Supplementary Figures



Supplementary Figure 1. Overview of the data flow in the study. Flowchart displaying the data selection and stratification process and showing the final numbers of cases analyzed in the study.

Gene	Ν	Total events	p-value	Lean (%)	Overweight (%)	p-value	Lean (%)	Obese (%)		p−value
AKT1											
Model 1	392	18	0.773	7 (4.58%)	5 (3.65%)		0.715	7 (4.58%)	6 (5.88%)		0.621
Model 2	386	17	0.691	6 (4.03%)	5 (3.7%)		0.937	6 (4.03%)	6 (5.88%)		0.638
ARID1A			~	7 (4 500)	0 (4 000()		0.004	7 (4 500()	7 (0.000()	_	0.400
Model 1	392	20	0.444	7 (4.58%)	6 (4.38%)		0.931	7 (4.58%)	7 (6.86%)		0.430
CBEB	300	20	0.555	7 (4.7%)	0 (4.44 %)		0.916	7 (4.7%)	7 (0.00%)		0.045
Model 1	392	16	0.299	5 (3.27%)	5 (3.65%)		0.851	5 (3.27%)	6 (5.88%)		0.313
Model 2	386	15	0.171	4 (2.68%)	5 (3.7%)		0.651	4 (2.68%)	6 (5.88%)		0.183
CDH1											
Model 1	392	10	0.002*	3 (1.96%)	2 (1.46%)		0.776	3 (1.96%)	5 (4.9%)		0.198
Model 2	386	10	0.002*	3 (2.01%)	2 (1.48%)		0.754	3 (2.01%)	5 (4.9%)		0.205
CTCF		-				_				_	
Model 1	392	5	0.416	1 (0.65%)	2 (1.46%)		0.534	1 (0.65%)	2 (1.96%)		0.362
FRRR2	300	5	0.407	1 (0.07 %)	2 (1.40%)		0.575	1 (0.07 %)	2 (1.90%)		0.555
Model 1	392	13	0.968	5 (3 27%)	5 (3 65%)		0.855	5 (3 27%)	3 (2.94%)	_	0.940
Model 2	386	13	0.95	5 (3.36%)	5 (3.7%)		0.866	5 (3.36%)	3 (2.94%)		0.844
ERBB3				. ,	. ,			. ,	. ,		
Model 1	392	8	0.533	2 (1.31%)	2 (1.46%)		0.881	2 (1.31%)	4 (3.92%)		0.186
Model 2	386	8	0.445	2 (1.34%)	2 (1.48%)		0.902	2 (1.34%)	4 (3.92%)		0.124
GATA3											
Model 1	392	36	0.748	14 (9.15%)	11 (8.03%)		0.707	14 (9.15%)	11 (10.78%)	-	0.665
	386	35	0.601	13 (8.72%)	11 (8.15%)	-	0.826	13 (8.72%)	11 (10.78%)	-	0.527
Model 1	392	5	0.908	2 (1.31%)	2 (1 46%)		0.897	2 (1 31%)	1 (0.98%)		0.917
Model 2	386	5	0.930	2 (1.34%)	2 (1.48%)		0.938	2 (1.34%)	1 (0.98%)		0.915
MAP2K4		T		- (,	_(,	T		_(,	. (,	T	
Model 1	392	11	0.409	3 (1.96%)	3 (2.19%)		0.895	3 (1.96%)	5 (4.9%)		0.199
Model 2	386	11 -	0.501	3 (2.01%)	3 (2.22%)		0.920	3 (2.01%)	5 (4.9%)		0.277
MAP3K1											
Model 1	392	24	0.233	12 (7.84%)	9 (6.57%)		0.680	12 (7.84%)	3 (2.94%)		0.110
Model 2	386	23	0.126	12 (8.05%)	8 (5.93%)	-	0.541	12 (8.05%)	3 (2.94%)		0.057
Model 1	302	8	0.929	5 (3 27%)	1 (0 73%)		0.160	5 (3 27%)	2 (1 06%)		0.608
Model 2	386	8	0.901	5 (3.36%)	1 (0.74%)		0.175	5 (3.36%)	2 (1.96%)		0.594
NF1	000	- -	0.001	0 (0.00 /0)	1 (0.1470)	-	0.110	0 (0.00 /0)	2 (1.0070)		0.004
Model 1	392	10 -	0.083	5 (3.27%)	4 (2.92%)		0.906	5 (3.27%)	1 (0.98%)		0.292
Model 2	386	10	0.075	5 (3.36%)	4 (2.96%)		0.920	5 (3.36%)	1 (0.98%)		0.270
NOTCH1											
Model 1	392	6	0.352	2 (1.31%)	1 (0.73%)		0.688	2 (1.31%)	3 (2.94%)		0.365
Model 2	386	6	0.326	2 (1.34%)	1 (0.74%)		0.666	2 (1.34%)	3 (2.94%)		0.317
PIK3CA Model 1	202	162	0.125	70 /45 75%)	50 (42 07%)		0.670	70 (45 75%)	24 (22 220/)		0.050
Model 2	386	161	0.125	69 (46 31%)	58 (42 96%)		0.570	69 (46 31%)	34 (33 33%)		0.039*
PIK3R1	000	-	0.111	00 (10.0170)	00 (12:00 /0)	T	0.010	00 (10:0170)	01 (0010070)	-	0.000
Model 1	392	6	0.451	3 (1.96%)	2 (1.46%)		0.776	3 (1.96%)	1 (0.98%)		0.635
Model 2	386	6 -	0.426	3 (2.01%)	2 (1.48%)		0.750	3 (2.01%)	1 (0.98%)		0.605
PTEN											
Model 1	392	14	0.888	3 (1.96%)	8 (5.84%)		0.091	3 (1.96%)	3 (2.94%)		0.590
Model 2	386	13	0.982	2 (1.34%)	8 (5.93%)		0.034*	2 (1.34%)	3 (2.94%)		0.360
KB1 Model 1	202	6	0.910	2 (1 06%)	1 (0 72%)		0.426	2 (1 06%)	2 (1 06%)		0.021
Model 2	386	6	0.916	3 (2.01%)	1 (0.74%)		0.454	3 (2.01%)	2 (1.96%)		0.962
RUNX1		-	51010	0 (=:01/0)	. (0	-		0 (=.0170)	- (Ī	0.004
Model 1	392	6	0.252	1 (0.65%)	2 (1.46%)		0.529	1 (0.65%)	3 (2.94%)		0.170
Model 2	386	6	0.297	1 (0.67%)	2 (1.48%)		0.534	1 (0.67%)	3 (2.94%)		0.212
SF3B1											
Model 1	392	12	0.849	5 (3.27%)	5 (3.65%)	_ <u>+</u>	0.861	5 (3.27%)	2 (1.96%)		0.597
Model 2	386	12	0.713	5 (3.36%)	5 (3.7%)		0.848	5 (3.36%)	2 (1.96%)		0.460
IBX3 Model 1	302	12	0.003*	1 (0 65%)	3 (2 10%)		0.303	1 (0 65%)	8 (7 8/9/)		0.003*
Model 2	386	12	0.005*	1 (0.67%)	3 (2.22%)		0.290	1 (0.67%)	8 (7.84%)		0.008*
TP53	000		5.000	. (0.07 /0)	- (/0)	-	0.200	(0.0770)	- (1.5-170)	-	0.000
Model 1	392	73	0.116	35 (22.88%)	24 (17.52%)	-	0.271	35 (22.88%)	14 (13.73%)	-	0.072
Model 2	386	71 —	0.232	33 (22.15%)	24 (17.78%)		0.377	33 (22.15%)	14 (13.73%)		0.192
		r1					1		r		1
		0.8 1 1.3	25			0.01 0.1 1 10 1	00		0.0	1 0.1 1 10 10	DO
		Odds ratio (per 1kg/m ²)				Odds ratio (Overweight vs Lean)			Udds ratio (Obese vs Lean)	
		More prevalent More prevalent				More prevalent More prevalent				More prevalent More prevalent	
		as bmi decréases as BMI incréase	5			in lean in overweight				in obese	
			Model	1 - corrected fo	r Cohort	Model 2 - corrected fe	or Cohort, Age ar	nd Grade			

Supplementary Figure 2. Association of BMI as a categorical variable with oncogenic mutations of breast cancerspecific driver genes in NST ER+/HER2- patients. Forest plots showing the associations evaluated using Firth's logistic regression between BMI, as a categorical variable (overweight vs lean, and obese vs lean), and driver gene mutations. Merged data from two cohorts, METABRIC and ICGC, was used. Gene mutations with at least 5 events detected in the respective cohorts were evaluated. Color-coded boxes indicate point estimates of odds ratios, and whiskers indicate their corresponding 95% confidence intervals. All statistical tests were two-sided. p-values shown were not corrected for multiple testing.



Supplementary Figure 3. Association of BMI with oncogenic mutations of breast cancer-specific driver genes in NST **ER-/HER2- patients.** Forest plots showing the associations evaluated using Firth's logistic regression between BMI, as a categorical variable (overweight vs lean, and obese vs lean), and driver gene mutations. Merged data from two cohorts, METABRIC and ICGC, was used. Gene mutations with at least 5 events detected in the respective cohorts were evaluated. Color-coded boxes indicate point estimates of odds ratios, and whiskers indicate their corresponding 95% confidence intervals. All statistical tests were two-sided. p-values shown were not corrected for multiple testing.

Gene	N	Total e	events	p-value	Lean (%)	Overweight (%)	p-value	Lean (%)	Obese (%)			p−value
AKT1													
Model 1	339	15		0.447	11 (5.21%)	2 (2.11%)		0.248	11 (5.21%)	2 (6.06%)		-	0.663
Model 2	338	15		0.379	11 (5.24%)	2 (2.11%)		0.228	11 (5.24%)	2 (6.06%)		-	0.760
ARID1A													
Model 1	339	23		0.131	14 (6.64%)	3 (3.16%)		0.249	14 (6.64%)	6 (18.18%)		-	0.033*
Model 2	338	23		0.211	14 (6.67%)	3 (3.16%)		0.164	14 (6.67%)	6 (18.18%)	-	-	0.056
BRCA2						- ()				- (,			
Model 1	339	6	* 	0.160	6 (2.84%)	0 (0%)	← _	0.117	6 (2.84%)	0 (0%)			0.573
Model 2	338	6		0.280	6 (2.86%)	0 (0%)	< -	0.150	6 (2.86%)	0 (0%)			0.746
CDH1		-	_		- ()	- ()			- ()	- ()	_		
Model 1	339	203		0.250	130 (61.61%)	52 (54.74%)	-	0.257	130 (61.61%)	21 (63.64%)	-	-	0.851
Model 2	338	202		0.236	129 (61.43%)	52 (54.74%)		0.272	129 (61.43%)	21 (63.64%)	-	-	0.883
CDKN1B			_			(,				_ (,	T		
Model 1	339	5		0 214	4 (1.9%)	0 (0%)		0.255	4 (1.9%)	1 (3.03%)		-	0.461
Model 2	338	5		0.176	4 (1.9%)	0 (0%)	← −	0.196	4 (1.9%)	1 (3.03%)		- ·	0.429
FRBR2	000	0	-	0.170	4 (1.070)	0 (070)	-	0.100	4 (1.070)	1 (0.0070)		-	0.120
Model 1	339	14		0.456	7 (3.32%)	4 (4 21%)		0.634	7 (3.32%)	3 (9.09%)	_	-	0 116
Model 2	338	14		0.946	7 (3 33%)	4 (4.21%)		0.761	7 (3 33%)	3 (9.09%)	_		0.210
FRRR3	000	14		0.040	7 (0.0070)	+ (+.2170)	_	0.701	7 (0.0070)	0 (0.00 %)		-	0.210
Model 1	330	12		0.501	8 (3 70%)	4 (4 21%)		0.786	8 (3 70%)	0 (0%)		_	0.415
Model 2	338	12		0.362	8 (3.81%)	4 (4.21%)		0.860	8 (3.81%)	0 (0%)		_	0.329
FOXA1	550	12	•	0.302	0 (0.01 %)	4 (4.2176)	-	0.009	0 (5.0176)	0 (0 %)	•		0.520
Model 1	220	22		0.706	16 (7 600/)	2 (2 169/)		0.151	16 (7 600/)	4 (10 100/)			0.210
Model 2	228	20		0.700	16 (7.50%)	3 (3.10%)		0.151	16 (7.50%)	4 (12.12%)			0.319
CATA 2	330	23		0.713	10 (7.02%)	3 (3.16%)		0.150	10 (7.02%)	4 (12.1276)			0.330
GAIAS Madal 4	220	04	-	0.450	45 (7 440/)	E (E 000())	_	0.005	45 (7 440/)	4 (2.028/)	_		0.540
Nodel 1	339	21		0.450	15 (7.11%)	5 (5.26%)		0.605	15 (7.11%)	1 (3.03%)		_	0.513
Wodel 2	330	21		0.565	15 (7.14%)	5 (5.26%)		0.672	15 (7.14%)	1 (3.03%)		_	0.605
MAP3K1	000	40	_	0.750	10 (0 100()	0 (0 400()	_	0.045	10 (0 100()	0 (0 000()			0.000
Model 1	339	18		0.753	13 (6.16%)	3 (3.16%)		0.315	13 (6.16%)	2 (6.06%)			0.832
Model 2	338	18		0.939	13 (6.19%)	3 (3.16%)		0.182	13 (6.19%)	2 (6.06%)		—	0.932
PIK3CA			_								_		
Model 1	339	134		0.159	91 (43.13%)	34 (35.79%)		0.230	91 (43.13%)	9 (27.27%)			0.088
Model 2	338	133		0.110	90 (42.86%)	34 (35.79%)	-	0.206	90 (42.86%)	9 (27.27%)			0.061
PTEN			_				_					_	
Model 1	339	13		0.400	10 (4.74%)	1 (1.05%)		0.123	10 (4.74%)	2 (6.06%)			0.579
Model 2	338	13		0.680	10 (4.76%)	1 (1.05%)		0.211	10 (4.76%)	2 (6.06%)	_		0.418
RUNX1			_				_				_		
Model 1	339	10		0.054	10 (4.74%)	0 (0%)	<	0.024*	10 (4.74%)	0 (0%)	<hr/>	_	0.301
Model 2	338	10		0.051	10 (4.76%)	0 (0%)	< ─■ ──	0.023*	10 (4.76%)	0 (0%)		_	0.274
SF3B1													
Model 1	339	5	< ■	0.657	3 (1.42%)	2 (2.11%)		0.584	3 (1.42%)	0 (0%)			0.938
Model 2	338	5	· · · · · · · · · · · · · · · · · · ·	0.935	3 (1.43%)	2 (2.11%)		0.329	3 (1.43%)	0 (0%)	\leftarrow		0.845
TBX3													
Model 1	339	43		0.108	24 (11.37%)	10 (10.53%)		0.874	24 (11.37%)	9 (27.27%)			0.018*
Model 2	338	42		0.154	23 (10.95%)	10 (10.53%)		0.813	23 (10.95%)	9 (27.27%)		-	0.027*
TP53													
Model 1	339	18	←	0.032*	14 (6.64%)	4 (4.21%)		0.456	14 (6.64%)	0 (0%)	<hr/>	-	0.158
Model 2	338	18		0.005*	14 (6.67%)	4 (4.21%)		0.119	14 (6.67%)	0 (0%)	<hr/>	-	0.114
USP9X													
Model 1	339	7		0.887	4 (1.9%)	2 (2.11%)		0.795	4 (1.9%)	1 (3.03%)		-	0.461
Model 2	338	7		0.663	4 (1.9%)	2 (2.11%)		0.682	4 (1.9%)	1 (3.03%)			0.329
			r									1	_
			0.8 1 1.2	5			0.01 0.1 1 10 100			(0.01 0.1 1	10	100
			Odds ratio (per 1kg/m ²)				Odds ratio (Overweight vs Lean)				Odds ratio (Ob	ese vs Lear)
			More prevalent More prevalent				More prevalent More prevalent				More prevalent	More preval	ent
			as BMI decreases as BMI increases				in lean in overweight				in lean	in obese	
				Mode	l 1- Univariable		Model 2 - corrected for	Ane and Grade					

Supplementary Figure 4. Association of BMI with oncogenic mutations of breast cancer-specific driver genes in ILC ER+/HER2- patients. Forest plots showing the associations evaluated using Firth's logistic regression between BMI, as a categorical variable (overweight vs lean, and obese vs lean), and driver gene mutations. Data from the ELBC cohort was used. Gene mutations with at least 5 events detected in the respective cohorts were evaluated. Color-coded boxes indicate point estimates of odds ratios, and whiskers indicate their corresponding 95% confidence intervals. All statistical tests were two-sided. p-values shown were not corrected for multiple testing.





BMI BMI p-value: 0.0253

ILC ER+/HER2- ERBB2 mutation



Supplementary Figure 5. Non-linear association of gene mutations with BMI. Plots showing fitted lines of the logOR of gene mutations against continuous BMI (baseline BMI of 20) for those indicated to be better associated with BMI in a non-linear model. Data are presented for point estimates of log-odds ratio (logOR; blue solid line) and their 95% confidence interval (grey shaded band). p-values shown were determined for coefficients estimated by generalized additive models fitted with a spline term of BMI and adjusted for cohort, age, and tumor grade. All statistical tests were two-sided.

NST ER+/HER2- PTEN mutation

ILC ER+/HER2- ARID1A mutation



Supplementary Figure 6. Co-occurrence and mutual exclusivity of genomic alterations in NST ER+/HER2- tumors from patients of different BMI categories. Pairwise analyses of recurrent gene mutations and mutations, mutations and CNAs (either amp or hemiLoss) were performed. The color scale represents -log(q-value), which were derived from a Poisson-Binomial distribution-based test and adjusted for multiple testing using the Benjamin-Hochberg method. A grey cell indicates that one of the alterations in the pair did not have enough number of events (3 events) in the respective sub-cohort and thus was not analyzed. Merged data from two cohorts, METABRIC and ICGC, was used.



Supplementary Figure 7. Co-occurrence and mutual exclusivity of genomic alterations in NST ER-/HER2- tumors from patients of different BMI categories. Pairwise analyses of recurrent gene mutations and mutations, mutations and CNAs (either amp or hemiLoss) were performed. The color scale represents -log(q-value), which were derived from a Poisson-Binomial distribution-based test and adjusted for multiple testing using the Benjamin-Hochberg method. A grey cell indicates that one of the alterations in the pair did not have enough number of events (3 events) in the respective sub-cohort and thus was not analyzed. Merged data from two cohorts, METABRIC and ICGC, was used.



Supplementary Figure 8. Non-linear association of gene-level CNAs with BMI. Plots showing fitted lines of the logOR of gene-level CNAs against continuous BMI (baseline BMI of 20) for those indicated to be better associated with BMI in a non-linear model. Data are presented for point estimates of log-odds ratio (logOR; blue solid line) and their 95% confidence interval (grey shaded band). p-values shown were determined for coefficients estimated by generalized additive models fitted with a spline term of BMI and adjusted for cohort, age, and tumor grade. All statistical tests were two-sided.



Supplementary Figure 9. Association of BMI with the age-associated mutational signature (Signature.1) in patients with NST ER+/HER2- in different age groups, \leq 50 (a-c) and >50 years (d-f), from the ICGC cohort. a-b, d-e Violin/box plots showing the contribution in absolute count (left) and relative percentage (right) of the mutational signature 1 (MS1) (a, d) and the sequence context N[C>T]G (b, e) according to BMI categories (age \leq 50 lean, n = 26; overweight, n = 20; obese, n = 8; age >50 lean, n = 41; overweight, n = 44; obese, n = 38). In each boxplot, the box denotes the range from the 25th to the 75th percentile, the center line indicates the median value, and the whiskers specify the

maxima and minima excluding outliers. All statistical tests were two-sided. Wald test p-values determined for coefficients estimated by linear regressions adjusted for age continuous) and tumor grade (G3 vs G1/G2), are reported and were not corrected for multiple testing. **c**, **f** Bar plots presenting the number of oncogenic mutations occurring in BC-specific driver genes in each tumor. The count of mutations having the sequence context N[C>T]G is highlighted in bold colors. Each bar represents a tumor.



Supplementary Figure 10. Gene expression of relevant genes in the BC-obesity axis in NST ER+/HER2- tumors from patients of different BMI categories in the MINDACT cohort. Violin/box plots showing the expression levels of selected genes according to BMI categories (lean, n = 354; overweight, n = 250; obese, n = 131). The expression values (log10-transformed) presented here had been normalized prior to data retrieval. In each boxplot, the box denotes the range from the 25th to the 75th percentile, the center line indicates the median value, and the whiskers specify the maxima and minima excluding outliers.



Supplementary Figure 11. Gene expression of relevant genes in the BC-obesity axis in NST ER-/HER2- tumors from patients of different BMI categories in the MINDACT cohort. Violin/box plots showing the expression levels of selected genes according to BMI categories (lean, n = 53; overweight, n = 54; obese, n = 11). The expression values (log10-transformed) presented here had been normalized prior to data retrieval. In each boxplot, the box denotes the range from the 25th to the 75th percentile, the center line indicates the median value, and the whiskers specify the maxima and minima excluding outliers.



Supplementary Figure 12. Gene expression of relevant genes in the BC-obesity axis in ILC ER+/HER2- tumors from patients of different BMI categories in the MINDACT cohort. Violin/box plots showing the expression levels of selected genes according to BMI categories (lean, n = 65; overweight, n = 32; obese, n = 7). The expression values (log10-transformed) presented here had been normalized prior to data retrieval. In each boxplot, the box denotes the range from the 25th to the 75th percentile, the center line indicates the median value, and the whiskers specify the maxima and minima excluding outliers.



Supplementary Figure 13. Differentially enriched hallmarks in NST ER+/HER2- tumors from obese patients compared to lean patients. Lollipop plots displaying differentially enriched molecular hallmarks detected by GSEA (q-value < 0.05) in at least one of the analyzed cohorts. The signs of the normalized enrichment score (NES) indicate the orientation of the differential enrichments (positive: enriched in tumors from obese patients, negative: enriched in tumors from lean patients). Lollipops with solid segments represent the main cohort discussed in the main text (i.e. MINDACT) and those with dashed segments represent the other cohorts.



Supplementary Figure 14. Differentially enriched hallmarks in NST ER-/HER2- tumors from obese patients compared

to lean patients. Lollipop plots displaying differentially enriched molecular hallmarks detected by GSEA (q-value < 0.05) in at least one of the analyzed cohorts. The signs of the normalized enrichment score (NES) indicate the orientation of the differential enrichments (positive: enriched in tumors from obese patients, negative: enriched in tumors from lean patients). Lollipops with solid segments represent the main cohort discussed in the main text (i.e. MINDACT) and those with dashed segments represent the other cohorts.



Supplementary Figure 15. Differentially enriched hallmarks in ILC ER+/HER2- tumors from obese patients compared to lean patients. Lollipop plots displaying differentially enriched molecular hallmarks detected by GSEA (q-value < 0.05) in at least one of the analyzed cohorts. The signs of the normalized enrichment score (NES) indicate the orientation of the differential enrichments (positive: enriched in tumors from obese patients, negative: enriched in tumors from lean patients). Lollipops with solid segments represent the main cohort discussed in the main text (i.e. MINDACT) and those with dashed segments represent the other cohorts.



Supplementary Figure 16. Differentially enriched hallmarks in NST ER+/HER2- tumors from overweight patients compared to lean patients. Lollipop plots displaying differentially enriched molecular hallmarks detected by GSEA (q-value < 0.05) in at least one of the analyzed cohorts. The signs of the normalized enrichment score (NES) indicate the orientation of the differential enrichments (positive: enriched in tumors from overweight patients, negative: enriched in tumors from lean patients). Lollipops with solid segments represent the main cohort discussed in the main text (i.e. MINDACT) and those with dashed segments represent the other cohorts.



Supplementary Figure 17. Differentially enriched hallmarks in NST ER-/HER2- tumors from overweight patients compared to lean patients. Lollipop plots displaying differentially enriched molecular hallmarks detected by GSEA (q-value < 0.05) in at least one of the analyzed cohorts. The signs of the normalized enrichment score (NES) indicate the orientation of the differential enrichments (positive: enriched in tumors from overweight patients, negative: enriched in tumors from lean patients). Lollipops with solid segments represent the main cohort discussed in the main text (i.e. MINDACT) and those with dashed segments represent the other cohorts.



Supplementary Figure 18. Differentially enriched hallmarks in ILC ER+/HER2- tumors from overweight patients compared to lean patients. Lollipop plots displaying differentially enriched molecular hallmarks detected by GSEA (q-value < 0.05) in at least one of the analyzed cohorts. The signs of the normalized enrichment score (NES) indicate the orientation of the differential enrichments (positive: enriched in tumors from overweight patients, negative: enriched in tumors from lean patients). Lollipops with solid segments represent the main cohort discussed in the main text (i.e. MINDACT) and those with dashed segments represent the other cohorts.



Supplementary Figure 19. Cell fractions of 22 immune cell types in the tumor bulk of NST ER+/HER2- tumors from the MINDACT cohort. Violin/box plots showing relative frequency of 22 immune cells inferred by deconvolution of the bulk profiling data using CIBERSORTx according to BMI categories (lean, n = 354; overweight, n = 250; obese, n = 65). In each boxplot, the box denotes the range from the 25th to the 75th percentile, the center line indicates the median value, and the whiskers specify the maxima and minima excluding outliers. Comparisons with p-value < 0.05 are indicated. p-values shown were derived from Wilcoxon's ranked sum tests. All statistical tests were two-sided.



Supplementary Figure 20. Cell fractions of 22 immune cell types in the tumor bulk of NST ER-/HER2- tumors from the MINDACT cohort. Violin plots showing relative frequency of 22 immune cells inferred by deconvolution of the bulk profiling data using CIBERSORTx according to BMI categories (lean, n = 53; overweight, n = 54; obese, n = 11). In each boxplot, the box denotes the range from the 25th to the 75th percentile, the center line indicates the median value, and the whiskers specify the maxima and minima excluding outliers.



Supplementary Figure 21. Cell fractions of 22 immune cell types in the tumor bulk of ILC ER+/HER2- tumors from the MINDACT cohort. Violin plots showing relative frequency of 22 immune cells inferred by deconvolution of the bulk profiling data using CIBERSORTx according to BMI categories (lean, n = 65; overweight, n = 32; obese, n = 7). In each boxplot, the box denotes the range from the 25th to the 75th percentile, the center line indicates the median value, and the whiskers specify the maxima and minima excluding outliers.



Supplementary Figure 22. Uniform Manifold Approximation and Projection (UMAP) of cells in tumors from NST ER+/HER2- and NST ER-/HER2- patients from the Biokey cohort. a-c UMAP of cells from all patients color-coded according to cell type (a), tumor subtype (b), and BMI category of the patient (c). d-g UMAPs of cells from NST ER+/HER2- (d-e) and NST ER-/HER2- (f-g) color-coded according to cell type and BMI category.



Supplementary Figure 23. Cell type-specific differential gene expression in overweight versus lean patients with NST ER+/HER2- and NST ER-/HER2- from the BioKey cohort. a-b Volcano plots highlighting cancer cell-specific DEGs between overweight and lean in the NST ER+/HER2- (a) and NST ER-/HER2- (b) subgroups. Genes with absolute logFC > 0.5 and q-value < 0.05 are colored (red: upregulated in cancer cells from overweight patients, green: upregulated in

cancer cells from lean patients). The top 20 up-regulated (sorted by q-value), 20 down-regulated genes, and genes discussed in the main text (in bold) are labeled. **c** Heatmaps showing differential expression of a selection of genes involved in several immune and cancer pathways in non-malignant cell populations. The cell color is scaled based on the log-fold change (logFC) values (overweight vs lean) estimated by the MAST test. Gray cells indicate genes not being tested due to expression in less than 10% of the corresponding cell type in both BMI categories. *, q-value < 0.05

Denditic cell



Fibroblast

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q-value

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B cell

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Endothelial cell

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prostanoid metabolic process	-		
icosanoid biosynthetic process	-		
b cell mediated immunity	-		•
peptide antigen assembly with mhc protein complex	-		
chemokine production	-		
immunoglobulin production involved in immunoglobulin mediated immune response	-		
attisted muscle adaptation			-
strated muscle adaptable			
noosone assentio	-		
negative regulation of leukocyte migration	-		-
icosanoid metabolic process	-		-
adaptive immune response based on somatic recombination of immune receptors built from immunoglobulin superfamily domains	-		•
response to muscle stretch	-		•
cellular response to gamma radiation	-		•
unsaturated fatty acid biosynthetic process	-		<u> </u>
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acidic amino acid transport	-	_	
ear morphogenesis	-	_	
digestive system development	-	_	
camera type eye morphogenesis	-	_	
aorta development	-	_	
artery morphogenesis	-	_	
embryonic organ morphogenesis	-	_	
amino acid transport	-	_	
artery development		_	
angiogenesis involved in wound healing	- 6	_	
cell differentiation involved in kidney development	-	_	
cellular response to acid chemical	-		
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Mf/Mono

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icosanció biosynthetic process intermediate filament based process		actin polymerization or depolymerization aminogiycan biosynthetic process - carbohydrate nol weisiana
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Supplementary Figure 24. Gene set enrichment analysis (GSEA) on Gene Ontology biological process (GOBP) gene sets of non-malignant cells from obese versus lean patients with NST ER+/HER2- from the BioKey cohort. Lollipop plots displaying top 20 upregulated (sorted by q-value, NES > 0) and top 20 downregulated (NES < 0) GOBP gene sets according to BMI category (obese vs lean) detected by GSEA (q-value < 0.1). p-values were computed by permutation and adjusted for multiple testing using the Benjamin-Hochberg method (presented as q-values).



Supplementary Figure 25. Gene set enrichment analysis (GSEA) on REACTOME gene sets of nonmalignant cells from obese versus lean patients with NST ER+/HER2- from the BioKey cohort. Lollipop plots displaying top 20 upregulated (sorted by q-value, NES > 0) and top 20 downregulated (NES < 0) REACTOME gene sets according to BMI category (obese vs lean) detected by GSEA (q-value < 0.1). p-values were computed by permutation and adjusted for multiple testing using the Benjamin-Hochberg method (presented as q-values).



Supplementary Figure 26. Gene set enrichment analysis (GSEA) on GO biological process gene sets of non-malignant cells from obese versus lean patients with NST ER-/HER2- from the BioKey cohort. Lollipop plots displaying top 20 upregulated (sorted by q-value, NES > 0) and top 20 downregulated (NES < 0) GOBP gene sets according to BMI category (obese vs lean) detected by GSEA (q-value < 0.1). p-values were computed by permutation and adjusted for multiple testing using the Benjamin-Hochberg method (presented as q-values).



Supplementary Figure 27. Gene set enrichment analysis (GSEA) on REACTOME gene sets of nonmalignant cells from obese versus lean patients with NST ER-/HER2- from the BioKey cohort. Lollipop plots displaying top 20 upregulated (sorted by q-value, NES > 0) and top 20 downregulated (NES < 0) REACTOME gene sets according to BMI category (obese vs lean) detected by GSEA (q-value < 0.1). p-values were computed by permutation and adjusted for multiple testing using the Benjamin-Hochberg method (presented as q-values).



Supplementary Figure 28. Total intercellular interactions in tumors from lean and obese patients in the BioKey cohort. a-b Sum of signaling interactions in terms of number and strength inferred by CellChat in NST ER+/HER2- (a) and NST ER-/HER2- (b) tumors from lean and obese patients.



Supplementary Figure 29. Differences in the cell composition and intercellular interactions within the tumor microenvironment between overweight and lean patients with NST ER+/HER2- (a-d) and NST ER-/HER2- (e-h) tumors from the BioKey cohort. a, e Frequency of non-malignant cell types relative to the non-malignant cell pool for lean and overweight patients (NST ER+/HER2- lean, n = 6; overweight, n = 3; NST ER-/HER2- lean, n = 8; overweight, n = 2). In each boxplot, the box denotes the range from the 25th to the 75th percentile, the center line indicates the median value, and the whiskers specify the maxima and minima excluding outliers. b, f CellChat-derived outgoing and incoming interaction strength from and to cancer cells and non-malignant cells in tumors from lean and overweight patients. c, g Differential number of interactions detected by CellChat between lean and overweight. d, h Relative Information flow of signaling pathways in the intercellular communication network in tumors from lean and overweight patients. The relative information flow was estimated by the sum of CellChat-derived communication

probability between all pairs of cell compartments in the network. Signaling pathways with non-zero information in at least one of the BMI categories are shown.