriamycin); **E** = Epirubicin

Other agents: **C** = cyclophosphamide; **F** = fluorouracil; **M** = methotrexate; **Mel** = Melphalan; **V** = vincristine
(Not shown: antibiotic, hormonal, local or steroid therapies)

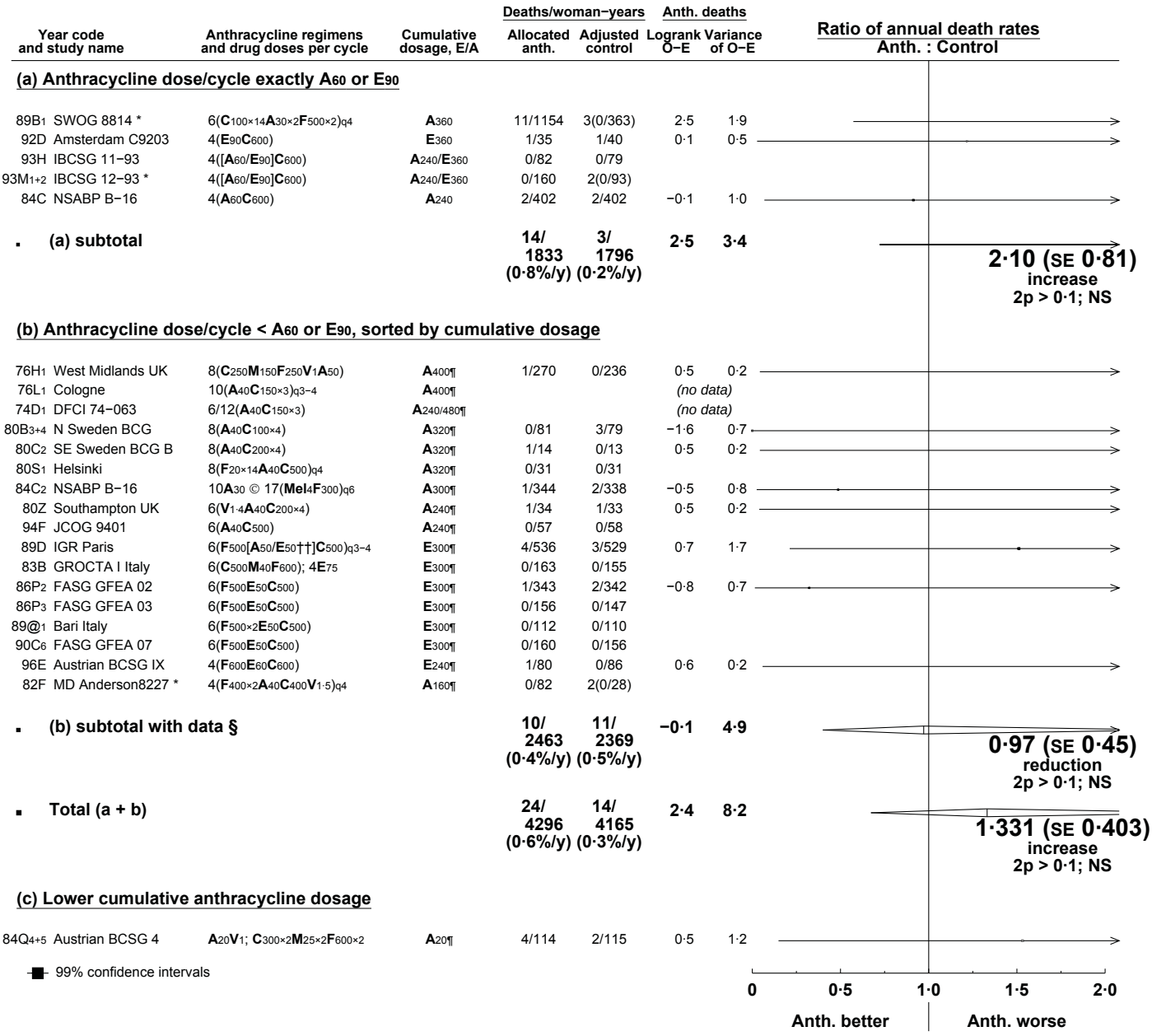
All regimens q3week (unless specified as q4). Semicolon [;] indicates treatment sequence, © indicates concurrent regimens

×2 means d1,8 iv; ×4 means d3−6 iv

¶ Dose less than **A**60 or **E**90 per cycle

††91% given **E**, 9% given **A**

P 36: MORTALITY WITHOUT RECURRENCE IN FIRST YEAR in trials of any anthracycline-based regimen vs. No chemotherapy



§ 2 trials with no data do not contribute to subtotals or to the overall total.

* For balance, subtotals and totals count control patients 2 or 3 times in trials with 2 or 3 times as many allocated chemotherapy; logrank statistics are unaffected.

Anthracyclines: **A** = doxorubicin (Adriamycin); **E** = Epirubicin

Other agents: **C** = cyclophosphamide; **F** = fluorouracil; **M** = methotrexate; **Mel** = Melphalan; **V** = vincristine
(Not shown: antibiotic, hormonal, local or steroid therapies)

All regimens q3week (unless specified as q4). Semicolon [;] indicates treatment sequence, © indicates concurrent regimens

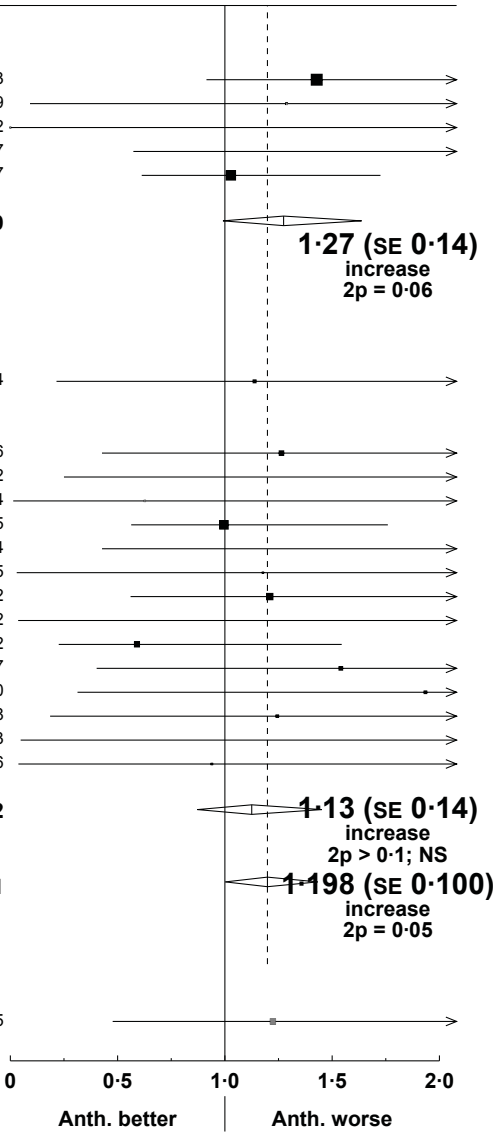
×2 means d1,8 iv; ×4 means d3−6 iv

¶ Dose less than **A**60 or **E**90 per cycle

††91% given **E**, 9% given **A**

P 37: MORTALITY WITHOUT RECURRENCE in trials of any anthracycline-based regimen vs. No chemotherapy

Year code and study name	Anthracycline regimens and drug doses per cycle	Cumulative dosage, E/A	Deaths/woman−years: Allocated anth.	Deaths/woman−years: Adjusted control	Anth. deaths: Logrank O−E	Anth. deaths: Variance of O−E
(a) Anthracycline dose/cycle exactly A_{60} or E_{90}						
89B$_1$ SWOG 8814 *	6(**C**$_{100\times14}$**A**$_{30\times2}$**F**$_{500\times2}$)$_{q4}$	**A**$_{360}$	162/10308	3(33/3065)	11·9	33·3
92D Amsterdam C9203	4(**E**$_{90}$**C**$_{600}$)	**E**$_{360}$	2/177	2/174	0·2	0·9
93H IBCSG 11−93	4([**A**$_{60}$/**E**$_{90}$]**C**$_{600}$)	**A**$_{240}$/**E**$_{360}$	0/628	1/608	−0·4	0·2
93M$_{1+2}$ IBCSG 12−93 *	4([**A**$_{60}$/**E**$_{90}$]**C**$_{600}$)	**A**$_{240}$/**E**$_{360}$	8/1353	2(1/684)	2·4	1·7
84C NSABP B−16	4(**A**$_{60}$**C**$_{600}$)	**A**$_{240}$	61/4101	51/3632	0·7	24·7
(a) subtotal			**233/ 16567 (1·4%/y)**	**155/ 14977 (1·0%/y)**	**14·8**	**60·9**
(b) Anthracycline dose/cycle < A_{60} or E_{90}, sorted by cumulative dosage						
76H$_1$ West Midlands UK	8(**C**$_{250}$**M**$_{150}$**F**$_{250}$**V**$_1$**A**$_{50}$)	**A**$_{400}$¶	6/2324	4/1691	0·3	2·4
76L$_1$ Cologne	10(**A**$_{40}$**C**$_{150\times3}$)$_{q3-4}$	**A**$_{400}$¶			*(no data)*	
74D$_1$ DFCI 74−063	6/12(**A**$_{40}$**C**$_{150\times3}$)	**A**$_{240/480}$¶	2/46	1/16		
80B$_{3+4}$ N Sweden BCG	8(**A**$_{40}$**C**$_{100\times4}$)	**A**$_{320}$¶	14/721	11/616	1·3	5·6
80C$_2$ SE Sweden BCG B	8(**A**$_{40}$**C**$_{200\times4}$)	**A**$_{320}$¶	7/272	3/187	1·2	1·2
80S$_1$ Helsinki	8(**F**$_{20\times14}$**A**$_{40}$**C**$_{500}$)$_{q4}$	**A**$_{320}$¶	2/308	6/249	−0·2	0·4
84C$_2$ NSABP B−16	10**A**$_{30}$ © 17(**Mel**$_4$**F**$_{300}$)$_{q6}$	**A**$_{300}$¶	46/3330	43/2948	−0·1	20·5
80Z Southampton UK	6(**V**$_{1\cdot4}$**A**$_{40}$**C**$_{200\times4}$)	**A**$_{240}$¶	5/452	2/391	1·9	1·4
94F JCOG 9401	6(**A**$_{40}$**C**$_{500}$)	**A**$_{240}$¶	1/235	2/210	0·1	0·5
89D IGR Paris	6(**F**$_{500}$[**A**$_{50}$/**E**$_{50}$††]**C**$_{500}$)$_{q3-4}$	**E**$_{300}$¶	25/4401	21/4116	2·1	11·2
83B GROCTA I Italy	6(**C**$_{500}$**M**$_{40}$**F**$_{600}$); 4**E**$_{75}$	**E**$_{300}$¶	1/1668	0/1526	0·5	0·2
86P$_2$ FASG GFEA 02	6(**F**$_{500}$**E**$_{50}$**C**$_{500}$)	**E**$_{300}$¶	13/2780	20/2619	−3·8	7·2
86P$_3$ FASG GFEA 03	6(**F**$_{500}$**E**$_{50}$**C**$_{500}$)	**E**$_{300}$¶	9/1185	6/1078	1·6	3·7
89@$_1$ Bari Italy	6(**F**$_{500\times2}$**E**$_{50}$**C**$_{500}$)	**E**$_{300}$¶	5/1058	6/1090	1·3	2·0
90C$_6$ FASG GFEA 07	6(**F**$_{500}$**E**$_{50}$**C**$_{500}$)	**E**$_{300}$¶	5/1134	3/1010	0·4	1·8
96E Austrian BCSG IX	4(**F**$_{600}$**E**$_{60}$**C**$_{600}$)	**E**$_{240}$¶	1/212	1/217	0·5	0·3
82F MD Anderson8227 *	4(**F**$_{400\times2}$**A**$_{40}$**C**$_{400}$**V**$_{1\cdot5}$)$_{q4}$	**A**$_{160}$¶	2/596	2(2/259)	0·0	0·6
(b) subtotal with data §			**144/ 20722 (0·7%/y)**	**133/ 18482 (0·7%/y)**	**7·0**	**59·2**
Total (a + b)			**377/ 37289 (1·0%/y)**	**288/ 33459 (0·9%/y)**	**21·7**	**120·1**
(c) Lower cumulative anthracycline dosage						
84Q$_{4+5}$ Austrian BCSG 4	**A**$_{20}$**V**$_1$; **C**$_{300\times2}$**M**$_{25\times2}$**F**$_{600\times2}$	**A**$_{20}$¶	20/764	16/761	1·5	7·5



§ 1 trial with no data does not contribute to subtotals or to the overall total.

* For balance, subtotals and totals count control patients 2 or 3 times in trials with 2 or 3 times as many allocated chemotherapy; logrank statistics are unaffected.

Anthracyclines: **A** = doxorubicin (Adriamycin); **E** = Epirubicin

Other agents: **C** = cyclophosphamide; **F** = fluorouracil; **M** = methotrexate; **Mel** = Melphalan; **V** = vincristine
(Not shown: antibiotic, hormonal, local or steroid therapies)

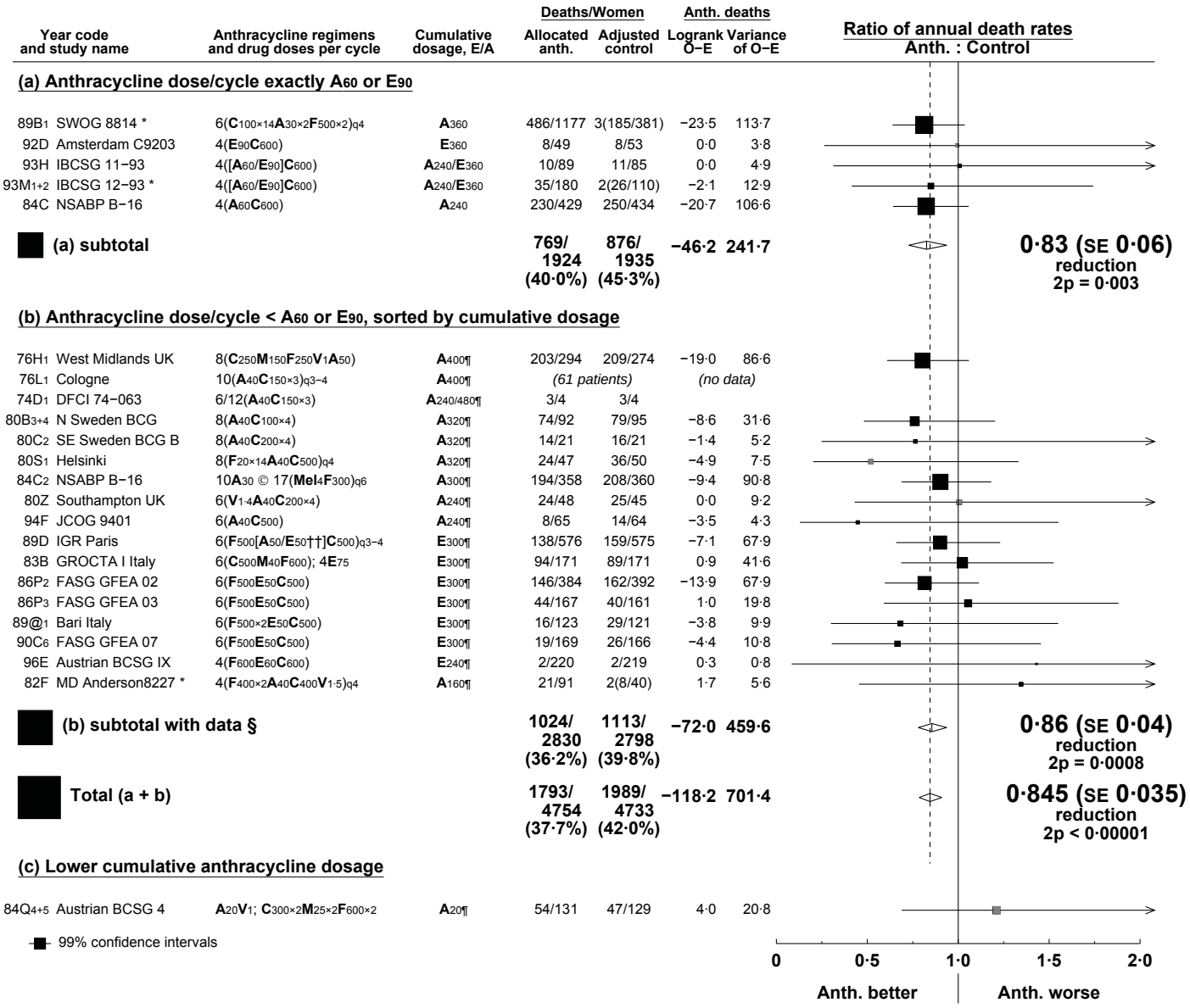
All regimens q3week (unless specified as q4). Semicolon [;] indicates treatment sequence, © indicates concurrent regimens

×2 means d1,8 iv; ×4 means d3−6 iv

¶ Dose less than A_{60} or E_{90} per cycle

††91% given **E**, 9% given **A**

P 38: OVERALL MORTALITY in trials of any anthracycline-based regimen vs. No chemotherapy



§ 1 trial with no data does not contribute to subtotals or to the overall total.

* For balance, subtotals and totals count control patients 2 or 3 times in trials with 2 or 3 times as many allocated chemotherapy; logrank statistics are unaffected.

Anthracyclines: **A** = doxorubicin (Adriamycin); **E** = Epirubicin

Other agents: **C** = cyclophosphamide; **F** = fluorouracil; **M** = methotrexate; **Mel** = Melphalan; **V** = vincristine
(Not shown: antibiotic, hormonal, local or steroid therapies)

All regimens q3week (unless specified as q4). Semicolon [;] indicates treatment sequence, © indicates concurrent regimens

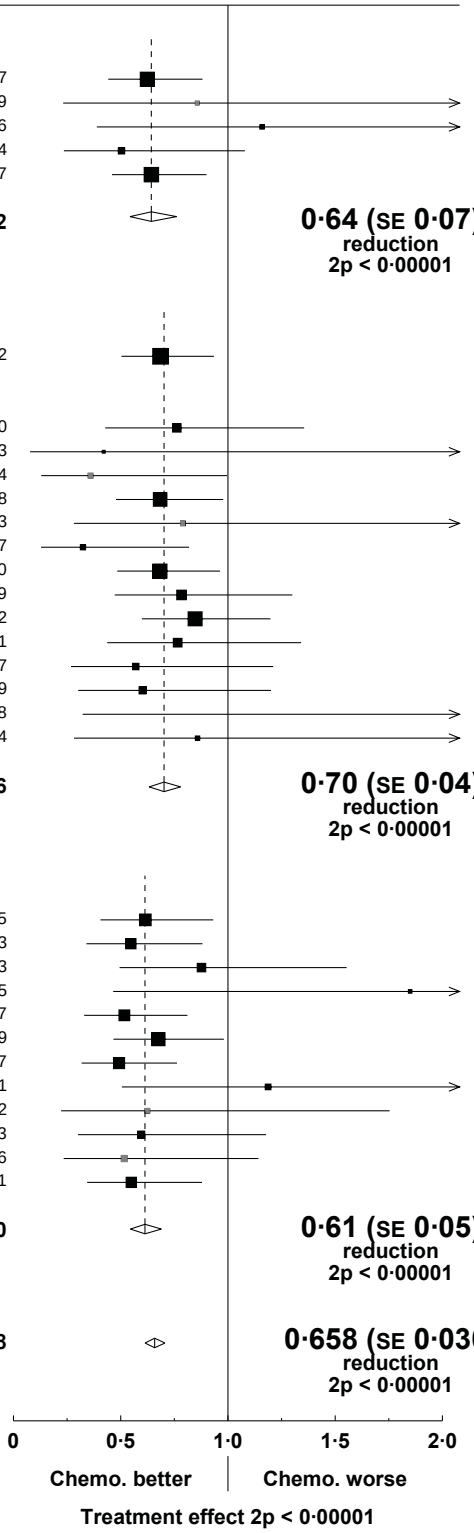
×2 means d1,8 iv; ×4 means d3−6 iv

¶ Dose less than **A**60 or **E**90 per cycle

††91% given **E**, 9% given **A**

P 39: EARLY RECURRENCE (first 5 years) in trials of anthracycline-based regimen (eg, standard 4AC) or standard CMF (or near-standard CMF) vs. No chemotherapy

Year code and study name	Regimens and drug doses per cycle	Cumulative dosage, E/A	Events/woman-years: Allocated chemo.	Events/woman-years: Adjusted control	Chemo. events: Logrank O−E	Chemo. events: Variance of O−E
(a) Anthracycline dose/cycle exactly A_{60} or E_{90}						
89B$_1$ SWOG 8814 *	6(**C**$_{100\times14}$**A**$_{30\times2}$**F**$_{500\times2}$)$_{q4}$	**A**$_{360}$	231/5196	3(108/1595)	−26·2	55·7
92D Amsterdam C9203	4(**E**$_{90}$**C**$_{600}$)$_{q3}$	**E**$_{360}$	9/170	9/169	−0·6	3·9
93H IBCSG 11−93	4([**A**$_{60}$/**E**$_{90}$]**C**$_{600}$)$_{q3}$	**A**$_{240}$/**E**$_{360}$	12/407	12/390	0·8	5·6
93M$_{1+2}$ IBCSG 12−93 *	4([**A**$_{60}$/**E**$_{90}$]**C**$_{600}$)$_{q3}$	**A**$_{240}$/**E**$_{360}$	24/829	2(28/462)	−7·8	11·4
84C NSABP B−16	4(**A**$_{60}$**C**$_{600}$)$_{q3}$	**A**$_{240}$	118/1819	156/1647	−25·9	58·7
(a) subtotal			**394/ 8421 (4·7%/y)**	**557/ 7915 (7·0%/y)**	**−59·8**	**135·2**
(b) Anthracycline dose/cycle < A_{60} or E_{90}, sorted by cumulative dosage §						
76H$_1$ West Midlands UK	8(**C**$_{250}$**M**$_{150}$**F**$_{250}$**V**$_1$**A**$_{50}$)	**A**$_{400¶}$	183/868	198/676	−26·1	69·2
76L$_1$ Cologne	10(**A**$_{40}$**C**$_{150\times3}$)$_{q3-4}$	**A**$_{400¶}$			*(no data)*	
74D$_1$ DFCI 74−063	6/12(**A**$_{40}$**C**$_{150\times3}$)$_{q3}$	**A**$_{240/480¶}$	1/13	1/9		
80B$_{3+4}$ N Sweden BCG	8(**A**$_{40}$**C**$_{100\times4}$)$_{q3}$	**A**$_{320¶}$	49/319	56/274	−5·4	20·0
80C$_2$ SE Sweden BCG B	8(**A**$_{40}$**C**$_{200\times4}$)$_{q3}$	**A**$_{320¶}$	5/77	8/68	−2·0	2·3
80S$_1$ Helsinki	8(**F**$_{20\times14}$**A**$_{40}$**C**$_{500}$)$_{q4}$	**A**$_{320¶}$	18/171	29/149	−6·5	6·4
84C$_2$ NSABP B−16	10**A**$_{30}$ © 17(**Mel**$_4$**F**$_{300}$)$_{q6}$	**A**$_{300¶}$	104/1491	133/1355	−19·7	51·8
80Z Southampton UK	6(**V**$_{1\cdot4}$**A**$_{40}$**C**$_{200\times4}$)$_{q3}$	**A**$_{240¶}$	17/187	19/156	−1·5	6·3
94F JCOG 9401	6(**A**$_{40}$**C**$_{500}$)$_{q3}$	**A**$_{240¶}$	12/223	26/200	−8·7	7·7
89D IGR Paris	6(**F**$_{500}$[**A**$_{50}$/**E**$_{50}$††]**C**$_{500}$)$_{q3-4}$	**E**$_{300¶}$	102/2464	146/2319	−21·4	56·0
83B GROCTA I Italy	6(**C**$_{500}$**M**$_{40}$**F**$_{600}$)$_{q3}$; 4**E**$_{75q3}$	**E**$_{300¶}$	53/727	64/658	−6·3	25·9
86P$_2$ FASG GFEA 02	6(**F**$_{500}$**E**$_{50}$**C**$_{500}$)$_{q3}$	**E**$_{300¶}$	128/1526	137/1436	−9·2	55·2
86P$_3$ FASG GFEA 03	6(**F**$_{500}$**E**$_{50}$**C**$_{500}$)$_{q3}$	**E**$_{300¶}$	45/658	49/609	−5·6	21·1
89@$_1$ Bari Italy	6(**F**$_{500\times2}$**E**$_{50}$**C**$_{500}$)$_{q3}$	**E**$_{300¶}$	20/546	33/520	−6·6	11·7
90C$_6$ FASG GFEA 07	6(**F**$_{500}$**E**$_{50}$**C**$_{500}$)$_{q3}$	**E**$_{300¶}$	23/758	35/695	−7·1	13·9
96E Austrian BCSG IX	4(**F**$_{600}$**E**$_{60}$**C**$_{600}$)$_{q3}$	**E**$_{240¶}$	5/212	3/217	1·4	1·8
82F MD Anderson8227 *	4(**F**$_{400\times2}$**A**$_{40}$**C**$_{400}$**V**$_{1\cdot5}$)$_{q4}$	**A**$_{160¶}$	20/371	2(9/154)	−0·8	5·4
(b) subtotal with data §			**785/ 10611 (7·4%/y)**	**955/ 9649 (9·9%/y)**	**−125·4**	**354·6**
(c) Standard CMF (or near-standard CMF)						
73B INT Milan 7205	12(**C**$_{100\times14}$**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$		95/787	98/555	−18·7	38·5
78K$_3$ IBCSG/Ludwig III	12(**C**$_{100\times14}$**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$		59/608	88/488	−17·6	29·3
78V$_2$ ECOG EST6177	12(**C**$_{100\times14}$**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$		52/264	57/268	−2·7	20·3
79U$_{1+3}$ Vienna Gyn.	6(**C**$_{100\times14}$**M**$_{50\times2}$**F**$_{750\times2}$)$_{q4}$		14/109	9/108	2·1	3·5
81H EST1180/SW.8294	6(**C**$_{100\times14}$**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$		53/1153	89/1009	−21·6	32·7
86H$_2$ IBCSG VII	6(**C**$_{100\times14}$**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$		96/1248	126/1177	−18·7	47·9
88C NSABP B−20	6(**C**$_{100\times14}$**M**$_{100\times2}$**F**$_{600\times2}$)$_{q4}$		48/3756	95/3681	−24·6	34·7
89A$_2$ SITAM−01	6([**C**$_{100\times14}$/**C**$_{600\times2}$]**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$		26/208	19/185	1·6	9·1
89E$_{4+9}$ GROCTA V Italy	6(**C**$_{600\times2}$**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$		14/152	20/124	−2·9	6·2
89V Romagnolo Italy	6(**C**$_{100\times14}$**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$		23/621	38/603	−7·4	14·3
90P Amsterdam C8913	6(**C**$_{100\times14}$**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$		20/542	27/398	−7·0	10·6
90S IBCSG VIII	6(**C**$_{100\times14}$**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$		49/1834	82/1721	−18·0	30·1
(c) subtotal			**549/ 11282 (4·9%/y)**	**748/ 10317 (7·3%/y)**	**−135·5**	**277·0**
Total (a + b + c)			**1728/ 30314 (5·7%/y)**	**2260/ 27881 (8·1%/y)**	**−320·7**	**766·8**



99% or 95% confidence intervals

Heterogeneity between 3 subtotals: $\chi^2_2 = 2{\cdot}9$; p > 0·1; NS

Heterogeneity within subtotals: $\chi^2_{29} = 32{\cdot}2$; p > 0·1; NS

Heterogeneity between 32 trials: $\chi^2_{31} = 35{\cdot}1$; p > 0·1; NS

§ 1 trial with no data does not contribute to subtotals or to the overall total.

Anthracyclines: **A** = doxorubicin (Adriamycin); **E** = Epirubicin

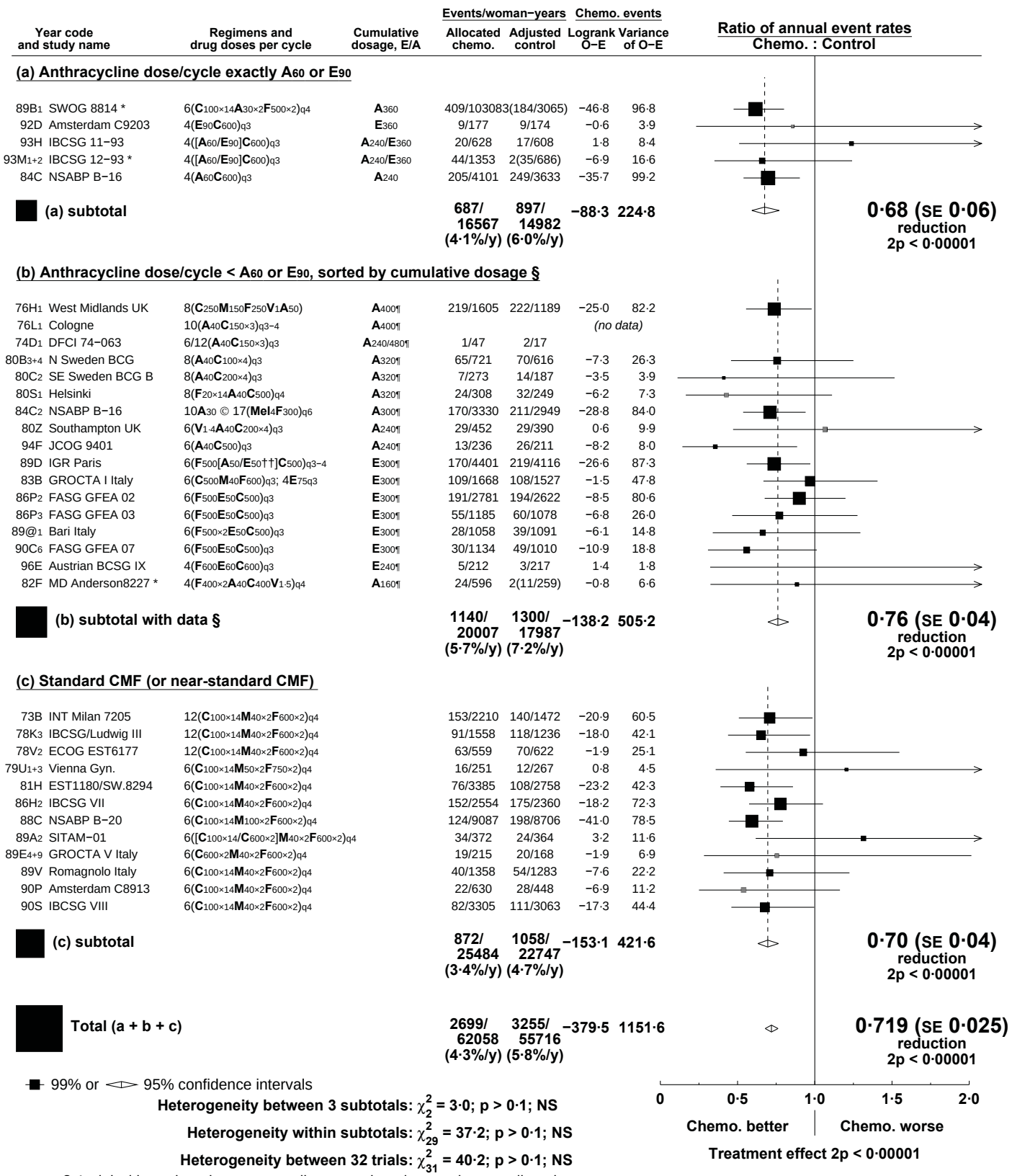
Other agents: **C** = cyclophosphamide; **F** = fluorouracil; **M** = methotrexate; **Mel** = Melphalan; **V** = vincristine
(Not shown: antibiotic, hormonal, local or steroid therapies)

×2 means d1,8 iv; ×4 means d3−6 iv

¶ Dose less than A_{60} or E_{90} per cycle

††91% given **E**, 9% given **A**

P 40: RECURRENCE in trials of anthracycline-based regimen (eg, standard 4AC) or standard CMF (or near-standard CMF) vs. No chemotherapy



Heterogeneity between 3 subtotals: $\chi^2_2 = 3{\cdot}0$; p > 0·1; NS

Heterogeneity within subtotals: $\chi^2_{29} = 37{\cdot}2$; p > 0·1; NS

Heterogeneity between 32 trials: $\chi^2_{31} = 40{\cdot}2$; p > 0·1; NS

§ 1 trial with no data does not contribute to subtotals or to the overall total.

Anthracyclines: **A** = doxorubicin (Adriamycin); **E** = Epirubicin

Other agents: **C** = cyclophosphamide; **F** = fluorouracil; **M** = methotrexate; **Mel** = Melphalan; **V** = vincristine

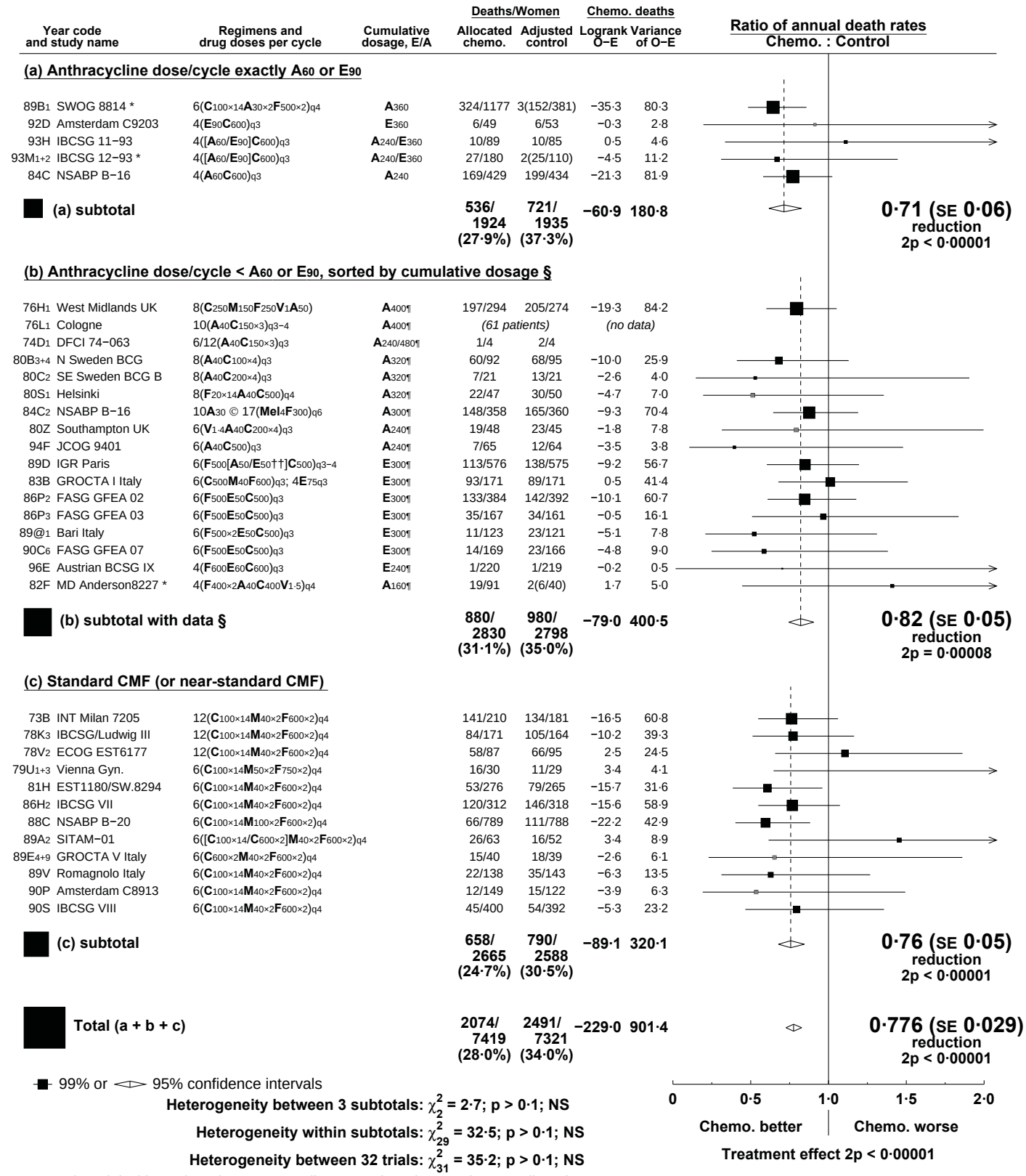
(Not shown: antibiotic, hormonal, local or steroid therapies)

×2 means d1,8 iv; ×4 means d3−6 iv

¶ Dose less than **A**60 or **E**90 per cycle

††91% given **E**, 9% given **A**

P 41: BREAST CANCER MORTALITY (MORTALITY WITH RECURRENCE) in trials of anthracycline-based regimen (eg, standard 4AC) or standard CMF (or near-standard CMF) vs. No chemotherapy



§ 1 trial with no data does not contribute to subtotals or to the overall total.

Anthracyclines: **A** = doxorubicin (Adriamycin); **E** = Epirubicin
Other agents: **C** = cyclophosphamide; **F** = fluorouracil; **M** = methotrexate; **MeI** = Melphalan; **V** = vincristine
(Not shown: antibiotic, hormonal, local or steroid therapies)
×2 means d1,8 iv; ×4 means d3−6 iv
¶ Dose less than **A**60 or **E**90 per cycle
††91% given **E**, 9% given **A**

P 42: MORTALITY WITHOUT RECURRENCE IN FIRST YEAR in trials of anthracycline-based regimen (eg, standard 4AC) or standard CMF (or near-standard CMF) vs. No chemotherapy

Year code and study name	Regimens and drug doses per cycle	Cumulative dosage, E/A	Deaths/woman−years: Allocated chemo.	Deaths/woman−years: Adjusted control	Chemo. deaths: Logrank O−E	Chemo. deaths: Variance of O−E
(a) Anthracycline dose/cycle exactly A_{60} or E_{90}						
89B$_1$ SWOG 8814 *	6(**C**$_{100\times14}$**A**$_{30\times2}$**F**$_{500\times2}$)$_{q4}$	**A**$_{360}$	11/1154	3(0/363)	2·5	1·9
92D Amsterdam C9203	4(**E**$_{90}$**C**$_{600}$)$_{q3}$	**E**$_{360}$	1/35	1/40	0·1	0·5
93H IBCSG 11−93	4([**A**$_{60}$/**E**$_{90}$]**C**$_{600}$)$_{q3}$	**A**$_{240}$/**E**$_{360}$	0/82	0/79		
93M$_{1+2}$ IBCSG 12−93 *	4([**A**$_{60}$/**E**$_{90}$]**C**$_{600}$)$_{q3}$	**A**$_{240}$/**E**$_{360}$	0/160	2(0/93)		
84C NSABP B−16	4(**A**$_{60}$**C**$_{600}$)$_{q3}$	**A**$_{240}$	2/402	2/402	−0·1	1·0
▪ **(a) subtotal**			**14/ 1833 (0·8%/y)**	**3/ 1796 (0·2%/y)**	**2·5**	**3·4**
(b) Anthracycline dose/cycle < A_{60} or E_{90}, sorted by cumulative dosage §						
76H$_1$ West Midlands UK	8(**C**$_{250}$**M**$_{150}$**F**$_{250}$**V**$_1$**A**$_{50}$)	**A**$_{400}$¶	1/270	0/236	0·5	0·2
76L$_1$ Cologne	10(**A**$_{40}$**C**$_{150\times3}$)$_{q3-4}$	**A**$_{400}$¶			*(no data)*	
74D$_1$ DFCI 74−063	6/12(**A**$_{40}$**C**$_{150\times3}$)$_{q3}$	**A**$_{240/480}$¶			*(no data)*	
80B$_{3+4}$ N Sweden BCG	8(**A**$_{40}$**C**$_{100\times4}$)$_{q3}$	**A**$_{320}$¶	0/81	3/79	−1·6	0·7
80C$_2$ SE Sweden BCG B	8(**A**$_{40}$**C**$_{200\times4}$)$_{q3}$	**A**$_{320}$¶	1/14	0/13	0·5	0·2
80S$_1$ Helsinki	8(**F**$_{20\times14}$**A**$_{40}$**C**$_{500}$)$_{q4}$	**A**$_{320}$¶	0/31	0/31		
84C$_2$ NSABP B−16	10**A**$_{30}$ © 17(**Mel**$_4$**F**$_{300}$)$_{q6}$	**A**$_{300}$¶	1/344	2/338	−0·5	0·8
80Z Southampton UK	6(**V**$_{1\cdot4}$**A**$_{40}$**C**$_{200\times4}$)$_{q3}$	**A**$_{240}$¶	1/34	1/33	0·5	0·2
94F JCOG 9401	6(**A**$_{40}$**C**$_{500}$)$_{q3}$	**A**$_{240}$¶	0/57	0/58		
89D IGR Paris	6(**F**$_{500}$[**A**$_{50}$/**E**$_{50}$††]**C**$_{500}$)$_{q3-4}$	**E**$_{300}$¶	4/536	3/529	0·7	1·7
83B GROCTA I Italy	6(**C**$_{500}$**M**$_{40}$**F**$_{600}$)$_{q3}$; 4**E**$_{75q3}$	**E**$_{300}$¶	0/163	0/155		
86P$_2$ FASG GFEA 02	6(**F**$_{500}$**E**$_{50}$**C**$_{500}$)$_{q3}$	**E**$_{300}$¶	1/343	2/342	−0·8	0·7
86P$_3$ FASG GFEA 03	6(**F**$_{500}$**E**$_{50}$**C**$_{500}$)$_{q3}$	**E**$_{300}$¶	0/156	0/147		
89@$_1$ Bari Italy	6(**F**$_{500\times2}$**E**$_{50}$**C**$_{500}$)$_{q3}$	**E**$_{300}$¶	0/112	0/110		
90C$_6$ FASG GFEA 07	6(**F**$_{500}$**E**$_{50}$**C**$_{500}$)$_{q3}$	**E**$_{300}$¶	0/160	0/156		
96E Austrian BCSG IX	4(**F**$_{600}$**E**$_{60}$**C**$_{600}$)$_{q3}$	**E**$_{240}$¶	1/80	0/86	0·6	0·2
82F MD Anderson8227 *	4(**F**$_{400\times2}$**A**$_{40}$**C**$_{400}$**V**$_{1\cdot5}$)$_{q4}$	**A**$_{160}$¶	0/82	2(0/28)		
▪ **(b) subtotal with data §**			**10/ 2463 (0·4%/y)**	**11/ 2369 (0·5%/y)**	**−0·1**	**4·9**
(c) Standard CMF (or near-standard CMF)						
73B INT Milan 7205	12(**C**$_{100\times14}$**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$		1/198	1/160	−0·1	0·5
78K$_3$ IBCSG/Ludwig III	12(**C**$_{100\times14}$**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$		6/148	1/138	2·5	1·7
78V$_2$ ECOG EST6177	12(**C**$_{100\times14}$**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$		1/78	0/77	0·5	0·2
79U$_{1+3}$ Vienna Gyn.	6(**C**$_{100\times14}$**M**$_{50\times2}$**F**$_{750\times2}$)$_{q4}$		0/18	0/19		
81H EST1180/SW.8294	6(**C**$_{100\times14}$**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$		3/258	1/248	0·9	1·0
86H$_2$ IBCSG VII	6(**C**$_{100\times14}$**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$		3/292	2/289	0·7	1·2
88C NSABP B−20	6(**C**$_{100\times14}$**M**$_{100\times2}$**F**$_{600\times2}$)$_{q4}$		1/774	0/777	0·5	0·2
89A$_2$ SITAM−01	6([**C**$_{100\times14}$/**C**$_{600\times2}$]**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$		0/45	0/39		
89E$_{4+9}$ GROCTA V Italy	6(**C**$_{600\times2}$**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$		0/32	0/28		
89V Romagnolo Italy	6(**C**$_{100\times14}$**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$		1/132	0/137	0·5	0·2
90P Amsterdam C8913	6(**C**$_{100\times14}$**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$		0/141	0/112		
90S IBCSG VIII	6(**C**$_{100\times14}$**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$		0/377	0/371		
▪ **(c) subtotal**			**16/ 2493 (0·6%/y)**	**5/ 2395 (0·2%/y)**	**5·5**	**5·2**
▪ **Total (a + b + c)**			**40/ 6789 (0·6%/y)**	**19/ 6560 (0·3%/y)**	**7·8**	**13·4**

Ratio of annual death rates
Chemo. : Control

2·10 (SE 0·81)
increase
2p > 0·1; NS

0·97 (SE 0·45)
reduction
2p > 0·1; NS

2·88 (SE 0·78)
increase
2p = 0·02

1·792 (SE 0·371)
increase
2p = 0·03

0 0·5 1·0 1·5 2·0

Chemo. better | **Chemo. worse**

Treatment effect 2p = 0·03, adverse

■ 99% or ◁▷ 95% confidence intervals

Heterogeneity between 3 subtotals: χ^2_2 = 3·1; p > 0·1; NS

Heterogeneity within subtotals: χ^2_{15} = 12·9; p > 0·1; NS

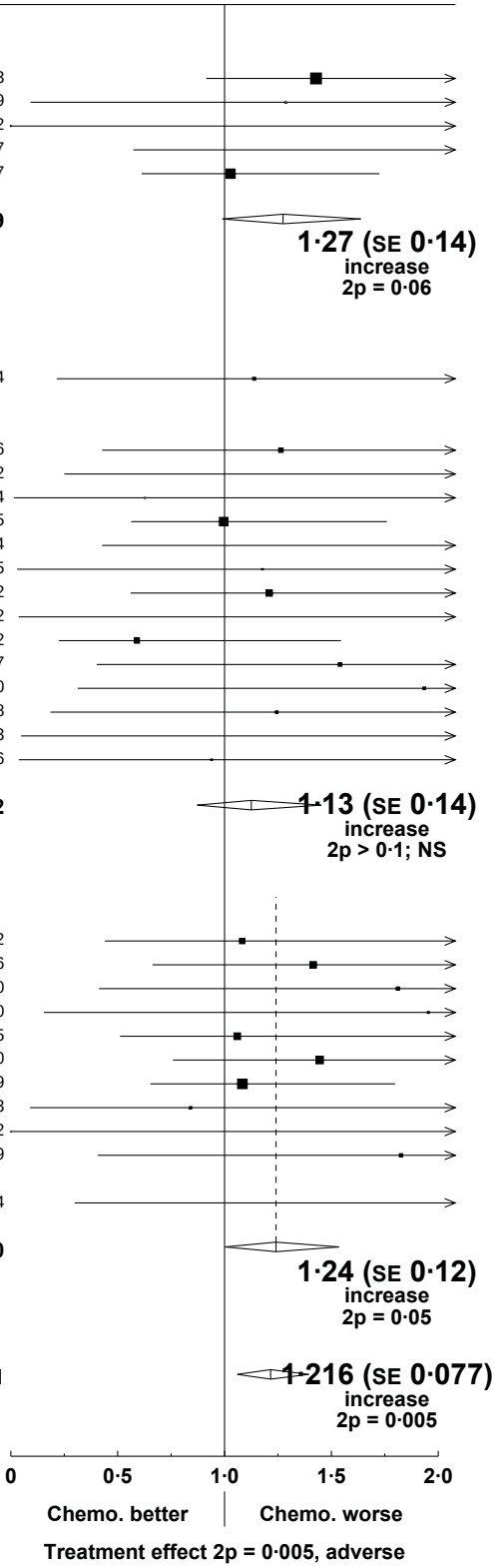
Heterogeneity between 18 trials: χ^2_{17} = 16·0; p > 0·1; NS

§ 2 trials with no data do not contribute to subtotals or to the overall total.

Anthracyclines: **A** = doxorubicin (Adriamycin); **E** = Epirubicin
Other agents: **C** = cyclophosphamide; **F** = fluorouracil; **M** = methotrexate; **Mel** = Melphalan; **V** = vincristine
(Not shown: antibiotic, hormonal, local or steroid therapies)
×2 means d1,8 iv; ×4 means d3−6 iv
¶ Dose less than A_{60} or E_{90} per cycle
††91% given **E**, 9% given **A**

P 43: MORTALITY WITHOUT RECURRENCE in trials of anthracycline-based regimen (eg, standard 4AC) or standard CMF (or near-standard CMF) vs. No chemotherapy

Year code and study name	Regimens and drug doses per cycle	Cumulative dosage, E/A	Deaths/woman-years: Allocated chemo.	Deaths/woman-years: Adjusted control	Chemo. deaths: Logrank O−E	Chemo. deaths: Variance of O−E
(a) Anthracycline dose/cycle exactly A_{60} or E_{90}						
89B$_1$ SWOG 8814 *	6(**C**$_{100\times14}$**A**$_{30\times2}$**F**$_{500\times2}$)$_{q4}$	**A**$_{360}$	162/10308	3(33/3065)	11·9	33·3
92D Amsterdam C9203	4(**E**$_{90}$**C**$_{600}$)$_{q3}$	**E**$_{360}$	2/177	2/174	0·2	0·9
93H IBCSG 11−93	4([**A**$_{60}$/**E**$_{90}$]**C**$_{600}$)$_{q3}$	**A**$_{240}$/**E**$_{360}$	0/628	1/608	−0·4	0·2
93M$_{1+2}$ IBCSG 12−93 *	4([**A**$_{60}$/**E**$_{90}$]**C**$_{600}$)$_{q3}$	**A**$_{240}$/**E**$_{360}$	8/1353	2(1/684)	2·4	1·7
84C NSABP B−16	4(**A**$_{60}$**C**$_{600}$)$_{q3}$	**A**$_{240}$	61/4101	51/3632	0·7	24·7
(a) subtotal			**233/ 16567 (1·4%/y)**	**155/ 14977 (1·0%/y)**	**14·8**	**60·9**
(b) Anthracycline dose/cycle < A_{60} or E_{90}, sorted by cumulative dosage §						
76H$_1$ West Midlands UK	8(**C**$_{250}$**M**$_{150}$**F**$_{250}$**V**$_1$**A**$_{50}$)	**A**$_{400}$¶	6/2324	4/1691	0·3	2·4
76L$_1$ Cologne	10(**A**$_{40}$**C**$_{150\times3}$)$_{q3-4}$	**A**$_{400}$¶			*(no data)*	
74D$_1$ DFCI 74−063	6/12(**A**$_{40}$**C**$_{150\times3}$)$_{q3}$	**A**$_{240/480}$¶	2/46	1/16		
80B$_{3+4}$ N Sweden BCG	8(**A**$_{40}$**C**$_{100\times4}$)$_{q3}$	**A**$_{320}$¶	14/721	11/616	1·3	5·6
80C$_2$ SE Sweden BCG B	8(**A**$_{40}$**C**$_{200\times4}$)$_{q3}$	**A**$_{320}$¶	7/272	3/187	1·2	1·2
80S$_1$ Helsinki	8(**F**$_{20\times14}$**A**$_{40}$**C**$_{500}$)$_{q4}$	**A**$_{320}$¶	2/308	6/249	−0·2	0·4
84C$_2$ NSABP B−16	10**A**$_{30}$ © 17(**Mel**$_4$**F**$_{300}$)$_{q6}$	**A**$_{300}$¶	46/3330	43/2948	−0·1	20·5
80Z Southampton UK	6(**V**$_{1\cdot4}$**A**$_{40}$**C**$_{200\times4}$)$_{q3}$	**A**$_{240}$¶	5/452	2/391	1·9	1·4
94F JCOG 9401	6(**A**$_{40}$**C**$_{500}$)$_{q3}$	**A**$_{240}$¶	1/235	2/210	0·1	0·5
89D IGR Paris	6(**F**$_{500}$[**A**$_{50}$/**E**$_{50}$††]**C**$_{500}$)$_{q3-4}$	**E**$_{300}$¶	25/4401	21/4116	2·1	11·2
83B GROCTA I Italy	6(**C**$_{500}$**M**$_{40}$**F**$_{600}$)$_{q3}$; 4**E**$_{75q3}$	**E**$_{300}$¶	1/1668	0/1526	0·5	0·2
86P$_2$ FASG GFEA 02	6(**F**$_{500}$**E**$_{50}$**C**$_{500}$)$_{q3}$	**E**$_{300}$¶	13/2780	20/2619	−3·8	7·2
86P$_3$ FASG GFEA 03	6(**F**$_{500}$**E**$_{50}$**C**$_{500}$)$_{q3}$	**E**$_{300}$¶	9/1185	6/1078	1·6	3·7
89@$_1$ Bari Italy	6(**F**$_{500\times2}$**E**$_{50}$**C**$_{500}$)$_{q3}$	**E**$_{300}$¶	5/1058	6/1090	1·3	2·0
90C$_6$ FASG GFEA 07	6(**F**$_{500}$**E**$_{50}$**C**$_{500}$)$_{q3}$	**E**$_{300}$¶	5/1134	3/1010	0·4	1·8
96E Austrian BCSG IX	4(**F**$_{600}$**E**$_{60}$**C**$_{600}$)$_{q3}$	**E**$_{240}$¶	1/212	1/217	0·5	0·3
82F MD Anderson8227 *	4(**F**$_{400\times2}$**A**$_{40}$**C**$_{400}$**V**$_{1\cdot5}$)$_{q4}$	**A**$_{160}$¶	2/596	2(2/259)	0·0	0·6
(b) subtotal with data §			**144/ 20722 (0·7%/y)**	**133/ 18482 (0·7%/y)**	**7·0**	**59·2**
(c) Standard CMF (or near-standard CMF)						
73B INT Milan 7205	12(**C**$_{100\times14}$**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$		24/2210	19/1472	0·7	8·2
78K$_3$ IBCSG/Ludwig III	12(**C**$_{100\times14}$**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$		37/1558	20/1235	4·0	11·6
78V$_2$ ECOG EST6177	12(**C**$_{100\times14}$**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$		8/559	7/622	1·8	3·0
79U$_{1+3}$ Vienna Gyn.	6(**C**$_{100\times14}$**M**$_{50\times2}$**F**$_{750\times2}$)$_{q4}$		4/250	10/266	0·7	1·0
81H EST1180/SW.8294	6(**C**$_{100\times14}$**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$		31/3385	25/2758	0·7	12·5
86H$_2$ IBCSG VII	6(**C**$_{100\times14}$**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$		40/2554	28/2359	5·9	16·0
88C NSABP B−20	6(**C**$_{100\times14}$**M**$_{100\times2}$**F**$_{600\times2}$)$_{q4}$		54/9087	51/8706	2·1	25·9
89A$_2$ SITAM−01	6([**C**$_{100\times14}$/**C**$_{600\times2}$]**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$		5/370	3/364	−0·2	1·3
89E$_{4+9}$ GROCTA V Italy	6(**C**$_{600\times2}$**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$		0/215	1/167	−0·6	0·2
89V Romagnolo Italy	6(**C**$_{100\times14}$**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$		8/1358	4/1283	1·8	2·9
90P Amsterdam C8913	6(**C**$_{100\times14}$**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$		0/630	0/448		
90S IBCSG VIII	6(**C**$_{100\times14}$**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$		4/3305	2/3063	1·4	1·4
(c) subtotal			**215/ 25481 (0·8%/y)**	**170/ 22743 (0·7%/y)**	**18·1**	**84·0**
Total (a + b + c)			**592/ 62770 (0·9%/y)**	**458/ 56202 (0·8%/y)**	**39·9**	**204·1**



■ 99% or ◁▷ 95% confidence intervals

Heterogeneity between 3 subtotals: χ^2_2 = 0·5; p > 0·1; NS

Heterogeneity within subtotals: χ^2_{28} = 19·1; p > 0·1; NS

Heterogeneity between 31 trials: χ^2_{30} = 19·7; p > 0·1; NS

§ 1 trial with no data does not contribute to subtotals or to the overall total.

Anthracyclines: **A** = doxorubicin (Adriamycin); **E** = Epirubicin

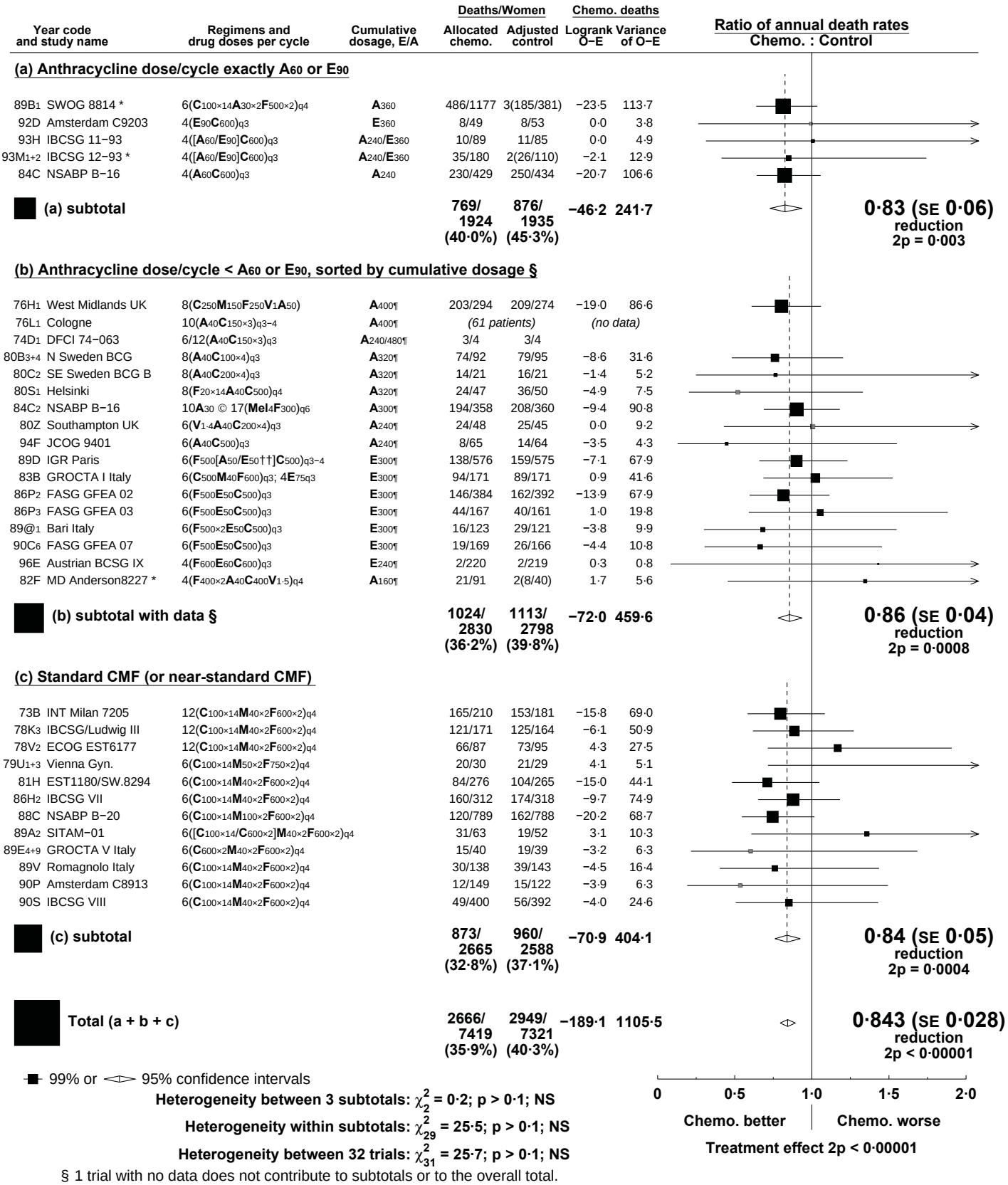
Other agents: **C** = cyclophosphamide; **F** = fluorouracil; **M** = methotrexate; **Mel** = Melphalan; **V** = vincristine
(Not shown: antibiotic, hormonal, local or steroid therapies)

×2 means d1,8 iv; ×4 means d3−6 iv

¶ Dose less than **A**$_{60}$ or **E**$_{90}$ per cycle

††91% given **E**, 9% given **A**

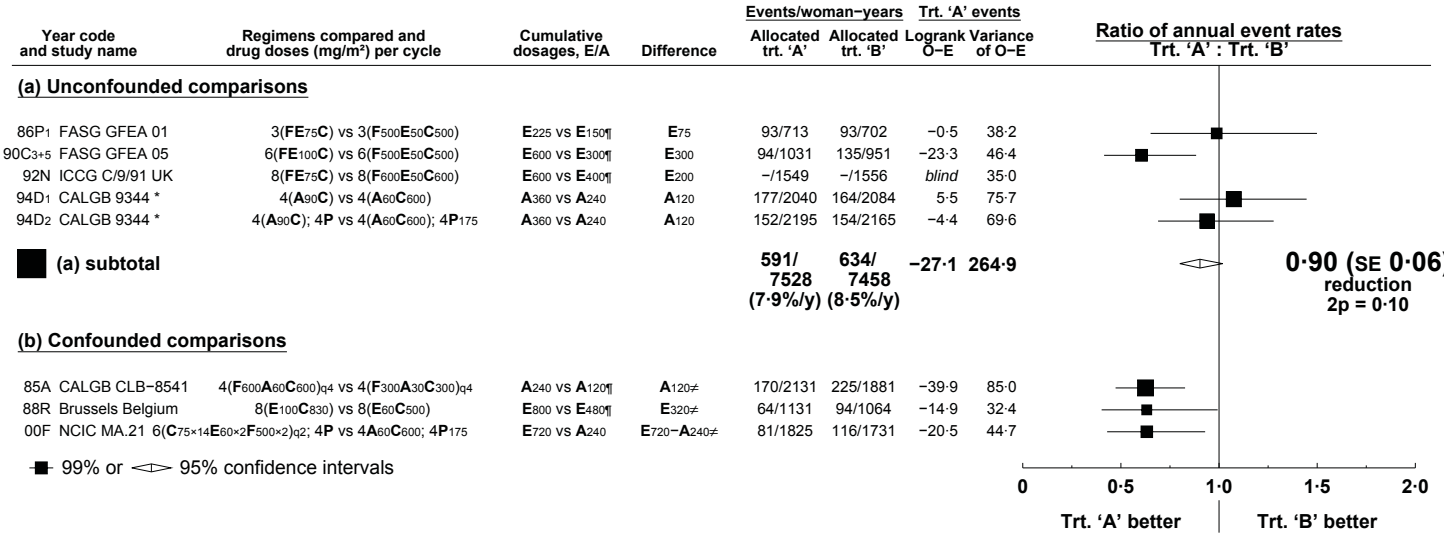
P 44: OVERALL MORTALITY in trials of anthracycline-based regimen (eg, standard 4AC) or standard CMF (or near-standard CMF) vs. No chemotherapy



§ 1 trial with no data does not contribute to subtotals or to the overall total.

Anthracyclines: **A** = doxorubicin (Adriamycin); **E** = Epirubicin
Other agents: **C** = cyclophosphamide; **F** = fluorouracil; **M** = methotrexate; **Mel** = Melphalan; **V** = vincristine
(Not shown: antibiotic, hormonal, local or steroid therapies)
×2 means d1,8 iv; ×4 means d3−6 iv
¶ Dose less than **A**60 or **E**90 per cycle
††91% given **E**, 9% given **A**

P 45: EARLY RECURRENCE (first 5 years) in trials of anthracycline dosage



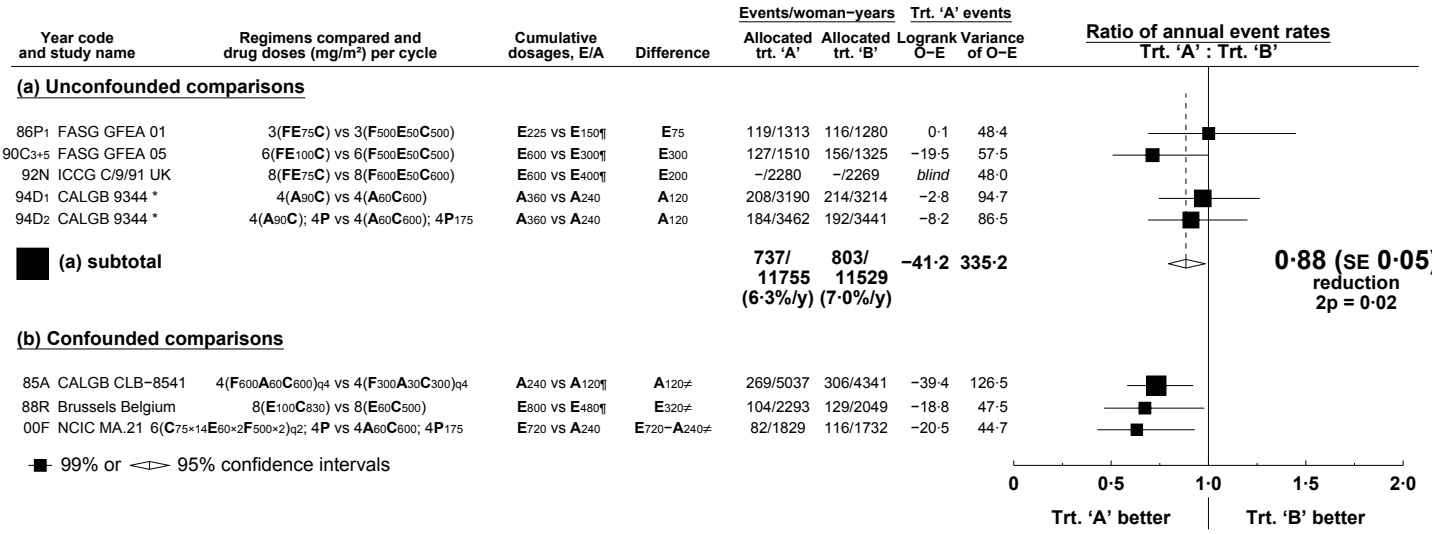
Anthracyclines: **A** = doxorubicin (Adriamycin); **E** = Epirubicin
Other agents: **C** = cyclophosphamide; **F** = fluorouracil; **P** = paclitaxel
(Not shown: antibiotic, hormonal, local or steroid therapies)
All regimens q3w (unless specified as q4). Semicolon [;] indicates treatment sequence
×2 means d1,8 iv; ×4 means d3−6 iv

¶ Dose less than **E**90 or **A**60 per q3w (**E**120 or **A**75 per q4w) cycle

≠ Taxane and control regimens differ in ways other than cumulative anthracycline dose

* These analyses compare the highest and lowest of the 3 anthracycline doses studied in 94D CALGB 9344, ignoring the middle dose

P 46: RECURRENCE in trials of anthracycline dosage



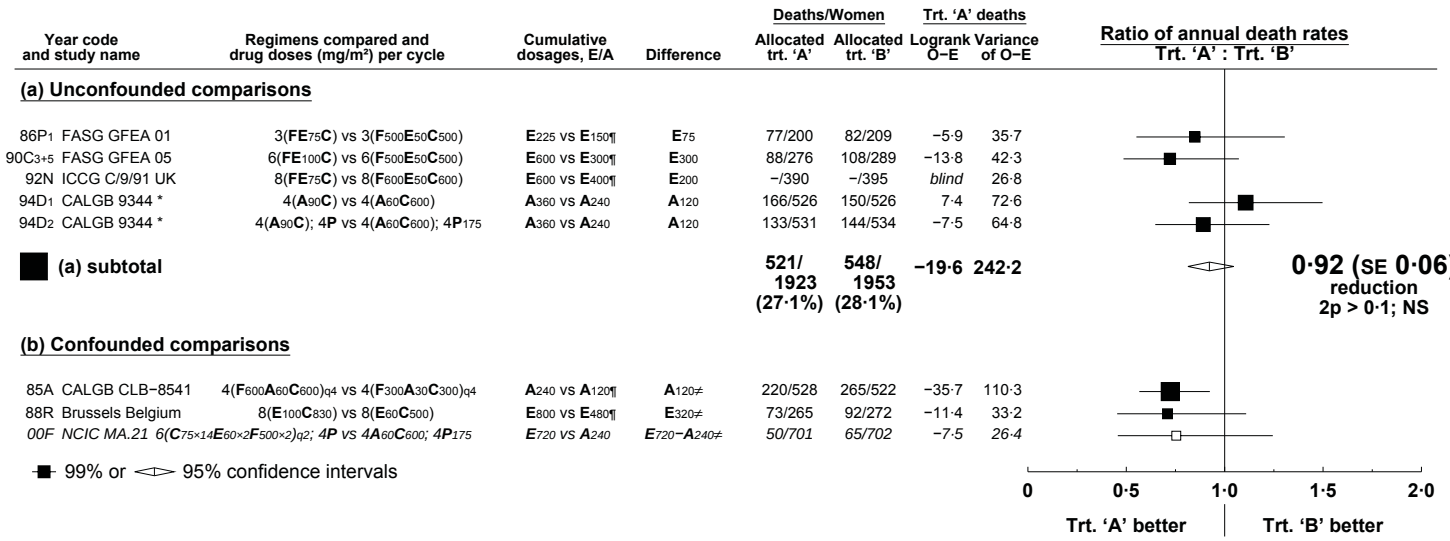
Anthracyclines: **A** = doxorubicin (Adriamycin); **E** = Epirubicin
Other agents: **C** = cyclophosphamide; **F** = fluorouracil; **P** = paclitaxel
(Not shown: antibiotic, hormonal, local or steroid therapies)
All regimens q3w (unless specified as q4). Semicolon [;] indicates treatment sequence
×2 means d1,8 iv; ×4 means d3−6 iv

¶ Dose less than **E**90 or **A**60 per q3w (**E**120 or **A**75 per q4w) cycle

≠ Taxane and control regimens differ in ways other than cumulative anthracycline dose

* These analyses compare the highest and lowest of the 3 anthracycline doses studied in 94D CALGB 9344, ignoring the middle dose

P 47: BREAST CANCER MORTALITY (MORTALITY WITH RECURRENCE) in trials of anthracycline dosage



Anthracyclines: **A** = doxorubicin (Adriamycin); **E** = Epirubicin
Other agents: **C** = cyclophosphamide; **F** = fluorouracil; **P** = paclitaxel
(Not shown: antibiotic, hormonal, local or steroid therapies)
All regimens q3w (unless specified as q4). Semicolon [;] indicates treatment sequence
×2 means d1,8 iv; ×4 means d3−6 iv

¶ Dose less than **E**90 or **A**60 per q3w (**E**120 or **A**75 per q4w) cycle

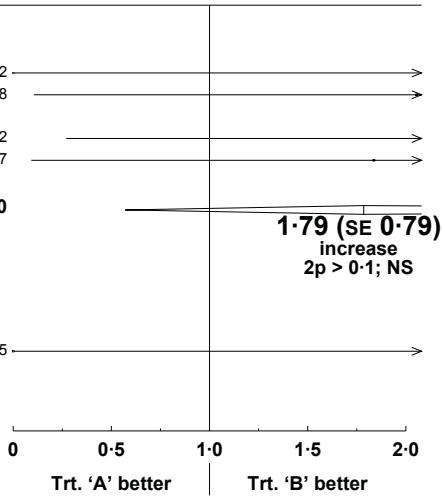
≠ Taxane and control regimens differ in ways other than cumulative anthracycline dose

* These analyses compare the highest and lowest of the 3 anthracycline doses studied in 94D CALGB 9344, ignoring the middle dose

P 48: MORTALITY WITHOUT RECURRENCE IN FIRST YEAR in trials of anthracycline dosage

Year code and study name	Regimens compared and drug doses (mg/m²) per cycle	Cumulative dosages, E/A	Difference	Deaths/woman−years: Allocated trt. 'A'	Deaths/woman−years: Allocated trt. 'B'	Trt. 'A' deaths: Logrank O−E	Trt. 'A' deaths: Variance of O−E
(a) Unconfounded comparisons							
86P1 FASG GFEA 01	3(**FE**$_{75}$**C**) vs 3(**F**$_{500}$**E**$_{50}$**C**$_{500}$)	**E**$_{225}$ vs **E**$_{150}$¶	**E**$_{75}$	0/183	1/183	−0·5	0·2
90C3+5 FASG GFEA 05	6(**FE**$_{100}$**C**) vs 6(**F**$_{500}$**E**$_{50}$**C**$_{500}$)	**E**$_{600}$ vs **E**$_{300}$¶	**E**$_{300}$	2/244	1/245	0·5	0·8
92N ICCG C/9/91 UK	8(**FE**$_{75}$**C**) vs 8(**F**$_{600}$**E**$_{50}$**C**$_{600}$)	**E**$_{600}$ vs **E**$_{400}$¶	**E**$_{200}$	−/339	−/343		
94D1 CALGB 9344 *	4(**A**$_{90}$**C**) vs 4(**A**$_{60}$**C**$_{600}$)	**A**$_{360}$ vs **A**$_{240}$	**A**$_{120}$	4/508	1/506	1·2	1·2
94D2 CALGB 9344 *	4(**A**$_{90}$**C**); 4**P** vs 4(**A**$_{60}$**C**$_{600}$); 4**P**$_{175}$	**A**$_{360}$ vs **A**$_{240}$	**A**$_{120}$	2/513	1/518	0·4	0·7
(a) subtotal				**8/ 1787 (0·4%/y)**	**4/ 1795 (0·2%/y)**	**1·7**	**3·0**
(b) Confounded comparisons							
85A CALGB CLB−8541	4(**F**$_{600}$**A**$_{60}$**C**$_{600}$)$_{q4}$ vs 4(**F**$_{300}$**A**$_{30}$**C**$_{300}$)$_{q4}$	**A**$_{240}$ vs **A**$_{120}$¶	**A**$_{120}$≠	0/498	2/483	−1·0	0·5
88R Brussels Belgium	8(**E**$_{100}$**C**$_{830}$) vs 8(**E**$_{60}$**C**$_{500}$)	**E**$_{800}$ vs **E**$_{480}$¶	**E**$_{320}$≠	0/230	0/236		
00F NCIC MA.21	*6(**C**$_{75\times14}$**E**$_{60\times2}$**F**$_{500\times2})_{q2}$; 4**P** vs 4**A**$_{60}$**C**$_{600}$; 4**P**$_{175}$*	*E*$_{720}$ *vs A*$_{240}$	*E*$_{720}$−*A*$_{240}$≠			*(no data)*	

■ 99% or ◁▷ 95% confidence intervals



§ 1 trial with no data does not contribute to subtotals or to the overall total.

Anthracyclines: **A** = doxorubicin (Adriamycin); **E** = Epirubicin

Other agents: **C** = cyclophosphamide; **F** = fluorouracil; **P** = paclitaxel
(Not shown: antibiotic, hormonal, local or steroid therapies)

All regimens q3w (unless specified as q4). Semicolon [;] indicates treatment sequence

×2 means d1,8 iv; ×4 means d3−6 iv

¶ Dose less than **E**$_{90}$ or **A**$_{60}$ per q3w (**E**$_{120}$ or **A**$_{75}$ per q4w) cycle

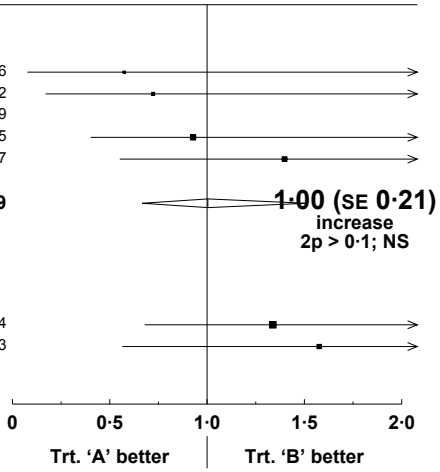
≠ Taxane and control regimens differ in ways other than cumulative anthracycline dose

* These analyses compare the highest and lowest of the 3 anthracycline doses studied in 94D CALGB 9344, ignoring the middle dose

P 49: MORTALITY WITHOUT RECURRENCE in trials of anthracycline dosage

Year code and study name	Regimens compared and drug doses (mg/m²) per cycle	Cumulative dosages, E/A	Difference	Deaths/woman−years: Allocated trt. 'A'	Deaths/woman−years: Allocated trt. 'B'	Trt. 'A' deaths: Logrank O−E	Trt. 'A' deaths: Variance of O−E
(a) Unconfounded comparisons							
86P1 FASG GFEA 01	3(**FE**$_{75}$**C**) vs 3(**F**$_{500}$**E**$_{50}$**C**$_{500}$)	**E**$_{225}$ vs **E**$_{150}$¶	**E**$_{75}$	3/1312	4/1278	−0·9	1·6
90C3+5 FASG GFEA 05	6(**FE**$_{100}$**C**) vs 6(**F**$_{500}$**E**$_{50}$**C**$_{500}$)	**E**$_{600}$ vs **E**$_{300}$¶	**E**$_{300}$	6/1509	7/1324	−1·0	3·2
92N ICCG C/9/91 UK	8(**FE**$_{75}$**C**) vs 8(**F**$_{600}$**E**$_{50}$**C**$_{600}$)	**E**$_{600}$ vs **E**$_{400}$¶	**E**$_{200}$	−/2280	−/2268	*blind*	0·9
94D1 CALGB 9344 *	4(**A**$_{90}$**C**) vs 4(**A**$_{60}$**C**$_{600}$)	**A**$_{360}$ vs **A**$_{240}$	**A**$_{120}$	19/3190	20/3214	−0·7	9·5
94D2 CALGB 9344 *	4(**A**$_{90}$**C**); 4**P** vs 4(**A**$_{60}$**C**$_{600}$); 4**P**$_{175}$	**A**$_{360}$ vs **A**$_{240}$	**A**$_{120}$	19/3462	14/3441	2·6	7·7
■ **(a) subtotal**				**49/ 11753 (0·4%/y)**	**47/ 11525 (0·4%/y)**	**0·1**	**22·9**
(b) Confounded comparisons							
85A CALGB CLB−8541	4(**F**$_{600}$**A**$_{60}$**C**$_{600}$)$_{q4}$ vs 4(**F**$_{300}$**A**$_{30}$**C**$_{300}$)$_{q4}$	**A**$_{240}$ vs **A**$_{120}$¶	**A**$_{120}$≠	39/5037	25/4340	4·2	14·4
88R Brussels Belgium	8(**E**$_{100}$**C**$_{830}$) vs 8(**E**$_{60}$**C**$_{500}$)	**E**$_{800}$ vs **E**$_{480}$¶	**E**$_{320}$≠	18/2293	10/2049	2·9	6·3
00F NCIC MA.21	*6(**C**$_{75\times14}$**E**$_{60\times2}$**F**$_{500\times2}$)$_{q2}$; 4**P** vs 4**A**$_{60}$**C**$_{600}$; 4**P**$_{175}$*	***E**$_{720}$ vs **A**$_{240}$*	***E**$_{720}$−**A**$_{240}$*≠			*(no data)*	

■ 99% or ◁▷ 95% confidence intervals



§ 1 trial with no data does not contribute to subtotals or to the overall total.

Anthracyclines: **A** = doxorubicin (Adriamycin); **E** = Epirubicin

Other agents: **C** = cyclophosphamide; **F** = fluorouracil; **P** = paclitaxel

(Not shown: antibiotic, hormonal, local or steroid therapies)

All regimens q3w (unless specified as q4). Semicolon [;] indicates treatment sequence

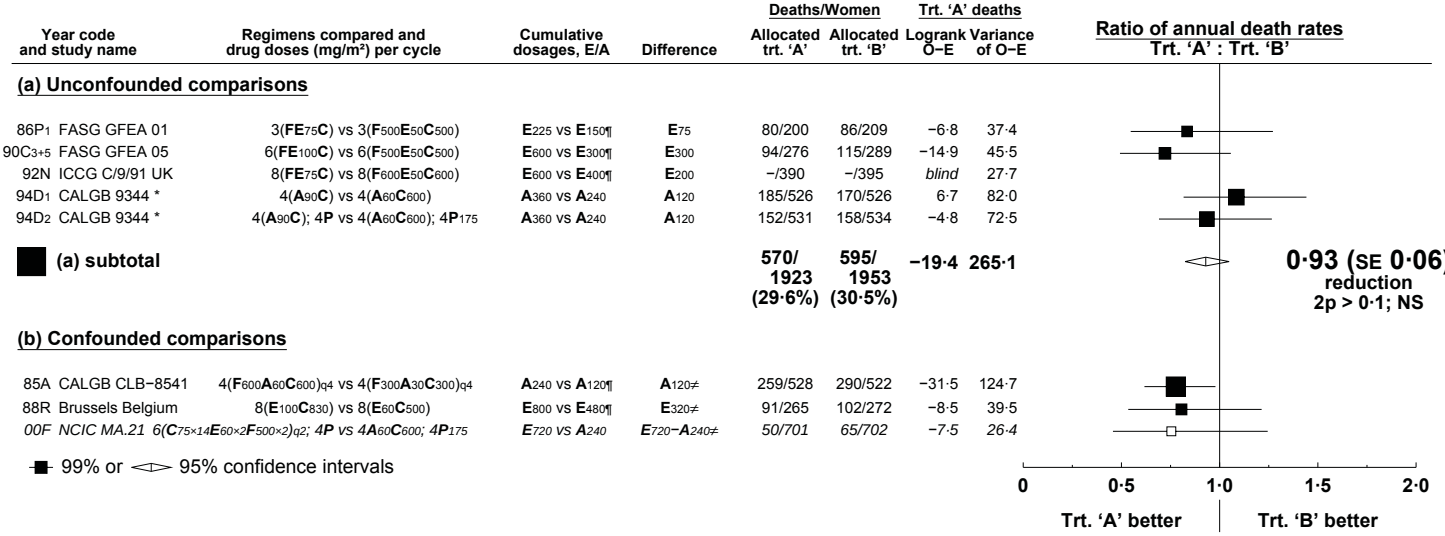
×2 means d1,8 iv; ×4 means d3−6 iv

¶ Dose less than **E**$_{90}$ or **A**$_{60}$ per q3w (**E**$_{120}$ or **A**$_{75}$ per q4w) cycle

≠ Taxane and control regimens differ in ways other than cumulative anthracycline dose

* These analyses compare the highest and lowest of the 3 anthracycline doses studied in 94D CALGB 9344, ignoring the middle dose

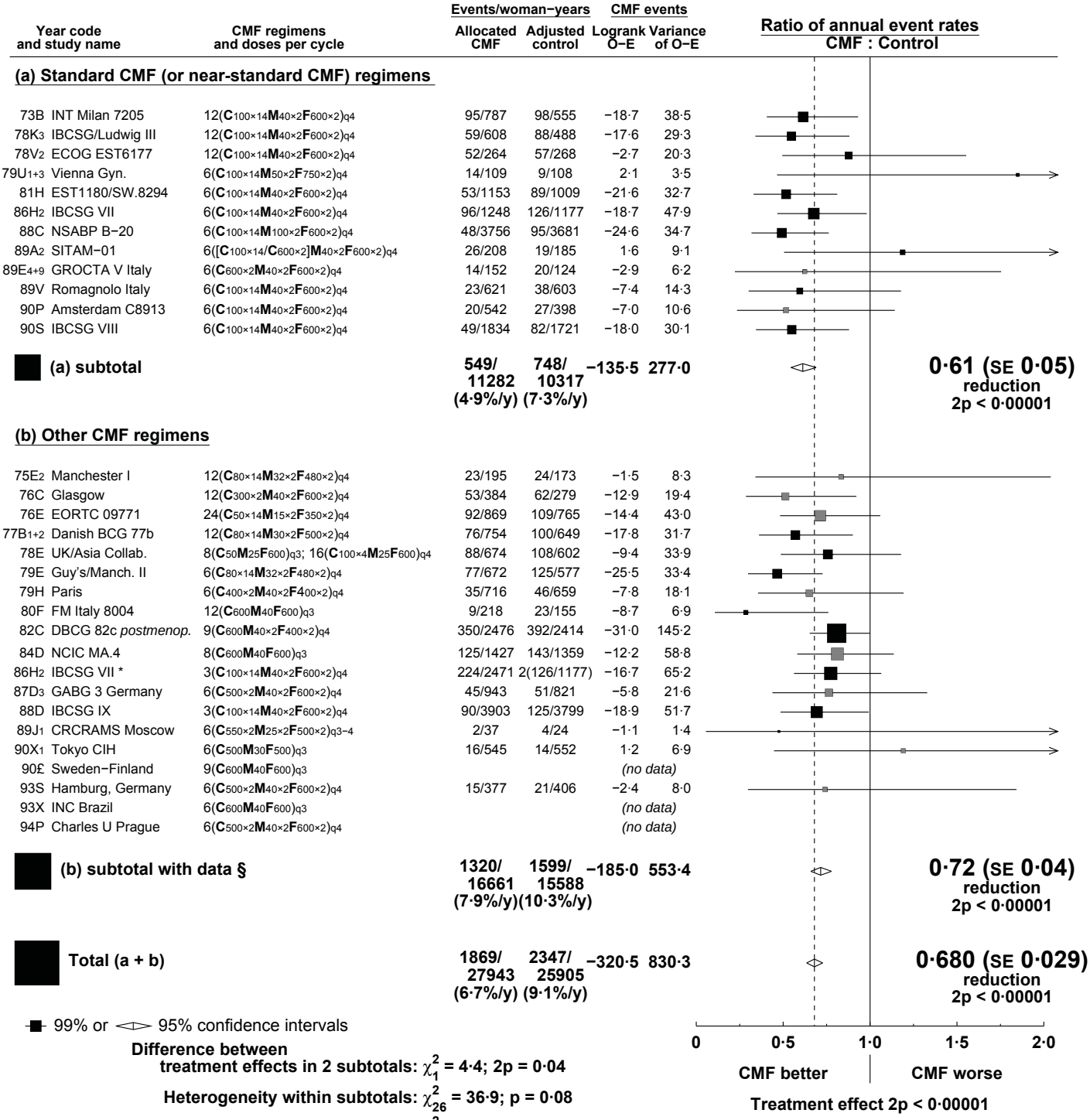
P 50: OVERALL MORTALITY in trials of anthracycline dosage



Anthracyclines: **A** = doxorubicin (Adriamycin); **E** = Epirubicin
Other agents: **C** = cyclophosphamide; **F** = fluorouracil; **P** = paclitaxel
(Not shown: antibiotic, hormonal, local or steroid therapies)
All regimens q3w (unless specified as q4). Semicolon [;] indicates treatment sequence
×2 means d1,8 iv; ×4 means d3−6 iv

¶ Dose less than **E**90 or **A**60 per q3w (**E**120 or **A**75 per q4w) cycle
≠ Taxane and control regimens differ in ways other than cumulative anthracycline dose
* These analyses compare the highest and lowest of the 3 anthracycline doses studied in 94D CALGB 9344, ignoring the middle dose

P 51: EARLY RECURRENCE (first 5 years) in trials of CMF regimen vs. No chemotherapy



Difference between treatment effects in 2 subtotals: $\chi^2_1 = 4{\cdot}4$; 2p = 0·04

Heterogeneity within subtotals: $\chi^2_{26} = 36{\cdot}9$; p = 0·08

Heterogeneity between 28 trials: $\chi^2_{27} = 41{\cdot}3$; p = 0·04

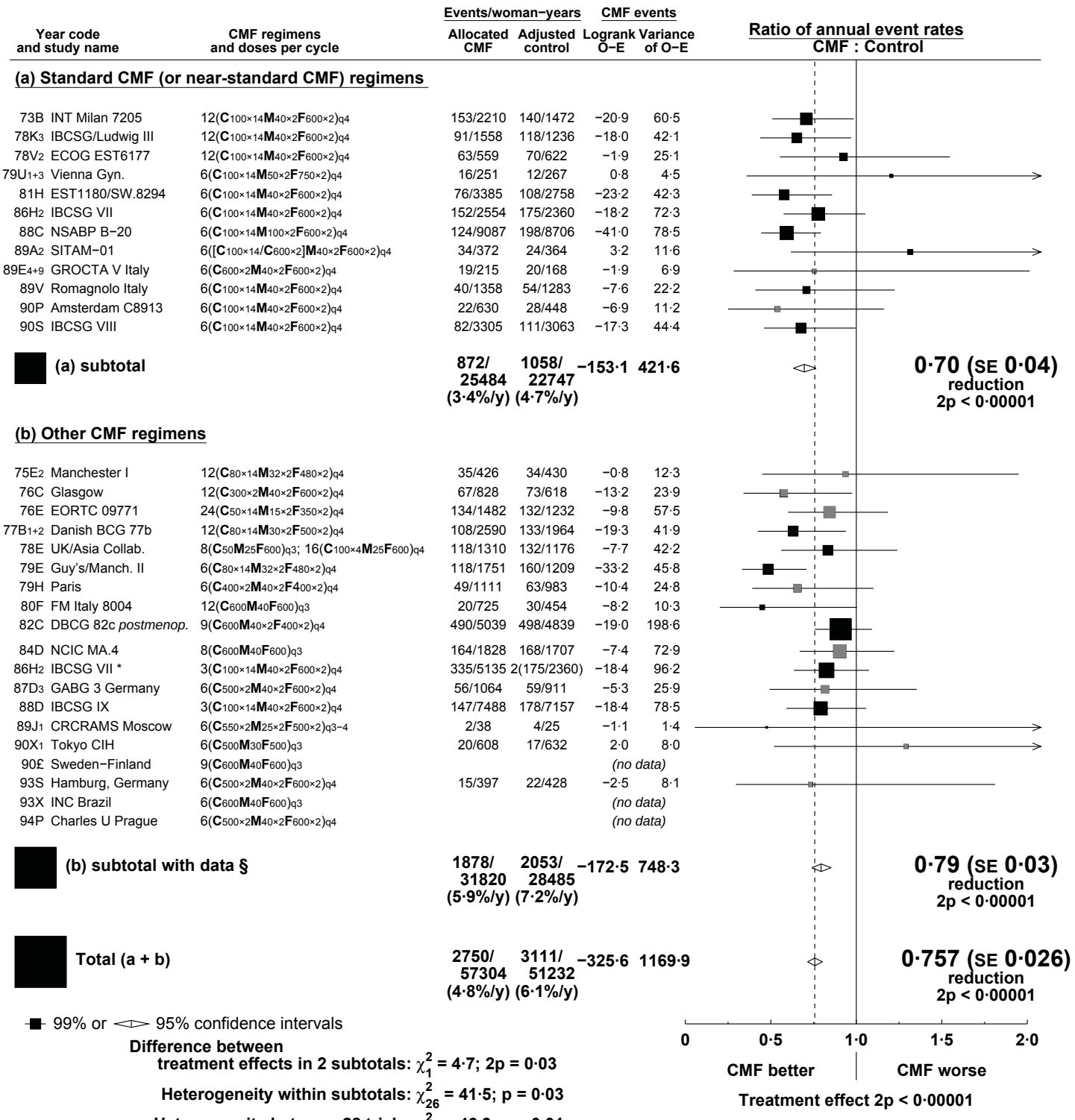
§ 3 trials with no data do not contribute to subtotals or to the overall total.

* For balance, control patients in 3−way trials or trial strata count half or twice in subtotal(s) and in final total of events/woman−years.

Agents: **C** = cyclophosphamide; **F** = fluorouracil; **M** = methotrexate
(Not shown: antibiotic, hormonal, local or steroid therapies)

Semicolon [;] indicates treatment sequence; ×2 means d1,8 iv; ×4 means d3−6 iv

P 52: RECURRENCE in trials of CMF regimen vs. No chemotherapy



Difference between treatment effects in 2 subtotals: $\chi^2_1 = 4{\cdot}7$; 2p = 0·03

Heterogeneity within subtotals: $\chi^2_{26} = 41{\cdot}5$; p = 0·03

Heterogeneity between 28 trials: $\chi^2_{27} = 46{\cdot}3$; p = 0·01

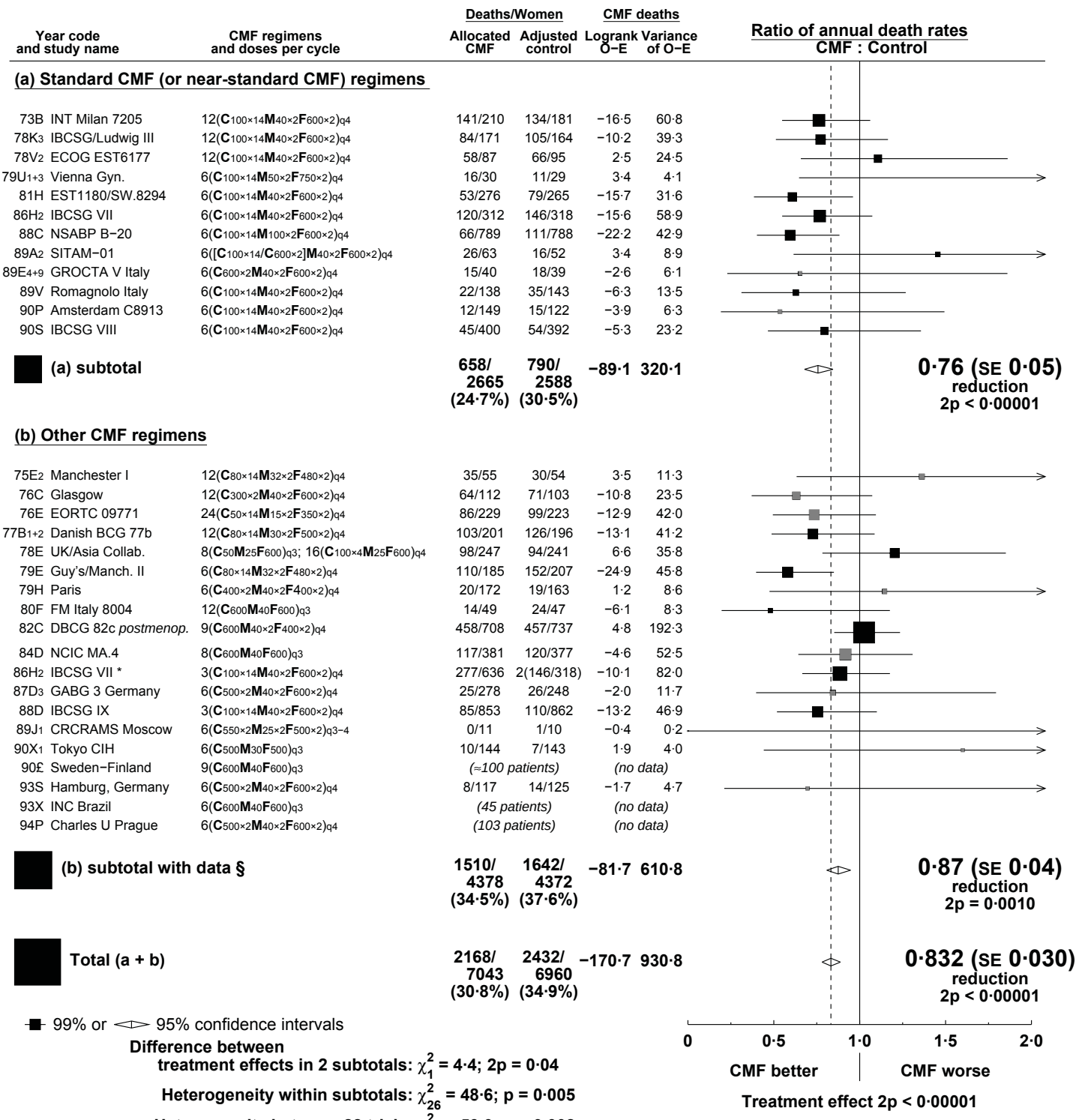
§ 3 trials with no data do not contribute to subtotals or to the overall total.

* For balance, control patients in 3−way trials or trial strata count half or twice in subtotal(s) and in final total of events/woman−years.

Agents: **C** = cyclophosphamide; **F** = fluorouracil; **M** = methotrexate
(Not shown: antibiotic, hormonal, local or steroid therapies)

Semicolon [;] indicates treatment sequence; ×2 means d1,8 iv; ×4 means d3−6 iv

P 53: BREAST CANCER MORTALITY (MORTALITY WITH RECURRENCE) in trials of CMF regimen vs. No chemotherapy



Difference between treatment effects in 2 subtotals: $\chi^2_1 = 4{\cdot}4$; 2p = 0·04

Heterogeneity within subtotals: $\chi^2_{26} = 48{\cdot}6$; p = 0·005

Heterogeneity between 28 trials: $\chi^2_{27} = 53{\cdot}0$; p = 0·002

§ 3 trials with no data do not contribute to subtotals or to the overall total.

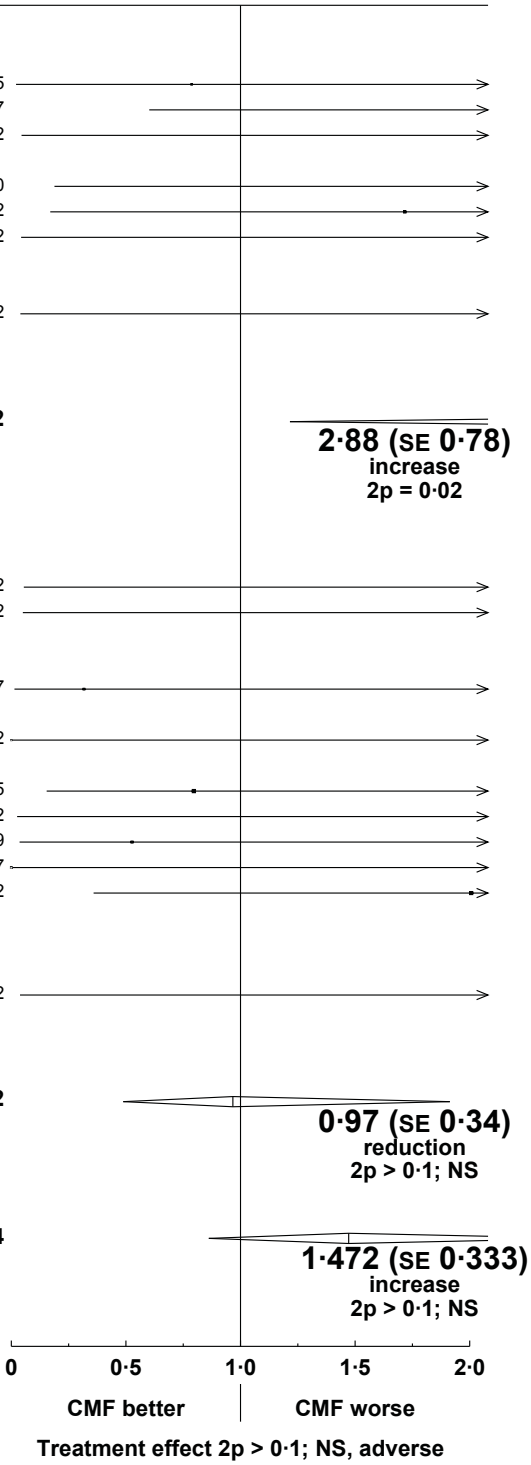
* For balance, control patients in 3−way trials or trial strata count half or twice in subtotal(s) and in final total of deaths/women.

Agents: **C** = cyclophosphamide; **F** = fluorouracil; **M** = methotrexate
(Not shown: antibiotic, hormonal, local or steroid therapies)

Semicolon [;] indicates treatment sequence; ×2 means d1,8 iv; ×4 means d3−6 iv

P 54: MORTALITY WITHOUT RECURRENCE IN FIRST YEAR in trials of CMF regimen vs. No chemotherapy

Year code and study name	CMF regimens and doses per cycle	Deaths/woman−years: Allocated CMF	Deaths/woman−years: Adjusted control	CMF deaths: Logrank O−E	CMF deaths: Variance of O−E
(a) Standard CMF (or near-standard CMF) regimens					
73B INT Milan 7205	12(**C**$_{100\times14}$**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$	1/198	1/160	−0·1	0·5
78K$_3$ IBCSG/Ludwig III	12(**C**$_{100\times14}$**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$	6/148	1/138	2·5	1·7
78V$_2$ ECOG EST6177	12(**C**$_{100\times14}$**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$	1/78	0/77	0·5	0·2
79U$_{1+3}$ Vienna Gyn.	6(**C**$_{100\times14}$**M**$_{50\times2}$**F**$_{750\times2}$)$_{q4}$	0/18	0/19		
81H EST1180/SW.8294	6(**C**$_{100\times14}$**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$	3/258	1/248	0·9	1·0
86H$_2$ IBCSG VII	6(**C**$_{100\times14}$**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$	3/292	2/289	0·7	1·2
88C NSABP B−20	6(**C**$_{100\times14}$**M**$_{100\times2}$**F**$_{600\times2}$)$_{q4}$	1/774	0/777	0·5	0·2
89A$_2$ SITAM−01	6([**C**$_{100\times14}$/**C**$_{600\times2}$]**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$	0/45	0/39		
89E$_{4+9}$ GROCTA V Italy	6(**C**$_{600\times2}$**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$	0/32	0/28		
89V Romagnolo Italy	6(**C**$_{100\times14}$**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$	1/132	0/137	0·5	0·2
90P Amsterdam C8913	6(**C**$_{100\times14}$**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$	0/141	0/112		
90S IBCSG VIII	6(**C**$_{100\times14}$**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$	0/377	0/371		
▪ **(a) subtotal**		**16/ 2493 (0·6%/y)**	**5/ 2395 (0·2%/y)**	**5·5**	**5·2**
(b) Other CMF regimens					
75E$_2$ Manchester I	12(**C**$_{80\times14}$**M**$_{32\times2}$**F**$_{480\times2}$)$_{q4}$	1/34	0/35	0·6	0·2
76C Glasgow	12(**C**$_{300\times2}$**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$	1/90	0/78	0·5	0·2
76E EORTC 09771	24(**C**$_{50\times14}$**M**$_{15\times2}$**F**$_{350\times2}$)$_{q4}$	0/212	0/205		
77B$_{1+2}$ Danish BCG 77b	12(**C**$_{80\times14}$**M**$_{30\times2}$**F**$_{500\times2}$)$_{q4}$	0/148	0/153		
78E UK/Asia Collab.	8(**C**$_{50}$**M**$_{25}$**F**$_{600}$)$_{q3}$; 16(**C**$_{100\times4}$**M**$_{25}$**F**$_{600}$)$_{q4}$	1/180	3/169	−0·8	0·7
79E Guy's/Manch. II	6(**C**$_{80\times14}$**M**$_{32\times2}$**F**$_{480\times2}$)$_{q4}$	0/138	0/151		
79H Paris	6(**C**$_{400\times2}$**M**$_{40\times2}$**F**$_{400\times2}$)$_{q4}$	0/160	1/154	−0·6	0·2
80F FM Italy 8004	12(**C**$_{600}$**M**$_{40}$**F**$_{600}$)$_{q3}$	0/44	0/42		
82C DBCG 82c *postmenop.*	9(**C**$_{600}$**M**$_{40\times2}$**F**$_{400\times2}$)$_{q4}$	4/651	6/656	−0·6	2·5
84D NCIC MA.4	8(**C**$_{600}$**M**$_{40}$**F**$_{600}$)$_{q3}$	1/356	0/349	0·4	0·2
86H$_2$ IBCSG VII *	3(**C**$_{100\times14}$**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$	2/592	2(2/289)	−0·6	0·9
87D$_3$ GABG 3 Germany	6(**C**$_{500\times2}$**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$	0/250	3/220	−1·3	0·7
88D IBCSG IX	3(**C**$_{100\times14}$**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$	6/832	3/836	1·6	2·2
89J$_1$ CRCRAMS Moscow	6(**C**$_{550\times2}$**M**$_{25\times2}$**F**$_{500\times2}$)$_{q3-4}$	0/7	0/6		
90X$_1$ Tokyo CIH	6(**C**$_{500}$**M**$_{30}$**F**$_{500}$)$_{q3}$	0/132	0/132		
90£ Sweden−Finland	9(**C**$_{600}$**M**$_{40}$**F**$_{600}$)$_{q3}$			*(no data)*	
93S Hamburg, Germany	6(**C**$_{500\times2}$**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$	1/110	0/119	0·5	0·2
93X INC Brazil	6(**C**$_{600}$**M**$_{40}$**F**$_{600}$)$_{q3}$			*(no data)*	
94P Charles U Prague	6(**C**$_{500\times2}$**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$			*(no data)*	
▪ **(b) subtotal with data §**		**17/ 3936 (0·4%/y)**	**20/ 3883 (0·5%/y)**	**−0·3**	**8·2**
▪ **Total (a + b)**		**33/ 6429 (0·5%/y)**	**25/ 6278 (0·4%/y)**	**5·2**	**13·4**



■ 99% or ◁▷ 95% confidence intervals

Difference between treatment effects in 2 subtotals: χ^2_1 = 3·8; 2p = 0·05

Heterogeneity within subtotals: χ^2_{15} = 12·2; p > 0·1; NS

Heterogeneity between 17 trials: χ^2_{16} = 15·9; p > 0·1; NS

§ 3 trials with no data do not contribute to subtotals or to the overall total.

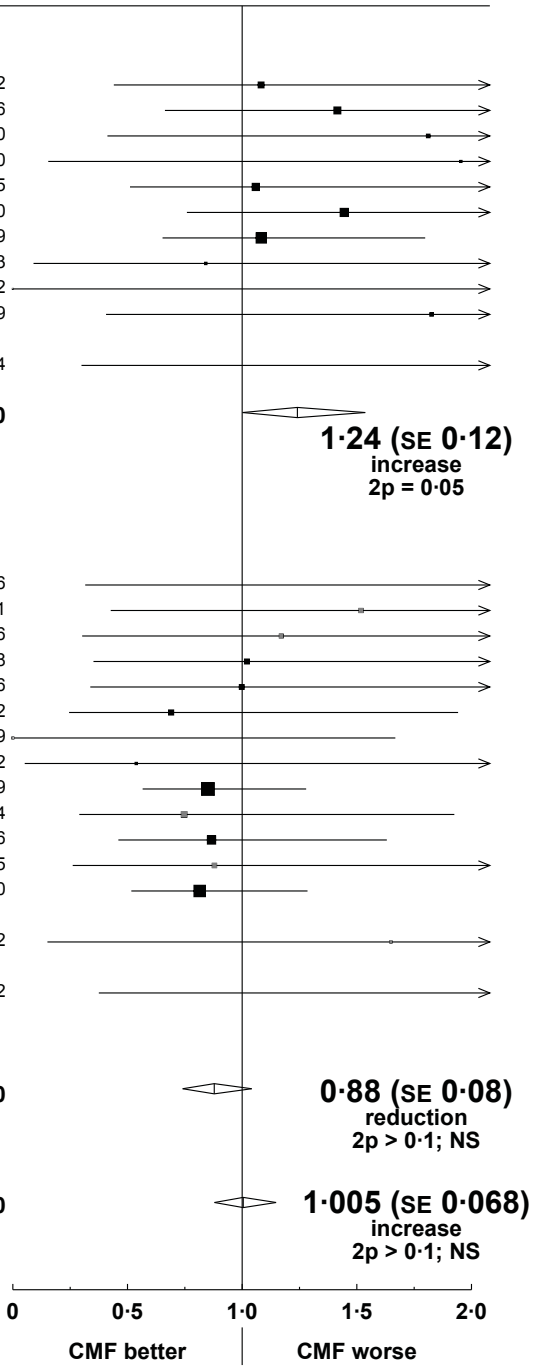
* For balance, control patients in 3−way trials or trial strata count half or twice in subtotal(s) and in final total of deaths/woman−years.

Agents: **C** = cyclophosphamide; **F** = fluorouracil; **M** = methotrexate
(Not shown: antibiotic, hormonal, local or steroid therapies)

Semicolon [;] indicates treatment sequence; ×2 means d1,8 iv; ×4 means d3−6 iv

P 55: MORTALITY WITHOUT RECURRENCE in trials of CMF regimen vs. No chemotherapy

Year code and study name	CMF regimens and doses per cycle	Deaths/woman−years: Allocated CMF	Deaths/woman−years: Adjusted control	CMF deaths: Logrank O−E	CMF deaths: Variance of O−E
(a) Standard CMF (or near-standard CMF) regimens					
73B INT Milan 7205	12(**C**$_{100\times14}$**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$	24/2210	19/1472	0·7	8·2
78K$_3$ IBCSG/Ludwig III	12(**C**$_{100\times14}$**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$	37/1558	20/1235	4·0	11·6
78V$_2$ ECOG EST6177	12(**C**$_{100\times14}$**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$	8/559	7/622	1·8	3·0
79U$_{1+3}$ Vienna Gyn.	6(**C**$_{100\times14}$**M**$_{50\times2}$**F**$_{750\times2}$)$_{q4}$	4/250	10/266	0·7	1·0
81H EST1180/SW.8294	6(**C**$_{100\times14}$**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$	31/3385	25/2758	0·7	12·5
86H$_2$ IBCSG VII	6(**C**$_{100\times14}$**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$	40/2554	28/2359	5·9	16·0
88C NSABP B−20	6(**C**$_{100\times14}$**M**$_{100\times2}$**F**$_{600\times2}$)$_{q4}$	54/9087	51/8706	2·1	25·9
89A$_2$ SITAM−01	6([**C**$_{100\times14}$/**C**$_{600\times2}$]**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$	5/370	3/364	−0·2	1·3
89E$_{4+9}$ GROCTA V Italy	6(**C**$_{600\times2}$**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$	0/215	1/167	−0·6	0·2
89V Romagnolo Italy	6(**C**$_{100\times14}$**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$	8/1358	4/1283	1·8	2·9
90P Amsterdam C8913	6(**C**$_{100\times14}$**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$	0/630	0/448		
90S IBCSG VIII	6(**C**$_{100\times14}$**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$	4/3305	2/3063	1·4	1·4
(a) subtotal		**215/ 25481 (0·8%/y)**	**170/ 22743 (0·7%/y)**	**18·1**	**84·0**
(b) Other CMF regimens					
75E$_2$ Manchester I	12(**C**$_{80\times14}$**M**$_{32\times2}$**F**$_{480\times2}$)$_{q4}$	6/426	3/430	1·4	1·6
76C Glasgow	12(**C**$_{300\times2}$**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$	14/827	6/616	1·7	4·1
76E EORTC 09771	24(**C**$_{50\times14}$**M**$_{15\times2}$**F**$_{350\times2}$)$_{q4}$	9/1482	7/1232	0·6	3·6
77B$_{1+2}$ Danish BCG 77b	12(**C**$_{80\times14}$**M**$_{30\times2}$**F**$_{500\times2}$)$_{q4}$	19/2590	14/1963	0·1	5·8
78E UK/Asia Collab.	8(**C**$_{50}$**M**$_{25}$**F**$_{600}$)$_{q3}$; 16(**C**$_{100\times4}$**M**$_{25}$**F**$_{600}$)$_{q4}$	14/1432	16/1234	0·0	5·6
79E Guy's/Manch. II	6(**C**$_{80\times14}$**M**$_{32\times2}$**F**$_{480\times2}$)$_{q4}$	17/1751	15/1203	−2·3	6·2
79H Paris	6(**C**$_{400\times2}$**M**$_{40\times2}$**F**$_{400\times2}$)$_{q4}$	0/1111	4/983	−2·0	0·9
80F FM Italy 8004	12(**C**$_{600}$**M**$_{40}$**F**$_{600}$)$_{q3}$	2/725	3/454	−0·8	1·2
82C DBCG 82c *postmenop.*	9(**C**$_{600}$**M**$_{40\times2}$**F**$_{400\times2}$)$_{q4}$	78/5039	96/4837	−6·4	39·9
84D NCIC MA.4	8(**C**$_{600}$**M**$_{40}$**F**$_{600}$)$_{q3}$	15/1827	17/1707	−2·2	7·4
86H$_2$ IBCSG VII *	3(**C**$_{100\times14}$**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$	51/5135	2(28/2359)	−2·4	16·6
87D$_3$ GABG 3 Germany	6(**C**$_{500\times2}$**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$	11/1064	9/911	−0·6	4·5
88D IBCSG IX	3(**C**$_{100\times14}$**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$	61/7488	69/7157	−6·6	32·0
89J$_1$ CRCRAMS Moscow	6(**C**$_{550\times2}$**M**$_{25\times2}$**F**$_{500\times2}$)$_{q3-4}$	0/38	0/25		
90X$_1$ Tokyo CIH	6(**C**$_{500}$**M**$_{30}$**F**$_{500}$)$_{q3}$	3/608	2/632	0·6	1·2
90£ Sweden−Finland	9(**C**$_{600}$**M**$_{40}$**F**$_{600}$)$_{q3}$			*(no data)*	
93S Hamburg, Germany	6(**C**$_{500\times2}$**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$	4/397	1/428	1·6	1·2
93X INC Brazil	6(**C**$_{600}$**M**$_{40}$**F**$_{600}$)$_{q3}$			*(no data)*	
94P Charles U Prague	6(**C**$_{500\times2}$**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$			*(no data)*	
(b) subtotal with data §		**304/ 31940 (1·0%/y)**	**318/ 28530 (1·1%/y)**	**−17·1**	**132·0**
Total (a + b)		**519/ 57421 (0·9%/y)**	**488/ 51273 (1·0%/y)**	**1·0**	**216·0**



■ 99% or ◁▷ 95% confidence intervals

Difference between treatment effects in 2 subtotals: $\chi^2_1 = 6{\cdot}1$; **2p = 0·01**

Heterogeneity within subtotals: $\chi^2_{24} = 16{\cdot}8$; **p > 0·1; NS**

Heterogeneity between 26 trials: $\chi^2_{25} = 22{\cdot}9$; **p > 0·1; NS**

§ 3 trials with no data do not contribute to subtotals or to the overall total.

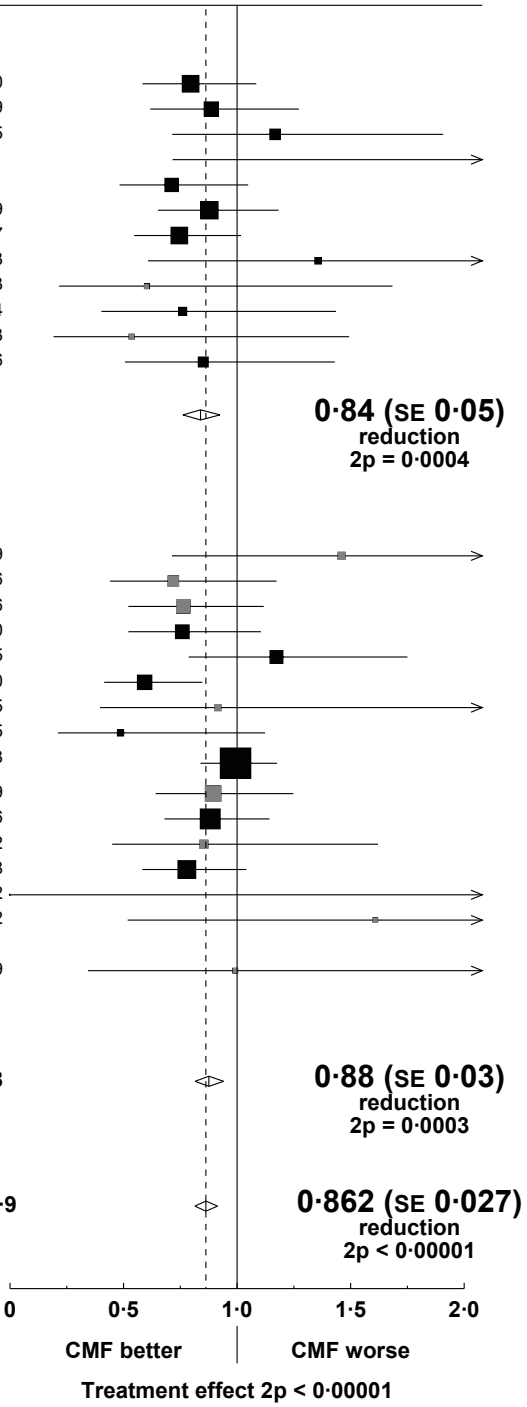
* For balance, control patients in 3−way trials or trial strata count half or twice in subtotal(s) and in final total of deaths/woman−years.

Agents: **C** = cyclophosphamide; **F** = fluorouracil; **M** = methotrexate
(Not shown: antibiotic, hormonal, local or steroid therapies)

Semicolon [;] indicates treatment sequence; ×2 means d1,8 iv; ×4 means d3−6 iv

P 56: OVERALL MORTALITY in trials of CMF regimen vs. No chemotherapy

Year code and study name	CMF regimens and doses per cycle	Deaths/Women: Allocated CMF	Deaths/Women: Adjusted control	CMF deaths: Logrank O−E	CMF deaths: Variance of O−E
(a) Standard CMF (or near-standard CMF) regimens					
73B INT Milan 7205	12(**C**$_{100\times14}$**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$	165/210	153/181	−15·8	69·0
78K$_3$ IBCSG/Ludwig III	12(**C**$_{100\times14}$**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$	121/171	125/164	−6·1	50·9
78V$_2$ ECOG EST6177	12(**C**$_{100\times14}$**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$	66/87	73/95	4·3	27·5
79U$_{1+3}$ Vienna Gyn.	6(**C**$_{100\times14}$**M**$_{50\times2}$**F**$_{750\times2}$)$_{q4}$	20/30	21/29	4·1	5·1
81H EST1180/SW.8294	6(**C**$_{100\times14}$**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$	84/276	104/265	−15·0	44·1
86H$_2$ IBCSG VII	6(**C**$_{100\times14}$**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$	160/312	174/318	−9·7	74·9
88C NSABP B−20	6(**C**$_{100\times14}$**M**$_{100\times2}$**F**$_{600\times2}$)$_{q4}$	120/789	162/788	−20·2	68·7
89A$_2$ SITAM−01	6([**C**$_{100\times14}$/**C**$_{600\times2}$]**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$	31/63	19/52	3·1	10·3
89E$_{4+9}$ GROCTA V Italy	6(**C**$_{600\times2}$**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$	15/40	19/39	−3·2	6·3
89V Romagnolo Italy	6(**C**$_{100\times14}$**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$	30/138	39/143	−4·5	16·4
90P Amsterdam C8913	6(**C**$_{100\times14}$**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$	12/149	15/122	−3·9	6·3
90S IBCSG VIII	6(**C**$_{100\times14}$**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$	49/400	56/392	−4·0	24·6
(a) subtotal		**873/ 2665 (32·8%)**	**960/ 2588 (37·1%)**	**−70·9**	**404·1**
(b) Other CMF regimens					
75E$_2$ Manchester I	12(**C**$_{80\times14}$**M**$_{32\times2}$**F**$_{480\times2}$)$_{q4}$	41/55	33/54	4·9	12·9
76C Glasgow	12(**C**$_{300\times2}$**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$	78/112	77/103	−9·1	27·6
76E EORTC 09771	24(**C**$_{50\times14}$**M**$_{15\times2}$**F**$_{350\times2}$)$_{q4}$	95/229	106/223	−12·3	45·6
77B$_{1+2}$ Danish BCG 77b	12(**C**$_{80\times14}$**M**$_{30\times2}$**F**$_{500\times2}$)$_{q4}$	122/201	140/196	−13·0	47·0
78E UK/Asia Collab.	8(**C**$_{50}$**M**$_{25}$**F**$_{600}$)$_{q3}$; 16(**C**$_{100\times4}$**M**$_{25}$**F**$_{600}$)$_{q4}$	112/247	110/241	6·6	41·5
79E Guy's/Manch. II	6(**C**$_{80\times14}$**M**$_{32\times2}$**F**$_{480\times2}$)$_{q4}$	127/185	167/207	−27·2	52·0
79H Paris	6(**C**$_{400\times2}$**M**$_{40\times2}$**F**$_{400\times2}$)$_{q4}$	20/172	23/163	−0·8	9·5
80F FM Italy 8004	12(**C**$_{600}$**M**$_{40}$**F**$_{600}$)$_{q3}$	16/49	27/47	−6·8	9·5
82C DBCG 82c *postmenop.*	9(**C**$_{600}$**M**$_{40\times2}$**F**$_{400\times2}$)$_{q4}$	536/708	553/737	−1·6	232·3
84D NCIC MA.4	8(**C**$_{600}$**M**$_{40}$**F**$_{600}$)$_{q3}$	132/381	137/377	−6·7	59·9
86H$_2$ IBCSG VII *	3(**C**$_{100\times14}$**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$	328/636	2(174/318)	−12·4	98·6
87D$_3$ GABG 3 Germany	6(**C**$_{500\times2}$**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$	36/278	35/248	−2·6	16·2
88D IBCSG IX	3(**C**$_{100\times14}$**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$	146/853	179/862	−19·7	78·8
89J$_1$ CRCRAMS Moscow	6(**C**$_{550\times2}$**M**$_{25\times2}$**F**$_{500\times2}$)$_{q3-4}$	0/11	1/10	−0·4	0·2
90X$_1$ Tokyo CIH	6(**C**$_{500}$**M**$_{30}$**F**$_{500}$)$_{q3}$	13/144	9/143	2·5	5·2
90£ Sweden−Finland	9(**C**$_{600}$**M**$_{40}$**F**$_{600}$)$_{q3}$	*(≈100 patients)*		*(no data)*	
93S Hamburg, Germany	6(**C**$_{500\times2}$**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$	12/117	15/125	0·0	5·9
93X INC Brazil	6(**C**$_{600}$**M**$_{40}$**F**$_{600}$)$_{q3}$	*(45 patients)*		*(no data)*	
94P Charles U Prague	6(**C**$_{500\times2}$**M**$_{40\times2}$**F**$_{600\times2}$)$_{q4}$	*(103 patients)*		*(no data)*	
(b) subtotal with data §		**1814/ 4378 (41·4%)**	**1960/ 4372 (44·8%)**	**−98·7**	**742·8**
Total (a + b)		**2687/ 7043 (38·2%)**	**2920/ 6960 (42·0%)**	**−169·7**	**1146·9**



99% or 95% confidence intervals

Difference between treatment effects in 2 subtotals: χ^2_1 = 0·5; 2p > 0·1; NS

Heterogeneity within subtotals: χ^2_{26} = 43·6; p = 0·02

Heterogeneity between 28 trials: χ^2_{27} = 44·1; p = 0·02

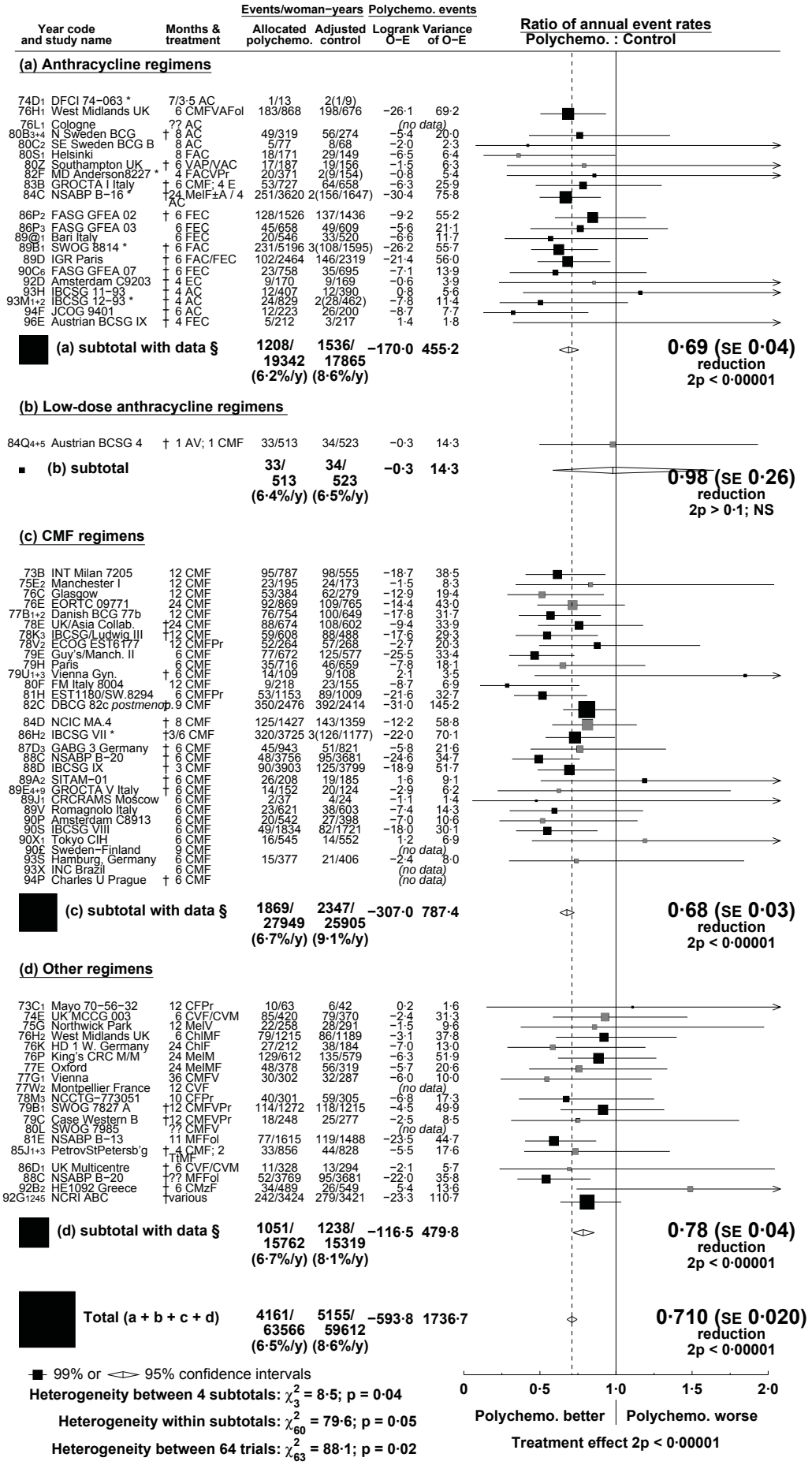
§ 3 trials with no data do not contribute to subtotals or to the overall total.

* For balance, control patients in 3−way trials or trial strata count half or twice in subtotal(s) and in final total of deaths/women.

Agents: **C** = cyclophosphamide; **F** = fluorouracil; **M** = methotrexate
(Not shown: antibiotic, hormonal, local or steroid therapies)

Semicolon [;] indicates treatment sequence; ×2 means d1,8 iv; ×4 means d3−6 iv

P 57: EARLY RECURRENCE (first 5 years) in trials of polychemotherapy vs. No chemotherapy

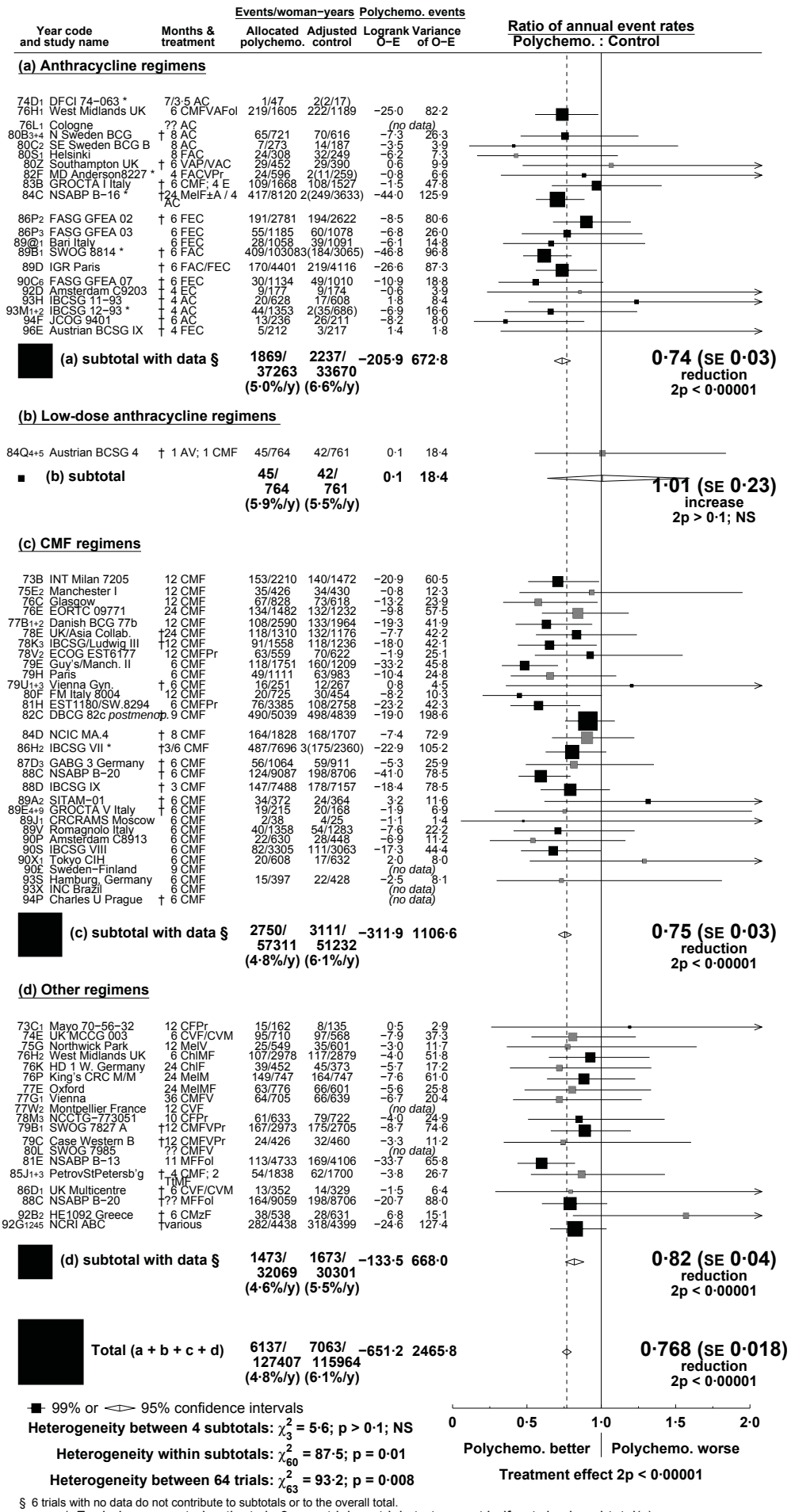


§ 6 trials with no data do not contribute to subtotals or to the overall total.

* For balance, control patients in 3−way trials or trial strata count half or twice in subtotal(s) and in final total of events/woman−years.

† Chemotherapy plus tamoxifen *versus* same tamoxifen alone

P 58: RECURRENCE in trials of polychemotherapy vs. No chemotherapy

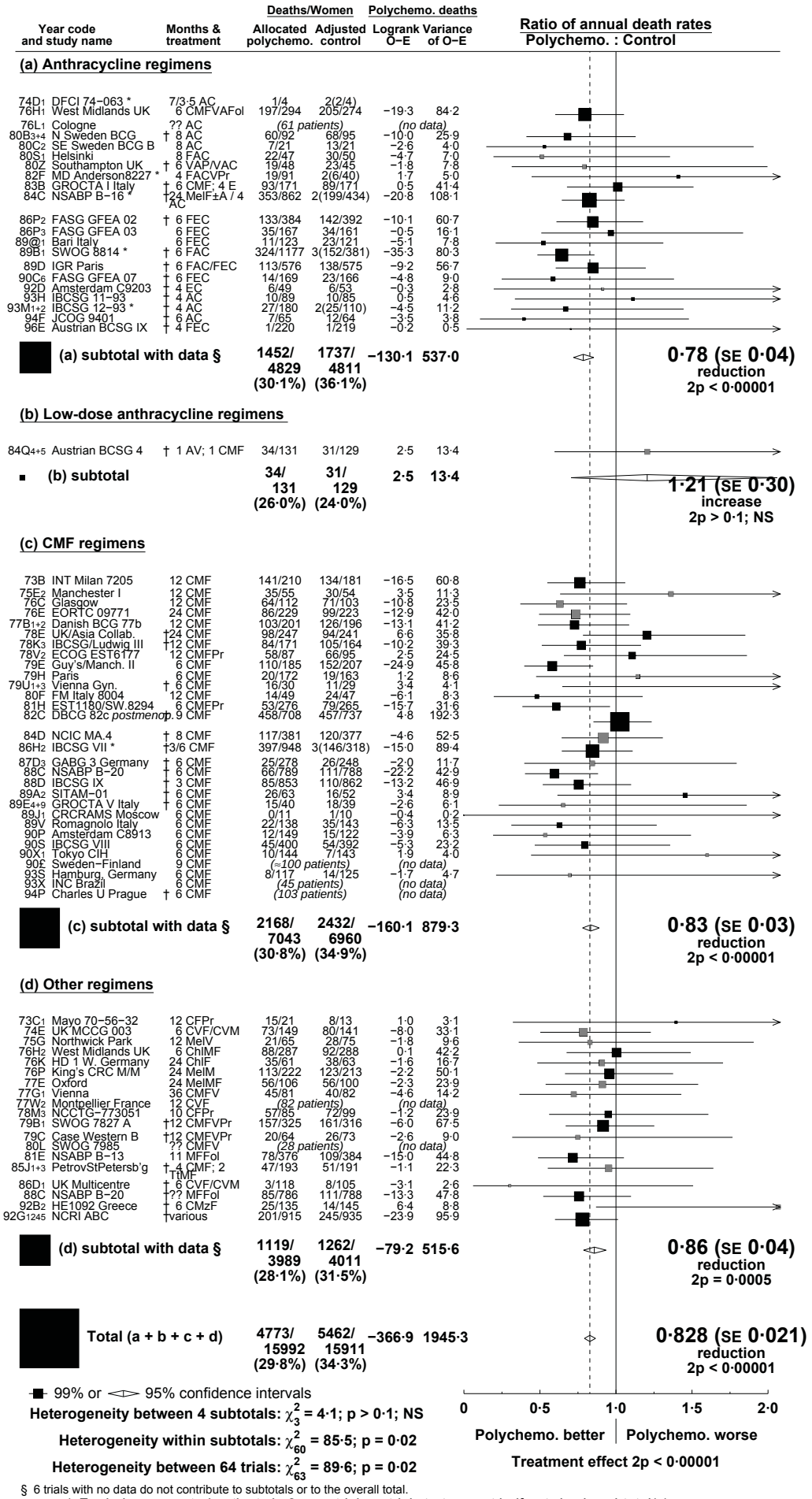


§ 6 trials with no data do not contribute to subtotals or to the overall total.

* For balance, control patients in 3−way trials or trial strata count half or twice in subtotal(s) and in final total of events/woman−years.

† Chemotherapy plus tamoxifen *versus* same tamoxifen alone

P 59: BREAST CANCER MORTALITY (MORTALITY WITH RECURRENCE) in trials of polychemotherapy vs. No Chemotherapy

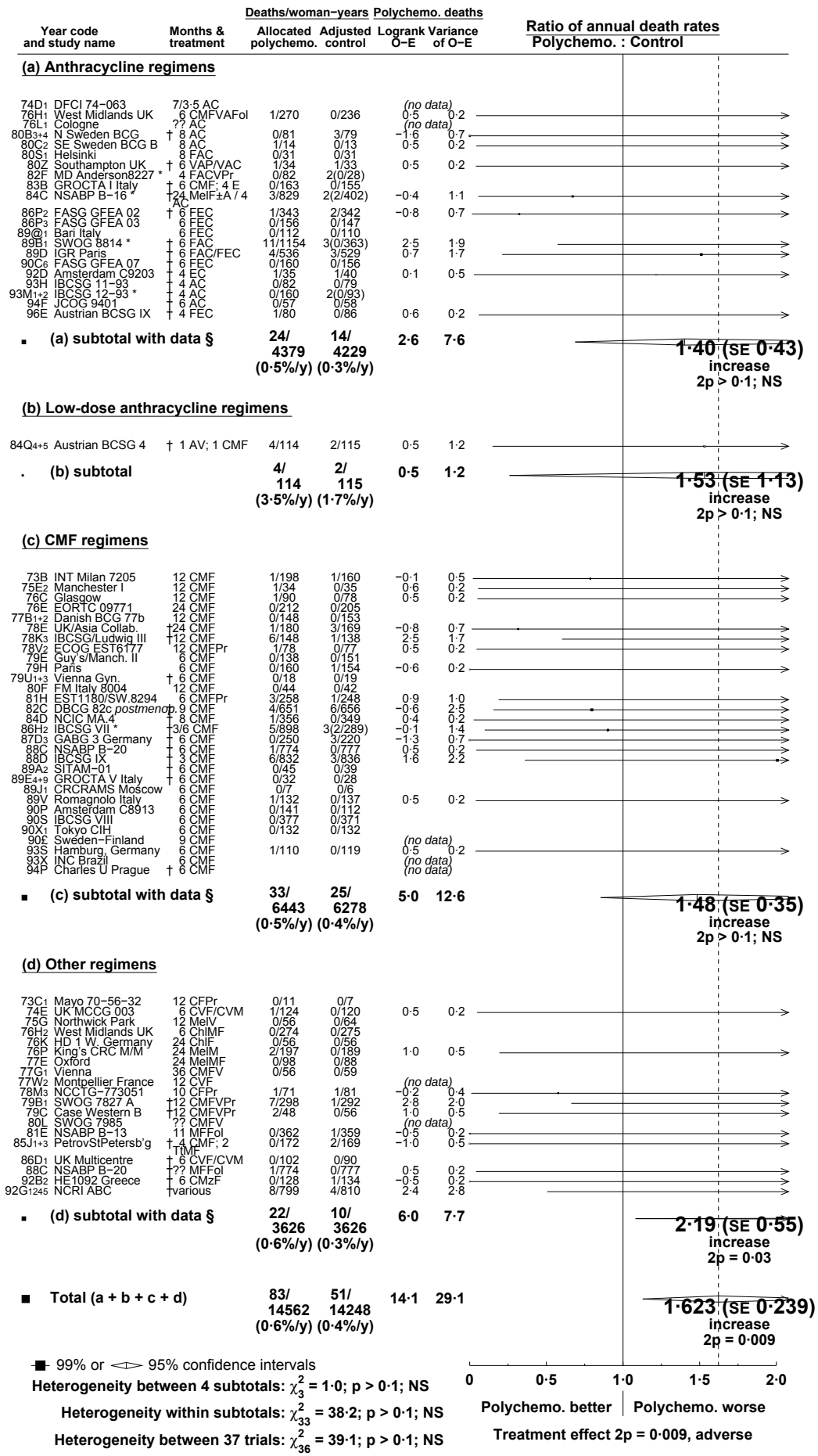


§ 6 trials with no data do not contribute to subtotals or to the overall total.

* For balance, control patients in 3−way trials or trial strata count half or twice in subtotal(s) and in final total of deaths/women.

† Chemotherapy plus tamoxifen *versus* same tamoxifen alone

P 60: MORTALITY WITHOUT RECURRENCE IN FIRST YEAR in trials of polychemotherapy vs. No chemotherapy

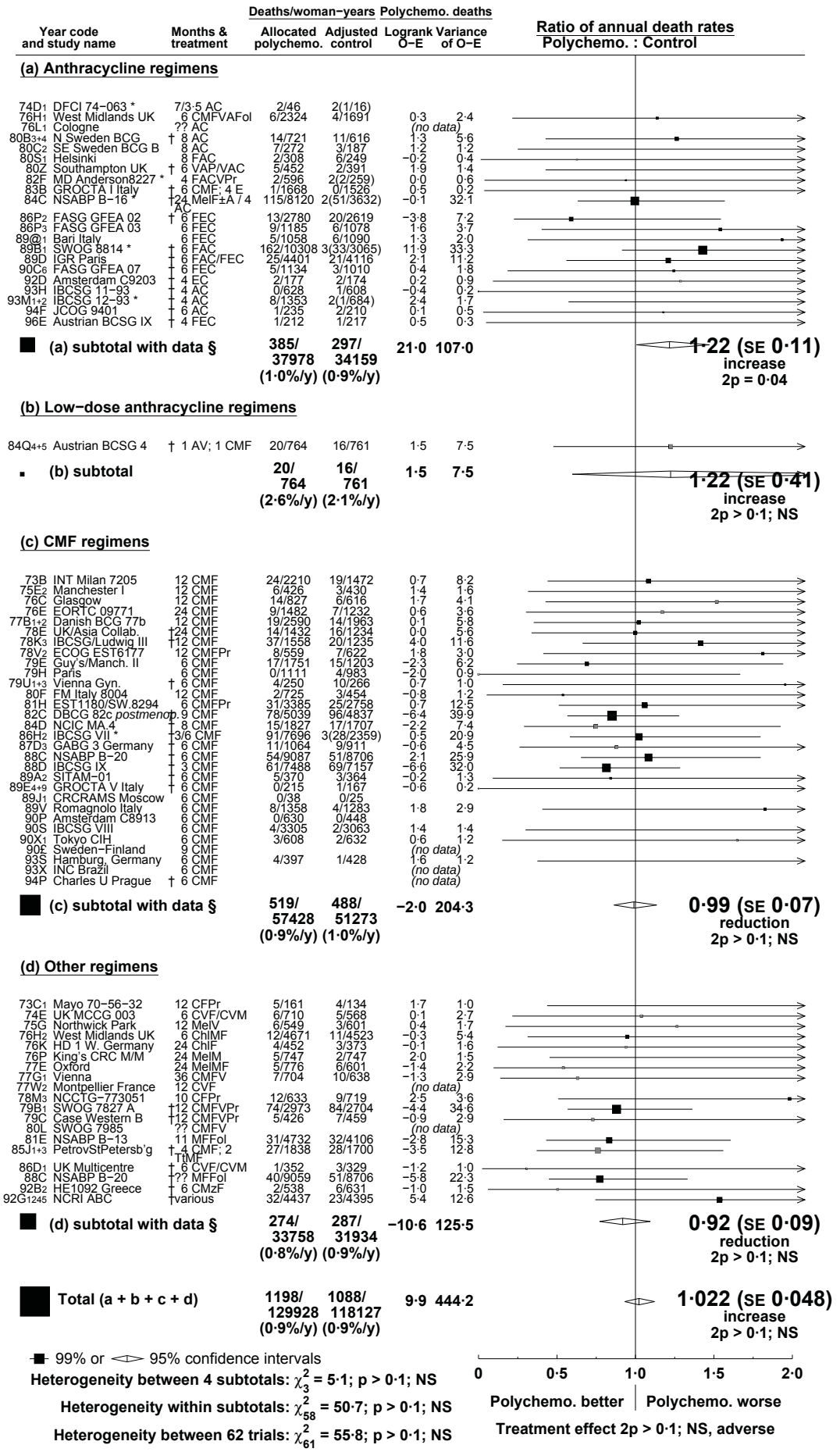


§ 7 trials with no data do not contribute to subtotals or to the overall total.

* For balance, control patients in 3−way trials or trial strata count half or twice in subtotal(s) and in final total of deaths/woman−years.

† Chemotherapy plus tamoxifen *versus* same tamoxifen alone

P 61: MORTALITY WITHOUT RECURRENCE in trials of polychemotherapy vs. No chemotherapy

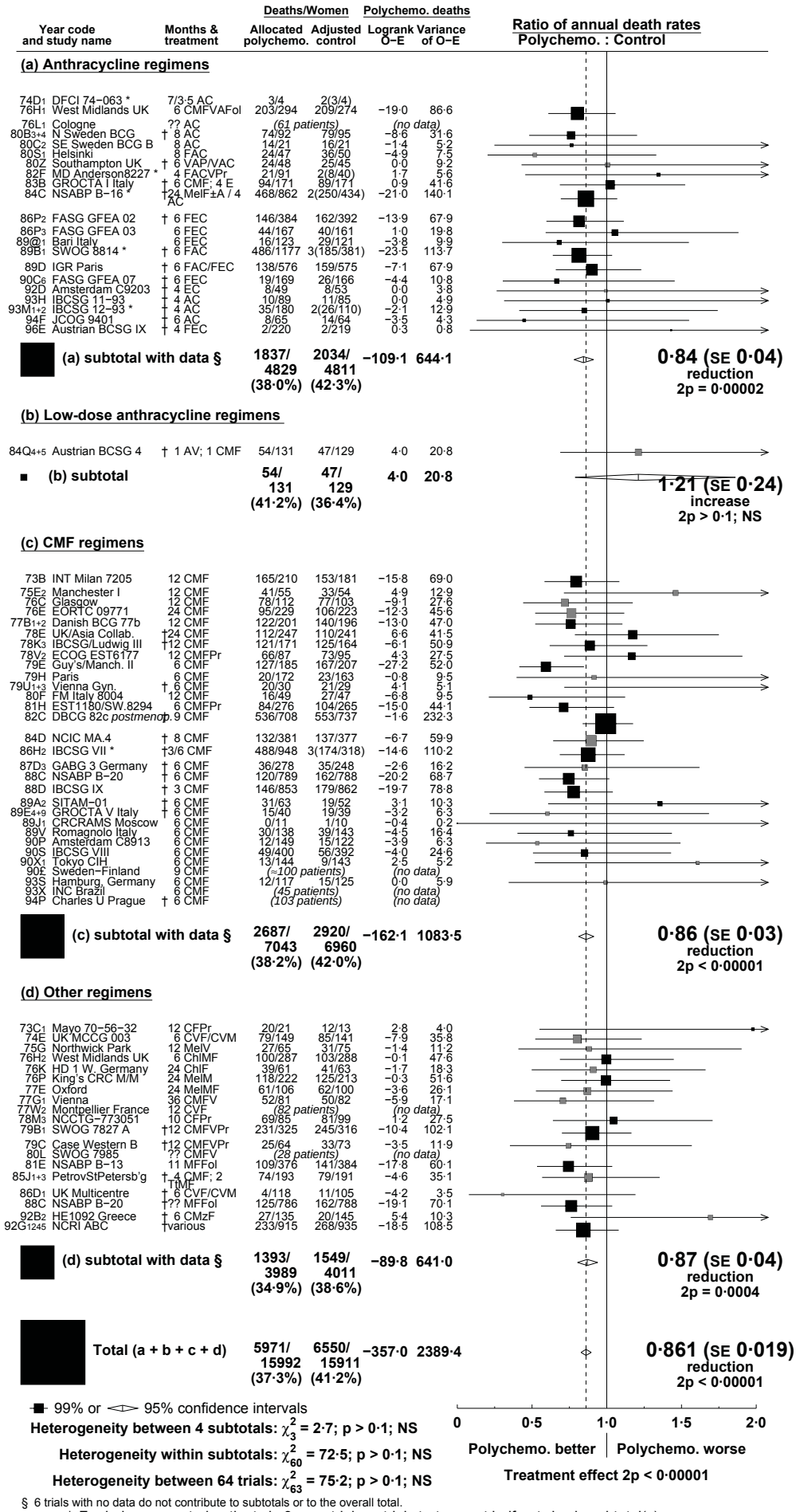


§ 6 trials with no data do not contribute to subtotals or to the overall total.

* For balance, control patients in 3−way trials or trial strata count half or twice in subtotal(s) and in final total of deaths/woman−years.

† Chemotherapy plus tamoxifen *versus* same tamoxifen alone

P 62: OVERALL MORTALITY in trials of polychemotherapy vs. No chemotherapy



§ 6 trials with no data do not contribute to subtotals or to the overall total.

* For balance, control patients in 3−way trials or trial strata count half or twice in subtotal(s) and in final total of deaths/women.

† Chemotherapy plus tamoxifen *versus* same tamoxifen alone

P63: Table of non-breast-cancer mortality without recurrence during the first year after randomisation, by age for various chemotherapy comparisons

Treatments compared (Active *vs* Control)	Entry age (years)*	Deaths/woman-years Active		Control**	
1. Taxane-plus-anthracycline-based regimen *vs* same or more non-taxane chemotherapy	<55	28/13174	(0·2%)	21/13117	(0·2%)
	55-69	31/6303	(0·5%)	19/6269	(0·3%)
	70+	7/244	(2·9%)	6/264	(2·3%)
	All	**66/19721**	**(0·3%)**	**46/19650**	**(0·2%)**
2. Any anthracycline-based regimen* *vs* standard CMF	<55	12/6416	(0·2%)	13/6405	(0·2%)
	55-69	11/1821	(0·6%)	13/1780	(0·7%)
	70+	0/78	(0·0%)	1/80	(1·3%)
	All	**23/8358**	**(0·3%)**	**27/8321**	**(0·3%)**
3. Any anthracycline-based regimen *vs* no chemotherapy	<55	3/1356	(0·2%)	4/1324	(0·3%)
	55-69	17/2766	(0·6%)	10/2677	(0·4%)
	70+	4/168	(2·4%)	0/162	(0·0%)
	All	**24/4296**	**(0·6%)**	**14/4165**	**(0·3%)**
4. Any CMF regimen *vs* no chemotherapy†	<55	3/2748	(0·1%)	5/2613	(0·2%)
	55-69	27/3452	(0·8%)	15/3435	(0·4%)
	70+	3/228	(1·3%)	5/231	(2·2%)
	All	**33/6429**	**(0·5%)**	**25/6279**	**(0·4%)**

* The few women of unknown age are excluded from the age-specific subgroups but included in the totals; none of them died in year 0 without recurrence.

** For balance, control patients count twice in the few trials with allocation ratio 2:1.

† 8/468 (2·1%) *vs* 2/540 (0·4%) in 3 small, old (began 1973-78) trials of 12 cycles of standard CMF,
8/2194 (0·4%) *vs* 3/2047 (0·15%) in trials of 6 cycles of standard CMF, and
14/4374 (0·4%) *vs* 20/4370 (0·5%) in trials of other CMF regimens.

P 64: One or more references for each trial in the forest plots on pp 21-50 of breast cancer mortality (in the same order as in those forest plots)

Trials of TAXANES (see webappendix page 23):

(a) Taxane-plus-anthracycline-based regimen (with taxane courses NOT overlapping with any other chemo. courses) vs the SAME non-taxane cytotoxic regimen, but without the taxane courses

Year Code	Trial name	Publication(s)
98B	Taxit216 Italy	Cognetti F, De Laurentiis M, De Matteis A, et al. Sequential epirubicin-docetaxel-CMF as adjuvant therapy for node-positive early stage breast cancer: updated results of the Taxit216 randomized trial. *Ann Oncol* 2008; **19:** viii77, A1820 (abstract). Bianco AR, De Laurentiis M, De Placido S, et al. Sequential epirubicin-docetaxel-CMF as adjuvant therapy for node-positive early-stage breast cancer: Subgroup analysis of the Taxit216 randomized trial. Breast Cancer Symposium 5-7 Sep 2008, A187 (abstract); Washington DC, USA.
99T	GOIM 9902 Italy	Lopez M, Brandi M, Foggi P, et al. Toxicity of epirubicin and cyclophosphamide (EC) vs. docetaxel (D) followed by EC in the adjuvant (adj) treatment of node positive breast cancer. A multicenter randomized phase III study (GOIM9902). *J Clin Oncol* 2006; **24:** A10526 (abstract).
95J[1-2]	NSABP B-27	Bear HD, Anderson S, Smith RE, et al. Sequential preoperative or postoperative docetaxel added to preoperative doxorubicin plus cyclophosphamide for operable breast cancer: National Surgical Adjuvant Breast and Bowel Project Protocol B-27. *J Clin Oncol* 2006; **24:** 2019-27.
95K	NSABP B-28	Mamounas EP, Bryant J, Lembersky B, et al. Paclitaxel after doxorubicin plus cyclophosphamide as adjuvant chemotherapy for node-positive breast cancer: results from NSABP B-28. *J Clin Oncol* 2005; **23:** 3686-96.
94D[1-3]	CALGB 9344	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:** 976-83. Berry DA, Thor A, Jewell SD, et al. Benefits of adding paclitaxel to adjuvant doxorubicin/cyclophosphamide depending on HER2 & ER status: analysis of tumor tissue microarrays and immunohistochemistry in CALGB 9344 (Intergroup 0148). *Cancer Res* 2009; **69:** A606 (abstract).

(b) Taxane-plus-anthracycline-based regimen (with taxane courses NOT overlapping with any other chemo. courses) vs MORE (but < doubled) non-taxane cytotoxic chemotherapy

Year Code	Trial name	Publication(s)
00S	WSG/AGO AM-02	Nitz U, Huober J, Lisboa B, et al. Superiority of sequential docetaxel over standard FE100C in patients with intermediate risk breast cancer: survival results of the randomized intergroup phase III trial EC-Doc. *Cancer Res* 2009; **69:** A78 (abstract).
95T	HORG Greece	Polyzos A, Malamos N, Boukovinas I, et al. FEC versus sequential docetaxel followed by epirubicin/cyclo-phosphamide as adjuvant chemotherapy in women with axillary node-positive early breast cancer: a randomized study of the Hellenic Oncology Research Group (HORG). *Breast Cancer Res Treat* 2010; **119:** 95-104.
00E	FinHer/FBCG 00-01	Joensuu H, Bono P, Kataja V, et al. Fluorouracil, epirubicin, and cyclophosphamide with either docetaxel or vinorelbine, with or without trastuzumab, as adjuvant treatments of breast cancer: final results of the FinHer Trial. *J Clin Oncol* 2009; **27:** 5685-92.
98D[1]	BIG 02-98	Francis P, Crown J, Di Leo A, et al. Adjuvant chemotherapy with sequential or concurrent anthracycline and docetaxel: Breast International Group 02-98 randomized trial. *J Natl Cancer Inst* 2008; **100:** 121-33. Di Leo A, Francis P, Crown JP, et al. Overall survival benefit for sequential doxorubicin-docetaxel compared to concomitant doxorubicin and docetaxel in node-positive breast cancer. 8-year results of the Breast International Group (BIG) 2-98 phase III adjuvant trial. *Cancer Res* 2009; **69:** A601 (abstract).
99K	GEICAM 9906 Spain	Rodriguez-Lescure A, Martin M, Ruiz A, et al. Subgroup analysis of GEICAM 9906 trial comparing six cycles of FE90C (FEC) to four cycles of FE90C followed by 8 weekly paclitaxel administrations (FECP): Relevance of HER2 and hormonal status (HR). *J Clin Oncol* 2007; **25:** A10598 (abstract).
97R	HE1097 Greece	Fountzilas G, Skarlos D, Dafni U, et al. Postoperative dose-dense sequential chemotherapy with epirubicin, followed by CMF with or without paclitaxel, in patients with high-risk operable breast cancer: a randomized phase III study conducted by the Hellenic Cooperative Oncology Group. *Ann Oncol* 2005; **16:** 1762-71.
00F[1]	NCIC MA.21	Burnell M, Levine MN, Chapman JAW, et al. Cyclophosphamide, epirubicin, and fluorouracil versus dose-dense epirubicin and cyclophosphamide followed by paclitaxel versus doxorubicin and cyclophosphamide followed by paclitaxel in node-positive or high-risk node-negative breast cancer. *J Clin Oncol* 2010; **28:** 77-82.
00U	AERO B−2000 France	Delbaldo C, Serin D, Mousseau M, et al. A phase III adjuvant randomized trial of 6 cycles of 5-fluorouracil - epirubicine-cyclophosphamide (FEC100) versus 4 FEC 100 followed by 4 taxol (FEC-T) in node positive breast cancer patients (trial B2000). *Cancer Res* 2010; **70:** P5-10-05 (abstract).
03R	GIM 1 Italy	http://www.slidefinder.net/c/clinical_trials_breast_cancer_italy/8472086

(c) Taxane-plus-anthracycline-based regimen (with taxane given CONCURRENTLY with other cytotoxic drugs) vs MORE (but < doubled) non-taxane cytotoxic chemotherapy

Year Code	Trial name	Publication(s)
01E[1+3]	PACS 04 France	Roché H, Allouache D, Romieu G, et al. Five-year analysis of the FNCLCC-PACS04 trial: FEC100 vs ED75 for the adjuvant treatment of node positive breast cancer. *Cancer Res* 2009; **69:** A602 (abstract).
97L	BCIRG 001	Martin M, Pienkowski T, Mackey J, et al. Adjuvant docetaxel for node-positive breast cancer. *N Engl J Med* 2005; **352:** 2302-13. Hugh J, Hanson J, Cheang MCU, et al. Breast cancer subtypes and response to docetaxel in node-positive breast cancer: Use of an immunohistochemical definition in the BCIRG 001 trial. *J Clin Oncol* 2009; **27**: 1168-76.
99%	GEICAM 9805 Spain	Martín M, Seguí MA, Antón A, et al. Adjuvant docetaxel for high-risk, node-negative breast cancer. *N Engl J Med* 2010; **363:** 2200-10.

[Trials of taxanes continue on the next page]

98D[2]	BIG 02-98	Francis P, Crown J, Di Leo A, et al. Adjuvant chemotherapy with sequential or concurrent anthracycline and docetaxel: Breast International Group 02-98 randomized trial. *J Natl Cancer Inst* 2008; **100:** 121-33. Di Leo A, Francis P, Crown JP, et al. Overall survival benefit for sequential doxorubicin-docetaxel compared to concomitant doxorubicin and docetaxel in node-positive breast cancer. 8-yr. Results of the Breast International Group (BIG) 2-98 phase III adjuvant trial. *Cancer Res* 2009; **69:** A601 (abstract).
99N	RAPP-01 France	Brain EGC, Bachelot T, Serin D, et al. Life-threatening sepsis associated with adjuvant doxorubicin plus docetaxel for intermediate-risk breast cancer. *JAMA* 2005; **293:** 2367-71. Brain EG, Debled M, Eymard J, et al. Final results of the RAPP-01 phase III trial comparing doxorubicin and docetaxel with doxorubicin and cyclophosphamide in the adjuvant treatment of high-risk node negative and limited node positive (<=3) breast cancer patients. *Cancer Res* 2009; **69:** A4101.
98T	ECOG EST2197	Goldstein LJ, O'Neill A, Sparano JA, et al. Concurrent doxorubicin plus docetaxel is not more effective than concurrent doxorubicin plus cyclophosphamide in operable breast cancer with 0 to 3 positive axillary nodes: North American Breast Cancer Intergroup trial E 2197. *J Clin Oncol* 2008; **26:** 4092-99. Badve SS, Baehner FL, Gray RP, et al. Estrogen- and progesterone-receptor status in ECOG 2197: comparison of immunohistochemistry by local and central laboratories and quantitative reverse transcription polymerase chain reaction by central laboratory. *J Clin Oncol* 2008; **26:** 2473-81.
96W[1-2]	ECTO Italy	Gianni L, Baselga J, Eiermann W, et al. Phase III trial evaluating the addition of paclitaxel to doxorubicin followed by cyclophosphamide, methotrexate, and fluorouracil, as adjuvant or primary systemic therapy: European Cooperative Trial in Operable Breast Cancer. *J Clin Oncol* 2009; **27:** 2474-81.
96%	Multicentre Germany	Kümmel S, Krocker J, Kohls A, et al. Randomised trial: survival benefit and safety of adjuvant dose-dense chemotherapy for node-positive breast cancer. *Br J Cancer* 2006; **94:** 1237-44.
96X	GONO Italy MIG 5	Del Mastro L, Costantini M, Durando A, et al. Cyclophosphamide, epirubicin, and 5-fluorouracil versus epirubicin plus paclitaxel in node-positive early breast cancer patients: A randomized, phase III study of Gruppo Oncologico Nord Ovest-Mammella Intergruppo Group. *J Clin Oncol* 2008; **26:** 10s, A516 (abstract).

(d) Taxane-plus-anthracycline-based regimen (with taxane courses NOT overlapping with any other chemo. courses) vs DOUBLED (or ≈ doubled) non−taxane cytotoxic chemotherapy

Year Code	Trial name	Publication(s)
01F	TACT UK (Control A)	Ellis P, Barrett-Lee P, Johnson L, et al. Sequential docetaxel as adjuvant chemotherapy for early breast cancer (TACT): an open-label, phase III, randomised controlled trial. *Lancet* 2009; **373:** 1681-92. Tutt A, Gillett C, Pinder S, et al. Microtubule associated protein tau expression as a predictive and prognostic marker in a trial assessing sequential docetaxel as adjuvant chemotherapy for early breast cancer (TACT). *Cancer Res* 2009; **69:** A607 (abstract).
01G	TACT UK (Control B)	Ellis P, Barrett-Lee P, Johnson L, et al. Sequential docetaxel as adjuvant chemotherapy for early breast cancer (TACT): an open-label, phase III, randomised controlled trial. *Lancet* 2009; **373:** 1681-92. Tutt A, Gillett C, Pinder S, et al. Microtubule associated protein tau expression as a predictive and prognostic marker in a trial assessing sequential docetaxel as adjuvant chemotherapy for early breast cancer (TACT). *Cancer Res* 2009; **69:** A607 (abstract).
01T	LMU Munich ADEBAR	Sommer HL, Jueckstock JK, Genss E, et al. Influence of sequencing of chemotherapy and radiotherapy regarding adverse effects of cytostatic treatment: Results of the ADEBAR trial. *J Clin Oncol* 2007; **25:** 17s, A559 (abstract). Janni WJ, Harbeck N, Sommer H, et al. Sequential treatment with epirubicin/cyclophosphamide followed by docetaxel is equi-effective, but less toxic, than FEC120 in the adjuvant treatment of breast cancer patients with extensive lymph node involvement: The German ADEBAR phase III study. *Cancer Res* 2009; **69:** A604 (abstract).
96F	Aberdeen Scotland	Walker LG, Walker MB, Anderson J, et al. Quality of life during primary chemotherapy for breast cancer with continuing cyclophosphamide, vincristine, adriamycin and prednisolone versus sequential docetaxel: a randomised trial. *Breast Cancer Res Treat* 2002; **76:** S52, A160 (abstract).
97J	PACS 01 France	Coudert B, Campone M, Spielmann M, et al. Benefit of the sequential administration of docetaxel after standard FEC regimen for node-positive breast cancer: long-term follow-up results of the FNCLCC-PACS 01 trial. *Cancer Res* 2009; **69:** A603 (abstract).
97A	DEVA UK	Coombes RC, Bliss JM, Espie M, et al. DEVA: Randomized trial of sequential epirubicin and docetaxel versus epirubicin alone in node-positive postmenopausal early breast cancer (EBC) patients. *J Clin Oncol* 2010; **28:** 76S, A536 (abstract).
94B	MD Anderson	Buzdar AU, Singletary SE, Valero V, et al. Evaluation of paclitaxel in adjuvant chemotherapy for patients with operable breast cancer: preliminary data of a prospective randomized trial. *Clin Cancer Res* 2002; **8**: 1073-79.
00F[2]	NCIC MA.21	Burnell M, Levine MN, Chapman JAW, et al. Cyclophosphamide, epirubicin, and fluorouracil versus dose-dense epirubicin and cyclophosphamide followed by paclitaxel versus doxorubicin and cyclophosphamide followed by paclitaxel in node-positive or high-risk node-negative breast cancer. *J Clin Oncol* 2010; **28:** 77-82.
02D	GBG 42 / NNBC 3−Eur.	Thomssen C, Kantelhardt EJ, Plueckhahn K, et al. Report of toxicities from the multicenter, randomized NNBC 3-Europe trial: 6xFEC versus 3xFEC-3xDoc for high-risk node-negative breast cancer patients. *J Clin Oncol* 2010; **28:** 80S, A554 (abstract). Kantelhardt EJ, Thomssen C, Vetter M, et al. Molecular types and prognostic markers uPA/PAI-1 for 2,497 early breast cancer patients in the multicenter, randomized NNBC 3-Europe trial. *J Clin Oncol* 2010; **28:** A10539.

(e) Taxane trial with no anthracycline in one allocation

Year Code	Trial name	Publication(s)
00S	WSG/AGO AM-02	Nitz U, Huober J, Lisboa B, et al. Superiority of sequential docetaxel over standard FE100C in patients with intermediate risk breast cancer: survival results of the randomized intergroup phase III trial EC-Doc. *Cancer Res* 2009; **69:** A78 (abstract).
97N	USO 97-35	Jones S, Holmes FA, O'Shaughnessy J, et al. Docetaxel with cyclophosphamide is associated with an overall survival benefit compared with doxorubicin and cyclophsphamide: 7-year follow-up of US Oncology Research Trial 9735. *J Clin Oncol* 2009; **27:** 1177-83.

Trials of any anthracycline-based regimen vs. standard CMF (or near-standard CMF) (see webappendix page 29):

(a) Anthracycline dose/cycle ≥ A60 or E90

i. Cumulative anthracycline dose A360 or E720-800

Year Code	Trial name	Publication(s)
88R	Brussels Belgium	Bernard Marty C, Mano M, Paesmans M, et al. Second malignancies following adjuvant chemotherapy: 6-year results from a Belgian randomized study comparing cyclophosphamide, methotrexate and 5-fluorouracil (CMF) with an anthracycline-based regimen in adjuvant treatment of node-positive breast cancer patients. *Ann Oncol* 2003; **14:** 693-98.
89R	NCIC MA.5	Pritchard KI, Shepherd LE, O'Malley FP, et al. *HER2* and responsiveness of breast cancer to adjuvant chemotherapy. *N Engl J Med* 2006; **354:** 2103-11.
89B2	SWOG 8897	Hutchins LF, Green SJ, Ravdin PM, et al. Randomized, controlled trial of cyclophosphamide, methotrexate, and fluorouracil versus cyclophosphamide, doxorubicin, and fluorouracil with and without tamoxifen for high-risk, node-negative breast cancer: treatment results of Intergroup protocol INT-0102. *J Clin Oncol* 2005; **23:** 8313-21.

ii. Cumulative anthracycline dose A300 or E400-480

Year Code	Trial name	Publication(s)
86S	GOCCNE Italy	Galligioni E, Cetto G, Nascimben O, et al. High dose epirubicin and cyclophosphamide (EC) vs cyclophosphamide, methotrexate, fluorouracil (CMF) as adjuvant chemotherapy in high risk premenopausal breast cancer patients (PTS). A prospective randomized trial. *Eur J Cancer* 1998; **34 (suppl 1):** 84 (abstract).
97G	FM Italy GMB1	*Personal communication*
90Z	GOIRC SANG2 Italy	Colozza M, Bisagni G, Mosconi AM, et al. Epirubicin versus CMF as adjuvant therapy for stage I and II breast cancer: a prospective randomised study. *Eur J Cancer* 2002; **38:** 2279-88.
84K1	GUN-3 Naples	De Placido S, Perrone F, Carlomagno C, et al. CMF vs alternating CMF/EV in the adjuvant treatment of operable breast cancer. A single centre randomised clinical trial (Naples GUN-3 study). *Br J Cancer* 1995; **71:** 1283-87.
96N	GOCSI MAM2 Italy	De Matteis A, De Laurentiis M, Nuzzo F, et al. Preliminary results from the IMPACT-B01/MAM2 GOCSI randomized trial of adjuvant therapy for breast cancer. *Ann Oncol* 2002; **13:** 16, A53 (abstract).
96A	NEAT, UK	Earl HM, Hiller L, Dunn JA, et al. NEAT: National Epirubicin Adjuvant Trial-toxicity, delivered dose intensity and quality of life. *Br J Cancer* 2008; **99:** 1226-31.
97U1+2	IBIS 03 Italy	Cyclophosphamide, Methotrexate, and Fluorouracil, With or Without Epirubicin Hydrochloride, in Treating Women Who Have Undergone Surgery for Breast Cancer [Internet] 2009 [updated 2009 Dec 13; cited 2011 Jun 16]. Available from: http://clinicaltrials.gov/ct2/show/study/NCT01031030?term=ibis+03&rank=1 Amadori D, Silvestrini R, De Lena M, et al. Randomized phase III trial of adjuvant epirubicin followed by cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) versus CMF followed by epirubicin in patients with node-negative or 1–3 node-positive rapidly proliferating breast cancer. *Breast Cancer Res Treat* 2011; **125:** 775-84.
91Q	GOCSI MAM1 Italy	De Placido S, De Laurentiis M, De Lena M, et al. A randomised factorial trial of sequential doxorubicin and CMF vs CMF and chemotherapy alone vs chemotherapy followed by goserelin plus tamoxifen as adjuvant treatment of node-positive breast cancer. *Br J Cancer* 2005; **92:** 467-74.

iii. Cumulative anthracycline dose A240

Year Code	Trial name	Publication(s)
84B1	NSABP B-15	Wickerham D, Fisher B, Brown A, et al. Two months of adriamycin + cyclophosphamide (AC) with and without interval reinduction therapy vs 6 months of conventional CMF in positive node breast cancer patients (pts) nonresponsive to tamoxifen: results of NSABP B-15. *Proc Annu Meet Am Soc Clin Oncol* 1990; **9:** A73 (abstract).
84B2	NSABP B-15	Wickerham D, Fisher B, Brown A, et al. Two months of adriamycin + cyclophosphamide (AC) with and without interval reinduction therapy vs 6 months of conventional CMF in positive node breast cancer patients (pts) nonresponsive to tamoxifen: results of NSABP B-15. *Proc Annu Meet Am Soc Clin Oncol* 1990; **9:** A73 (abstract).
91H	NSABP B-23	Fisher B, Anderson S, Tan Chiu E, et al. Tamoxifen and chemotherapy for axillary node-negative, estrogen receptor-negative breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-23. *J Clin Oncol* 2001; **19:** 931-42.

(b) Anthracycline dose/cycle < A60 or E90

Year Code	Trial name	Publication(s)
78L2	ONCOFRANCE	Misset JL, di Palma M, Delgado M, et al. Adjuvant treatment of node-positive breast cancer with cyclophosphamide, doxorubicin, fluorouracil, and vincristine versus cyclophosphamide, methotrexate, and fluorouracil: final report after a 16-year median follow-up duration. *J Clin Oncol* 1996; **14:** 1136-45.
88R	Brussels Belgium	Bernard Marty C, Mano M, Paesmans M, et al. Second malignancies following adjuvant chemotherapy: 6-year results from a Belgian randomized study comparing cyclophosphamide, methotrexate and 5-fluorouracil (CMF) with an anthracycline-based regimen in adjuvant treatment of node-positive breast cancer patients. *Ann Oncol* 2003; **14:** 693-98.
94J1+2+3	GOIRC SANG 2B R1	*Personal communication*
84L	ICCG C/2/84 UK	Coombes RC, Bliss JM, Wils J, et al. Adjuvant cyclophosphamide, methotrexate, and fluorouracil versus fluorouracil, epirubicin, and cyclophosphamide chemotherapy in premenopausal women with axillary node-positive operable breast cancer: results of a randomized trial. The International Collaborative Cancer Group. *J Clin Oncol* 1996; **14:** 35-45.
80C1	SE Sweden BCG A	Hrafnkelsson J, Nilsson K, Soderberg M. Tolerance of radiotherapy combined with adjuvant chemotherapy in breast cancer. *Acta Oncol* 1987; **26:** 269-72.
84N	ICCG C/6/89 UK	Marty M, Hall E, Wils J, et al. Evaluation of tolerability of CMF versus FEC in a randomised trial in node negative poor risk primary breast cancer patients. *Proc Annu Meet Am Soc Clin Oncol* 2002; **21:** 69a, A273 (abstract).

[End of anthracycline vs CMF; anthracycline vs nil follows]

Trials of Anthracycline−based regimen vs. No chemotherapy (see webappendix page 35):

(a) Anthracycline dose/cycle exactly A60 or E90

Year Code	Trial Name	Publication(s)
89B1	SWOG 8814	Albain KS, Barlow WE, Ravdin PM, et al. Adjuvant chemotherapy and timing of tamoxifen in postmenopausal patients with endocrine-responsive, node-positive breast cancer: a phase 3, open-label, randomised controlled trial. *Lancet* 2009; **374:** 2055-63.
92D	Amsterdam C9203	Nortier JWR; Slee PHTh; Veenhof CHN, et al. Adjuvant Tamoxifen plus combination chemotherapy with epirubicin and cyclophosphamide versus tamoxifen alone in postmenopausal node-positive breast cancer patients. Amsterdam Integraal Kankercentrum, The Netherlands, Sep 1993. (Protocol 12706, supplied by trialists)
93H	IBCSG 11-93	Thürlimann B, Price KN, Gelber RD, et al. Is chemotherapy necessary for premenopausal women with lower-risk node-positive, endocrine responsive breast cancer? 10-year update of International Breast Cancer Study Group Trial 11-93. *Breast Cancer Res Treat* 2009; **113:** 137-44.
93M1+2	IBCSG 12-93	International Breast Cancer Study Group. Toremifene and tamoxifen are equally effective for early-stage breast cancer: first results of International Breast Cancer Study Group Trials 12-93 and 14-93. *Ann Oncol* 2004; **15:**1749-1759
84C	NSABP B-16	Fisher B, Redmond C, Legault Poisson S, et al. Postoperative chemotherapy and tamoxifen compared with tamoxifen alone in the treatment of positive node breast cancer patients aged 50 years and older with tumors responsive to tamoxifen: Results from the National Surgical Adjuvant Breast and Bowel Project B-16. *J Clin Oncol* 1990; **8:** 1005-18.

(b) Anthracycline dose/cycle < A60 or E90, sorted by cumulative dose

Year Code	Trial Name	Publication(s)
76H1	West Midlands UK	Morrison JM, Howell A, Kelly KA, et al. West Midlands Oncology Association trials of adjuvant chemotherapy in operable breast cancer: Results after a median follow up of 7 years. I Patients with involved axillary lymph nodes. *Br J Cancer* 1989; **60:** 911-18.
76L1	Cologne	*Personal communication*
74D1	DFCI 74-063	Henderson IC, Gelman R, Parker LM, et al. 15 vs. 30 weeks (wks) of adjuvant chemotherapy for breast cancer patients (pts) with a high risk of reucrrence: A randomized trial. *Proc Ann Meet Am Soc Clin Oncol* 1982: C-290 (abstract).
80B3+4	N Sweden BCG	*Personal communication*
80C2	SE Sweden BCG B	Hrafnkelsson J, Nilsson K, Soderberg M. Tolerance of radiotherapy combined with adjuvant chemotherapy in breast cancer. *Acta Oncol* 1987; **26:** 269-72.
80S1	Helsinki	Blomqvist C, Tiusanen K, Elomaa I, et al. The combination of radiotherapy, adjuvant chemotherapy (cyclophosphamide doxorubicin ftorafur) and tamoxifen in stage II breast cancer. Long term follow up results of a randomised trial. *Br J Cancer* 1992; **66:** 1171-76.
84C2	NSABP B-16	Fisher B, Redmond C, Legault Poisson S, et al. Postoperative chemotherapy and tamoxifen compared with tamoxifen alone in the treatment of positive node breast cancer patients aged 50 years and older with tumors responsive to tamoxifen: Results from the National Surgical Adjuvant Breast and Bowel Project B-16. *J Clin Oncol* 1990; **8:** 1005-18.
80Z	Southampton UK	Williams CJ, Buchanan RB, Hall V, Taylor I. Adjuvant chemotherapy for T1-2, N0, M0 estrogen receptor (ER) negative breast cancer: preliminary results of a randomized trial. Fifth International Conference on the Adjuvant Therapy of Cancer. March 11-14 1987, Tucson, Arizona. page 46 (abstract).
94F	JCOG 9401	*Personal communication*
89D	IGR Paris	Arriagada R, Spielmann M, Koscielny S, et al. Patterns of failure in a randomized trial of adjuvant chemotherapy in postmenopausal patients with early breast cancer treated with tamoxifen. *Ann Oncol* 2002; **13:** 1378-1386 Arriagada R, Spielmann M, Koscielny S et al. Results of two randomized trials evaluating adjuvant anthracycline-based chemotherapy in 1146 patients with early breast cancer. *Acta Oncol* 2005; **44:** 458-466 Andre F, Khalil A, Slimane K, et al. Mitotic index and benefit of adjuvant anthracycline-based chemotherapy in patients with early breast cancer. *J Clin Oncol* 2005; **23:** 2996-3000.
83B	GROCTA I Italy	Boccardo F, Rubagotti A, Amoroso D, et al. Italian Breast Cancer Adjuvant Chemo-Hormone Therapy Cooperative Group Trials. GROCTA Trials. *Recent Results Cancer Res* 1998; **152:** 453-70.
86P2	FASG GFEA 02	Namer M, Fargeot P, Roche H, et al. Improved disease-free survival with epirubicin-based chemoendocrine adjuvant therapy compared with tamoxifen alone in one to three node-positive, estrogen-receptor-positive, postmenopausal breast cancer patients: results of French Adjuvant Study Group 02 and 07 trials. *Ann Oncol* 2006; **17:** 65-73.
86P3	FASG GFEA 03	Hery M, Bonneterre J, Roche H, et al. Epirubicin-based chemotherapy as adjuvant treatment for poor prognosis, node-negative breast cancer: 10-year follow-up results of the French Adjuvant Study Group 03 trial. *Bull Cancer* 2006; **93:** E109-14.
89@1	Bari Italy	Paradiso A, Schittulli F, Cellamare G, et al. Randomized clinical trial of adjuvant fluorouracil, epirubicin, and cyclophosphamide chemotherapy for patients with fast-proliferating, node-negative breast cancer. *J Clin Oncol* 2001; **19:** 3929-37.
90C6	FASG GFEA 07	Namer M, Fargeot P, Roche H, et al. Improved disease-free survival with epirubicin-based chemoendocrine adjuvant therapy compared with tamoxifen alone in one to three node-positive, estrogen-receptor-positive, postmenopausal breast cancer patients: results of French Adjuvant Study Group 02 and 07 trials. *Ann Oncol* 2006; **17:** 65-73.
96E	Austrian BCSG IX	Taucher S, Salat A, Gnant M, et al. Impact of pretreatment thrombocytosis on survival in primary breast cancer. *Thromb Haemost* 2003; **89:** 1098-1106.
82F	MD Anderson 8227	*Personal communication*

(c) Lower cumulative anthracycline dose

Year Code	Trial Name	Publication
84Q4+5	Austrian BCSG 4	Jakesz R, Hausmaninger H, et al. Randomized trial of low-dose chemotherapy added to tamoxifen in patients with receptor-positive and lymph node-positive breast cancer. *J Clin Oncol* 1999; **17:** 1701-09.

Trials of Standard CMF vs. No chemotherapy (see webappendix page 41):

Year Code	Trial name	Publication(s)
73B	INT Milan 7205	Bonadonna G, Zambetti M, Moliterni A, et al. Clinical relevance of different sequencing of doxorubicin and cyclophosphamide, methotrexate, and fluorouracil in operable breast cancer. J Clin Oncol 2004; 22:1614-20. Bonadonna G, Moliterni A, Zambetti M, et al. 30 years' follow up of randomised studies of adjuvant CMF in operable breast cancer: cohort study. *BMJ* 2005; **330:** 217-23.
78K3	IBCSG/Ludwig III	Pagani O, Price KN, Gelber RD, et al. Patterns of recurrence of early breast cancer according to estrogen receptor status: A therapeutic target for a quarter of a century. *Breast Cancer Res Treat* 2009; **117:** 319–324.
78V2	ECOG EST6177	Taylor SG, Knuiman MW, Sleeper LA, et al. Six-year results of the Eastern Cooperative Oncology Group trial of observation versus CMFP versus CMFPT in postmenopausal patients with node-positive breast cancer. *J Clin Oncol* 1989; **7:** 879-89.
79U1+3	Vienna Gyn.	Kubista E, Salzer H, Fischl F, et al. [Treatment of breast cancer at the 1st Gynecology Clinic at the University of Vienna]. *Wien Med Wochenschr* 1984; **134:** 251-5.
81H	EST1180/SW.8294	Mansour EG, Gray R, Shatila AH, et al. Efficacy of adjuvant chemotherapy in high-risk node-negative breast cancer. An Intergroup study. *N Engl J Med* 1989; **320:** 485-90.
86H2	IBCSG VII	The International Breast Cancer Study Group. Effectiveness of adjuvant chemotherapy in combination with tamoxifen for node-positive postmenopausal breast cancer patients. *J Clin Oncol* 1997; **15:** 1385-93.
88C	NSABP B-20	Mamounas EP, Tang G, Fisher B, et al. Association between the 21-gene recurrence score assay and risk of locoregional recurrence in node-negative, estrogen receptor-positive breast cancer: results from NSABP B-14 and NSABP B-20. *J Clin Oncol* 2010; **28:** 1677-83.
89A2	SITAM-01	Belfiglio M, Mari E, Nicolucci A, et al. Sitam-01 adjuvant breast trial for patients > 50 years. *Eur J Cancer* 1996; **32 (suppl 1):** 21 (abstract).
89E4+9	GROCTA V Italy	Boccardo F, Rubagotti A, Amoroso D, et al. Italian Breast Cancer Adjuvant Chemo-Hormone Therapy Cooperative Group Trials. GROCTA Trials. *Recent Results Cancer Res* 1998; **152:** 453-70.
89V	Romagnolo Italy	Amadori D, Nanni O, Volpi A, et al. Phase III randomized multicenter study on the effects of adjuvant CMF in patients with node-negative, rapidly proliferating breast cancer: twelve-year results and retrospective subgroup analysis. *Breast Cancer Res Treat* 2008; **108:** 259-64.
90P	Amsterdam C8913	*Personal communication*
90S	IBCSG VIII	Karlsson P, Sun Z, Braun D, et al. Long term results of International Breast Cancer Study Group Trial VIII: adjuvant chemotherapy plus goserelin compared with either therapy alone for premenopausal patients with node-negative breast cancer, *Ann Oncol* 2011; **22:** 2216-26.

Trials of Anthracycline Dosage (see webappendix page 47):

(a) Unconfounded comparisons

Year Code	Trial name	Publication(s)
86P1	FASG GFEA 01	Benchalal M, Le Prise E, De Lafontan B, et al. Influence of the time between surgery and radiotherapy on local recurrence in patients with lymph node-positive, early-stage, invasive breast carcinoma undergoing breast-conserving surgery: Results of the French Adjuvant Study Group. *Cancer* 2005; **104:** 240-250. Fumoleau P, Devaux Y, Vo-Van ML, et al. Premenopausal patients with node positive resectable breast cancer: a randomized trial comparing three adjuvant regimens: FEC50 x 6 cycles vs FEC50 x 3 cycles vs FEC75 x 3 cycles, preliminary results. *Ann Oncol* 1992; **3:** 203 (abstract).
90C3+5	FASG GFEA 05	Bonneterre J, Roche H, Kerbrat P, et al. French Adjuvant Study Group 05 trial (FEC 50 vs FEC 100): 10-year update of benefit/risk ratio after adjuvant chemotherapy (CT) in node-positive (N+), early breast cancer (EBC) patients (pts). *Proc Annu Meet Am Soc Clin Oncol* 2003; **22:** 24, A93 (abstract). Bonneterre JM, French Adjuvant Study Group. Long-term efficacy and toxicity of the FEC100 regimen. *Oncology (Williston Park)* 2004; **18(14), suppl 14:** 56-58.
92N	ICCG C/9/91 UK	Bliss JM, Wils J, Marty M, et al. Evaluation of the tolerability of FE50C versus FE75C in a prospective randomised trial in adjuvant breast cancer patients. *Proc Annu Meet Am Soc Clin Oncol* 2002; **21:** 51b, A2017 (abstract).
94D1&2	CALGB 9344	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:** 976-83. Berry DA, Thor A, Jewell SD, et al. Benefits of adding paclitaxel to adjuvant doxorubicin/cyclophosphamide depending on HER2 & ER status: analysis of tumor tissue microarrays and immunohistochemistry in CALGB 9344 (Intergroup 0148). *Cancer Res* 2009; **69:** A606 (abstract).

(b) Confounded comparisons

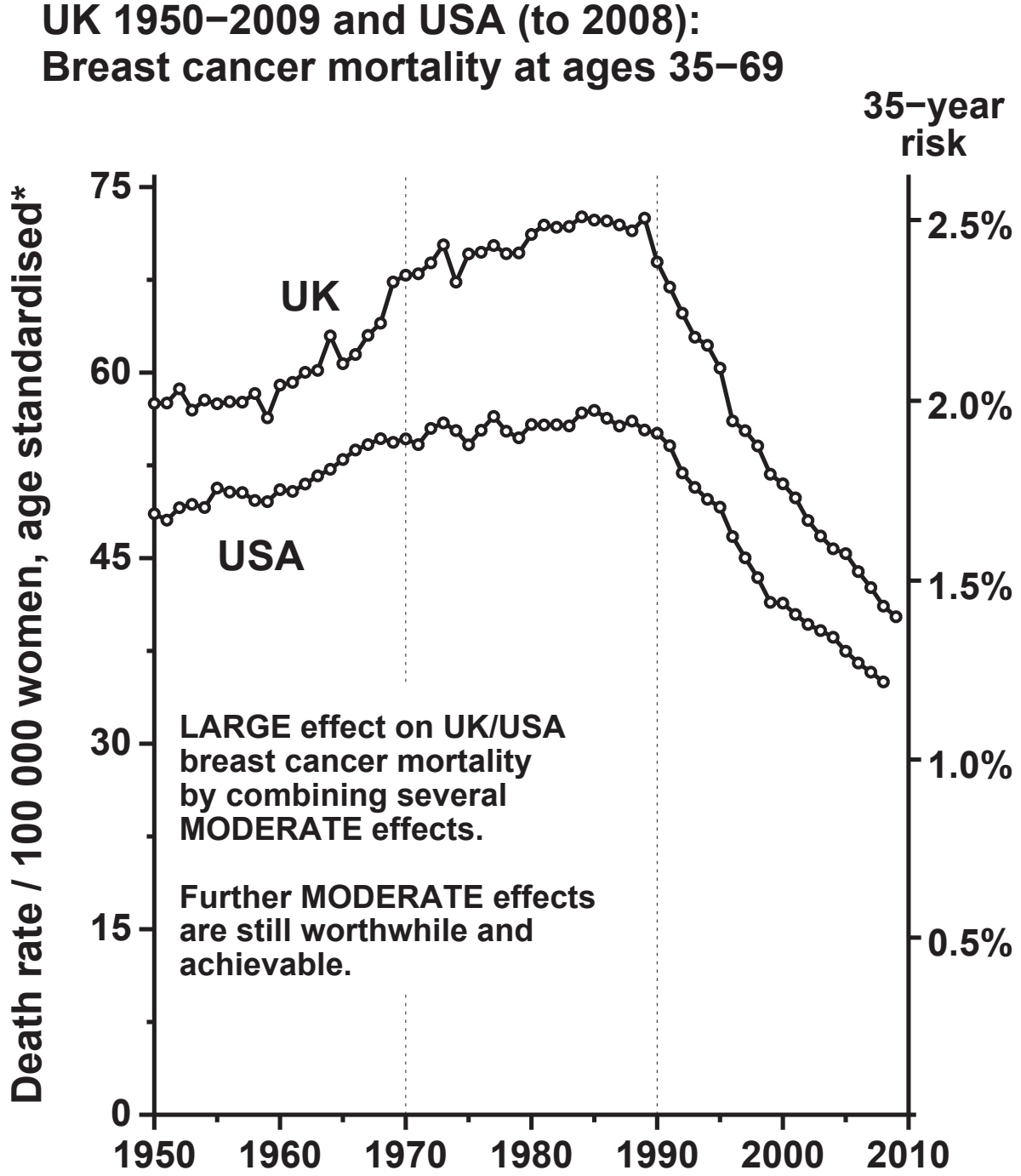
Year Code	Trial name	Publication(s)
85A	CALGB CLB-8541	Muss HB, Berry DA, Cirrincione C, et al. Toxicity of older and younger patients treated with adjuvant chemotherapy for node-positive breast cancer: the Cancer and Leukemia Group B experience. *J Clin Oncol* 2007; **25:** 3699-3704. Wood WC, Budman DR, Korzun AH, et al. Dose and dose intensity of adjuvant chemotherapy for stage II, node positive breast carcinoma. *N Engl J Med* 1994; **330:** 1253-59.
88R	Brussels Belgium	Bernard Marty C, Mano M, Paesmans M, et al. Second malignancies following adjuvant chemotherapy: 6-year results from a Belgian randomized study comparing cyclophosphamide, methotrexate and 5-fluorouracil (CMF) with an anthracycline-based regimen in adjuvant treatment of node-positive breast cancer patients. *Ann Oncol* 2003; **14:** 693-98.
00F	NCIC MA21	Burnell M, Levine MN, Chapman JAW, et al. Cyclophosphamide, epirubicin, and fluorouracil versus dose-dense epirubicin and cyclophosphamide followed by paclitaxel versus doxorubicin and cyclophosphamide followed by paclitaxel in node-positive or high-risk node-negative breast cancer. *J Clin Oncol* 2010; **28:** 77-82.

[End of webappendix]

Local and systemic therapies: several MODERATE survival gains

MODERATE improvements in early detection, in local control, in endocrine therapy and in chemotherapy have, in aggregate, SUBSTANTIALLY reduced national mortality rates

EBCTCG, Lancet 2011



*Mean of annual rates in the seven component 5−year age groups

WHO (& 2008 US NCHS) mortality and UN population estimates

EBCTCG, Lancet 2011

Reliable assessment of MODERATE differences in LONG-TERM survival by the 5-yearly worldwide overview (with tens of thousands randomised)

Need all the main randomised trial results, both to get big enough numbers and to avoid undue emphasis on particular studies

EBCTCG, Lancet 2011

Early Breast Cancer Trialists' Collaborative Group (EBCTCG)

So as not to miss any MODERATE differences in long-term survival, the world's trialists have shared their data every 5 years since 1985

1985, 1990, 1995, 2000, 2005, 2010

EBCTCG, Lancet 2011

620 names of EBCTCG collaborators in local and systemic therapy trials, listed alphabetically by institution, then name. Lancet 2011; 378: 771-84.

ACETBC, Tokyo, Japan O Abe, R Abe, K Enomoto, K Kikuchi, H Koyama, H Masuda, Y Nomura, Y Ohashi, K Sakai, K Sugimachi, M Toi, T Tominaga, J Uchino, M Yoshida. *Addenbrooke's Hospital, Cambridge, UK* J L Haybittle. *Anglo-Celtic Cooperative Oncology Group, UK* C F Leonard. *ARCOSEIN Group, France* G Calais, P Geraud. *ATLAS Trial Collaborative Study Group, Oxford, UK* V Collett, C Davies, A Delmestri, J Sayer. *Auckland Breast Cancer Study Group, New Zealand* V J Harvey, I M Holdaway, R G Kay, B H Mason. *Australian New Zealand Breast Cancer Trials Group, Sydney, Australia* J F Forbes, N Wilcken. *Austrian Breast Cancer Study Group, Vienna, Austria* R Bartsch, P Dubsky, C Fesl, H Fohler, M Gnant, R Greil, R Jakesz, A Lang, G Luschin-Ebengreuth, C Marth, B Mlineritsch, H Samonigg, C F Singer, G G Steger, H Stoger. *Beatson Oncology Centre, Glasgow, UK* P Canney, H M A Yosef. *Belgian Adjuvant Breast Cancer Project, Liège, Belgium* C Focan. *Berlin-Buch Akademie der Wissenschaften, Germany* U Peek. *Birmingham General Hospital, UK* G D Oates, J Powell. *Bordeaux Institut Bergonié, France* M Durand, L Mauriac. *Bordet Institute, Brussels, Belgium* A Di Leo, S Dolci, D Larsimont, J M Nogaret, C Philippson, M J Piccart. *Bradford Royal Infirmary, UK* M B Masood, D Parker, J J Price. *Breast Cancer International Research Group (BCIRG)* M A Lindsay, J Mackey, M Martin. *Breast Cancer Study Group of the Comprehensive Cancer Centre, Limburg, Netherlands* P S G J Hupperets. *British Association of Surgical Oncology BASO II Trialists, London, UK* T Bates, R W Blamey, U Chetty, I O Ellis, E Mallon, D A L Morgan, J Patnick, S Pinder. *British Columbia Cancer Agency, Vancouver, Canada* I Olivotto, J Ragaz. *Cancer and Leukemia Group B, Washington DC, USA* D Berry, G Broadwater, C Cirrincione, H Muss, L Norton, R B Weiss. *Cancer Care Ontario, Canada* H T Abu-Zahra. *Cancer Research Centre of the Russian Academy of Medical Sciences, Moscow, Russia* S M Portnoj. *Cancer Research UK Clinical Trials Unit (CRCTU), NCRI, Birmingham, UK* S Bowden, C Brookes, J Dunn, I Fernando, M Lee, C Poole, D Rea, D Spooner. *Cardiff Trialists Group, UK* P J Barrett-Lee, R E Mansel, I J Monypenny. *Case Western Reserve University, Cleveland, OH, USA* N H Gordon. *Central Oncology Group, Milwaukee, WI, USA* H L Davis. *Centre for Cancer Prevention, Wolfson Institute of Preventive Medicine, Queen Mary, University of London, UK* J Cuzick. *Centre Léon-Bérard, Lyon, France* Y Lehingue, P Romestaing. *Centre Paul Lamarque, Montpellier, France* J B Dubois. *Centre Regional François Baclesse, Caen, France* T Delozier, B Griffon, J Mace Lesec'h. *Centre René Huguenin, Paris, St Cloud, France* P Rambert. *Centro Oncologico, Trieste, Italy* G Mustacchi. *Charles University in Prague, First Faculty of Medicine, Department of Oncology of the First Faculty of Medicine and General Teaching Hospital, Czech Republic* L Petruzelka, O Pribylova. *Cheltenham General Hospital, UK* J R Owen. *Chemo N0 Trial Group, Germany* N Harbeck, F Janicke, C Meisner, M Schmitt, C Thomssen. *Chicago University, IL, USA* P Meier. *Chinese Academy of Medical Sciences, Beijing, People's Republic of China (in collaboration with the Oxford CTSU)* Y Shan, Y F Shao, X Wang, D B Zhao (CTSU: Z M Chen, H C Pan). *Christie Hospital and Holt Radium Institute, Manchester, UK* A Howell, R Swindell. *Clinical Trial Service Unit, Oxford, UK (ie, EBCTCG Secretariat)* J A Burrett, M Clarke, R Collins, C Correa, D Cutter, S Darby, C Davies, K Davies, A Delmestri, P Elphinstone, V Evans, L Gettins, J Godwin, R Gray, C Gregory, D Hermans, C Hicks, S James, A Kerr, E MacKinnon, M Lay, P McGale, T McHugh, R Peto, J Sayer, C Taylor, Y Wang. *Coimbra Instituto de Oncologia, Portugal* J Albano, C F de Oliveira, H Gervasio, J Gordilho. *Copenhagen Radium Centre, Denmark* H Johansen, H T Mouridsen. *Dana-Farber Cancer Institute, Boston, MA, USA* R S Gelman, J R Harris, D Hayes, C Henderson, C L Shapiro, E Winer. *Danish Breast Cancer Cooperative Group, Copenhagen, Denmark* P Christiansen, B Ejlertsen, M Ewertz, M-B Jensen, S Moller, H T Mouridsen. *Danish Cancer Registry, Copenhagen, Denmark* B Carstensen, T Palshof. *Düsseldorf University, Germany* H J Trampisch. *Dutch Working Party for Autologous Bone Marrow Transplant in Solid Tumours, Amsterdam & Groningen, Netherlands* O Dalesio, E G E de Vries, S Rodenhuis, H van Tinteren. *Eastern Cooperative Oncology Group, Boston, MA, USA* R L Comis, N E Davidson, R Gray, N Robert, G Sledge, L J Solin, J A Sparano, D C Tormey, W Wood. *Edinburgh Breast Unit, UK* D Cameron, U Chetty, J M Dixon, P Forrest, W Jack, I Kunkler. *Elim Hospital, Hamburg, Germany* J Rossbach. *Erasmus MC/Daniel den Hoed Cancer Center, Rotterdam, Netherlands* J G M Klijn, A D Treurniet-Donker, W L J van Putten. *European Institute of Oncology, Milan, Italy* N Rotmensz, U Veronesi, G Viale. *European Organization for Research and Treatment of Cancer, Brussels, Belgium* H Bartelink, N Bijker, J Bogaerts, F Cardoso, T Cufer, J P Julien, E Rutgers, C J H van de Velde. *Evanston Hospital, IL, USA* M P Cunningham. *Finnish Breast Cancer Group, Finland* R Huovinen, H Joensuu. *Fondazione Maugeri Pavia, Italy* A Costa, C Tinterri. *Fondazione Michelangelo, Milan, Italy* G Bonadonna, L Gianni, P Valagussa. *Fox Chase Cancer Center, Philadelphia, PA, USA* L J Goldstein. *French Adjuvant Study Group (GFEA), Guyancourt, France* J Bonneterre, P Fargeot, P Fumoleau, P Kerbrat, E Luporsi, M Namer. *German Adjuvant Breast Group (GABG), Frankfurt, Germany* W Eiermann, J Hilfrich, W Jonat, M Kaufmann, R Kreienberg, M Schumacher.

German Breast Cancer Study Group (BMFT), Freiburg, Germany G Bastert, H Rauschecker, R Sauer, W Sauerbrei, A Schauer, M Schumacher. *German Breast Group (GBG), Neulsenburg, Germany* J U Blohmer, S D Costa, H Eidtmann, B Gerber, C Jackisch, S Loibl, G von Minckwitz. *Ghent University Hospital, Belgium* A de Schryver, L Vakaet. *GIVIO Interdisciplinary Group for Cancer Care Evaluation, Chieti, Italy* M Belfiglio, A Nicolucci, F Pellegrini, M C Pirozzoli, M Sacco, M Valentini. *Glasgow Victoria Infirmary, UK* C S McArdle, D C Smith, S Stallard. *Groote Schuur Hospital, Cape Town, South Africa* D M Dent, C A Gudgeon, A Hacking, E Murray, E Panieri, ID Werner. *Grupo Español de Investigación en Cáncer de Mama (GEICAM), Spain* E Carrasco, M Martin, M A Segui. *Gruppo Oncologico Clinico Cooperativo del Nord Est, Aviano, Italy* E Galligioni. *Gruppo Oncologico Dell'Italia Meridionale (GOIM), Rome, Italy* M Lopez. *Guadalajara Hospital de 20 Noviembre, Mexico* A Erazo, J Y Medina. *Gunma University, Japan* J Horiguchi, H Takei. *Guy's Hospital, London, UK* I S Fentiman, J L Hayward, R D Rubens, D Skilton. *Heidelberg University I, Germany* H Scheurlen. *Heidelberg University II, Germany* M Kaufmann, H C Sohn. *Helios Klinikum Berlin-Buch, Germany* M Untch. *Hellenic Breast Surgeons Society, Greece* U Dafni, C Markopoulos. *Hellenic Cooperative Oncology Group, Athens, Greece* U Dafni, G Fountzilas. *Hellenic Oncology Research Group, Greece* D Mavroudis. *Helsinki Deaconess Medical Centre, Finland* P Klefstrom. *Helsinki University, Finland* C Blomqvist, T Saarto. *Hospital del Mar, Barcelona, Spain* M Gallen. *Innsbruck University, Austria* R Margreiter. *Institut Claudius Regaud, Toulouse, France* B de Lafontan, J Mihura, H Roche. *Institut Curie, Paris, France* B Asselain, R J Salmon, J R Vilcoq. *Institut Gustave-Roussy, Paris, France* R Arriagada, C. 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Department of Obstetrics and Gynaecology and Department of Medicine I, Vienna, Austria* M Janauer, M Seifert, P Sevelda, C C Zielinski. *Memorial Sloan-Kettering Cancer Center, New York, NY, USA* T Hakes, C A Hudis, L Norton, R Wittes. *Metaxas Memorial Cancer Hospital, Athens, Greece* G Giokas, D Kondylis, B Lissaios. *Mexican National Medical Center, Mexico City, Mexico* R de la Huerta, M G Sainz. *National Cancer Institute, Bethesda, MD, USA* R Altemus, K Camphausen, K Cowan, D Danforth, A Lichter, M Lippman, J O'Shaughnessy, L J Pierce, S Steinberg, D Venzon, J A Zujewski. *National Cancer Institute of Bari, Italy* C D'Amico, M Lioce, A Paradiso. *NCIC Clinical Trials Group, Kingston, Ontario, Canada* J-A W Chapman, K Gelmon, P E Goss, M N Levine, R Meyer, W Parulekar, J L Pater, K I Pritchard, L E Shepherd, D Tu, T Whelan. *National Kyushu Cancer Center, Japan* Y Nomura, S Ohno. *National Surgical Adjuvant Breast and Bowel Project (NSABP), Pittsburgh, PA, USA* S Anderson, G Bass, A Brown (deceased), J Bryant (deceased), J Costantino, J Dignam, B Fisher, C Geyer, E P Mamounas, S Paik, C Redmond, S Swain, L Wickerham, N Wolmark. *Nolvadex Adjuvant Trial Organisation, London, UK* M Baum, I M Jackson (deceased), M K Palmer. *North Central Cancer Treatment Group, Mayo Clinic, Rochester, MN, USA* E Perez, J N Ingle, V J Suman. *North Sweden Breast Cancer Group, Umeå, Sweden* N O Bengtsson, S Emdin, H Jonsson. *North-West Oncology Group (GONO), Italy* L Del Mastro, M Venturini. *North-Western British Surgeons, Manchester, UK* J P Lythgoe, R Swindell. *Northwick Park Hospital, London, UK* M Kissin. *Norwegian Breast Cancer Group, Oslo, Norway* B Erikstein, E Hannisdal, A B Jacobsen, J E Varhaug. *Norwegian Radium Hospital, Oslo, Norway* B Erikstein, S Gundersen, M Hauer-Jensen, H Host, A B Jacobsen, R Nissen-Meyer. *Nottingham City Hospital, UK* R W Blamey, A K Mitchell, D A L Morgan, J F R Robertson. *Oita Prefectural Hospital, Japan* H Ueo. *Oncofrance, Paris, France* M Di Palma, G Mathe (deceased), J L Misset. *Ontario Clinical Oncology Group, Hamilton, Canada* M Levine, K I Pritchard, T Whelan. *Osaka City University, Japan* K Morimoto. *Osaka National Hospital, Japan* K Sawa, Y Takatsuka. *Oxford Radcliffe Hospitals NHS Trust, Churchill Hospital, Oxford, UK* E Crossley, A Harris, D Talbot, M Taylor. *PACS Adjuvant Study Group, France* A L Martin, H Roche. *Parma Hospital, Italy* G Cocconi, B di Blasio. *Petrov Research Institute of Oncology, St Petersburg, Russia* V Ivanov, R Paltuev, V Semiglazov. *Piedmont Oncology Association, Winston-Salem, NC, USA* J Brockschmidt, M R Cooper. *Pretoria University, South Africa* C I Falkson. *Royal Marsden NHS Trust, London and Sutton, UK* R A'Hern, S Ashley, M Dowsett, A Makris, T J Powles, I E Smith, J R Yarnold. *St George's Hospital, London, UK* J C Gazet.

St George Hospital, Sydney, Australia L Browne, P Graham. *St Luke's Hospital, Dublin, Ireland* N Corcoran. *Sardinia Oncology Hospital A Businico, Cagliari, Sardinia* N Deshpande, L di Martino. *SASIB International Trialists, Cape Town, South Africa* P Douglas, A Hacking, H Host, A Lindtner, G Notter. *Saskatchewan Cancer Foundation, Regina, Canada* A J S Bryant, G H Ewing, L A Firth, J L Krushen-Kosloski. *Scandinavian Adjuvant Chemotherapy Study Group, Oslo, Norway* R Nissen-Meyer. *South Sweden Breast Cancer Group, Lund,* H Anderson, F Killander, P Malmstrom, L Ryden. *South-East Sweden Breast Cancer Group, Linköping, Sweden* L-G Arnesson, J Carstensen, M Dufmats, H Fohlin, B Nordenskjold, M Soderberg. *South-Eastern Cancer Study Group and Alabama Breast Cancer Project, Birmingham, AL, USA* J T Carpenter. *Southampton Oncology Centre, UK* N Murray, G T Royle, P D Simmonds. *Southwest Oncology Group, San Antonio, TX, USA* K Albain, W Barlow, J Crowley, D Hayes, J Gralow, S Green, G Hortobagyi, R Livingston, S Martino, C K Osborne, P M Ravdin. *Stockholm Breast Cancer Study Group, Sweden* J Adolfsson, J Bergh, T Bondesson, F Celebioglu, K Dahlberg, T Fornander, I Fredriksson, J Frisell, E Goransson, M Iiristo, U Johansson, E Lenner, L Lofgren, P Nikolaidis, L Perbeck, S Rotstein, K Sandelin, L Skoog, G Svane, E af Trampe, C Wadstrom. *Swiss Group for Clinical Cancer Research (SAKK), Bern, and OSAKO, St Gallen, Switzerland* M Castiglione, A Goldhirsch, R Maibach, H J Senn, B Thurlimann. *Tampere University Hospital, Finland* M Hakama, K Holli, J Isola, K Rouhento, R Saaristo. *Tel Aviv University, Israel* H Brenner, A Hercbergs. *The High-Dose Chemotherapy for Breast Cancer Study Group (PEGASE), France* A L Martin, H Roche. *Tokyo Cancer Institute Hospital, Japan* M Yoshimoto. *Toronto-Edmonton Breast Cancer Study Group, Canada* A H G Paterson, K I Pritchard. *Toronto Princess Margaret Hospital, Canada* A Fyles, J W Meakin, T Panzarella, K I Pritchard. *Tunis Institut Salah Azaiz, Tunisia* J Bahi. *UK Multicentre Cancer Chemotherapy Study Group, London, UK* M Reid, M Spittle. *UK/ANZ DCIS Trial* H Bishop, N J Bundred, J Cuzick, I O Ellis, I S Fentiman, J F Forbes, S Forsyth, W D George, S E Pinder, I Sestak. *UK/Asia Collaborative Breast Cancer Group, London, UK* G P Deutsch, R Gray, D L W Kwong, V R Pai, R Peto, F Senanayake. *University and Istituto Nazionale per la Ricerca sul Cancro, Genoa, Italy on behalf of GROCTA trialists* F Boccardo, A Rubagotti. *University College London, UK* M Baum, S Forsyth, A Hackshaw, J Houghton, J Ledermann, K Monson, JS Tobias. *University Federico II, Naples, Italy* C Carlomagno, M De Laurentiis, S De Placido. *University of Edinburgh, UK* L Williams. *University of Michigan, USA* D Hayes, L J Pierce. *University of Texas MD Anderson Cancer Center, Houston, TX, USA* K Broglio, A U Buzdar. *University of Wisconsin, USA* R R Love. *Uppsala-Örebro Breast Cancer Study Group, Sweden* J Ahlgren, H Garmo, L Holmberg, G Liljegren, H Lindman, F Warnberg. *US Oncology, Houston, USA* L Asmar, S E Jones. *West German Study Group (WSG), Germany* O Gluz, N Harbeck, C Liedtke, U Nitz. *West of Scotland Breast Trial Group, Glasgow, UK* A Litton. *West Sweden Breast Cancer Study Group, Gothenburg, Sweden* A Wallgren, P Karlsson, B K Linderholm. *Western Cancer Study Group, Torrance, CA, USA* R T Chlebowski. *Würzburg University, Germany* H Caffier.

EBCTCG, Lancet 2011

Comparisons between different polychemo-therapy regimens for early breast cancer:

meta-analyses of long-term outcome among 100,000 women in 123 randomised trials

Early Breast Cancer Trialists' Collaborative Group (EBCTCG)

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Direct and indirect comparisons between different polychemotherapy regimens, based on ~100,000 randomised women

45,000 taxane vs no taxane*
(44,000 with anthracycline in both arms)

22,000 anthracycline vs CMF
(18,000 vs “standard” CMF)

5,000 more vs less anthracycline
(2000 comparing currently relevant doses)

31,000 polychemotherapy vs no adjuvant chemo
(13,000 CMF vs Nil; 10,000 anthr.-based regimen vs Nil)

* Excludes trials of one taxane regimen vs another

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Taxane trials

Data on 44,000 women in randomised trials of a taxane-plus-anthracycline-based regimen vs the SAME, or MORE, non-taxane chemotherapy

11,000 in trials where the non-taxane regimen was the SAME, and 33,000 in trials where it was MORE

[15% node-negative; mean follow-up only 5 years; mean recurrence rate about 5% per year]

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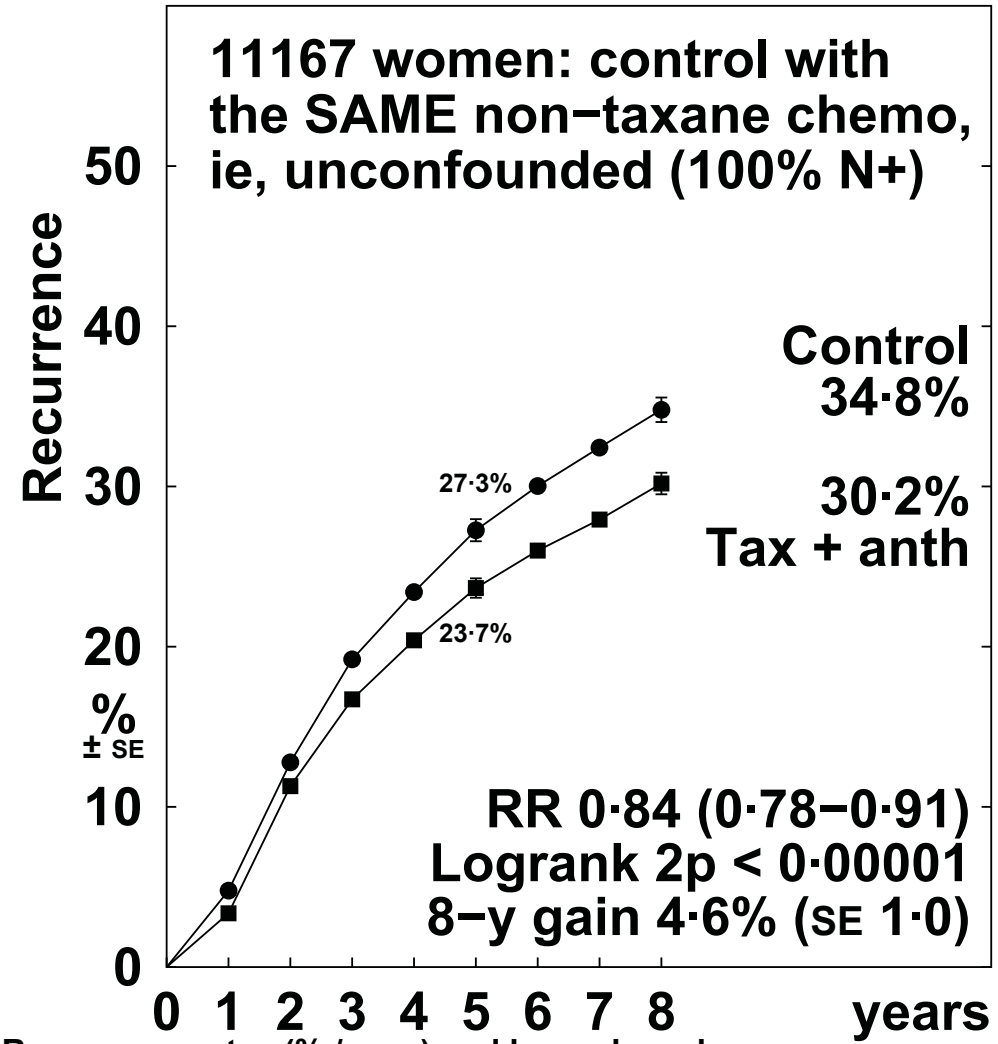
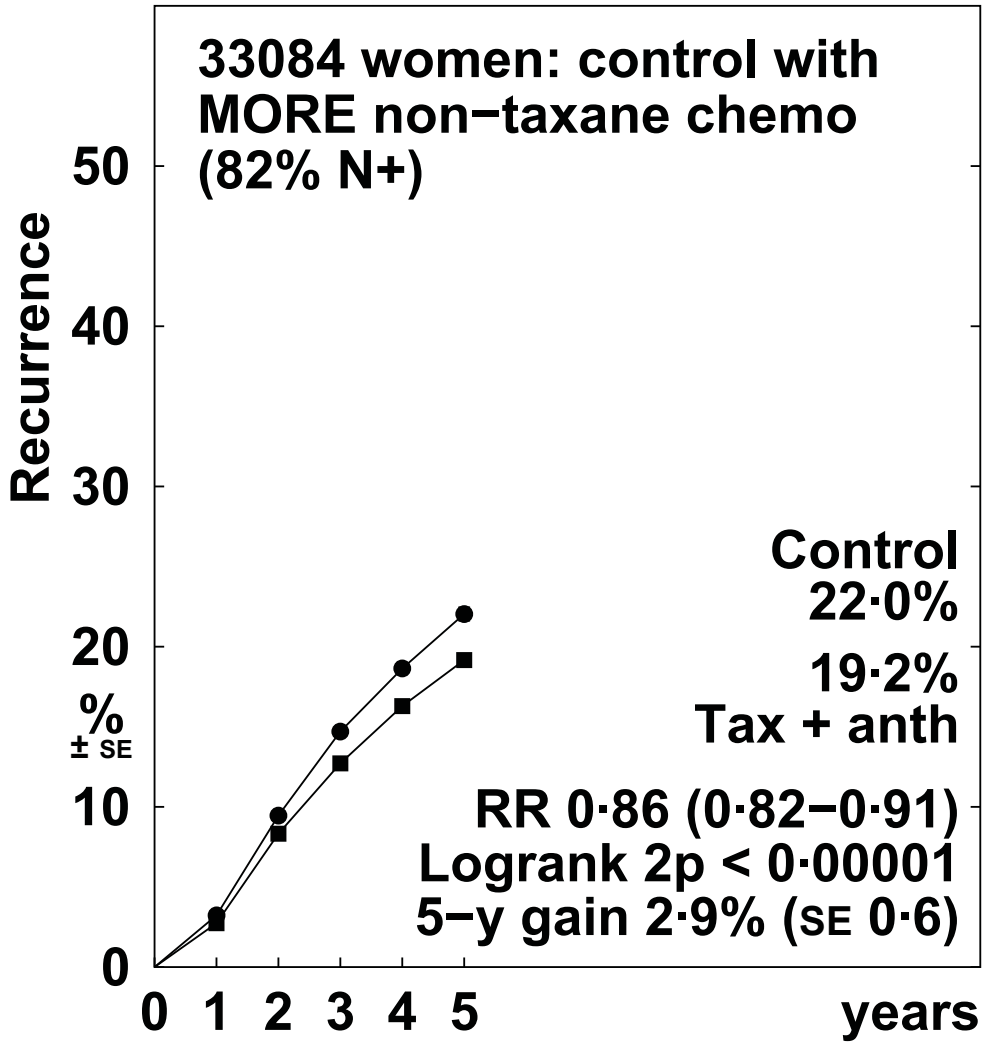
Taxane-plus-anthracycline-based regimens vs (L) the SAME, or (R) MORE, non-taxane chemo.





Recurrence rates (% / year) and logrank analyses

Allocation	Years 0 − 4	Year 5+
Tax + anth	5·51 (1280 / 23249)	3·10 (413 / 13343)
Control	6·43 (1239 / 19259)	3·62 (381 / 10534)
Rate ratio	0·84 SE 0·04	0·85 SE 0·07
(O−E) / V	−95·5 / 557·3	−30·5 / 182·8

Years 0 − 4	Year 5+
4·37 (2607 / 59665)	3·01 (153 / 5082)
5·02 (2586 / 51508)	2·69 (127 / 4727)
0·85 SE 0·03	1·03 SE 0·13
−181·4 / 1153·8	1·9 / 63·6

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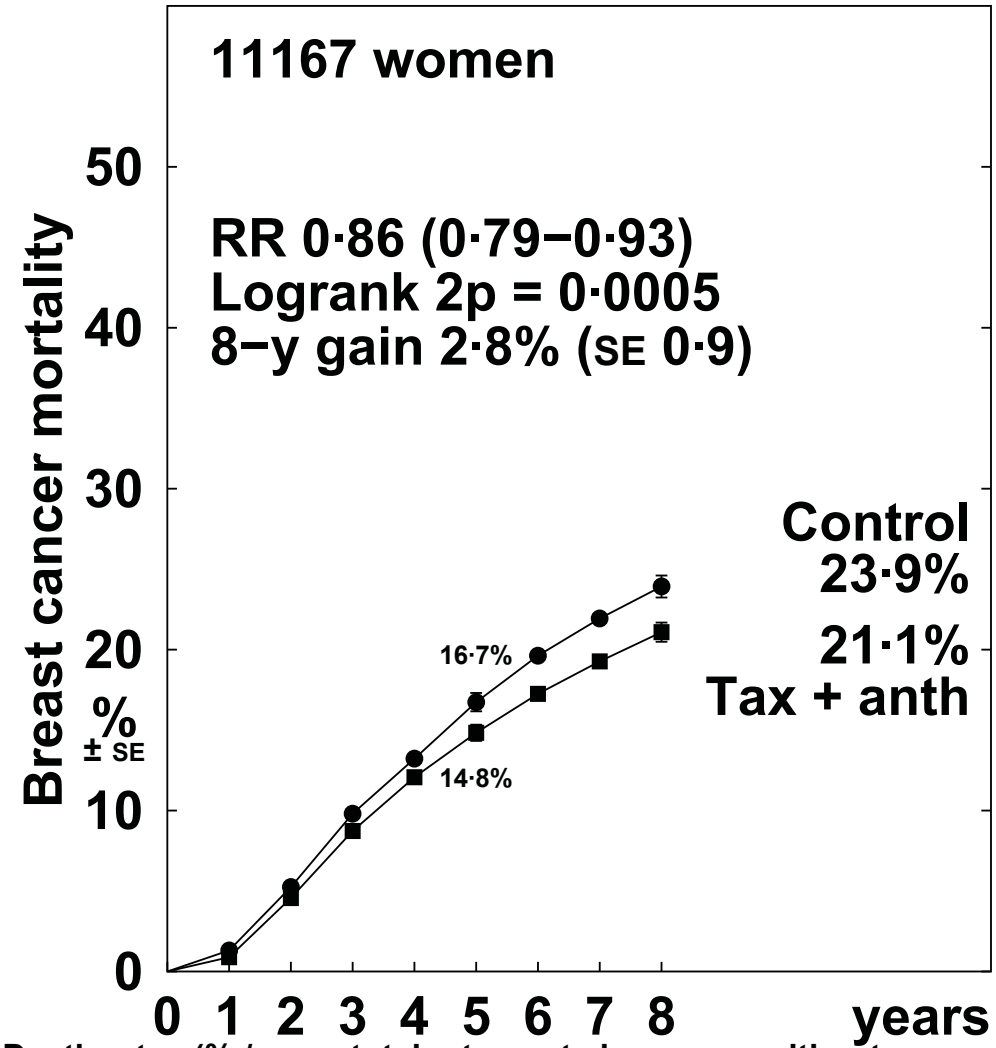
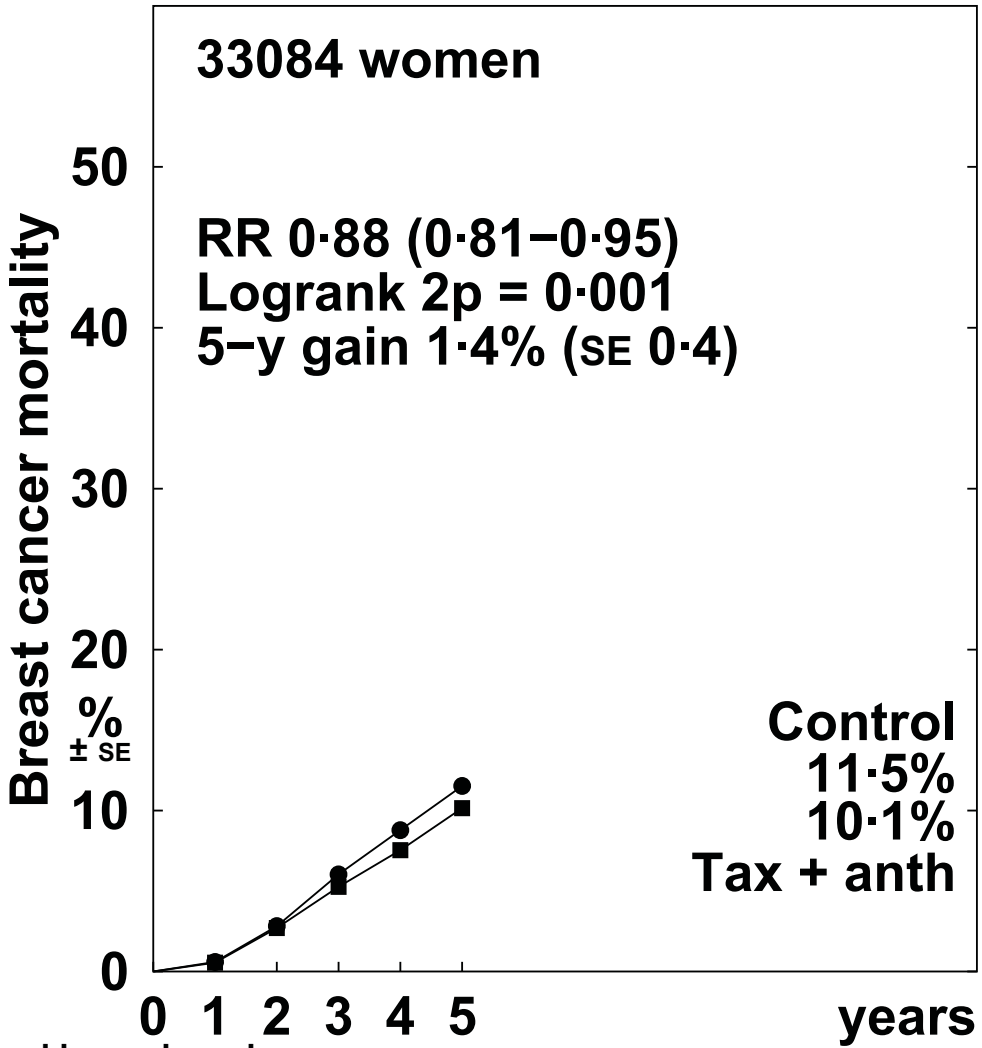
Taxane-plus-anthracycline-based regimens vs (L) the SAME, or (R) MORE, non-taxane chemo.





Death rates (% / year: total rate − rate in women without recurrence) and logrank analyses

Allocation	Years 0 − 4	Year 5+	Years 0 − 4	Year 5+
Tax + anth	3·21 SE 0·11	2·48 SE 0·13	2·01 SE 0·06	2·37 SE 0·20
Control	3·58 SE 0·13	3·06 SE 0·16	2·30 SE 0·07	2·26 SE 0·21
Rate ratio	0·88 SE 0·05	0·82 SE 0·07	0·87 SE 0·04	0·97 SE 0·13
(O−E) / V	−46·4 / 348·5	−33·3 / 172·3	−77·0 / 549·5	−1·7 / 57·4

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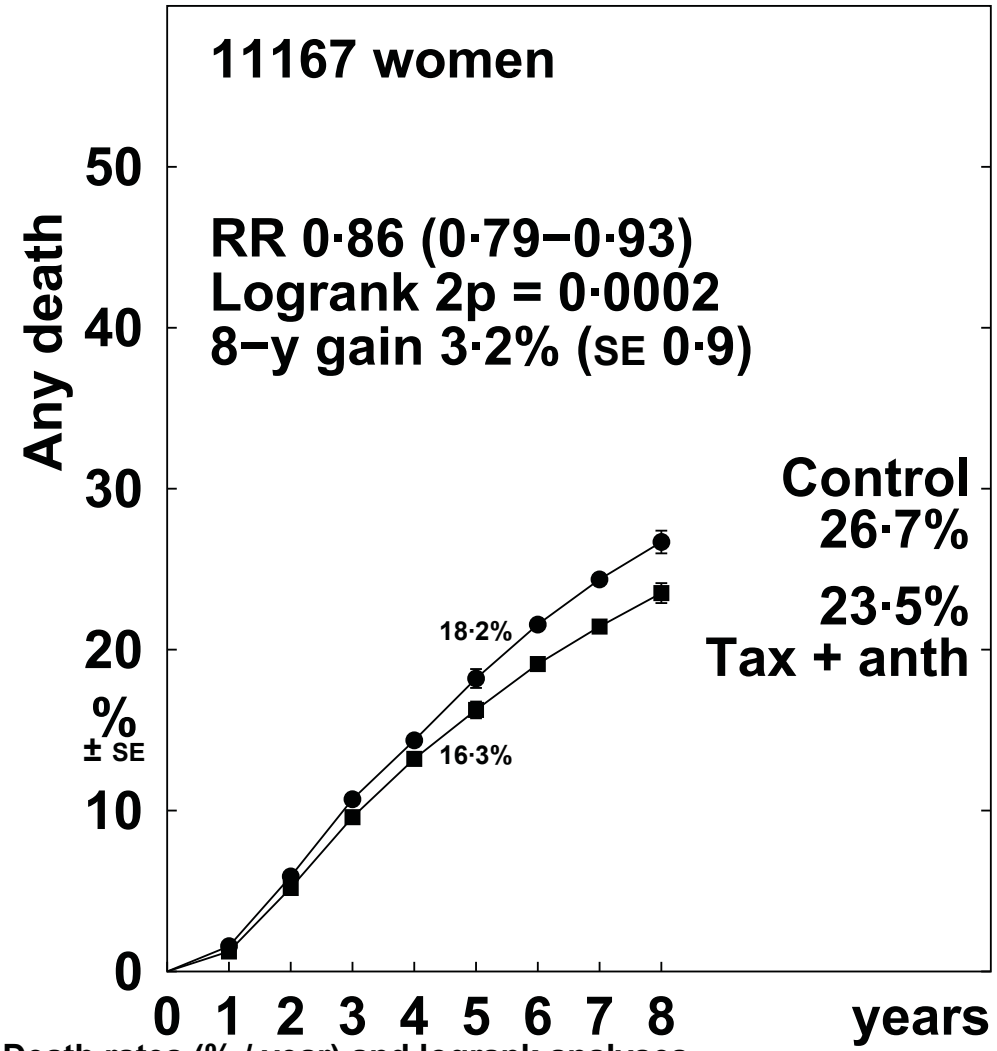
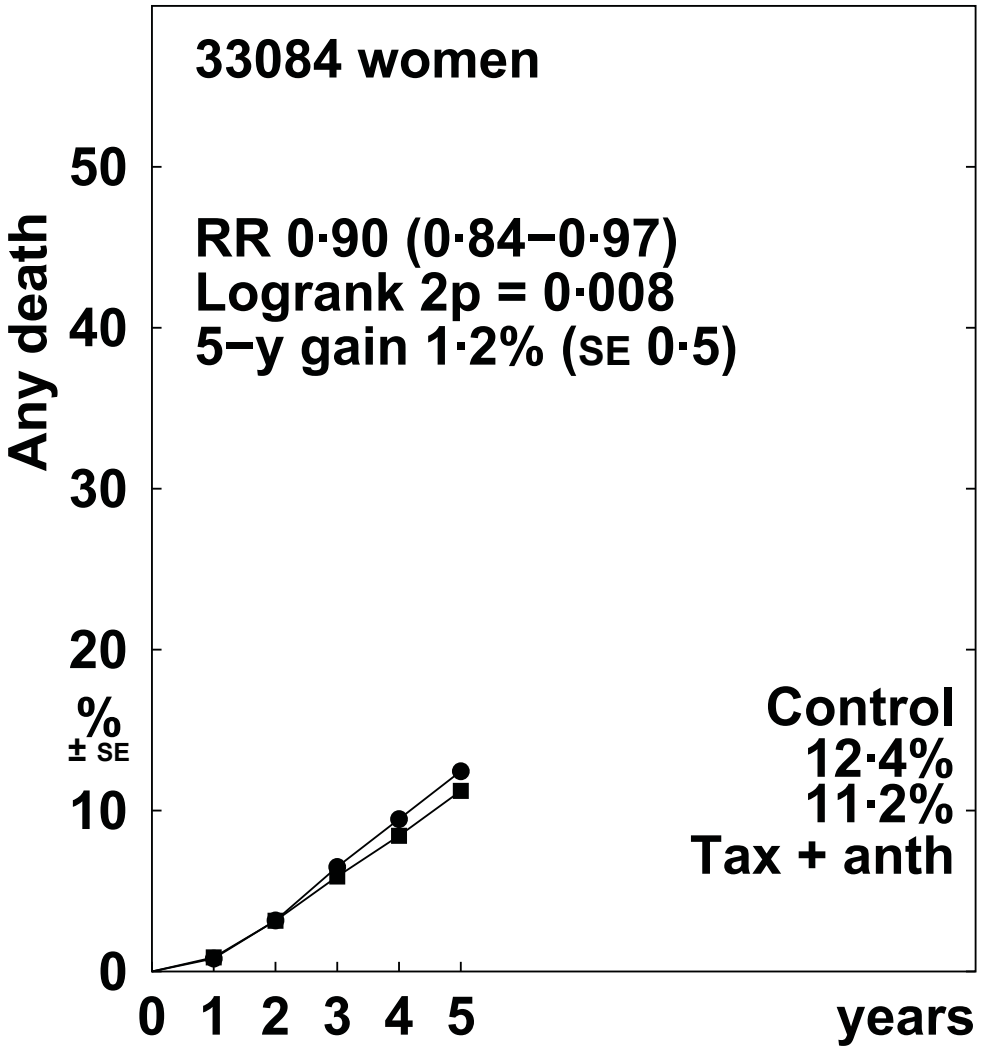
Taxane-plus-anthracycline-based regimens vs (L) the SAME, or (R) MORE, non-taxane chemo.





Death rates (% / year) and logrank analyses

Allocation	Years 0 – 4	Year 5+	Years 0 – 4	Year 5+
Tax + anth	3·55 (881 / 24821)	3·09 (465 / 15061)	2·24 (1326 / 59104)	2·85 (161 / 5658)
Control	3·93 (819 / 20850)	3·76 (458 / 12178)	2·51 (1326 / 52888)	2·84 (152 / 5358)
Rate ratio	0·88 SE 0·05	0·82 SE 0·06	0·90 SE 0·04	0·96 SE 0·12
(O–E) / V	−48·6 / 386·0	−41·3 / 213·4	−66·3 / 608·4	−3·1 / 70·9

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Taxane comparisons, subdivided according to:

(a) how the non-taxane treatments compare (active = control, active = ½ control, or an intermediate ratio), and

(b) whether the cycles of taxane are given <u>concurrently</u> (©) with the anthracycline, or whether taxanes are given alone (†).

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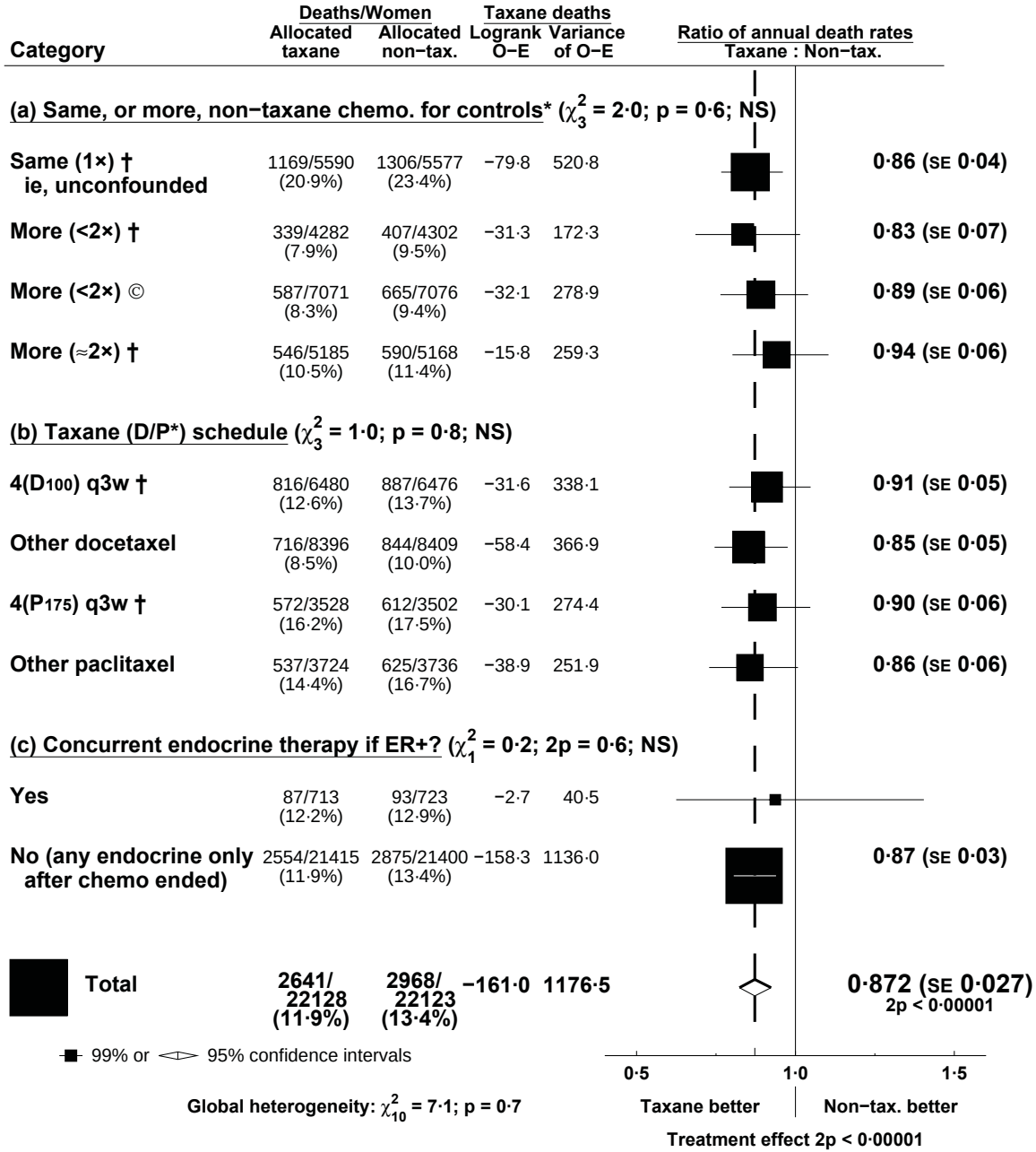
Breast cancer mortality ratio in taxane trials, by TYPE of treatment comparison



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Taxane trials: subgroup analyses by age, stage and ER status

Taxane-plus-anthracycline-based regimen
vs
an anthracycline-based control regimen
with the SAME, or MORE, of each
non-taxane cytotoxic drug

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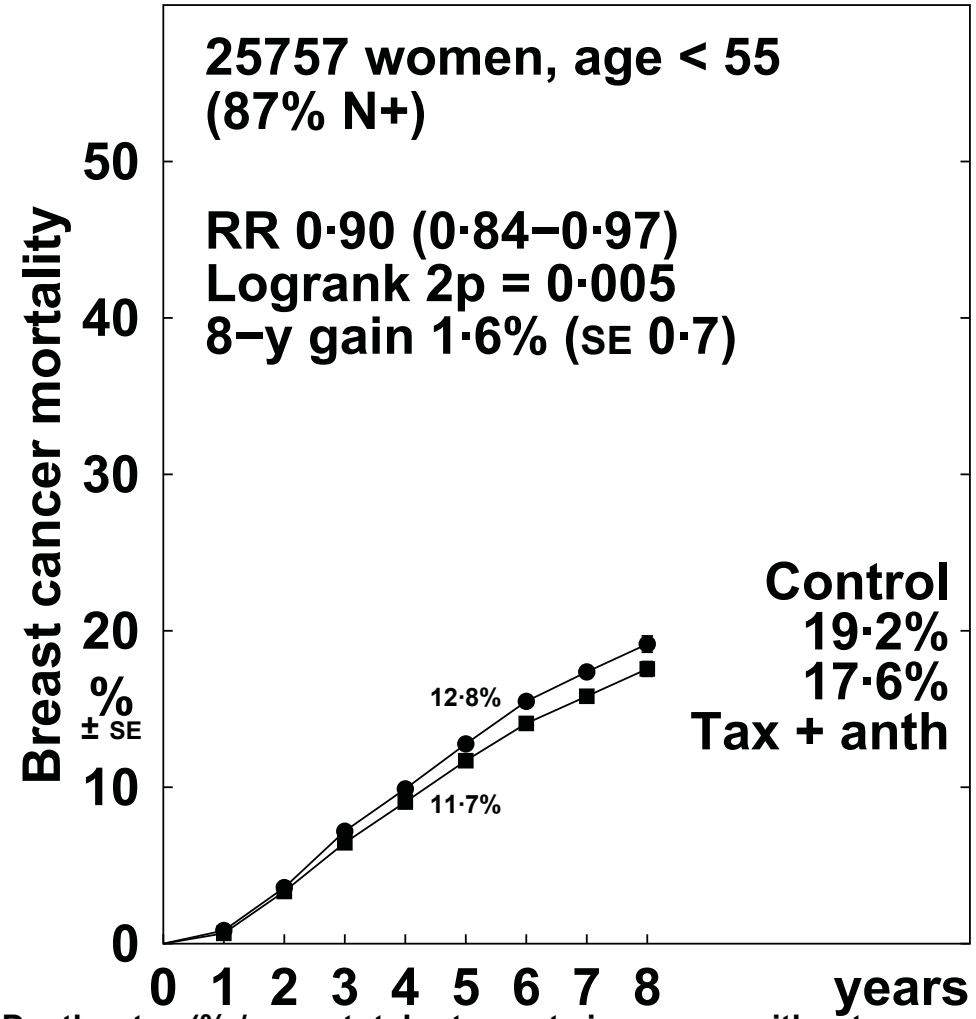
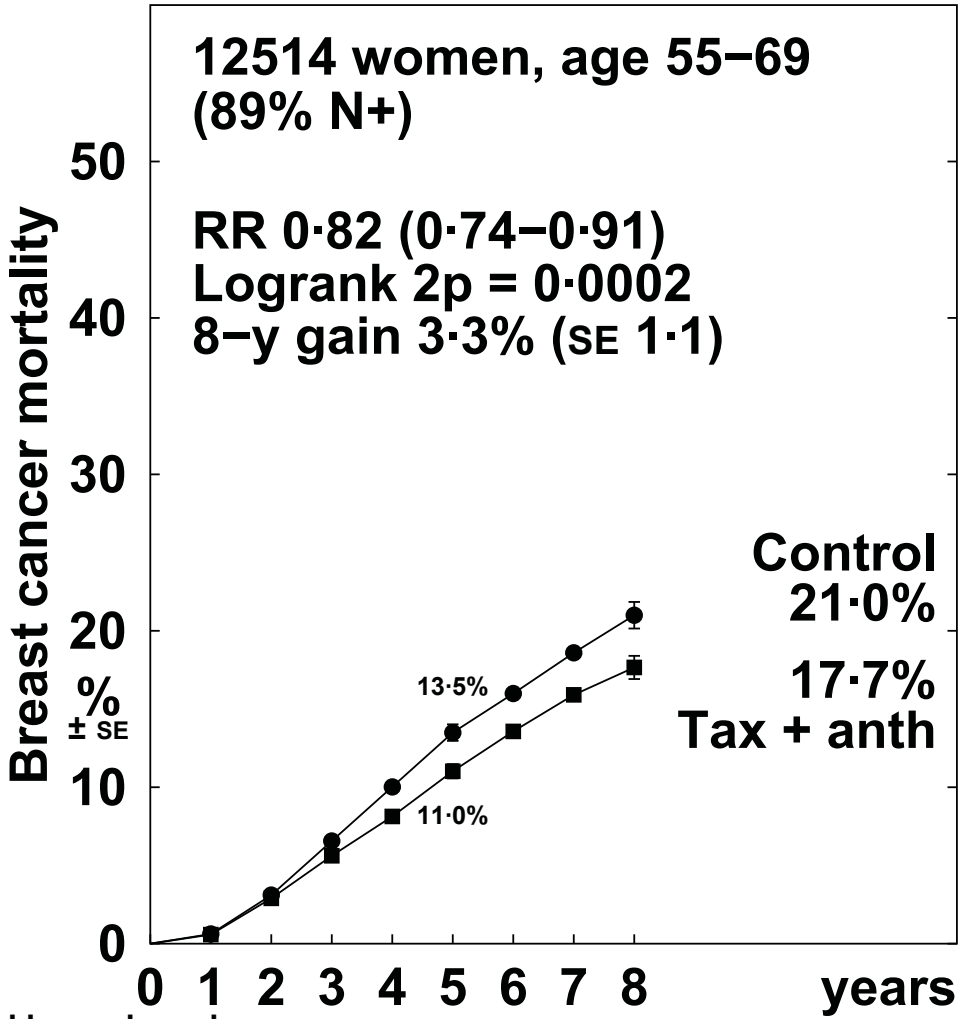
Taxane-plus-anthracycline-based regimen vs the SAME, or MORE, non-taxane chemo, by ENTRY AGE





Death rates (% / year: total rate − rate in women without recurrence) and logrank analyses

Allocation	Years 0 − 4	Year 5+	Years 0 − 4	Year 5+
Tax + anth	2·42 SE 0·07	2·36 SE 0·13	2·21 SE 0·09	2·64 SE 0·21
Control	2·62 SE 0·07	2·63 SE 0·15	2·69 SE 0·11	3·14 SE 0·25
Rate ratio	0·91 SE 0·04	0·88 SE 0·08	0·81 SE 0·05	0·85 SE 0·11
(O−E) / V	−58·4 / 604·0	−19·6 / 152·8	−57·7 / 275·4	−11·4 / 71·0

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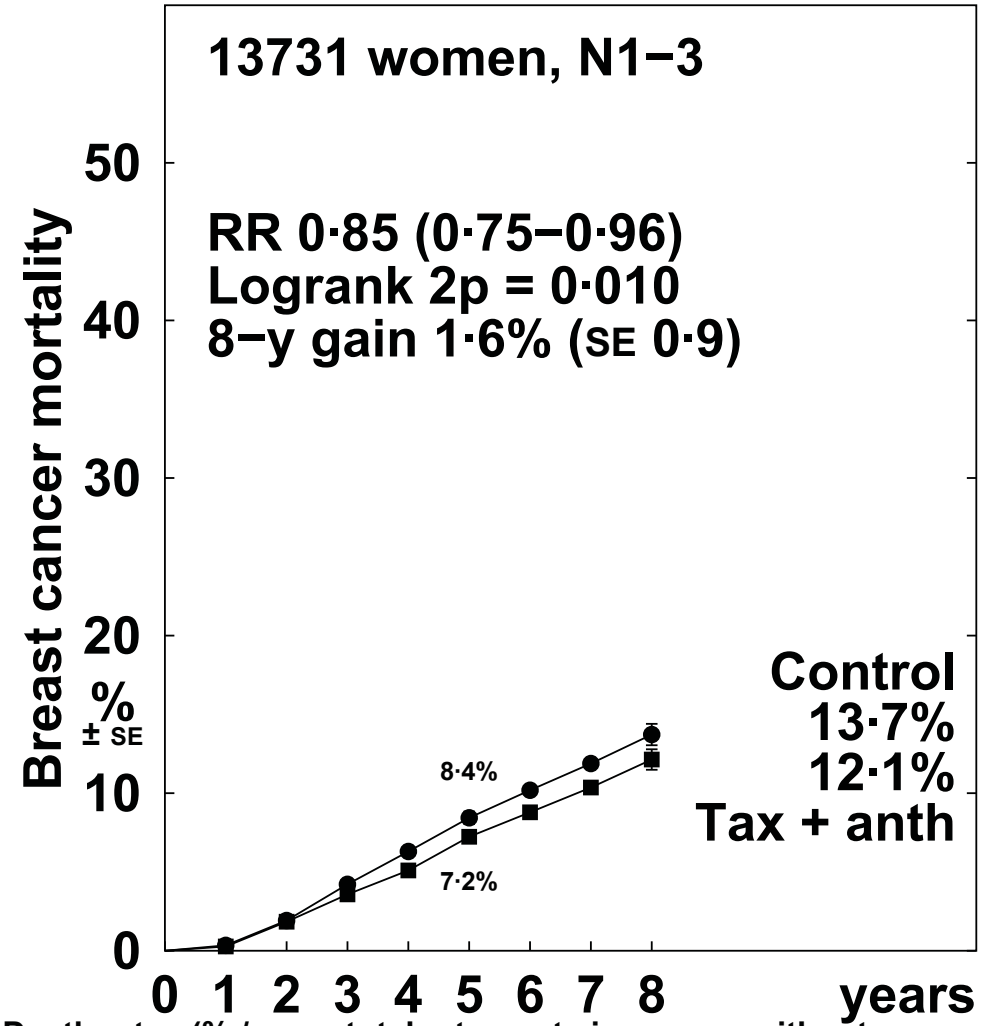
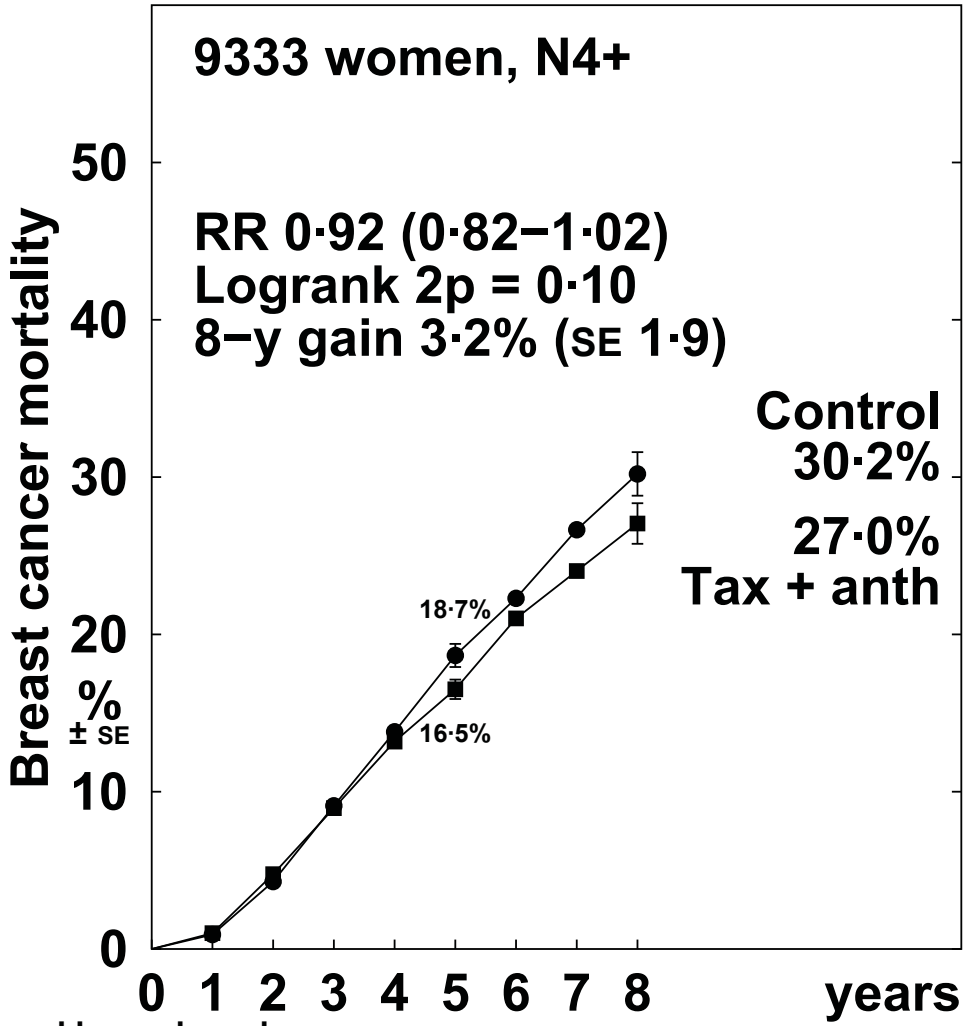
Taxane-plus-anthracycline-based regimen vs the SAME, or MORE, non-taxane chemo, by NODAL STATUS before chemotherapy





Death rates (% / year: total rate − rate in women without recurrence) and logrank analyses

Allocation	Years 0 − 4	Year 5+	Years 0 − 4	Year 5+
Tax + anth	1·39 SE 0·07	1·76 SE 0·17	3·41 SE 0·13	4·58 SE 0·41
Control	1·68 SE 0·08	1·96 SE 0·18	3·82 SE 0·15	4·72 SE 0·45
Rate ratio	0·84 SE 0·06	0·89 SE 0·13	0·91 SE 0·06	0·96 SE 0·14
(O−E) / V	−35·7 / 206·9	−6·3 / 55·1	−27·9 / 286·1	−2·0 / 52·6

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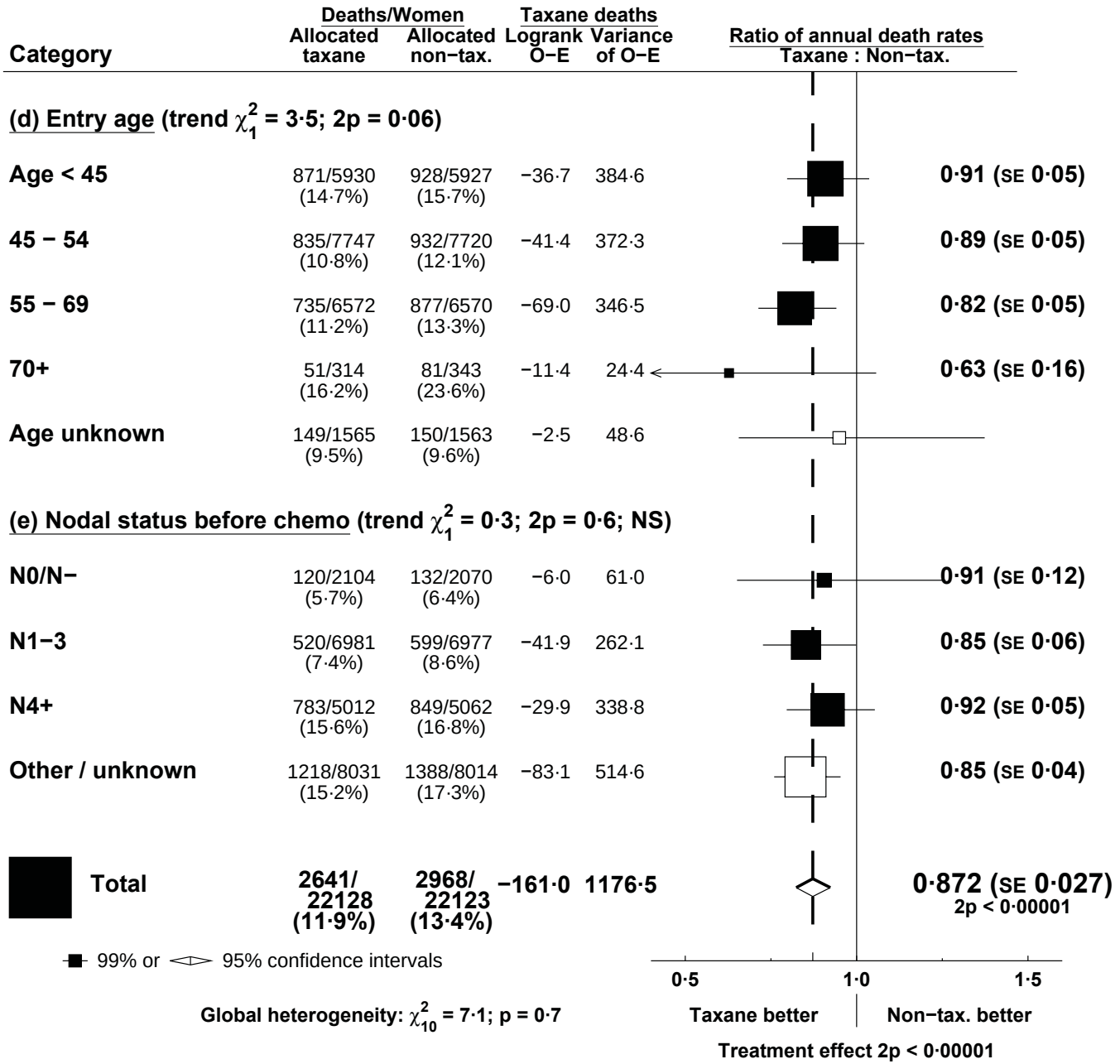
Breast cancer mortality ratio in taxane trials, by AGE and STAGE



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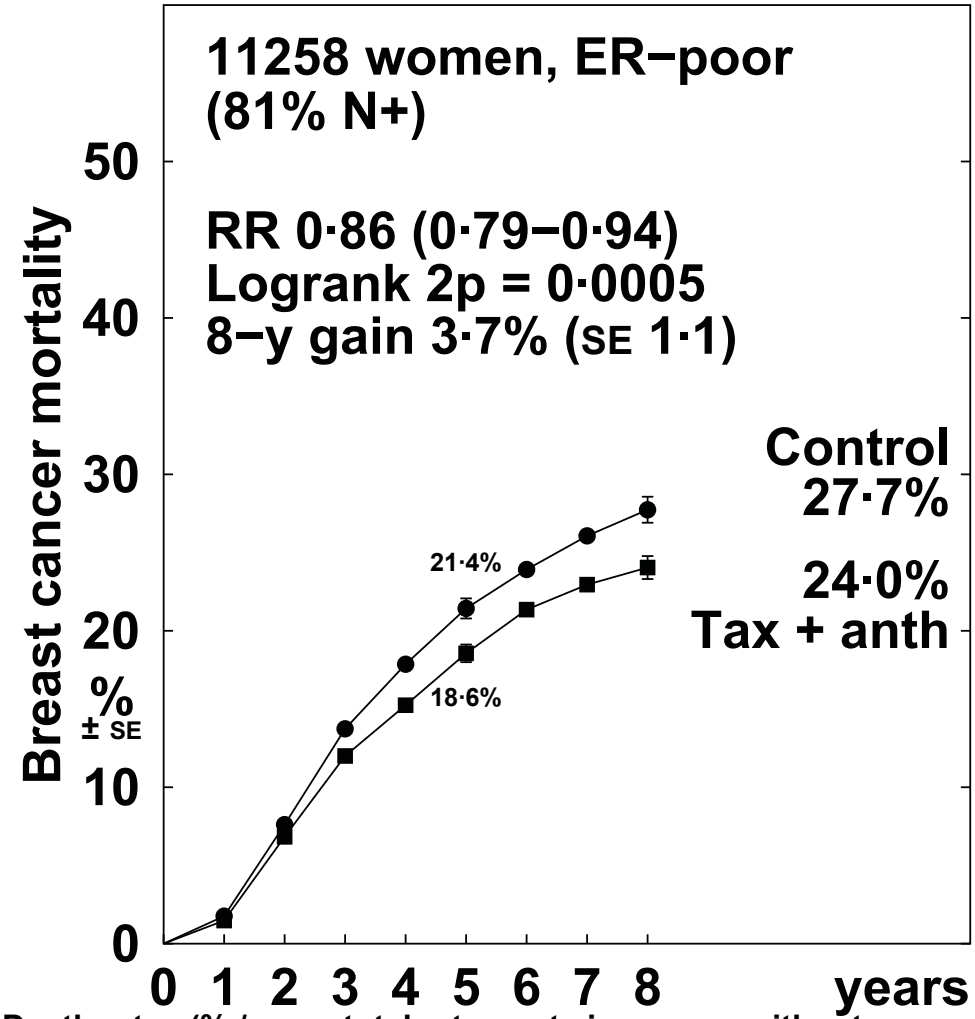
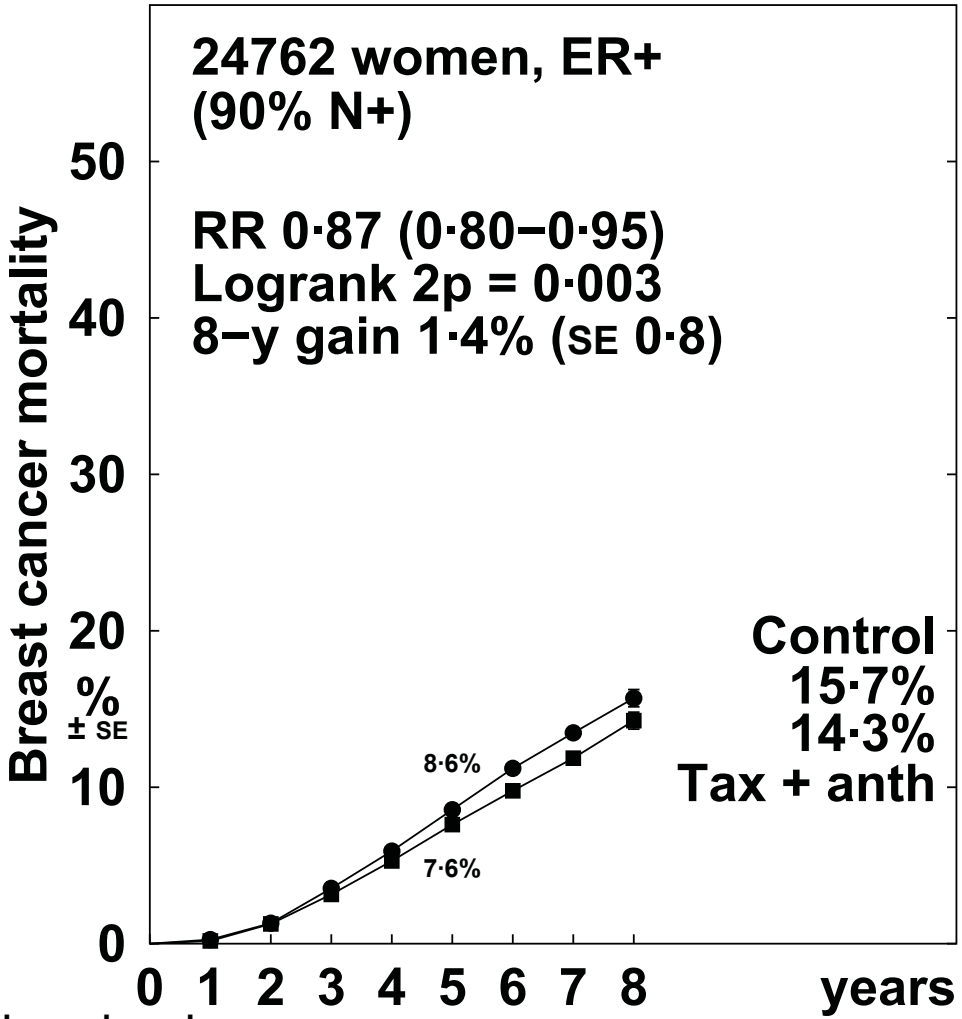
Taxane-plus-anthracycline-based regimen vs the SAME, or MORE, non-taxane chemo, by ER STATUS





Death rates (% / year: total rate − rate in women without recurrence) and logrank analyses

Allocation	Years 0 − 4	Year 5+	Years 0 − 4	Year 5+
Tax + anth	4·00 SE 0·13	2·44 SE 0·20	1·45 SE 0·05	2·51 SE 0·15
Control	4·86 SE 0·15	2·67 SE 0·23	1·62 SE 0·06	2·87 SE 0·16
Rate ratio	0·85 SE 0·04	0·91 SE 0·12	0·89 SE 0·05	0·85 SE 0·08
(O−E) / V	−71·7 / 438·8	−6·2 / 66·1	−44·3 / 365·5	−22·8 / 136·8

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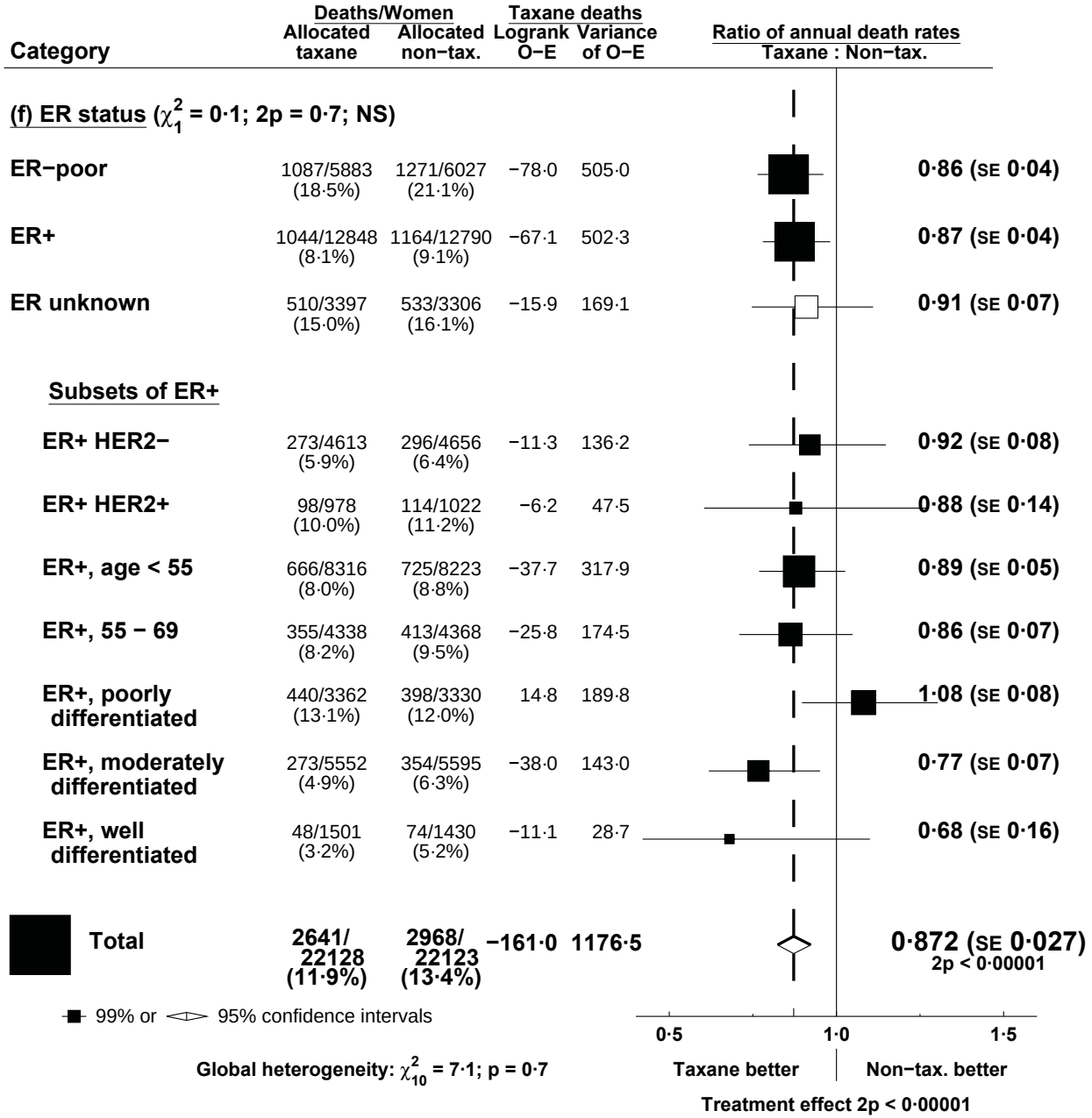
Breast cancer mortality ratio in taxane trials, by ER STATUS and subsets of ER+



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Trials of any anthracycline-based regimen* vs standard CMF

***Standard 4AC, standard 4EC, or higher-cumulative-dosage regimens (eg, CAF or CEF)**

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Definitions of “standard” CMF and 4AC

(mg/m^2 x frequency/cycle)

Standard CMF:

Six 4-weekly cycles of **C**100x14 oral **M**40x2 iv **F**600x2 iv

Standard 4AC:

Four 3-weekly cycles of **A**60 iv **C**600 iv

Approximate equivalence:
in the trials of standard AC vs standard CMF,
both appeared to be of comparable efficacy

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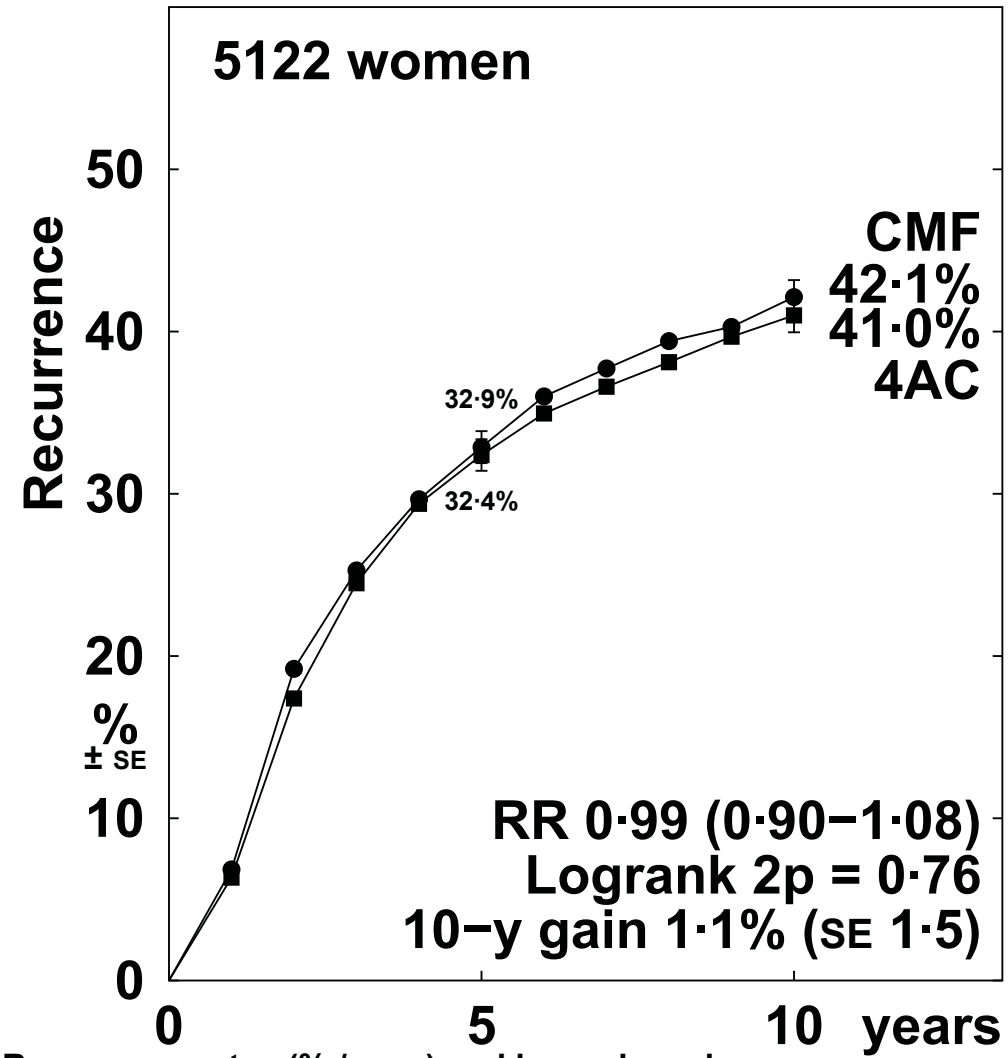
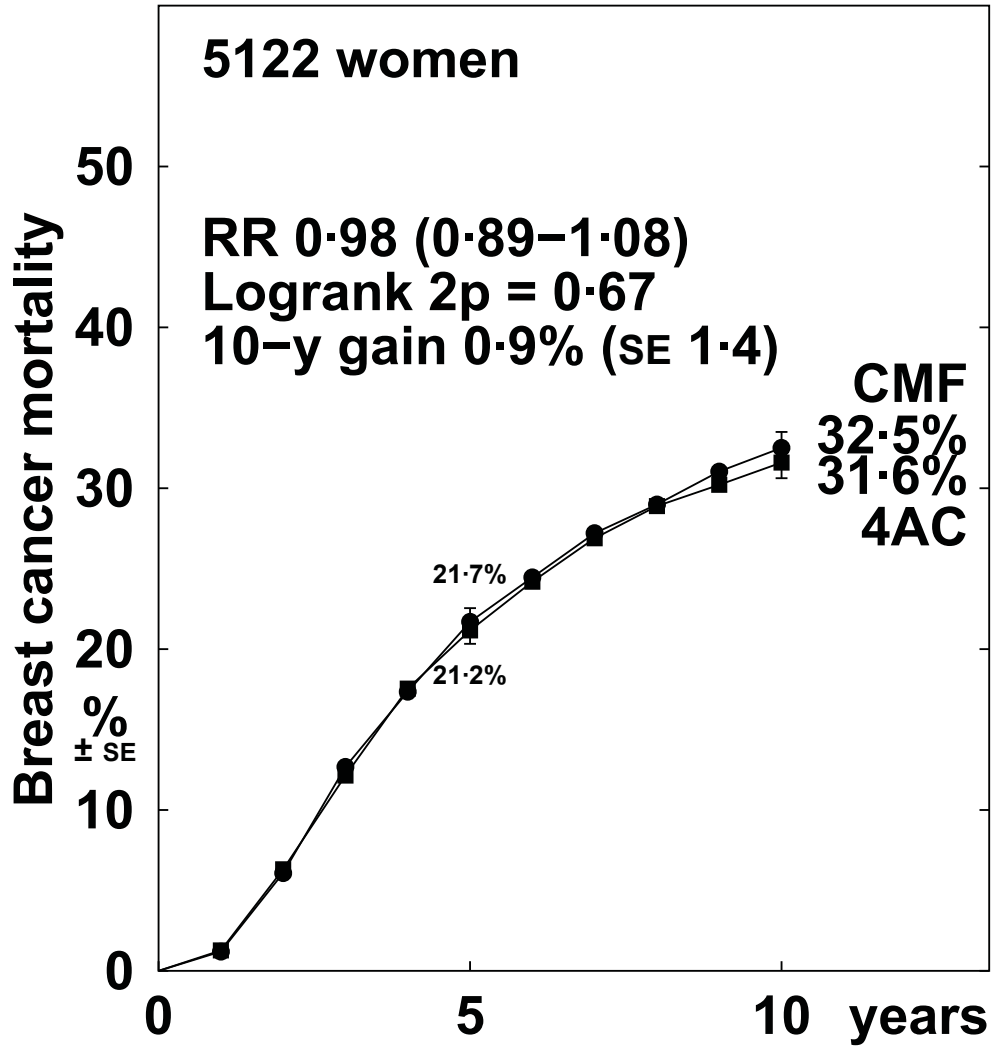
Standard 4AC vs standard CMF: approximate equivalence



Recurrence rates (% / year) and logrank analyses

Allocation	Years 0 – 4	Years 5 – 9	Year 10+
4AC	7·97 (820 / 10292)	2·86 (194 / 6795)	2·36 (100 / 4237)
CMF	8·21 (830 / 10108)	2·99 (199 / 6658)	1·87 (76 / 4054)
Rate ratio	0·98 SE 0·05	0·91 SE 0·10	1·28 SE 0·17
(O–E) / V	−8·7 / 355·5	−8·5 / 92·1	10·4 / 42·3



Years 0 – 4	Years 5 – 9	Year 10+
4·65 SE 0·20	2·94 SE 0·19	2·06 SE 0·20
4·81 SE 0·21	3·04 SE 0·20	1·96 SE 0·20
0·97 SE 0·06	0·97 SE 0·09	1·03 SE 0·15
−6·3 / 245·2	−3·7 / 111·6	1·5 / 48·9

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Examples of higher-cumulative-dosage* anthracycline-based regimens

(mg/m^2 x frequency/cycle)

CAF:

Six 4-weekly cycles of **C**100x14 oral **A**40x2 iv **F**500x2 iv

CEF:

Six 4-weekly cycles of **C**75x14 oral **E**60x2 iv **F**500x2 iv

* Higher dosage than standard 4AC not only of anthracycline but also of other cytotoxic drugs; scheduled dosages could be reduced for toxicity

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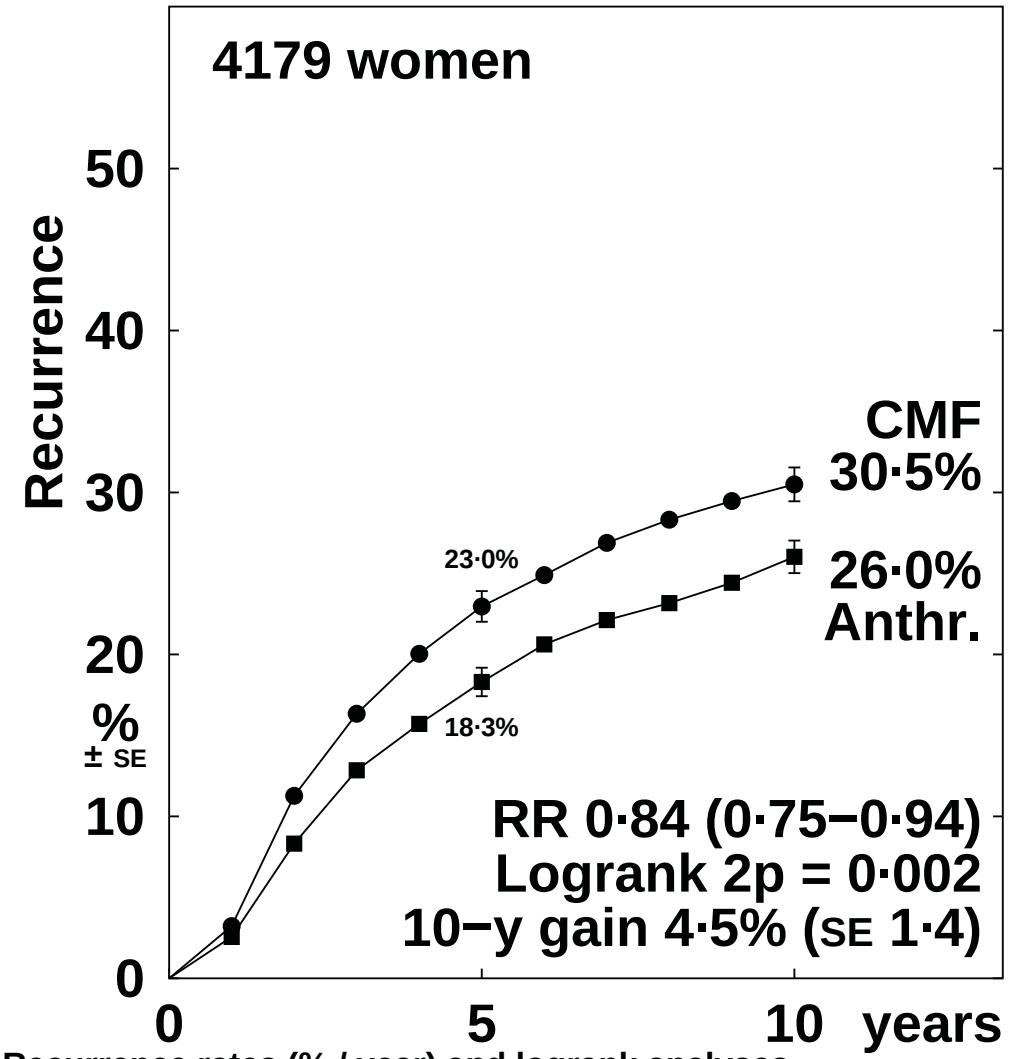
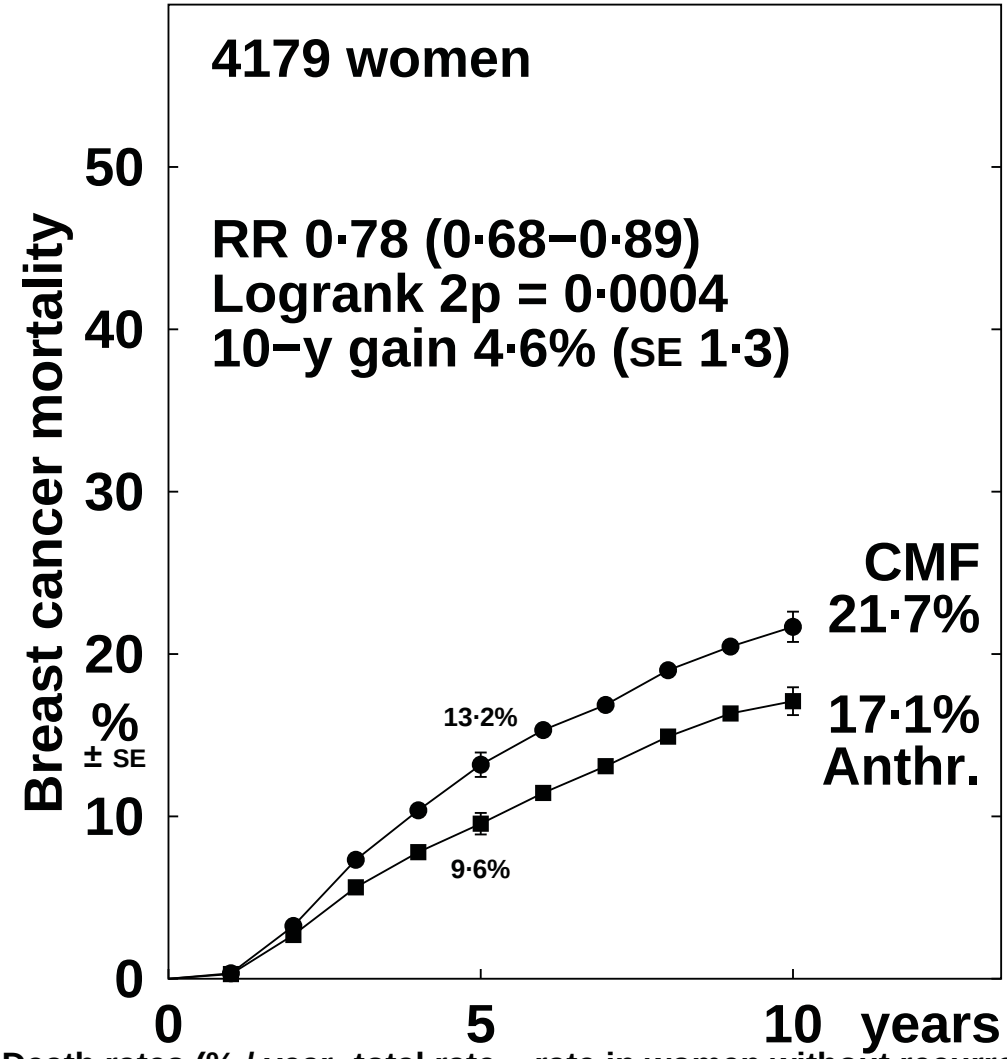
Anthracycline-based regimens with higher cumulative dosage (eg CAF/CEF) vs standard CMF





Recurrence rates (% / year) and logrank analyses

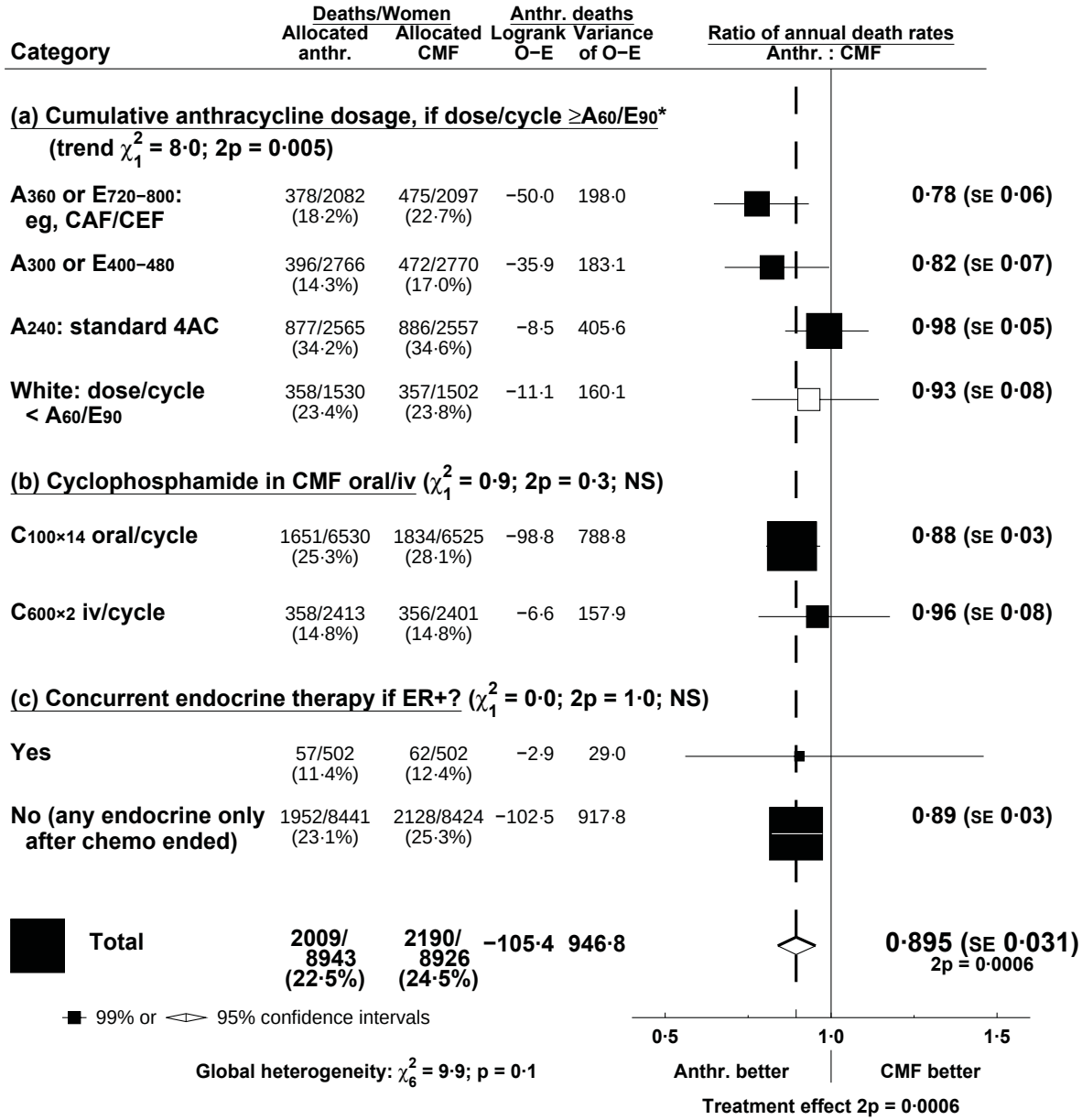
Allocation	Years 0 − 4	Years 5 − 9	Year 10+
Anthr.	4·11 (381 / 9268)	2·00 (146 / 7312)	1·60 (58 / 3623)
CMF	5·21 (473 / 9082)	2·10 (147 / 7012)	1·37 (50 / 3644)
Rate ratio	0·77 SE 0·06	0·96 SE 0·12	1·11 SE 0·21
(O−E) / V	−50·9 / 194·3	−3·2 / 69·6	2·6 / 24·2

Death rates (% / year: total rate − rate in women without recurrence)

Allocation	Years 0 − 4	Years 5 − 9	Year 10+
Anthr.	2·03 SE 0·14	1·75 SE 0·15	0·88 SE 0·15
CMF	2·76 SE 0·17	2·11 SE 0·16	0·93 SE 0·15
Rate ratio	0·71 SE 0·08	0·85 SE 0·11	0·94 SE 0·24
(O−E) / V	−37·0 / 109·0	−11·8 / 72·2	−1·1 / 16·7

EBCTCG, Lancet 2011

Breast cancer mortality ratio: anthracycline-based regimen vs standard CMF, by TYPE of treatment comparison



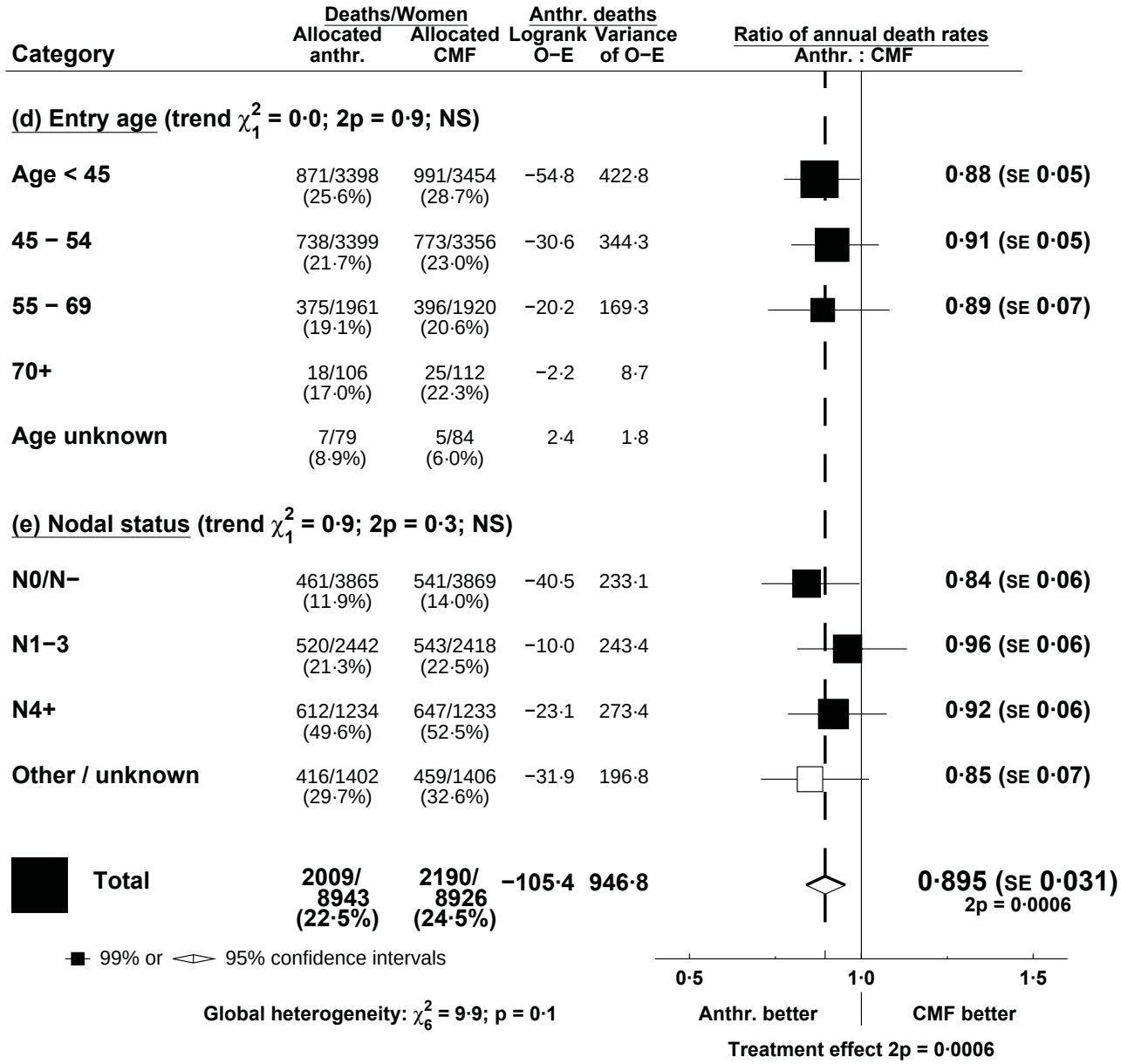
EBCTCG, Lancet 2011

Trials of any anthracycline-based regimen vs standard CMF:

subgroup analyses by age, stage and ER status

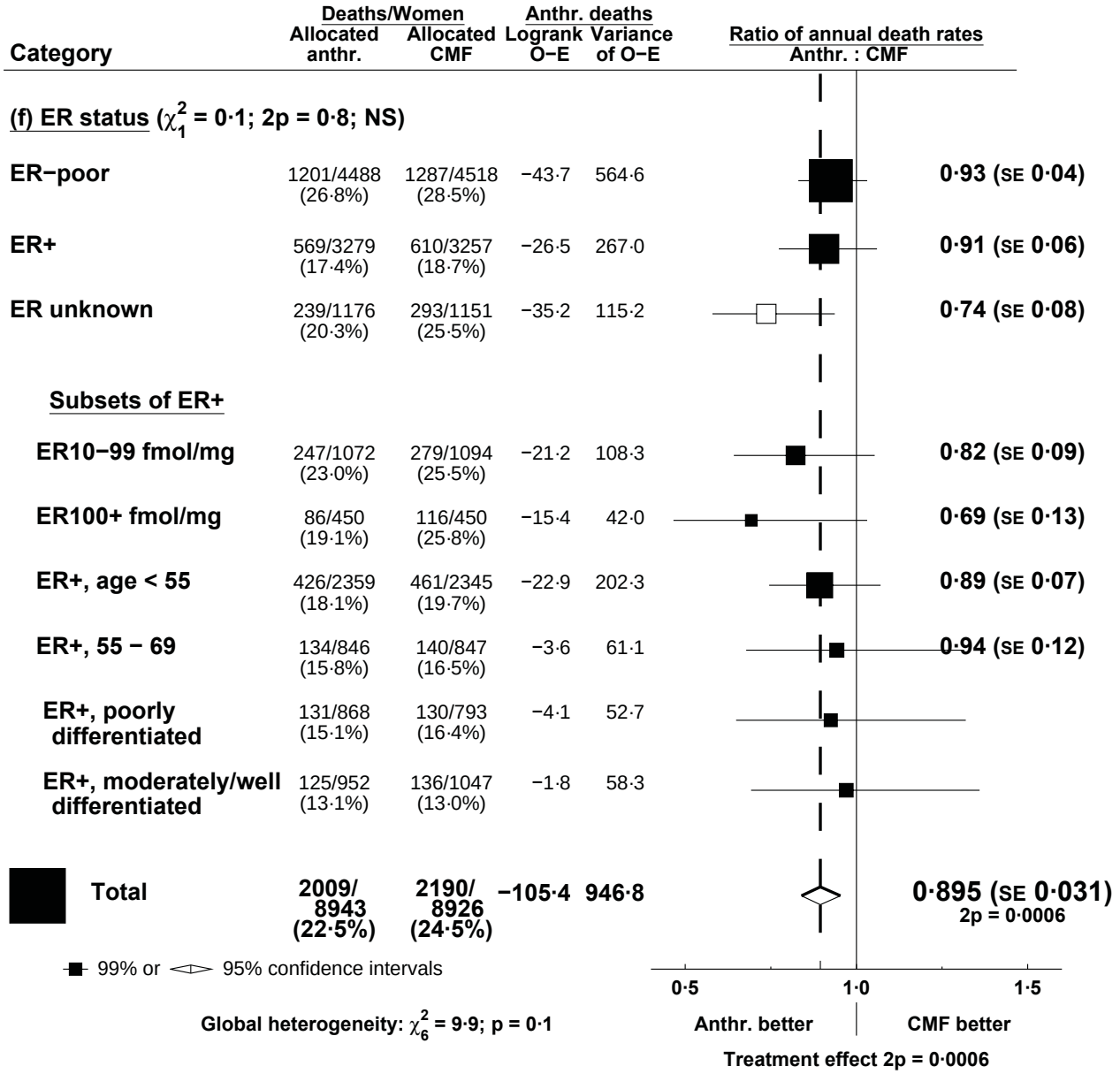
EBCTCG, Lancet 2011

Breast cancer mortality ratio: anthracycline-based regimen vs standard CMF, by AGE and STAGE



EBCTCG, Lancet 2011

Breast cancer mortality ratio: anthracycline-based regimen vs standard CMF, by ER STATUS and subsets of ER+



EBCTCG, Lancet 2011

Trials of chemotherapy vs no adjuvant chemotherapy

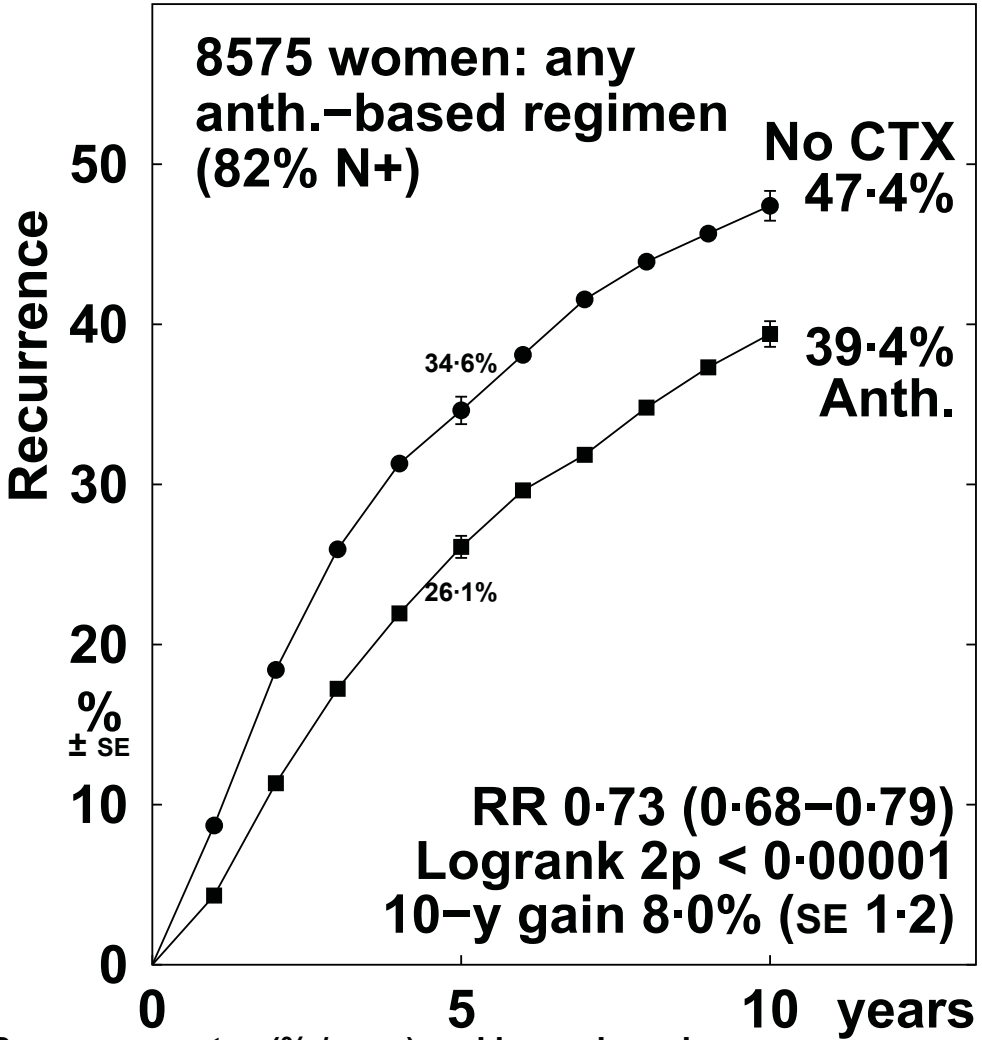
- Any anthracycline-based regimen (eg, standard 4AC) vs nil

- Standard CMF vs nil

EBCTCG, Lancet 2011

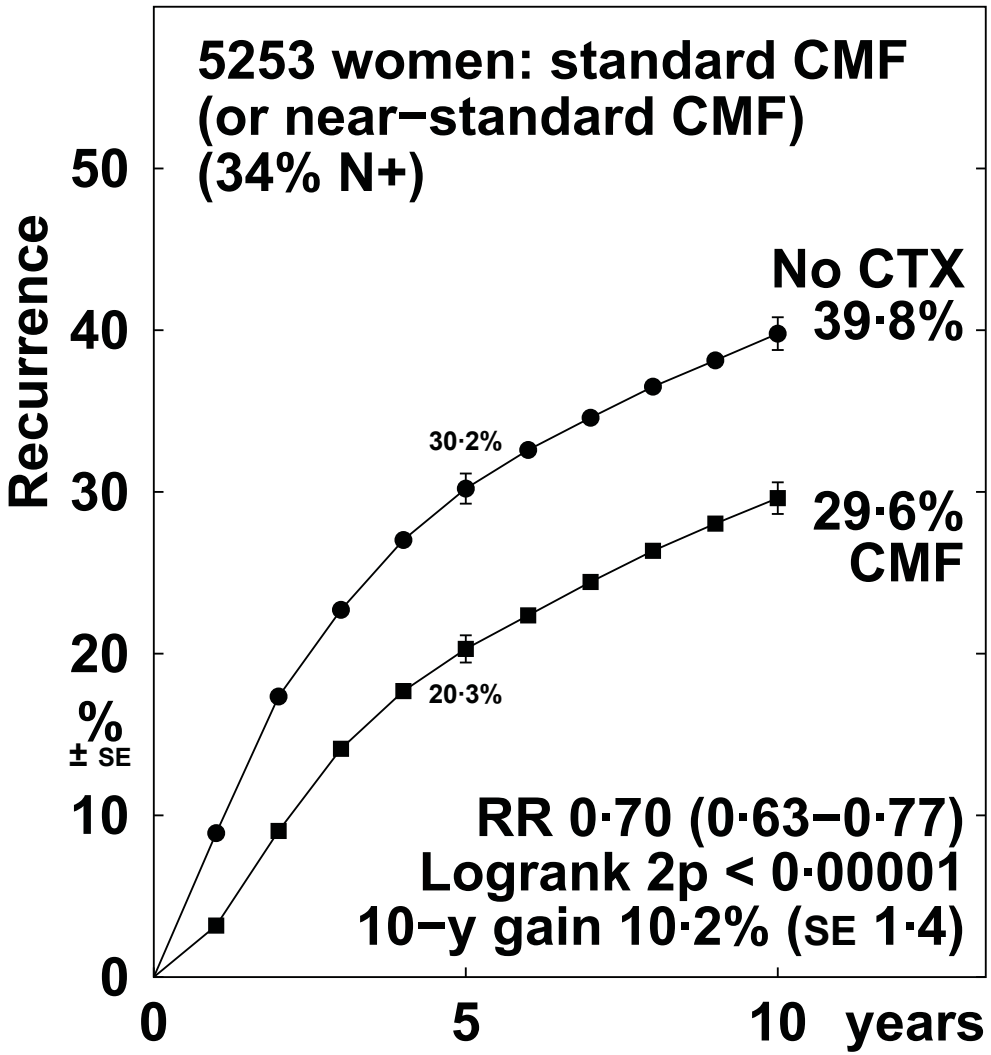
Chemotherapy vs no adjuvant chemotherapy

L: anthracycline-based regimen (eg, standard 4AC), R: standard CMF



Recurrence rates (% / year) and logrank analyses

Allocation	Years 0 − 4	Years 5 − 9	Year 10+
Anth.	6·14 (1179 / 19190)	4·06 (487 / 11981)	2·91 (161 / 5530)
No CTX	9·06 (1259 / 13899)	4·56 (365 / 8011)	3·87 (159 / 4104)
Rate ratio	0·69 SE 0·04	0·89 SE 0·07	0·72 SE 0·11
(O−E) / V	−185·2 / 489·8	−20·0 / 174·7	−21·2 / 65·5

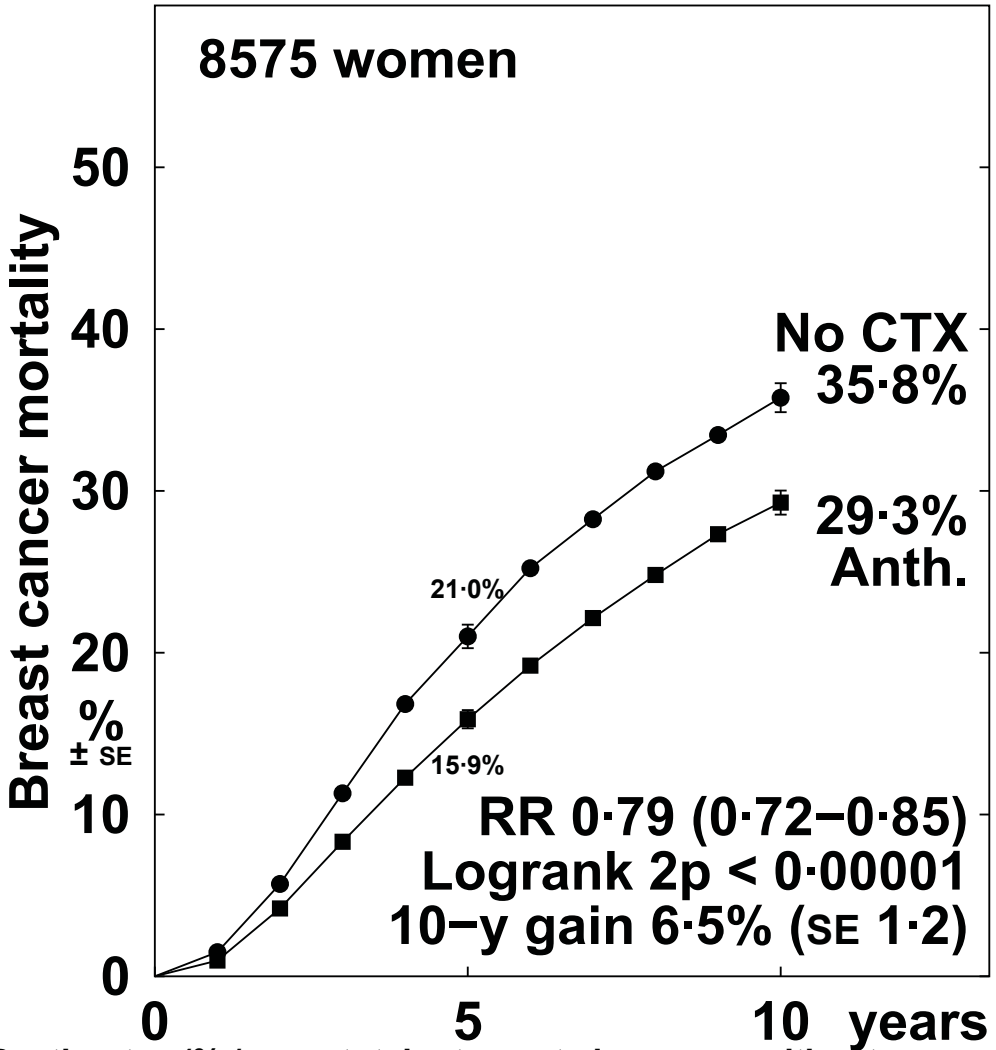


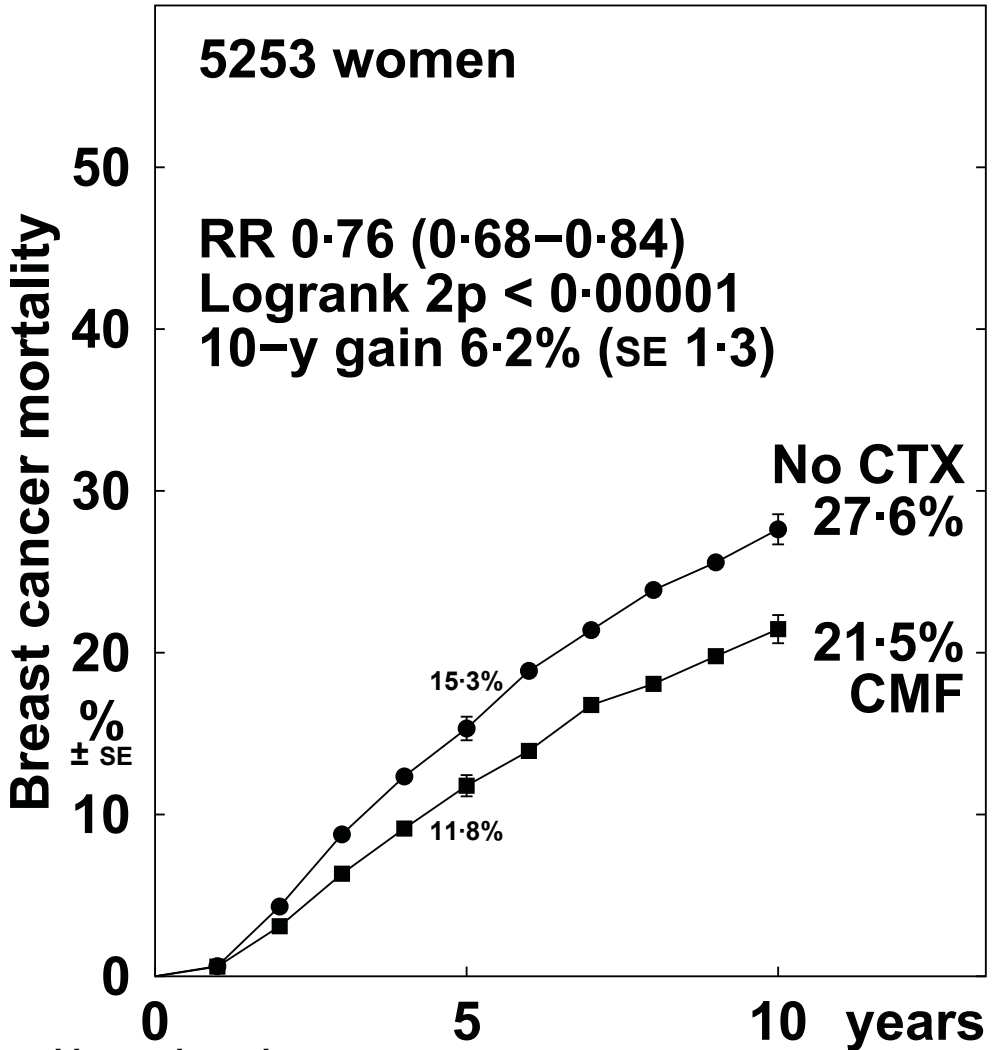
Allocation	Years 0 − 4	Years 5 − 9	Year 10+
CMF	4·83 (549 / 11357)	2·58 (207 / 8038)	1·88 (116 / 6155)
No CTX	7·20 (748 / 10385)	2·93 (210 / 7158)	1·90 (100 / 5260)
Rate ratio	0·61 SE 0·05	0·84 SE 0·09	0·99 SE 0·14
(O−E) / V	−135·5 / 277·0	−16·9 / 95·9	−0·7 / 48·7

EBCTCG, Lancet 2011

Chemotherapy vs no adjuvant chemotherapy

L: anthracycline-based regimen (eg, standard 4AC), R: standard CMF





Death rates (% / year: total rate − rate in women without recurrence) and logrank analyses

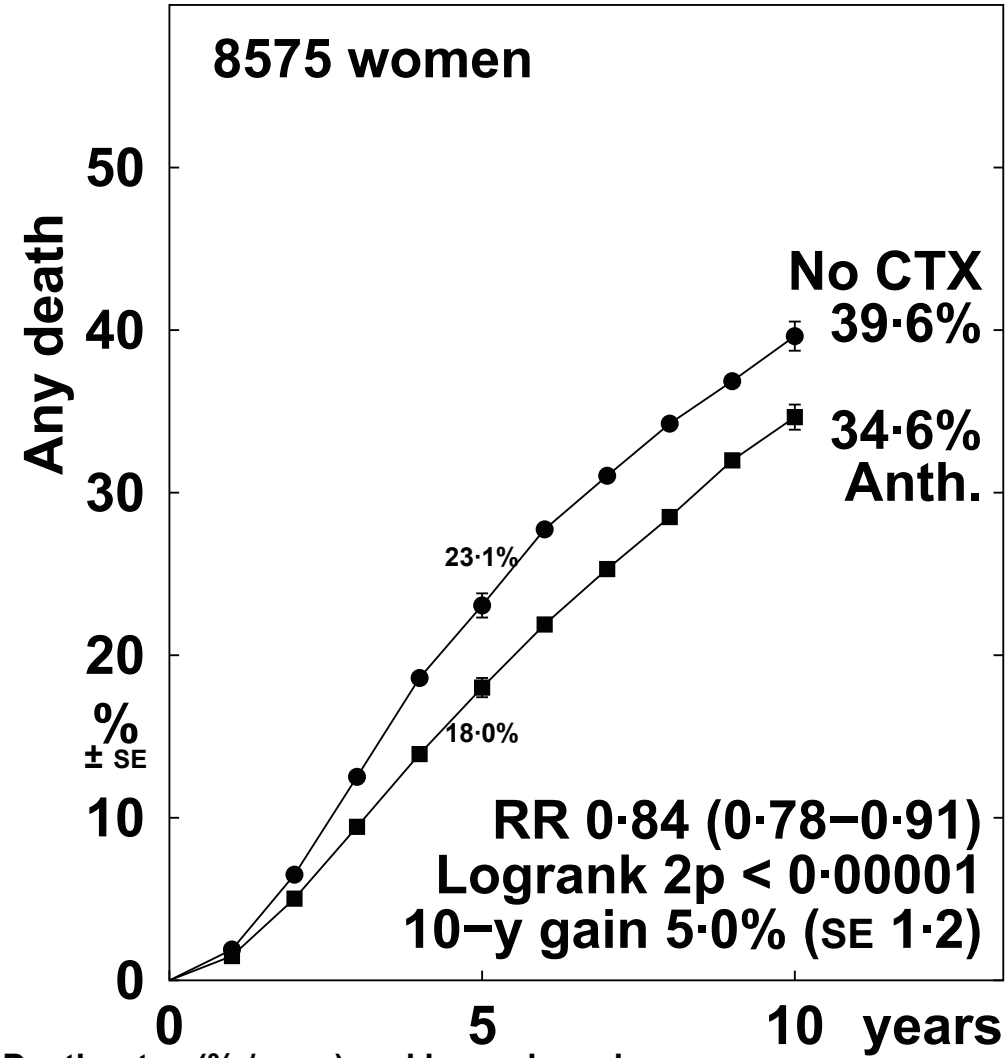
Allocation	Years 0 − 4	Years 5 − 9	Year 10+
Anth.	3·38 SE 0·13	3·57 SE 0·16	2·83 SE 0·19
No CTX	4·77 SE 0·17	4·31 SE 0·21	2·98 SE 0·22
Rate ratio	0·73 SE 0·05	0·83 SE 0·07	0·92 SE 0·11
(O−E) / V	−97·5 / 307·0	−35·9 / 193·2	−6·7 / 81·0

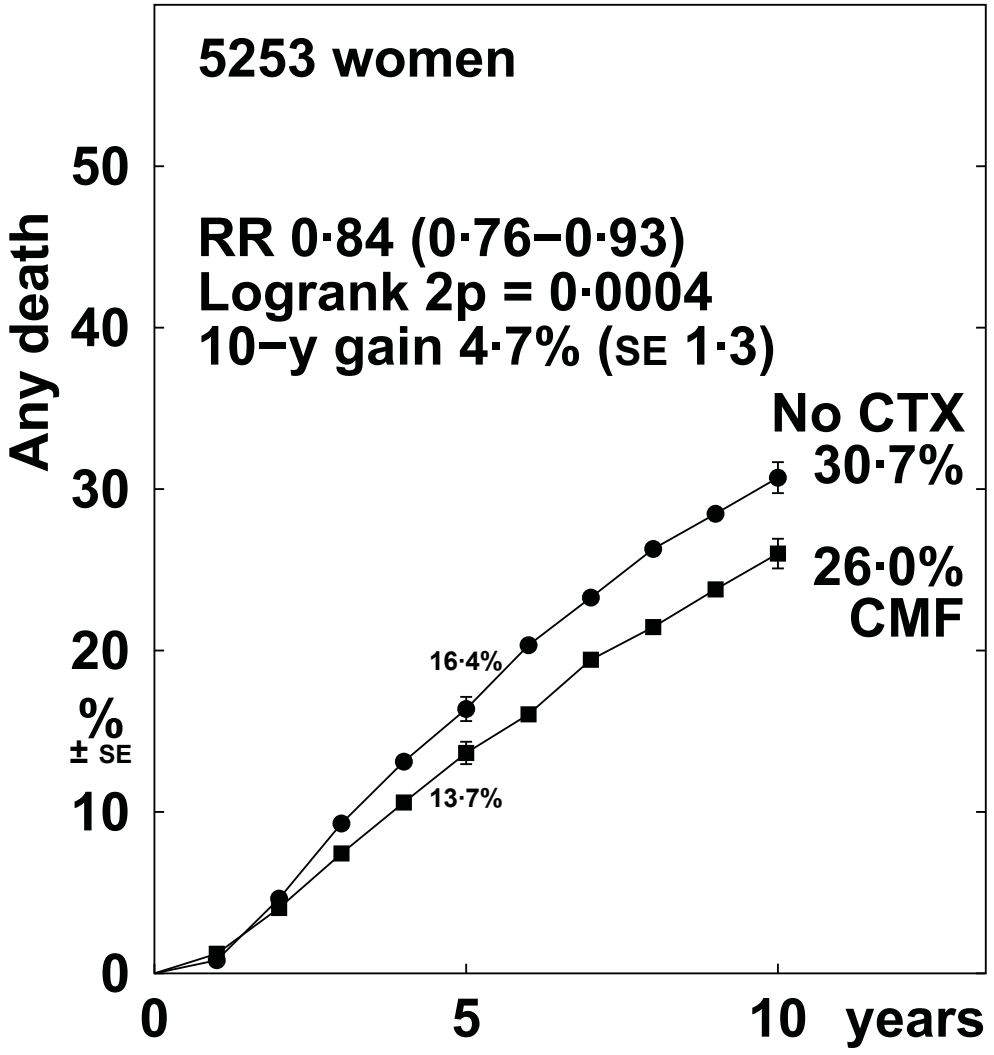
Allocation	Years 0 − 4	Years 5 − 9	Year 10+
CMF	2·51 SE 0·14	2·42 SE 0·16	1·80 SE 0·16
No CTX	3·23 SE 0·17	3·14 SE 0·19	2·10 SE 0·18
Rate ratio	0·75 SE 0·07	0·74 SE 0·08	0·82 SE 0·12
(O−E) / V	−43·5 / 151·3	−33·7 / 109·6	−11·9 / 59·1

EBCTCG, Lancet 2011

Chemotherapy vs no adjuvant chemotherapy

L: anthracycline-based regimen (eg, standard 4AC), R: standard CMF





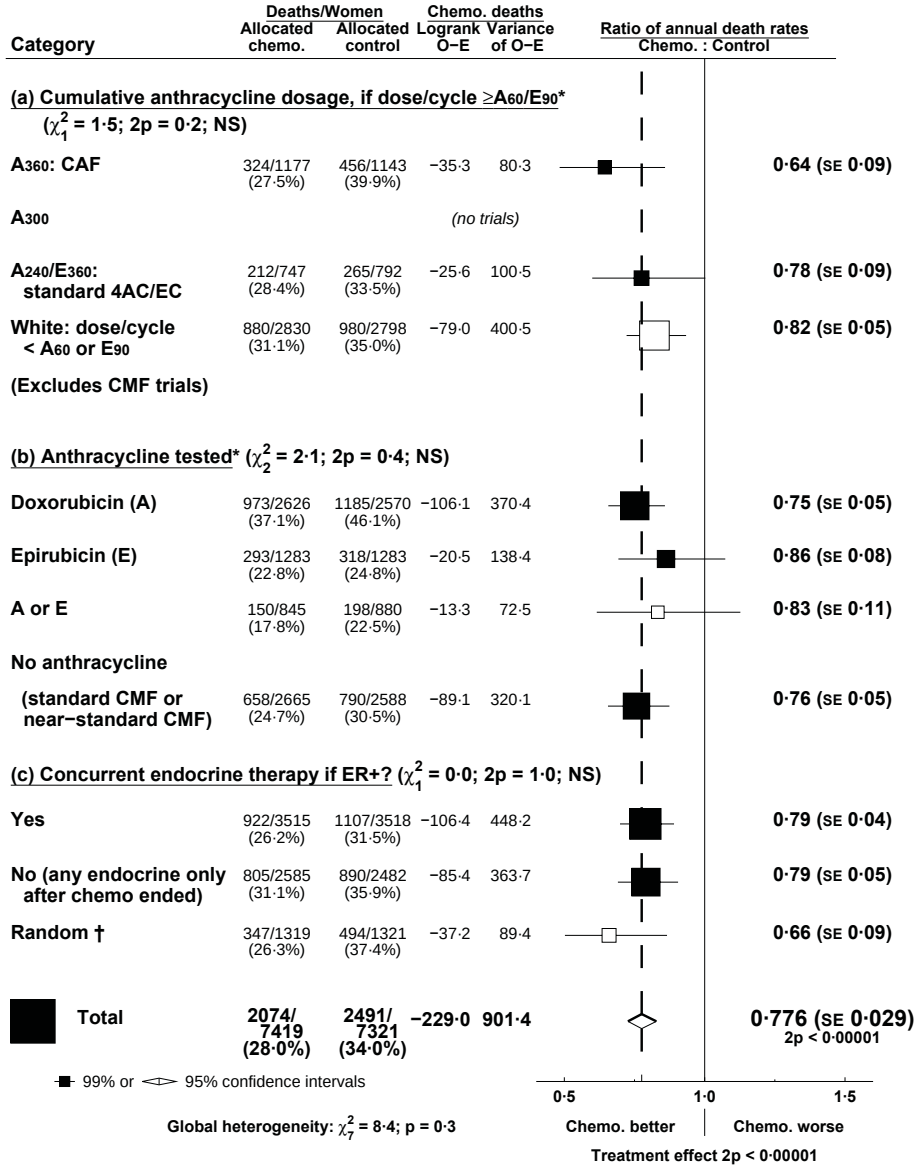
Death rates (% / year) and logrank analyses

Allocation	Years 0 − 4	Years 5 − 9	Year 10+
Anth.	3·91 (811 / 20718)	4·62 (645 / 13969)	4·39 (337 / 7680)
No CTX	5·25 (834 / 15889)	4·93 (492 / 9975)	4·34 (259 / 5969)
Rate ratio	0·75 SE 0·05	0·92 SE 0·06	1·00 SE 0·09
(O−E) / V	−99·0 / 346·4	−19·1 / 234·6	−0·1 / 120·2

Allocation	Years 0 − 4	Years 5 − 9	Year 10+
CMF	2·93 (357 / 12167)	3·15 (286 / 9091)	3·14 (230 / 7318)
No CTX	3·49 (410 / 11756)	3·78 (326 / 8617)	3·39 (224 / 6612)
Rate ratio	0·82 SE 0·07	0·81 SE 0·08	0·91 SE 0·10
(O−E) / V	−33·6 / 170·7	−28·5 / 137·2	−8·8 / 96·2

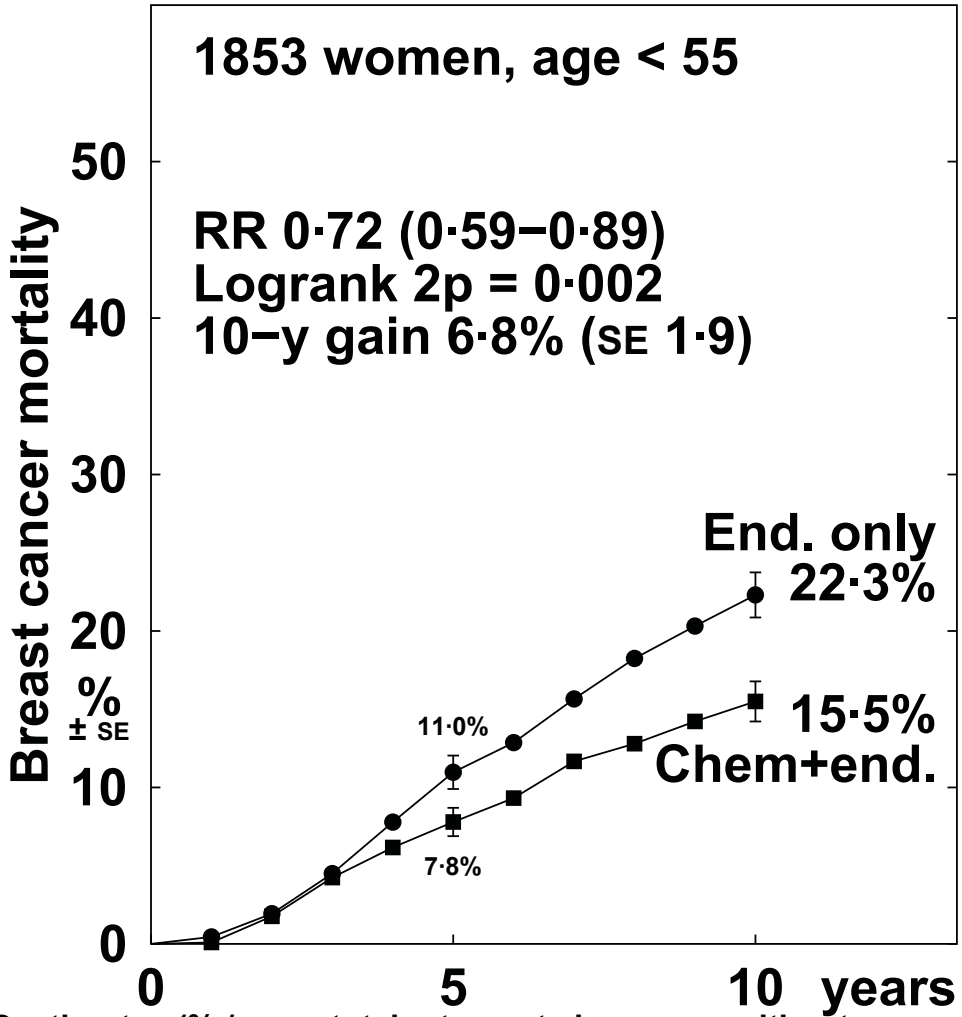
EBCTCG, Lancet 2011

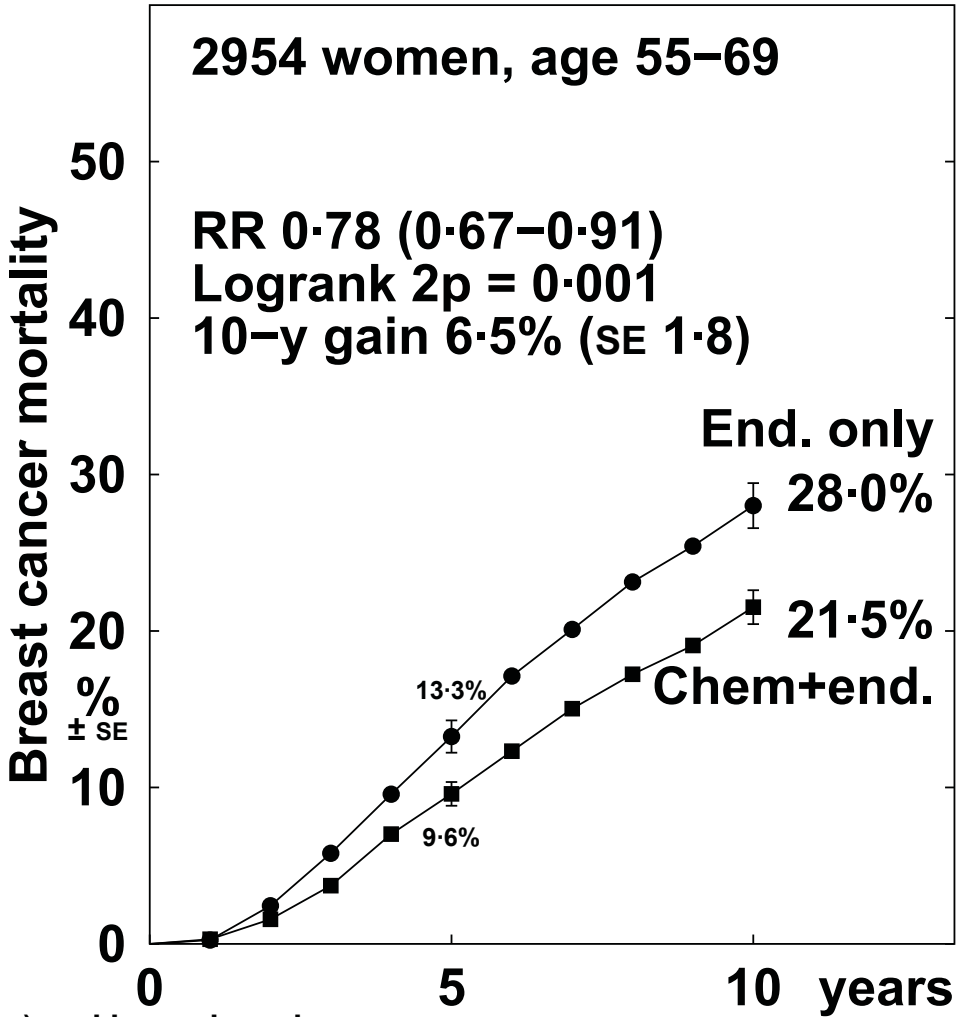
Breast cancer mortality ratio: anthracycline-based regimen (eg, standard 4AC) or standard CMF vs no chemotherapy, by TYPE of treatment comparison



EBCTCG, Lancet 2011

Chemotherapy (anthracycline-based regimen or standard CMF) + 5 year endocrine therapy vs 5 year endocrine therapy only, ER+ disease only: by ENTRY AGE





Death rates (% / year: total rate − rate in women without recurrence) and logrank analyses

Allocation	Years 0 − 4	Years 5 − 9	Year 10+	Years 0 − 4	Years 5 − 9	Year 10+
Chem+end.	1·72 SE 0·19	1·99 SE 0·23	1·77 SE 0·28	2·09 SE 0·16	2·88 SE 0·22	3·03 SE 0·31
End. only	2·20 SE 0·23	2·53 SE 0·28	1·69 SE 0·29	2·75 SE 0·23	3·96 SE 0·32	2·88 SE 0·35
Rate ratio	0·71 SE 0·14	0·65 SE 0·14	0·96 SE 0·24	0·70 SE 0·10	0·75 SE 0·10	1·03 SE 0·17
(O−E) / V	−13·0 / 37·8	−14·7 / 33·8	−0·6 / 16·2	−23·1 / 66·0	−19·7 / 69·4	1·0 / 34·5

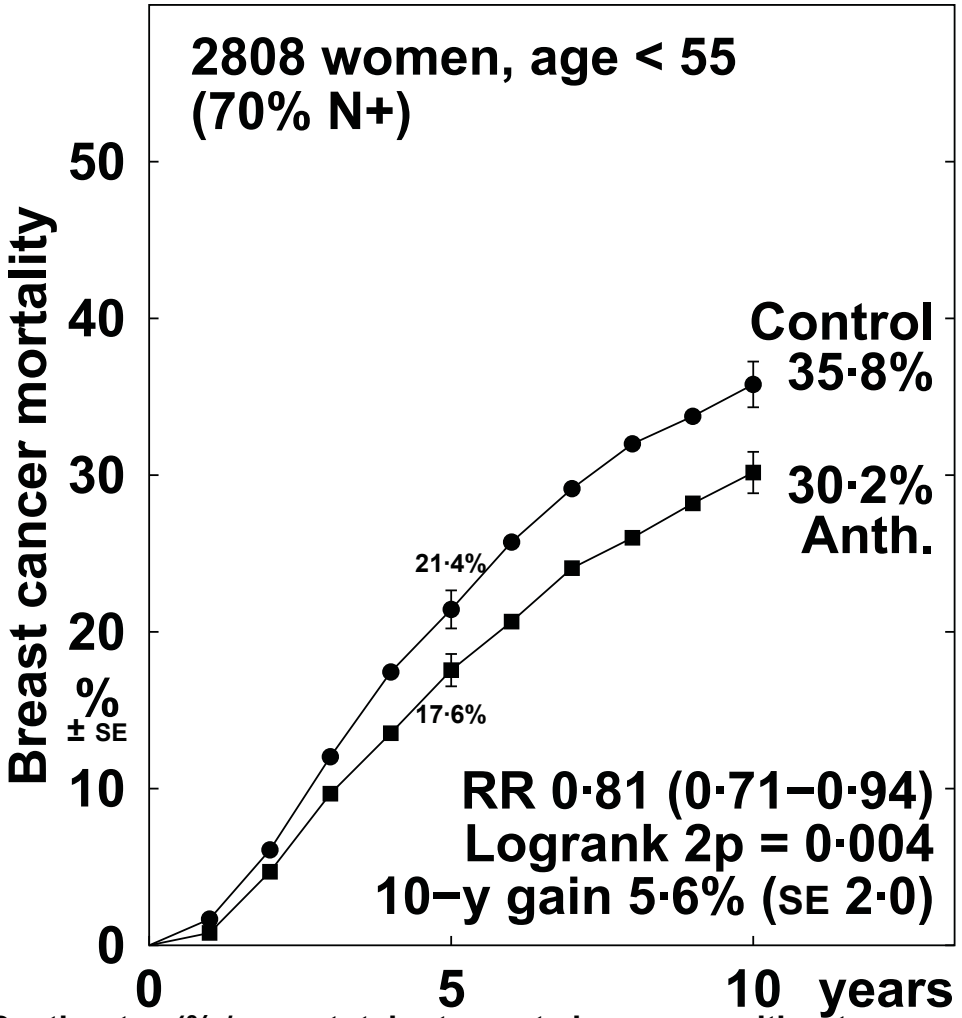
EBCTCG, Lancet 2011

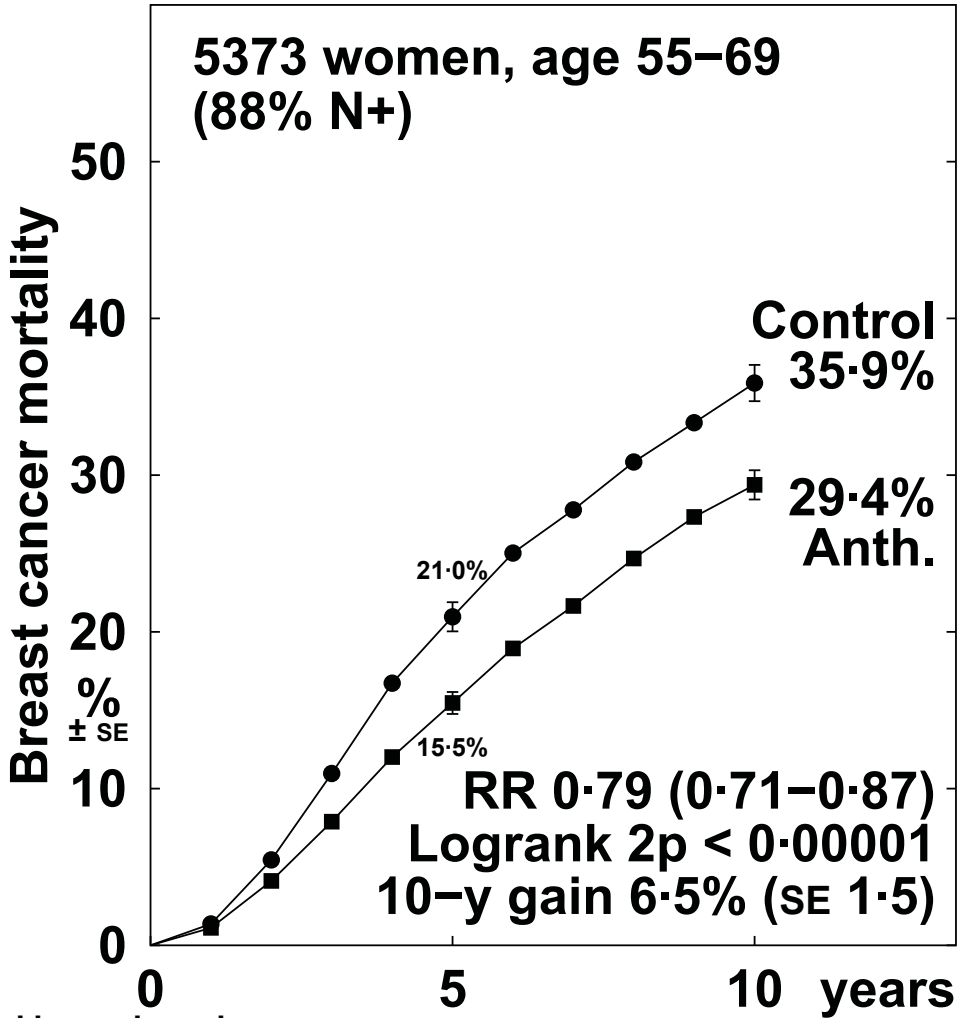
Trials of any anthracycline-based regimen (eg, standard 4AC) vs no adjuvant chemotherapy:

Subgroup analyses by age, stage and ER status, and by subsets of ER+ disease

EBCTCG, Lancet 2011

Any anthracycline-based regimen (eg, standard 4AC) vs no adjuvant chemotherapy, by ENTRY AGE



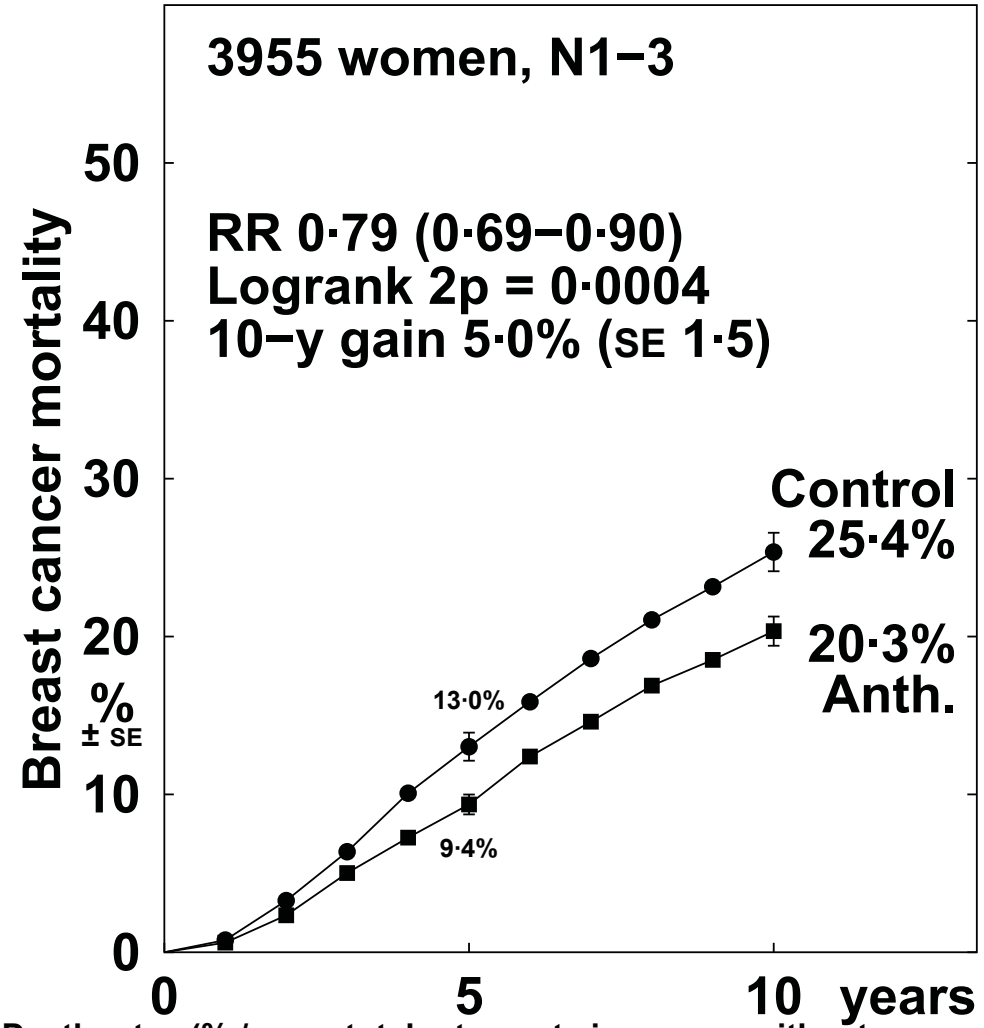


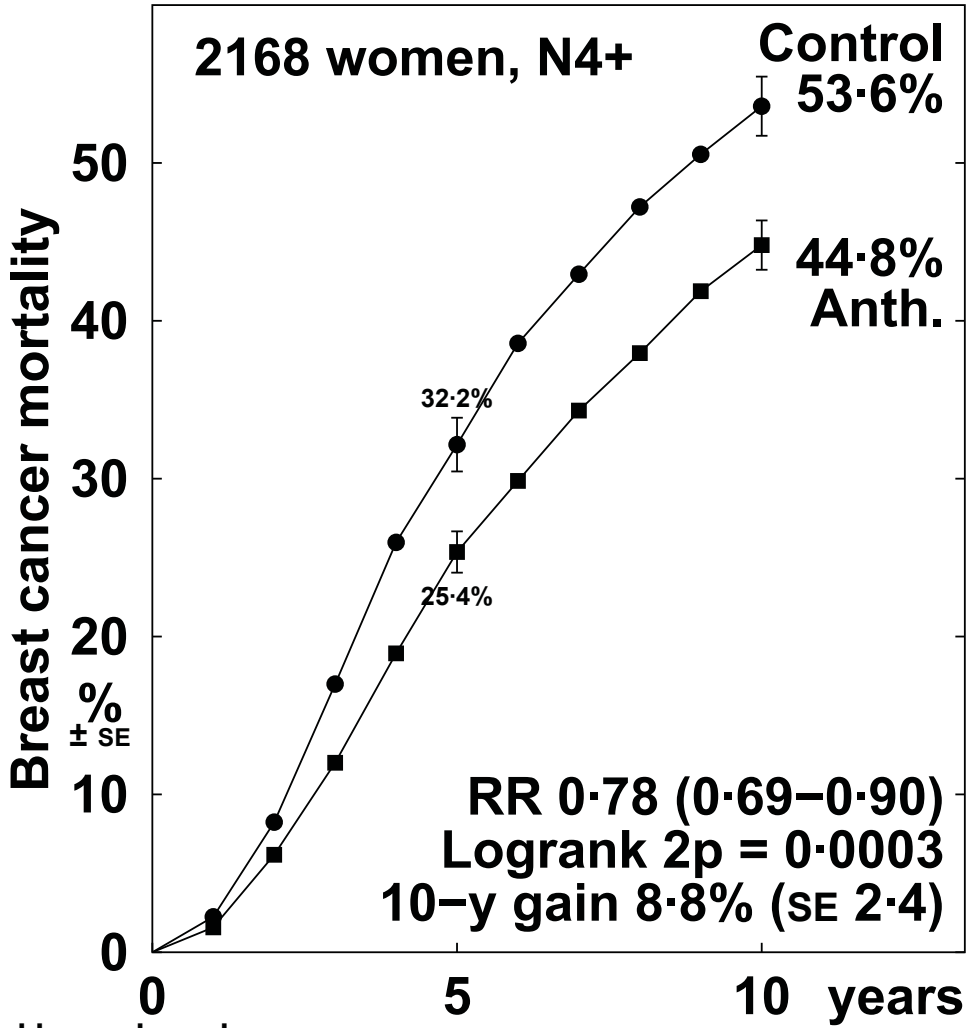
Death rates (% / year: total rate − rate in women without recurrence) and logrank analyses

Allocation	Years 0 − 4	Years 5 − 9	Year 10+	Years 0 − 4	Years 5 − 9	Year 10+
Anth.	3·81 SE 0·24	3·53 SE 0·28	1·85 SE 0·25	3·26 SE 0·16	3·63 SE 0·20	3·43 SE 0·28
Control	4·77 SE 0·29	4·11 SE 0·34	2·01 SE 0·28	4·79 SE 0·22	4·40 SE 0·27	3·65 SE 0·33
Rate ratio	0·79 SE 0·09	0·81 SE 0·11	0·96 SE 0·21	0·71 SE 0·06	0·86 SE 0·08	0·94 SE 0·13
(O−E) / V	−25·5 / 108·4	−13·5 / 63·4	−0·9 / 21·0	−65·9 / 193·2	−19·2 / 125·4	−3·5 / 58·3

EBCTCG, Lancet 2011

Any anthracycline-based regimen (eg, standard 4AC) vs no adjuvant chemotherapy, by NODAL STATUS



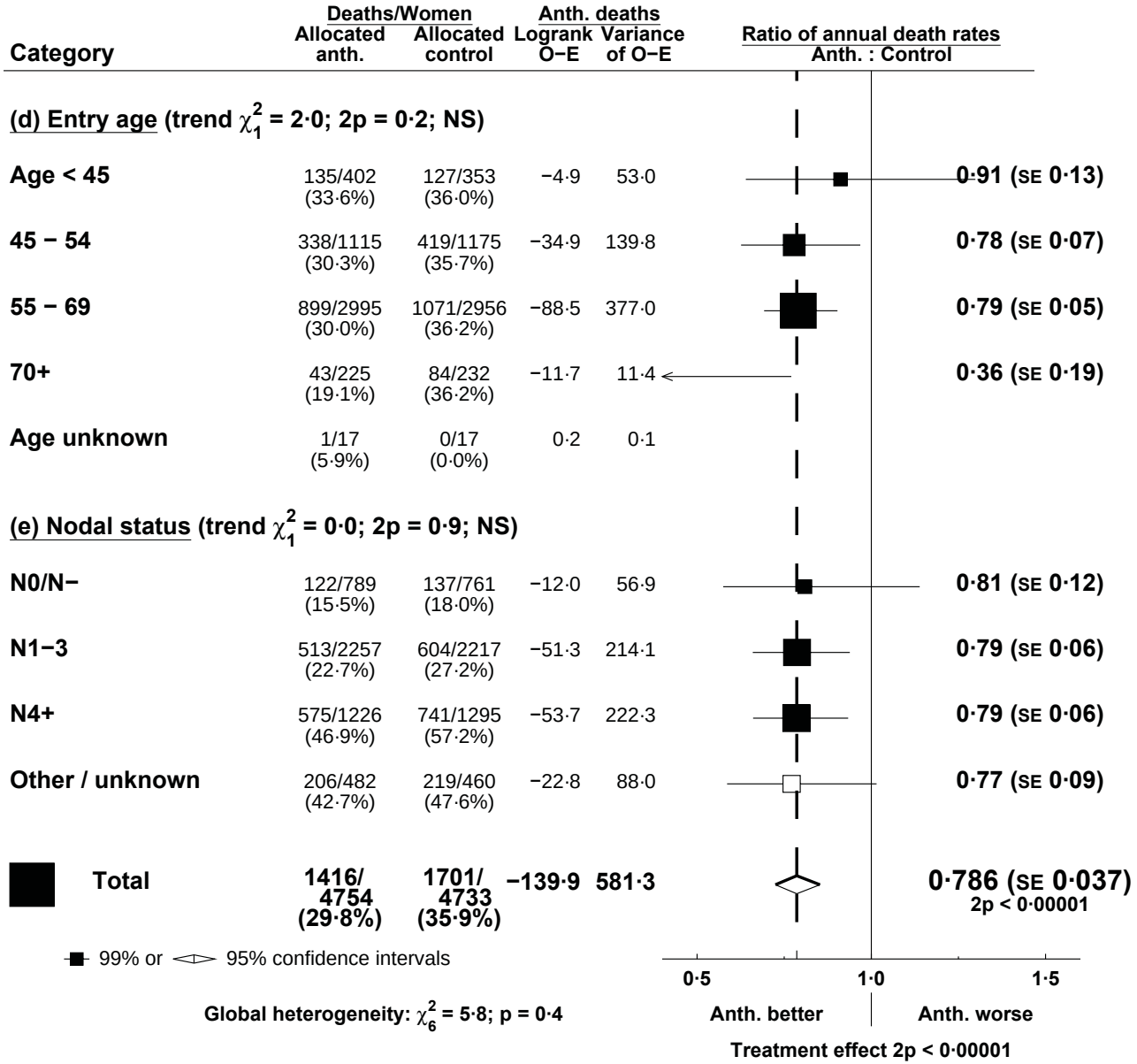


Death rates (% / year: total rate − rate in women without recurrence) and logrank analyses

Allocation	Years 0 − 4	Years 5 − 9	Year 10+	Years 0 − 4	Years 5 − 9	Year 10+
Anth.	1·91 SE 0·14	2·62 SE 0·19	2·91 SE 0·27	5·53 SE 0·32	6·15 SE 0·43	4·61 SE 0·53
Control	2·92 SE 0·20	3·22 SE 0·25	3·16 SE 0·33	7·87 SE 0·45	8·11 SE 0·61	4·72 SE 0·61
Rate ratio	0·71 SE 0·09	0·85 SE 0·10	0·86 SE 0·14	0·74 SE 0·08	0·78 SE 0·10	1·07 SE 0·20
(O−E) / V	−32·3 / 92·9	−12·4 / 78·4	−6·6 / 42·7	−36·7 / 120·7	−19·0 / 75·5	1·9 / 26·0

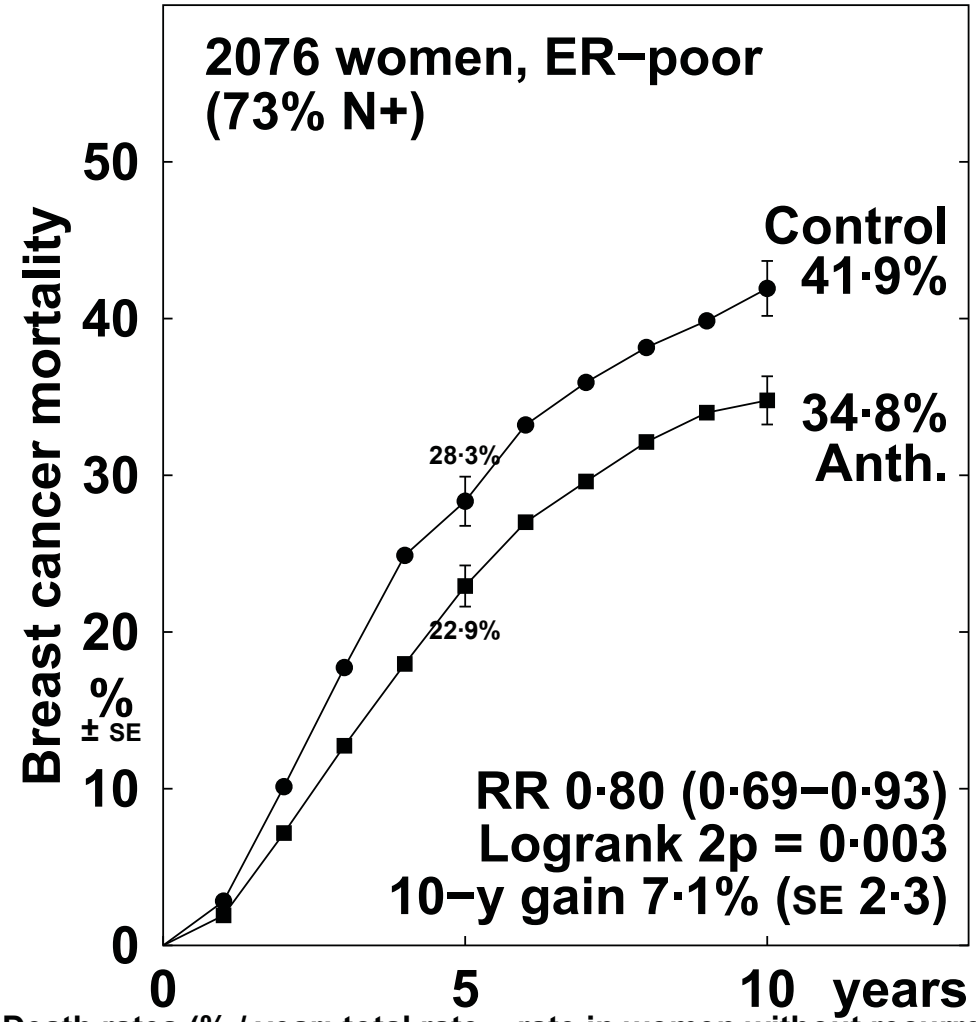
EBCTCG, Lancet 2011

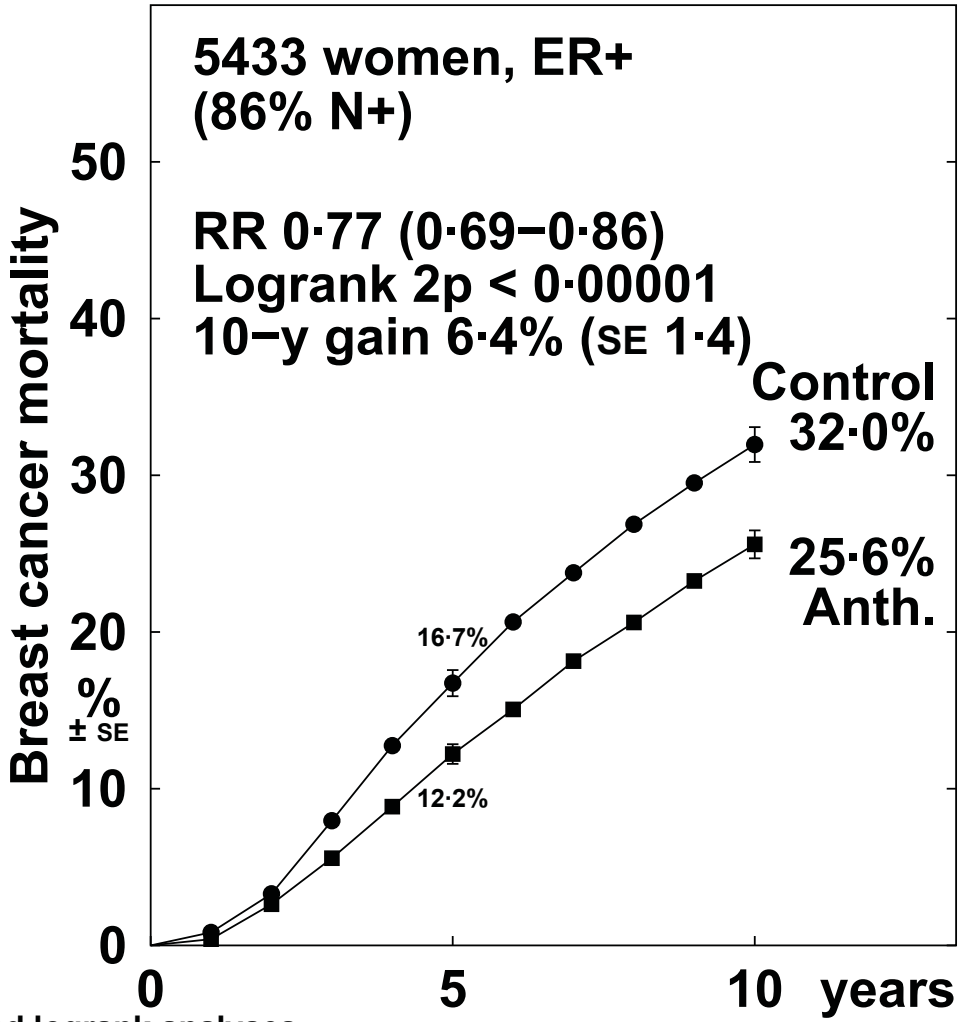
Breast cancer mortality ratio: any anthracycline-based regimen (eg, standard 4AC) vs no adjuvant chemotherapy, by AGE and STAGE



EBCTCG, Lancet 2011

Any anthracycline-based regimen (eg, standard 4AC) vs no adjuvant chemotherapy, by ER STATUS



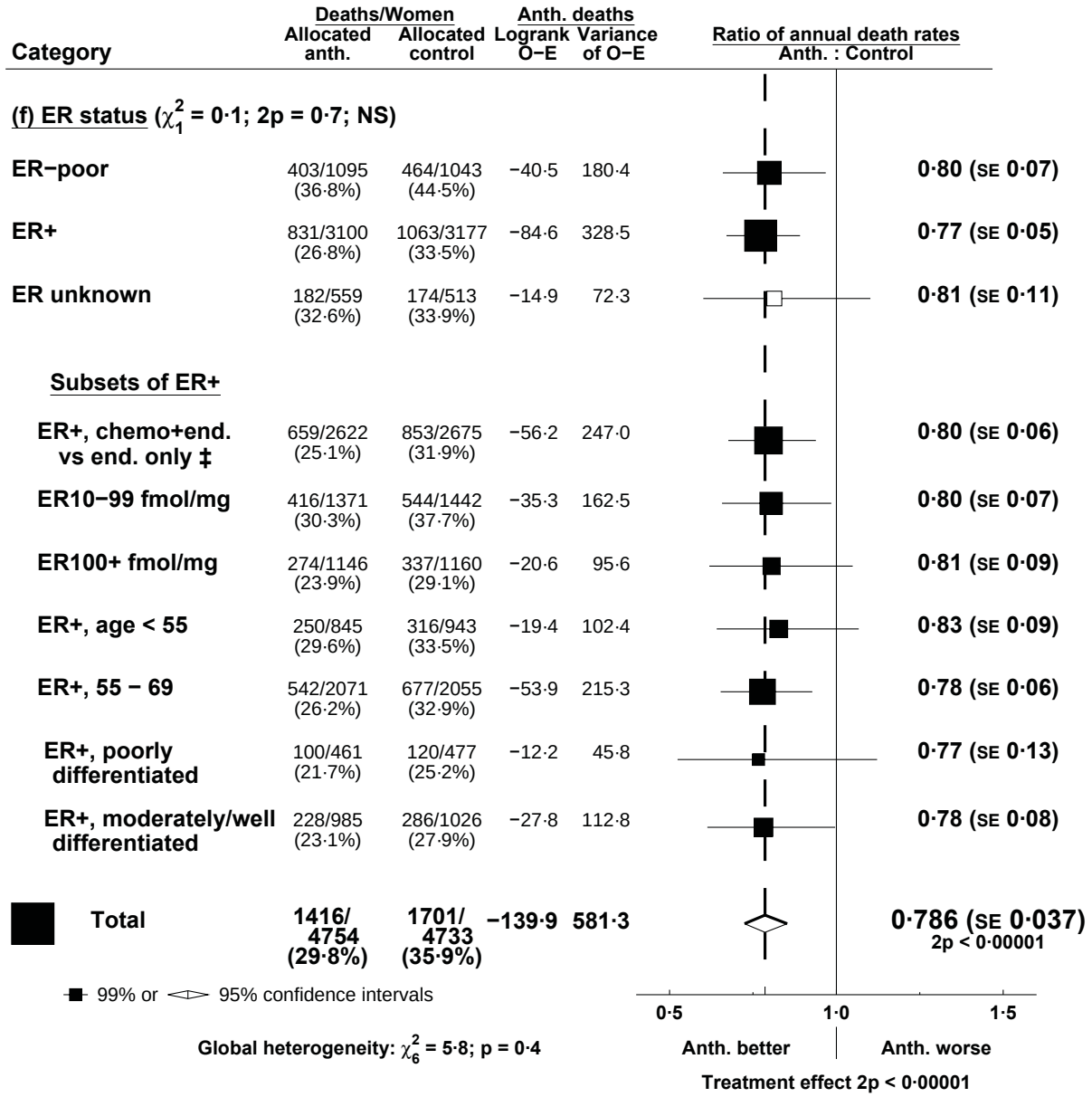


Death rates (% / year: total rate − rate in women without recurrence) and logrank analyses

Allocation	Years 0 − 4	Years 5 − 9	Year 10+	Years 0 − 4	Years 5 − 9	Year 10+
Anth.	4·96 SE 0·32	3·50 SE 0·33	2·64 SE 0·36	2·60 SE 0·14	3·40 SE 0·19	3·09 SE 0·26
Control	6·84 SE 0·41	4·47 SE 0·42	2·92 SE 0·41	3·63 SE 0·19	4·17 SE 0·25	3·14 SE 0·30
Rate ratio	0·76 SE 0·08	0·80 SE 0·13	0·98 SE 0·20	0·71 SE 0·07	0·81 SE 0·08	0·92 SE 0·14
(O−E) / V	−29·2 / 107·7	−10·8 / 48·7	−0·5 / 24·1	−54·3 / 156·2	−26·4 / 123·3	−4·0 / 48·9

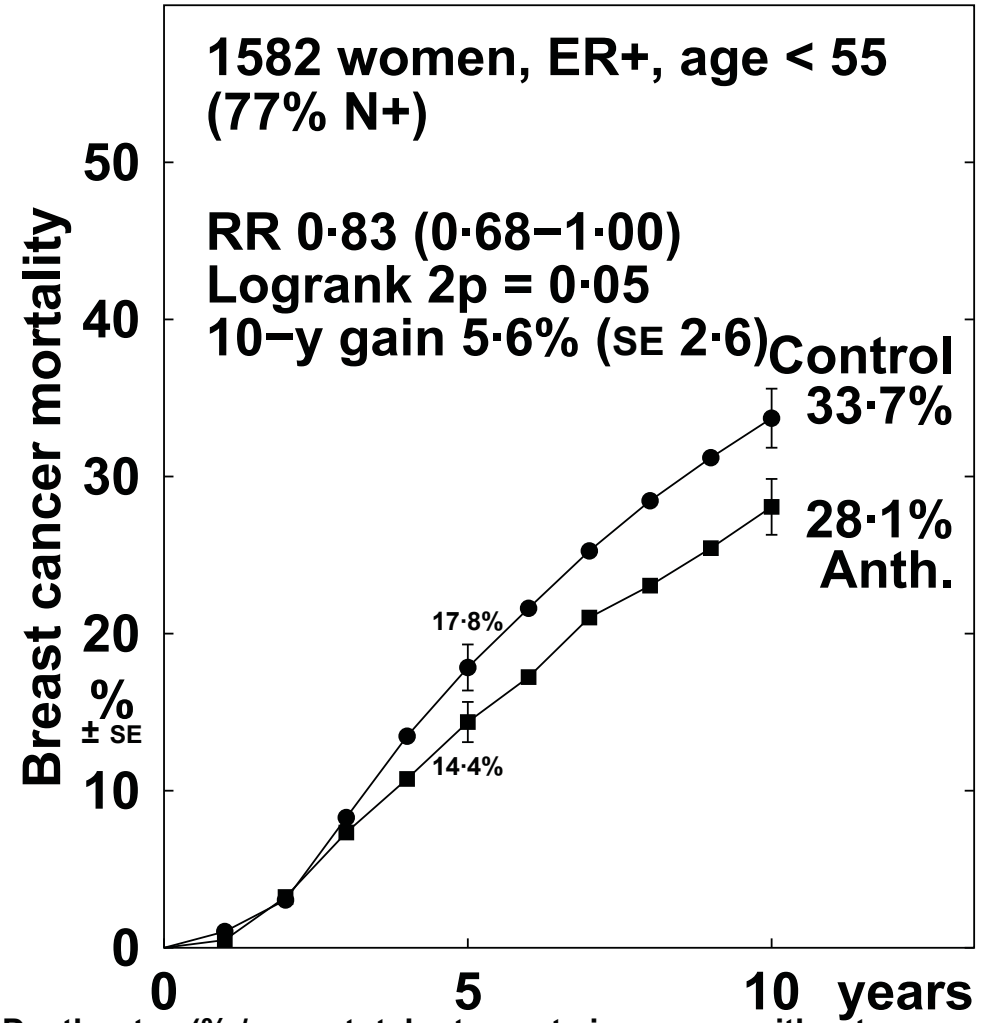
EBCTCG, Lancet 2011

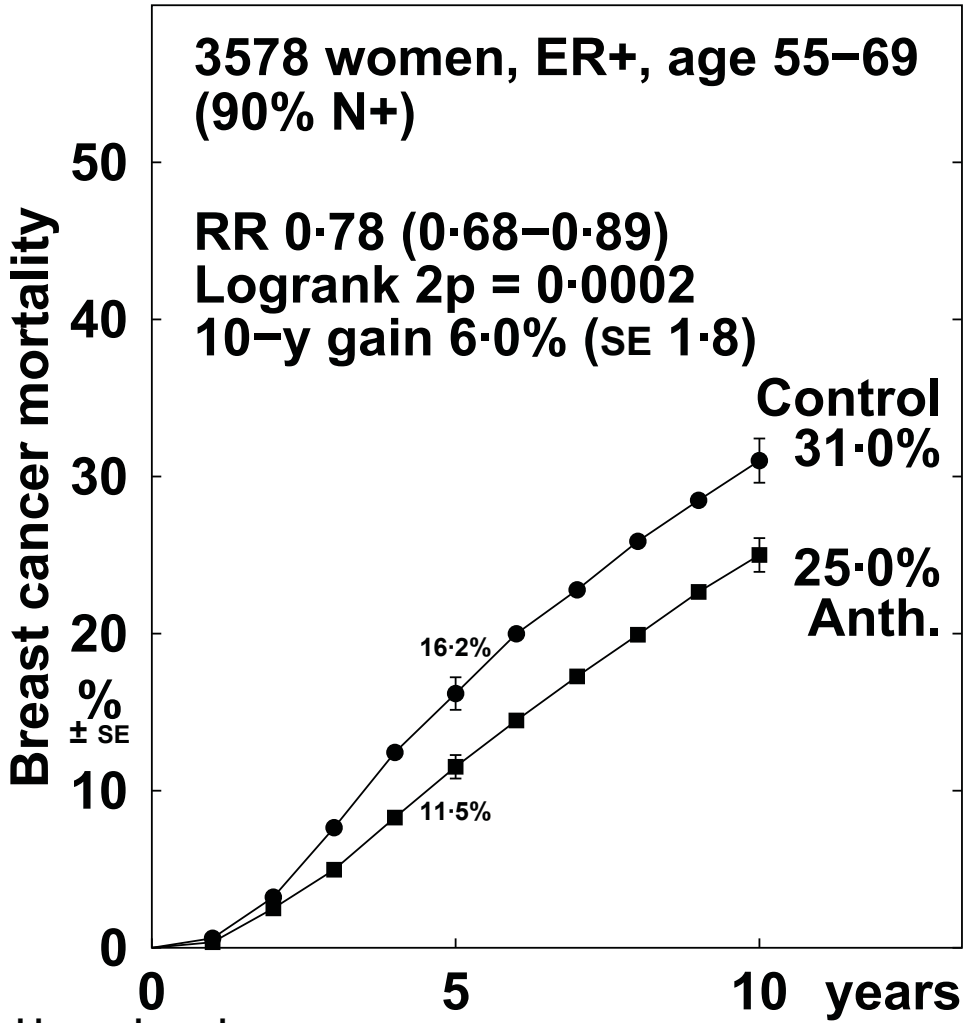
Breast cancer mortality ratio: any anthracycline-based regimen (eg, standard 4AC) vs no adjuvant chemotherapy, by ER STATUS and subsets of ER+



EBCTCG, Lancet 2011

Any anthracycline-based regimen (eg, standard 4AC) vs no adjuvant chemotherapy,
ER+ disease only: by ENTRY AGE





Death rates (% / year: total rate − rate in women without recurrence) and logrank analyses

Allocation	Years 0 − 4	Years 5 − 9	Year 10+	Years 0 − 4	Years 5 − 9	Year 10+
Anth.	3·12 SE 0·28	3·76 SE 0·38	2·19 SE 0·39	2·44 SE 0·16	3·31 SE 0·23	3·42 SE 0·34
Control	3·76 SE 0·34	4·14 SE 0·44	1·93 SE 0·39	3·54 SE 0·23	4·12 SE 0·32	3·76 SE 0·43
Rate ratio	0·79 SE 0·12	0·80 SE 0·14	1·14 SE 0·33	0·69 SE 0·08	0·84 SE 0·10	0·92 SE 0·16
(O−E) / V	−12·4 / 52·9	−8·5 / 38·8	1·4 / 10·8	−36·8 / 98·4	−14·0 / 80·4	−3·1 / 36·4

EBCTCG, Lancet 2011

Halving big risks and halving small risks by chemotherapy

- **Proportional risk reduction does not depend much on age, ER status or nodal status (or on tumour grade or tumour diameter)**
- **Absolute risk reduction, however, depends on the prognosis – and, for ER+ disease, this is the prognosis with endocrine therapy**
- Information lacking on tumour gene expression and on quantitative immunohistochemistry

EBCTCG, Lancet 2011