

S10 Table. Cox proportional hazards model of survival for patients with and without insulin and/or metformin exposure before the diagnosis of breast cancer (included HER2-available patients only)

Variable	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	p-value	Hazard ratio (95% CI)	p-value
Histologic type				
IDC	1		1	
ILC	2.206 (0.683-7.127)	0.186	1.216 (0.267-3.945)	0.775
Others	0.230 (0.056-0.948)	0.042	0.392 (0.044-1.491)	0.197
Stage: T				
T1	1		1	
T0	1.609 (0.013-12.408)	0.759	0.767 (0.005-9.917)	0.865
T2	2.447 (1.277-5.029)	0.006	1.973 (0.993-4.173)	0.052
T3	5.197 (1.974-12.875)	0.002	2.298 (0.753-6.715)	0.140
T4	4.923 (0.532-20.742)	0.132	0.936 (0.073-6.838)	0.952
Tis	0.701 (0.076-2.937)	0.669	2.064 (0.155-27.602)	0.552
Stage: N				
N0	1		1	
N1	1.344 (0.652-2.771)	0.423	1.100 (0.508-2.307)	0.803
N2	2.214 (0.826-5.932)	0.114	2.080 (0.681-5.431)	0.184
N3	8.262 (4.137-16.499)	< 0.001	5.135 (2.151-11.825)	< 0.001
Stage: M				
M0	1		1	
M1	7.990 (2.479-25.755)	< 0.001	2.781 (0.656-8.975)	0.150
ER				
Negative	1		1	
Positive	0.838 (0.476-1.478)	0.543	0.989 (0.424-2.173)	0.978
PR				
Negative	1		1	

Positive	0.758 (0.432-1.330)	0.335	0.627 (0.292-1.425)	0.255
HER2				
Negative	1		1	
Positive	0.497 (0.242-1.023)	0.058	0.434 (0.191-0.904)	0.025
Age at diagnosis				
<40 years old	1		1	
40≤ years <50	0.598 (0.162-2.210)	0.440	0.644 (0.193-2.678)	0.512
≥50 years old	0.700 (0.216-2.272)	0.553	0.519 (0.173-2.051)	0.315
CCI	1.137 (1.011-1.279)	0.032	1.060 (0.921-1.215)	0.411
Exposure before breast cancer				
Reference: no exposure to either drug	1		1	
Exposure to insulin	4.389 (1.314-14.665)	0.016	4.478 (0.995-15.096)	0.051
Exposure to metformin	1.138 (0.585-2.213)	0.704	0.977 (0.481-1.922)	0.947
Exposure to insulin and metformin	2.143 (1.019-4.504)	0.044	1.927 (0.828-4.195)	0.124

CCI, Charlson comorbidity index; CI, confidence interval; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; M, metastasis; N, node; PR, progesterone receptor; T, tumor.