

Supplementary Material

Elevated aromatase (*CYP19A1*) expression is associated with a poor survival of patients with estrogen receptor positive breast cancer

Hormones and Cancer

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Supplementary Table 1 Representation of the indicated clinical characteristics in human breast cancer patients with SNP rs10046 genotypes CC, CT and TT

		Sum	CC	CT	TT
All patients		119	28 (23.5%)	55 (46.2%)	36 (30.3%)
Age	<50	44	13 (29.5%)	19 (43.2%)	12 (27.3%)
	≥50	75	15 (20.0%)	36 (48.0%)	24 (32.0%)
Menopausal status	pre	33	9 (27.3%)	14 (42.4%)	10 (30.3%)
	post	67	15 (20.9%)	30 (44.8%)	23 (34.3%)
	na	19	5	11	3
Tumor size	pT1	37	9 (24.3%)	15 (40.5%)	13 (35.1%)
	pT2-4	80	18 (22.5%)	39 (48.8%)	23 (28.8%)
	na	2	1	1	0
Tumor type	ductal	83	17 (20.5%)	43 (51.8%)	23 (27.7%)
	lobular	32	10 (31.3%)	10 (31.3%)	12 (37.5%)
	na	4	1	2	1
Stage	1	24	5 (20.8%)	10 (41.7%)	9 (37.5%)
	2-4	84	21 (25.0%)	38 (45.2%)	25 (29.8%)
	na	11	2	7	2
Grade	pG1-2	70	15 (21.4%)	35 (50.0%)	20 (28.6%)
	pG3	47	12 (25.5%)	19 (40.4%)	16 (34.0%)
	na	2	1	1	0
Lymph node status	pN0	41	10 (24.4%)	18 (43.9%)	13 (31.7%)
	pN+	70	17 (24.3%)	33 (47.1%)	20 (28.6%)
	na	8	1	4	3
ER status	pos	52	12 (23.1%)	21 (40.4%)	19 (36.5%)
	neg	61	13 (21.3%)	31 (50.8%)	17 (27.9%)
	na	6	3	3	0
PR status	pos	24	5 (20.8%)	12 (50.0%)	7 (29.2%)
	neg	60	13 (21.7%)	29 (48.3%)	18 (30.0%)
	na	35	10	14	11
HER2 status	pos	17	3 (17.6%)	9 (52.9%)	5 (29.4%)
	neg	73	16 (21.9%)	35 (47.9%)	22 (30.1%)
	na	29	9	11	9
p53 status	pos	33	10 (30.3%)	16 (48.5%)	7 (21.2%)
	neg	58	9 (15.5%)	28 (48.3%)	21 (36.2%)
	na	28	9	11	8
Tumor Subtype	HER2 type	12	2 (16.7%)	6 (50.0%)	4 (33.3%)
	Luminal	42	9 (21.4%)	21 (50.0%)	12 (28.6%)
	Triple neg	31	8 (25.8%)	16 (51.6%)	7 (22.6%)
	na	34	9	12	13

Supplementary Table 2 Details of the analyses of the overall, disease-free and metastasis-free survival in the indicated patient subpopulations

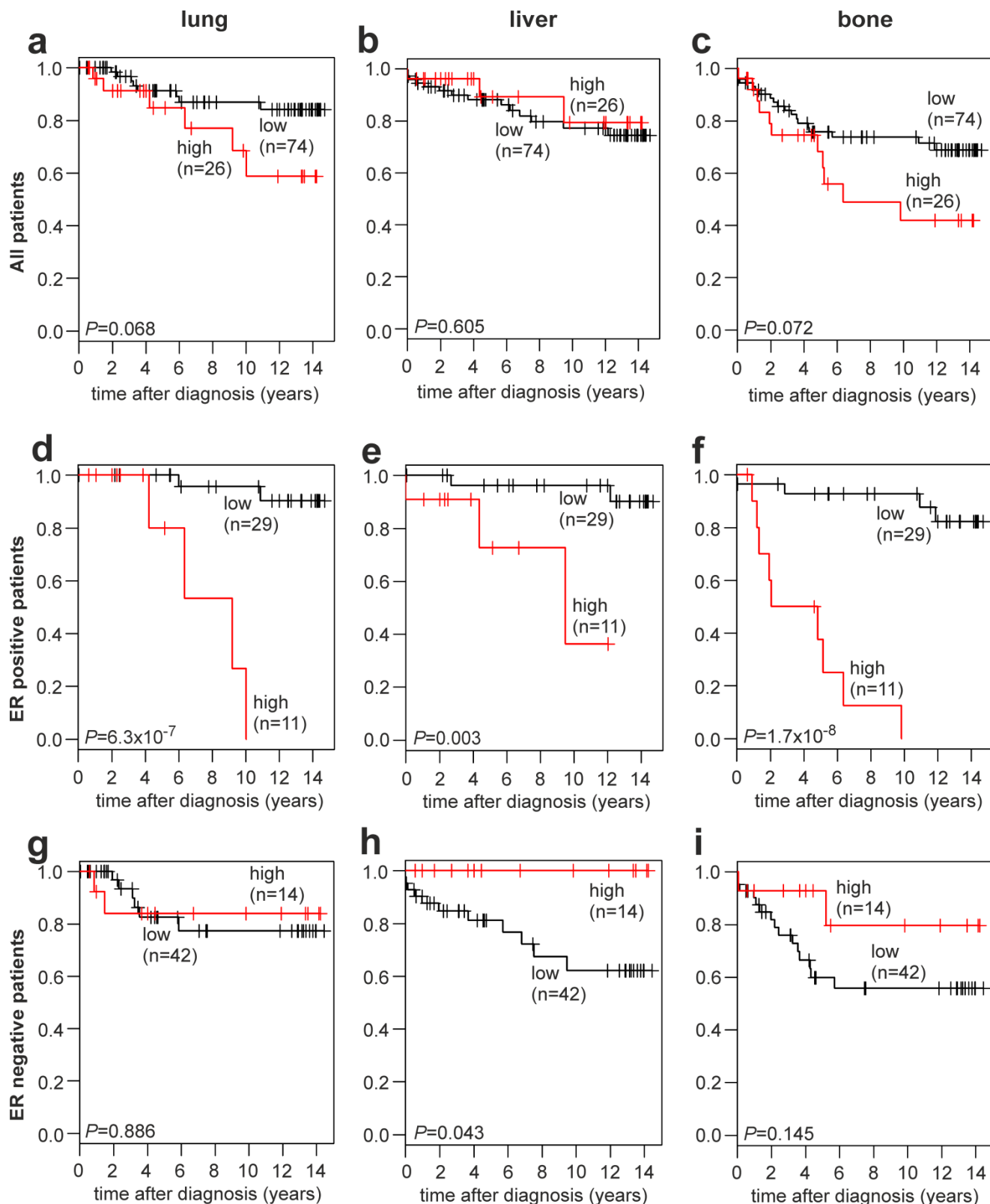
Overall Survival		All patients		CYP19A1 high		CYP19A1 low		CC (rs10046)		CT (rs10046)		TT (rs10046)	
		All	event-free	All	event-free	All	event-free	All	event-free	All	event-free	All	event-free
All patients	number (n)	100	43	26	8	74	35	28	13	55	22	36	14
	events (n)	57	0	18	0	39	0	15	0	33	0	22	0
	mean (y)	7,55	10,96	6,53	11,68	7,92	10,83	6,46	7,63	6,99	10,54	6,63	10,36
	median (y)	6,70	13,13	4,88	13,33	7,49	13,13	5,40	12,55	5,15	13,03	5,62	13,54
	range (y)	0-14.7	0-14.7	0.6-14.2	1.0-14.2	0-14.7	0-14.7	0-16.6	0-16.6	0-14.4	0-14.4	0-14.3	0-14.3
ER pos patients	number (n)	40	17	11	1	29	16	12	3	21	8	19	8
	events (n)	23	0	10	0	13	0	9	0	13	0	11	0
	mean (y)	8,81	12,68	4,65	12,04	10,39	12,72	8,01	12,83	7,11	10,50	6,90	10,46
	median (y)	10,50	13,32	3,86	12,04	12,55	13,33	9,23	12,58	5,48	12,96	6,12	13,75
	range (y)	0-14.7	0-14.7	0.6-12.0	12.0	0-14.7	0-14.7	1.1-13.4	2.6-13.4	0-14.4	0-14.4	0-14.3	0-14.3
ER neg patients	number (n)	56	23	14	6	42	17	13	8	31	11	17	6
	events (n)	33	0	8	0	25	0	5	0	20	0	11	0
	mean (y)	6,55	9,70	7,53	11,35	6,26	9,20	6,52	7,58	6,29	9,78	6,32	10,23
	median (y)	4,56	12,88	6,08	13,43	4,49	12,88	4,43	7,27	4,52	12,93	4,74	13,19
	range (y)	0-14.5	0-14.5	0.6-14.2	1.0-14.2	0-14.5	0-14.5	0-16.6	0-16.6	0-14.4	0-14.4	0.4-14.2	3.1-14.2
Disease-free survival													
All patients	number (n)	100	38	26	6	74	32	28	14	55	24	36	16
	events (n)	62	0	20	0	42	0	14	0	31	0	20	0
	mean (y)	5,48	10,06	4,29	10,03	5,90	10,07	4,94	7,20	5,31	8,91	5,67	9,13
	median (y)	3,39	12,82	2,18	13,40	3,86	12,63	2,25	9,52	3,14	12,53	3,76	12,08
	range (y)	0-14.7	0-14.7	0-14.2	0.6-14.2	0-14.7	0-14.7	0-14.5	0-14.5	0-14.4	0-14.4	0-14.3	0-14.3
ER pos patients	number (n)	40	14	11	0	29	14	12	4	21	9	19	9
	events (n)	26	0	11	0	15	0	8	0	12	0	10	0
	mean (y)	6,67	11,85	2,91		8,10	11,85	6,42	12,31	6,21	8,61	5,84	8,37
	median (y)	4,86	13,33	2,06		10,77	13,33	4,86	12,57	4,84	12,51	5,43	11,56
	range (y)	0-14.7	0-14.7	0-7.5		0-14.7	0-14.7	0-13.4	0.8-13.4	0-14.4	0-14.4	0-14.3	0-14.3
ER neg patients	number (n)	56	22	14	5	42	17	13	7	31	12	17	7
	events (n)	34	0	9	0	25	0	6	0	19	0	10	0
	mean (y)	4,44	8,68	4,73	9,37	4,35	8,47	4,73	7,36	3,91	8,00	5,47	10,11
	median (y)	2,11	12,20	1,89	13,49	2,18	11,85	1,67	8,27	2,29	8,22	3,25	12,60
	range (y)	0-14.5	0-14.5	0.1-14.2	0.6-14.2	0-14.5	0-14.5	0-14.5	0-14.5	0-14.4	0-14.4	0-14.2	0.5-14.2
Metastasis-free survival													
All patients	number (n)	100	48	26	8	74	40	28	16	55	28	36	19
	events (n)	52	0	18	0	34	0	12	0	27	0	17	0
	mean (y)	6,30	9,91	4,60	8,10	6,90	10,27	5,66	7,55	5,75	8,31	6,02	9,23
	median (y)	4,38	12,80	3,08	8,88	5,03	12,80	3,86	9,52	3,68	12,18	3,76	12,60
	range (y)	0-14.7	0-14.7	0-14.2	0.6-14.2	0-14.7	0-14.7	0-16.6	0-16.6	0-14.4	0-14.4	0-14.3	0-14.3
ER pos patients	number (n)	40	19	11	0	29	19	12	4	21	9	19	12
	events (n)	21	0	11		10	0	8	0	12	0	7	0
	mean (y)	7,78	11,95	3,19		9,52	11,95	6,78	12,31	6,38	8,61	6,41	8,72
	median (y)	7,37	13,31	2,06		11,57	13,31	5,58	12,57	5,45	12,51	5,57	12,12
	range (y)	0-14.7	0-14.7	0-7.5		0-14.7	0-14.7	0-13.4	0.8-13.4	0-14.4	0-14.4	0-14.3	0-14.3
ER neg patients	number (n)	56	27	14	7	42	20	13	9	31	16	17	7
	events (n)	29	0	7	0	22	0	4	0	15	0	10	0
	mean (y)	5,08	8,25	5,08	7,36	5,08	8,57	5,94	7,95	4,58	7,19	5,57	10,12
	median (y)	3,11	11,85	3,08	4,45	3,11	12,20	3,46	8,27	2,93	4,57	3,25	12,60
	range (y)	0-14.5	0-14.5	0-14.2	0.6-14.2	0-14.5	0-14.5	0-16.6	0-16.6	0-14.4	0-14.4	0-14.2	0.5-14.2

All, all patients in the indicated analysis; event-free, those patients without an event in the indicated analysis; ER, estrogen receptor; pos, positive; neg, negative. The number of patients (n), the number of events (n), as well as the mean, median, and range for the follow-up time in years (y) is indicated in each analysis and subgroup

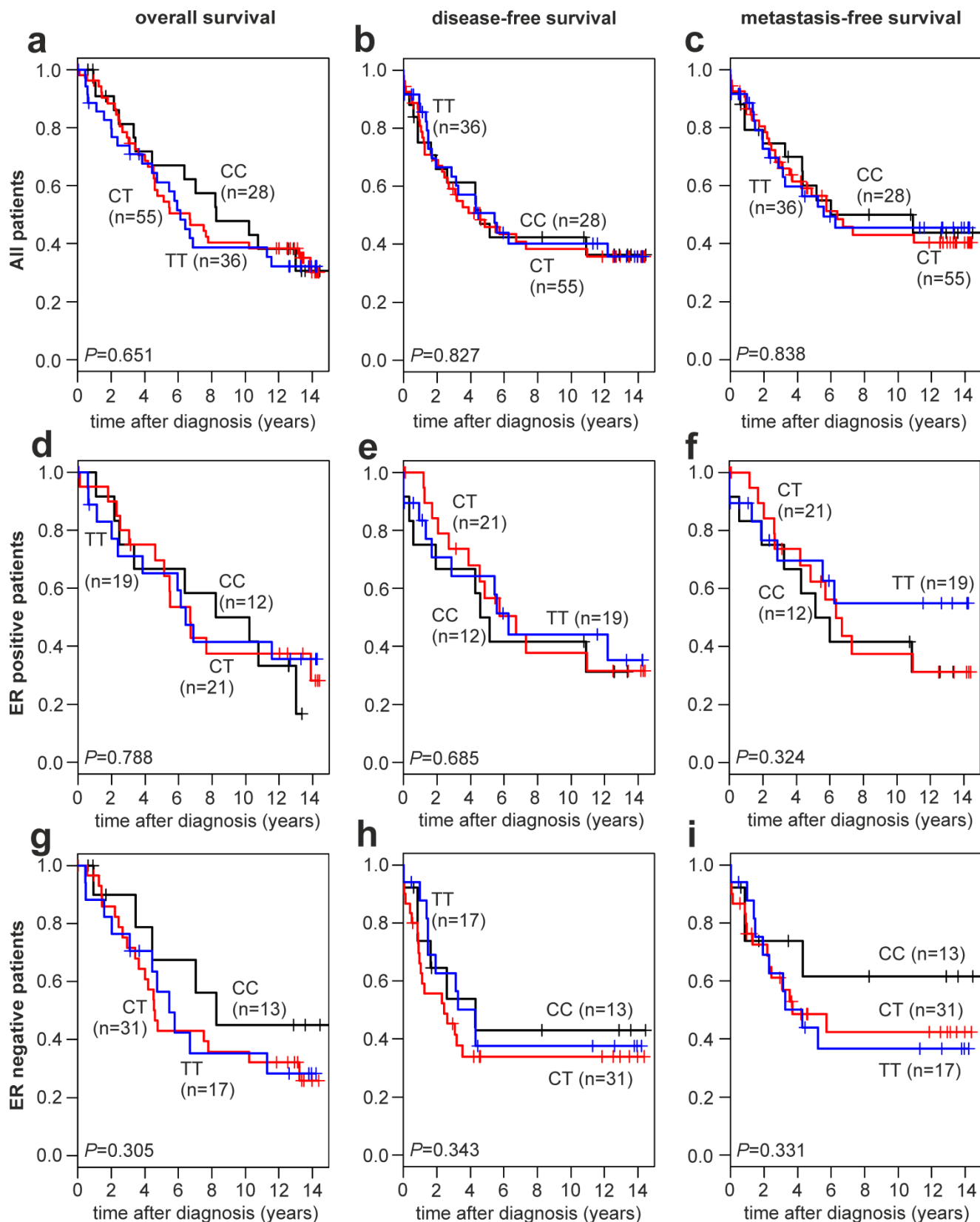
Supplementary Table 3 Details of the analyses of the survival free of lung, liver and bone metastasis in the indicated patient subpopulations

Lung metastasis-free survival		All patients		CYP19A1 high		CYP19A1 low		CC (rs10046)		CT (rs10046)		TT (rs10046)	
		All	event-free	All	event-free	All	event-free	All	event-free	All	event-free	All	event-free
All patients	number (n)	100	86	26	20	74	66	28	24	55	49	36	30
	events (n)	14	0	6	0	8	0	4	0	6	0	6	0
	mean (y)	7,33	7,72	6,16	6,41	7,74	8,11	6,37	6,27	6,77	7,10	6,44	7,09
	median (y)	6,07	6,94	4,34	4,23	6,94	7,66	5,22	3,95	4,60	5,16	5,12	6,04
	range (y)	0-14.7	0-14.7	0.6-14.2	0.6-14.2	0-14.7	0-14.7	0-16.6	0-16.6	0-14.4	0-14.4	0-14.3	0-14.3
ER pos patients	number (n)	40	34	11	7	29	27	12	9	21	19	19	18
	events (n)	6	0	4	0	2	0	3	0	2	0	1	0
	mean (y)	8,66	8,81	4,30	2,50	10,31	10,45	7,79	7,39	7,08	7,27	6,90	6,91
	median (y)	9,62	11,17	3,86	2,30	12,52	12,55	9,13	8,22	5,49	5,49	6,13	6,04
	range (y)	0-14.7	0-14.7	0.6-10.0	0.6-5.2	0-14.7	0-14.7	1.1-13.4	1.1-13.4	0-14.4	0-14.4	0-14.3	0-14.3
ER neg patients	number (n)	56	48	14	12	42	36	13	12	31	27	17	12
	events (n)	8	0	2	0	6	0	1	0	4	0	5	0
	mean (y)	6,27	6,85	7,12	8,11	5,99	6,43	6,52	6,99	5,92	6,28	5,91	7,37
	median (y)	4,44	4,57	5,58	8,28	4,31	4,53	4,43	5,74	4,01	4,20	3,25	6,25
	range (y)	0-14.5	0-14.5	0.6-14.2	0.6-14.2	0-14.5	0-14.5	0-16.6	0-16.6	0-14.4	0-14.4	0.5-14.3	0.5-14.3
Liver metastasis-free survival													
All patients	number (n)	100	83	26	23	74	60	28	23	55	48	36	30
	events (n)	17	0	3	0	14	0	5	0	7	0	6	0
	mean (y)	7,39	8,03	6,33	6,55	7,76	8,60	6,24	6,21	6,87	7,18	6,47	7,36
	median (y)	6,54	7,53	4,41	4,45	7,49	11,17	4,92	3,46	4,77	4,96	5,22	6,28
	range (y)	0-14.7	0-14.7	0-14.2	0-14.2	0-14.7	0-14.7	0-16.6	0-16.6	0-14.4	0-14.4	0-14.3	0-14.3
ER pos patients	number (n)	40	35	11	8	29	27	12	9	21	17	19	18
	events (n)	5	0	3	0	2	0	3	0	4	0	1	0
	mean (y)	8,68	9,10	4,50	4,46	10,27	10,48	7,87	7,73	6,92	7,57	6,87	7,25
	median (y)	10,14	11,57	3,86	3,19	12,52	12,55	8,86	8,22	5,45	6,71	6,13	6,28
	range (y)	0-14.7	0-14.7	0-12.0	1.1-12.0	0-14.7	0-14.7	1.1-13.4	1.1-13.4	0-14.4	0-14.4	0-14.3	0-14.3
ER neg patients	number (n)	56	45	14	14	42	31	13	11	31	28	17	12
	events (n)	11	0	0	0	11	0	2	0	3	0	5	0
	mean (y)	6,37	7,11	7,26	7,26	6,07	7,03	6,18	6,67	6,21	6,27	6,03	7,52
	median (y)	4,53	4,60	5,58	5,58	4,53	4,60	3,46	3,46	4,53	4,36	4,45	5,72
	range (y)	0-14.5	0-14.5	0.6-14.3	0.6-14.3	0-14.5	0-14.5	0-16.6	0-16.6	0-14.4	0-14.4	0-14.3	0.5-14.3
Bone metastasis-free survival													
All patients	number (n)	100	70	26	15	74	55	28	21	55	39	36	23
	events (n)	30	0	11	0	19	0	7	0	16	0	13	0
	mean (y)	6,97	8,53	5,50	6,93	7,48	8,97	5,90	6,65	6,38	7,61	6,26	8,16
	median (y)	5,33	10,31	4,53	4,61	6,60	11,85	3,89	6,37	4,60	5,49	4,36	11,31
	range (y)	0-14.7	0-14.7	0.1-14.2	0.6-14.2	0-14.7	0-14.7	0-16.6	0-16.6	0-14.4	0-14.4	0-14.3	0-14.3
ER pos patients	number (n)	40	27	11	2	29	25	12	7	21	14	19	13
	events (n)	13	0	9	0	4	0	5	0	7	0	6	0
	mean (y)	8,27	10,06	3,54	2,62	10,07	10,65	7,29	9,47	6,77	7,73	6,50	8,09
	median (y)	9,03	12,52	2,06	2,62	12,01	12,55	7,30	10,77	5,49	6,11	5,94	11,57
	range (y)	0-14.7	0-14.7	0.6-9.8	0.6-4.6	0-14.7	0-14.7	0-13.4	2.5-13.4	0-14.4	0-14.4	0-14.3	0-14.3
ER neg patients	number (n)	56	39	14	12	42	27	13	11	31	22	17	10
	events (n)	17	0	2	0	15	0	2	0	9	0	7	0
	mean (y)	5,90	7,44	6,48	7,12	5,71	7,59	5,99	6,67	5,43	6,75	6,00	8,25
	median (y)	4,23	5,46	4,83	4,95	3,92	7,46	3,46	3,46	3,68	4,53	4,27	8,38
	range (y)	0-14.5	0-14.5	0.1-14.2	0.6-14.2	0-14.5	0-14.5	0-16.6	0-16.6	0-14.4	0-14.4	0-14.2	0.5-14.2

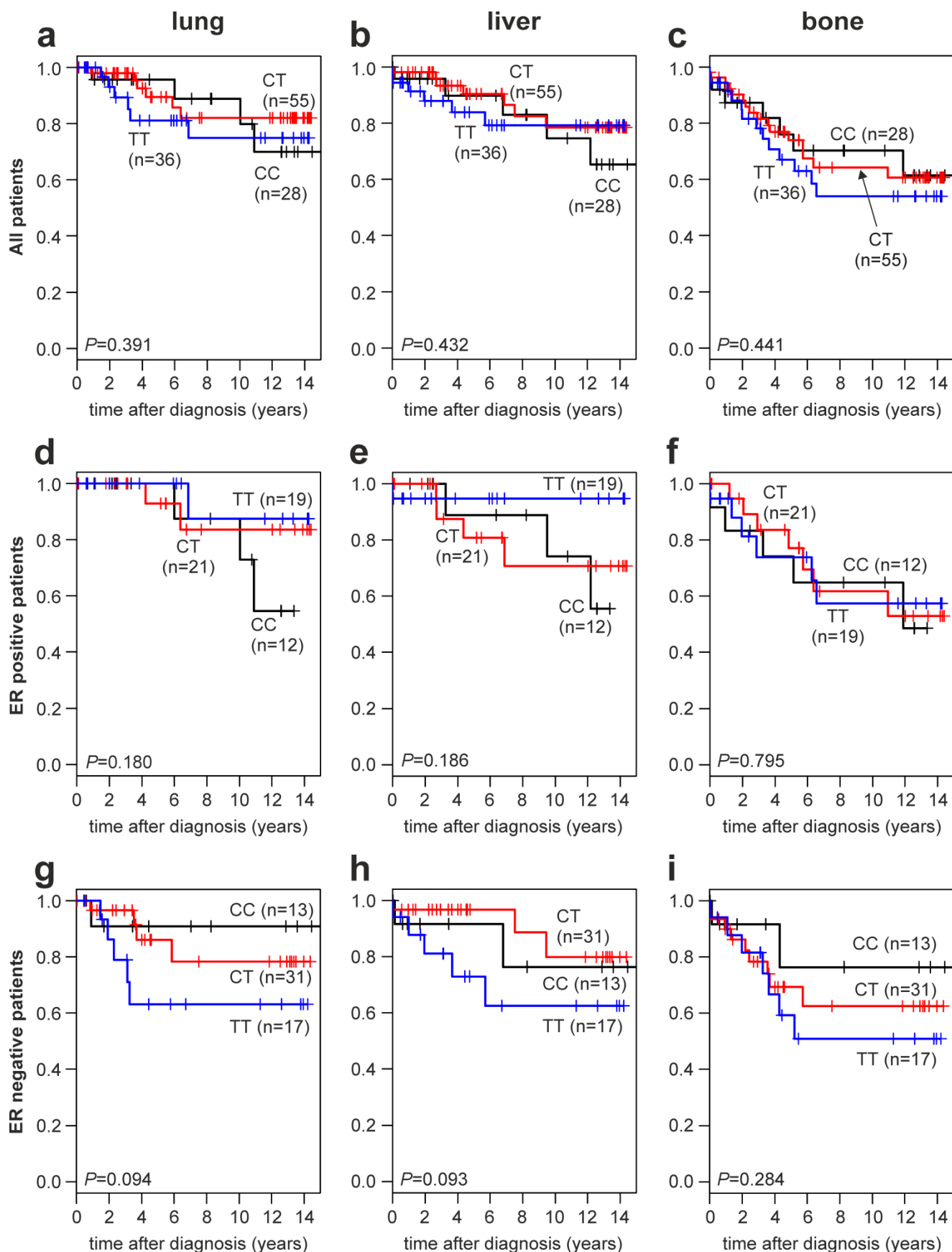
All, all patients in the indicated analysis; event-free, those patients without an event in the indicated analysis; ER, estrogen receptor; pos, positive; neg, negative. The number of patients (n), the number of events (n), as well as the mean, median, and range for the follow-up time in years (y) is indicated in each analysis and subgroup



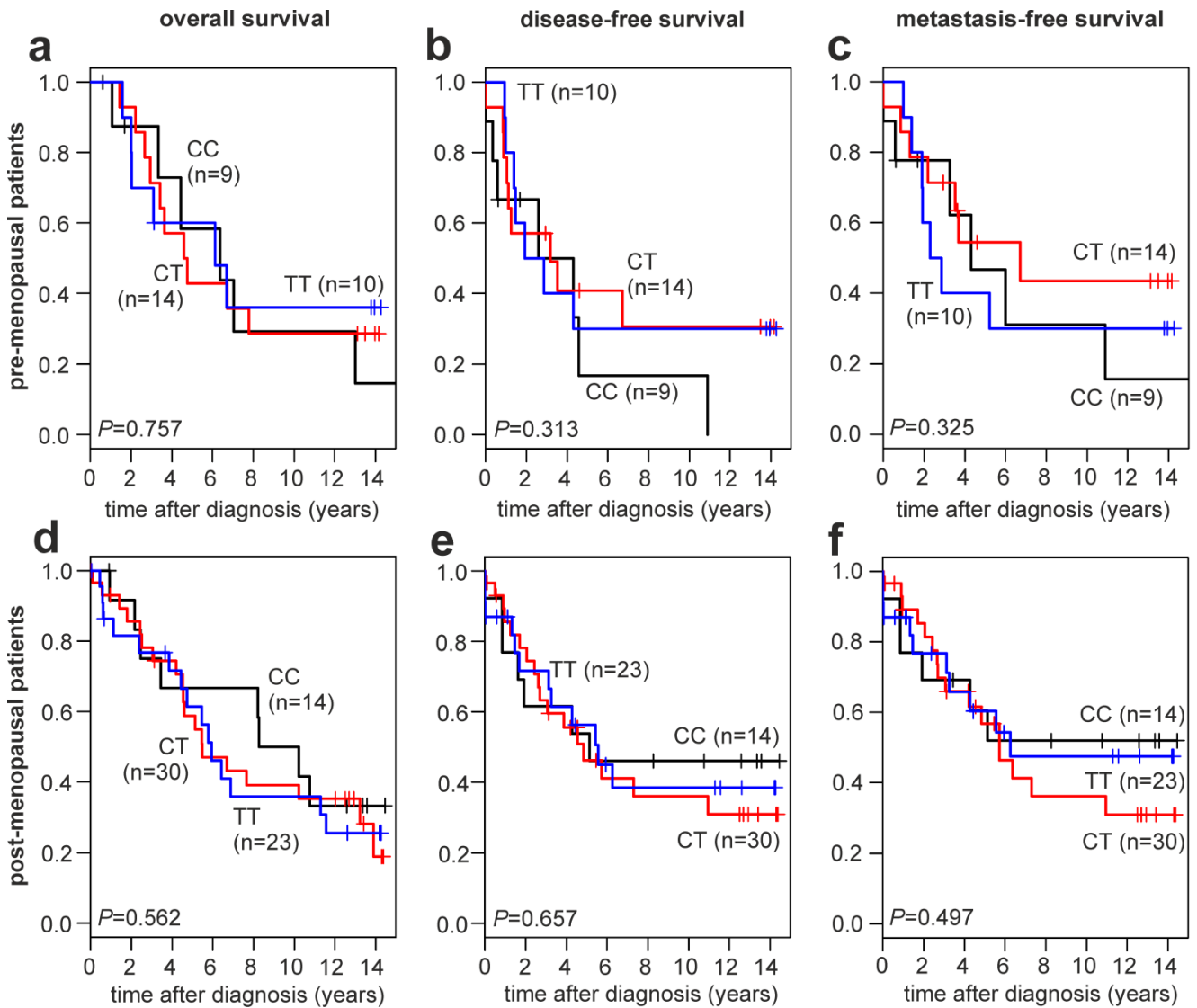
Supplementary Fig. 1 Association of *CYP19A1* mRNA expression with the metastasis-free survival of human breast cancer patients. Kaplan-Meier analyses of the lung metastasis-free survival (a, d, g), liver metastasis-free survival (b, e, h) and bone metastasis-free survival (c, f, i) in unselected patients (a-c; n=100), ER-positive patients (d-f; n=40) and ER-negative patients (g-i; n=56) are shown. Patient subgroups with high and low *CYP19A1* expression and their numbers (n) are indicated in each panel. ER, estrogen receptor



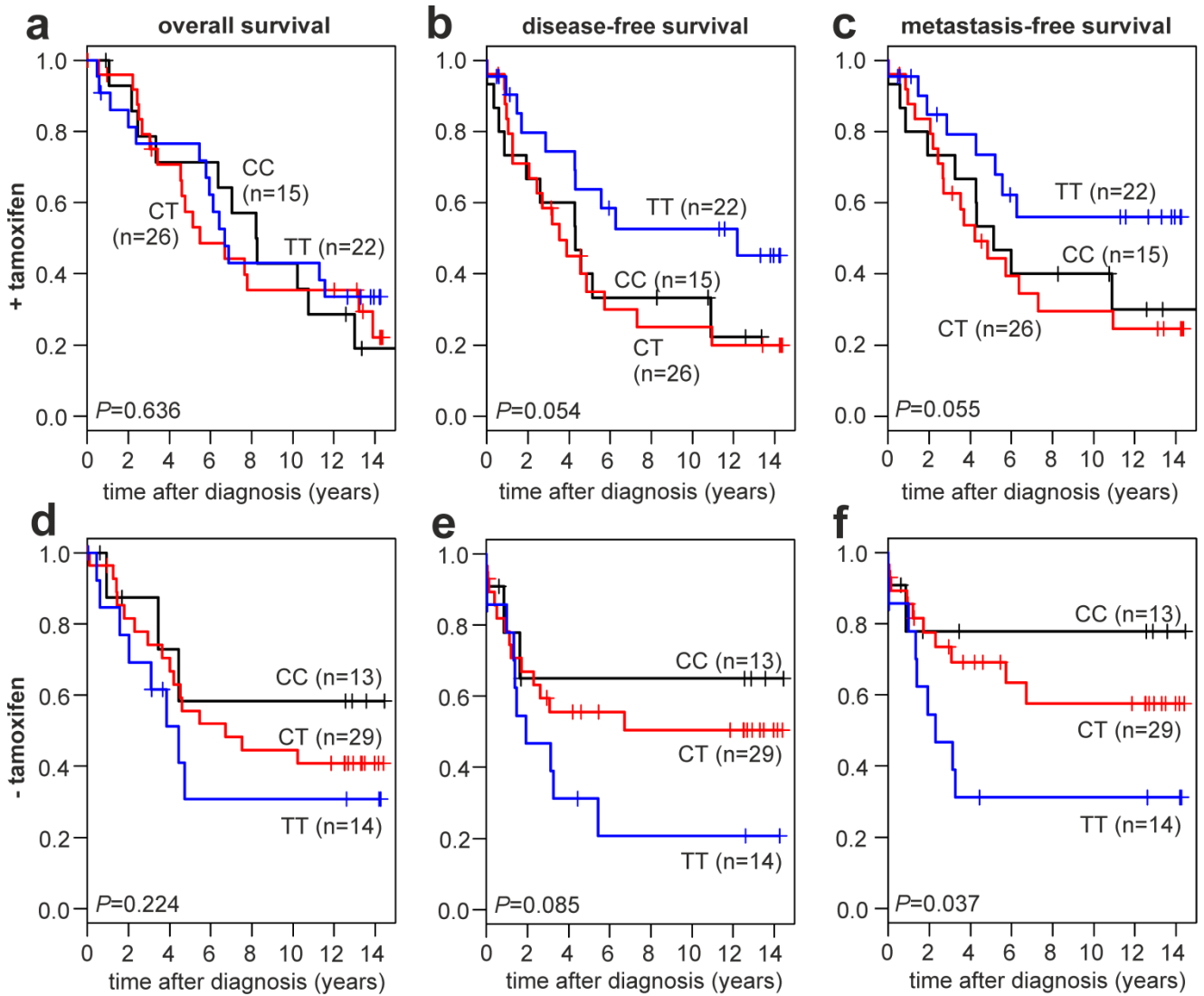
Supplementary Fig. 2 Association of *CYP19A1* rs10046 genotypes with the survival of human breast cancer patients. Kaplan-Meier analyses of the overall survival (a, d, g), disease-free survival (b, e, h) and metastasis-free survival (c, f, i) in unselected patients (a-c; $n=119$), ER positive patients (d-f; $n=52$) and ER negative patients (g-i; $n=61$) are shown. Patient subgroups with rs10046 genotypes CC, CT and TT as well as their numbers (n) are indicated in each panel. ER, estrogen receptor



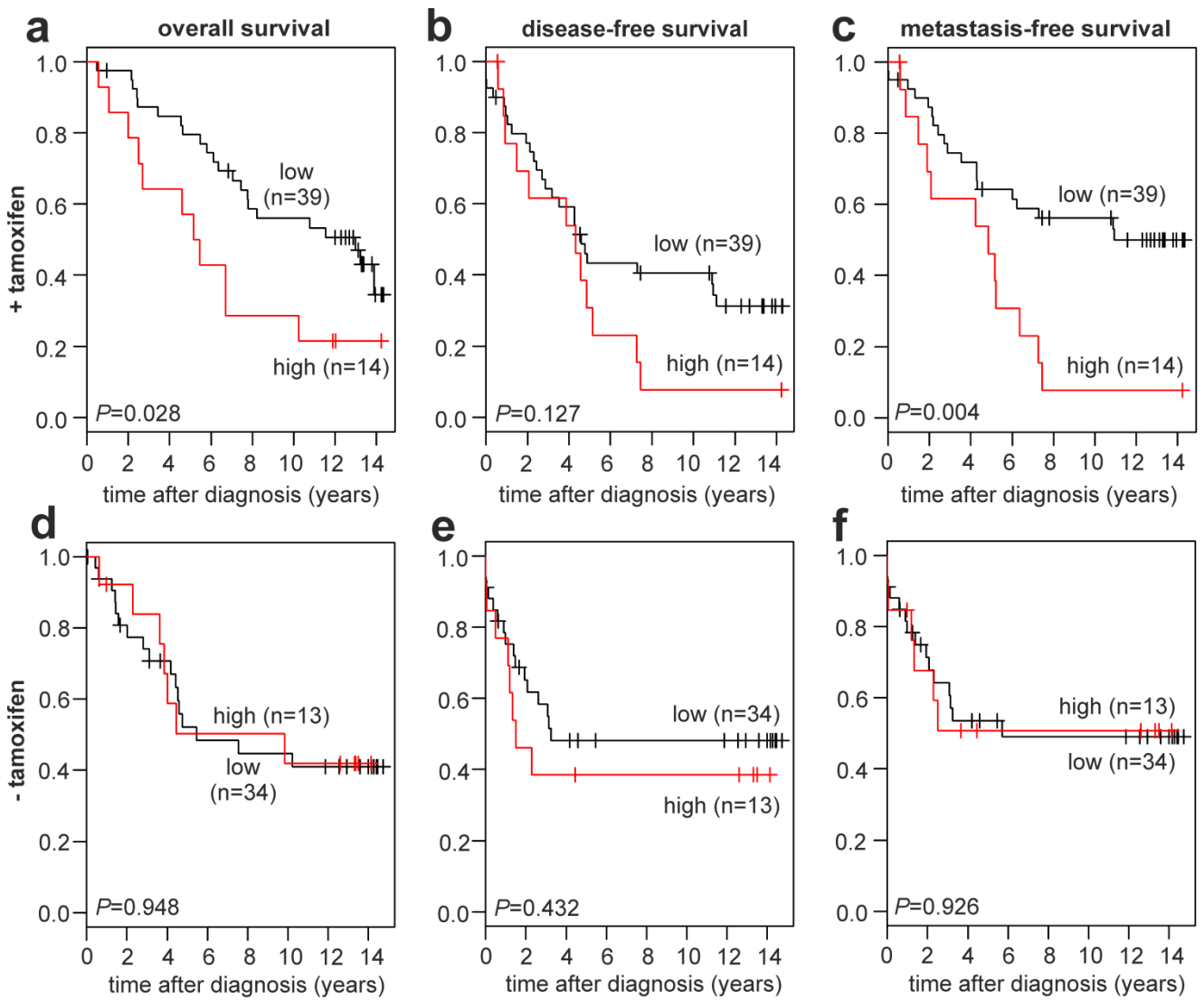
Supplementary Fig. 3 Association of *CYP19A1* rs10046 genotypes with the metastasis-free survival of human breast cancer patients. Kaplan-Meier analyses of the lung metastasis-free survival (a, d, g), liver metastasis-free survival (b, e, h) and bone metastasis-free survival (c, f, i) in unselected patients (a-c; n=119), ER positive patients (d-f; n=52) and ER negative patients (g-i; n=61) are shown. Patient subgroups with rs10046 genotypes CC, CT and TT as well as their numbers (n) are indicated in each panel. ER, estrogen receptor



Supplementary Fig. 4 Association of *CYP19A1* rs10046 genotypes with the survival of human breast cancer patients. Kaplan-Meier analyses of the overall survival (a, d), disease-free survival (b, e) and metastasis-free survival (c, f) in pre-menopausal patients (a-c; n=33) and post-menopausal patients (d-f; n=67) are shown. Patient subgroups with rs10046 genotypes CC, CT and TT as well as their numbers (n) are indicated in each panel.



Supplementary Fig. 5 Association of *CYP19A1* rs10046 genotypes with the survival of human breast cancer patients. Kaplan-Meier analyses of the overall survival (a, d), disease-free survival (b, e) and metastasis-free survival (c, f) in patients treated with tamoxifen (a-c; n=63) and patients not treated with tamoxifen (d-f; n=56) are shown. Patient subgroups with rs10046 genotypes CC, CT and TT as well as their numbers (n) are indicated in each panel.



Supplementary Fig. 6 Association of *CYP19A1* mRNA expression with the survival of human breast cancer patients. Kaplan-Meier analyses of the overall survival (a, d), disease-free survival (b, e) and metastasis-free survival (c, f) in patients treated with tamoxifen (a-c; n=53) and patients not treated with tamoxifen (d-f; n=47) are shown. Patient subgroups with high and low *CYP19A1* expression and their numbers (n) are indicated in each panel.