Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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The writing committee designed the study and drafted the report, circulated it for comment to the Early Breast Cancer Trialists' Collaborative Group (EBCTCG), then revised it. The data were analyzed by the EBCTCG Secretariat within the MRC PHRU, Nuffield Department of Population Health, Oxford, UK (HP, RG, JB, CD, CT, PM, and RP), who vouch for the data and the analysis. Funders had no role in study design, data collection, data analysis, data interpretation or report writing. The EBCTCG secretariat had full access to the data and the writing committee had full access to analyses and final responsibility for deciding to submit for publication. There are no commercial sponsors or confidentiality agreements.

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Table S1: **Characteristics of women with ER+ disease scheduled to stop ET at 5 years, and of the 62,923 who remained disease free at the end of 5 years of ET**

	In year 0-5 analyses (N = 74,194)		In year 5-20 analyses (N = 62,923)	
Characteristics	**n**	**%**	**n**	**%**
Age at diagnosis (years)				
<35	1585	2.1	1009	1.6
35-44	10344	13.9	7859	12.5
45-54	22568	30.4	19326	30.7
55-64	25439	34.3	22337	35.5
65-74	14258	19.2	12392	19.7
Tumor diameter (mm)				
1-10 (T1a/b)	10135	13.7	9418	15.0
11-20 (T1c)	31751	42.8	28158	44.7
21-30 (T2)	20708	27.9	16461	26.2
31-50 (T2)	11600	15.6	8886	14.1
Axillary nodal status				
N0	29925	40.3	28847	45.8
N1-3	31936	43.0	25292	40.2
N4-9	12333	16.6	8784	14.0
Tumor grade (differentiation)				
Low (well differentiated)	8913	12.0	8023	12.8
Moderate	29158	39.3	23490	37.3
High (poorly differentiated)	17137	23.1	12077	19.2
Unknown grade	18986	25.6	19333	30.7
Ki-67 status				
0-9%	3166	4.3	2796	4.4
10-19%	3379	4.6	2824	4.5
≥20%	2919	3.9	2072	3.3
Unknown	64730	87.2	55231	87.8
Progesterone receptor status				
ER+, PgR-poor	11733	15.8	8875	14.1
ER+, PgR+	56608	76.3	45240	71.9
PgR unknown	5853	7.9	8808	14.0
HER2 over-expression				
HER2-negative	27975	37.7	20014	31.8
HER2-positive	6182	8.3	4131	6.6
HER2 unknown	40037	54.0	38778	61.6
Original breast surgery				
Breast-conserving surgery	37412	50.4	31849	50.6
Mastectomy	33933	45.7	29024	46.1
Unknown	2849	3.8	2050	3.3
Year of diagnosis				
Before 1995	11199	15.1	10404	16.5
1995-99	18182	24.5	21778	34.6
2000-04	34864	47.0	26189	41.6
Since 2005	9949	13.4	4552	7.2
Endocrine therapy scheduled				
Tamoxifen only	47837	64.5	41647	66.2
Aromatase inhibitors (AI)	9563	12.9	6828	10.9
Tamoxifen and AI	16434	22.2	14169	22.5
Toremifene only	360	0.5	279	0.4
Ovarian ablation or suppression in premenopausal women	1771	2.4	1363	2.2
Chemotherapy scheduled?				
Yes	47247	63.7	33080	52.6
No	26947	36.3	29843	47.4

Table S2: **A) Numbers with chemotherapy scheduled, by TN status and (if T1N0) grade**
B) Numbers with trastuzumab scheduled, by trial design and HER2 status

NB This study cannot assess reliably effects of chemotherapy or trastuzumab: see footnotes

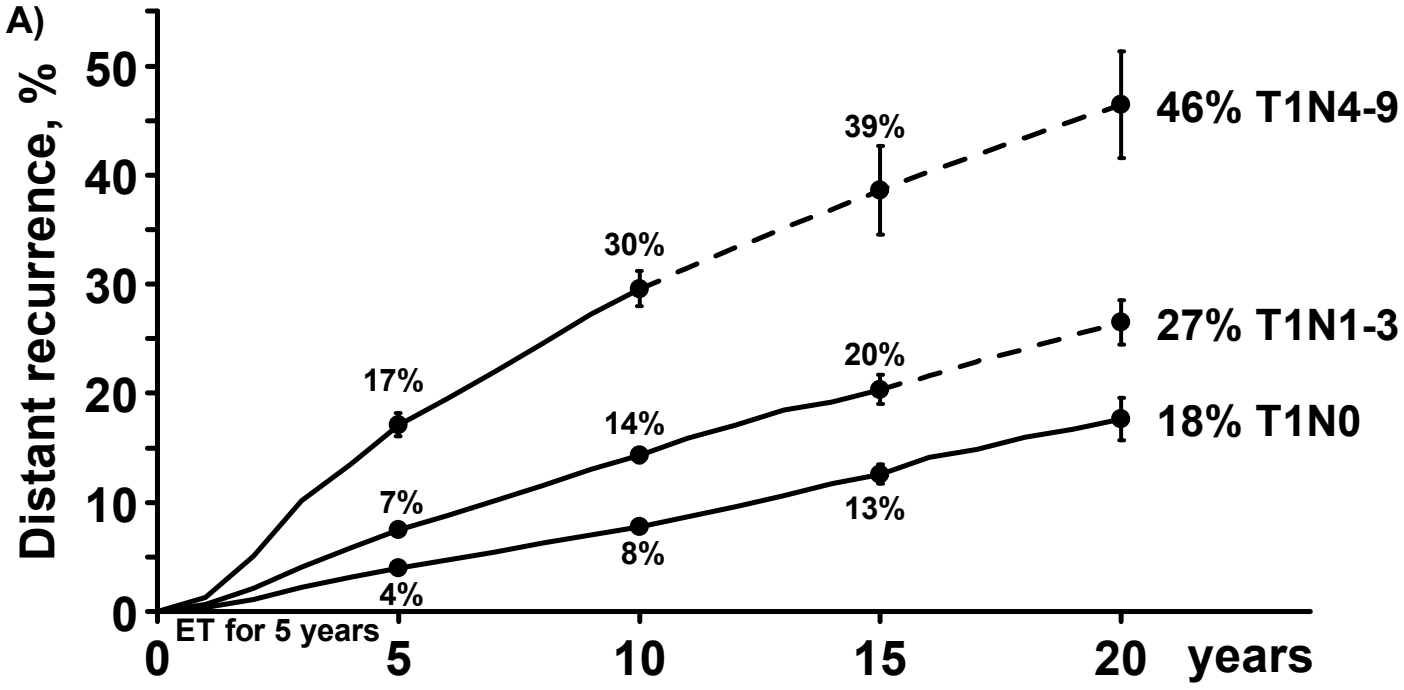
A)		**In year 0-5 analyses**		**In year 5-20 analyses**	
		Total	**Chemotherapy scheduled***	**Total**	**Chemotherapy scheduled***
Nodal involvement	**N0**	29,925	12,176 (41%)	28,847	9,136 (32%)
	N1-3	31,936	24,467 (77%)	25,292	17,280 (68%)
	N4-9	12,333	10,604 (86%)	8,784	6,664 (76%)
Diameter in mm, N0 only	**≤10 (T1a/b)**	5,602	1,232 (22%)	5,527	910 (16%)
	11-20 (T1c)	14,080	5,337 (38%)	13,875	4,034 (29%)
	21-30 (T2)	7,311	3,837 (52%)	6,700	2,859 (43%)
	31-50 (T2)	2,932	1,770 (60%)	2,745	1,333 (49%)
Tumor grade, T1N0 only	**Low**	3,552	517 (15%)	3,524	401 (11%)
	Moderate	7,867	2,492 (32%)	7,363	1,861 (25%)
	High (poorly differentiated)	3,655	1,903 (52%)	3,054	1,414 (46%)

* Much of this chemotherapy was not randomly allocated and many trials of chemotherapy vs not are absent, so chemotherapy effects cannot be assessed reliably from comparisons in this study.

B)		**In year 0-5 analyses**		**In year 5-20 analyses**	
		Total	**Trastuzumab scheduled†**	**Total**	**Trastuzumab scheduled†**
Trials with no scheduled trastuzumab	**HER2-negative**	17,448	0	13,262	0
	HER2-positive	3,200	0	2,156	0
	HER2 unknown	39,167	0	38,215	0
Trials with some scheduled trastuzumab	**HER2-negative**	10,527	0	6,752	0
	HER2-positive	2,982	1564 (52%)	1,975	993 (50%)
	HER2 unknown	870	0	563	0

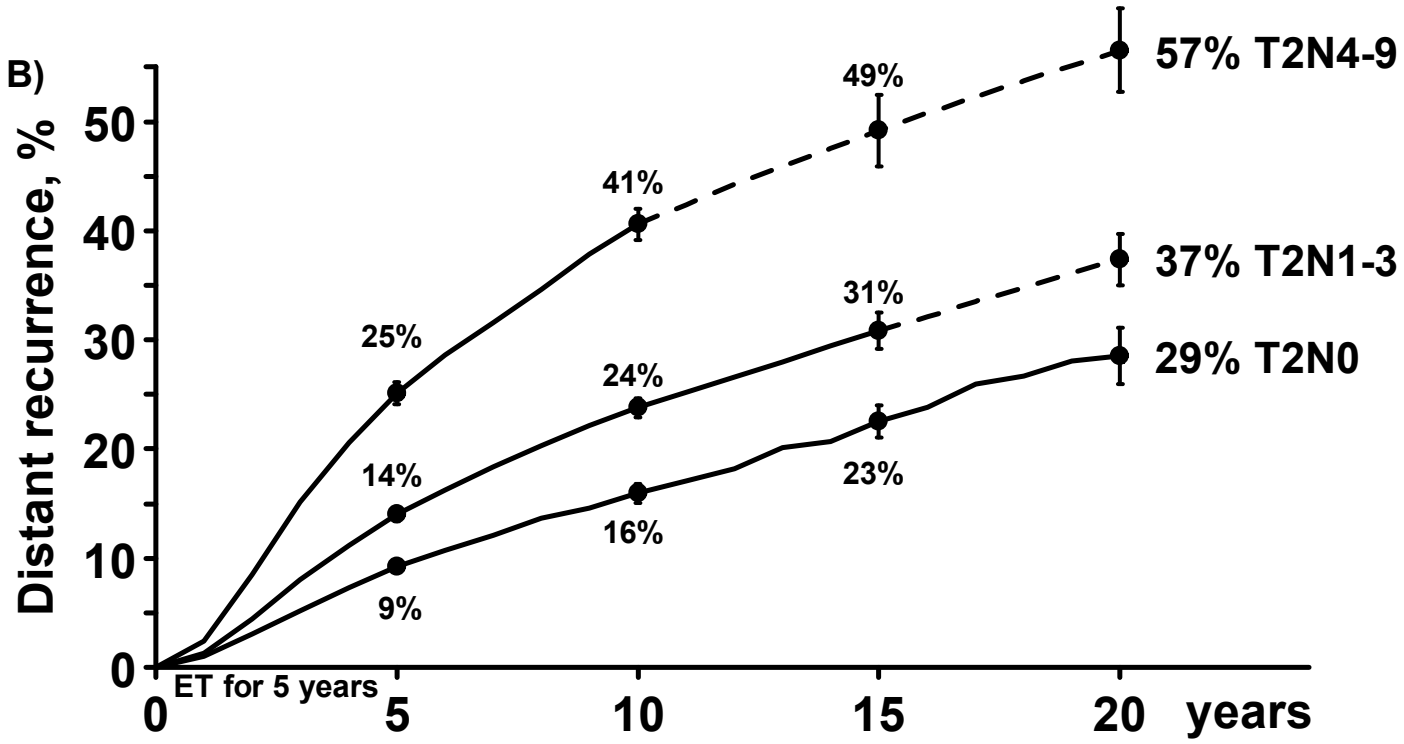
† Much of this trastuzumab was not randomly allocated and many trials of trastuzumab vs not are absent, so trastuzumab effects cannot be assessed reliably from comparisons in this study.

Figure S1: **Association of pathological nodal status (N0, N1-3 or N4-9) with risk from diagnosis to year 20 of distant recurrence for: A) T1 tumors, and B) T2 tumors.** 74,194 women with T1/T2 N0-9 ER+ disease entered at year 0 and scheduled 5 years of ET. Bars are 95% CIs. Dashed lines indicate that event rate is that for whole 5-year period.



No. at risk (and, in each 5-year period, no. of events and annual rate)

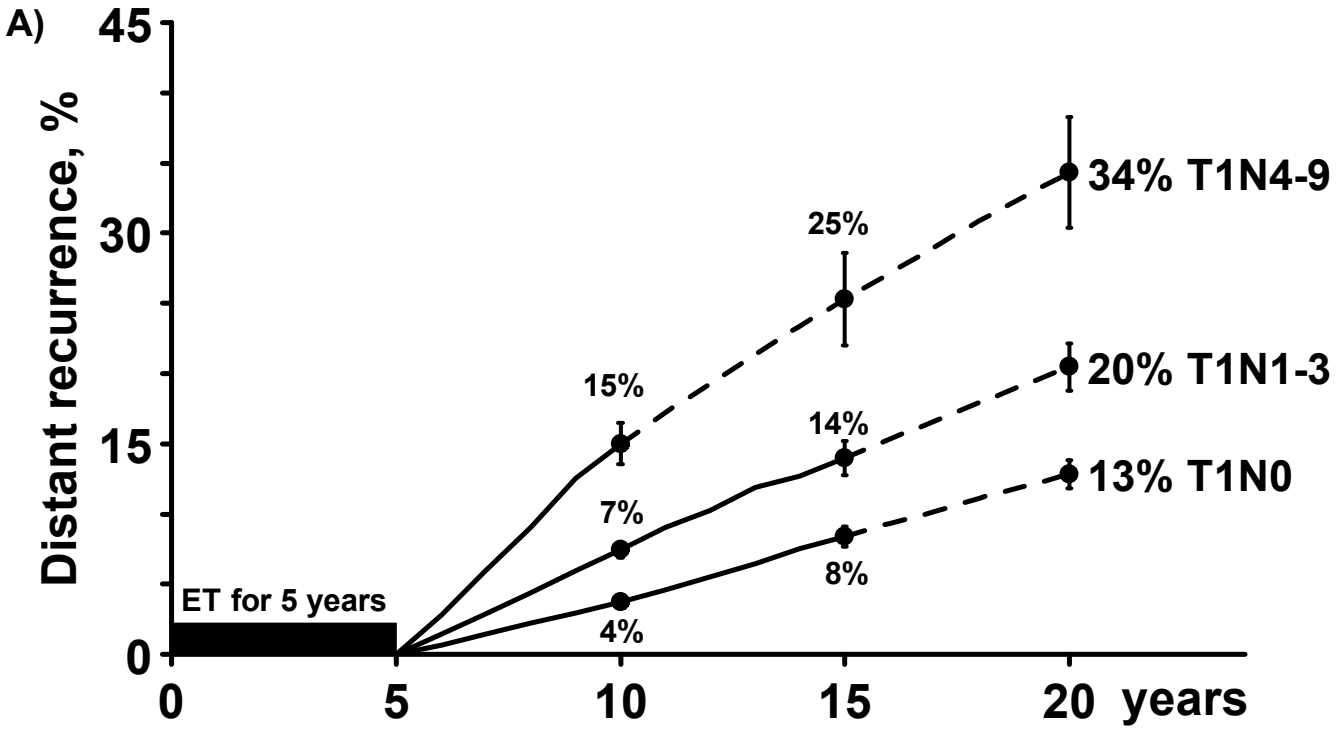
T1N4-9	5033	(818, 3.7%)	3517	(340, 3.2%)	956	(47, 2.6%)	115	(7, 2.9%)	18
T1N1-3	17171	(1203, 1.5%)	13305	(652, 1.5%)	4282	(130, 1.6%)	552	(20, 1.5%)	102
T1N0	19682	(744, 0.8%)	16107	(425, 0.8%)	5701	(153, 1.1%)	1323	(39, 1.3%)	263



No. at risk (and, in each 5-year period, no. of events and annual rate)

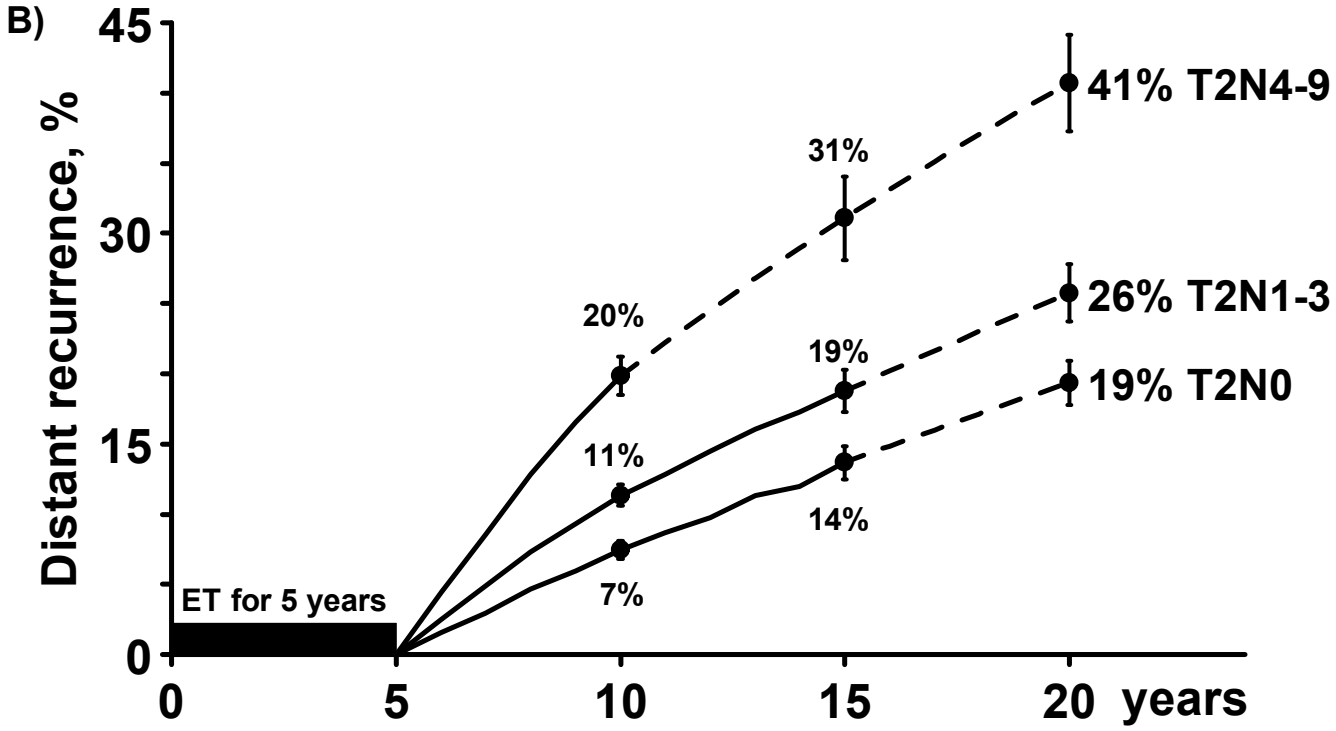
T2N4-9	7300	(1750, 5.7%)	4599	(629, 4.6%)	1209	(74, 3.5%)	144	(6, 1.7%)	34
T2N1-3	14765	(1923, 3.0%)	10271	(769, 2.5%)	2968	(111, 1.9%)	397	(19, 2.1%)	81
T2N0	10243	(902, 1.9%)	7974	(410, 1.6%)	2870	(119, 1.6%)	659	(29, 1.7%)	151

Figure S2: **Association of pathological nodal status with risk in years 5-20 of distant recurrence for: A) T1 tumors, and B) T2 tumors.** 62,923 women with ER+ disease scheduled 5 years of ET and event-free and being followed at year 5. Bars are 95% CIs. Dashed lines indicate that event rate is that for whole 5-year period. ET: endocrine therapy; T1 or T2: diameter 1-20 or 21-50 mm; N: no. involved nodes.



No. at risk (and, in each 5-year period, no. of events and annual rate)

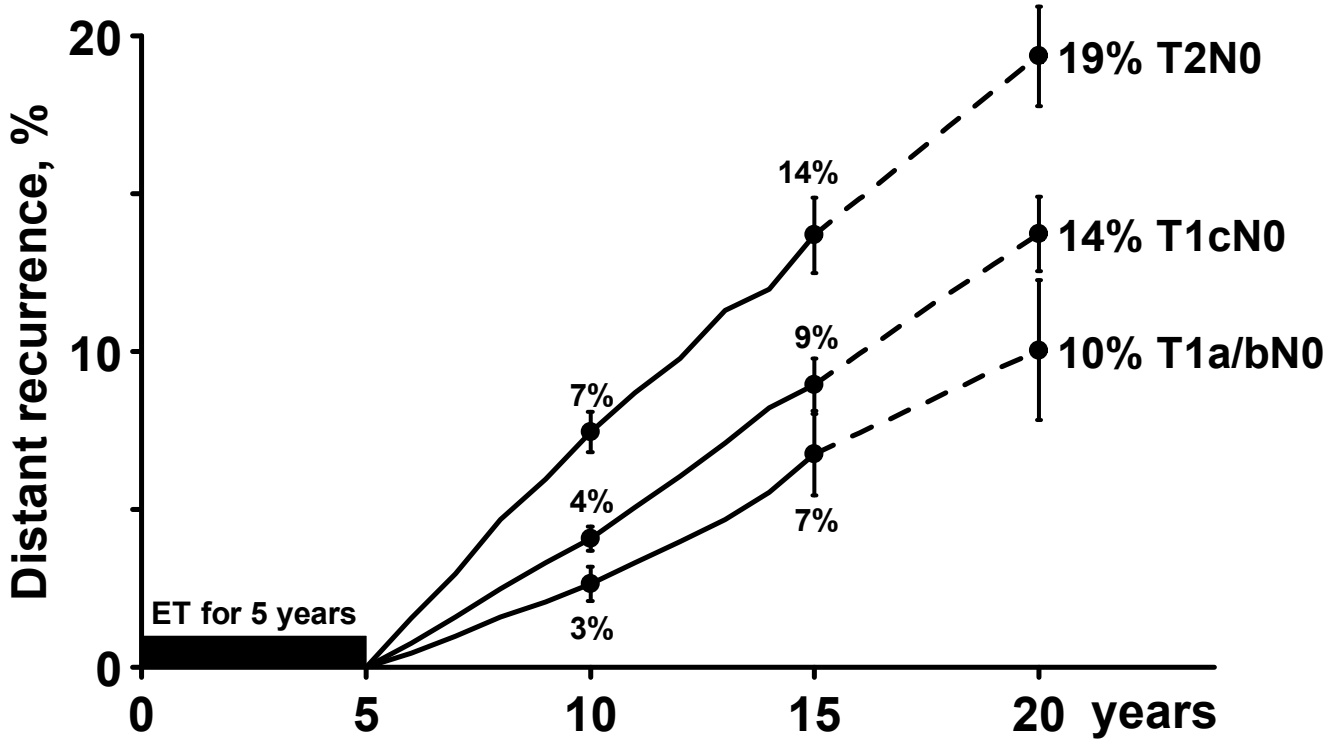
T1N4-9	3832	(391, 3.2%)	1193	(68, 2.6%)	214	(11, 2.2%)	32
T1N1-3	14342	(734, 1.5%)	5138	(162, 1.5%)	817	(35, 1.7%)	154
T1N0	19402	(509, 0.8%)	8020	(218, 1.0%)	2345	(58, 1.0%)	440



No. at risk (and, in each 5-year period, no. of events and annual rate)

T2N4-9	4952	(688, 4.5%)	1517	(106, 3.3%)	285	(12, 1.7%)	51
T2N1-3	10950	(842, 2.4%)	3551	(134, 1.8%)	614	(28, 1.9%)	114
T2N0	9445	(512, 1.6%)	3901	(152, 1.4%)	1129	(37, 1.3%)	218

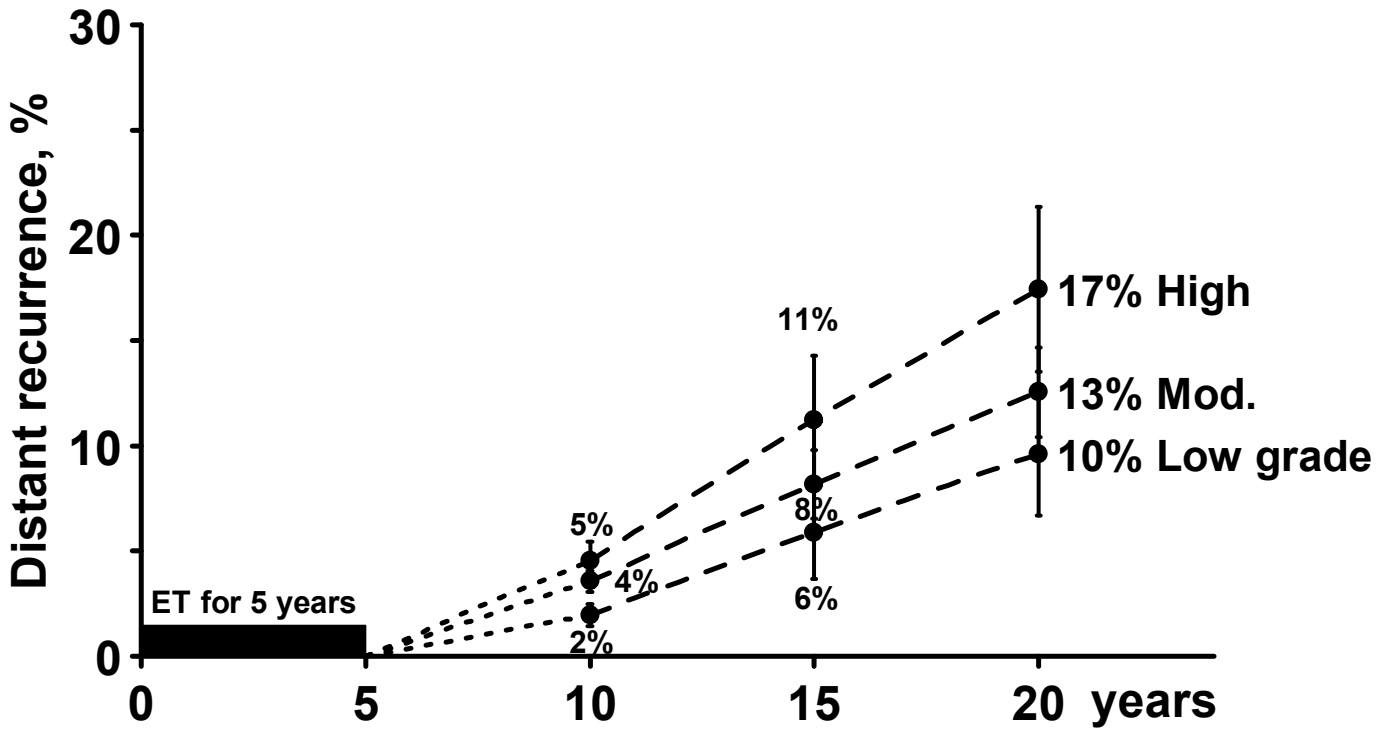
Figure S3: **Association of tumor diameter (T1a/b, T1c, and T2) in N0 disease with risk in years 5-20 of distant recurrence.** 28,847 women with N0 ER+ disease scheduled 5 years of ET and event-free and being followed at year 5. Bars are 95% CIs. Dashed lines indicate that event rate is that for whole 5-year period. ET: endocrine therapy; T1a/b, T1c, or T2: tumor diameter 1-10, 11-20, or 21-50 mm; N0: node-negative.



No. at risk (and, in each 5-year period, no. of events and annual rate)

T2N0	9445	(512, 1.6%)	3901	(152, 1.4%)	1129	(37, 1.3%)	218
T1cN0	13875	(413, 0.8%)	5967	(171, 1.1%)	1641	(46, 1.2%)	309
T1a/bN0	5527	(96, 0.5%)	2053	(47, 0.8%)	704	(12, 0.7%)	131

Figure S4: **Association of tumor grade in T1N0 disease with risk in years 5-20 of distant recurrence.** 13,941 women with grade known and T1N0 ER+ disease scheduled 5 years of ET and event-free and followed at year 5. Bars are 95% CIs. Dashed lines indicate that event rate is that for whole 5-year period. ET: endocrine therapy



No. at risk (and, in each 5-year period, no. of events and annual rate)

High	3054	(92, 0.9%)	1010	(32, 1.3%)	188	(6, 2.6%)	2
Mod.	7363	(186, 0.7%)	2761	(60, 1.0%)	474	(6, 1.1%)	6
Low grade	3524	(49, 0.4%)	1258	(23, 0.8%)	239	(2, 0.6%)	6

Figure S5: **Independent associations of various factors with rate ratio of distant recurrence (RR) during the 5 years of endocrine therapy and after it.** 74,194 women entered at year 0 (plus some later); total 62,923 event-free and followed at year 5. Bars (and text) give 95% group-specific CIs. All RRs are stratified by treatment group. TN analyses have RR=1 for T2N0; others adjust for TN status, scaling RRs so that mean RR=1.

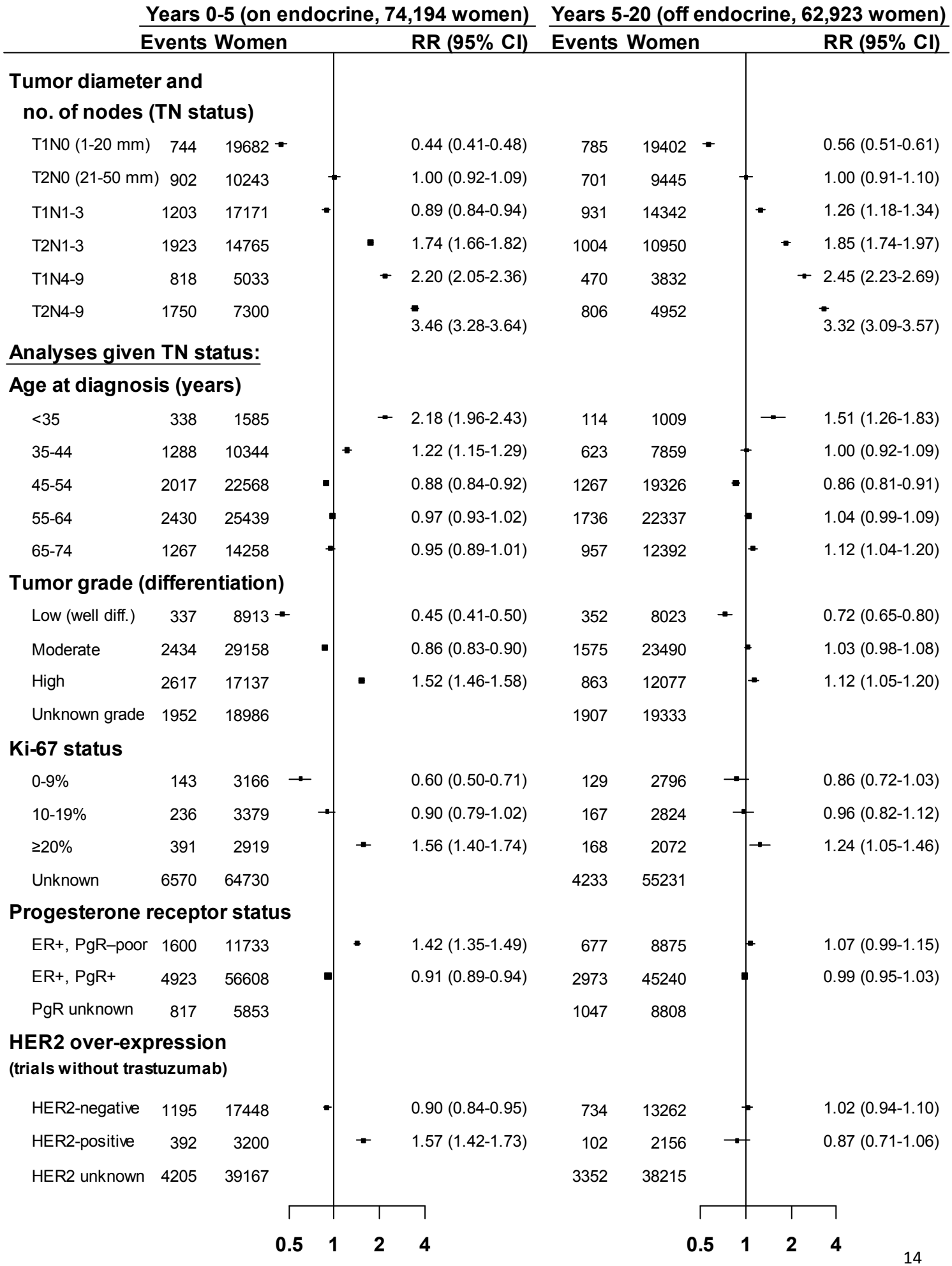
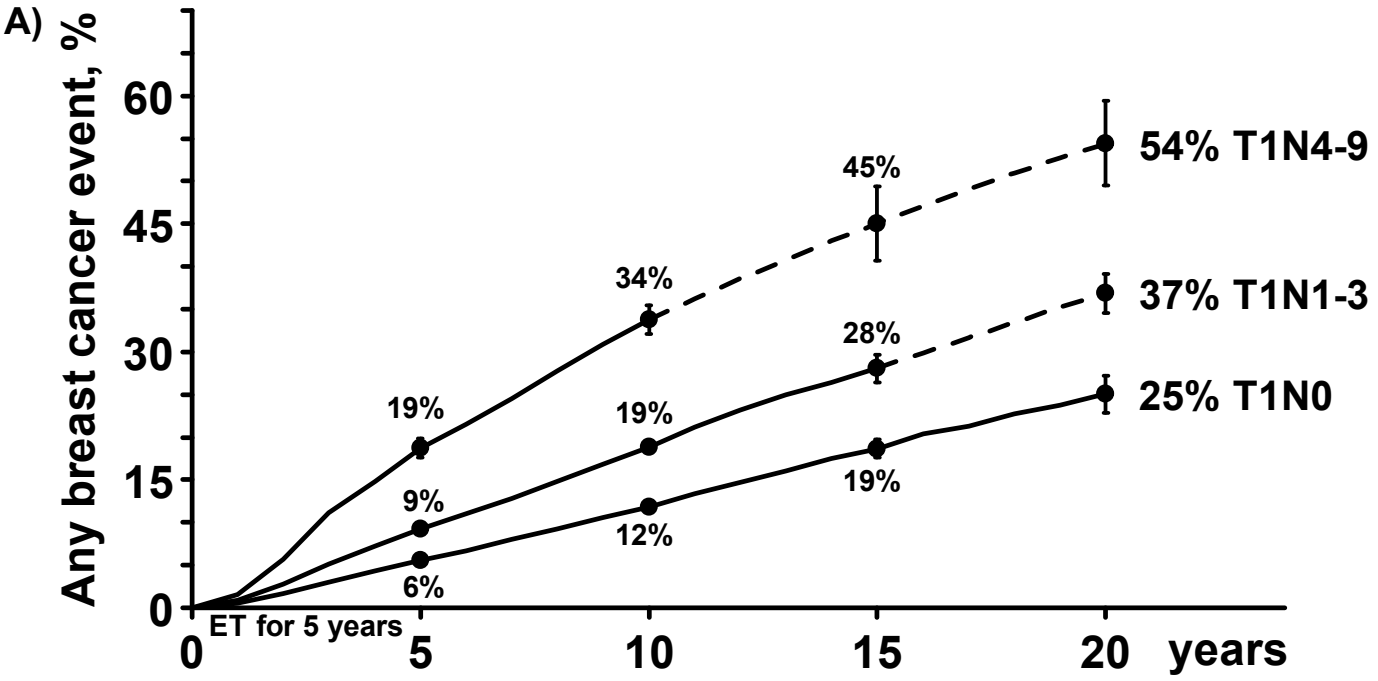
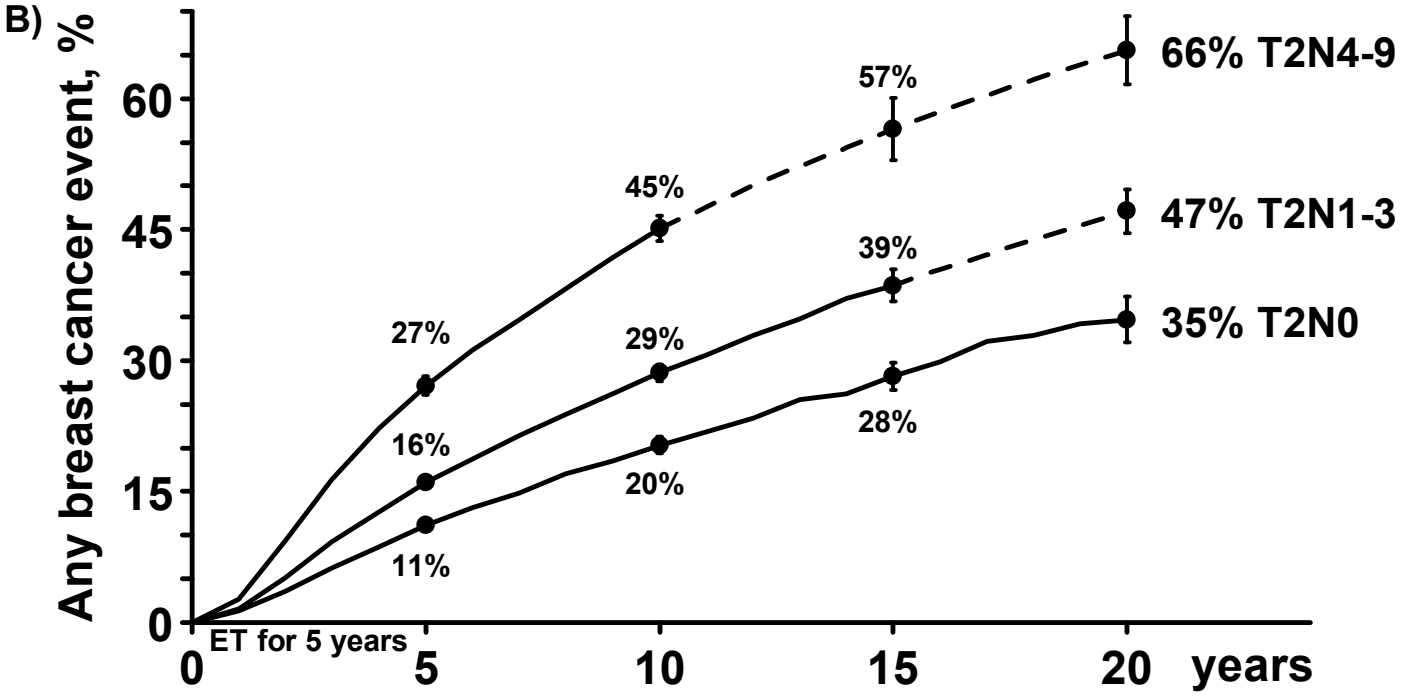


Figure S6: **Association of pathological nodal status (N0, N1-3 or N4-9) with risk from diagnosis to year 20 of any breast cancer event (distant or local recurrence or contralateral onset) for: A) T1 tumors, and B) T2 tumors.** 74,194 women with T1/T2 N0-9 ER+ disease entered at year 0 and scheduled 5 years of ET. Bars are 95% CIs. Dashed lines indicate that event rate is that for whole 5-year period.



No. at risk (and, in each 5-year period, no. of events and annual rate)

T1N4-9	5033	(898, 4.1%)	3461	(409, 4.0%)	905	(62, 3.7%)	111	(8, 3.4%)	18
T1N1-3	17171	(1502, 1.9%)	13070	(904, 2.2%)	4087	(195, 2.6%)	497	(29, 2.5%)	88
T1N0	19682	(1038, 1.1%)	15883	(708, 1.4%)	5519	(222, 1.6%)	1253	(49, 1.7%)	246

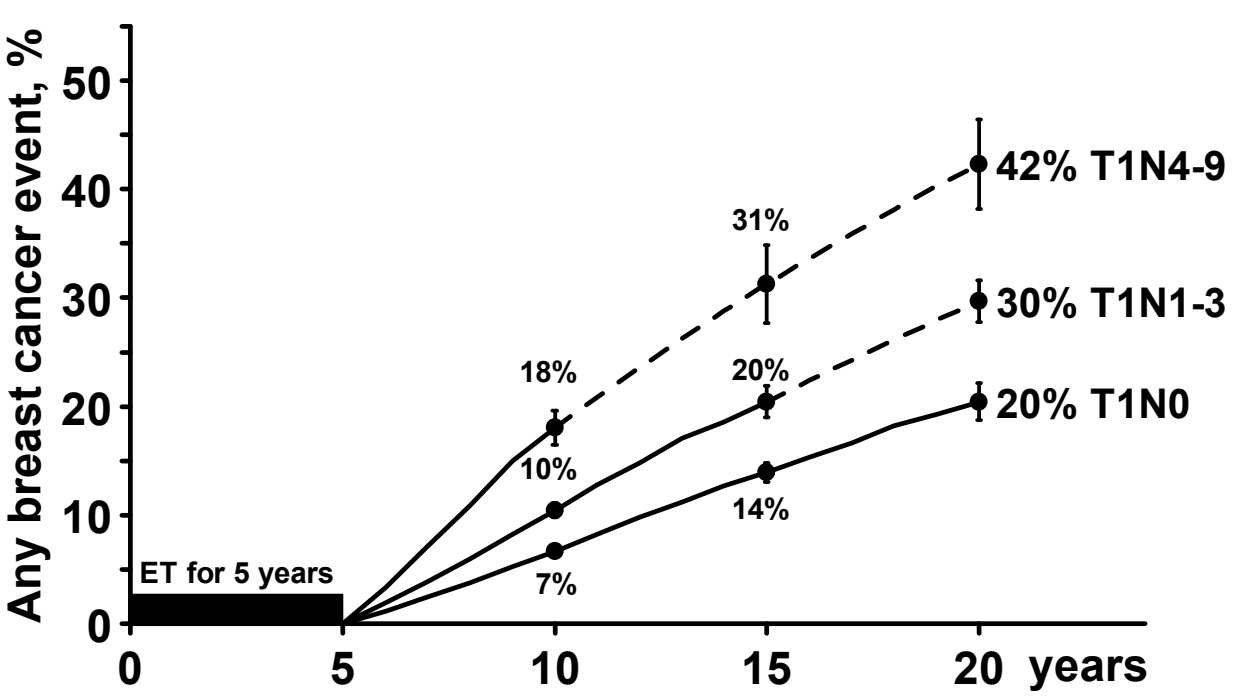


No. at risk (and, in each 5-year period, no. of events and annual rate)

T2N4-9	7300	(1894, 6.2%)	4491	(732, 5.6%)	1122	(95, 4.9%)	127	(12, 4.0%)	26
T2N1-3	14765	(2206, 3.4%)	10068	(979, 3.3%)	2829	(164, 3.1%)	364	(20, 2.4%)	77
T2N0	10243	(1092, 2.3%)	7817	(554, 2.2%)	2768	(149, 2.1%)	629	(34, 2.1%)	147

Figure S7: **Association of pathological nodal status with risk in years 5-20 of any breast cancer event for: A) T1 tumors, and B) T2 tumors.** 62,923 women with ER+ disease scheduled 5 years of ET and event-free and being followed at year 5. Bars are 95% CIs. Dashed lines indicate that event rate is that for whole 5-year period. ET: endocrine therapy; T1 or T2: diameter 1-20 or 21-50 mm; N: no. involved nodes.

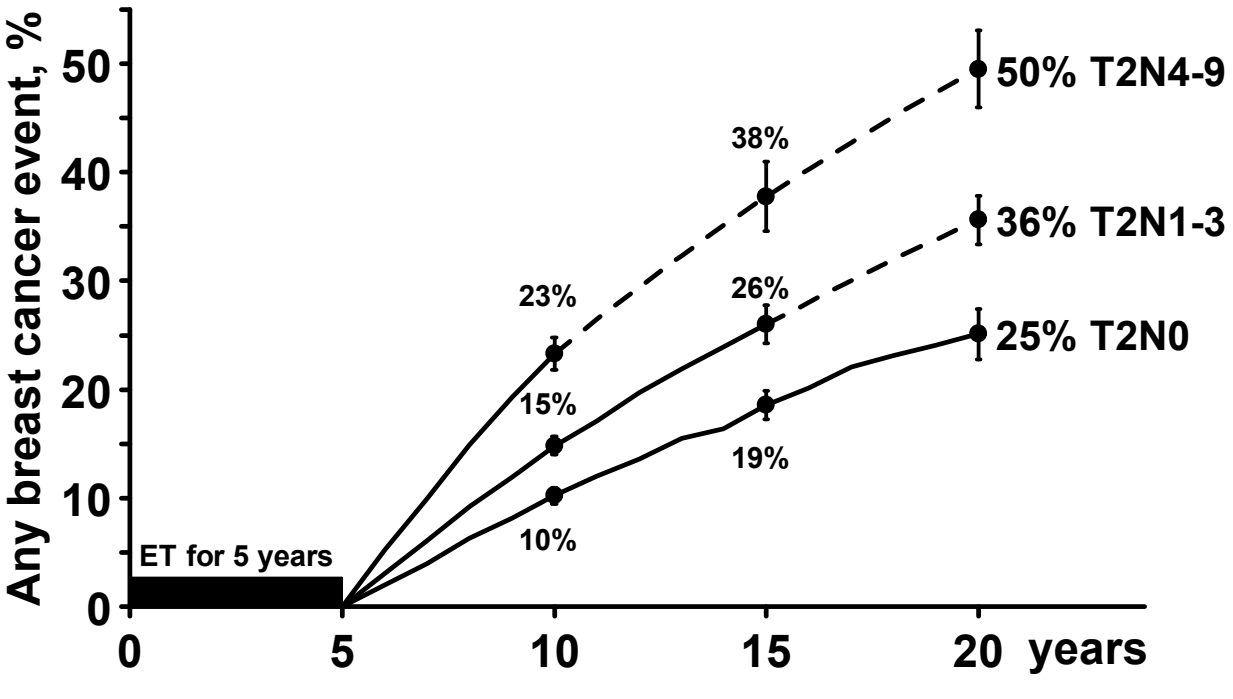
A)



No. at risk (and, in each 5-year period, no. of events and annual rate)

T1N4-9	3832	(470, 3.9%)	1158	(86, 3.4%)	208	(18, 3.8%)	30
T1N1-3	14342	(1023, 2.2%)	4995	(247, 2.4%)	761	(49, 2.6%)	137
T1N0	19402	(910, 1.4%)	7834	(350, 1.6%)	2228	(84, 1.6%)	413

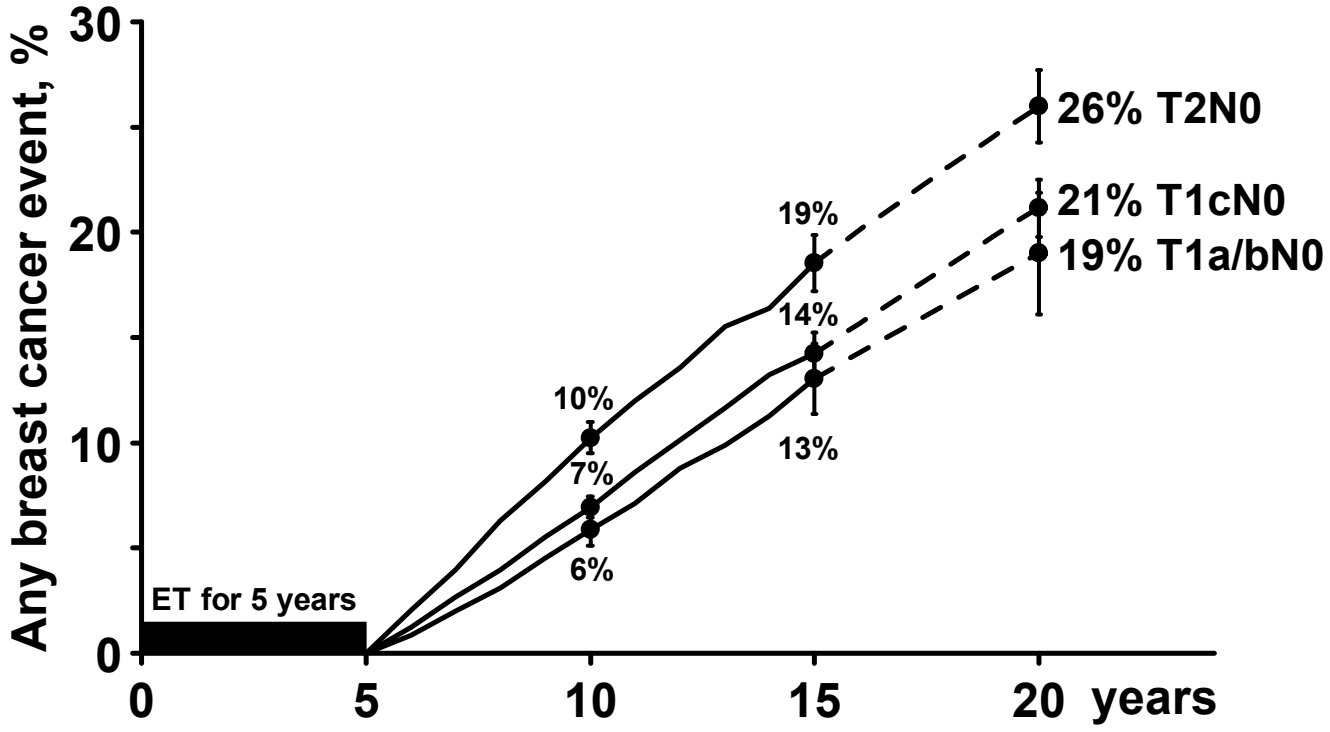
B)



No. at risk (and, in each 5-year period, no. of events and annual rate)

T2N4-9	4952	(804, 5.3%)	1459	(134, 4.4%)	266	(21, 3.4%)	44
T2N1-3	10950	(1089, 3.2%)	3438	(204, 2.8%)	566	(32, 2.4%)	107
T2N0	9445	(700, 2.2%)	3816	(208, 1.9%)	1079	(49, 1.8%)	208

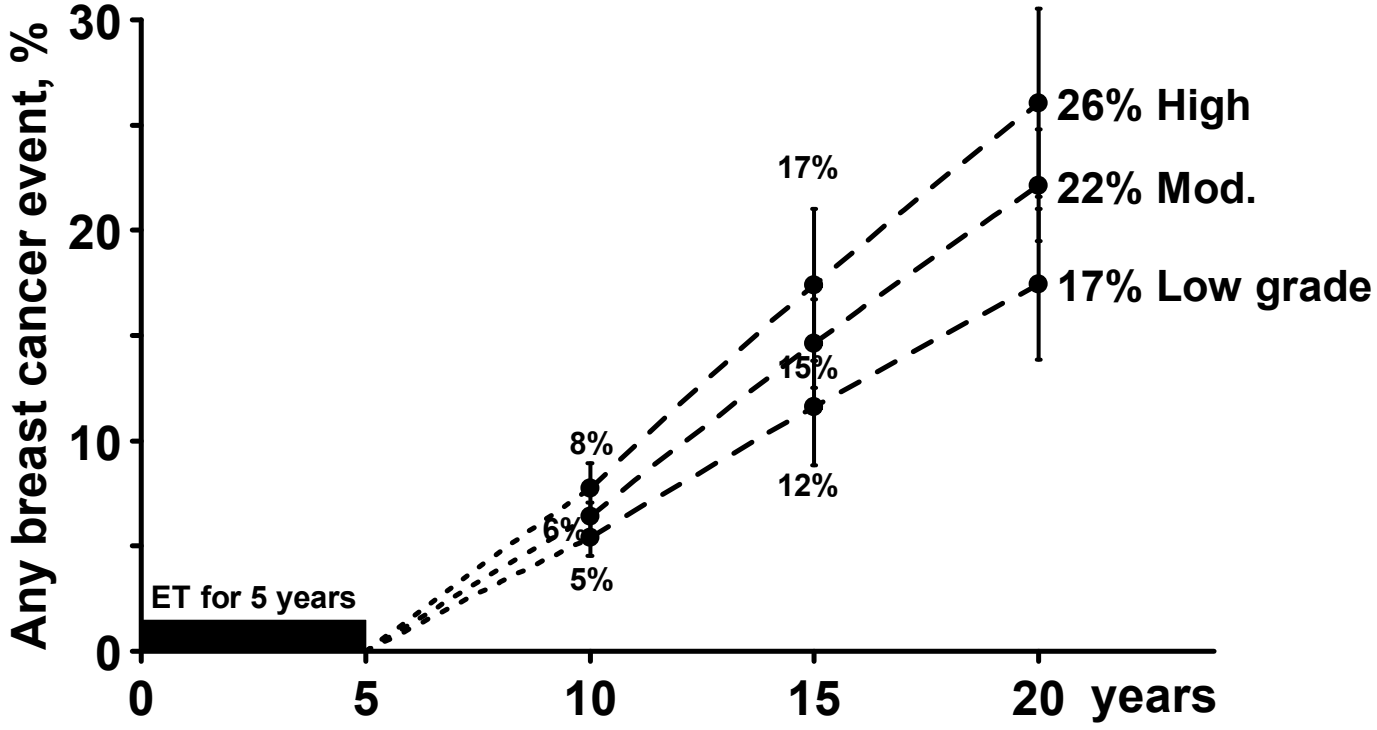
Figure S8: **Association of tumor diameter (T1a/b, T1c, and T2) in N0 disease with risk in years 5-20 of any breast cancer event.** 28,847 women with N0 ER+ disease scheduled 5 years of ET and event-free and being followed at year 5. Bars are 95% CIs. Dashed lines indicate that event rate is that for whole 5-year period. ET: endocrine therapy; T1a/b, T1c, or T2: tumor diameter 1-10, 11-20, or 21-50 mm; N0: node-negative.



No. at risk (and, in each 5-year period, no. of events and annual rate)

T2N0	9445	(700, 2.2%)	3816	(208, 1.9%)	1079	(49, 1.8%)	208
T1cN0	13875	(700, 1.4%)	5832	(264, 1.7%)	1569	(62, 1.7%)	294
T1a/bN0	5527	(210, 1.2%)	2002	(86, 1.5%)	659	(22, 1.4%)	119

Figure S9: **Association of tumor grade in T1N0 disease with risk in years 5-20 of any breast cancer event.** 13,941 women with grade known and T1N0 ER+ disease scheduled 5 years of ET and event-free and being followed at year 5. Bars are 95% CIs. Dashed lines indicate that event rate is that for whole 5-year period. ET: endocrine therapy



No. at risk (and, in each 5-year period, no. of events and annual rate)

High	3054	(158, 1.6%)	987	(49, 2.1%)	174	(6, 3.0%)	0
Mod.	7363	(337, 1.3%)	2693	(108, 1.8%)	449	(11, 2.1%)	6
Low grade	3524	(136, 1.1%)	1224	(36, 1.4%)	227	(4, 1.4%)	6

Figure S10: **Independent associations of various factors with rate ratio of any breast cancer event (RR) during the 5 years of endocrine therapy and after it.** 74,194 women entered at year 0 (plus some later); total 62,923 event-free and followed at year 5. Bars (and text) give 95% group-specific CIs. All RRs are stratified by treatment group. TN analyses have RR=1 for T2N0; others adjust for TN status, scaling RRs so that mean RR=1.

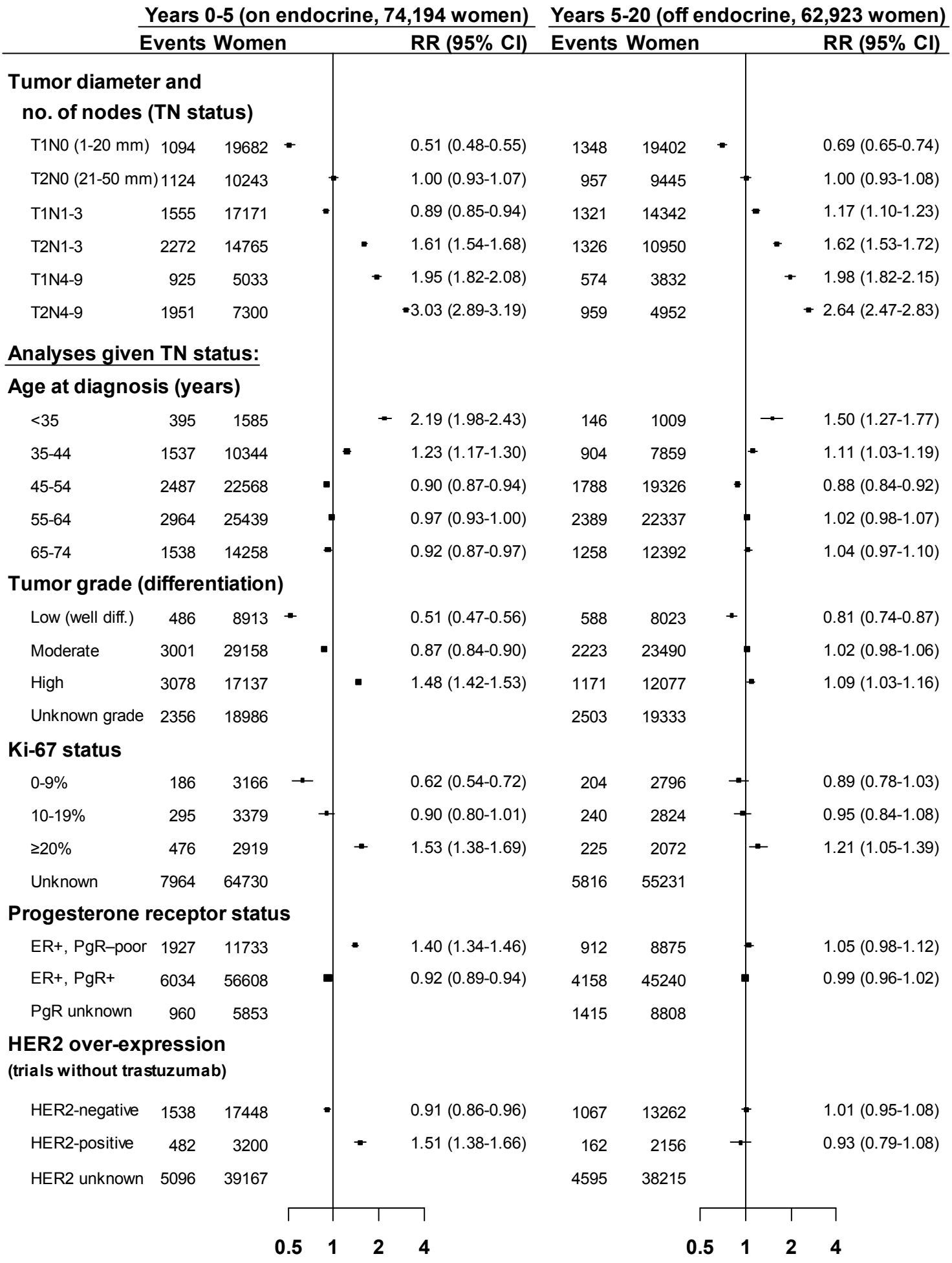
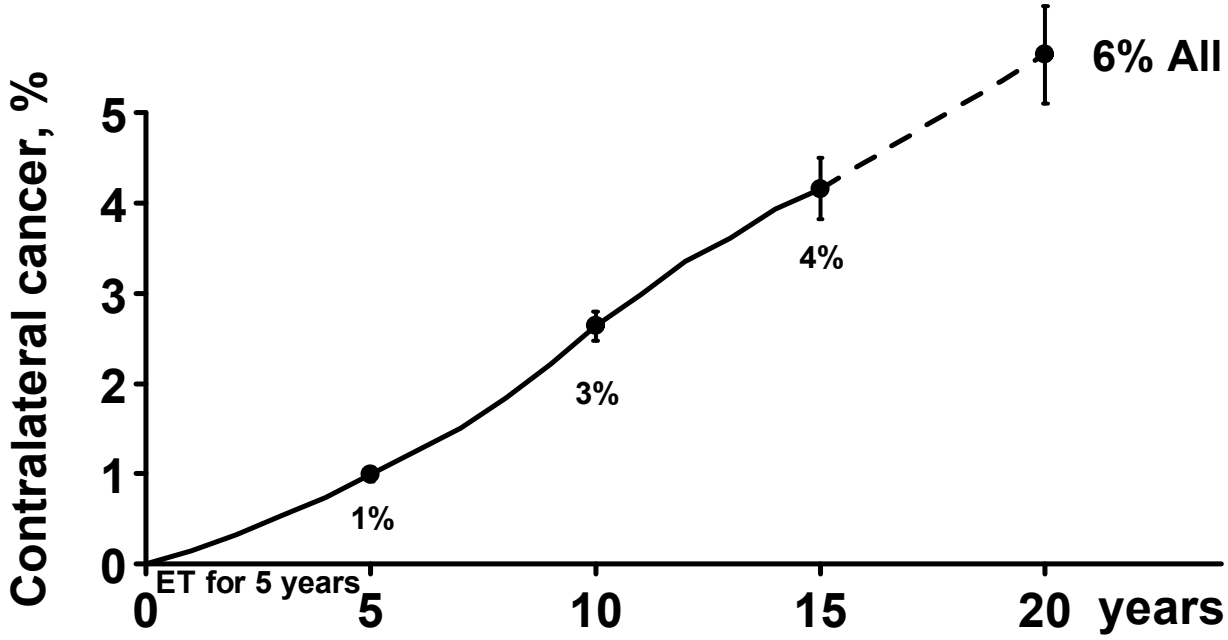


Figure S11: **Risk from diagnosis to year 20 of contralateral breast cancer.**

74,194 women with T1/T2 N0-9 ER+ disease entered at year 0 and scheduled 5 years of ET. Bars are 95% CIs. Dashed lines indicate that event rate is that for whole 5-year period.



No. at risk (and, in each 5-year period, no. of events and annual rate)

All	74194	(654, 0.2%)	54499	(536, 0.3%)	17108	(122, 0.3%)	2957	(15, 0.2%) 601

Figure S12: **Independent associations of various factors with rate ratio of contralateral breast cancer (RR) during the 5 years of endocrine therapy and after it.** 74,194 women entered at year 0 (plus some later); total 62,923 event-free and followed at year 5. Bars (and text) give 95% group-specific CIs. All RRs are stratified by treatment group. TN analyses have RR=1 for T2N0; others adjust for TN status, scaling RRs so that mean RR=1.

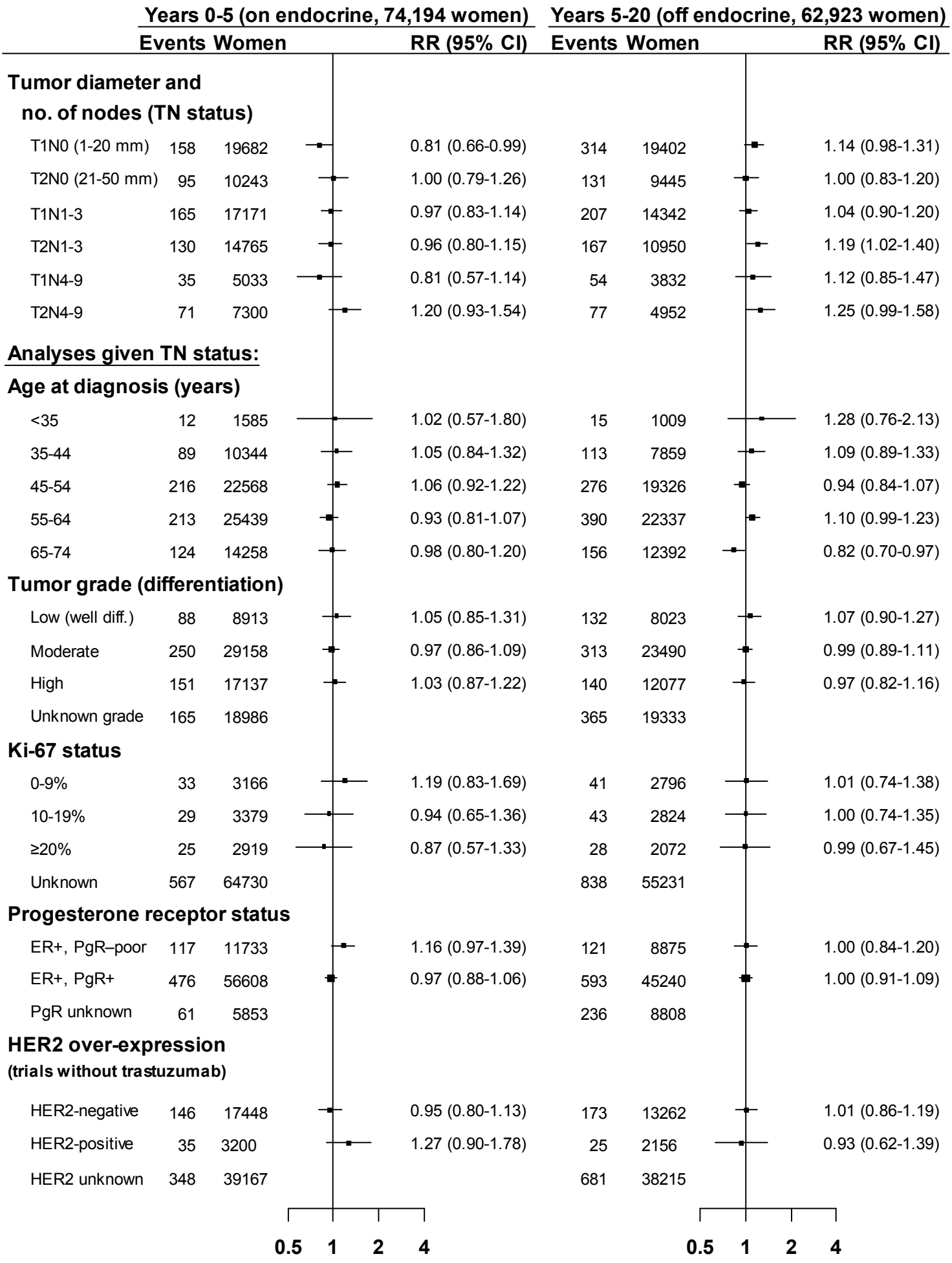
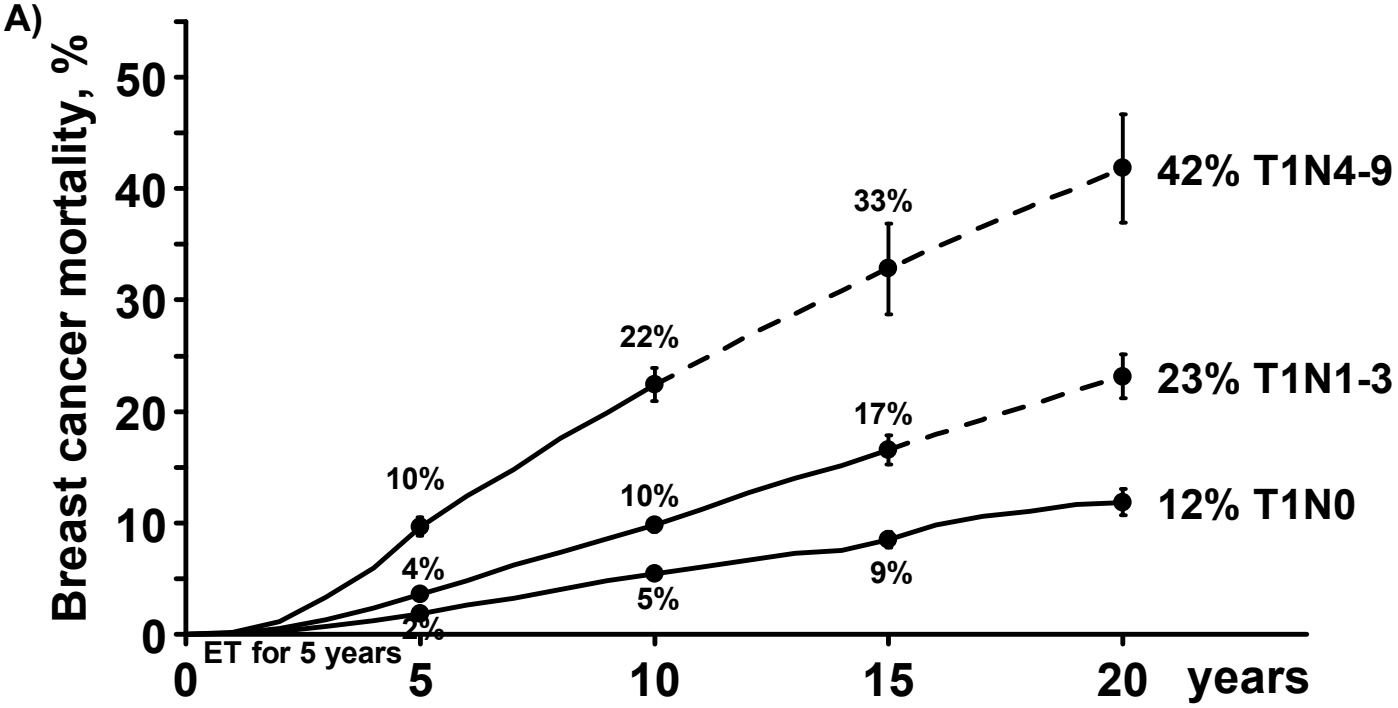
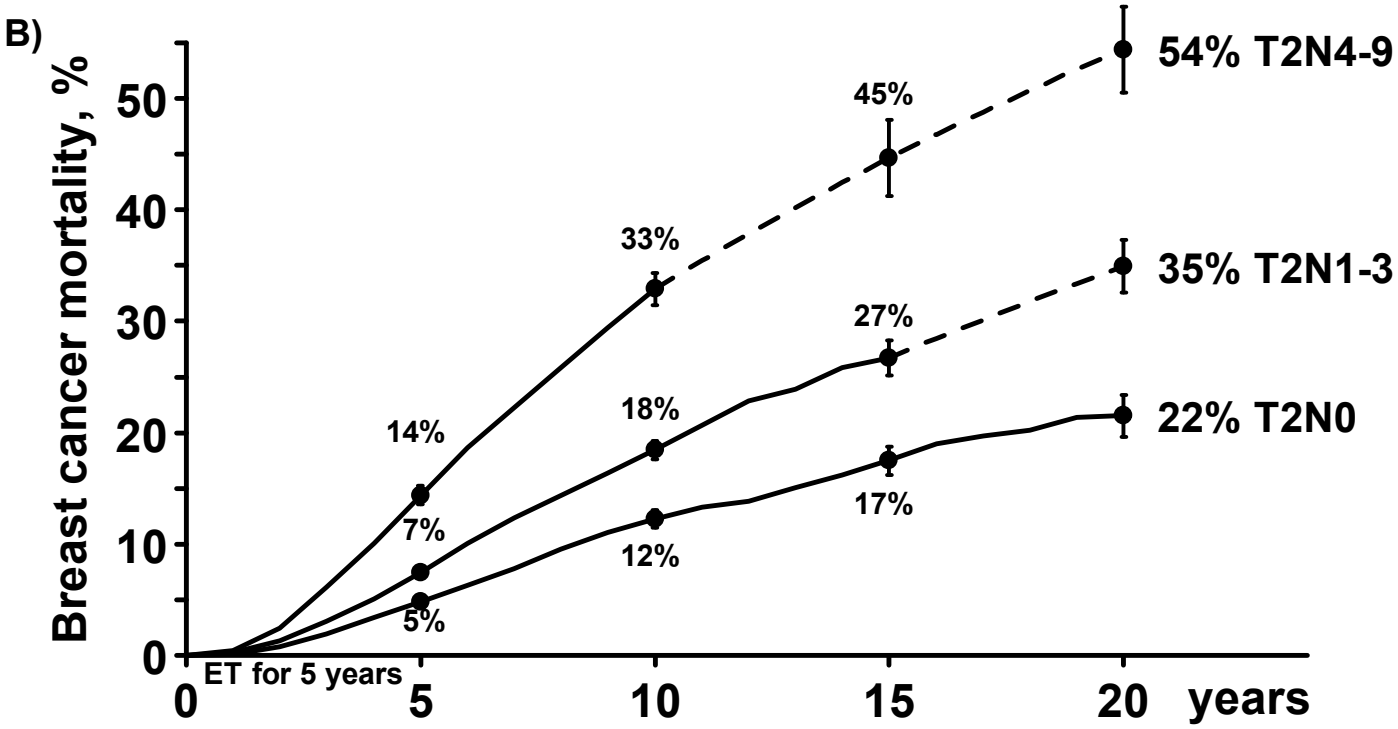


Figure S13: **Association of pathological nodal status (N0, N1-3 or N4-9) with risk from diagnosis to year 20 of breast cancer mortality for: A) T1 tumors, and B) T2 tumors.** 74,194 women with T1/T2 N0-9 ER+ disease entered at year 0 and scheduled 5 years of ET. Bars are 95% CIs. Dashed lines indicate that event rate is that for whole 5-year period. The breast cancer mortality rate in each separate time period is estimated by subtracting the mortality rate in women without recurrence from the rate in all women.



No. at risk (and, in each 5-year period, no. of events and annual rate)

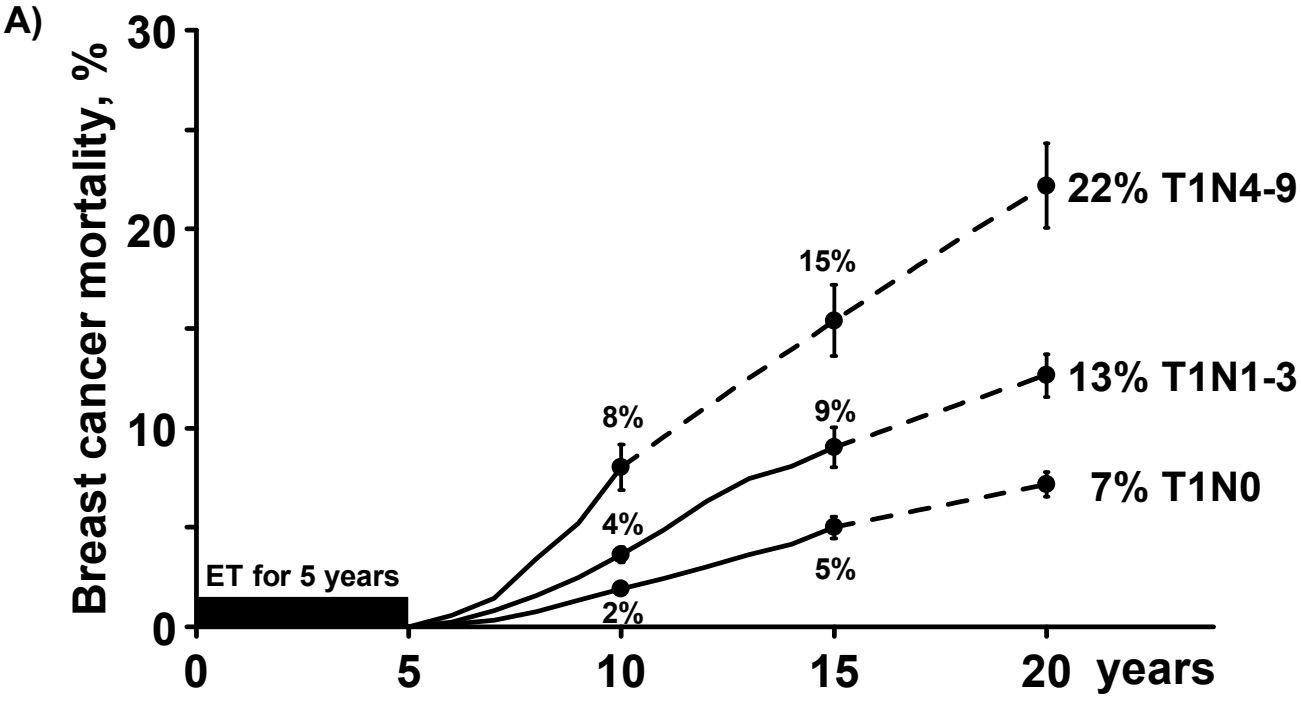
T1N4-9	5033	(460, 2.0%)	3834	(367, 3.0%)	1082	(67, 3.1%)	130	(6, 1.6%)	22
T1N1-3	17171	(576, 0.7%)	13839	(621, 1.3%)	4516	(156, 1.6%)	590	(28, 1.5%)	110
T1N0	19682	(354, 0.4%)	16452	(419, 0.7%)	5890	(120, 0.7%)	1424	(46, 0.9%)	298



No. at risk (and, in each 5-year period, no. of events and annual rate)

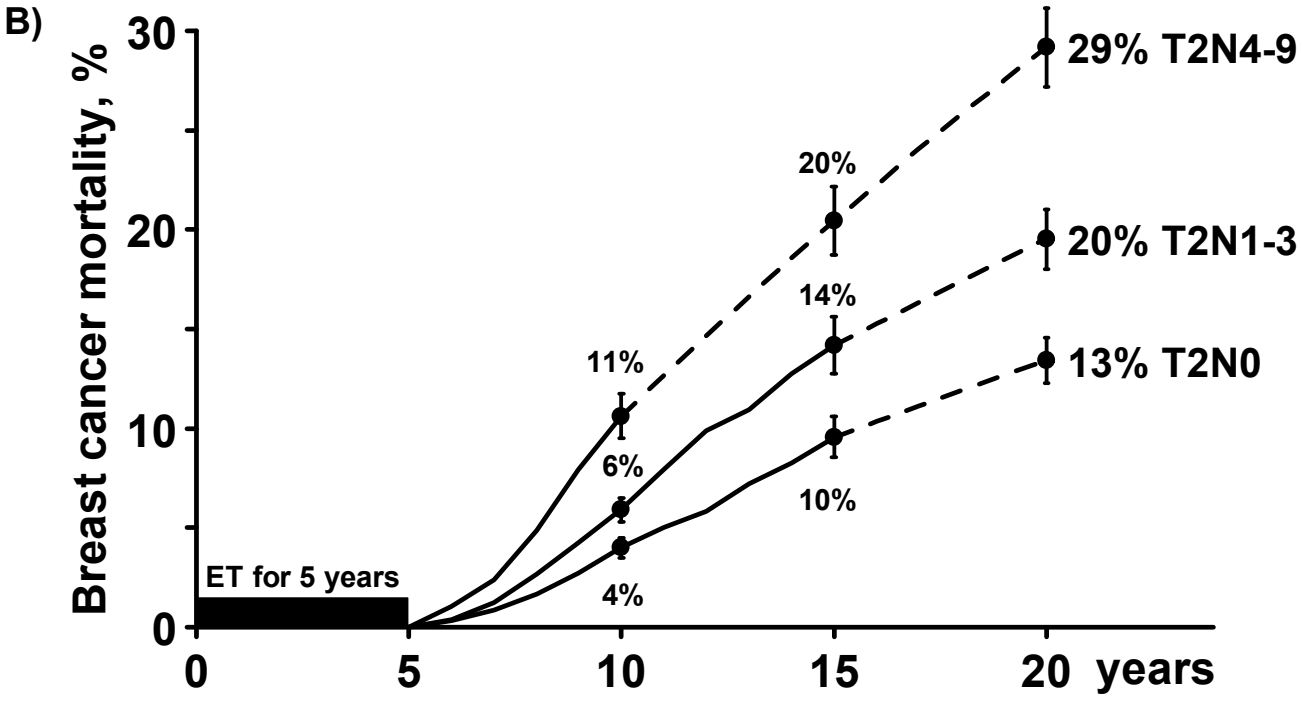
T2N4-9	7300	(1003, 3.0%)	5245	(787, 4.9%)	1399	(118, 4.2%)	164	(14, 2.8%)	35
T2N1-3	14765	(1024, 1.5%)	11027	(885, 2.6%)	3212	(163, 2.4%)	421	(24, 2.3%)	87
T2N0	10243	(472, 1.0%)	8367	(471, 1.6%)	3036	(108, 1.1%)	720	(31, 1.2%)	178

Figure S14: **Association of pathological nodal status with risk in years 5-20 of breast cancer mortality for: A) T1 tumors, and B) T2 tumors.** 62,923 women with ER+ disease scheduled 5 years of ET and event-free and followed at year 5. Bars are 95% CIs. Dashed lines indicate that event rate is that for whole 5-year period. The breast cancer mortality rate in each separate time period is estimated by subtracting the mortality rate in women without recurrence from the rate in all women. ET: endocrine therapy; T1 or T2: diameter 1-20 or 21-50 mm; N: no. involved nodes.



No. at risk (and, in each 5-year period, no. of events and annual rate)

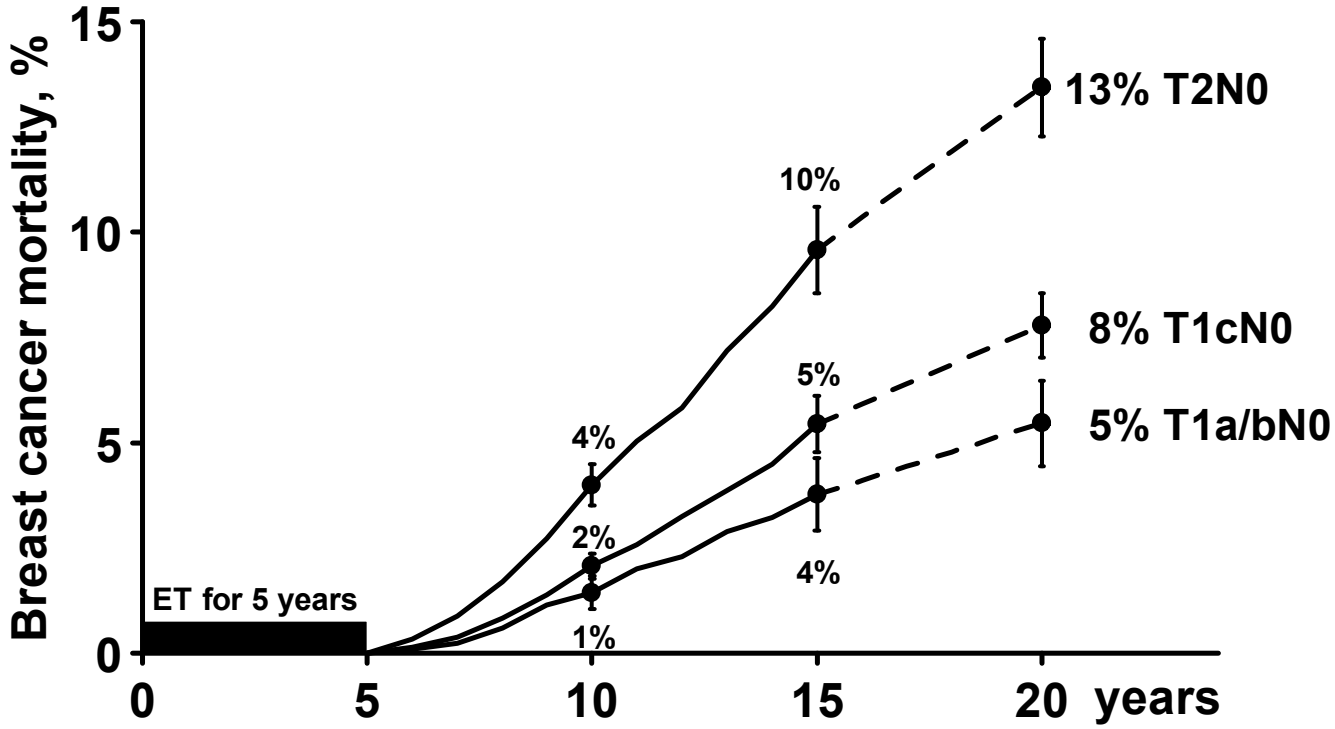
T1N4-9	3832	(189, 1.4%)	1307	(75, 2.5%)	241	(16, 2.3%)	39
T1N1-3	14342	(335, 0.7%)	5342	(155, 1.3%)	872	(40, 1.4%)	165
T1N0	19402	(250, 0.4%)	8184	(165, 0.6%)	2456	(70, 0.8%)	473



No. at risk (and, in each 5-year period, no. of events and annual rate)

T2N4-9	4952	(343, 2.0%)	1695	(147, 3.7%)	308	(15, 1.4%)	55
T2N1-3	10950	(399, 1.1%)	3769	(171, 1.9%)	645	(38, 2.0%)	121
T2N0	9445	(257, 0.7%)	4051	(149, 1.2%)	1189	(41, 1.0%)	243

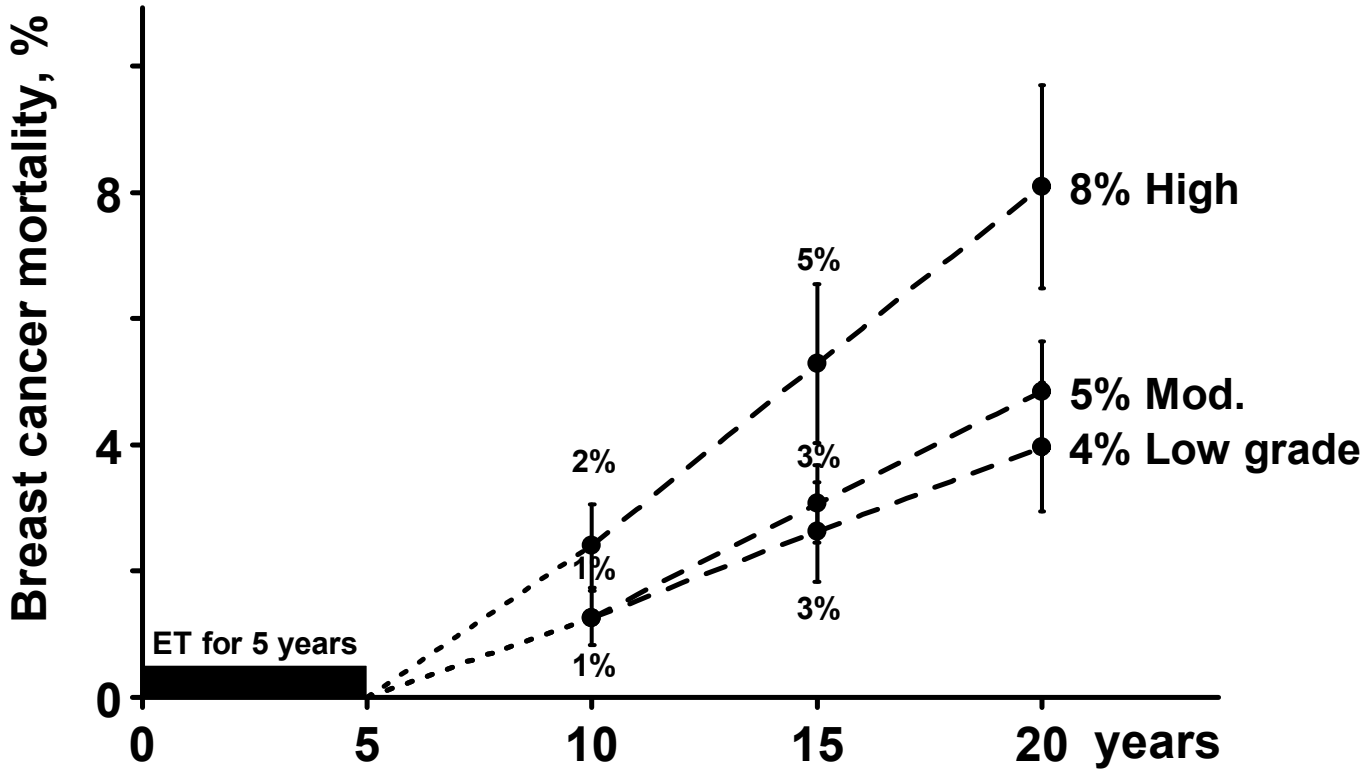
Figure S15: **Association of tumor diameter (T1a/b, T1c, and T2) in N0 disease with risk in years 5-20 of breast cancer mortality.** 28,847 women with N0 ER+ disease scheduled 5 years of ET and event-free and being followed at year 5. Bars are 95% CIs. Dashed lines indicate that event rate is that for whole 5-year period. The breast cancer mortality rate in each separate time period is estimated by subtracting the mortality rate in women without recurrence from the rate in all women. ET: endocrine therapy; T1a/b, T1c, or T2: tumor diameter 1-10, 11-20, or 21-50 mm; N0: node-negative.



No. at risk (and, in each 5-year period, no. of events and annual rate)

T2N0	9445	(257, 0.7%)	4051	(149, 1.2%)	1189	(41, 1.0%)	243
T1cN0	13875	(199, 0.4%)	6102	(129, 0.7%)	1726	(55, 1.0%)	335
T1a/bN0	5527	(51, 0.3%)	2082	(36, 0.5%)	730	(15, 0.5%)	138

Figure S16: **Association of tumor grade in T1N0 disease with risk in years 5-20 of breast cancer mortality.** 13,941 women with known grade in T1N0 ER+ disease scheduled 5 years of ET and event-free and being followed at year 5. Bars are 95% CIs. Dashed lines indicate that event rate is that for whole 5-year period. The breast cancer mortality rate in each separate time period is estimated by subtracting the mortality rate in women without recurrence from the rate in all women. ET: endocrine therapy



No. at risk (and, in each 5-year period, no. of events and annual rate)

High	3054	(50, 0.5%)	1027	(22, 0.8%)	198	(8, 2.8%)	4
Mod.	7363	(69, 0.3%)	2829	(53, 0.7%)	499	(8, 1.2%)	6
Low grade	3524	(33, 0.3%)	1270	(12, 0.3%)	248	(2, 0.3%)	6

Figure S17: **Independent associations of various factors with breast cancer mortality rate ratio (RR) during the 5 years of endocrine therapy and after it.** 74,194 women entered at year 0 (plus some later); total 62,923 event-free and followed at year 5. Bars (and text) give 95% group-specific CIs. All RRs are stratified by treatment group. TN analyses have RR=1 for T2N0; others adjust for TN status, scaling RRs so that mean RR=1. Events = deaths (from any cause) after any recurrence.

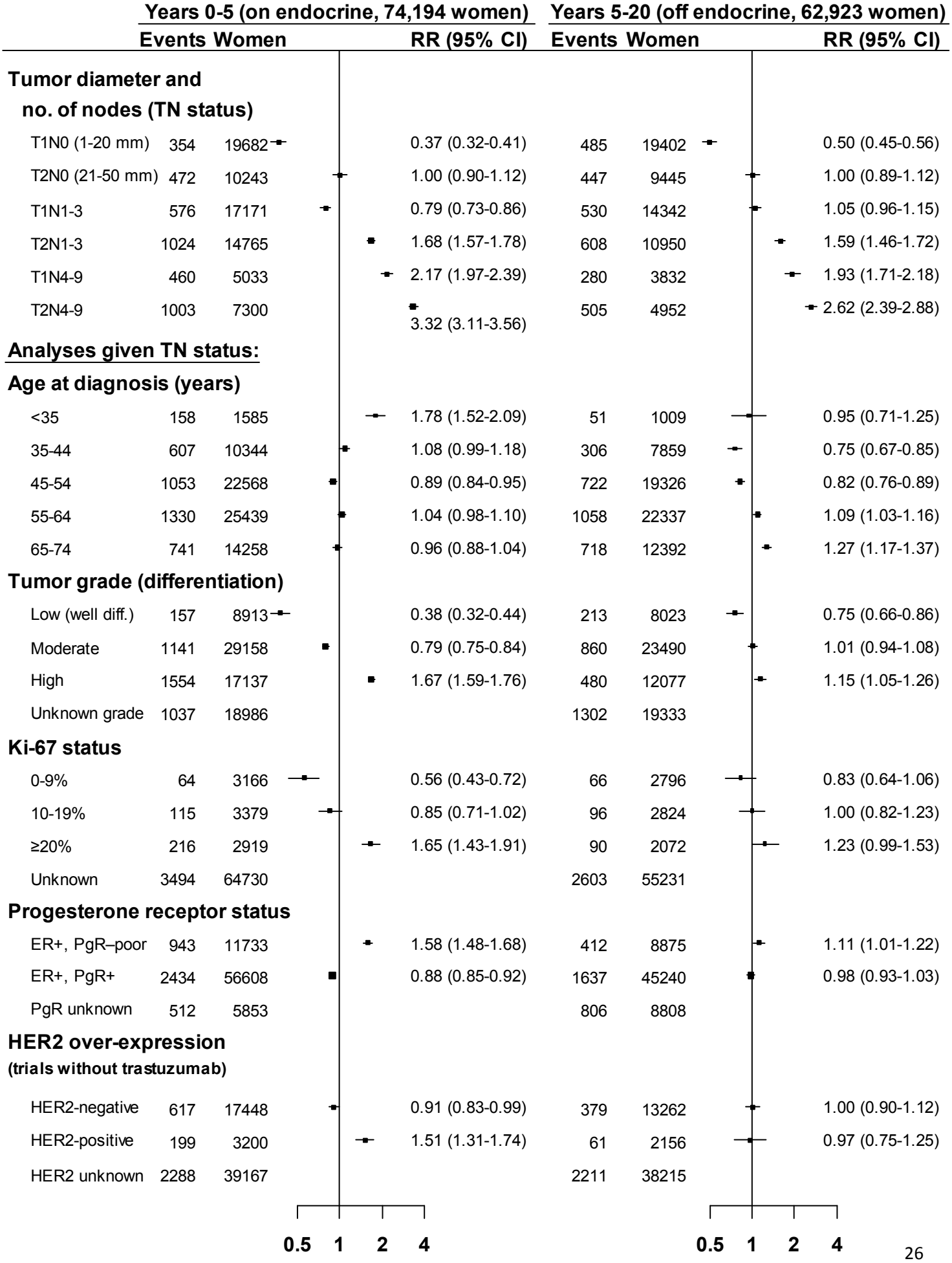
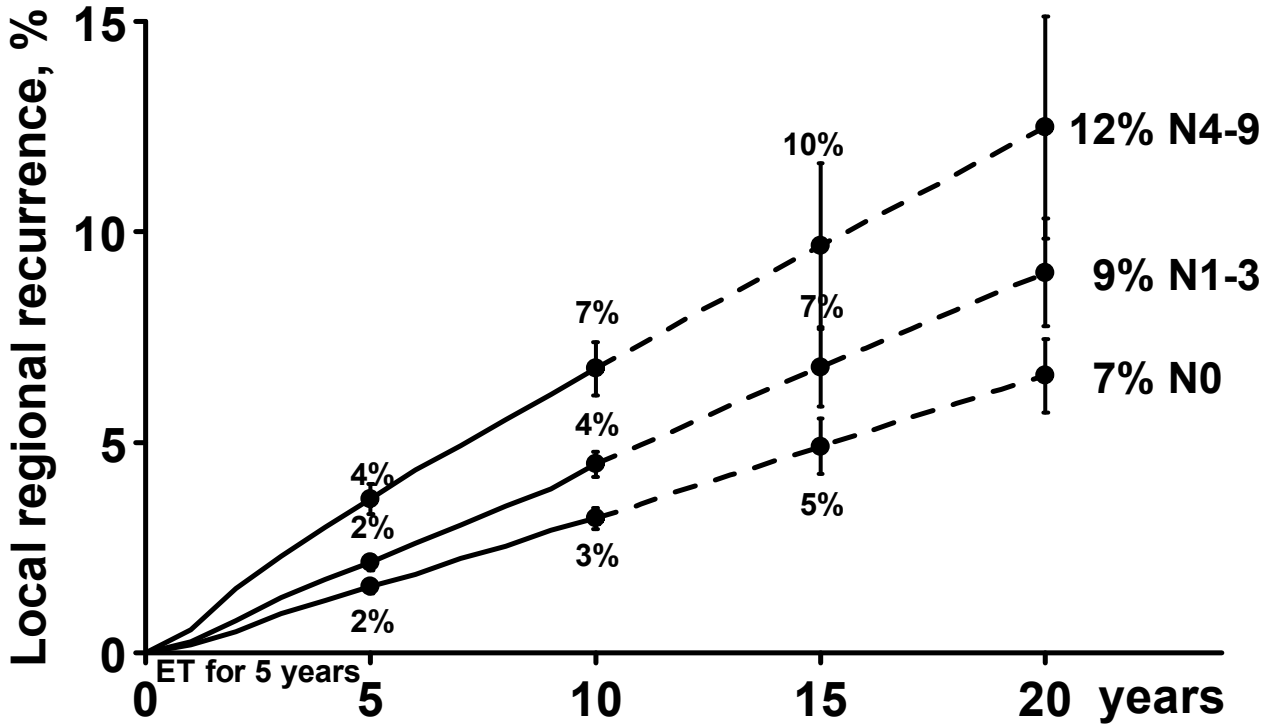


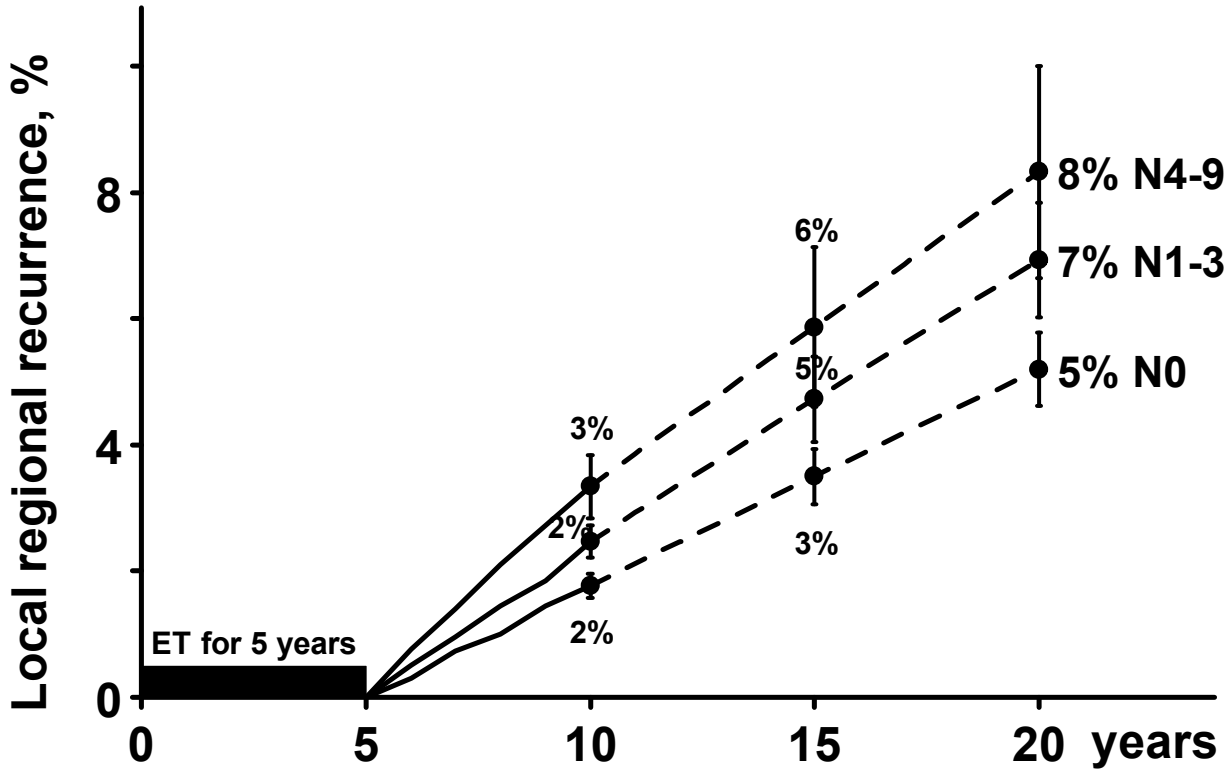
Figure S18: **Association of pathological nodal status (N0, N1-3 or N4-9) with risk from diagnosis to year 20 of loco-regional recurrence.** 74,194 women with T1/T2 N0-9 ER+ disease entered at year 0 and scheduled 5 years of ET. Bars are 95% CIs. Dashed lines indicate that event rate is that for whole 5-year period. ET: endocrine therapy



No. at risk (and, in each 5-year period, no. of events and annual rate)

N4-9	12333	(389, 0.7%)	7868	(152, 0.7%)	2001	(22, 0.6%)	236	(4, 0.7%)	44
N1-3	31936	(610, 0.4%)	23019	(338, 0.5%)	6860	(70, 0.5%)	852	(4, 0.2%)	164
N0	29925	(434, 0.3%)	23562	(256, 0.3%)	8239	(77, 0.4%)	1869	(15, 0.3%)	393

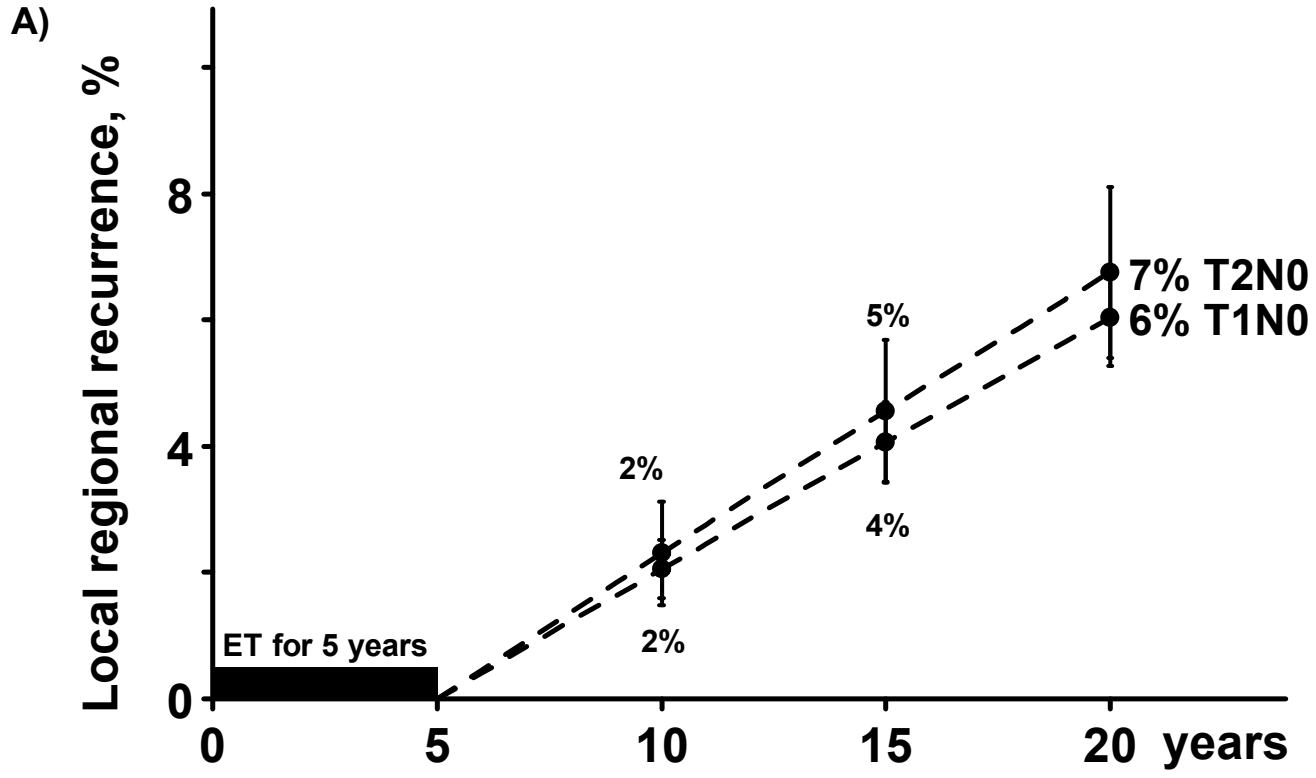
Figure S19: **Association of pathological nodal status with risk in years 5-20 of loco-regional recurrence.** 62,923 women with T1/T2 N0-9 ER+ disease scheduled 5 years of ET and event-free and being followed at year 5. Bars are 95% CIs. Dashed lines indicate that event rate is that for whole 5-year period. ET: endocrine therapy; T1 or T2: diameter 1-20 or 21-50 mm; N: no. involved nodes.



No. at risk (and, in each 5-year period, no. of events and annual rate)

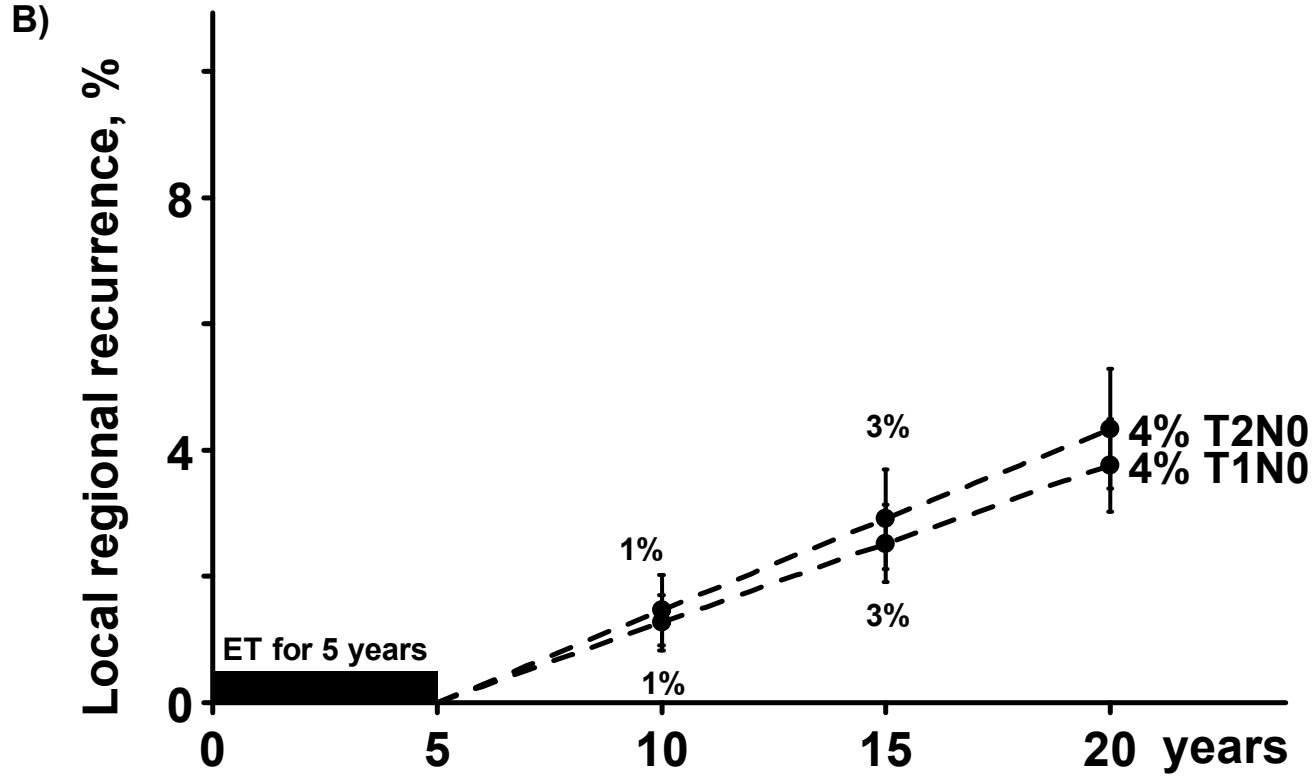
N4-9	8784	(186, 0.7%)	2593	(27, 0.5%)	473	(8, 0.7%)	74
N1-3	25292	(400, 0.5%)	8387	(89, 0.5%)	1313	(6, 0.2%)	241
N0	28847	(354, 0.4%)	11602	(119, 0.4%)	3283	(22, 0.3%)	617

Figure S20: **Association of tumor diameter (T1 or T2) in N0 disease with risk in years 5-20 of loco-regional recurrence for A) Breast-conserving surgery (BCS) and B) mastectomy.** 27,707 women with T1/T2 N0 ER+ disease scheduled 5 years of ET and event-free and being followed at year 5. Bars are 95% CIs. Dashed lines indicate that event rate is that for whole 5-year period. ET: endocrine therapy; T1 or T2: diameter 1-20 or 21-50 mm; N: no. involved nodes.



No. at risk (and, in each 5-year period, no. of events and annual rate)

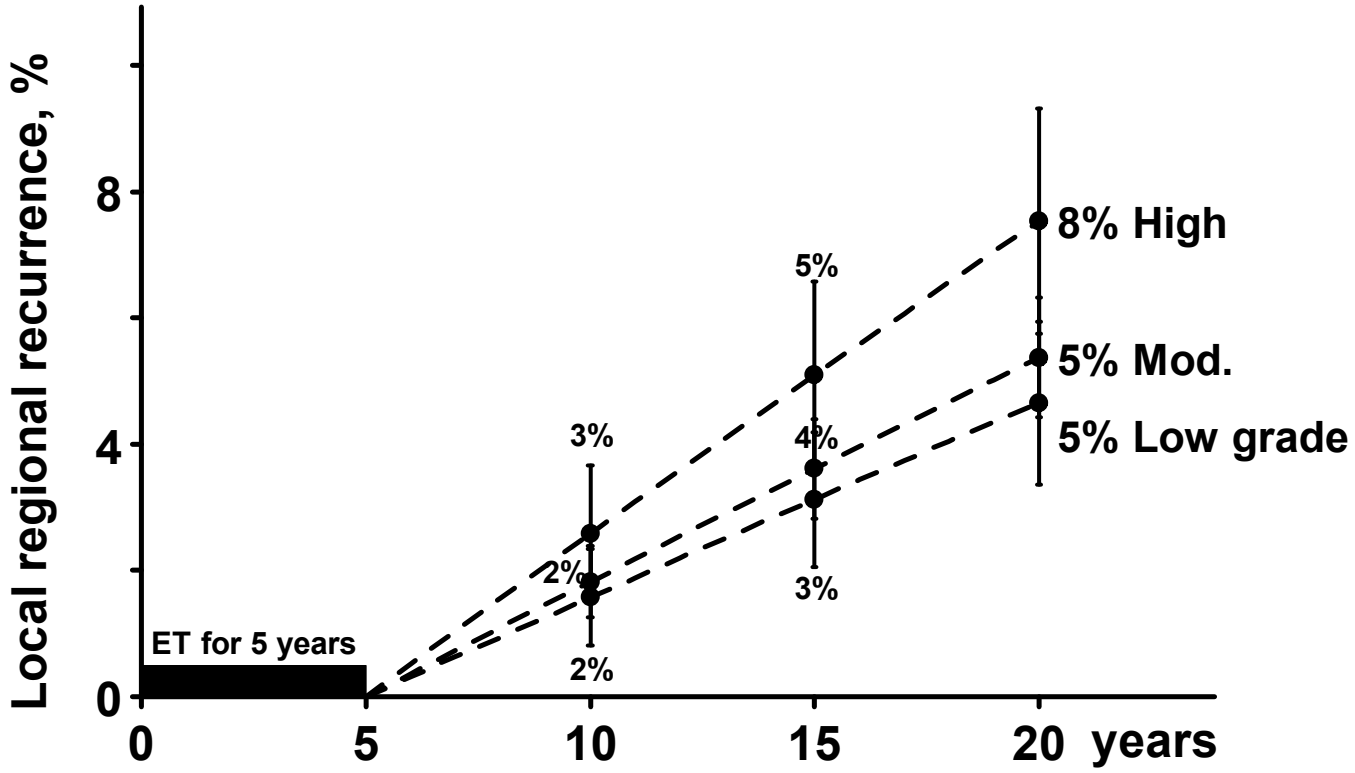
T2N0	4225	(70, 0.5%)	1549	(17, 0.4%)	401	(3, 0.3%)	91
T1N0	11424	(159, 0.4%)	4655	(60, 0.5%)	1268	(9, 0.3%)	226



No. at risk (and, in each 5-year period, no. of events and annual rate)

T2N0	4905	(54, 0.3%)	2244	(20, 0.3%)	671	(3, 0.2%)	117
T1N0	7281	(67, 0.3%)	3107	(22, 0.3%)	941	(7, 0.3%)	183

Figure S21: **Association of tumor grade in T1N0 disease with risk in years 5-20 of loco-regional recurrence.** 13,941 women with known grade in T1N0 ER+ disease scheduled 5 years of ET and event-free and being followed at year 5. Bars are 95% CIs. Dashed lines indicate that event rate is that for whole 5-year period. ET: endocrine therapy



No. at risk (and, in each 5-year period, no. of events and annual rate)

High	3054	(51, 0.5%)	983	(13, 0.6%)	172	(0, 0.0%)	0
Mod.	7363	(84, 0.3%)	2688	(29, 0.5%)	448	(4, 0.8%)	6
Low grade	3524	(36, 0.3%)	1218	(10, 0.4%)	227	(2, 0.7%)	6

Figure S22: **Independent associations of various factors with rate ratio of loco-regional recurrence (RR) during the 5 years of endocrine therapy and after it.** 74,194 women entered at year 0 (plus some later); total 62,923 event-free and followed at year 5. Bars (and text) give 95% group-specific CIs. All RRs are stratified by treatment group. TN analyses have RR=1 for T2N0; others adjust for TN status, scaling RRs so that mean RR=1.

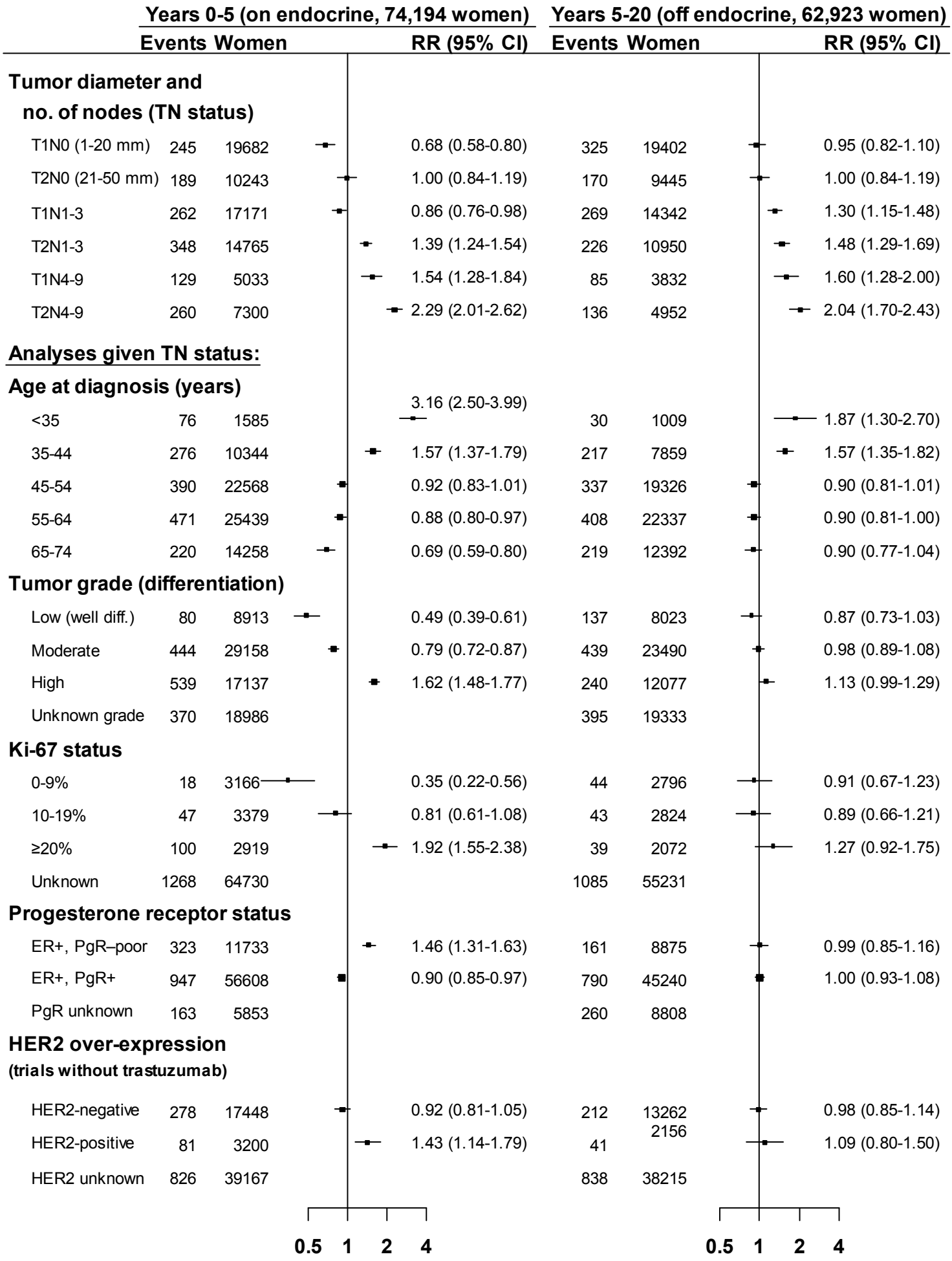


Figure S23A: **Independent associations of various factors with rate ratio (RR) of death from an unknown cause without recorded recurrence during the 5 years of endocrine therapy and after it.** 74,194 women entered at year 0 (plus some later); total 62,923 event-free and followed at year 5. Bars (and text) give 95% group-specific CIs. All RRs are stratified by treatment group. TN analyses have RR=1 for T2N0; others adjust for TN status, scaling RRs so that mean RR=1. Events = deaths from an unknown cause without recorded recurrence.

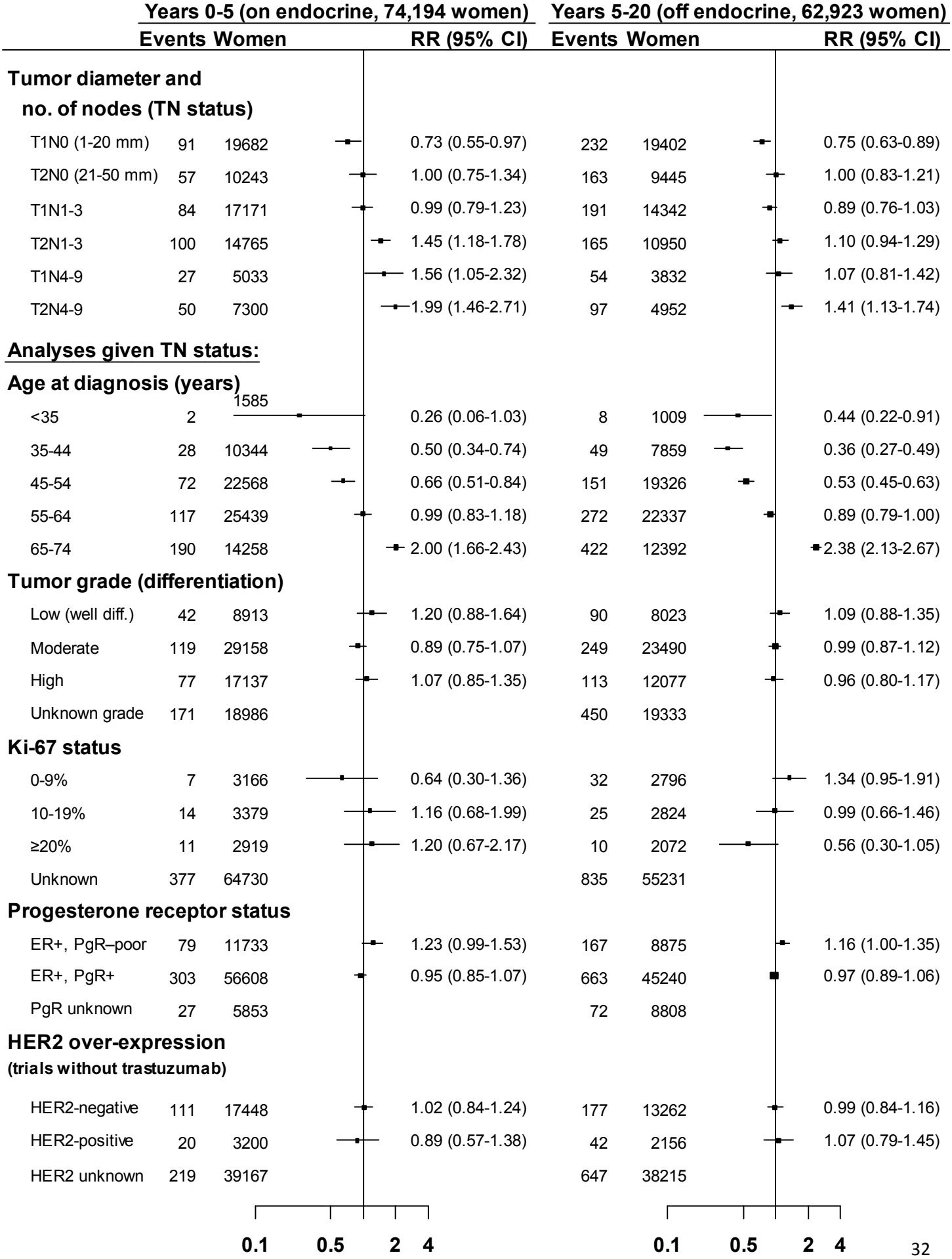


Figure S23B: **Independent associations of various factors with rate ratio (RR) of death from any cause without recorded recurrence during the 5 years of endocrine therapy and after it.** 74,194 women entered at year 0 (plus some later); total 62,923 event-free and followed at year 5. Bars (and text) give 95% group-specific CIs. All RRs are stratified by treatment group. TN analyses have RR=1 for T2N0; others adjust for TN status, scaling RRs so that mean RR=1. Events = death from any cause without recorded recurrence.

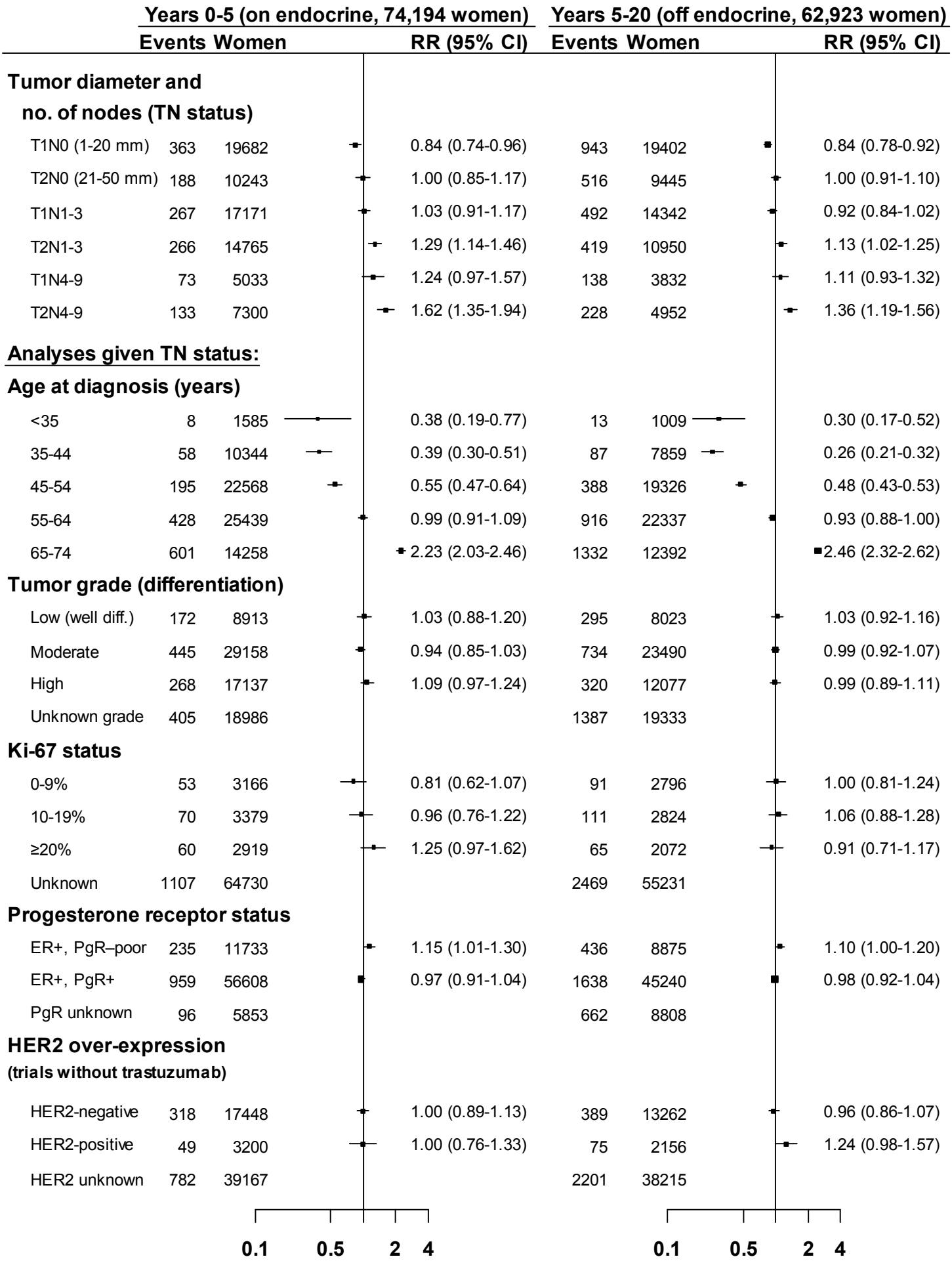


Table S3: **Characteristics of trials and women in analyses that begin at year 5** ET: endocrine therapy, AI: aromatase inhibitor, Tam: tamoxifen

Trial group or study name	Accrual period	Factor(s) evaluated	ET agents	Number random-ized	Characteristics of the selected women				First author, year, corresponding author's country [and number in list of references]
					Number selected	TN status	Median years of age (IQR)	Median years follow-up (IQR)	
Swedish BCCG	Nov 1976 - May 1990	ET	Tam	2738	242	T1/T2; N0, N1-9	61.0 (57.0-66.0)	20.8 (15.2-24.4)	Rutqvist, 2007, Sweden[1]
Scottish B	Apr 1978 - Sep 1984	ET	Tam	1323	63	T1/T2; N0, N1-9	58.0 (54.0-66.0)	13.7 (5.8-21.2)	Stewart, 2001, UK[2]
NSABP B-14	Jan 1982 - Jan 1988	ET	Tam	4127	1068	T1/T2; N0	56.0 (48.0-63.0)	18.5 (8.6-20.5)	Fisher, 1996, USA[3]
ECOG EST5181	Feb 1982 - Jun 1987	ET	Tam	658	91	T1/T2; N1-9	45.0 (39.0-48.0)	15.2 (7.6-19.1)	Tormey, 1992, USA[4]
ECOG EST4181	Mar 1982 - Dec 1986	ET	Tam	962	148	T1/T2; N1-9	61.0 (56.0-65.0)	9.6 (4.8-16.0)	Falkson, 1990, USA[5]
Swedish BCCG	Dec 1982 - Dec 1994	ET	Tam	3647	643	T1/T2; N0, N1-9	63.0 (58.0-68.0)	15.8 (8.3-20.2)	Swedish Breast Cancer Cooperative Group, 1996, Sweden[6]
GROCTA I Italy	Nov 1983 - Jun 1987	ET/Chemo	Tam	504	277	T1/T2; N1-9	53.0 (46.0-59.0)	16.0 (6.9-23.7)	Boccardo, 2011, Italy[7]
Scottish	Apr 1985 - Oct 1991	Radiotherapy	Tam	589	265	T1/T2; N0, N1-9	59.0 (52.0-63.0)	14.3 (10.6-16.7)	Forrest, 1996, UK[8]
IBCSG VII	Jul 1986 - Apr 1993	Chemo	Tam	1266	802	T1/T2; N1-9	61.0 (56.0-65.0)	12.3 (6.7-16.0)	International Breast Cancer Study Group, 1997, Switz.[9]
CRC, UK	Jan 1987 - Feb 1997	ET	Tam	3888	75	T1/T2; N0, N1-9	59.0 (52.0-65.0)	10.7 (9.3-12.2)	Hackshaw,, 2011, UK[10]
GRETA Trieste	Mar 1987 - Jun 1992	ET	Tam	474	41	T1/T2; N0, N1-9	72.0 (72.0-73.0)	9.1 (6.0-13.0)	Mustacchi, 2015, Italy[11]
Brussels Belgium	Jun 1988 - Apr 1997	Chemo	Tam	804	328	T1/T2; N1-9	49.0 (43.0-57.0)	13.7 (8.3-16.4)	Piccart, 2001, Belgium[12]
IBCSG IX	Oct 1988 - Aug 1999	ET/Chemo	Tam	1715	1275	T1/T2; N0	60.0 (56.0-65.0)	12.4 (9.6-15.4)	Aebi, 2011, Switz. [13]
NSABP B-20	Oct 1988 - Mar 1993	ET/Chemo	Tam	2363	2197	T1/T2; N0, N1-3	51.0 (44.0-60.0)	13.9 (12.1-15.2)	Fisher, 1997, USA[14]
GROCTA II Italy	Jan 1989 - Jan 1997	ET/Chemo	Tam/LHRHI	244	114	T1/T2; N0, N1-9	47.0 (43.0-49.0)	6.2 (4.3-8.6)	Boccardo, 2000, Italy[15]
SWOG 8814	Jun 1989 - Jul 1995	Chemo	Tam	1558	1191	T1/T2; N1-9	60.0 (55.0-66.0)	10.7 (7.0-12.8)	Albain, 2009, USA[16]
ECOG EST5188	Jul 1989 - Feb 1994	ET/Chemo	Tam/LHRHI	1537	386	T1/T2; N1-9	43.0 (39.0-47.0)	13.2 (8.9-14.8)	Davidson, 2005, USA[17]
SITAM-01	Jul 1989 - Dec 1996	ET	Tam	1901	385	T1/T2; N0, N1-9	62.0 (57.0-66.0)	12.0 (10.0-13.5)	Sacco, 2003, Italy[18]
SWOG 8897	Jul 1989 - Feb 1993	ET/Chemo	Tam	2690	663	T1/T2; N0	49.0 (42.0-58.0)	12.9 (11.3-13.9)	Hutchins, 2005, USA[19]
DBCG 89c	Jan 1990 - Dec 1996	ET	Tam	2322	337	T1/T2; N1-9	61.0 (55.0-67.0)	14.8 (8.4-16.2)	Andersen, 2008, Denmark[20](just 337 women with 5-yr ET)
RMH London	Feb 1990 - Aug 1995	ET/Chemo	Tam	305	107	T1/T2; N0	56.0 (49.0-63.0)	7.0 (5.3-8.3)	Powles, 1995, UK[21]
Austrian BCSG V	Dec 1990 - Jun 1999	ET/Chemo	Tam/LHRHI	1100	449	T1/T2; N0, N1-9	45.0 (42.0-49.0)	10.3 (7.6-12.8)	Jakesz, 2002, Austria[22]
Austrian BCSG VI	Dec 1990 - Dec 1995	ET	Tam	2021	1288	T1/T2; N0, N1-9	64.0 (58.0-69.0)	11.1 (9.0-12.8)	Schmid, 2003, Austria[23]
aTTom, UK	Jul 1991 - Mar 2005	ET	Tam	6953	725	T1/T2; N0	55.0 (50.0-62.0)	15.0 (14.2-16.1)	Gray, 2013, UK[24]
ICCG C/9/91 UK	Mar 1992 - Jul 2000	Chemo	Tam	785	136	T1/T2; N1-9	46.0 (42.0-49.0)	7.6 (5.3-10.0)	Bliss, 2002, UK[25]
NCI Hanoi 9201	Aug 1992 - Jun 1999	oophorectomy	Tam	709	56	T1/T2; N0	41.0 (36.5-44.0)	7.6 (6.4-8.9)	Love, 2002, USA[26]
GROCTA IV Italy	Sep 1992 - Jan 1998	ET	Tam/AI	380	264	T1/T2; N0, N1-9	62.0 (57.0-66.5)	11.9 (10.4-13.2)	Boccardo, 2001, Italy[27]
GONO Italy MIG 1	Nov 1992 - Jun 1997	Chemo	Tam	710	612	T1/T2; N0, N1-9	54.0 (46.0-60.0)	9.0 (7.3-14.4)	Venturini, 2005, Italy[28]
ICR-CTSU (NCRI BCSG)	Dec 1992 - Oct 2000	ET/Chemo	Tam	3854	1372	T1/T2; N0, N1-9	48.0 (43.0-55.0)	8.1 (5.8-10.0)	Bliss, 2007; UK[29, 30]
NCIC MA.12	Jan 1993 - Dec 1999	ET	Tam	672	43	T1/T2; N0	46.0 (42.0-49.0)	8.2 (7.4-8.9)	Bramwell, 2010, Canada[31]
GABG 4 Germany	Feb 1993 - Dec 2000	ET	Tam	829	46	T1/T2; N4-9	55.0 (53.0-63.0)	5.0 (3.1-6.7)	Kaufmann, 2005, Germany[32]
IBCSG 10-93	May 1993 - Dec 2002	Surgery	Tam	473	186	T1/T2; N0	72.0 (69.0-73.0)	5.5 (4.0-7.1)	International Breast Cancer Study Group, 2006, Sweden[33]
IBCSG 11-93	May 1993 - Nov 1998	Chemo	Tam/ovary supp	174	162	T1/T2; N1-9	45.0 (42.0-48.0)	13.5 (10.6-15.1)	Thürlimann, 2009, Switzerland[34]
IBCSG 12-93	May 1993 - Jul 1999	ET/Chemo	Tam/toremifene	452	402	T1/T2; N0, N1-9	59.0 (56.0-65.0)	10.7 (7.6-12.5)	International Breast Cancer Study Group, 2004, Switz.[35]
IBCSG 13-93	May 1993 - Aug 1999	ET/Chemo	Tam	1294	320	T1/T2; N1-9	44.0 (39.0-47.0)	11.6 (7.0-14.1)	International Breast Cancer Study Group, 2006, Italy[36]
IBCSG 14-93	May 1993 - Jul 1999	ET/Chemo	Tam/toremifene	969	489	T1/T2; N0, N1-9	57.0 (53.0-61.0)	10.0 (7.4-12.0)	International Breast Cancer Study Group, 2007, Italy[37]
MDA 94-002	May 1994 - Aug 1998	Chemo	Tam	524	39	T1/T2; N0, N1-3	57.0 (52.0-62.0)	12.7 (9.5-13.5)	Buzdar, 2002, USA[38]

Trial group or study name	Accrual period	Factor(s) evaluated	ET agents	Number random-ized	Characteristics of the selected women				First author, year, corresponding author's country [and number in list of references]
					Number selected	TN status	Median years of age (IQR)	Median years follow-up (IQR)	
CALGB 9343	Jul 1994 - Feb 1999	Radiotherapy	Tam	647	249	T1/T2; N0, N1-9	72.0 (71.0-74.0)	6.9 (5.9-7.8)	Hughes, 2004, USA[39]
EST3193/INT0142	Sep 1994 - Nov 1997	ET	Tam/ovary supp	345	333	T1/T2; N0	45.0 (41.0-48.0)	9.9 (8.9-10.6)	Tevaarwerk, 2014, USA[40]
GOIRC SANG 2B R1	Oct 1994 - Apr 2000	Chemo	Tam	489	335	T1/T2; N0, N1-9	54.0 (47.0-60.0)	7.6 (6.0-9.2)	Cocconi, 2000, Italy[41]
MDA 98-240	Nov 1994 - Jul 2001	Chemo	Tam	480	247	T1/T2; N0, N1-9	51.0 (44.0-57.0)	3.8 (3.2-4.9)	Green, 2005, USA[42]
GEICAM 9401 Spain	Jun 1995 - Jun 2000	ET	Tam	485	215	T1/T2; N0, N1-9	62.0 (58.0-66.0)	6.0 (4.2-7.9)	Pico, 2004, Spain[43]
HORG Greece	Jun 1995 - Oct 2004	Chemo	Tam	788	318	T1/T2; N1-9	56.0 (47.0-65.0)	5.3 (3.6-7.2)	Polyzos, 2010, Greece[44]
IBCSG 15-95	Jul 1995 - Mar 2000	Chemo	Tam	344	12	T1/T2; N4-9	49.0 (40.0-53.5)	11.5 (9.0-12.4)	Colleoni, 2009, Italy[45]
GOCS 08-BR-95-III	Aug 1995 - Apr 2004	Chemo	Tam	126	43	T1/T2; N0, N1-9	55.0 (42.0-64.0)	6.3 (3.3-9.5)	Leone, 2014, USA[46]
NSABP B-28	Aug 1995 - May 1998	Chemo	Tam	3060	982	T1/T2; N1-9	57.0 (53.0-62.0)	9.6 (8.6-10.3)	Mamounas, 2005, USA[47]
E-EB193/INT0151	Oct 1995 - Oct 1999	Fenretinide	Tam	426	309	T1/T2; N0, N1-9	67.0 (62.0-71.0)	6.8 (5.6-7.9)	Rao, 2011, USA[48]
ATAC, UK	Jul 1996 - Mar 2000	ET	Tam/AI	9366	4012	T1/T2; N0, N1-9	61.0 (56.0-67.0)	9.8 (7.3-10.1)	Baum, 2002, UK[49]
ECTO Italy	Nov 1996 - May 2002	Chemo	Tam	1355	629	T1/T2; N0, N1-9	51.0 (44.0-59.0)	8.9 (5.8-10.9)	Gianni, 2005, 2009, Italy[50, 51]
GONO Italy MIG 5	Nov 1996 - Jan 2001	Chemo	Tam	1055	762	T1/T2; N1-9	53.0 (45.0-61.0)	12.0 (9.8-13.4)	Del Mastro, 2016, Italy[52]
ATLAS	Dec 1996 - May 2005	ET	Tam	12894	2958	T1/T2; N0, N1-9	55.0 (47.0-63.0)	16.0 (12.7-18.0)	Davies, 2013, UK[53]
GABG/ARNO Germany	Dec 1996 - Aug 2002	ET	Tam/AI	1040	808	T1/T2; N0, N1-9	58.0 (54.0-62.0)	8.2 (6.9-10.1)	Kaufmann, 2007, Germany[54]
IBIS 02 Italy	Apr 1997 - Jan 2004	Chemo	Tam	244	126	T1/T2; N4-9	52.5 (47.0-59.0)	8.0 (6.2-9.7)	Boccardo, 2010, Italy[55]
BCIRG 001	Jun 1997 - Jun 1999	Chemo	Tam	1491	797	T1/T2; N1-9	49.0 (44.0-56.0)	10.4 (9.3-10.5)	Martin, 2005, Spain[56]
PACS 01 France	Jun 1997 - Mar 2000	Chemo	Tam	1999	983	T1/T2; N1-9	50.0 (45.0-56.0)	7.5 (6.7-8.1)	Roché, 2006, France[57]
USO 97-35	Jun 1997 - Dec 1999	Chemo	Tam	1016	642	T1/T2; N0, N1-9	52.0 (45.0-60.0)	5.4 (4.9-6.2)	Jones, 2006, USA[58]
DEVA UK	Aug 1997 -Aug 2005	Chemo	Tam	803	537	T1/T2; N0, N1-9	59.0 (55.0-64.0)	5.0 (3.5-6.8)	Coombes, 2011, UK[59]
IBIS 03 Italy	Nov 1997 - Dec 2004	Chemo	Tam	1066	782	T1/T2; N0, N1-3	52.0 (44.0-60.0)	5.7 (4.0-7.6)	Amadori, 2011. Italy[60]
Int Exemestane Study, IES	Feb 1998 - Feb 2003	ET	Tam/AI	4742	2942	T1/T2; N0, N1-9	61.0 (56.0-66.0)	9.6 (8.9-10.2)	Coombes, 2004, UK[61]
IBCSG BIG 1-98	Mar 1998 - May 2003	ET	Tam/AI	8010	6916	T1/T2; N0, N1-9	61.0 (56.0-66.0)	8.0 (7.1-9.1)	Regan, 2011, USA[62]
ITA Italy	Mar 1998 - Dec 2002	ET	Tam/AI	448	297	T1/T2; N1-9	61.0 (53.0-67.0)	12.3 (10.5-13.4)	Boccardo, 2005, Italy[63]
BIG 02-98	Jun 1998 - Jun 2001	Chemo	Tam	2202	1690	T1/T2; N1-9	50.0 (44.0-56.0)	5.0 (4.6-5.7)	Francis, 2008, Australia[64]
ECOG EST2197	Jul 1998 - Jan 2000	Chemo	Tam	2952	1826	T1/T2; N0, N1-9	51.0 (45.0-58.0)	11.9 (9.2-12.4)	Goldstein, 2008, USA[65]
NSABP B-30	Mar 1999 - Mar 2004	Chemo	Tam	5351	2421	T1/T2; N1-9	51.0 (45.0-58.0)	6.6 (5.5-7.9)	Swain, 2010, USA[66]
GEICAM 9805/TARGET 0	Jun 1999 - Mar 2003	Chemo	Tam	1060	576	T1/T2; N0	51.0 (44.0-58.0)	9.3 (8.7-10.3)	Martín, 2010, Spain[67]
GEPARDUO Germany	Jun 1999 - Sep 2001	Chemo	Tam	910	387	T1/T2; N0, N1-3	53.0 (45.0-61.0)	5.9 (5.6-6.3)	von Minckwitz, 2005, Germany[68]
ECOG EST1199	Oct 1999 - Jan 2002	Chemo	Tam/AI	5052	2821	T1/T2; N0, N1-9	52.0 (45.0-58.0)	10.2 (8.1-11.0)	Sparano, 2008, USA[69]
GEICAM 9906 Spain	Nov 1999 - Jun 2002	Chemo	Tam/AI	1246	878	T1/T2; N1-9	50.0 (43.0-58.0)	10.4 (9.4-11.0)	Martín, 2008, Spain[70]
USO 99-016	Jan 2000 - Mar 2002	Chemo	Tam/AI	1830	918	T1/T2; N0, N1-9	52.1 (45.5-58.6)	5.2 (3.9-5.5)	Loesch, 2010, USA[71]
NSABP B-31	Feb 2000 - Apr 2005	Trastuzumab	Tam	2101	873	T1/T2; N1-9	48.0 (42.0-55.0)	8.8 (7.4-10.3)	Romond, 2005, USA[72]
HE 10/00 Greece	Oct 2000 - Jun 2005	Chemo	Tam/AI	1121	598	T1/T2; N0, N1-9	52.0 (44.0-62.0)	7.9 (7.0-9.2)	Gogas, 2012, Greece[73]
NSABP B-34	Jan 2001 - Mar 2004	Bispho	Tam/AI	3323	2371	T1/T2; N0, N1-9	54.0 (47.0-61.0)	9.2 (8.2-10.1)	Paterson, 2012, USA[74]
TEAM	Jan 2001 - Jan 2006	ET	Tam/AI	9779	7513	T1/T2; N0, N1-9	62.0 (57.0-68.0)	5.1 (4.0-5.9)	van de Velde, 2011, Netherlands[75]
PACS 04 France	Feb 2001 - Aug 2004	Chemo/Trastz.	Tam/AI	3010	2140	T1/T2; N1-9	50.5 (44.0-56.0)	9.2 (6.8-10.0)	Spielmann, 2009, France[76]
TACT UK	Feb 2001 - Jul 2003	Chemo	Tam/AI	4162	2582	T1/T2; N0, N1-9	49.0 (43.0-54.0)	7.9 (6.3-8.7)	Ellis, 2009, UK[77]
EORTC10994/BIG 0-01	Apr 2001 - Nov 2006	Chemo	Tam/AI	1856	784	T1/T2; N0, N1-9	48.0 (43.0-55.0)	4.5 (3.5-5.6)	Bonnefoi, 2011, France[78]

Trial group or study name	Accrual period	Factor(s) evaluated	ET agents	Number random-ized	Characteristics of the selected women				First author, year, corresponding author's country [and number in list of references]
					Number selected	TN status	Median years of age (IQR)	Median years follow-up (IQR)	
NSABP B-33 \42	May 2001 - Oct 2003	ET	Tam/AI	1598	689	T1/T2; N0, N1-9	54.0 (49.0-62.0)	12.3 (11.7-12.9)	Mamounas, 2008, USA[79]
CALGB 49907	Sep 2001 - Dec 2006	Chemo	Tam/AI	633	288	T1/T2; N0, N1-9	69.0 (67.0-72.0)	6.4 (5.4-7.6)	Muss, 2009, USA[80]
LMU Munich ADEBAR	Sep 2001 - May 2005	Chemo	Tam/AI	1493	511	T1/T2; N1-9	55.0 (46.0-63.0)	5.2 (3.4-5.8)	Janni, 2016, Germany[81]
PACS 05 France	Aug 2002 - Sep 2006	Chemo	Tam/AI	1515	987	T1/T2; N0	50.0 (44.0-56.0)	6.0 (5.1-7.1)	Kerbrat, 2012, France[82]
GIM 2 Italy	Apr 2003 - Jul 2006	Chemo	Tam	2091	1332	T1/T2; N1-9	51.0 (44.0-59.0)	7.0 (6.0-7.7)	Del Mastro, 2015, Italy[83]
Novartis ZO-FAST	May 2003 - Aug 2004	Bisph	AI	1065	998	T1/T2; N0, N1-9	58.0 (52.0-64.0)	5.1 (5.0-5.5)	Bundred, 2008, UK[84]
ELDA Naples	Jul 2003 - Apr 2011	Chemo	Tam/AI	302	164	T1/T2; N0, N1-9	69.0 (67.0-71.5)	5.9 (4.1-7.3)	Perrone, 2015, Italy[85]
GEICAM 2003-02	Sep 2003 - Oct 2008	Chemo	Tam/AI	1925	1272	T1/T2; N0, N1-3	50.0 (44.0-59.0)	5.3 (4.3-6.1)	Martín, 2013, Spain[86]
IT Naples HOBOE	Mar 2004 - Jan 2010	ET/Bisph	Tam/AI	227	88	T1/T2; N0	61.5 (55.5-66.0)	5.7 (4.5-7.3)	Rossi, 2009, Italy/Nuzzo, 2012[87, 88]
Novartis E-ZO-FAST	Mar 2004 - Aug 2005	Bisph	AI	527	495	T1/T2; N0, N1-9	57.0 (52.0-63.0)	5.1 (5.0-5.5)	Llombart, 2012, Spain[89]
GAIN/GBG 33 Germany	Aug 2004 - Jul 2008	Bisph/Chemo	Tam/AI	3023	1956	T1/T2; N1-3	50.0 (43.0-58.0)	3.2 (2.4-4.3)	von Minckwitz, 2013, Germany[90]
TACT2	Dec 2005 - Dec 2008	Chemo	Tam/AI	4371	2900	T1/T2; N0, N1-9	51.0 (45.0-58.0)	7.1 (6.2-8.0)	Cameron, 2012, UK[91]

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