

Figure S1. Immunohistochemical analysis of L1 lactating mammary glands of wild-type mice and mice with conditional *ErbB4* knock-out under the mammary-specific WAP promoter (*ErbB4^{flox/flox}Wap-Cre^{+/-}*). Paraffin sections were stained with anti-ErbB4 (sc-283). Anti-phosphotyrosine (pTyr) antibody (4G10) was used as a positive control and nonspecific mouse IgG (clone 3G6) as a negative control.

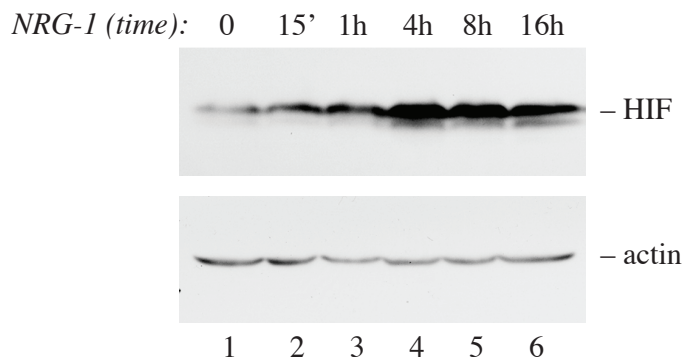
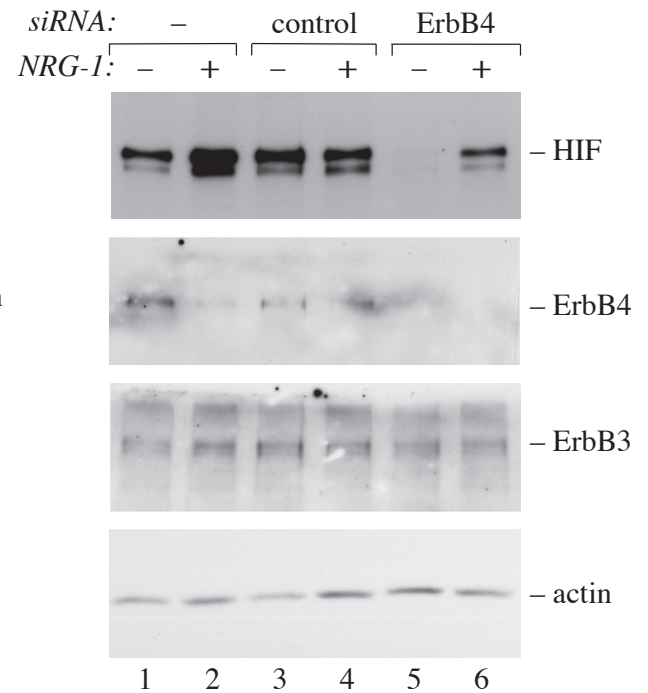
A**B**

Figure S2. A) Time course analysis of the effect of NRG-1 treatment on HIF-1 α protein level. MCF-7 cells were treated with 200 μ M CoCl₂ for 16 hours and with 50 ng/ml NRG-1 for the indicated periods of time and analyzed for HIF-1 α expression by Western blotting. B) Western analysis of the effect of ErbB4 knock-down by siRNAs on HIF-1 α protein accumulation in the presence of CoCl₂. MCF-7 cells were transfected with no siRNA, non-specific control siRNA or ErbB4-targeting siRNA. Twenty-four hours later, the cells were treated with 200 μ M CoCl₂ and with or without 50 ng/ml NRG-1 for another 24 hours.

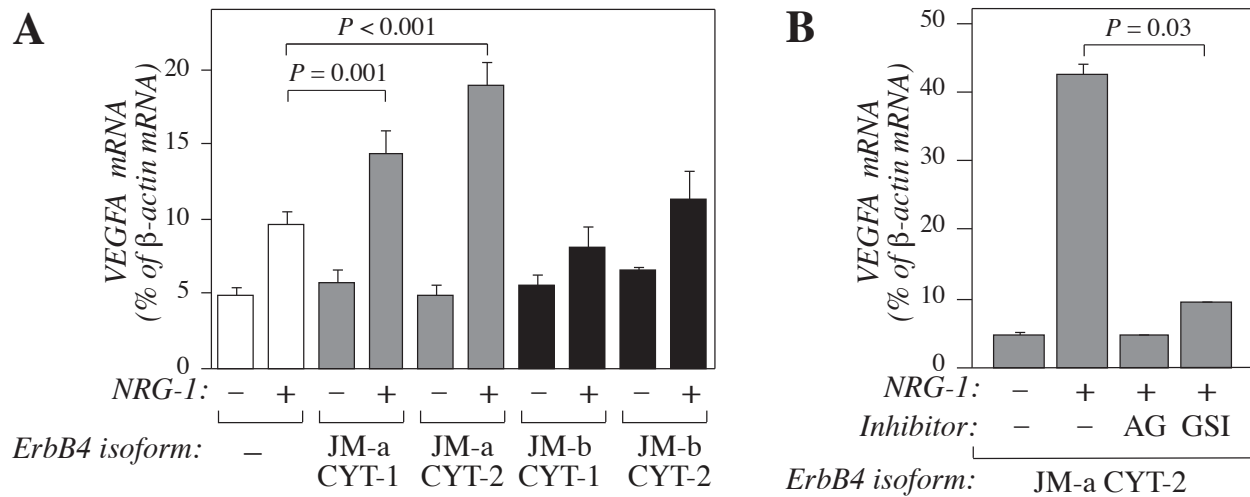


Figure S3. Cleaved ErbB4 isoforms promote *VEGFA* expression. A) MCF-7 cells were transfected with an empty vector or plasmids encoding the indicated isoforms of ErbB4. Cells were treated with 0 or 50 ng/ml NRG-1 for 24 hours in 0% FCS. *VEGFA* mRNA expression was analyzed by real-time RT-PCR. B) MCF-7 transfectants expressing ErbB4 JM-a CYT-2 were treated for 24 hours with 0 or 50 ng/ml NRG-1 to stimulate ErbB4 activity, and with 10 μ M AG 1478 or 25 μ M GSI IX, to block ErbB4 kinase activity and proteolytic release of soluble ErbB4 ICD, respectively. *VEGFA* mRNA expression was analyzed by real-time RT-PCR.

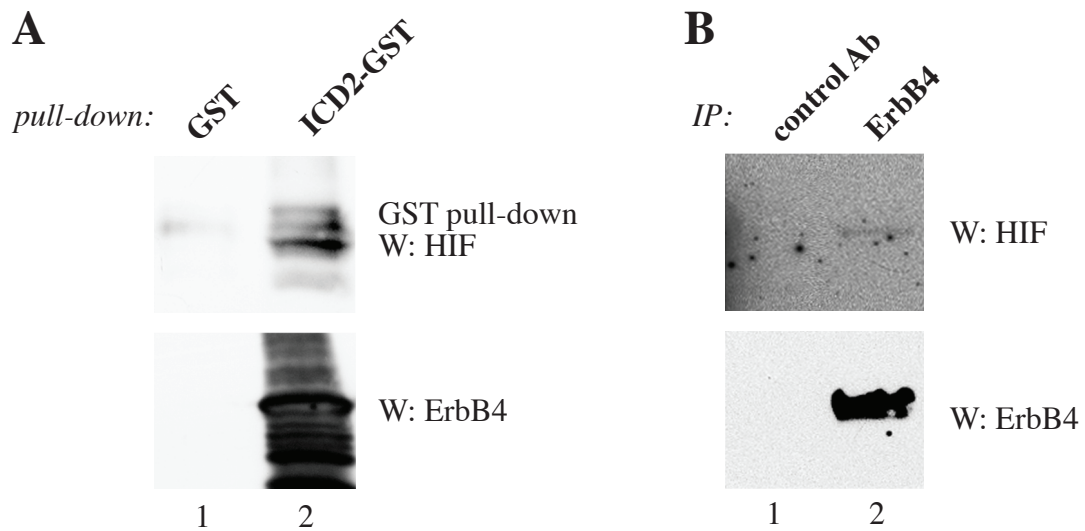


Figure S4. Interaction between HIF-1 α and ErbB4. A) Bacterially expressed HIF-1 α co-precipitated with bacterially expressed GST fusion of ErbB4 ICD2 (ICD2-GST) (lane 2) but not with GST alone (lane 1). Western analysis with anti-HIF1 α antibody and anti-ErbB4 antibody is shown. B) Parental MCF-7 cells were cultured for four hours in 1% O₂. Cell lysates were precipitated with an antibody against the Flag epitope (control Ab) or with anti-ErbB4 followed by Western blotting with anti-HIF-1 α or anti ErbB4.

ERBB4 correlations									
Normal tissue	EPO (n)	EPO (r)	EPO (p)	CAIX (n)	CAIX (r)	CAIX (p)	GLUT1 (n)	GLUT1 (r)	GLUT1 (p)
adipose tissue	2			2			2		
bladder	17	-0,053	0,84	17	0,118	0,65	17	0,599	0,011
blood lymphoid cell	41	-0,112	0,49	41	-0,046	0,78	41	0,082	0,61
blood myeloid cell	24	0,415	0,044	25	-0,414	0,039	26	0,165	0,42
blood unspecified leukocyte	2			2			2		
blood vessel	2			2			2		
bone	4	-0,905		4	0,872		4	-0,98	
bone marrow	5	0,53		5	0,932		5	0,995	
bone marrow lymphoid cell	43	-0,133	0,4	43	0,146	0,35	43	0,383	0,011
bone marrow myeloid cell	6	0,702	0,12	6	0,363	0,48	6	-0,512	0,3
breast	10	-0,234	0,52	10	0,467	0,17	10	0,323	0,36
colorectal	21	0,215	0,35	21	0,078	0,74	21	0,235	0,31
endocrine system	19	0,164	0,5	21	-0,123	0,6	24	0,445	0,029
heart	36	0,114	0,51	43	0,469	0,0015	46	0,04	0,8
kidney	25	0,271	0,19	26	0,445	0,023	27	0,459	0,016
liver	14	0,186	0,53	14	0,412	0,14	17	-0,19	0,47
lymphatic system	30	-0,021	0,91	35	-0,171	0,33	35	-0,02	0,9
muscle	105	0,043	0,67	105	0,333	0,00051	105	0,383	0,00055
nervous system	210	0,137	0,047	222	0,207	0,0019	227	0,092	0,17
other GI	12	0,192	0,55	12	0,712	0,0094	12	-0,05	0,88
other urogenital system				3			3		
ovary	12	0,14	0,66	12	-0,302	0,34	12	0,153	0,63
pancreas	20	0,121	0,61	21	0,255	0,27	21	0,375	0,094
placenta	8	0,143	0,74	12	0,078	0,81	13	-0,233	0,44
prostate	68	0,345	0,004	71	0,145	0,23	71	0,399	0,00057
respiratory system	177	0,099	0,19	181	0,376	0,0000019	181	0,426	2,2E-09
salivary gland	3			4	0,905		5	-0,28	
skin	5	0,971		5	0,662		5	0,904	
testis	17	-0,025	0,92	19	-0,078	0,75	19	0,203	0,41
tongue	2			2			2		
uterus	31	0,471	0,0075	32	0,403	0,022	33	0,362	0,039
Normal tissues	971			1018			1037		
Normal with P < 0.05	333			646			501		
Cancer	EPO (n)	EPO (r)	EPO (p)	CAIX (n)	CAIX (r)	CAIX (p)	GLUT1 (n)	GLUT1 (r)	GLUT1 (p)
adrenal gland cancer	11	-0,087	0,8	11	-0,3607	0,28	11	-0,001	1
ALL	716	0,198	9,90E-08	716	0,1893	3,40E-07	714	0,176	2,20E-06
AML	377	-0,086	0,095	377	0,2197	1,70E-05	379	0,074	0,15
bladder cancer	75	0,346	0,0023	100	0,0617	0,54	100	-0,1418	0,16
breast cancer	373	0,062	0,24	373	-0,0567	0,28	373	0,0117	0,82
colorectal cancer	132	0,029	0,74	132	-0,0313	0,72	132	0,2231	0,01
glioma	219	0,034	0,62	219	-0,1063	0,12	219	-0,0222	0,74
head and neck cancer	3			3			3		
kidney cancer	53	0,151	0,28	53	-0,03	0,83	53	0,1174	0,4
lung cancer	346	0,136	0,012	346	0,0868	0,11	346	0,0089	0,87
lung carcinoid tumor	20	-0,223	0,34	20	0,1136	0,63	20	-0,0226	0,92
lymphoma	103	-0,141	0,16	103	0,0141	0,89	103	0,1015	0,31
melanoma	11	-0,526	0,097	11	0,3859	0,24	11	-0,0833	0,8
mesothelioma	44	0,273	0,073	44	-0,0701	0,65	44	0,1367	0,38
myeloma	255	-0,07	0,27	255	-0,0308	0,62	255	0,1538	0,014
neuroblastoma	22	-0,066	0,77	22	0,4302	0,046	22	0,4132	0,056
other GI cancer	12	0,201	0,53	12	-0,4126	0,18	12	0,5271	0,078
other neuroectodermal cancer	80	-0,132		81	-0,0038		81	0,0541	
other urogenital tumor	11	-0,329	0,32	11	-0,478	0,14	11	-0,5956	0,053
ovarian cancer	239	0,095	0,14	239	-0,0593	0,36	239	0,1521	0,019
pancreatic cancer	23	0,491	0,017	23	-0,1606	0,46	23	-0,0982	0,66
prostate cancer	237	0,049	0,45	239	0,0327	0,62	241	0,2049	0,0014
sarcoma	64	0,078	0,54	64	0,4035	0,00095	64	0,4014	0,001
testicular cancer	75	0,264	0,022	75	0,1194	0,31	75	-0,1509	0,2
thyroid cancer	9	-0,32	0,4	9	-0,1136	0,77	9	0,1335	0,73
uterine cancer	62	0,107	0,41	62	0,0075	0,95	62	-0,0161	0,9
Cancers	3572			3600			3602		
Cancers with P < 0.05	1235			1179			1645		
TOTAL (normal + cancer)	4543			4618			4639		
TOTAL P < 0.05	1568			1825			2146		

Table S1. Correlation of *ERBB4* expression with the expression of HIF-1 α -regulated genes *in vivo*. mRNA expression levels of *ERBB4* and HIF-1 α -regulated genes *EPO*, *CAIX* and *GLUT1* were analyzed from published microarray data. Pearson's correlations from normal human tissues and clinical cancer samples were analyzed separately for each tissue and cancer type. Pearson's correlations (r), number of samples (n) and probability value associated with correlation (p) are displayed.

NRG1 correlations									
Normal tissue	EPO (n)	EPO (r)	EPO (p)	CAIX (n)	CAIX (r)	CAIX (p)	GLUT1 (n)	GLUT1 (r)	GLUT1 (p)
adipose tissue	2			2			2		
bladder	17	-0,127	0,63	17	0,095	0,72	17	0,357	0,16
blood lymphoid cell	41	0,136	0,39	41	0,148	0,36	41	-0,147	0,36
blood myeloid cell	24	0,089	0,68	24	0,505	0,012	24	0,083	0,7
blood unspecified leukocyte	2			2			2		
blood vessel	2			2			2		
bone	4	-0,897		4	0,874		4	-0,991	
bone marrow	5	0,891		5	0,187		5	0,261	
bone marrow lymphoid cell	43	0,049	0,76	43	0,173	0,27	43	0,201	0,2
bone marrow myeloid cell	6	0,591	0,22	6	0,783	0,066	6	-0,202	0,7
breast	10	-0,186	0,61	10	0,254	0,48	10	0,541	0,11
colorectal	21	0,27	0,24	21	-0,112	0,63	21	-0,144	0,53
endocrine system	19	0,091	0,71	21	0,204	0,37	25	0,173	0,41
heart	36	0,783	1,70E-08	43	0,334	0,029	46	0,681	1,90E-07
kidney	25	0,324	0,11	26	0,029	0,89	28	0,122	0,54
liver	14	0,267	0,36	15	0,537	0,039	18	0,222	0,38
lymphatic system	30	-0,124	0,52	36	0,068	0,69	36	-0,151	0,38
muscle	105	0,231	0,018	105	0,139	0,16	105	0,194	0,048
nervous system	210	-0,036	0,6	223	0,017	0,8	228	-0,024	0,72
other GI	12	0,372	0,23	12	0,608	0,036	12	0,156	0,63
other urogenital system	3			3			3		
ovary	12	0,619	0,032	12	-0,555	0,061	12	-0,109	0,74
pancreas	20	-0,253	0,28	22	0,513	0,015	22	0,476	0,025
placenta	9	-0,157	0,69	13	0,544	0,055	14	0,234	0,42
prostate	68	0,326	0,0066	71	0,379	0,0011	71	0,61	1,70E-08
respiratory system	177	0,024	0,76	181	0,072	0,33	181	-0,106	0,16
salivary gland	3			4	0,718		5	0,285	
skin	5	-0,286		5	-0,034		5	-0,604	
testis	17	-0,018	0,95	19	0,116	0,64	19	0,053	0,83
tongue	2			2			2		
uterus	31	0,345	0,058	32	0,319	0,075	33	0,11	0,54
Normal tissues	975			1022			1042		
Normal with P < 0.05	333			646			503		
Cancer	EPO (n)	EPO (r)	EPO (p)	CAIX (n)	CAIX (r)	CAIX (p)	GLUT1 (n)	GLUT1 (r)	GLUT1 (p)
adrenal gland cancer	11	-0,1647	0,63	11	-0,23	0,5	11	-0,171	0,61
ALL	716	0,0689	0,066	716	0,183	7,70E-07	714	0,13	0,00049
AML	377	-0,0502	0,33	378	0,224	1,10E-05	379	0,108	0,035
bladder cancer	80	0,3908	0,00034	95	0,02	0,84	95	-0,089	0,39
breast cancer	373	0,2093	4,60E-05	373	0,329	7,50E-11	373	0,291	1,10E-08
colorectal cancer	132	0,0782	0,37	132	-0,118	0,18	132	0,174	0,046
glioma	219	0,1597	0,018	219	0,197	0,0034	219	-0,062	0,36
head and neck cancer	3			3			3		
kidney cancer	53	-0,0575	0,68	53	-0,38	0,005	53	-0,098	0,49
lung cancer	346	0,2142	5,90E-05	346	0,03	0,57	346	0,211	7,50E-05
lung carcinoid tumor	20	-0,1164	0,63	20	0,039	0,87	20	-0,048	0,84
lymphoma	103	0,0914	0,36	103	0,317	0,0011	103	0,401	2,70E-05
melanoma	11	0,1963	0,56	11	0,269	0,42	11	0,424	0,19
mesothelioma	44	0,1211	0,43	44	-0,251	0,1	44	0,047	0,76
myeloma	255	0,0074	0,9	255	0,094	0,13	255	0,265	1,80E-05
neuroblastoma	22	-0,0882	0,7	22	-0,2	0,37	22	-0,187	0,4
other GI cancer	12	-0,0355	0,91	12	0,906	4,90E-05	12	-0,634	0,027
other neuroectodermal cancer	80	-0,0141		81	0,035		81	0,17	
other urogenital tumor	11	0,3366	0,31	11	0,288	0,39	11	0,454	0,16
ovarian cancer	239	0,0119	0,85	239	0,015	0,82	239	0,062	0,34
pancreatic cancer	23	0,5611	0,0053	23	-0,238	0,27	23	-0,406	0,055
prostate cancer	237	0,1947	0,0026	239	0,191	0,0031	241	0,583	0
sarcoma	64	0,0801	0,53	64	0,036	0,78	64	-0,127	0,32
testicular cancer	75	0,0228	0,85	75	0,185	0,11	75	0,033	0,78
thyroid cancer	9	-0,0274	0,94	9	-0,595	0,09	9	-0,206	0,6
uterine cancer	62	0,4672	0,00013	62	0,09	0,49	62	0,159	0,22
Cancers	3577			3596			3597		
Cancers with P < 0.05	1240			1180			1645		
TOTAL (normal + cancer)	4552			4618			4639		
TOTAL with P < 0.05	1573			1826			2148		

Table S2. Correlation of *NRG1* expression with the expression of HIF-1 α -regulated genes *in vivo*. mRNA expression levels of *NRG1* and HIF-1 α -regulated genes *EPO*, *CAIX* and *GLUT1* were analyzed from published microarray data. Pearson's correlations from normal human tissues and clinical cancer samples were analyzed separately for each tissue and cancer type. Pearson's correlations (r), number of samples (n) and probability value associated with correlation (p) are displayed.