

THE LANCET

Supplementary webappendix

This webappendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

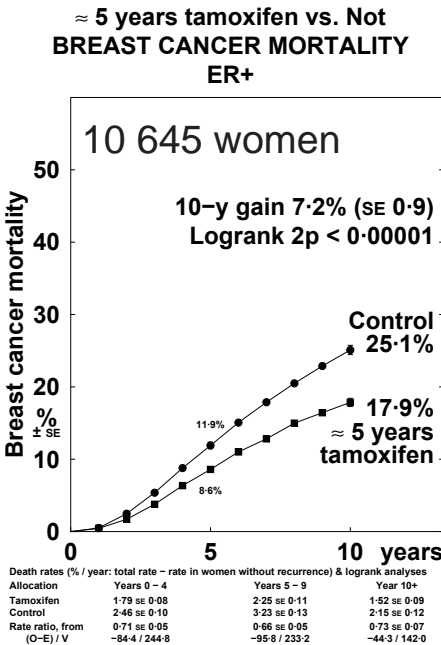
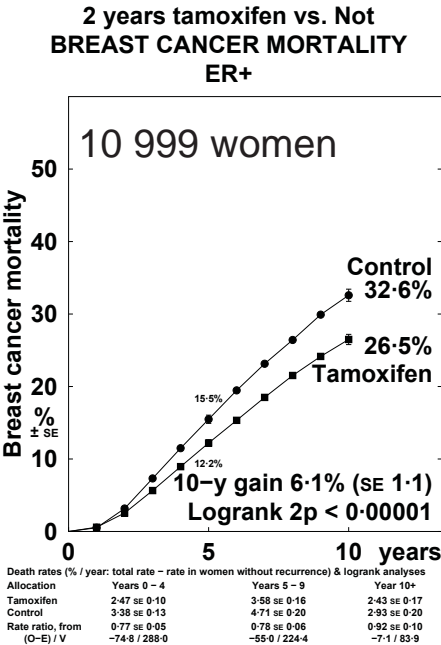
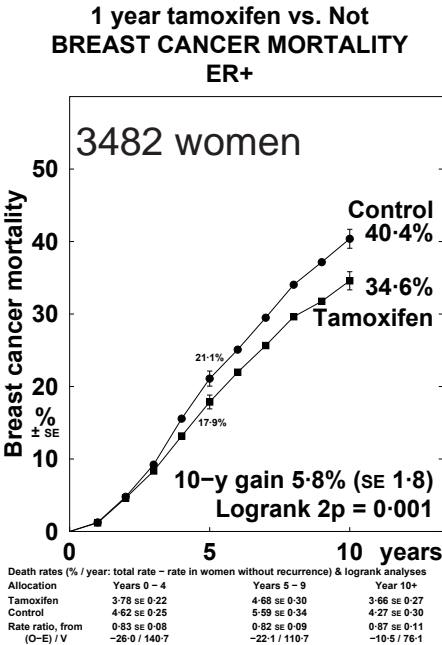
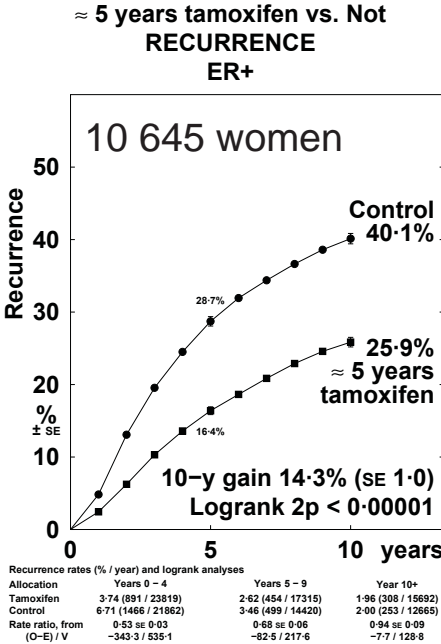
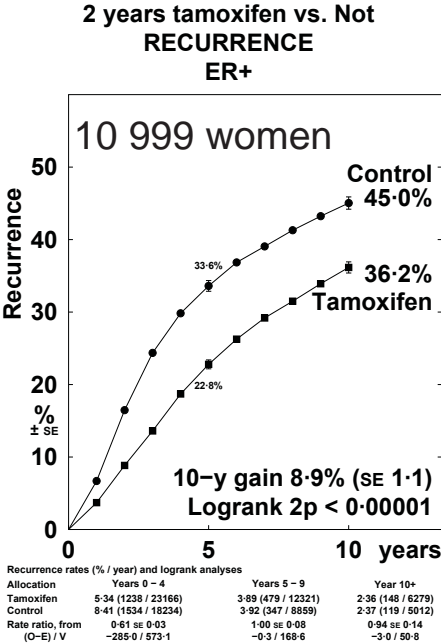
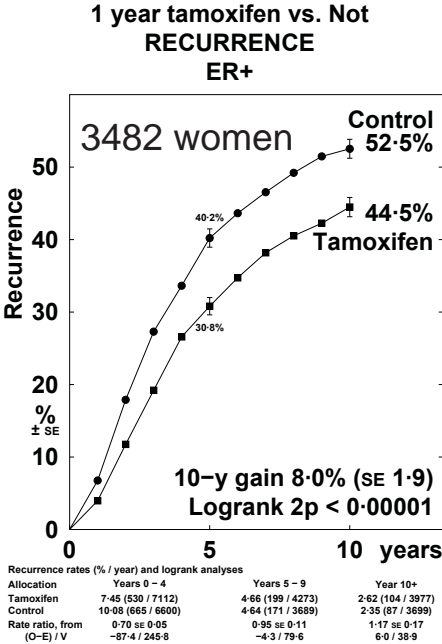
Supplement to: Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. *Lancet* 2011; published online July 29. DOI:10.1016/S0140-6736(11)60993-8.

Webappendix: Supplementary figures and tables for “Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials” *Analyses are by allocated treatment: tamoxifen vs control (no adjuvant tam.)*

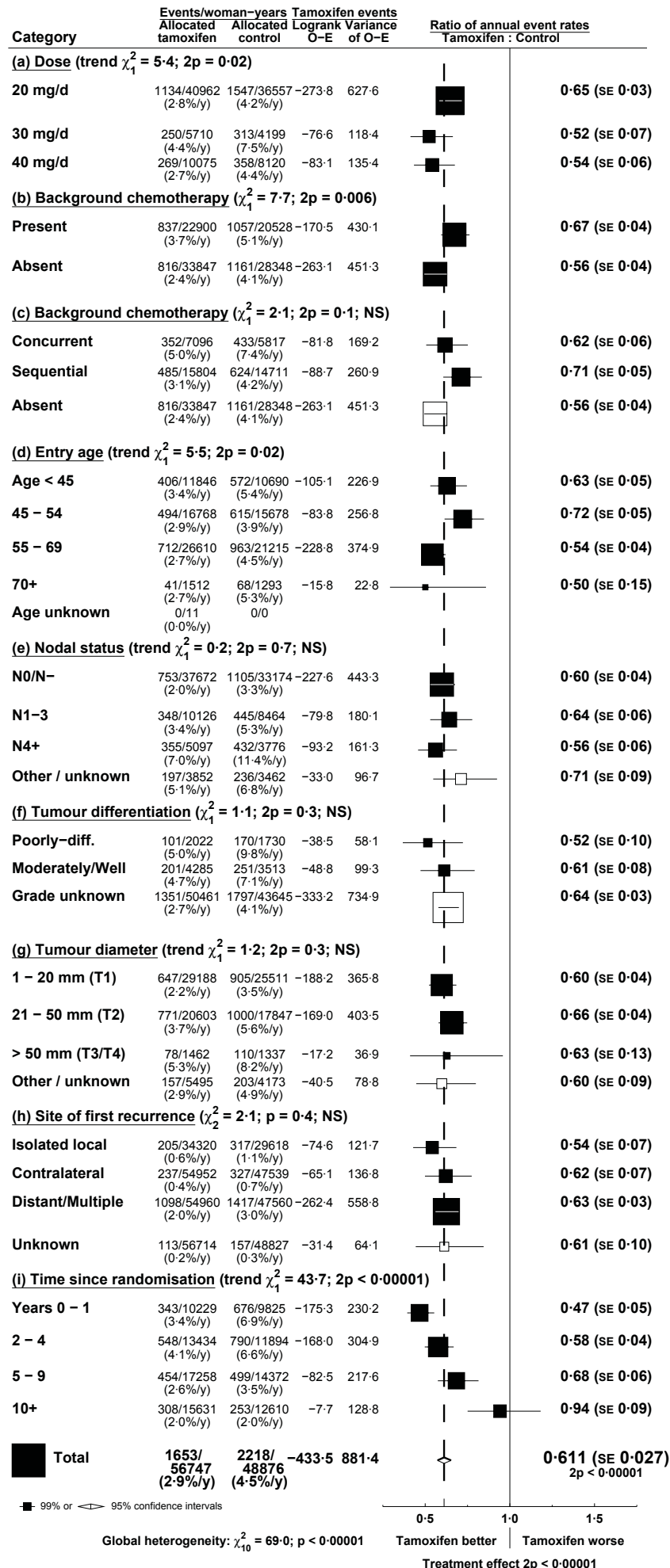
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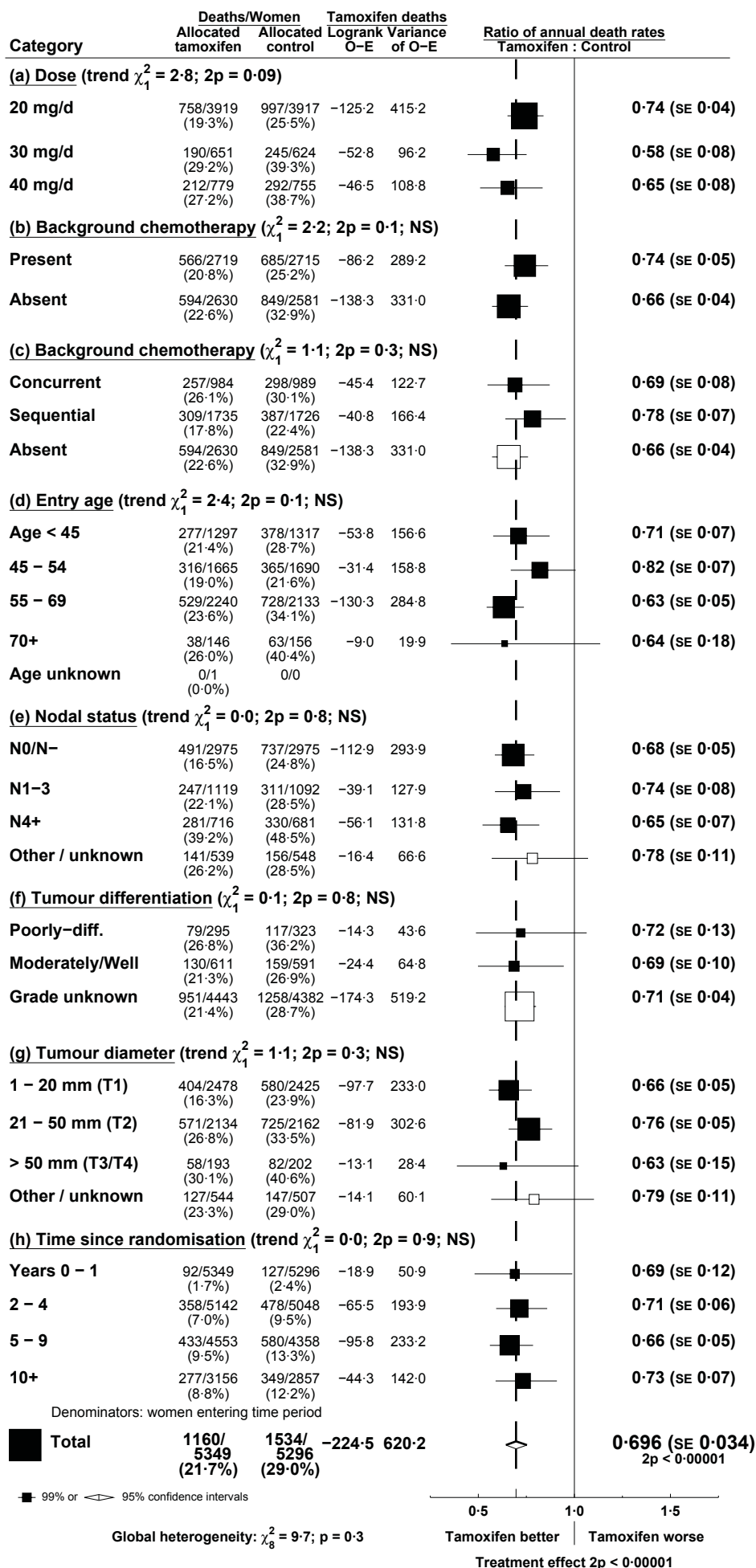
p 2: 10-year recurrence & breast cancer mortality, ER+ disease: 1, 2 or 5 years tam.



p 3: RRs for recurrence, multiple subgroup analyses, ER+ disease: ~5 years tam.

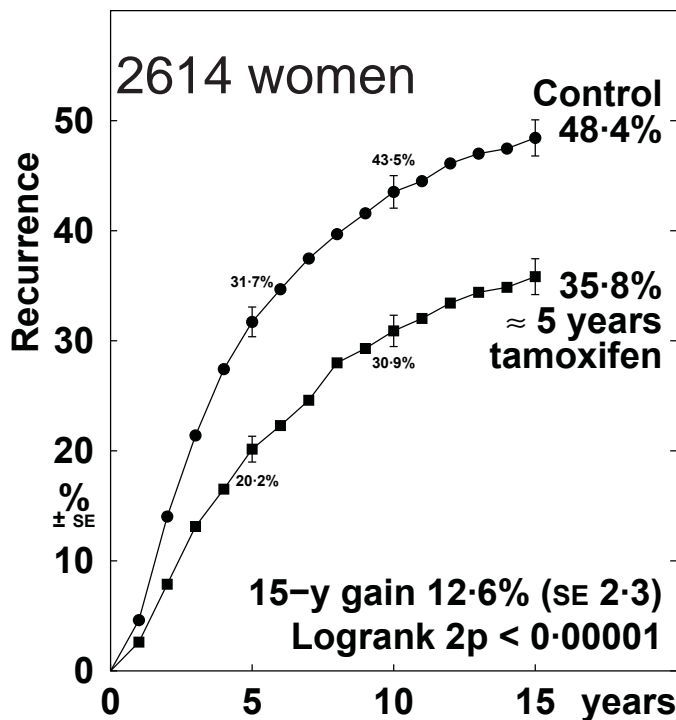


p 4: RRs for death with recurrence, multiple subgroup analyses, ER+ disease: ~5 years tam.

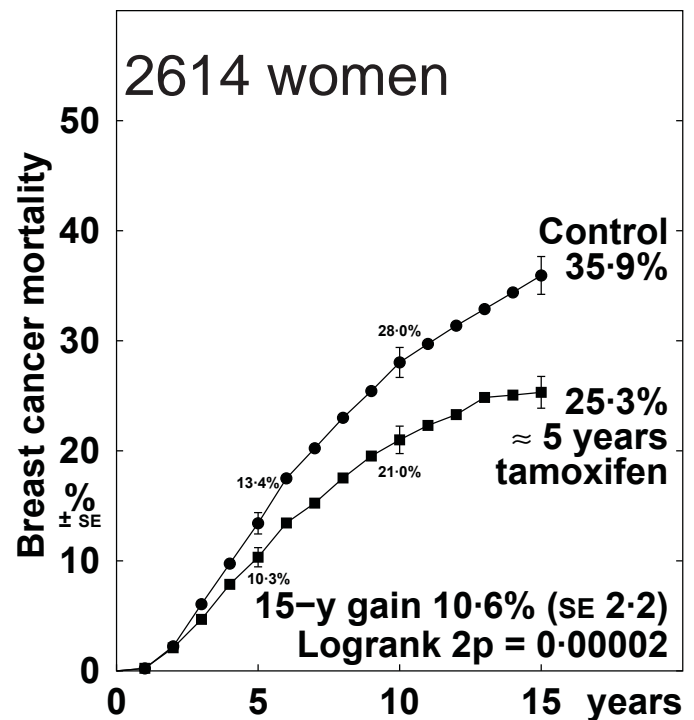


p 5: 15-year outcomes, age at entry <45 years, ER+ disease: ~5 years tam.

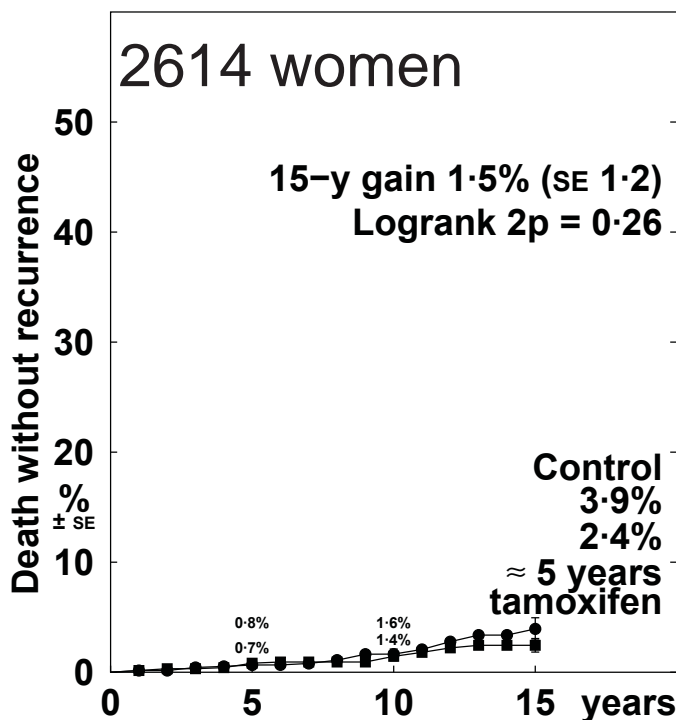
≈ 5 years tamoxifen vs. Not
RECURRENCE
Entry age < 45, ER+



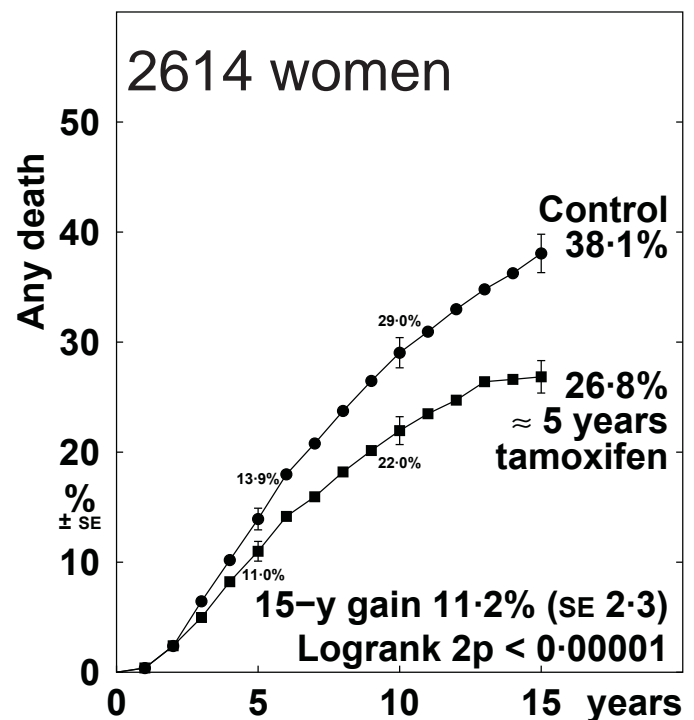
≈ 5 years tamoxifen vs. Not
BREAST CANCER MORTALITY
Entry age < 45, ER+



≈ 5 years tamoxifen vs. Not
DEATH WITHOUT RECURRENCE
Entry age < 45, ER+



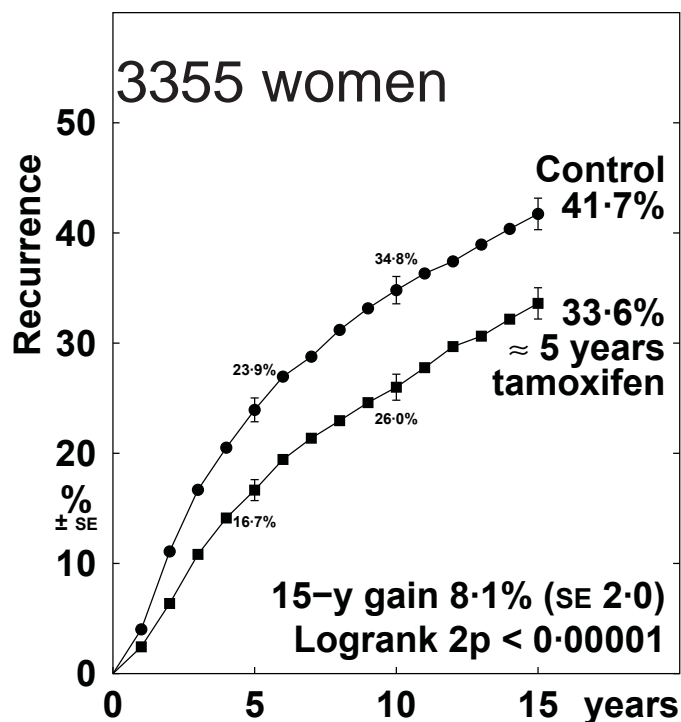
≈ 5 years tamoxifen vs. Not
ANY DEATH
Entry age < 45, ER+



≈ 5 years tamoxifen vs. Not

RECURRENCE

Entry age 45-54, ER+



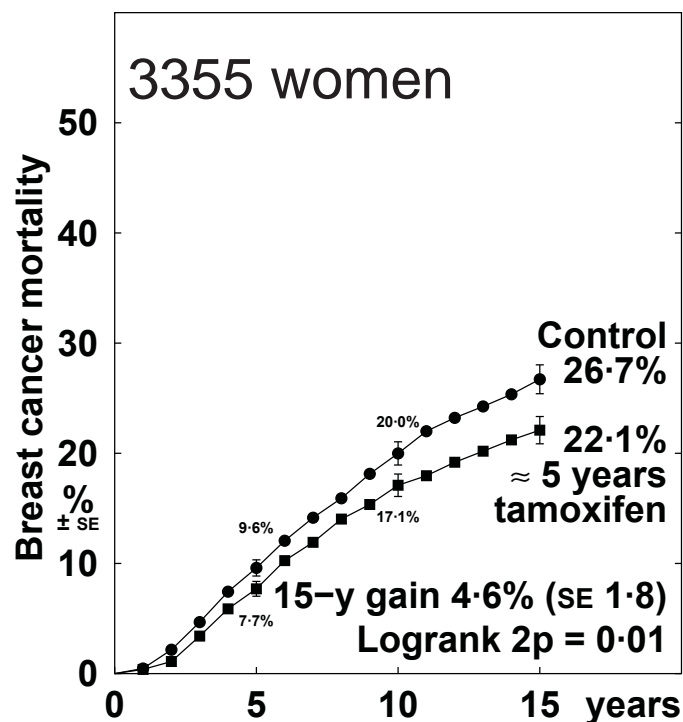
Recurrence rates (% / year) and logrank analyses

| Allocation | Years 0 - 4 | Years 5 - 9 | Years 10 - 14 | Year 15+ |
|----------------------------|-------------------------------|------------------------------|-----------------------------|-----------------------------|
| Tamoxifen | 3.69 (274 / 7420) | 2.60 (135 / 5200) | 2.18 (62 / 2849) | 1.74 (23 / 1322) |
| Control | 5.47 (392 / 7170) | 3.00 (143 / 4763) | 2.25 (58 / 2573) | 1.84 (22 / 1196) |
| Rate ratio, from (O-E) / V | 0.66 SE 0.07 -64.0 / 153.3 | 0.78 SE 0.11 -16.3 / 64.3 | 0.99 SE 0.18 -0.4 / 29.0 | 0.74 SE 0.27 -3.1 / 10.2 |

≈ 5 years tamoxifen vs. Not

BREAST CANCER MORTALITY

Entry age 45-54, ER+

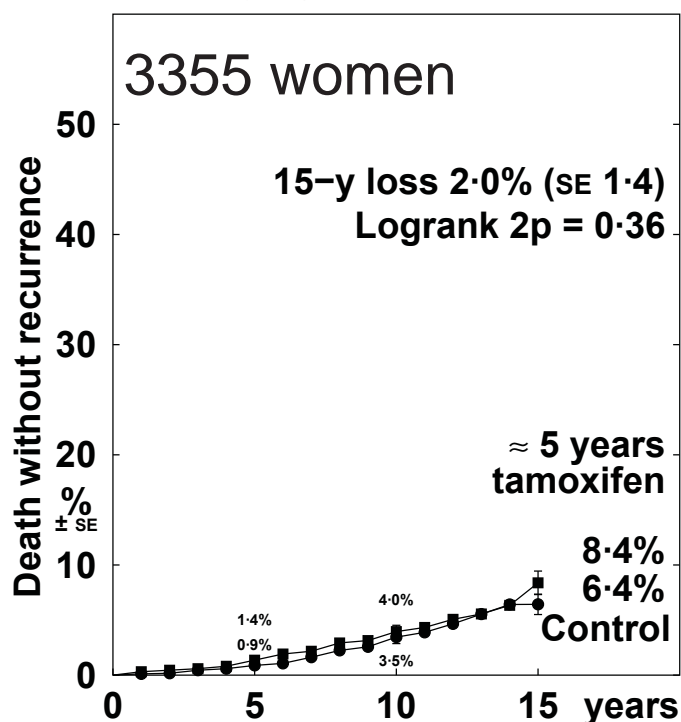


Death rates (% / year: total rate - rate in women without recurrence) & logrank analyses

| Allocation | Years 0 - 4 | Years 5 - 9 | Years 10 - 14 | Year 15+ |
|----------------------------|------------------------------|-----------------------------|-----------------------------|----------------------------|
| Tamoxifen | 1.59 SE 0.14 | 2.27 SE 0.20 | 1.26 SE 0.20 | 1.11 SE 0.26 |
| Control | 1.97 SE 0.16 | 2.37 SE 0.20 | 1.79 SE 0.24 | 1.02 SE 0.26 |
| Rate ratio, from (O-E) / V | 0.79 SE 0.11 -15.2 / 65.7 | 0.89 SE 0.12 -7.2 / 62.4 | 0.69 SE 0.17 -8.5 / 23.1 | 0.93 SE 0.35 -0.5 / 7.6 |

≈ 5 years tamoxifen vs. Not
DEATH WITHOUT RECURRENCE

Entry age 45-54, ER+



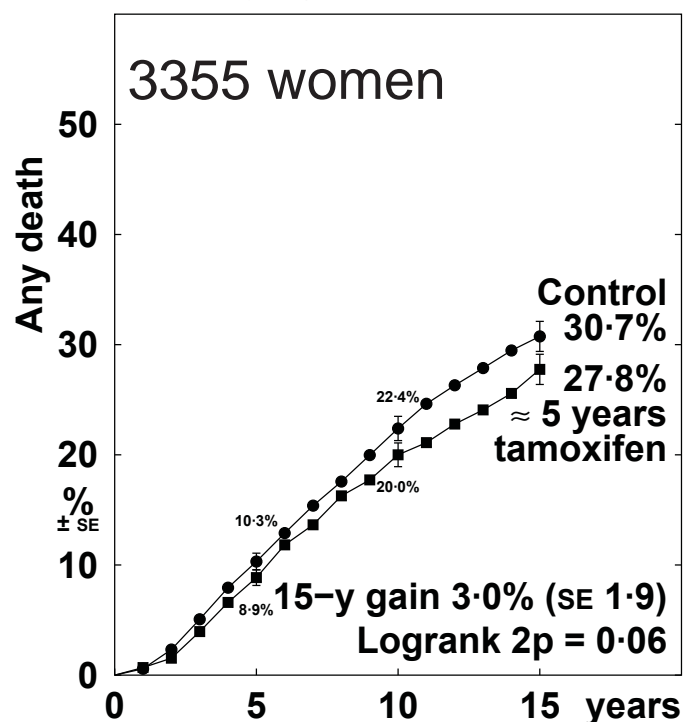
Death-without-recurrence rates (% / year) and logrank analyses

| Allocation | Years 0 - 4 | Years 5 - 9 | Years 10 - 14 | Year 15+ |
|----------------------------|---------------------------|----------------------------|---------------------------|----------------------------|
| Tamoxifen | 0.26 (19 / 7420) | 0.52 (27 / 5200) | 0.81 (23 / 2854) | 0.72 (10 / 1395) |
| Control | 0.18 (13 / 7170) | 0.50 (24 / 4763) | 0.66 (17 / 2574) | 0.89 (11 / 1235) |
| Rate ratio, from (O-E) / V | 1.54 SE 0.45 3.4 / 7.9 | 1.04 SE 0.29 0.5 / 12.6 | 1.26 SE 0.36 2.3 / 9.9 | 0.86 SE 0.42 -0.7 / 4.9 |

≈ 5 years tamoxifen vs. Not

ANY DEATH

Entry age 45-54, ER+



Death rates (% / year) and logrank analyses

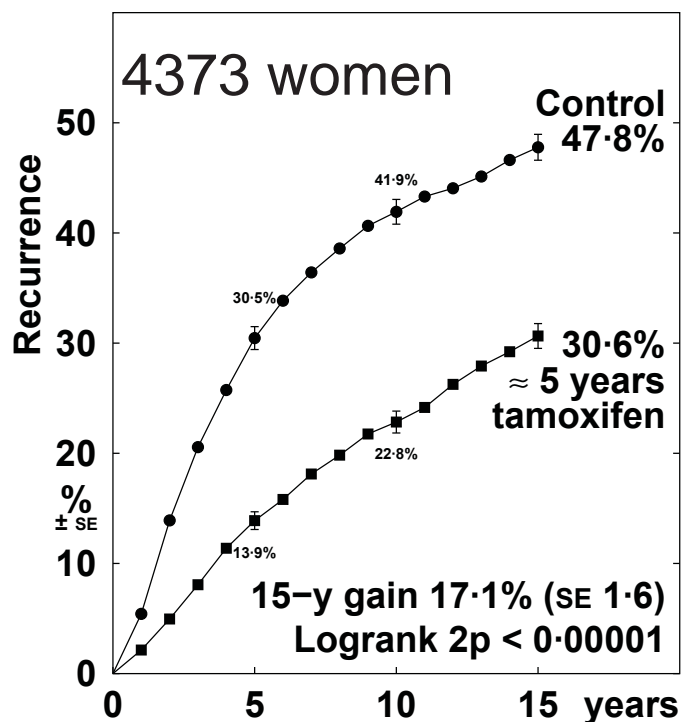
| Allocation | Years 0 - 4 | Years 5 - 9 | Years 10 - 14 | Year 15+ |
|----------------------------|------------------------------|-----------------------------|-----------------------------|-----------------------------|
| Tamoxifen | 1.83 (144 / 7862) | 2.73 (159 / 5823) | 1.97 (64 / 3256) | 1.73 (28 / 1623) |
| Control | 2.14 (169 / 7900) | 2.79 (160 / 5732) | 2.33 (74 / 3179) | 1.72 (27 / 1568) |
| Rate ratio, from (O-E) / V | 0.85 SE 0.11 -11.8 / 73.6 | 0.92 SE 0.11 -6.7 / 75.0 | 0.83 SE 0.16 -6.2 / 33.0 | 0.90 SE 0.27 -1.3 / 12.5 |

p 7: 15-year outcomes, age at entry 55-69 years, ER+ disease: ~5 years tam.

≈ 5 years tamoxifen vs. Not

RECURRENCE

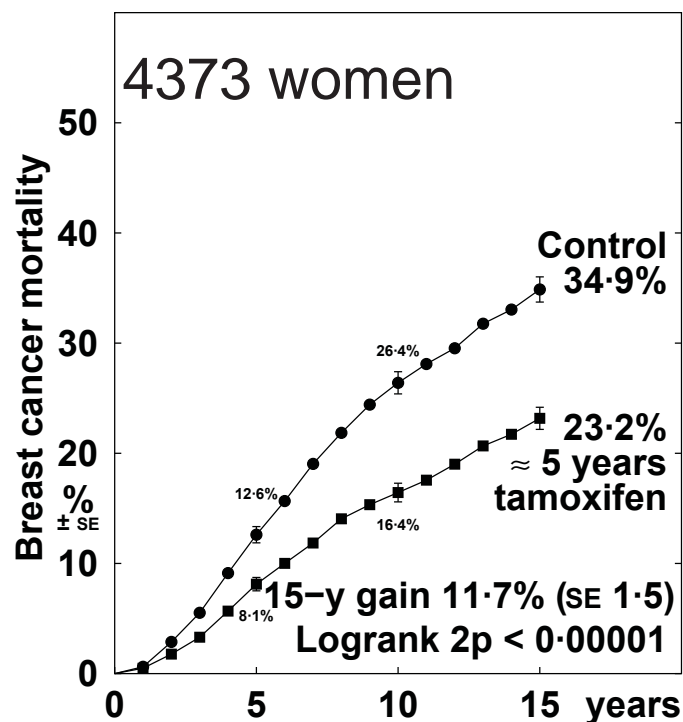
Entry age 55-69, ER+



≈ 5 years tamoxifen vs. Not

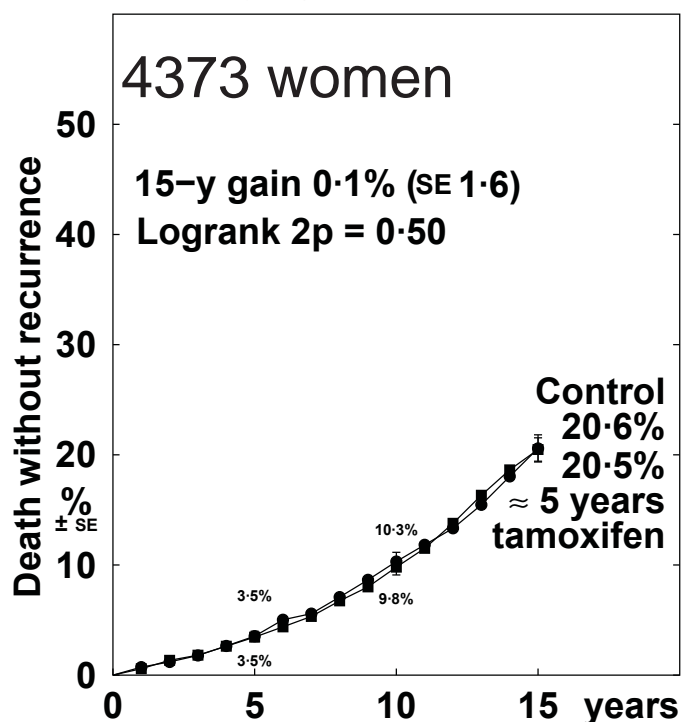
BREAST CANCER MORTALITY

Entry age 55-69, ER+



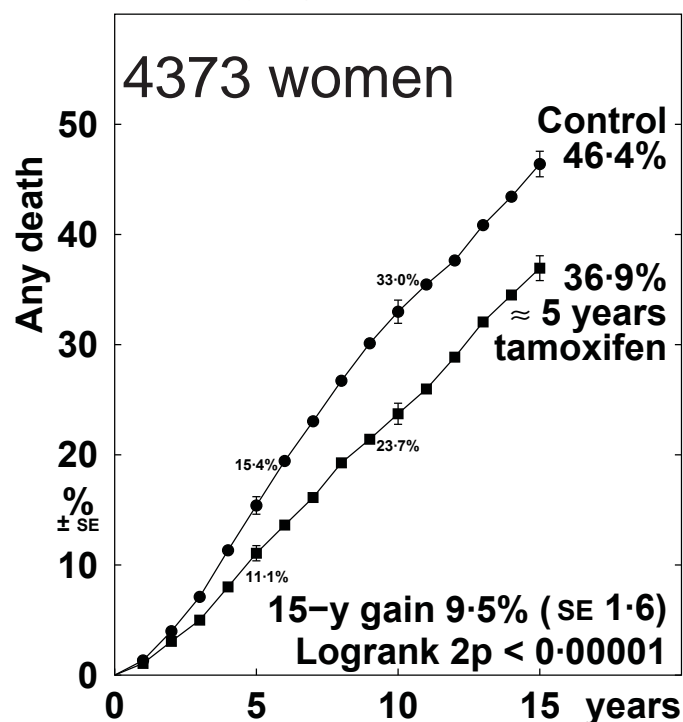
≈ 5 years tamoxifen vs. Not
DEATH WITHOUT RECURRENCE

Entry age 55-69, ER+



≈ 5 years tamoxifen vs. Not
ANY DEATH

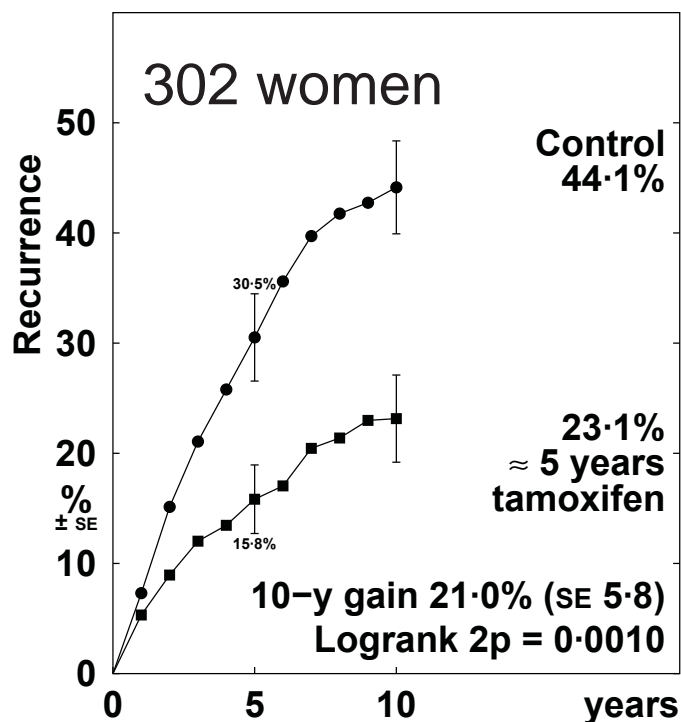
Entry age 55-69, ER+



≈ 5 years tamoxifen vs. Not

RECURRENCE

Entry age 70+, ER+



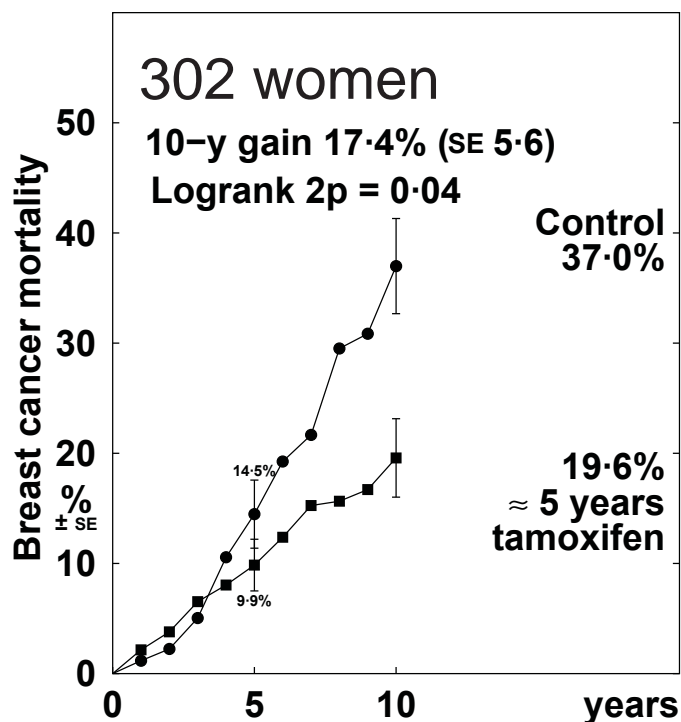
Recurrence rates (% / year) and logrank analyses

| Allocation | Years 0 - 4 | Years 5 - 9 | Year 10+ |
|----------------------------|------------------------------|----------------------------|----------------------------|
| Tamoxifen | 3.46 (22 / 635) | 2.52 (12 / 476) | 1.71 (7 / 409) |
| Control | 7.49 (46 / 614) | 4.08 (16 / 392) | 2.03 (6 / 296) |
| Rate ratio, from (O-E) / V | 0.49 SE 0.18 -10.7 / 14.9 | 0.45 SE 0.29 -4.4 / 5.5 | 0.74 SE 0.55 -0.7 / 2.4 |

≈ 5 years tamoxifen vs. Not

BREAST CANCER MORTALITY

Entry age 70+, ER+



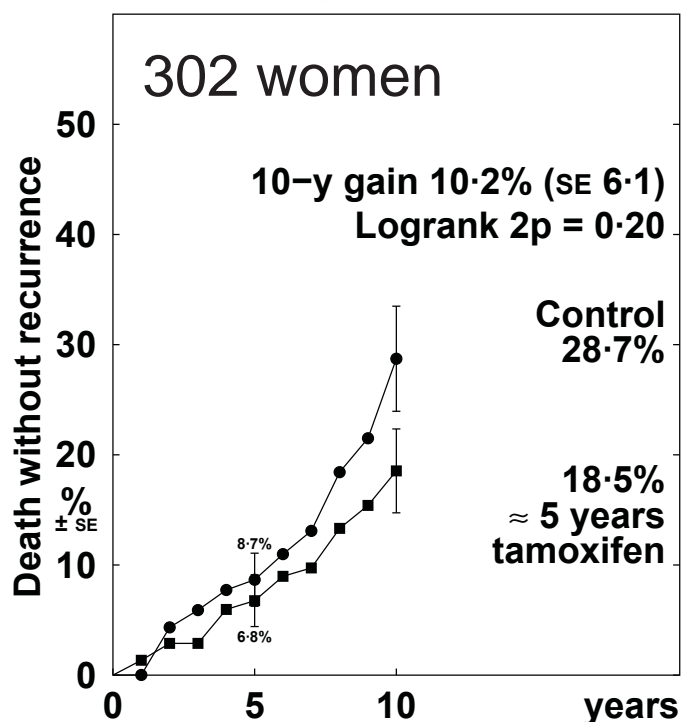
Death rates (% / year: total rate - rate in women without recurrence) & logrank analyses

| Allocation | Years 0 - 4 | Years 5 - 9 | Year 10+ |
|----------------------------|----------------------------|----------------------------|---------------------------|
| Tamoxifen | 1.79 SE 0.52 | 2.68 SE 0.72 | 2.68 SE 0.77 |
| Control | 3.27 SE 0.68 | 5.65 SE 1.07 | 3.17 SE 0.92 |
| Rate ratio, from (O-E) / V | 0.67 SE 0.31 -2.9 / 7.3 | 0.41 SE 0.23 -7.3 / 8.2 | 1.28 SE 0.54 1.1 / 4.5 |

≈ 5 years tamoxifen vs. Not

DEATH WITHOUT RECURRENCE

Entry age 70+, ER+



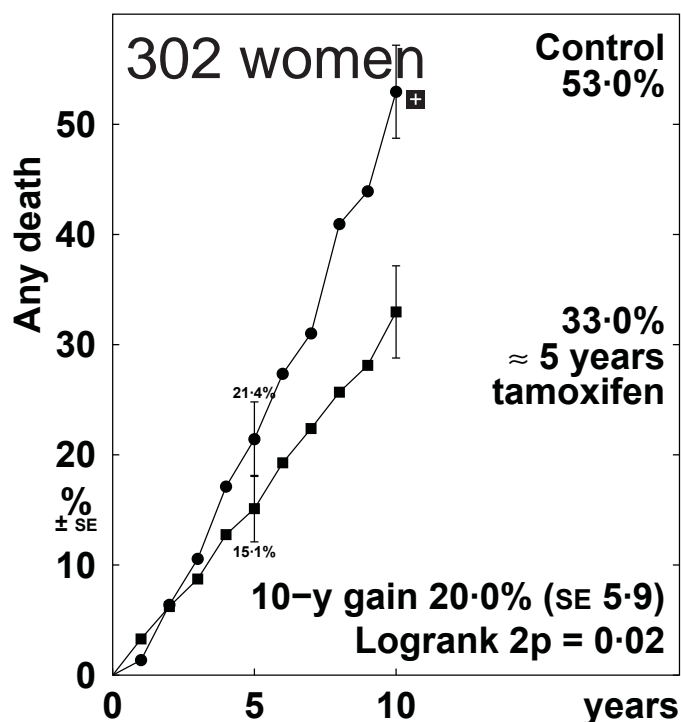
Death-without-recurrence rates (% / year) and logrank analyses

| Allocation | Years 0 - 4 | Years 5 - 9 | Year 10+ |
|----------------------------|----------------------------|----------------------------|-----------------------------|
| Tamoxifen | 1.57 (10 / 635) | 2.73 (13 / 476) | 9.25 (38 / 411) |
| Control | 1.63 (10 / 614) | 4.85 (19 / 392) | 8.79 (27 / 307) |
| Rate ratio, from (O-E) / V | 0.69 SE 0.41 -1.6 / 4.3 | 0.56 SE 0.29 -4.0 / 6.9 | 0.96 SE 0.29 -0.5 / 11.0 |

≈ 5 years tamoxifen vs. Not

ANY DEATH

Entry age 70+, ER+

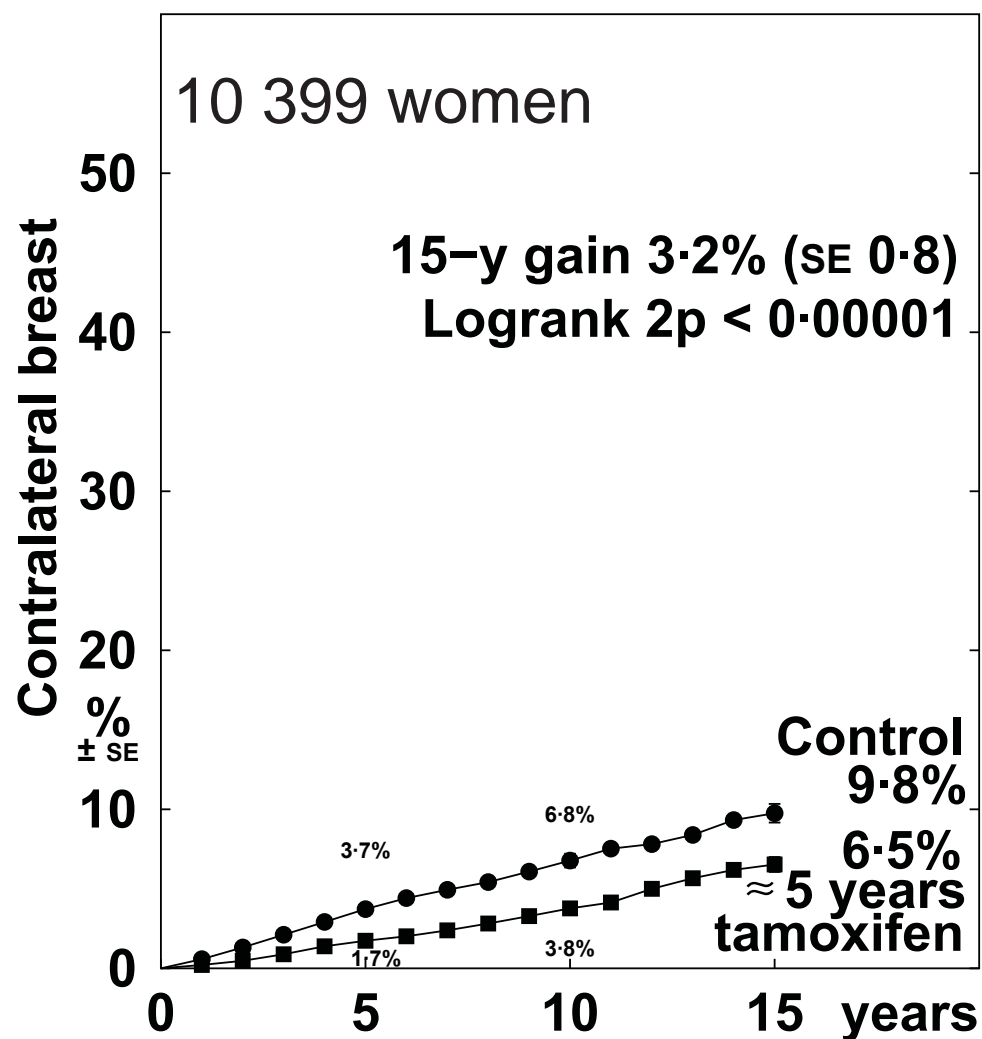


Death rates (% / year) and logrank analyses

| Allocation | Years 0 - 4 | Years 5 - 9 | Year 10+ |
|----------------------------|-----------------------------|------------------------------|----------------------------|
| Tamoxifen | 3.28 (22 / 670) | 5.17 (27 / 522) | 11.19 (50 / 447) |
| Control | 4.69 (33 / 704) | 9.48 (47 / 496) | 10.32 (39 / 378) |
| Rate ratio, from (O-E) / V | 0.68 SE 0.24 -4.5 / 11.5 | 0.47 SE 0.18 -11.3 / 15.0 | 1.04 SE 0.26 0.6 / 15.5 |

p 9: 15-year contralateral breast cancer incidence, all ages, by ER status: ~5 years tam.

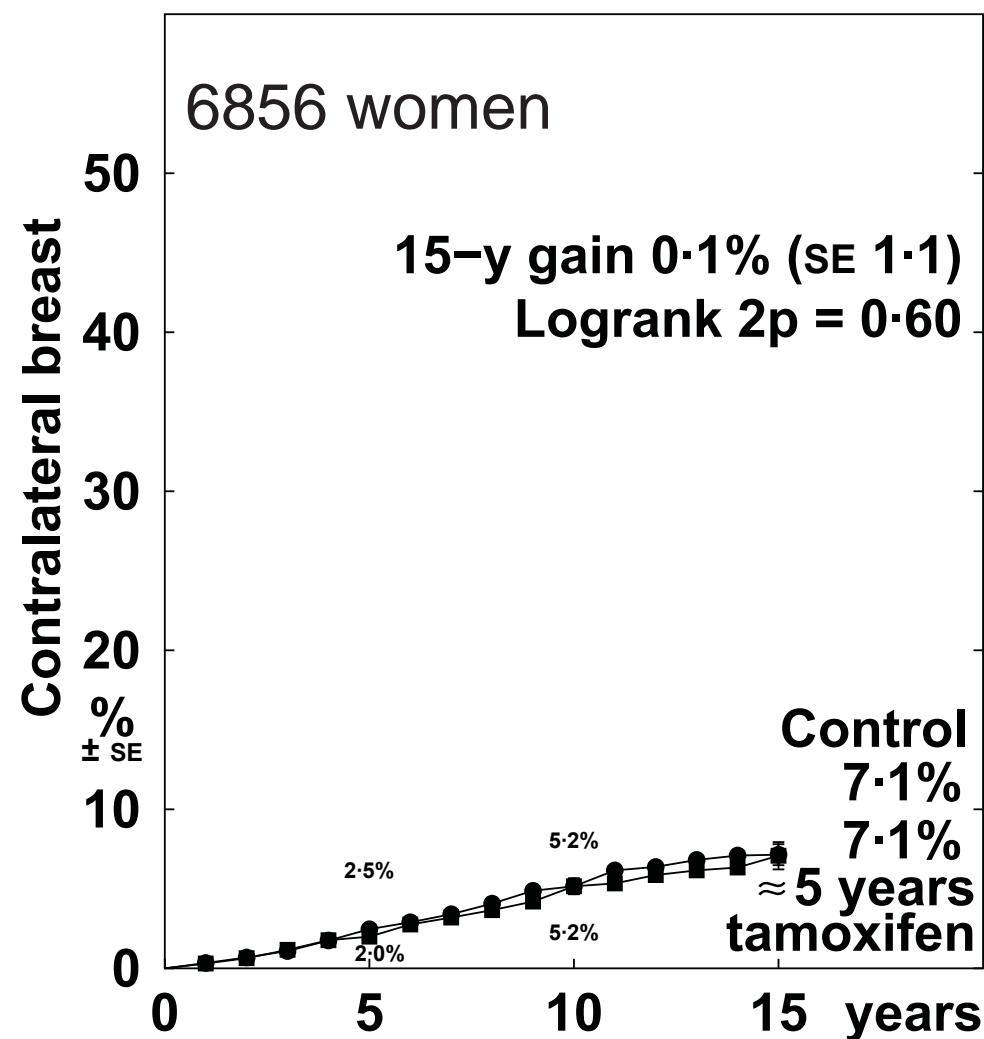
≈ 5 years tamoxifen vs. Not
CONTRALATERAL BREAST
ER+



Contralateral breast cancer rates (% / year) and logrank analyses

| Allocation | Years 0 – 4 | Years 5 – 9 | Years 10 – 14 | Year 15+ |
|----------------------------|------------------------------|------------------------------|-----------------------------|-----------------------------|
| Tamoxifen | 0.35 (80 / 23136) | 0.42 (70 / 16704) | 0.61 (62 / 10200) | 0.52 (25 / 4812) |
| Control | 0.77 (163 / 21301) | 0.65 (91 / 13959) | 0.64 (53 / 8321) | 0.51 (20 / 3938) |
| Rate ratio, from (O-E) / V | 0.47 SE 0.09 -44.9 / 59.9 | 0.64 SE 0.13 -17.1 / 38.8 | 0.91 SE 0.18 -2.5 / 27.5 | 0.95 SE 0.30 -0.5 / 10.6 |

≈ 5 years tamoxifen vs. Not
CONTRALATERAL BREAST
ER-poor

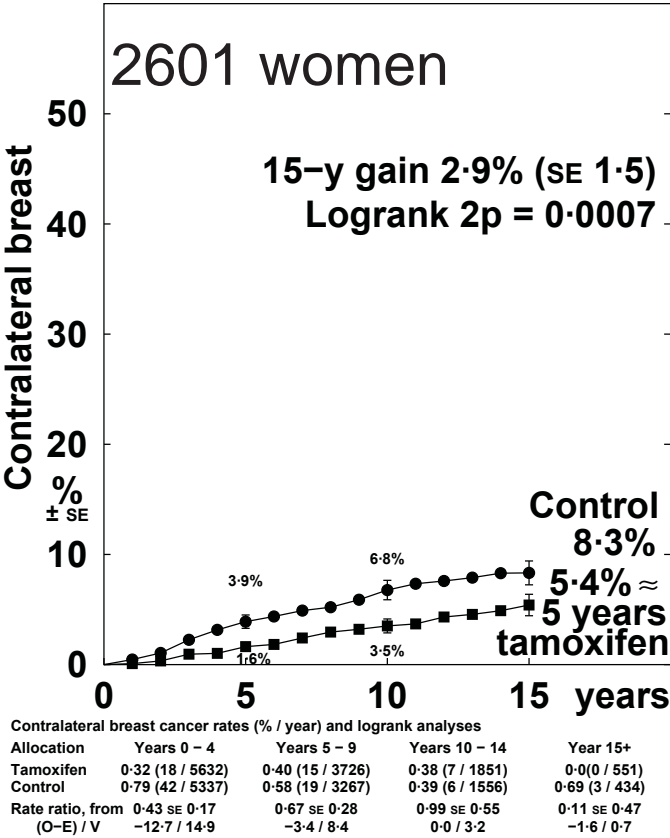


Contralateral breast cancer rates (% / year) and logrank analyses

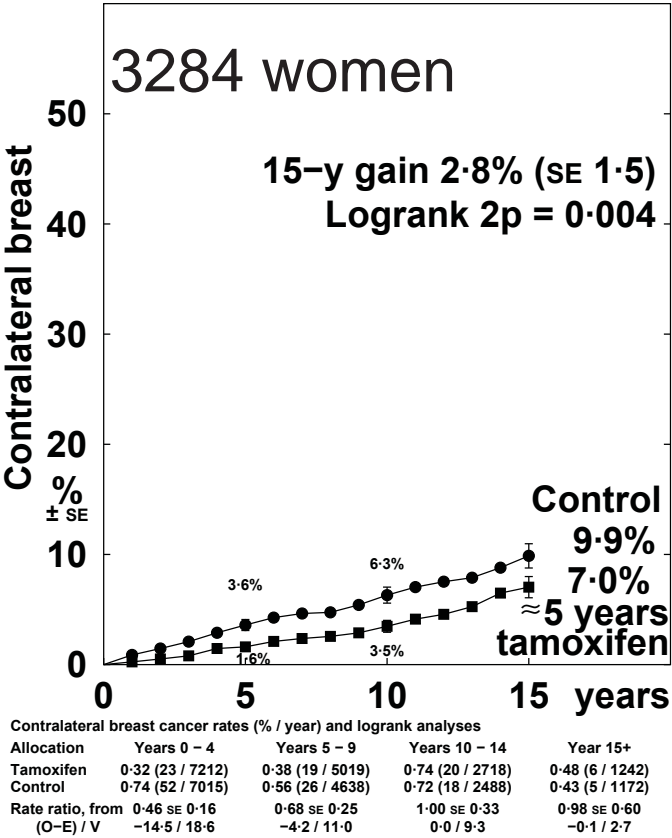
| Allocation | Years 0 – 4 | Years 5 – 9 | Years 10 – 14 | Year 15+ |
|----------------------------|-----------------------------|----------------------------|----------------------------|---------------------------|
| Tamoxifen | 0.41 (58 / 14091) | 0.64 (55 / 8601) | 0.37 (12 / 3209) | 0.58 (4 / 687) |
| Control | 0.47 (66 / 14044) | 0.56 (49 / 8702) | 0.53 (18 / 3369) | 0.26 (2 / 770) |
| Rate ratio, from (O-E) / V | 0.84 SE 0.17 -5.2 / 29.3 | 1.15 SE 0.21 3.5 / 25.1 | 0.64 SE 0.30 -3.2 / 7.2 | 1.94 SE 1.30 0.8 / 1.2 |

p 10: 15-year contralateral breast cancer incidence, ER+ disease, by age: ~5 years tam.

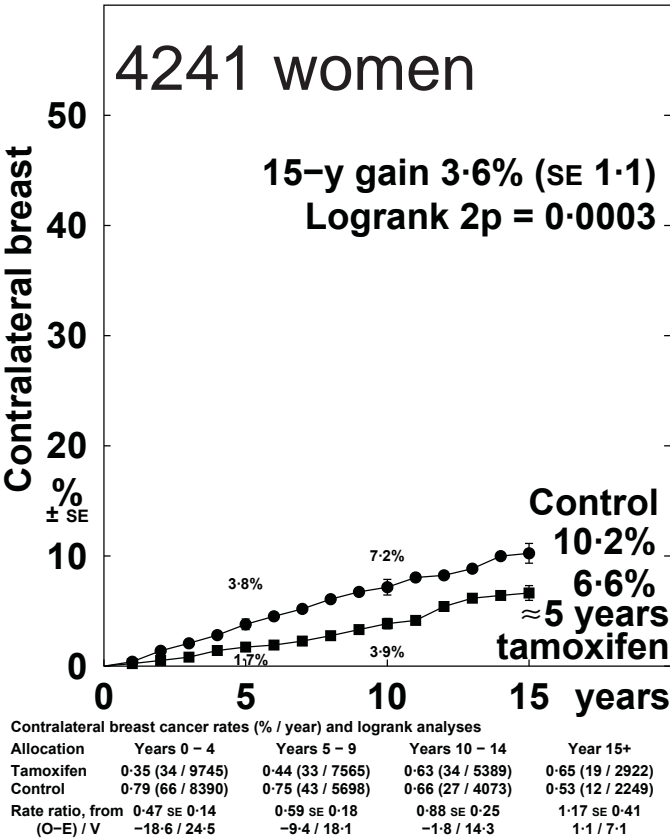
≈ 5 years tamoxifen vs. Not
CONTRALATERAL BREAST
Entry age < 45, ER+



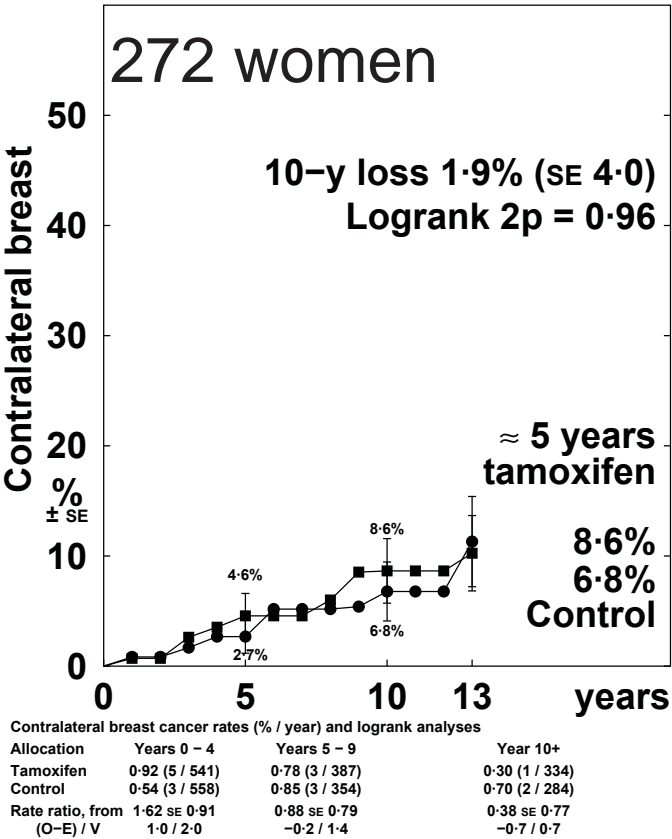
≈ 5 years tamoxifen vs. Not
CONTRALATERAL BREAST
Entry age 45-54, ER+



≈ 5 years tamoxifen vs. Not
CONTRALATERAL BREAST
Entry age 55-69, ER+

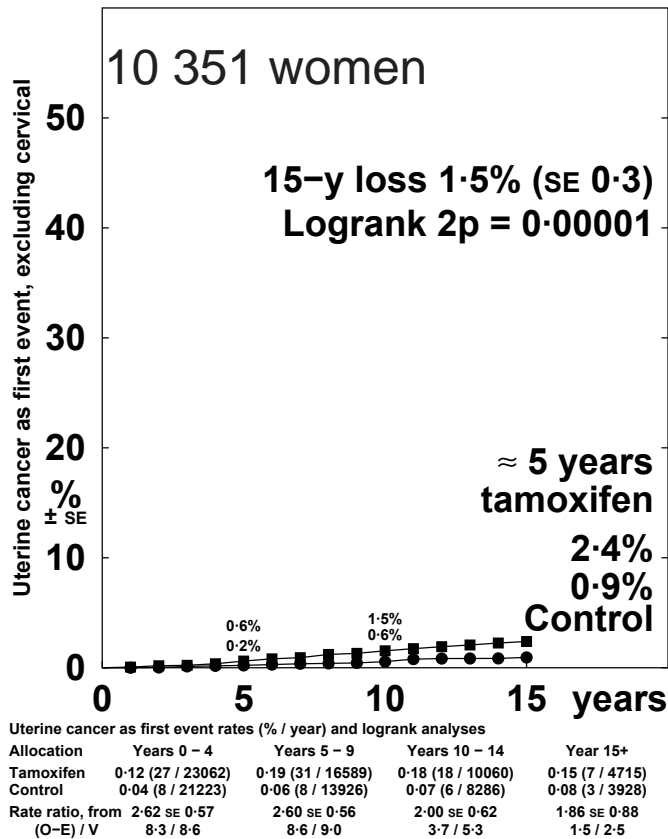


≈ 5 years tamoxifen vs. Not
CONTRALATERAL BREAST
Entry age 70+, ER+

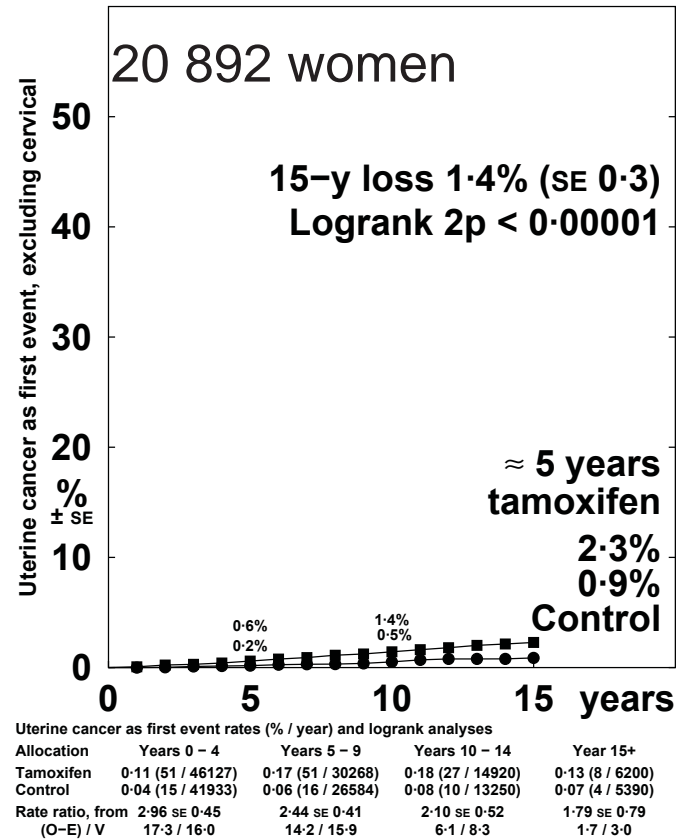


p 11: 15-year uterus (excl. cervix) ca. incidence & mortality, ER+ and all ER: ~5 years tam.

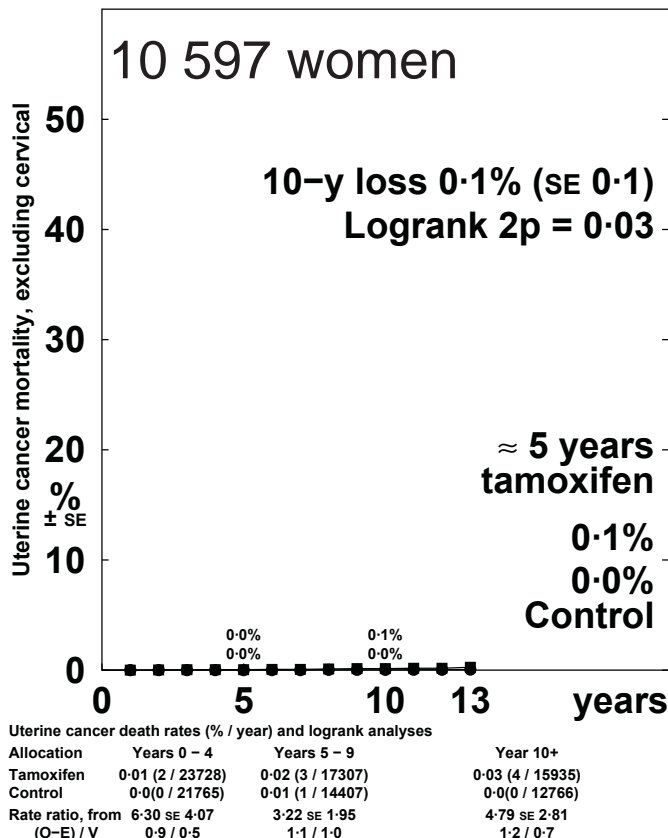
≈ 5 years tamoxifen vs. Not
UTERUS (not cervix) cancer INCIDENCE
ER+



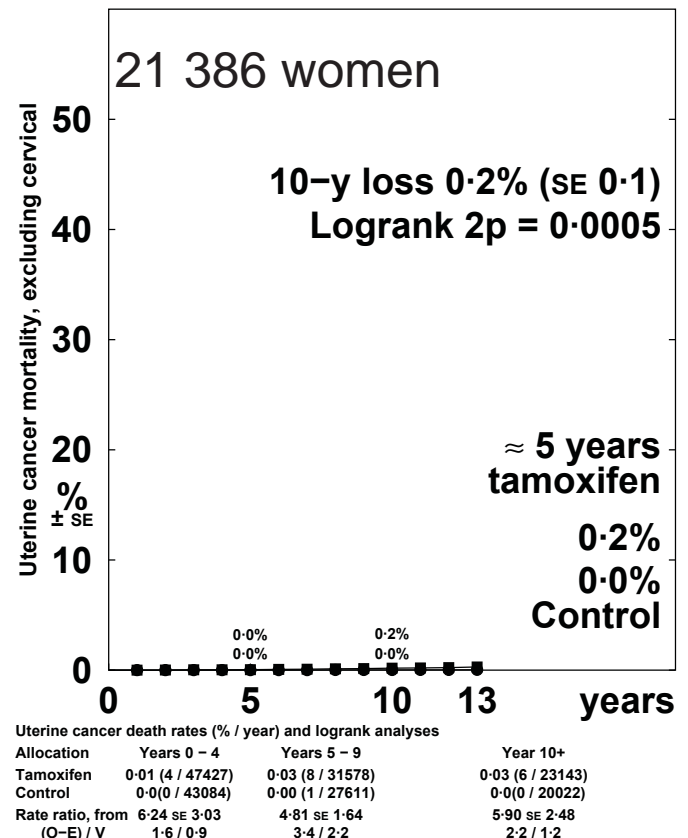
≈ 5 years tamoxifen vs. Not
UTERUS (not cervix) cancer INCIDENCE



≈ 5 years tamoxifen vs. Not
UTERUS (not cervix) cancer MORTALITY
ER+



≈ 5 years tamoxifen vs. Not
UTERUS (not cervix) cancer MORTALITY

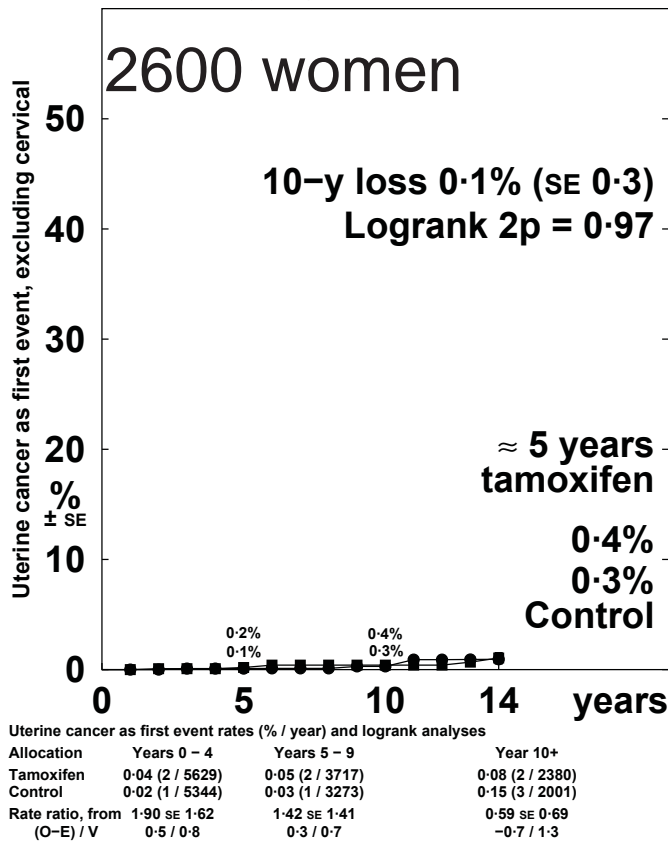


p 12: 15-year uterus (excl. cervix) ca. incidence, ER+ disease, by age: ~5 years tam.

≈ 5 years tamoxifen vs. Not

UTERUS (not cervix) cancer INCIDENCE

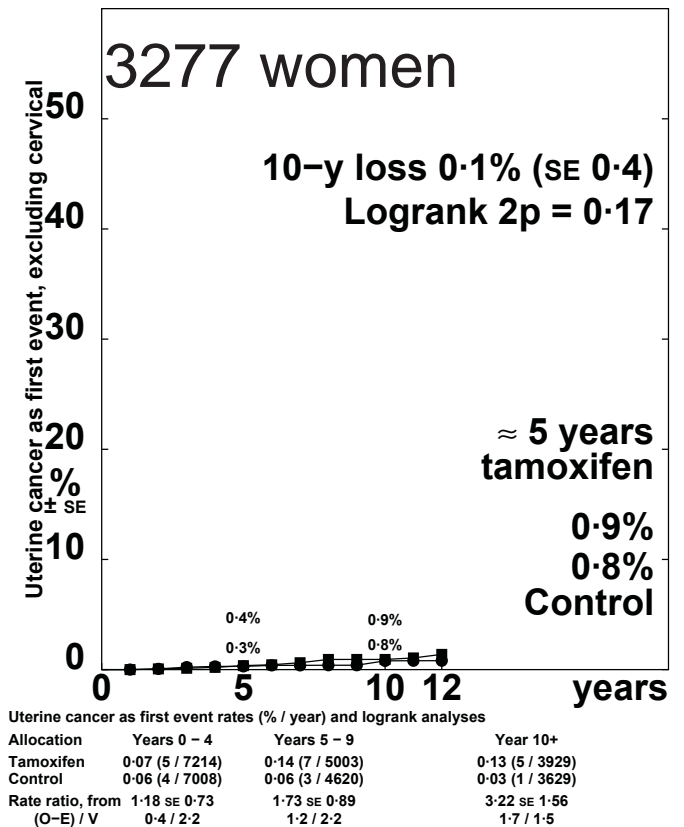
Entry age < 45, ER+



≈ 5 years tamoxifen vs. Not

UTERUS (not cervix) cancer INCIDENCE

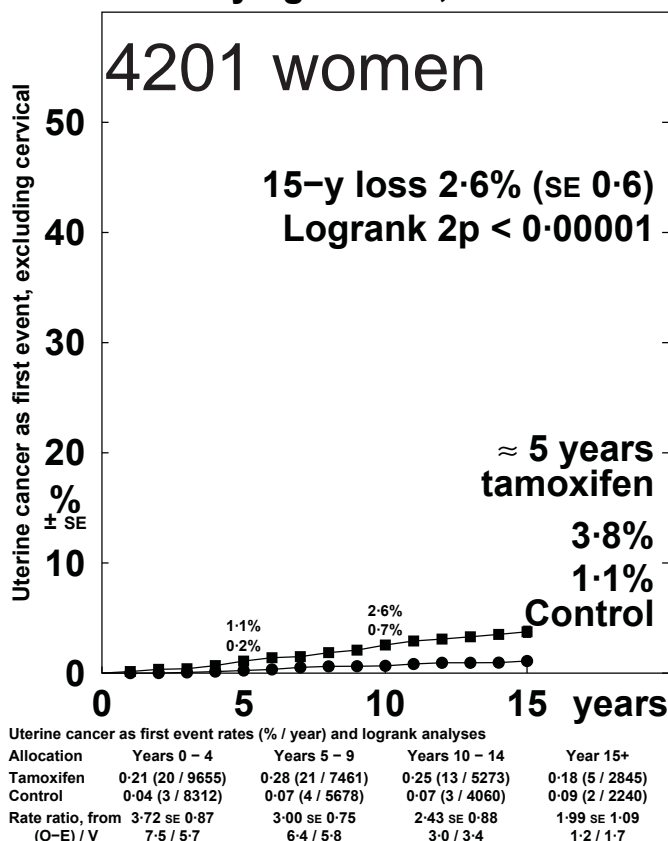
Entry age 45-54, ER+



≈ 5 years tamoxifen vs. Not

UTERUS (not cervix) cancer INCIDENCE

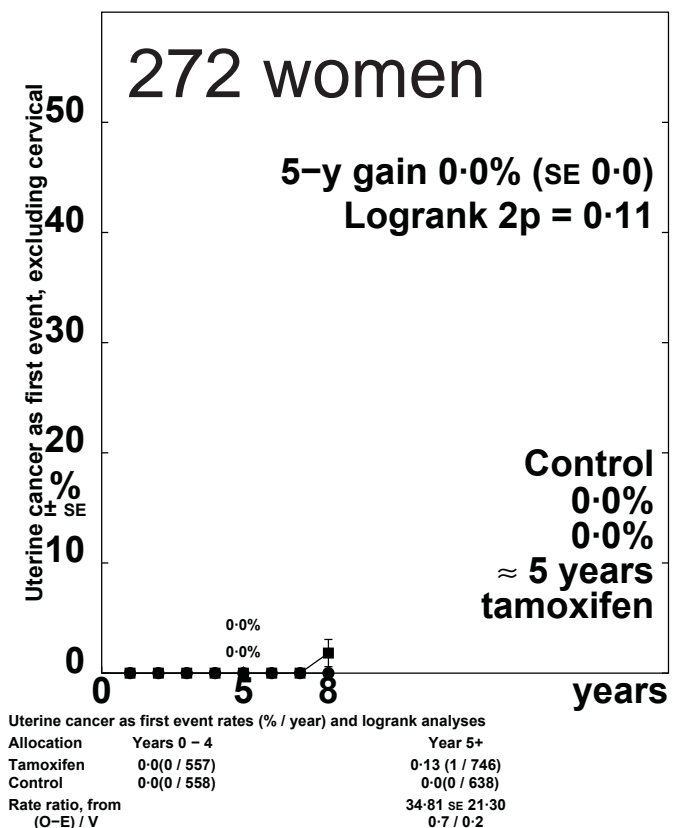
Entry age 55-69, ER+



≈ 5 years tamoxifen vs. Not

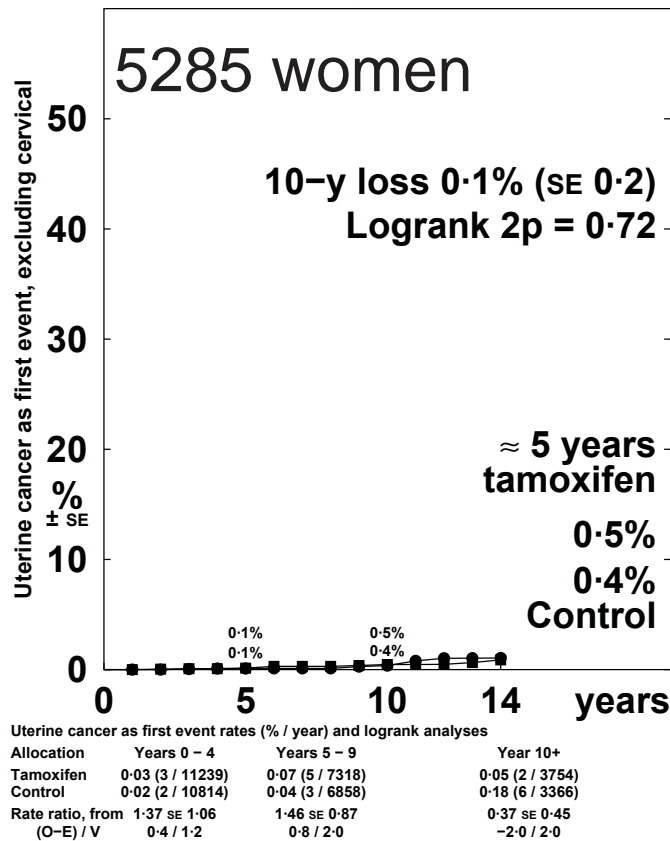
UTERUS (not cervix) cancer INCIDENCE

Entry age 70+, ER+

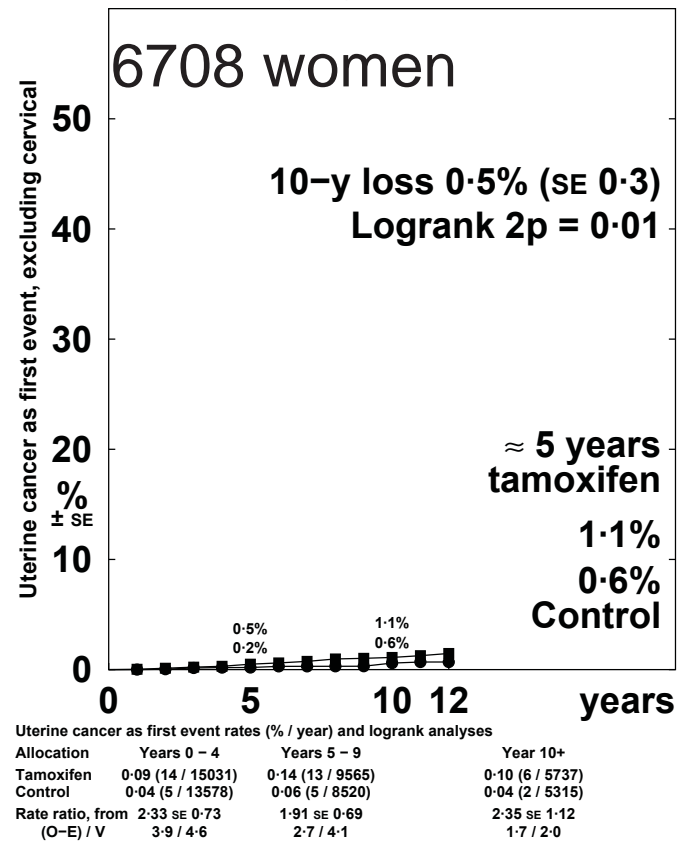


p 13: 15-year uterus (excl. cervix) ca. incidence, all ER, by age: ~5 years tam.

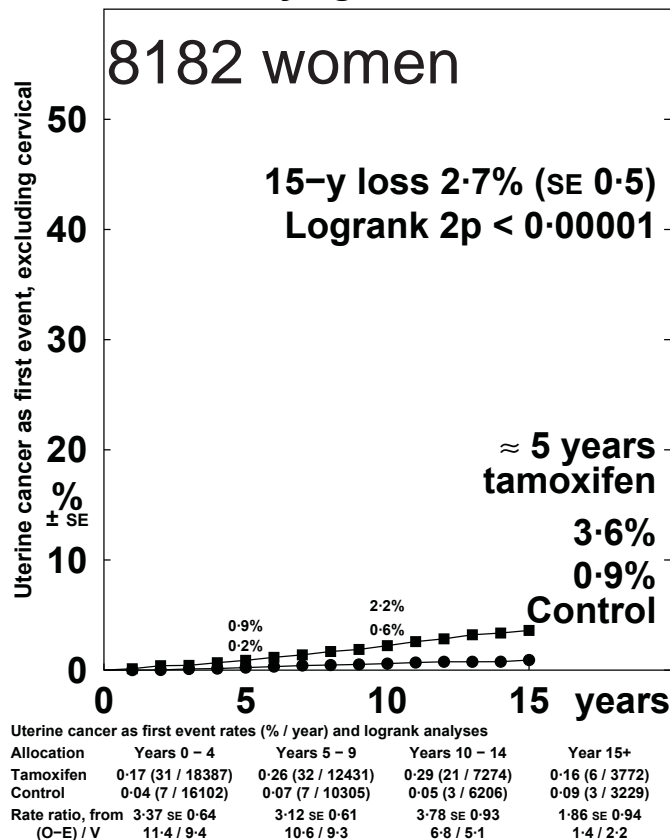
≈ 5 years tamoxifen vs. Not
UTERUS (not cervix) cancer INCIDENCE
Entry age < 45



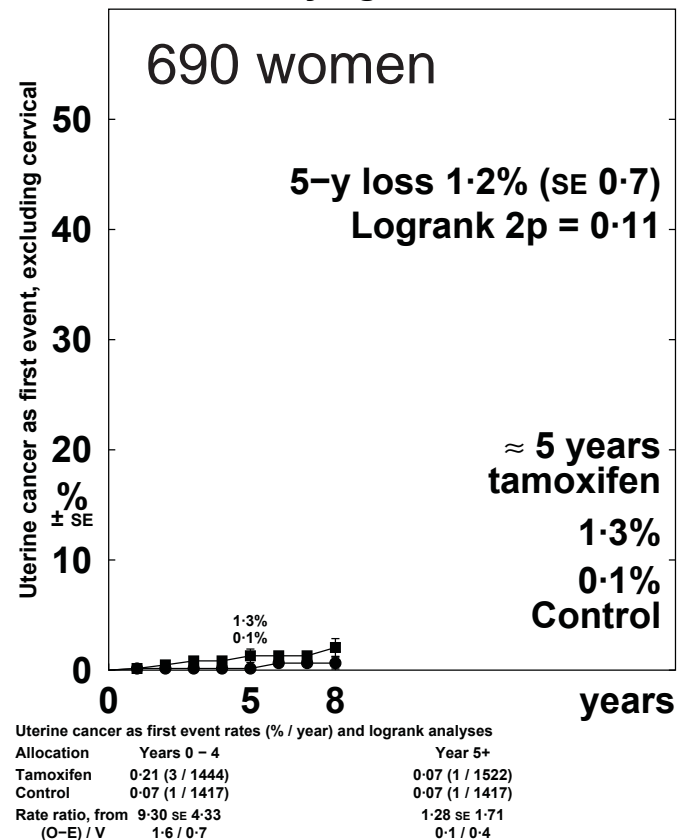
≈ 5 years tamoxifen vs. Not
UTERUS (not cervix) cancer INCIDENCE
Entry age 45-54



≈ 5 years tamoxifen vs. Not
UTERUS (not cervix) cancer INCIDENCE
Entry age 55-69

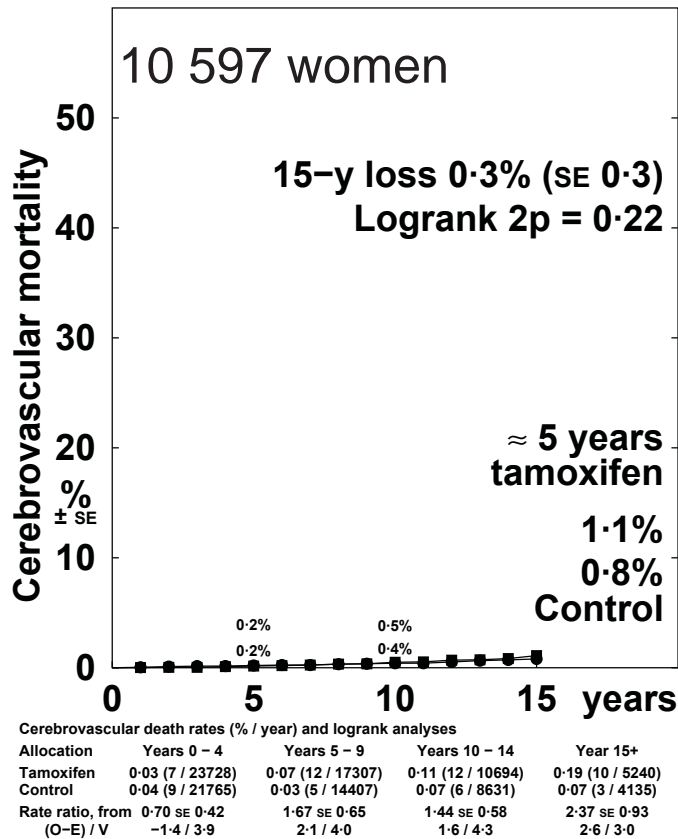


≈ 5 years tamoxifen vs. Not
UTERUS (not cervix) cancer INCIDENCE
Entry age 70+

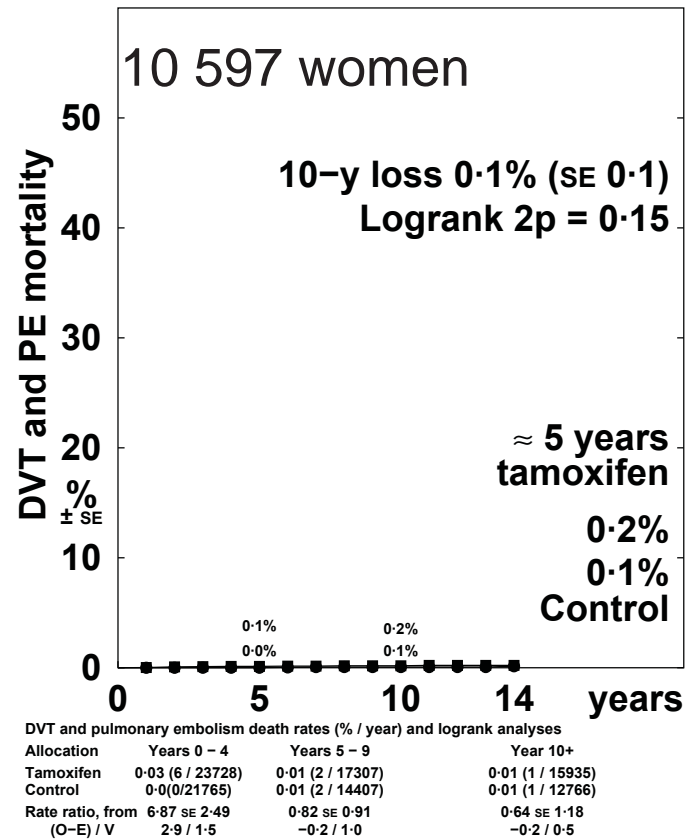


p 14: 15-year stroke, PE & other/all vascular mortality, ER+ disease: ~5 years tam.

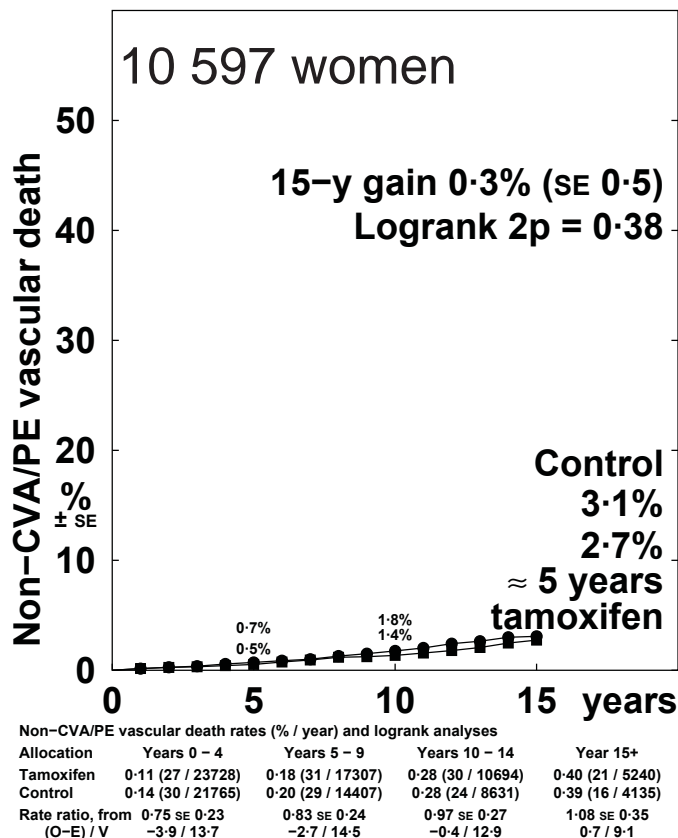
≈ 5 years tamoxifen vs. Not
CEREBROVASCULAR MORTALITY
ER+



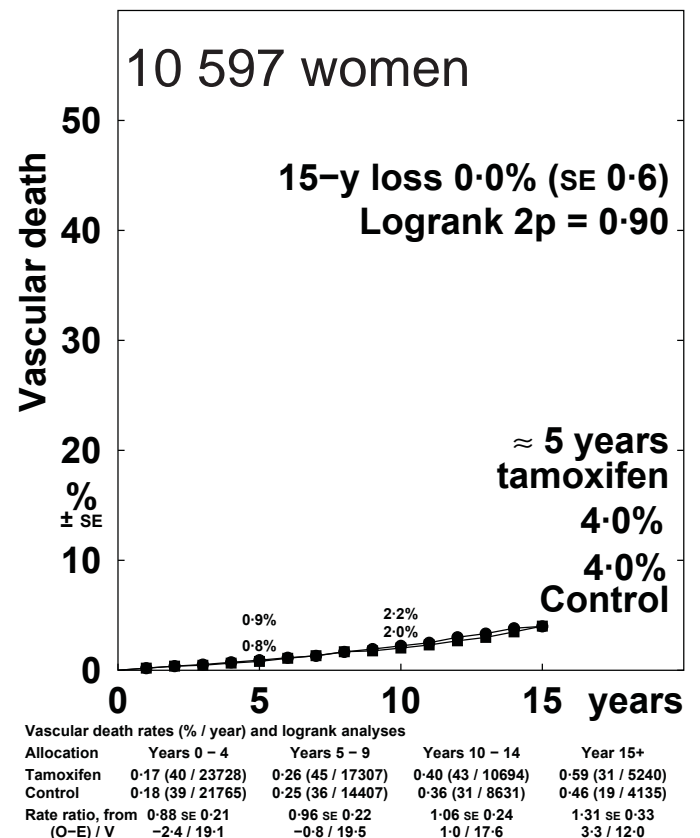
≈ 5 years tamoxifen vs. Not
DVT AND PE MORTALITY
ER+



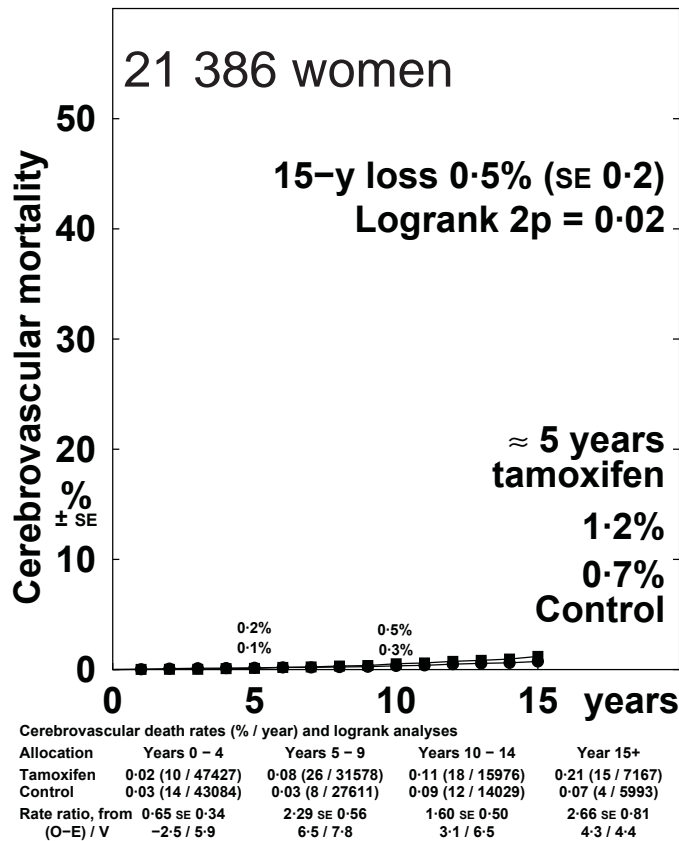
≈ 5 years tamoxifen vs. Not
VASCULAR (excl. stroke & PE) DEATH
ER+



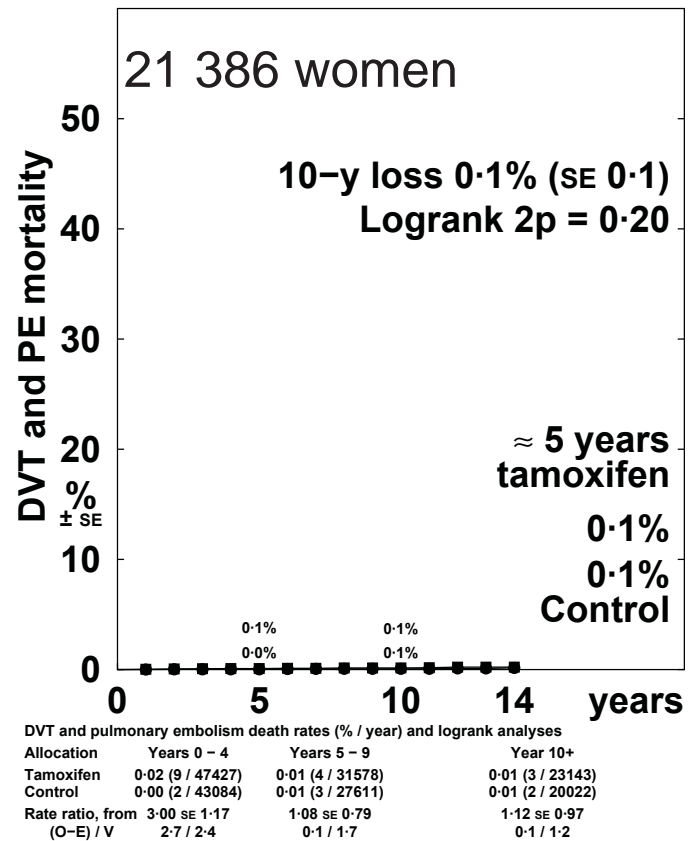
≈ 5 years tamoxifen vs. Not
VASCULAR DEATH
ER+



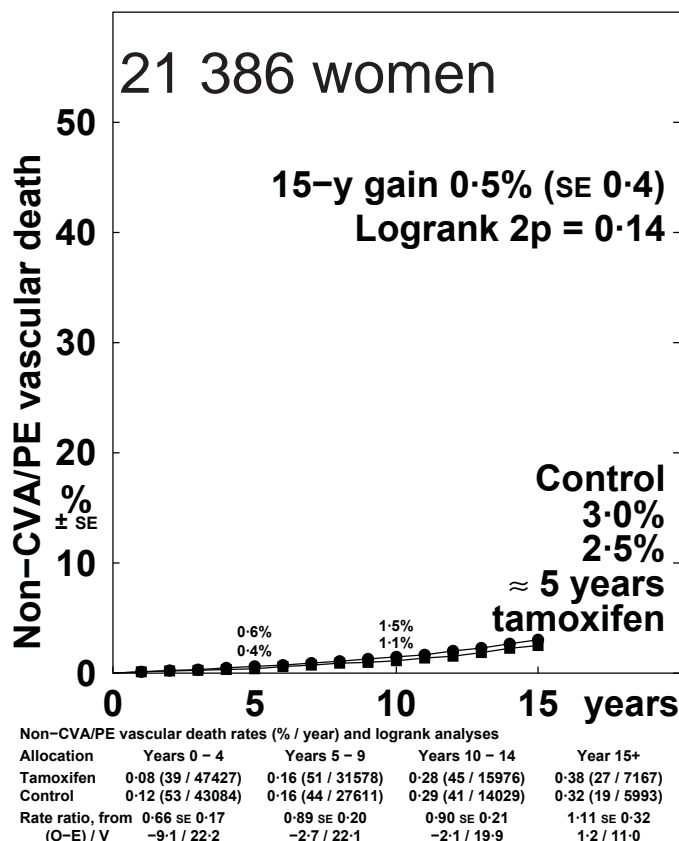
≈ 5 years tamoxifen vs. Not CEREBROVASCULAR MORTALITY



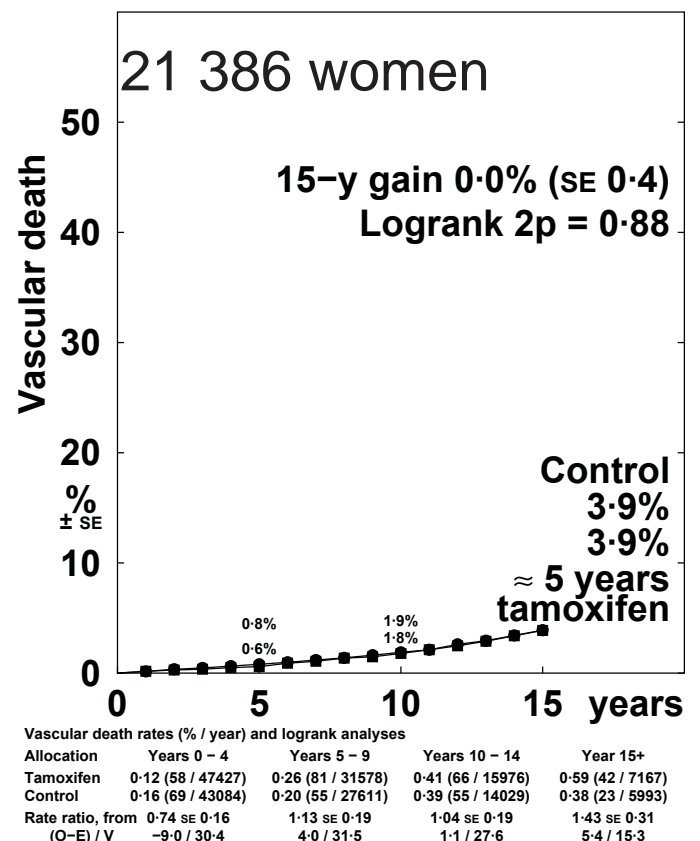
≈ 5 years tamoxifen vs. Not DVT AND PE MORTALITY



≈ 5 years tamoxifen vs. Not VASCULAR (excl. stroke & PE) DEATH



≈ 5 years tamoxifen vs. Not VASCULAR DEATH



p 16: Table 1: Mortality by cause and incidence of second cancers, ER+ disease. Outcome by allocated treatment in trials of about 5 years of adjuvant tamoxifen. (Webappendix p 17 gives results for all women, irrespective of ER status.)

| | Events | (O-E) | Variance | Rate Ratio & SE | | 2p* |
|---|--------|--------|----------|--------------------|------|-----------|
| Death without recurrence | 1117 | 4.9 | 258.6 | 1.02 | 0.06 | 0.79 |
| Death with recurrence | 2694 | -224.5 | 620.2 | 0.70 | 0.03 | < 0.00001 |
| Any death | 3811 | -219.6 | 878.8 | 0.78 | 0.03 | < 0.00001 |
| Death without recurrence (selected groups of causes) | | | | | | |
| Vascular disease: | | | | | | |
| Stroke | 64 | 4.8 | 15.2 | 1.37 | 0.30 | 0.27 |
| Pulmonary embolus† | 12 | 2.5 | 3.0 | 2.30 | 0.90 | 0.25 |
| Heart & other vascular | 212 | -6.1 | 50.1 | 0.89 | 0.13 | 0.43 |
| Neoplastic disease: | | | | | | |
| Uterus excluding cervix‡ | 10 | 3.2 | 2.2 | 4.28 | 1.52 | 0.07 |
| Other non-breast | 187 | -0.1 | 44.2 | 1.00 | 0.15 | 1.00 |
| Other specified cause | 312 | 4.6 | 71.0 | 1.07 | 0.12 | 0.63 |
| Unknown cause (but definitely not-breast cancer**) | 320 | -4.0 | 72.9 | 0.95 | 0.11 | 0.68 |
| Second cancer incidence without previous recurrence (selected sites) | | | | | | |
| Contralateral breast, | | | | | | |
| by age at entry (years) | | | | | | |
| < 45 | 110 | -17.7 | 27.2 | 0.52 | 0.14 | 0.001 |
| 45 - 54 | 169 | -18.8 | 41.5 | 0.64 | 0.12 | 0.004 |
| 55 - 69 | 268 | -28.7 | 64.0 | 0.64 | 0.10 | 0.00001 |
| ≥70 | 17 | 0.1 | 4.1 | - | - | - |
| All ages | 564 | -65.1 | 136.7 | 0.62 | 0.07 | < 0.00001 |
| Uterus excluding cervix,‡ | | | | | | |
| by age at entry (years) | | | | | | |
| < 45 | 11 | 0.1 | 2.7 | 1.04 | 0.62 | 1.00 |
| 45 - 54 | 25 | 3.3 | 5.9 | 1.75 | 0.55 | 0.25 |
| 55 - 69 | 71 | 18.0 | 16.6 | 2.96 | 0.44 | 0.00002 |
| ≥70 | 1 | 0.8 | 0.2 | - | - | - |
| All ages | 108 | 22.2 | 25.4 | 2.40 | 0.32 | 0.00002 |
| Other or unknown site | 606 | 2.6 | 143.6 | 1.02 | 0.08 | 0.86 |

* 2p, with continuity correction

† 6 vs 0 deaths from pulmonary embolus during years 0-4 (all with entry age 55-69 years) and 3 vs 3 later (all with entry age 55+ years).

‡ 9 vs 1 deaths (age at entry: 45-54 years, 1 vs 0; 55-69 years, 7 vs 1; 70+ years, 1 vs 0) and 83 vs 25 incident cases of uterine cancer, excluding cervix

** Deaths from an unknown cause that might possibly have been breast cancer were taken to have been immediately preceded by recurrence.

p 17: Table 2: Mortality by cause and incidence of second cancers, all ER. Outcome by allocated treatment in trials of about 5 years of adjuvant tamoxifen.

| | Events | (O-E) | Variance | Rate Ratio & SE | | 2p* |
|---|--------|--------|----------|--------------------|------|-----------|
| Death without recurrence | 1805 | 25.0 | 410.0 | 1.06 | 0.05 | 0.23 |
| Death with recurrence | 4789 | -265.6 | 1074.5 | 0.78 | 0.03 | < 0.00001 |
| Any death | 6594 | -240.5 | 1484.5 | 0.85 | 0.02 | < 0.00001 |
| Death without recurrence (selected groups of causes) | | | | | | |
| Vascular disease: | | | | | | |
| Stroke | 107 | 11.3 | 24.5 | 1.59 | 0.26 | 0.03 |
| Pulmonary embolus† | 23 | 3.0 | 5.4 | 1.74 | 0.58 | 0.28 |
| Heart & other vascular | 319 | -12.8 | 74.8 | 0.84 | 0.11 | 0.16 |
| Neoplastic disease: | | | | | | |
| Uterus excluding cervix‡ | 19 | 7.3 | 4.3 | 5.46 | 1.27 | 0.001 |
| Other non-breast | 324 | 2.4 | 76.5 | 1.03 | 0.11 | 0.41 |
| Other specified cause | 470 | 5.6 | 103.6 | 1.06 | 0.10 | 0.62 |
| Unknown cause (but definitely not-breast cancer**) | 543 | 8.2 | 120.9 | 1.07 | 0.09 | 0.60 |
| Second cancer incidence without previous recurrence (selected sites) | | | | | | |
| Contralateral breast, All ages | 940 | -77.2 | 223.6 | 0.71 | 0.06 | < 0.00001 |
| Uterus excluding cervix,‡ by age at entry (years) | | | | | | |
| < 45 | 21 | -0.8 | 5.2 | 0.86 | 0.41 | 0.90 |
| 45 - 54 | 45 | 3.3 | 5.9 | 1.75 | 0.55 | 0.02 |
| 55 - 69 | 110 | 30.2 | 25.9 | 3.21 | 0.37 | < 0.00001 |
| ≥70 | 6 | 1.6 | 1.1 | - | - | - |
| All ages | 182 | 39.3 | 42.9 | 2.50 | 0.25 | < 0.00001 |
| Other or unknown site | 1026 | -0.8 | 241.7 | 1.00 | 0.06 | 0.98 |

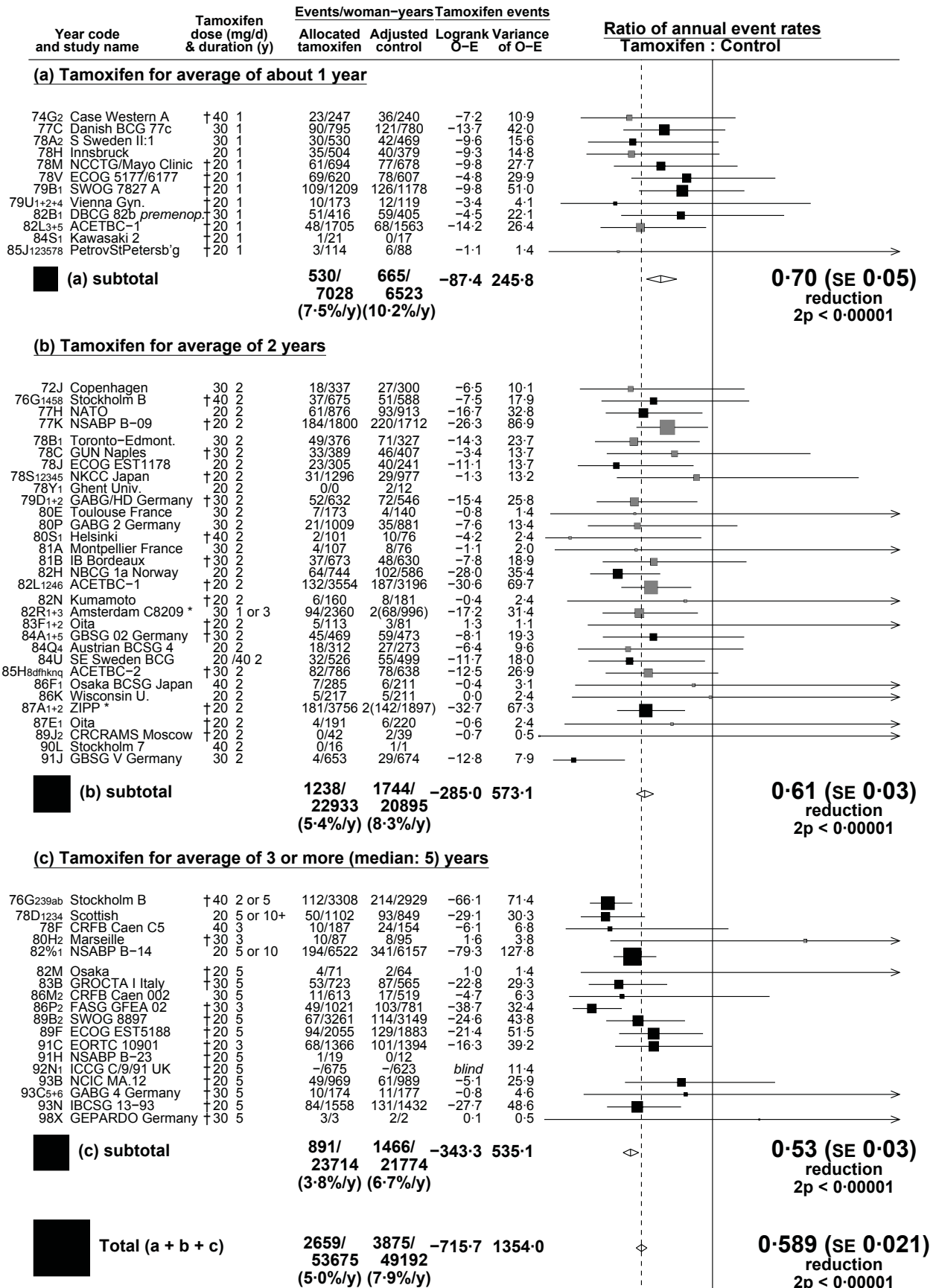
* 2p, with continuity correction

† 9 vs 2 deaths from pulmonary embolus during years 0-4 (age at entry: < 45 years 0 vs 1, 45-54 years 1 vs 0, 55-69 years 8 vs 1) and 7 vs 5 later (age at entry: < 45 1 vs 0, 55-69 5 vs 4, 70+ 1 vs 1).

‡ 18 vs 1 deaths (age at entry: 45-54 years, 4 vs 0; 55-69 years, 13 vs 1; 70+ years, 1 vs 0) and 137 vs 45 incident cases of uterine cancer, excluding cervix

** Deaths from an unknown cause that might possibly have been breast cancer were taken to have been immediately preceded by recurrence.

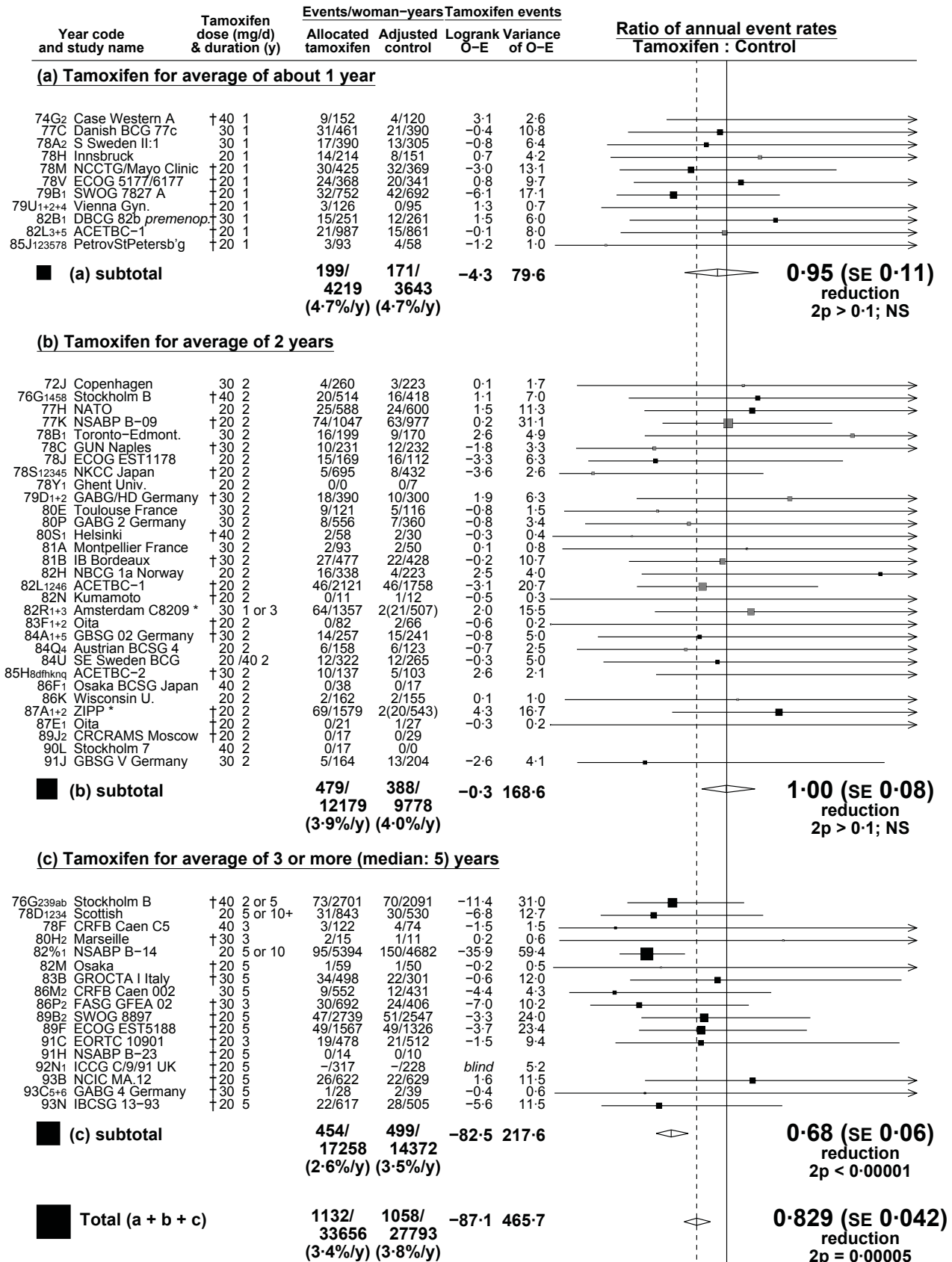
p 18: RRs for recurrence in years 0-4, one line / trial, ER+ disease: by tam. duration



* 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.

† Tamoxifen plus chemotherapy versus same chemotherapy alone

p 19: RRs for recurrence in years 5-9, one line / trial, ER+ disease: by tam. duration



■ 99% or ◊ 95% confidence intervals

Heterogeneity between 3 subtotals: $\chi^2 = 15.2$; p = 0.0005

Heterogeneity within subtotals: $\chi^2_{51} = 47.5$; p > 0.1; NS

Heterogeneity between 54 trials: $\chi^2_{53} = 62.8$; p > 0.1; NS

0 0.5 1.0 1.5 2.0
Tamoxifen better | Tamoxifen worse

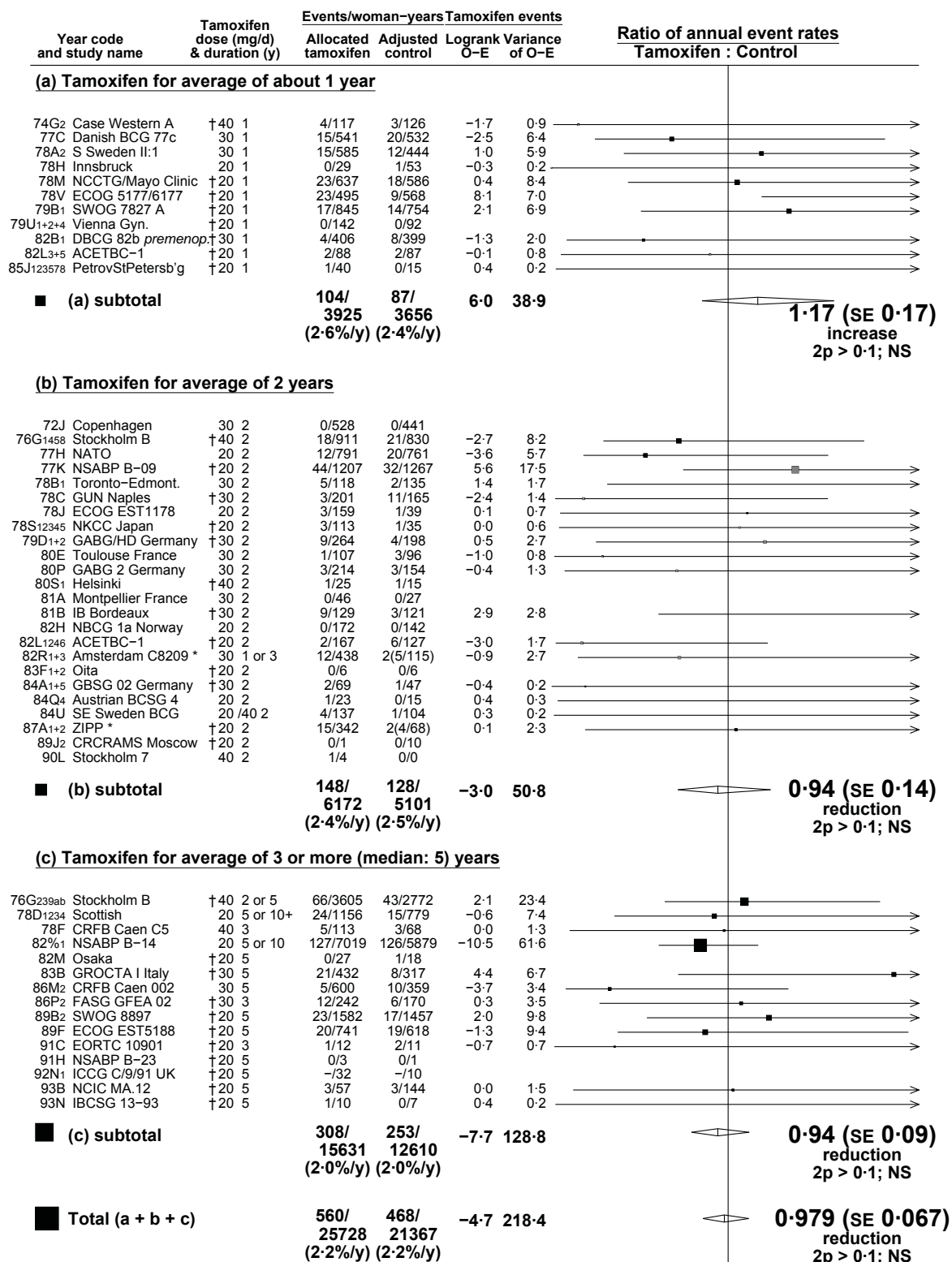
Treatment effect 2p = 0.00005

Trend between 3 subtotals: $\chi^2_1 = 10.7$; 2p = 0.001

* 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.

† Tamoxifen plus chemotherapy versus same chemotherapy alone

p 20: RRs for recurrence in years 10+, one line / trial, ER+ disease: by tam. duration



■ 99% or ◁ 95% confidence intervals

Heterogeneity between 3 subtotals: $\chi^2_2 = 1.5$; $p > 0.1$; NS

Heterogeneity within subtotals: $\chi^2_{36} = 47.9$; $p = 0.09$

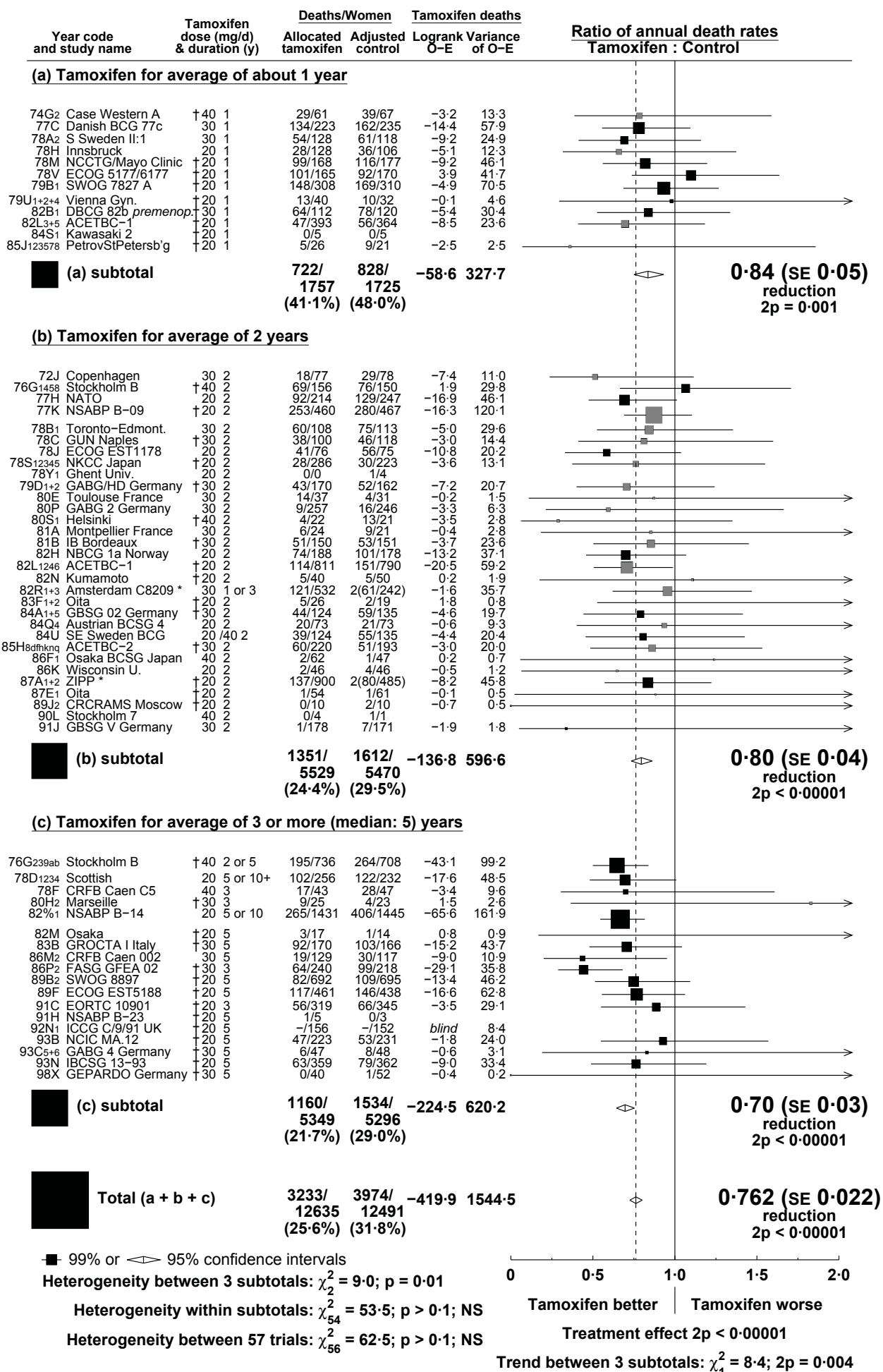
Heterogeneity between 39 trials: $\chi^2_{38} = 49.3$; $p > 0.1$; NS

Treatment effect $2p > 0.1$; NS
Trend between 3 subtotals: $\chi^2_1 = 1.1$; $2p > 0.1$; NS

* 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.

† Tamoxifen plus chemotherapy versus same chemotherapy alone

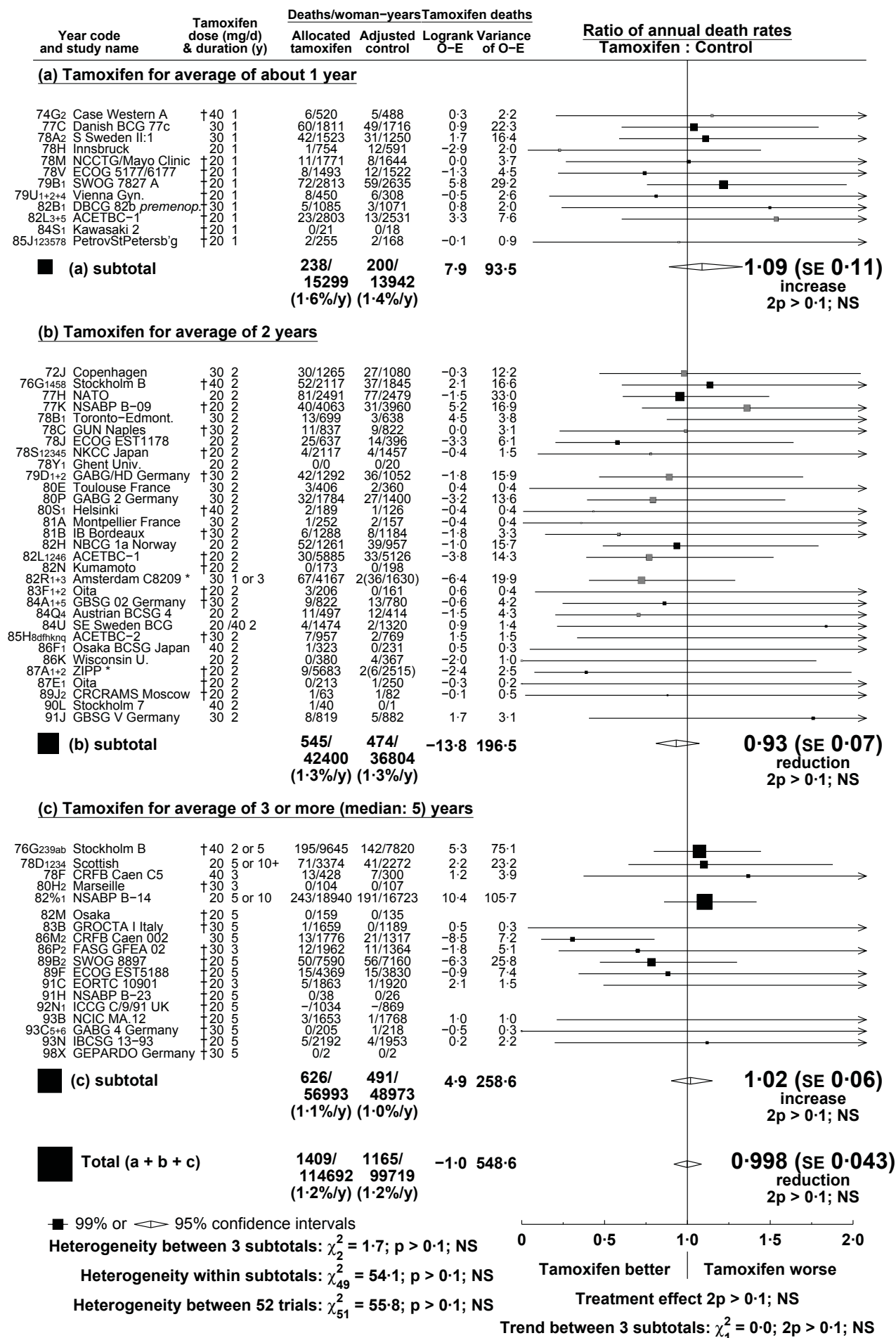
p 21: RRs for death with recurrence, one line / trial, ER+ disease: by tam. duration



* 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.

† Tamoxifen plus chemotherapy *versus* same chemotherapy alone

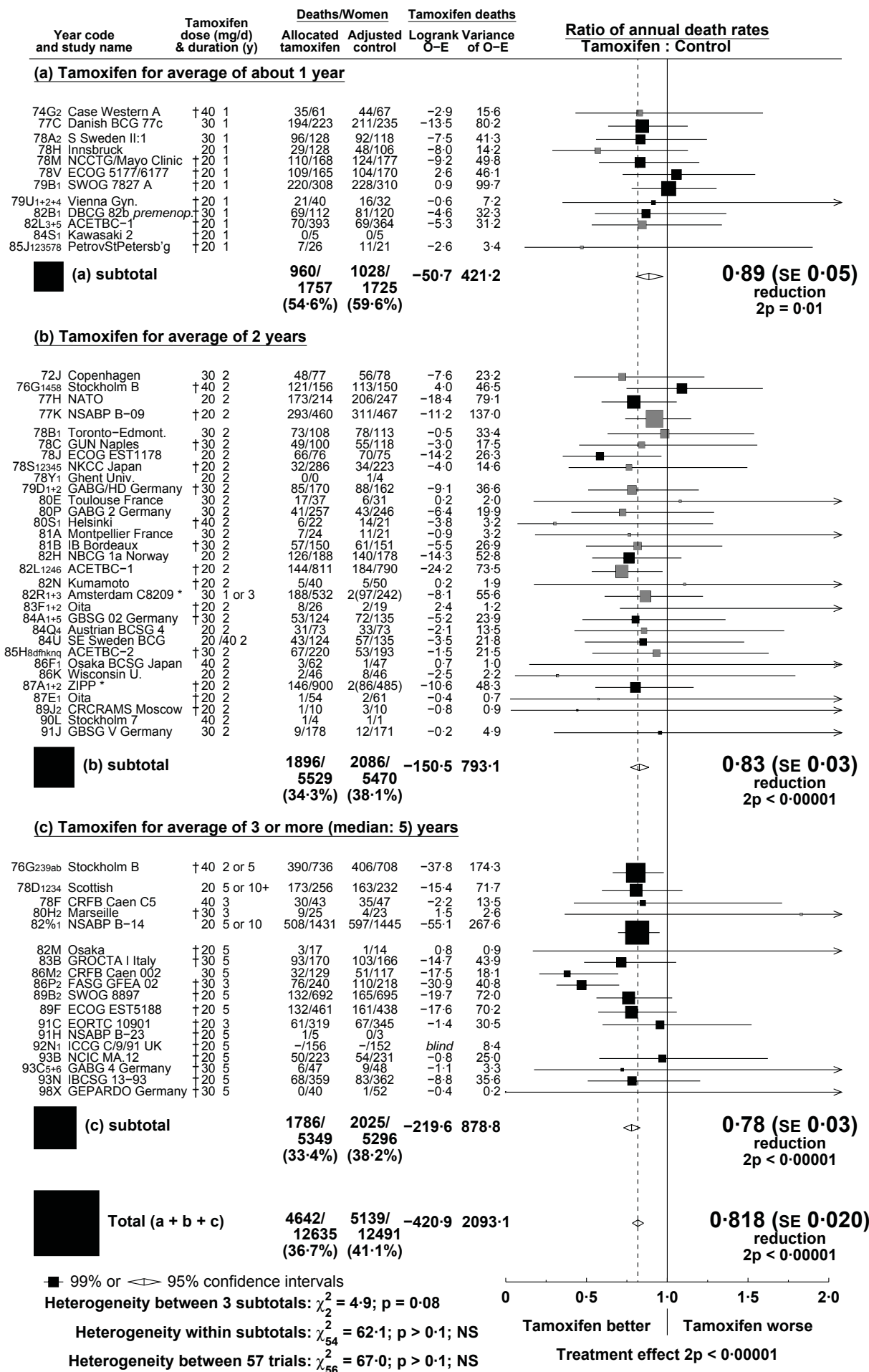
p 22: RRs for death without recurrence, one line / trial, ER+ disease: by tam. duration



* 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.

† Tamoxifen plus chemotherapy versus same chemotherapy alone

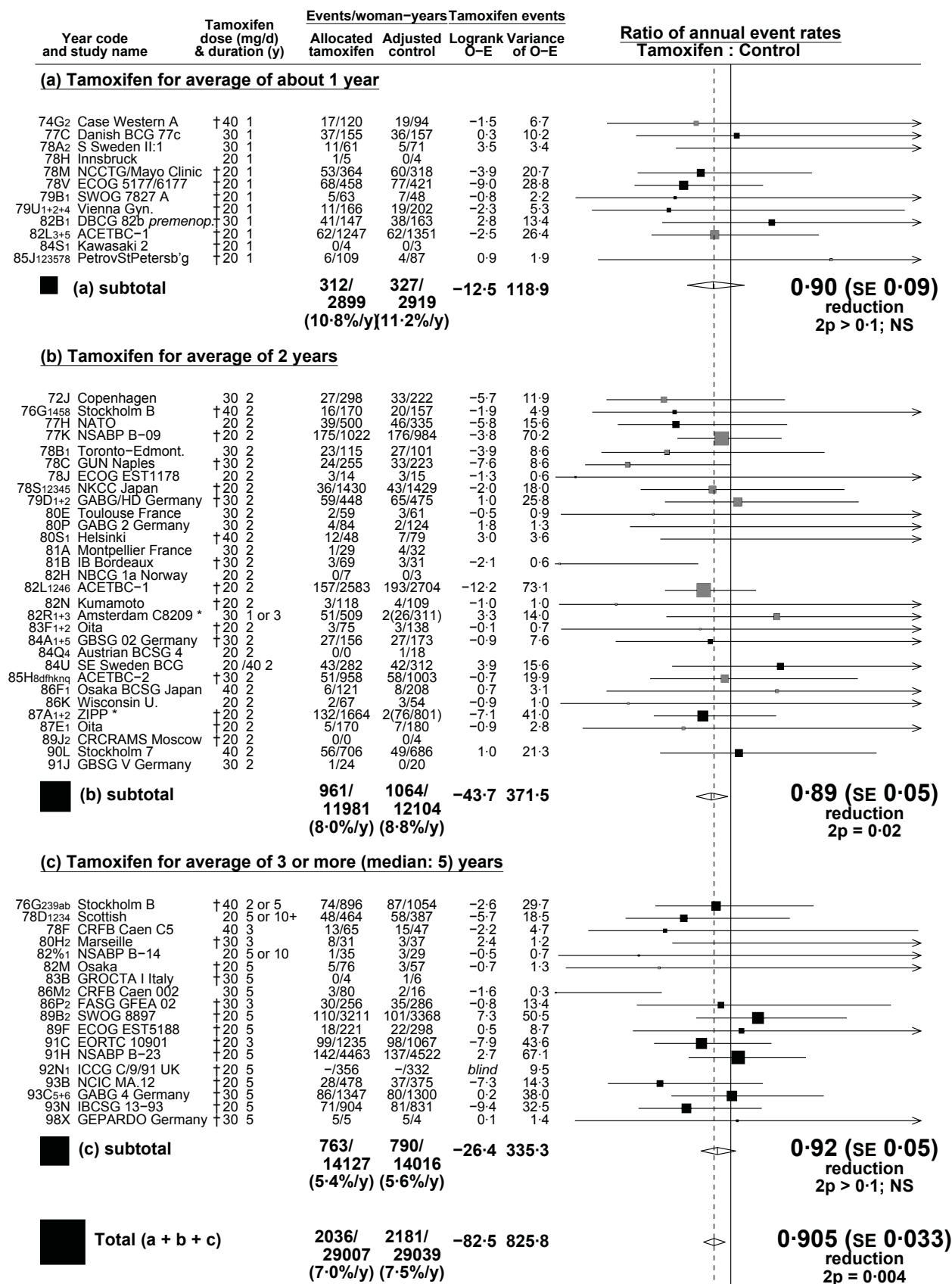
p 23: RRs for any death, one line / trial, ER+ disease: by tam. duration



* 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.

† Tamoxifen plus chemotherapy *versus* same chemotherapy alone

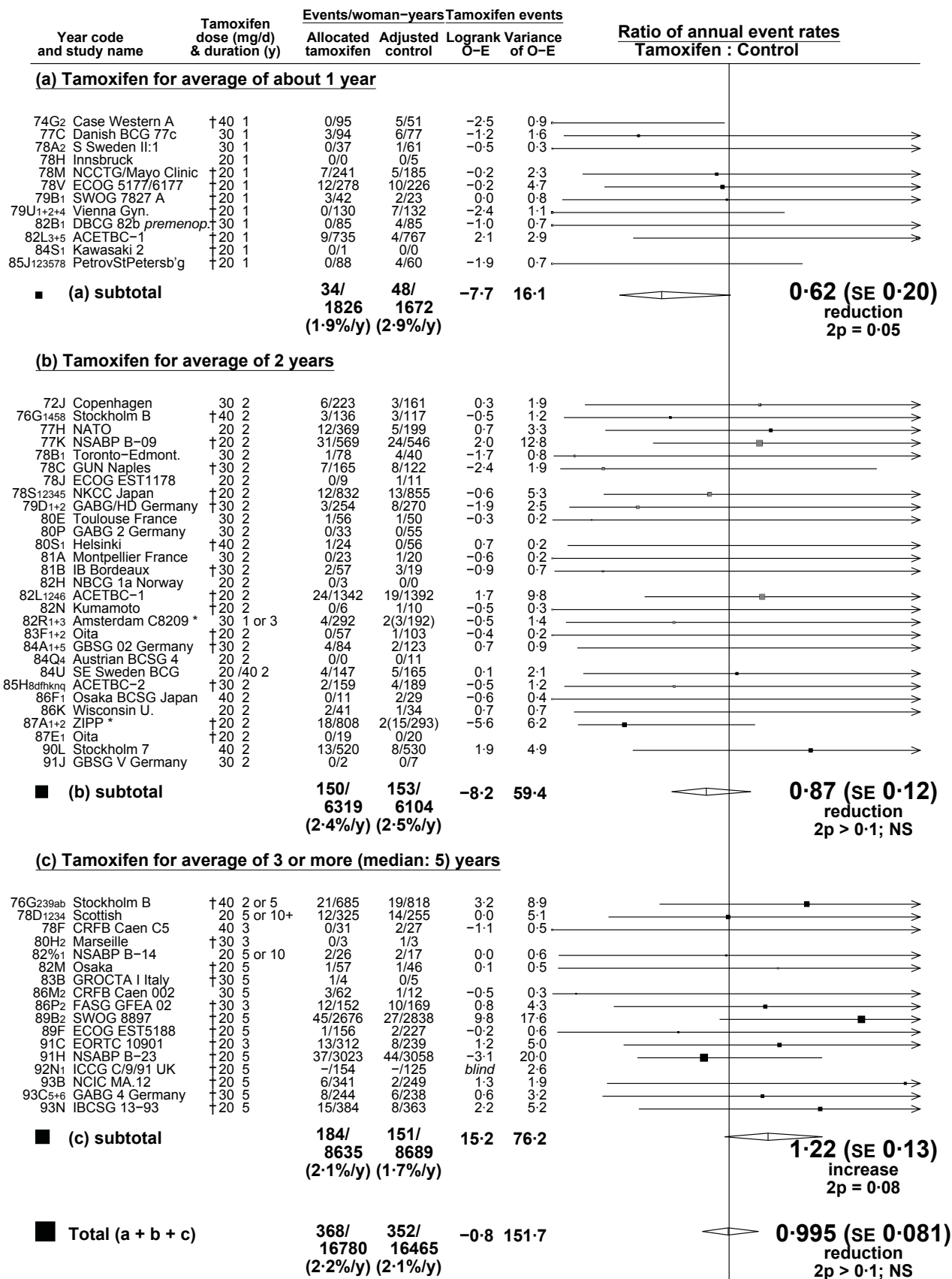
p 24: RRs for recurrence in years 0-4, one line / trial, ER-poor disease: by tam. duration



* 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.

† Tamoxifen plus chemotherapy versus same chemotherapy alone

p 25: RRs for recurrence in years 5-9, one line / trial, ER-poor disease: by tam. duration



■ 99% or ◊ 95% confidence intervals

Heterogeneity between 3 subtotals: $\chi^2_2 = 7.9$; $p = 0.02$

Heterogeneity within subtotals: $\chi^2_{45} = 51.7$; $p > 0.1$; NS

Heterogeneity between 48 trials: $\chi^2_{47} = 59.6$; $p > 0.1$; NS

0 0.5 1.0 1.5 2.0
Tamoxifen better | Tamoxifen worse

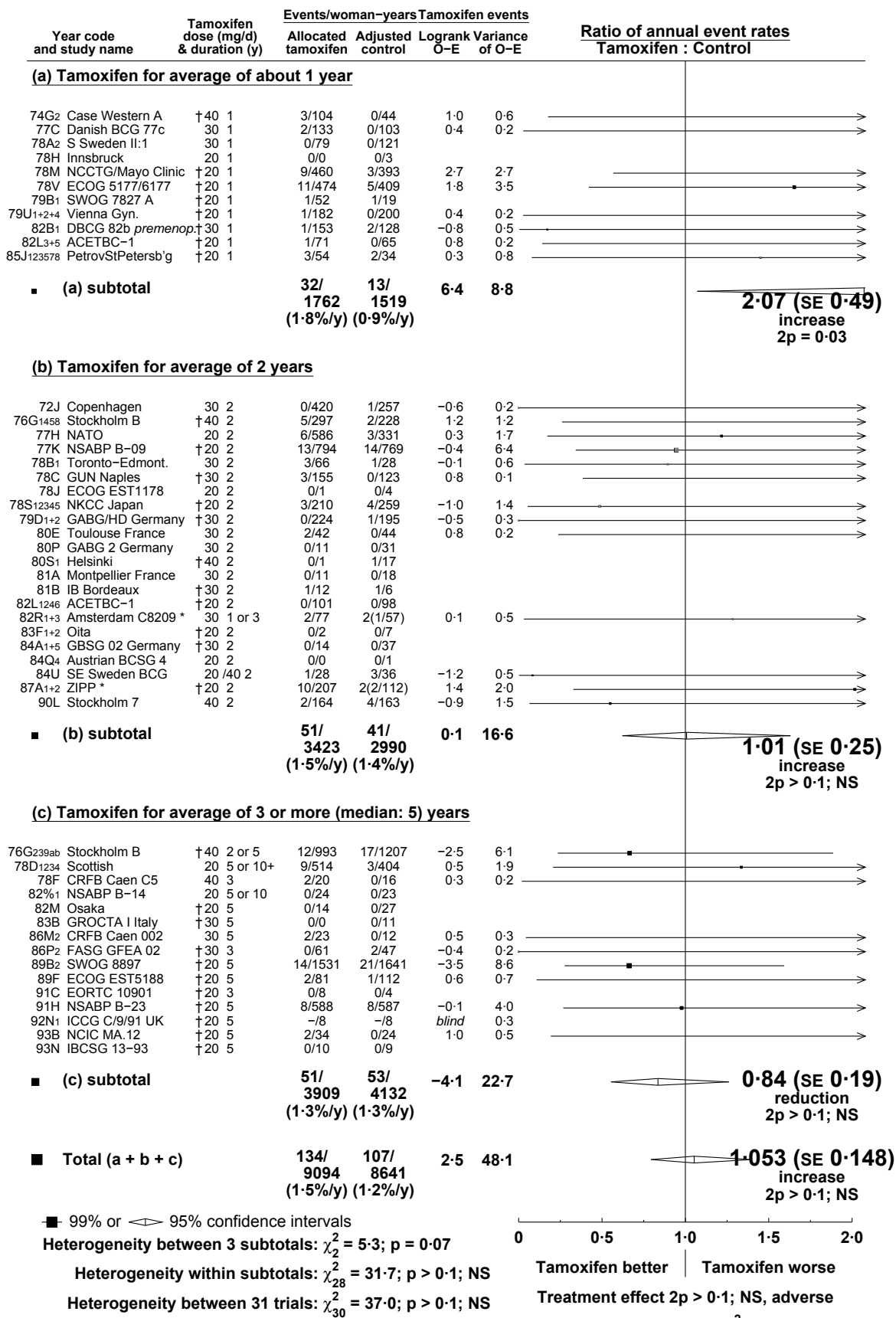
Treatment effect $2p > 0.1$; NS

Trend between 3 subtotals: $\chi^2_1 = 7.9$; $2p = 0.005$

* 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.

† Tamoxifen plus chemotherapy *versus* same chemotherapy alone

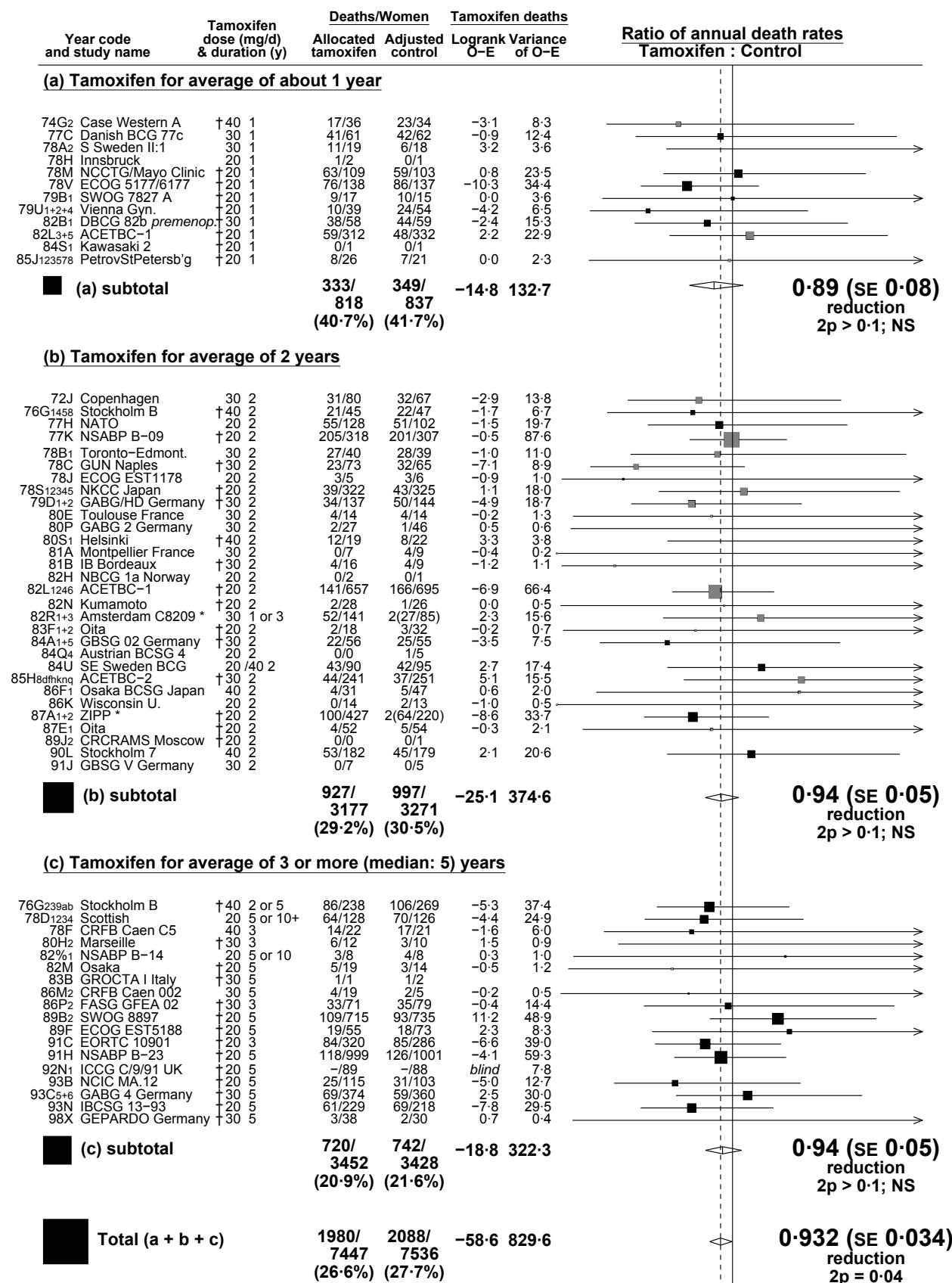
p 26: RRs for recurrence in years 10+, one line / trial, ER-poor disease: by tam. duration



* 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.

† Tamoxifen plus chemotherapy versus same chemotherapy alone

p 27: RRs for death with recurrence, one line / trial, ER-poor disease: by tam. duration



■ 99% or ◊ 95% confidence intervals

Heterogeneity between 3 subtotals: $\chi^2_2 = 0.3$; p > 0.1; NS

Heterogeneity within subtotals: $\chi^2_{50} = 45.4$; p > 0.1; NS

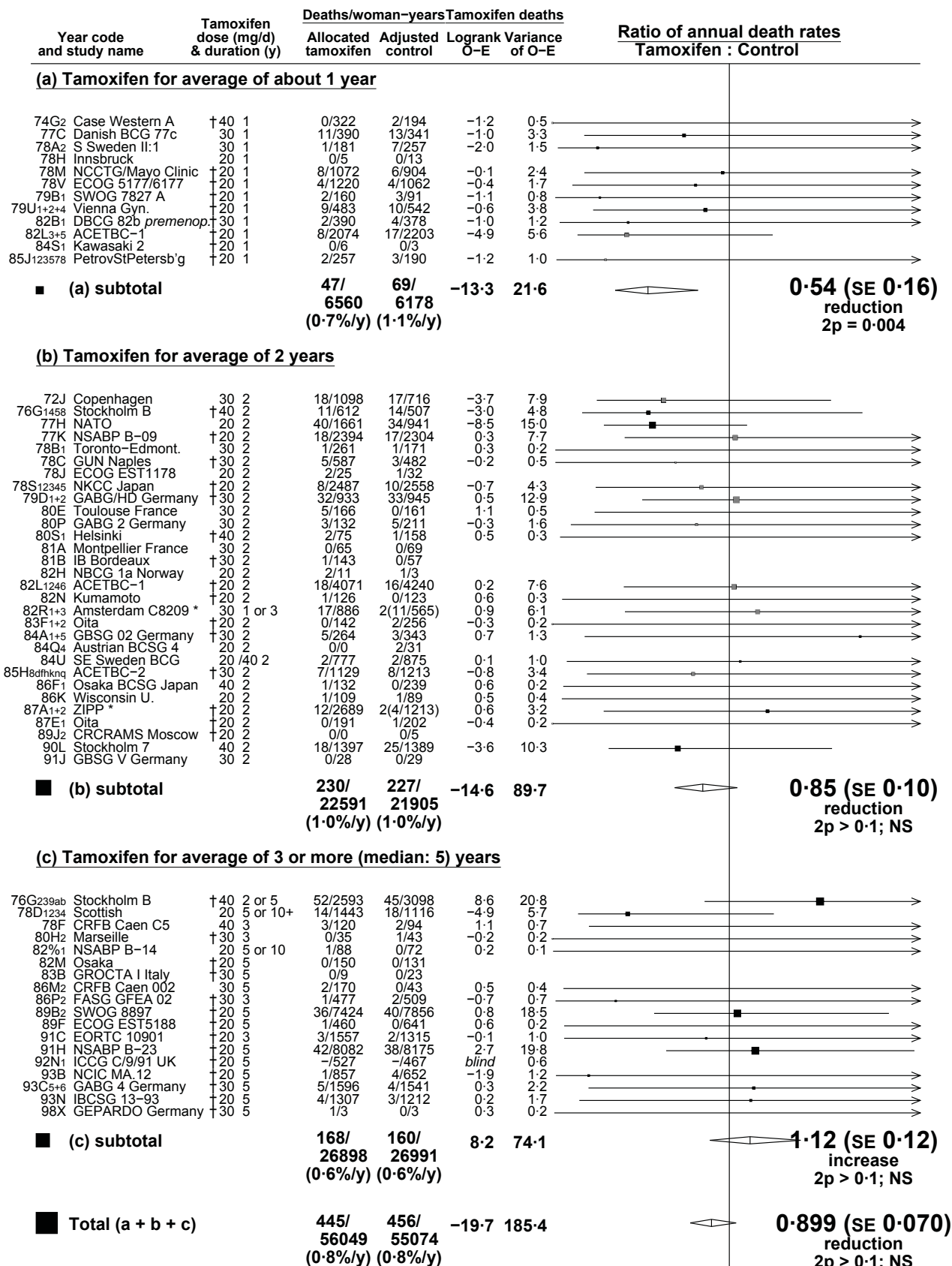
Heterogeneity between 53 trials: $\chi^2_{52} = 45.6$; p > 0.1; NS

Trend between 3 subtotals: $\chi^2_1 = 0.2$; 2p > 0.1; NS

* 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.

† Tamoxifen plus chemotherapy versus same chemotherapy alone

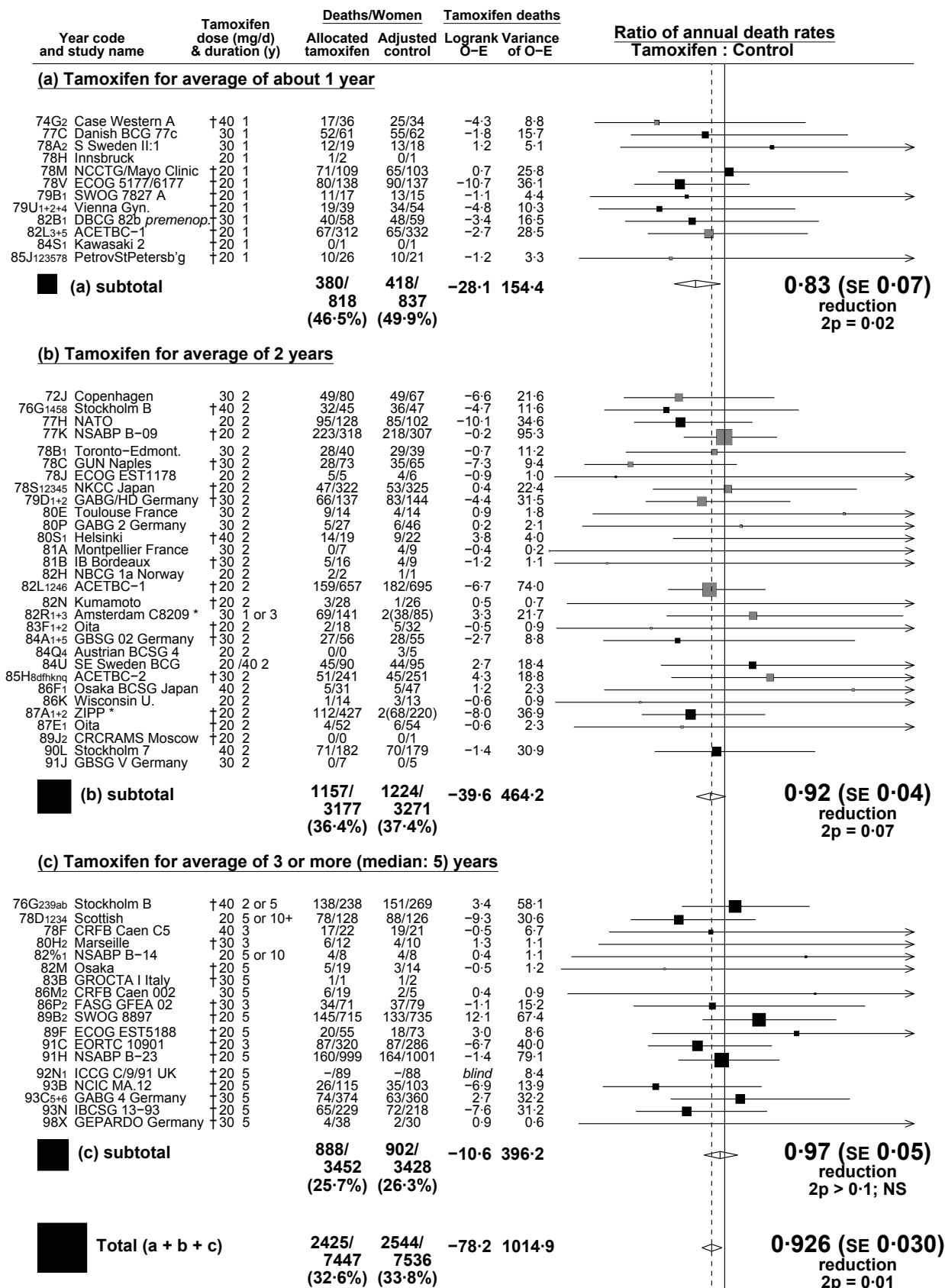
p 28: RRs for death without recurrence, one line / trial, ER-poor disease: by tam. duration



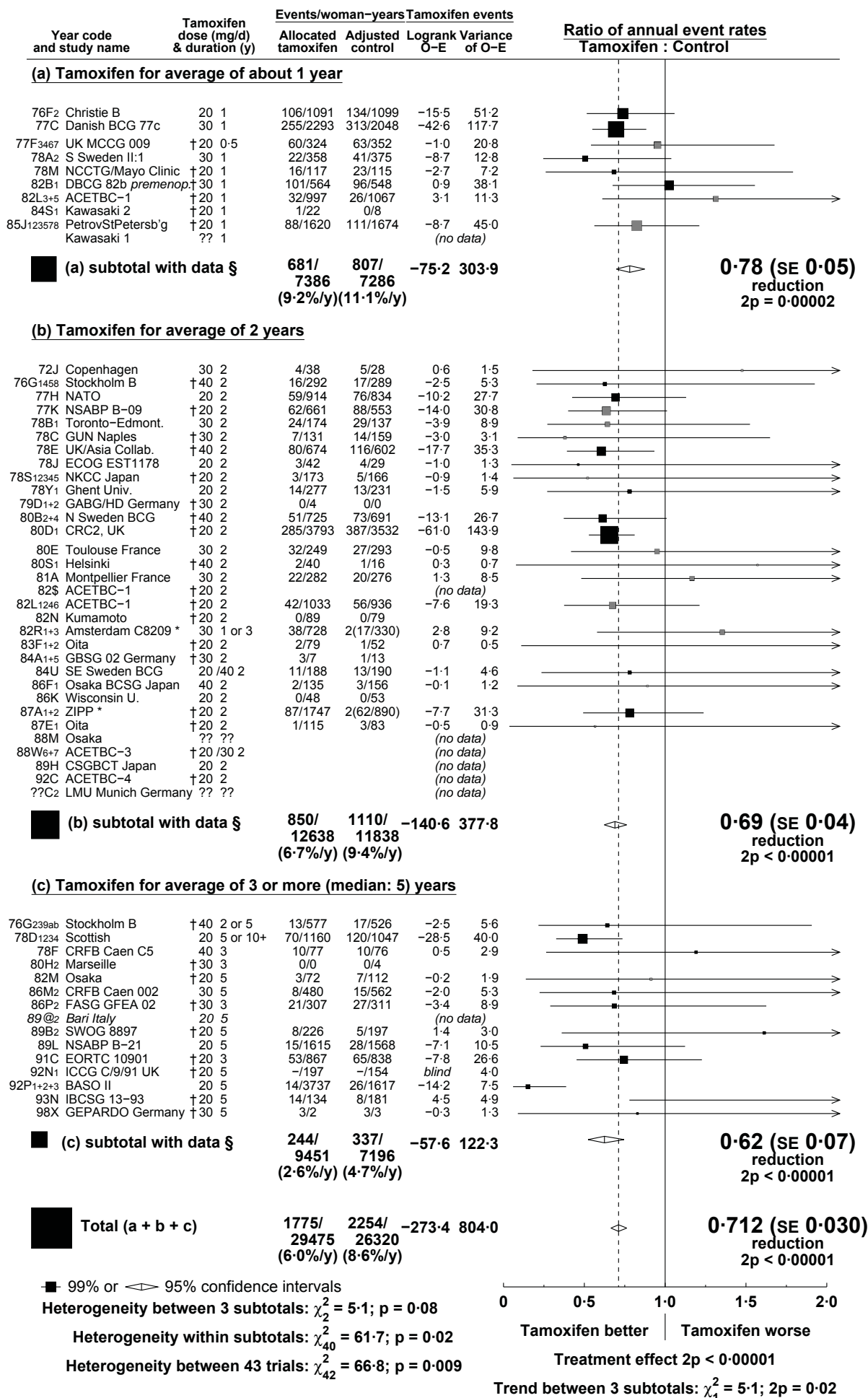
* For balance, control patients in 3-way trials or trial strata count half or twice in subtotal(s) and in final total of deaths/woman-years.

† Tamoxifen plus chemotherapy versus same chemotherapy alone

p 29: RRs for any death, one line / trial, ER-poor disease: by tam. duration



p 30: RRs for recurrence in years 0-4, one line / trial, ER-unknown disease: by tam. duration

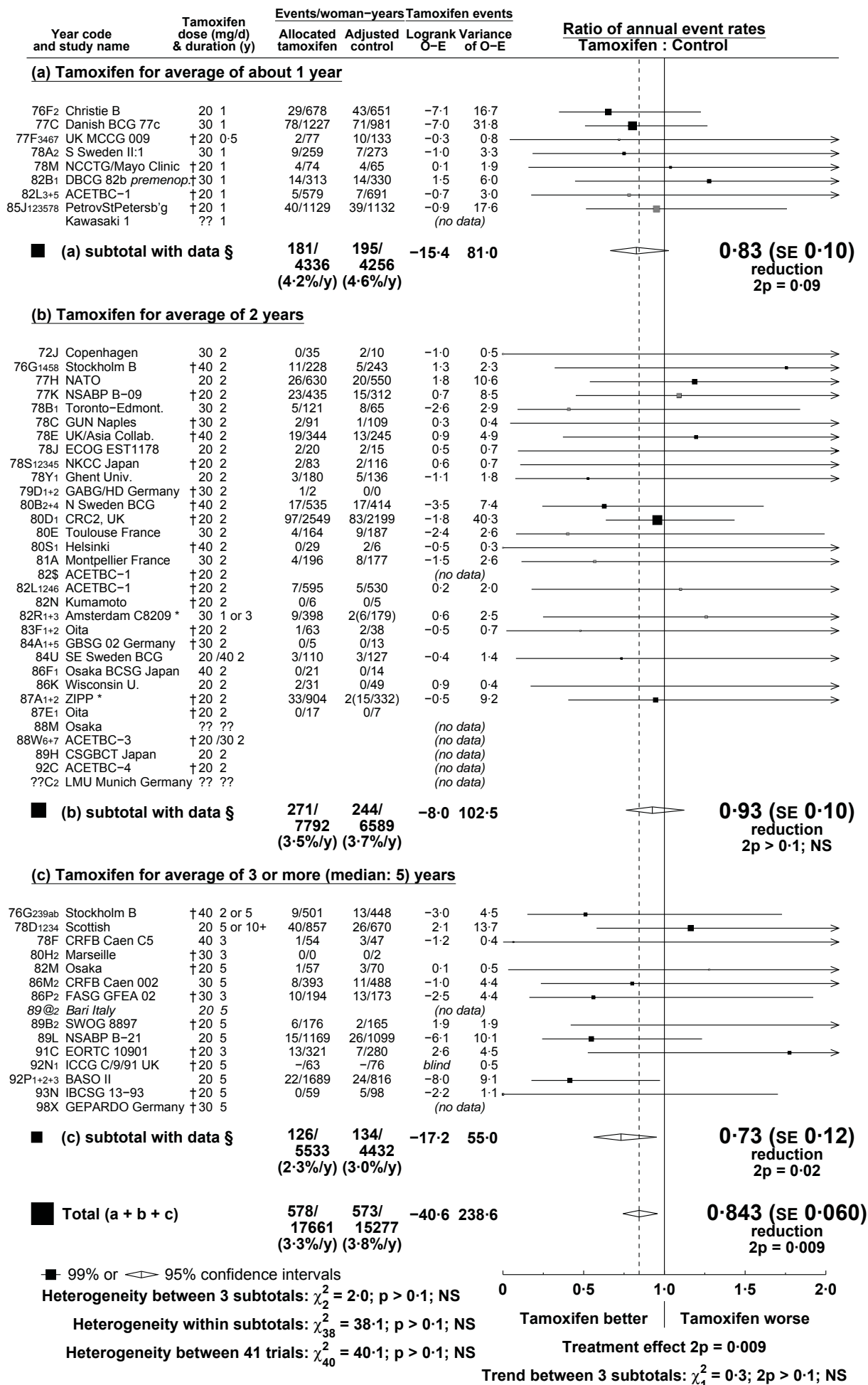


§ 1 trial with no data does not contribute to subtotals or to the overall total.

* 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.

† Tamoxifen plus chemotherapy versus same chemotherapy alone

p 31: RRs for recurrence in years 5-9, one line / trial, ER-unknown disease: by tam. duration

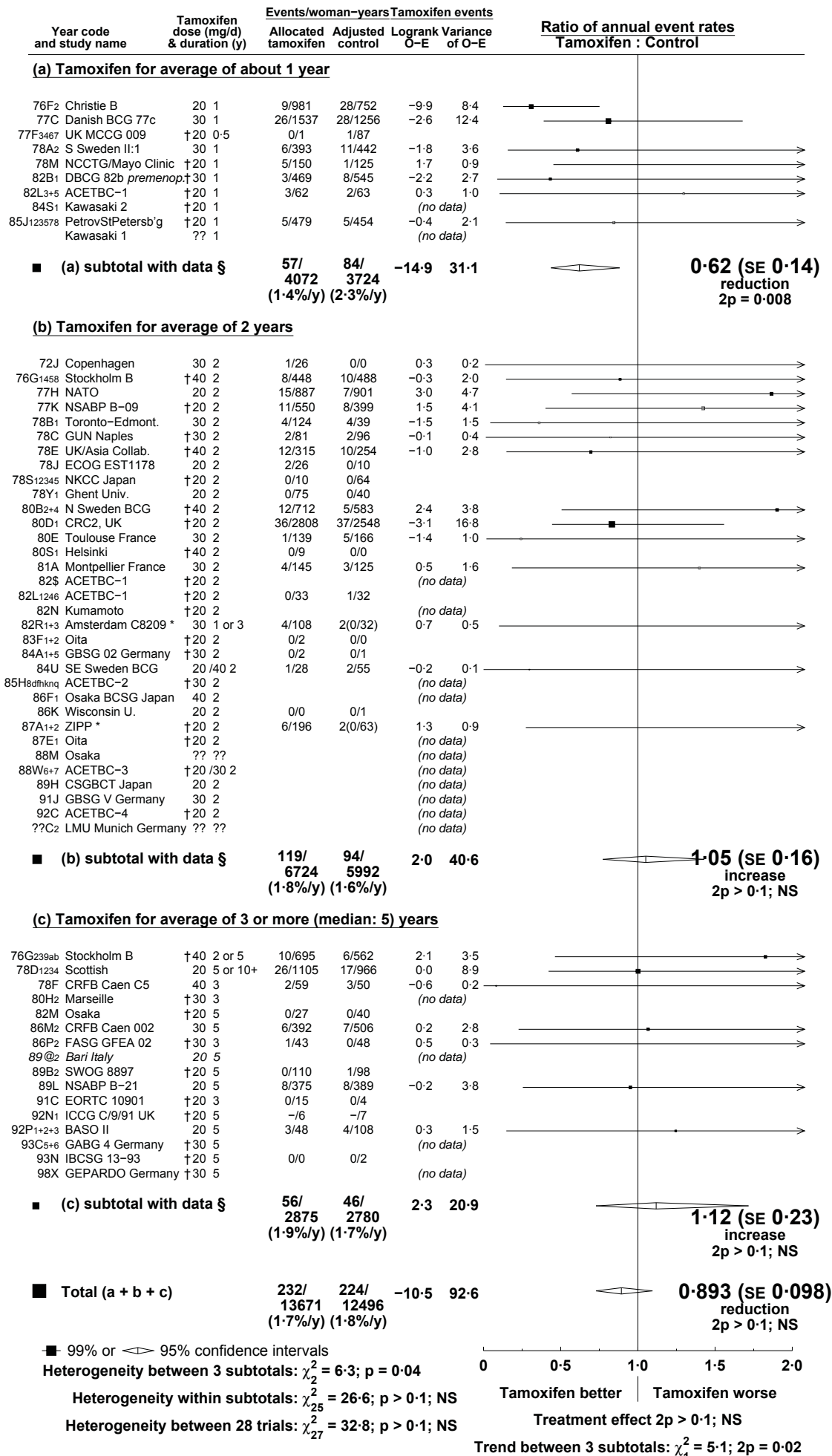


§ 1 trial with no data does not contribute to subtotals or to the overall total.

* 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.

† Tamoxifen plus chemotherapy *versus* same chemotherapy alone

p 32: RRs for recurrence in years 10+, one line / trial, ER-unknown disease: by tam. duration

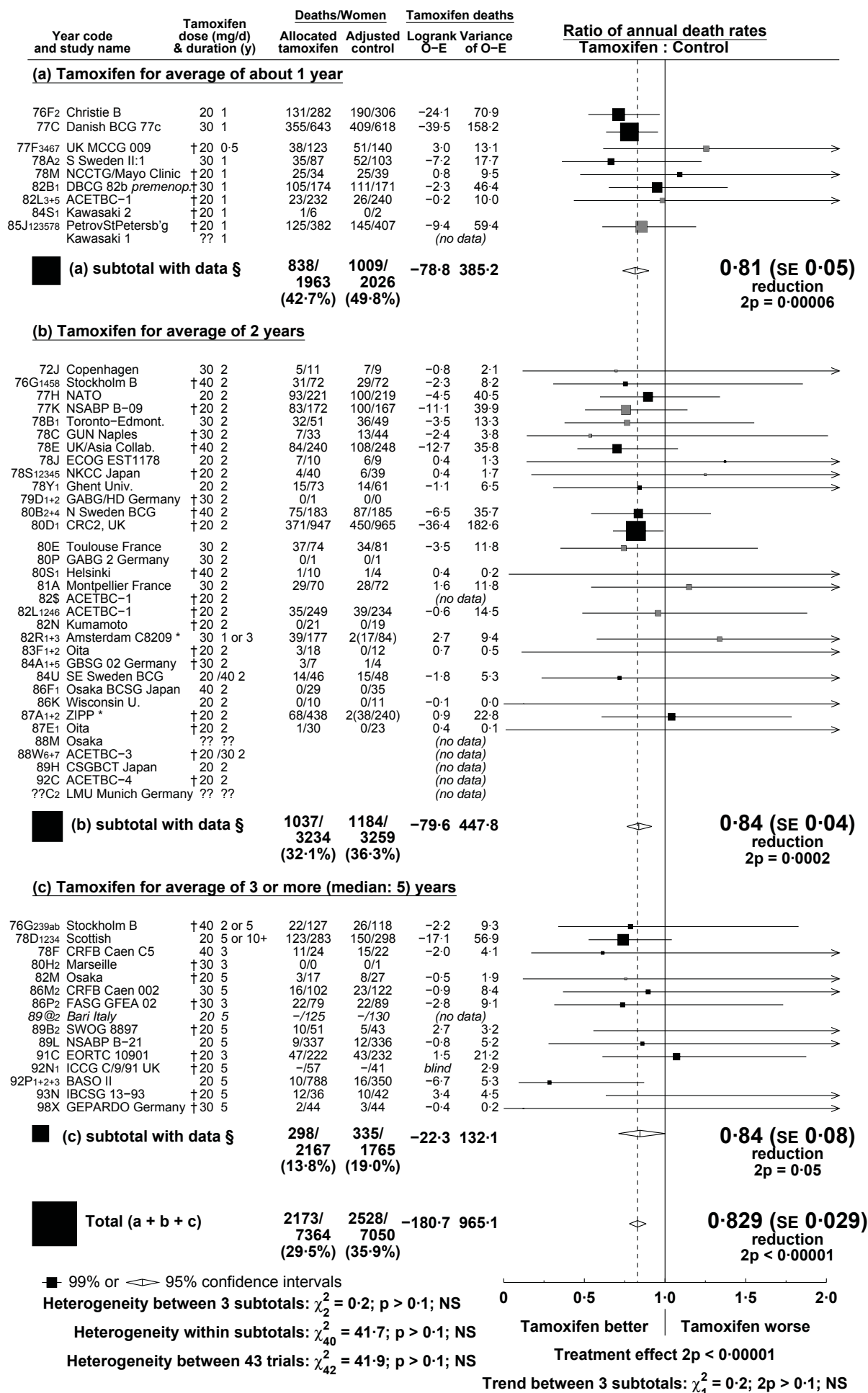


§ 1 trial with no data does not contribute to subtotals or to the overall total.

* 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.

† Tamoxifen plus chemotherapy versus same chemotherapy alone

p 33: RRs for death with recurrence, one line / trial, ER-unknown disease: by tam. duration

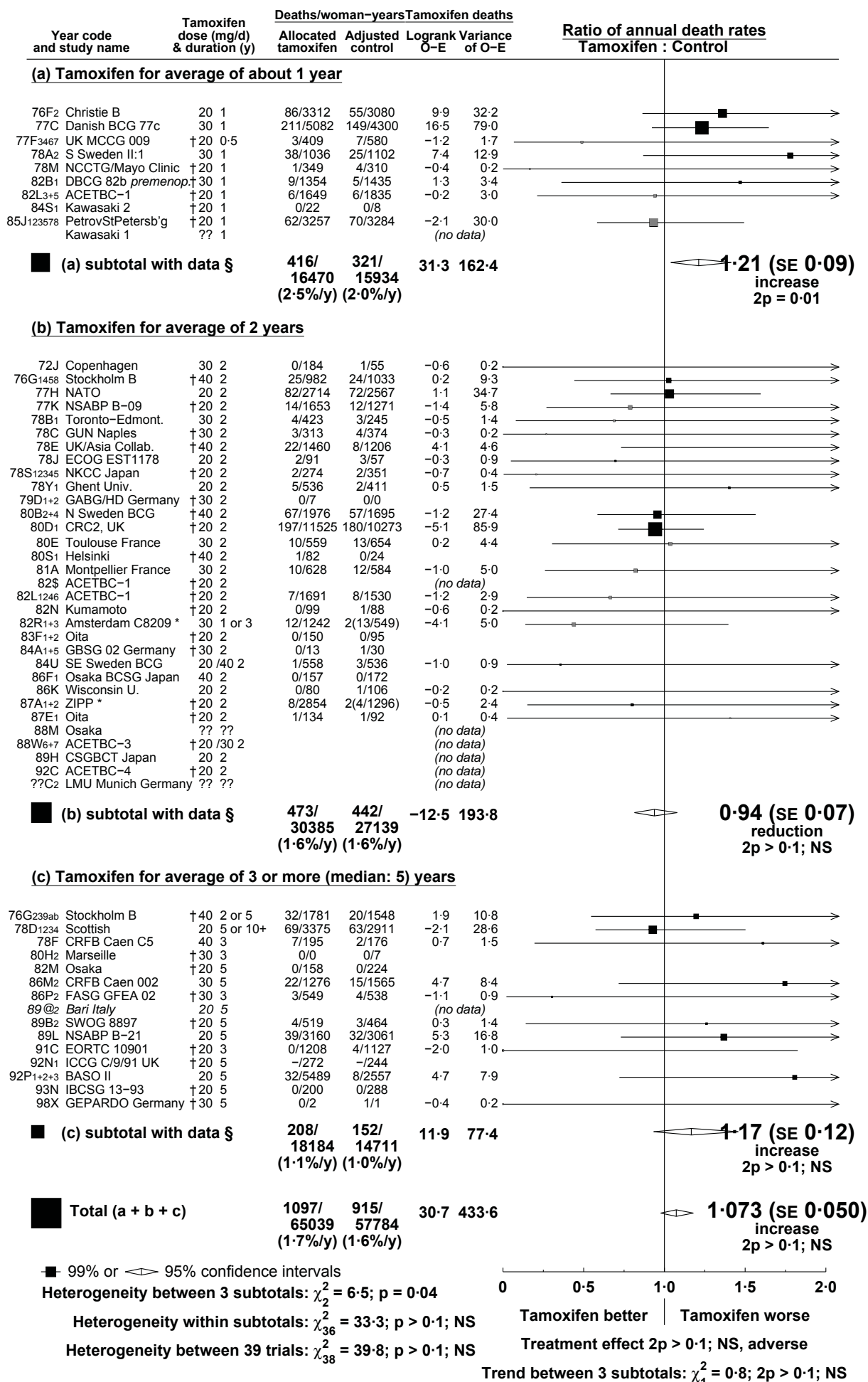


§ 1 trial with no data does not contribute to subtotals or to the overall total (allocated tamoxifen: 125; allocated control: 130)

* 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.

† Tamoxifen plus chemotherapy *versus* same chemotherapy alone

p 34: RRs for death without recurrence, one line / trial, ER-unknown disease: by tam. duration

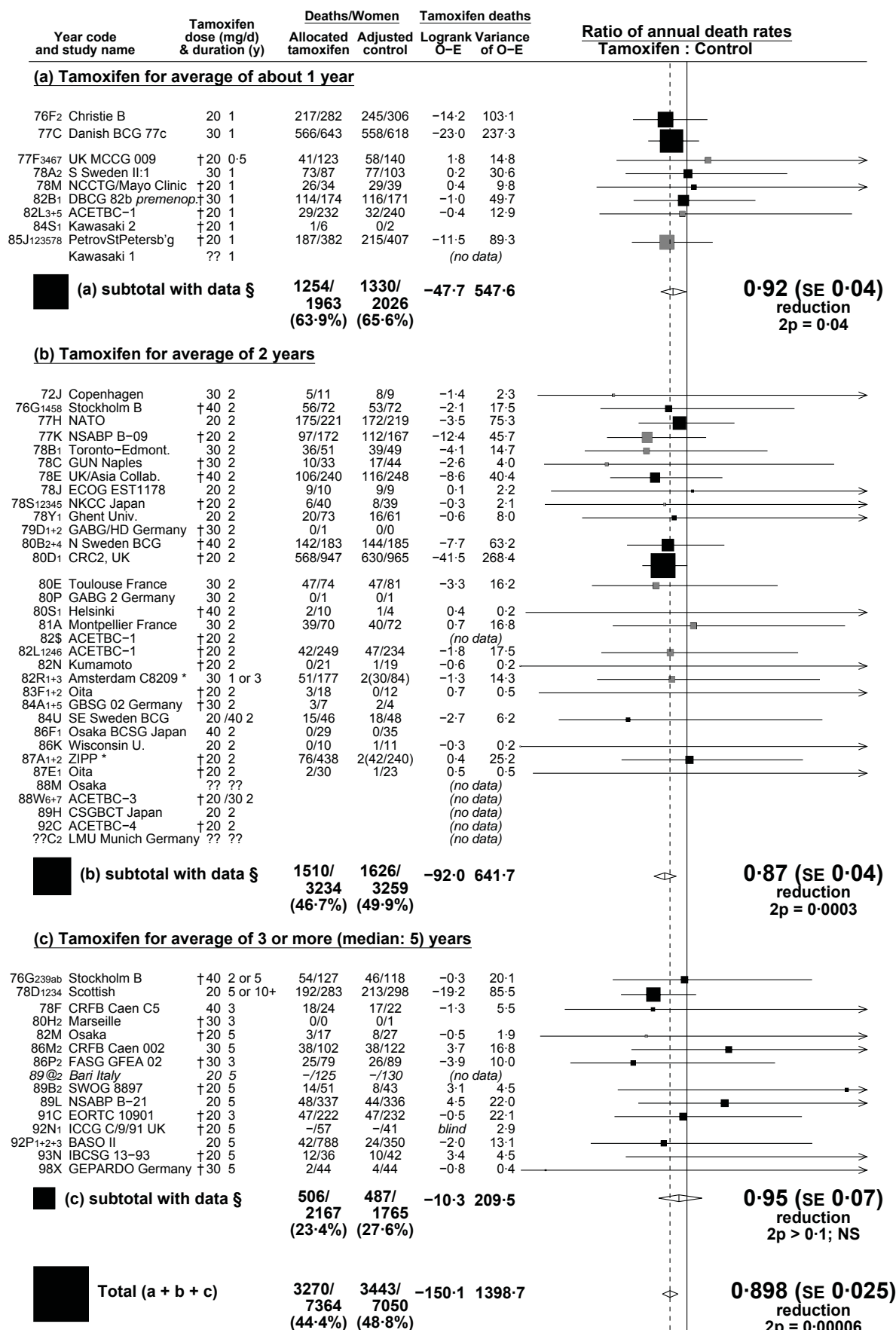


§ 1 trial with no data does not contribute to subtotals or to the overall total.

* 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.

† Tamoxifen plus chemotherapy versus same chemotherapy alone

p 35: RRs for any death, one line / trial, ER-unknown disease: by tam. duration



■ 99% or ◇ 95% confidence intervals

Heterogeneity between 3 subtotals: $\chi^2_2 = 1.8$; $p > 0.1$; NS

Heterogeneity within subtotals: $\chi^2_{41} = 30.3$; $p > 0.1$; NS

Heterogeneity between 44 trials: $\chi^2_{43} = 32.0$; $p > 0.1$; NS

Treatment effect $2p = 0.00006$

Trend between 3 subtotals: $\chi^2_1 = 0.0$; $2p > 0.1$; NS

§ 1 trial with no data does not contribute to subtotals or to the overall total (allocated tamoxifen: 125; allocated control: 130)

* 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.

† Tamoxifen plus chemotherapy versus same chemotherapy alone

Page 36: List of trials included in the EBCTCG meta-analysis of ~5 years of tamoxifen versus not: selected publications listed in chronological order of year starting

| Year code | Text ref. | Trial name | Publication(s) |
|-----------|-----------|------------------------------------|--|
| 76G | 22 | Stockholm Adjuvant Tamoxifen Trial | Rutqvist LE, Johansson H, for the Stockholm Breast Cancer Study Group. Long-term follow-up of the randomized Stockholm trial on adjuvant tamoxifen among postmenopausal patients with early stage breast cancer. <i>Acta Oncol</i> 2007; 46 : 133–45. |
| 78D | 23,24 | Scottish | Breast Cancer Trials Committee, Scottish Cancer Trials Office. Adjuvant tamoxifen in the management of operable breast cancer: the Scottish trial. <i>Lancet</i> 1987; 2 : 171–5. Stewart HJ, Prescott RJ, Forrest APM. Scottish Adjuvant Tamoxifen Trial: a randomized study updated to 15 years. <i>J Natl Cancer Inst</i> 2001; 93 : 456–62. |
| 78F | 17 | CRFB Caen C5 | Delozier T, Julien JP, Juret P, et al. Adjuvant tamoxifen in postmenopausal breast cancer: Preliminary results of a randomized trial. <i>Breast Cancer Res Treat</i> 1986; 7 : 105–09. |
| 80H | 18,19 | Marseille | Ayme Y, Spitalier JM, Amalric R, et al. Preliminary results of a three-arm randomized trial of adjuvant chemo- and/or hormone-therapy for high-risk breast cancer. Fourth EORTC breast cancer working conference 1987 C2A.1; 30 June-3 July 1987; Imperial College, London, UK. Martin PM, Romain S, Spyrtas F, et al. Re-evaluation of the indications of adjuvant hormonotherapy in high risk primary breast cancer patients. <i>Bull Cancer</i> 1991; 78 : 709–723. |
| 82% | 25,26 | NSABP B-14 | Fisher B, Dignam J, Bryant J, et al. Five versus more than five years of tamoxifen therapy for breast cancer patients with negative lymph nodes and estrogen receptor-positive tumors [see comments]. <i>J Natl Cancer Inst</i> 1996; 88 : 1529–42. Fisher B, Dignam J, Bryant J, Wolmark N. Five versus more than five years of tamoxifen for lymph node-negative breast cancer: updated findings from the National Surgical Adjuvant Breast and Bowel Project B-14 randomized trial. <i>J Natl Cancer Inst</i> 2001; 93 : 684–90. |
| 82M | | Osaka | Personal communication |
| 83B | 15 | GROCTA I | Boccardo F, Rubagotti A, Bruzzi P, et al. Chemotherapy versus tamoxifen versus chemotherapy plus tamoxifen in node-positive, estrogen receptor-positive breast cancer patients: Results of a multicentric Italian study. <i>J Clin Oncol</i> 1990; 8 : 1310–20. |
| 89@ | 6 | Bari, Italy | Paradiso A, De Lena M, Sambiasi M, et al. Adjuvant hormonotherapy for slow-proliferating node-negative breast cancer patients. Results of the phase III trial of NCI-Bari. <i>Breast</i> 2003; 12 : S40, P90. |
| 89L | 4 | NSABP B-21 | Fisher B, Bryant J, Dignam JJ, Wickerham DL, et al. Tamoxifen, radiation therapy, or both for prevention of ipsilateral breast tumor recurrence after lumpectomy in women with invasive breast cancers of one centimeter or less. <i>J Clin Oncol</i> 2002; 20 : 4141–49. |
| 86M | 16 | CRFB Caen 002 | Delozier T, Switers O, Genot JY et al. Late delayed adjuvant tamoxifen in breast cancer, a multicenter randomized trial. <i>Fourth International Congress on Anti-cancer Chemotherapy 1993 p.58; February 2-5, 1993; Paris, France.</i> |
| 86P | 20 | 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. <i>Ann Oncol</i> 2006; 17 : 65–73. |
| 89B | 7 | SWOG 8897 / INT 0102 | 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. <i>J Clin Oncol</i> 2005; 23 : 8313–21. |
| 89F | 8 | ECOG EST 5188 / INT 0101 | Davidson NE, O'Neill AM, Vukov AM, et al. Chemoendocrine therapy for premenopausal women with axillary lymph node-positive, steroid hormone receptor-positive breast cancer: results from INT 0101 (E5188). <i>J Clin Oncol</i> 2005; 23 : 5973–82. |
| 91C | 21 | EORTC 10901 | Morales L, Canney P, Dyczka J, et al. Postoperative adjuvant chemotherapy followed by adjuvant tamoxifen versus nil for patients with operable breast cancer: a randomised phase III trial of the European Organisation for Research and Treatment of Cancer Breast Group. <i>Eur J Cancer</i> 2007; 43 : 331–40. |
| 91H | 9 | 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. <i>J Clin Oncol</i> 2001; 19 : 931–42. |
| 92N1 | 10 | ICCG C/9/91 UK | Bliss JM, Wils J, Marty M et al. Evaluation of the tolerability of FE ₅₀ C versus FE ₇₅ C in a prospective randomised trial in adjuvant breast cancer patients. <i>Proc Ann Meet Am Soc Clin Oncol</i> 2002; 21 : 51b, A2017. |
| 92P | 5 | BASO II | Blamey RW, Chetty U, Bates T, et al. Radiotherapy and/or Tamoxifen after conserving surgery for breast cancers of excellent prognosis: BASO II trial. <i>Eur J Cancer Suppl</i> 2008; 6 : 55, A17. |
| 93B | 11 | NCIC MA.12 | Bramwell VHC, Pritchard KI, Tu D, et al. A randomized placebo-controlled study of tamoxifen after adjuvant chemotherapy in premenopausal women with early breast cancer (National Cancer Institute of Canada Clinical Trials Group Trial, MA.12). <i>Ann Oncol</i> 2010; 21 : 283-90. |
| 93C | 12 | GABG-4-D-93 | Kaufmann M, Graf E, Jonat W, et al. Tamoxifen versus control after adjuvant, risk-adapted chemotherapy in postmenopausal, receptor-negative patients with breast cancer: a randomized trial (GABG-IV D-93) - the German Adjuvant Breast Cancer Group. <i>J Clin Oncol</i> 2005; 23 : 7842–48. |
| 93N | 13 | IBCSG 13-93 | Colleoni M, Gelber S, Goldhirsch A, et al. Tamoxifen after adjuvant chemotherapy for premenopausal women with lymph node-positive breast cancer: International Breast Cancer Study Group Trial 13–93. <i>J Clin Oncol</i> 2006; 24 : 1332–41. |
| 98X | 14 | GEPARDO Germany | von Minckwitz G, Costa SD, Raab G, et al. Dose-dense doxorubicin, docetaxel, and granulocyte colony-stimulating factor support with or without tamoxifen as preoperative therapy in patients with operable carcinoma of the breast: a randomized, controlled, open phase IIb study. <i>J Clin Oncol</i> 2001; 19 : 3506–15. |