

Figure S1 Effects of oral intake of HRW on xenografted mice. Effects of oral intake of HRW on xenografted mice. All nine female BALB/c-nude mice weighing 18–25 g implanted with 1×10^7 AN3CA-LUC cells at right shoulder were fed with either HRW with the concentration of 1.0 ppm or control (NC) purified water (20 mL/kg/d) for 24 days. Six for HRW-fed groups (H1, H2, H3, H4, H5, H6); Three for purified water-fed groups (P1, P2, P3). (A) The tumor volume (mm^3) of the HRW group was decreased compared to the control group. (B) There was a trend in the relative tumor volume in the HRW group on day 1–24 compared to the control group. (C) The mice weight (g) in the HRW group was diminished on day 1–10, 19–24 compared to the control group. (D) Living tumor imaging after oral intake of HRW in xenografted mice. Photographs show tumor imaging in two groups, each containing three AN3CA-LUC cells—implanted mice per group in day 12 (H1, H2, H3, P1, P2, P3), day 13 (H1, H3, P2), day 24 (H2, P1, P3). The color scale is represented by ROI = radiance ($\text{p/sec/cm}^2/\text{sr}$). The color scale changes from blue to red, with the darker the color, the greater the tumor density. E. Mice subjected to HRW displayed a decreased ROI as assessed by luminescence analysis of Total Radiant Efficiency (day 12: HRW vs. NC, $5.90\text{E}+07$ vs. $4.60\text{E}+08$). Values are mean \pm SD of six mice per HRW group and three mice per NC group. HRW, hydrogen-rich water; NC, normal control.

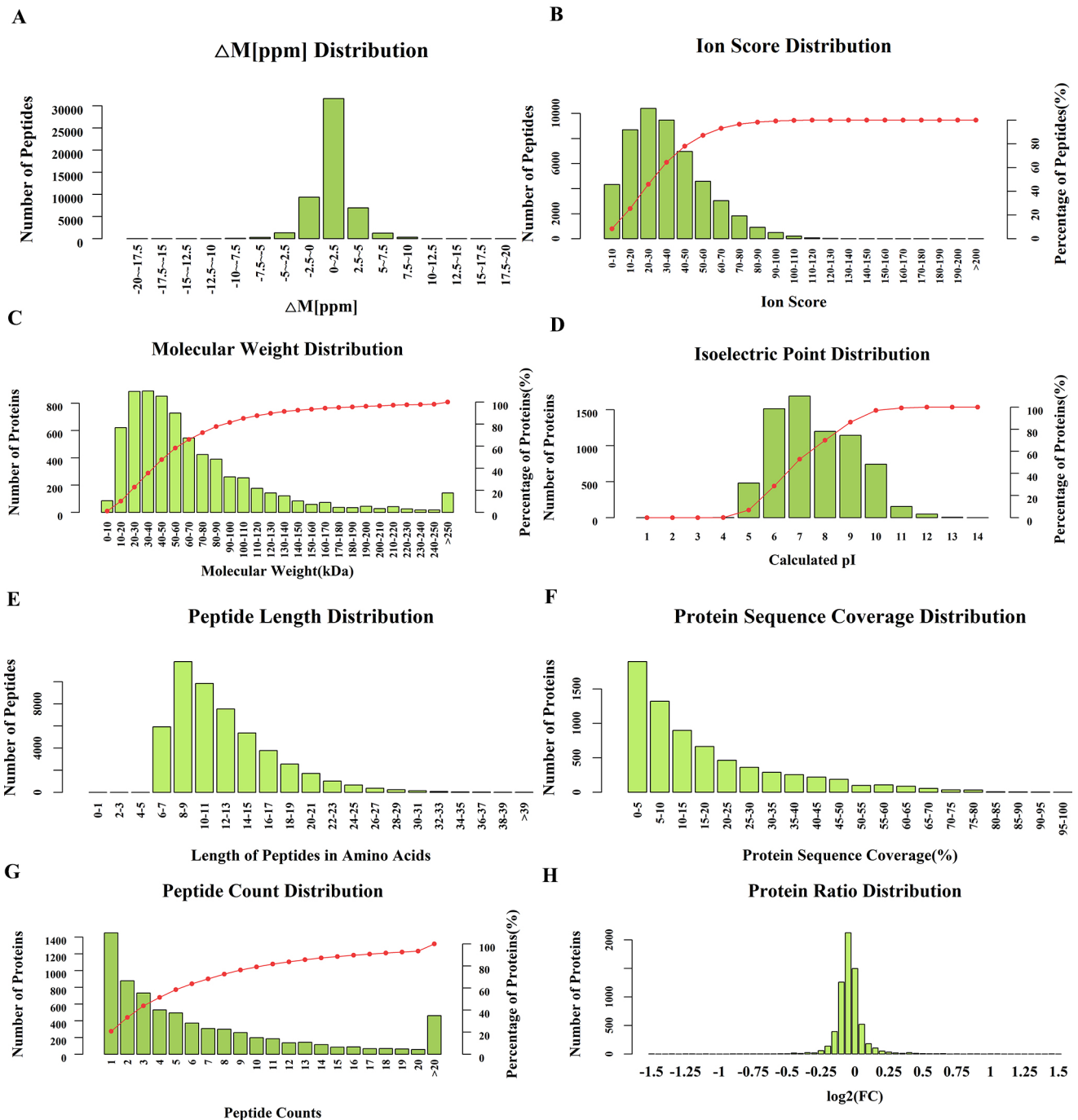


Figure S2 MASCOT derived protein and peptide identification profile. (A) DeltaM (ppm) distribution graph; (B) Ions score distribution; (C) molecular weight distribution; (D) isoelectric point distribution; (E) peptide length distribution; (F) protein sequence coverage distribution; (G) peptide count distribution; and (H) protein ratio distribution. Red lines indicate the percentage of peptides below the red spot.

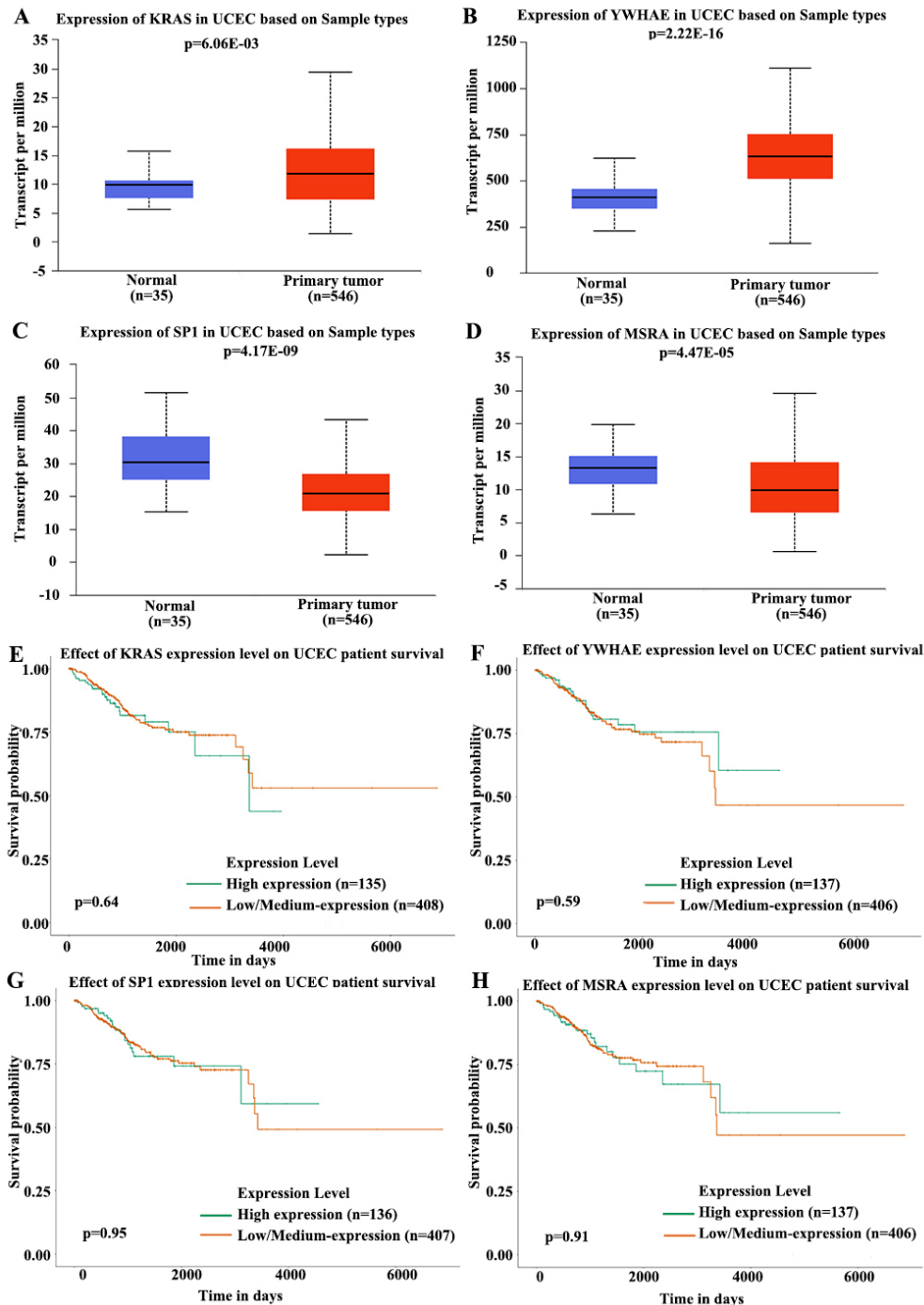


Figure S3 Expression and survival rate from the TCGA database of KRAS, YWHAE, SP1 and MSRA in the HRW group between EC and normal endometrial tissues. Expression of KRAS (A) (11.768 *vs.* 9.877, $P=6.06E-03$), YWHAE (B) (632.309 *vs.* 409.535, $P=2.22E-16$), SP1 (C) (20.929 *vs.* 30.431, $P=4.17E-09$), MSRA (D) (9.911 *vs.* 13.317, $P=4.47E-05$) were significantly different between EC and normal endometrial tissues. The 5-year survival rate between low/moderate expression versus high expression in KRAS (E) (0.78 *vs.* 0.75, $P=0.64$), YWHAE (F) (0.78 *vs.* 0.75, $P=0.59$), SP1 (G) (0.75 *vs.* 0.73, $P=0.95$), MSRA (H) (0.8 *vs.* 0.7, $P=0.91$) are also displayed. TCGA, The Cancer Genome Atlas; HRW, hydrogen-rich water; EC, endometrial cancer.

Table S1 Protein quantification and difference analysis

Accession	Gene name	Abundances A1	Abundances A2	Abundances A3	Abundances B1	Abundances B2	Abundances B3	Average A	Average B	A/B	P value
Q9D6Y7	<i>MSRA</i>	64.4	60.5	87.2	126.1	128.4	133.4	70.7	129.3	0.54679041	0.00242538
P32883	<i>KRAS</i>	84.8	70.7	80.6	113.9	112.3	137.7	78.7	121.3	0.64880462	0.00986105
O89090	<i>SP1</i>	90	80.7	98.1	99.8	117.8	113.7	89.6	110.433333	0.81134923	0.04827976
Q6PDM1	<i>Msl1</i>	80.7	91.5	93.7	101.8	118.5	113.8	88.6333333	111.366667	0.7958695	0.02366069
Q3UIL6	<i>Plekha7</i>	88.6	76.4	92.6	111.6	114.8	116	85.8666667	114.133333	0.75233645	0.00498638
Q9D0U1	<i>Dtwd2</i>	86.6	79.2	90.9	123.1	109.9	110.4	85.5666667	114.466667	0.74752475	0.00630704
Q920S3	<i>Gatad1</i>	114.5	131.5	113.7	61.2	99.4	79.7	119.9	80.1	1.4968789	0.03311027
Q6P5F7	<i>Ttyh3</i>	139.6	103.9	107.6	73.9	85.9	89.1	117.033333	82.9666667	1.41060667	0.04967401
Q9Z1J2	<i>Nek4</i>	126.9	101.8	120.9	76	85.5	88.9	116.533333	83.4666667	1.39616613	0.01765495
Q5U4C9	<i>Dyrk2</i>	109.6	116.9	111.8	76.7	100.2	84.8	112.766667	87.2333333	1.29270157	0.02412443
P70224	<i>Gimap1</i>	111.8	105.6	112.6	89.1	86.2	94.7	110	90	1.22222222	0.0038861
P62259	<i>YWHAE</i>	94.2	95.2	110.9	88.6	103.3	107.7	100.1	99.8666667	1.00233645	0.97788418

Table S2 The GO annotation—cellular component, molecular function and biological process analysis

Level	GO ID	GO name	GO type	#Seqs	Sequence names
Cellular component analysis					
2	GO:0016020	Membrane	C	1	P32883
2	GO:0044464	Cell part	C	3	O89090, Q6PDM1, P32883
2	GO:0043226	Organelle	C	3	O89090, Q6PDM1, P32883
2	GO:0032991	Protein-containing complex	C	2	O89090, Q6PDM1
2	GO:0044422	Organelle part	C	1	Q6PDM1
Molecular function analysis					
2	GO:0005488	Binding	F	8	O89090, Q3UIL6, Q9Z1J2, Q920S3, Q9D6Y7, P32883, P70224, Q5U4C9
2	GO:0003824	Catalytic activity	F	4	Q9D6Y7, P32883, Q9Z1J2, Q5U4C9
2	GO:0140110	Transcription regulator activity	F	1	O89090
Biological process analysis					
2	GO:0065007	Biological regulation	P	7	O89090, Q6PDM1, Q9Z1J2, Q920S3, P32883, Q9D6Y7, Q5U4C9
2	GO:0009987	Cellular process	P	5	Q6PDM1, Q9Z1J2, P32883, Q9D6Y7, Q5U4C9
2	GO:0008152	Metabolic process	P	5	Q6PDM1, Q9Z1J2, P32883, Q9D6Y7, Q5U4C9
2	GO:0071840	Cellular component organization or biogenesis	P	1	Q6PDM1

GO, Gene Ontology.

Table S3 The GO annotation—enrichment

GO ID	Term	Category	FDR	P value	#Diff	Over/under	Column1
GO:0043984	Histone H4-K16 acetylation	P	0.33224851	0.0016	1	Over	-2.8020893
GO:0008113	Peptide-methionine (S)-S-oxide reductase activity	F	0.21114953	0.0016	1	Over	-2.8020893
GO:0072487	MSL complex	C	0.3145793	0.0063	1	Over	-2.2009637
GO:0004672	Protein kinase activity	F	0.07579541	0.0141	2	Over	-1.8498393
GO:0006464	Cellular protein modification process	P	0.3145793	0.0172	1	Over	-1.7638098
GO:0005525	GTP binding	F	0.15025453	0.0383	2	Over	-1.4166951
GO:0006468	Protein phosphorylation	P	0.14046766	0.0478	2	Over	-1.3204971
GO:0006357	Regulation of transcription by RNA polymerase II	P	0.39015907	0.0614	1	Over	-1.2121453
GO:0043565	Sequence-specific DNA binding	F	0.39015907	0.0864	1	Over	-1.0635901
GO:0003700	DNA-binding transcription factor activity	F	0.3052702	0.1388	1	Over	-0.8577383
GO:0045449	Regulation of transcription, DNA-templated	P	0.1687281	0.1632	1	Over	-0.7871714
GO:0005667	Transcription factor complex	C	0.3145793	0.2014	1	Over	-0.6960365
GO:0003924	GTPase activity	F	0.3145793	0.2179	1	Over	-0.6616963
GO:0016020	Membrane	C	0.04616765	0.2192	1	Over	-0.6591897
GO:0007165	Signal transduction	P	0.01735016	0.2342	1	Over	-0.6304537
GO:0005524	ATP binding	F	1	0.2385	2	Over	-0.6225449
GO:0055114	Oxidation-reduction process	P	0.3145793	0.2513	1	Over	-0.5997396
GO:0006355	Regulation of transcription, DNA-templated	P	0.3145793	0.2574	1	Over	-0.58942
GO:0008270	Zinc ion binding	F	0.3145793	0.2869	1	Over	-0.542206
GO:0005634	Nucleus	C	0.01735016	0.3631	1	Over	-0.4400207
GO:0003676	Nucleic acid binding	F	0.3145793	0.3724	1	Over	-0.4289617
GO:0005515	Protein binding	F	0.07579541	1	1	Under	0

GO, Gene Ontology.

Table S4 KEGG pathway annotation

Map ID	Map name	P value	FDR	Over/under	DiffSeqs	Column1
ko04137	Mitophagy—animal	0.001881647	0.136636429	Over	O89090 P32883	-2.72546
ko01522	Endocrine resistance	0.002452453	0.05991131	Over	O89090 P32883	-2.6104
ko05224	Breast cancer	0.002452453	0.05991131	Over	O89090 P32883	-2.6104
ko04915	Estrogen signaling pathway	0.003443179	0.136636429	Over	O89090 P32883	-2.46304
ko05231	Choline metabolism in cancer	0.003443179	0.05991131	Over	O89090 P32883	-2.46304
ko05163	Human cytomegalovirus infection	0.014359787	0.136636429	Over	O89090 P32883	-1.84285
ko04320	Dorso-ventral axis formation	0.018778794	0.136636429	Over	P32883	-1.72633
ko05216	Thyroid cancer	0.028047455	0.136636429	Over	P32883	-1.55211
ko04960	Aldosterone-regulated sodium reabsorption	0.02958447	0.195717324	Over	P32883	-1.52894
ko04927	Cortisol synthesis and secretion	0.031119275	0.136636429	Over	O89090	-1.50697
ko05219	Bladder cancer	0.034182268	0.136636429	Over	P32883	-1.4662
ko05200	Pathways in cancer	0.044426876	0.136636429	Over	O89090 P32883	-1.35235
ko05218	Melanoma	0.044833546	0.05991131	Over	P32883	-1.3484
ko04730	Long-term depression	0.047857093	0.05991131	Over	P32883	-1.32005
ko04916	Melanogenesis	0.047857093	0.136636429	Over	P32883	-1.32005
ko04214	Apoptosis—fly	0.052376101	0.199170754	Over	P32883	-1.28087
ko04370	VEGF signaling pathway	0.052376101	0.136636429	Over	P32883	-1.28087
ko04720	Long-term potentiation	0.052376101	0.136636429	Over	P32883	-1.28087
ko04917	Prolactin signaling pathway	0.052376101	0.157759072	Over	P32883	-1.28087
ko05213	Endometrial cancer (EC)	0.053878099	0.155952366	Over	P32883	-1.26859
ko04213	Longevity regulating pathway—multiple species	0.056875603	0.155952366	Over	P32883	-1.24507
ko05214	Glioma	0.059864471	0.145143881	Over	P32883	-1.22283
ko05221	Acute myeloid leukemia	0.059864471	0.145143881	Over	P32883	-1.22283
ko04350	TGF-beta signaling pathway	0.061355674	0.145143881	Over	O89090	-1.21215
ko04726	Serotonergic synapse	0.061355674	0.136636429	Over	P32883	-1.21215
ko05223	Non-small cell lung cancer	0.061355674	0.156636655	Over	P32883	-1.21215
ko04650	Natural killer cell mediated cytotoxicity	0.062844726	0.151215165	Over	P32883	-1.20173
ko04664	Fc epsilon RI signaling pathway	0.06433163	0.207409211	Over	P32883	-1.19158
ko04725	Cholinergic synapse	0.06433163	0.151215165	Over	P32883	-1.19158
ko05230	Central carbon metabolism in cancer	0.06433163	0.136636429	Over	P32883	-1.19158
ko04928	Parathyroid hormone synthesis, secretion and action	0.06581639	0.136636429	Over	O89090	-1.18167
ko01521	EGFR tyrosine kinase inhibitor resistance	0.068779485	0.136636429	Over	P32883	-1.16254
ko04662	B cell receptor signaling pathway	0.068779485	0.158842749	Over	P32883	-1.16254
ko04540	Gap junction	0.070257826	0.136636429	Over	P32883	-1.15331
ko05211	Renal cell carcinoma	0.070257826	0.155952366	Over	P32883	-1.15331
ko05215	Prostate cancer	0.070257826	0.136636429	Over	P32883	-1.15331
ko04013	MAPK signaling pathway—fly	0.071734033	0.145143881	Over	P32883	-1.14427
ko04912	GnRH signaling pathway	0.071734033	0.136636429	Over	P32883	-1.14427
ko05235	PD-L1 expression and PD-1 checkpoint pathway in cancer	0.071734033	0.136636429	Over	P32883	-1.14427
ko04211	Longevity regulating pathway	0.07614988	0.136636429	Over	P32883	-1.11833
ko04012	ErbB signaling pathway	0.077617579	0.136636429	Over	P32883	-1.11004
ko04550	Signaling pathways regulating pluripotency of stem cells	0.077617579	0.136636429	Over	P32883	-1.11004
ko05220	Chronic myeloid leukemia	0.077617579	0.136636429	Over	P32883	-1.11004
ko04660	T cell receptor signaling pathway	0.079083158	0.136636429	Over	P32883	-1.10192
ko04914	Progesterone-mediated oocyte maturation	0.079083158	0.220457324	Over	P32883	-1.10192
ko05212	Pancreatic cancer	0.080546621	0.136636429	Over	P32883	-1.09395
ko04138	Autophagy—yeast	0.082007968	0.145143881	Over	P32883	-1.08614
ko05210	Colorectal cancer	0.082007968	0.136636429	Over	P32883	-1.08614
ko04934	Cushing syndrome	0.084924331	0.136636429	Over	O89090	-1.07097
ko04625	C-type lectin receptor signaling pathway	0.084924331	0.136636429	Over	P32883	-1.07097
ko04933	AGE-RAGE signaling pathway in diabetic complications	0.084924331	0.199170754	Over	P32883	-1.07097
ko05226	Gastric cancer	0.084924331	0.155952366	Over	P32883	-1.07097
ko04111	Cell cycle—yeast	0.086379352	0.136636429	Over	Q5U4C9	-1.06359
ko05202	Transcriptional misregulation in cancer	0.086379352	0.136636429	Over	O89090	-1.06359
ko05034	Alcoholism	0.086379352	0.136636429	Over	P32883	-1.06359
ko04926	Relaxin signaling pathway	0.095065396	0.136636429	Over	P32883	-1.02198
ko04072	Phospholipase D signaling pathway	0.097944018	0.145143881	Over	P32883	-1.00902
ko04921	Oxytocin signaling pathway	0.097944018	0.145143881	Over	P32883	-1.00902
ko04068	FoxO signaling pathway	0.099380205	0.145143881	Over	P32883	-1.0027
ko04919	Thyroid hormone signaling pathway	0.100814313	0.136636429	Over	P32883	-0.99648
ko04071	Sphingolipid signaling pathway	0.102246345	0.136636429	Over	P32883	-0.99035
ko04371	Apelin signaling pathway	0.103676303	0.136636429	Over	P32883	-0.98432
ko04722	Neurotrophin signaling pathway	0.10510419	0.151215165	Over	P32883	-0.97838
ko05206	MicroRNAs in cancer	0.109375453	0.156636655	Over	P32883	-0.96108
ko04210	Apoptosis	0.115041641	0.234178121	Over	P32883	-0.93914
ko04150	mTOR signaling pathway	0.116453058	0.184796687	Over	P32883	-0.93385
ko05160	Hepatitis C	0.116453058	0.161440513	Over	P32883	-0.93385
ko04360	Axon guidance	0.122078285	0.195312525	Over	P32883	-0.91336
ko04062	Chemokine signaling pathway	0.124878671	0.184796687	Over	P32883	-0.90351
ko04015	Rap1 signaling pathway	0.129064027	0.17757475	Over	P32883	-0.88919
ko04910	Insulin signaling pathway	0.129064027	0.148682256	Over	P32883	-0.88919
ko05225	Hepatocellular carcinoma	0.129064027	0.136636429	Over	P32883	-0.88919
ko04140	Autophagy—animal	0.131844146	0.136636429	Over	P32883	-0.87994
ko05161	Hepatitis B	0.133231178	0.136636429	Over	P32883	-0.87539
ko04014	Ras signaling pathway	0.1359992	0.136636429	Over	P32883	-0.86646
ko04218	Cellular senescence	0.138759183	0.136636429	Over	P32883	-0.85774
ko05167	Kaposi sarcoma-associated herpesvirus infection	0.142884132	0.136636429	Over	P32883	-0.84502
ko05205	Proteoglycans in cancer	0.159204948	0.136636429	Over	P32883	-0.79804
ko05166	Human T-cell leukemia virus 1 infection	0.169927988	0.136636429	Over	P32883	-0.76974
ko05203	Viral carcinogenesis	0.169927988	0.136636429	Over	P32883	-0.76974
ko05170	Human immunodeficiency virus 1 infection	0.181842696	0.136636429	Over	P32883	-0.7403
ko05016	Huntington disease	0.184469202	0.136636429	Over	O89090	-0.73408
ko04010	MAPK signaling pathway	0.191001967	0.136636429	Over	P32883	-0.71896
ko04810	Regulation of actin cytoskeleton	0.192302797	0.155952366	Over	P32883	-0.71601
ko04151	PI3K-Akt signaling pathway	0.202641183	0.136636429	Over	P32883	-0.69327
ko04714	Thermogenesis	0.217923332	0.136636429	Over	P32883	-0.6617
ko05165	Human papillomavirus infection	0.234178121	0.136636429	Over	P32883	-0.63045

KEGG, Kyoto Encyclopedia of Genes and Genomes.

Table S5 Clinical pathological factors of endometrial cancer patients

No.	Systemic therapy				Postoperative pathology				Invasion										IHC marker														
	EBRT	Vaginal brachytherapy	Chemotherapy	Hormone therapy	Grade	Age	Depth of myometrial invasion (cm)	Myometrial invasion (cm)	LVI	Parametrial	Adnexa	Endocervical glandular	Cervical stromal connective tissue	Lymph node	KRAS	YWHAE	SP1	MSRA	NLRP3	Caspase1	GSDMD	IL-1 β	ER	PR	Vim	CK7	Ki67	CD10	PAX-8	P16	P53	MLH1	
1	0	0	0	0	0	83	0.3	1	0	0	0	0	0	0	2	2	0	0	2	2	2	2	2	1	1	1	0	0	1	1	0	2	
2	1	0	0	0	0	52	1	2	0	0	0	0	0	0	2	2	2	0	2	2	2	2	2	2	1	1	1	1	1	2	0	0	
3	1	0	0	0	0	67	0.8	2	0	0	0	0	0	0	2	2	2	0	2	2	2	2	2	2	2	2	2	2	2	1	0	0	
4	0	0	0	0	0	56	0.5	1	0	0	0	0	0	0	2	2	2	0	2	1	1	0	2	2	1	2	2	1	2	0	1		
5	1	0	0	0	0	79	0.2	1	0	0	0	0	0	0	2	2	0	0	2	2	2	0	2	2	2	2	1	2	2	2	2	2	
6	1	0	0	0	0	69	0.2	1	0	0	0	0	0	0	2	2	0	0	2	2	2	2	2	2	2	2	1	1	2	0	2	2	
7	0	0	0	0	0	65	0	0	0	0	0	0	0	0	2	2	2	0	2	2	2	1	2	2	2	2	2	2	2	2	2	1	
8	1	0	0	0	0	68	0.5	1	0	0	0	0	0	0	0	2	2	0	2	2	2	0	2	2	1	2	0	1	2	1	1	1	
9	1	0	0	0	0	48	0.4	1	0	0	0	0	0	0	2	2	2	2	2	2	1	2	2	2	2	1	2	1	2	1	2	1	
10	1	0	0	0	1	60	0.2	1	0	0	0	0	0	0	2	2	0	0	2	1	2	0	2	2	2	2	2	1	2	1	1	1	
11	1	0	0	0	1	59	0.5	2	0	0	0	1	1	0	2	2	2	2	1	2	2	0	0	0	2	2	2	1	2	0	1	1	
12	1	0	0	0	1	50	0.3	1	0	0	0	1	1	0	2	2	2	0	2	2	2	0	1	1	2	1	1	2	0	1	1	1	
13	0	0	0	0	2	44	0	0	0	0	0	0	0	0	2	2	2	0	2	2	2	1	2	2	2	2	1	2	2	0	1	1	
14	1	0	0	0	2	72	0.6	2	0	0	0	0	0	0	2	2	2	0	1	1	2	0	2	1	1	0	2	1	0	1	0	0	
15	1	0	0	0	2	59	0.8	2	1	0	0	0	0	0	2	2	0	0	2	2	2	1	1	2	2	2	1	1	1	2	2	0	0
16	1	0	0	0	2	80	0.3	1	0	0	0	0	0	0	2	2	0	0	2	2	2	0	1	1	0	2	1	1	1	2	0	1	1
17	1	0	1	0	2	57	0.7	2	1	0	0	0	0	0	2	2	2	0	2	2	2	2	0	0	1	0	2	1	1	2	2	2	1