Supplementary Table 1: Characteristics of single nucleotide polymorphisms (SNPs) extracted from the GWAS statistical summary data.

Supplementary Table 1 | Characteristics of SNPs extracted from exposure (nine types of cathepsins) GWAS statistical summary data.

	SNP	EA	OA	EAF	se	F-Statistic	Association with exposure	
							Beta	P-value
Cathepsin B	rs75773690	A	G	0.02192	0.0857	21.19007	-0.3945	4.17E-06
	rs113646963	T	C	0.09708	0.0427	21.85070	0.1996	2.95E-06
	rs76089522	A	G	0.10475	0.0421	21.91841	-0.1971	2.88E-06
	rs13152767	A	G	0.02617	0.0867	23.00016	0.4158	1.62E-06
	rs36021960	A	G	0.12637	0.0374	21.81939	0.1747	3.02E-06
	rs11563944	G	A	0.26799	0.0278	21.56567	0.1291	3.55E-06
	rs148930853	C	T	0.01211	0.1181	21.81467	0.5516	3.02E-06
	rs1692819	A	G	0.29182	0.0274	240.13687	0.4246	5.25E-54
	rs72863882	A	G	0.08353	0.0475	29.25102	-0.2569	6.46E-08
	rs150811995	C	A	0.01878	0.1004	21.01912	0.4603	4.57E-06
	rs117345475	G	A	0.02062	0.0933	21.55826	-0.4332	3.47E-06
	rs150370599	T	C	0.08341	0.0457	22.81787	0.2183	1.78E-06
	rs143557119	A	G	0.02199	0.0946	20.92144	0.4327	4.79E-06
	rs117486267	C	T	0.02486	0.0834	23.03770	-0.4003	1.58E-06
	rs147881440	A	G	0.06428	0.051	20.89028	-0.2331	4.79E-06
	rs9905973	A	G	0.271	0.0276	25.91400	-0.1405	3.55E-07
	rs200652433	T	C	0.04112	0.0684	24.54884	0.3389	7.24E-07
	rs7249773	A	G	0.15121	0.0351	24.82935	0.1749	6.03E-07
	rs1065853	T	G	0.07778	0.0463	23.95288	0.2266	1.00E-06
Cathepsin E	rs149553686	C	T	0.06772	0.0525	21.33560	0.2425	3.89E-06
	rs13089837	C	T	0.49848	0.025	21.23366	-0.1152	4.17E-06
	rs57689619	G	A	0.08618	0.0444	21.90409	-0.2078	2.82E-06
	rs189009983	T	C	0.00831	0.1541	20.95988	0.7055	4.68E-06
	rs10900907	A	G	0.41707	0.0255	21.70464	0.1188	3.24E-06
	rs112918835	T	C	0.00706	0.1526	21.41639	0.7062	3.72E-06
	rs57135345	T	C	0.05697	0.0542	21.87547	0.2535	2.95E-06
	rs1936839	C	G	0.16937	0.0329	22.54085	0.1562	2.00E-06
	rs74677283	T	C	0.02151	0.0882	24.64976	0.4379	6.76E-07
	rs8066936	A	G	0.1792	0.0325	21.07516	-0.1492	4.27E-06
	rs10401027	A	G	0.45246	0.0259	22.37034	-0.1225	2.24E-06
Cathepsin F	rs647400	A	G	0.19253	0.0314	22.57763	0.1492	2.04E-06
	rs7564167	G	A	0.93594	0.0526	25.36252	-0.2649	4.90E-07
	rs115901379	G	T	0.02042	0.0927	21.57688	0.4306	3.39E-06
	rs1260326	C	T	0.59849	0.0252	42.45660	-0.1642	6.92E-11
	rs58531759	G	T	0.03949	0.0747	24.82627	-0.3722	6.31E-07
	rs186369051	T	C	0.01504	0.1026	22.05154	-0.4818	2.63E-06
	rs183683891	T	C	0.01536	0.1123	21.78886	-0.5242	3.02E-06
	rs112526544	G	A	0.02831	0.0766	24.62284	0.3801	6.92E-07
	rs61866943	G	T	0.01874	0.1012	24.10888	0.4969	9.12E-07
	rs1791679	A	C	0.28947	0.0269	76.25380	0.2349	2.51E-18
	rs10745925	C	T	0.29402	0.0268	115.00162	-0.2874	9.12E-27
	rs143015877	T	C	0.25734	0.0287	21.31415	-0.1325	3.98E-06
	rs9796775	G	A	0.50502	0.0249	22.15422	-0.1172	2.45E-06
Cathepsin G	rs10170044	G	A	0.39112	0.0251	20.99173	0.115	4.79E-06
	rs114418234	C	A	0.03719	0.065	22.40930	0.3077	2.24E-06
	rs192289769	G	C	0.01364	0.1093	25.02745	-0.5468	5.62E-07
	rs147099093	A	G	0.02053	0.0885	23.29017	0.4271	1.38E-06
	rs116142041	A	G	0.03645	0.0665	25.46834	-0.3356	4.57E-07
	rs548719719	G	A	0.03709	0.0708	21.87015	0.3311	2.88E-06
	rs4702448	A	C	0.66583	0.0265	23.14881	0.1275	1.45E-06
	rs497459	C	T	0.86534	0.0368	22.66588	-0.1752	1.95E-06
	rs62493038	T	C	0.03503	0.0725	21.87659	-0.3391	2.88E-06
	rs77893942	A	T	0.03128	0.0764	24.22042	-0.376	8.71E-07
	rs72773561	C	T	0.05703	0.0528	22.94192	-0.2529	1.70E-06
	rs35241999	G	A	0.02374	0.0869	21.81718	0.4059	2.95E-06
	rs117133380	A	C	0.01556	0.1065	22.05912	0.5002	2.63E-06
	rs56284011	C	G	0.03943	0.0656	22.85306	-0.3136	1.74E-06
	rs571991098	T	C	0.02347	0.0884	21.66881	0.4115	3.24E-06
Cathepsin H	rs35628511	T	C	0.3116	0.0272	21.22093	-0.1253	4.17E-06
	rs147991203	T	C	0.02671	0.0773	23.63494	0.3758	1.17E-06
	rs508807	C	G	0.81025	0.032	22.29610	-0.1511	2.40E-06
	rs62474230	C	G	0.06195	0.0506	22.06771	-0.2377	2.69E-06
	rs77977134	C	T	0.0493	0.0583	21.78311	-0.2721	3.02E-06
	rs62013235	A	G	0.091	0.0432	86.59336	0.402	1.35E-20
	rs34593439	A	G	0.11066	0.0346	1098.94166	-1.147	1.00E-200
	rs12911554	T	C	0.55027	0.0251	22.78065	-0.1198	1.82E-06
	rs60018174	T	C	0.1159	0.0395	24.52130	0.1956	7.24E-07
	rs146037740	A	G	0.02292	0.0929	25.98914	0.4736	3.47E-07
	rs74342103	T	A	0.02583	0.0812	21.51040	0.3766	3.47E-06
Cathepsin O	rs146963690	G	T	0.0101	0.1322	22.32241	0.6246	2.29E-06
	rs149159018	G	A	0.01105	0.134	27.55466	0.7034	1.55E-07
	rs17288007	G	A	0.06381	0.0521	22.22190	-0.2456	2.45E-06
	rs181844705	G	A	0.02318	0.0905	23.76697	0.4412	1.10E-06
	rs4297371	C	A	0.79306	0.0313	21.54977	0.1453	3.55E-06
	rs78943701	A	G	0.01536	0.1025	21.83852	-0.479	2.95E-06
	rs2439803	G	A	0.15304	0.0351	25.22844	0.1763	5.13E-07
	rs4076941	C	T	0.36872	0.0262	22.58063	-0.1245	2.14E-06
	rs10902420	G	A	0.89909	0.0432	23.56293	-0.2097	1.23E-06
	rs7140599	C	T	0.57698	0.0251	23.58631	-0.1219	1.17E-06
	rs1870736	G	C	0.42746	0.0249	24.08484	0.1222	9.33E-07
	rs9932172	T	C	0.10798	0.0401	22.80598	0.1915	1.74E-06
	rs4843804	A	G	0.0336	0.0673	21.54725	-0.3124	3.47E-06
Cathepsin S	rs41271951	G	A	0.08349	0.0419	421.76807	-0.8605	7.08E-94
	rs6657328	C	G	0.7184	0.0283	20.81036	-0.1291	4.90E-06
	rs4581957	A	G	0.13414	0.0365	23.64890	-0.1775	1.15E-06
	rs13411643	C	T	0.13712	0.0364	25.30311	0.1831	5.01E-07
	rs7614425	A	G	0.09254	0.0436	22.80282	-0.2082	1.82E-06
	rs13150189	A	G	0.21113	0.0306	25.85689	0.1556	3.47E-07
	rs989576	T	C	0.29483	0.0278	22.10353	0.1307	2.57E-06
	rs10516855	C	T	0.09552	0.0421	21.87395	-0.1969	2.95E-06
	rs113108135	C	G	0.06933	0.0491	22.88775	0.2349	1.70E-06
	rs116623438	C	T	0.02023	0.0876	24.09510	-0.43	9.12E-07
	rs13212873	C	T	0.0116	0.117	21.47570	0.5422	3.55E-06
	rs13196989	T	C	0.13099	0.0374	22.09503	-0.1758	2.57E-06
	rs2470994	C	T	0.28088	0.0281	21.53488	0.1304	3.39E-06
	rs529565	C	T	0.31269	0.0266	24.43927	-0.1315	7.76E-07
	rs61870690	G	A	0.04143	0.0684	24.50539	-0.3386	7.24E-07
	rs1060435	G	A	0.39793	0.0251	26.45483	-0.1291	2.75E-07
	rs12804405	A	G	0.01019	0.129	22.50730	0.612	2.09E-06
	rs74804137	C	T	0.01757	0.0987	27.52262	-0.5178	1.58E-07
	rs73099998	T	C	0.20811	0.0308	22.47006	-0.146	2.19E-06
	rs77792819	G	A	0.04096	0.0661	22.66682	0.3147	1.95E-06
	rs1022239	T	A	0.58887	0.025	21.41838	0.1157	3.72E-06
	rs4313886	C	T	0.13446	0.0365	21.36212	0.1687	3.89E-06
	rs78767885	C	T	0.08725	0.0477	22.01321	0.2238	2.69E-06
	rs118010753	C	T	0.01437	0.1081	21.54815	0.5018	3.47E-06
Cathepsin L2	rs114113108	C	G	0.0129	0.1172	25.53181	-0.5922	4.37E-07
	rs13068566	G	A	0.46617	0.0247	21.94183	0.1157	2.88E-06
	rs1523319	G	C	0.28541	0.0279	21.44453	-0.1292	3.55E-06
	rs151179824	A	G	0.02158	0.0943	22.25878	0.4449	2.34E-06
	rs7669728	C	T	0.43633	0.0254	26.23537	-0.1301	3.09E-07
	rs116407656	C	T	0.02439	0.0856	21.98909	0.4014	2.75E-06
	rs10817163	A	T	0.22045	0.0304	42.54987	0.1983	7.08E-11
	rs7898416	G	A	0.0705	0.0489	21.68245	-0.2277	3.24E-06
	rs148608463	A	G	0.35415	0.0257	21.00992	-0.1178	4.57E-06
	rs117714361	G	A	0.02685	0.0756	20.84961	-0.3452	4.90E-06
	rs2302837	G	A	0.92494	0.0498	26.03458	-0.2541	3.31E-07
Cathepsin Z	rs36128387	T	C	0.02261	0.0914	23.06942	0.439	1.55E-06
	rs114675081	G	A	0.01467	0.1075	22.97753	0.5153	1.66E-06
	rs148201372	T	A	0.01546	0.1063	23.81036	-0.5187	1.05E-06
	rs7656806	C	A	0.51592	0.0245	27.12496	-0.1276	1.86E-07
	rs1135945	A	G	0.20839	0.0301	21.17223	0.1385	4.17E-06
	rs770140	G	A	0.64195	0.0265	21.93067	-0.1241	2.82E-06
	rs298724	C	T	0.05507	0.0538	21.28330	0.2482	3.98E-06
	rs10761760	C	A	0.44944	0.0258	26.21599	0.1321	3.09E-07
	rs116920068	A	G	0.0289	0.0749	21.81102	-0.3498	3.02E-06
	rs4761709	G	A	0.40882	0.0249	23.92742	0.1218	1.00E-06
	rs10745925	C	T	0.29402	0.0266	185.61501	-0.3624	2.29E-42
	rs67845377	T	C	0.13855	0.0362	21.40979	0.1675	3.72E-06
	rs148370779	T	C	0.01316	0.1105	254.61184	-1.7632	2.57E-57

SNP: single nucleotide polymorphism; EA: effect Allele; OA: other Allele; EFA: effect allele frequency; SE: standard error.

Supplementary Table 2: Test for heterogeneity in the validation data.

Supplementary Table 2 | Heterogeneity test between nine different cathepsins and ovarian malignancies and their pathological subtypes in validation datasets				
		Cochran's Q test		
cancer	Outcome and method	Q	Q_df	Q-value
Ovarian cancer				
	Cathepsin B			
	Inverse variance weighted	13.40199	18	0.76716
	MR Egger	13.31804	17	0.71465
	Cathepsin E			
	Inverse variance weighted	13.84406	10	0.18022
	MR Egger	12.93914	9	0.16538
	Cathepsin F			
	Inverse variance weighted	13.27104	11	0.27598
	MR Egger	13.25342	10	0.20985
	Cathepsin G			
	Inverse variance weighted	4.66857	11	0.94615
	MR Egger	4.44379	10	0.92511
	Cathepsin H			
	Inverse variance weighted	6.04229	10	0.81170
	MR Egger	4.92200	9	0.84105
	Cathepsin O			
	Inverse variance weighted	6.74456	10	0.74932
	MR Egger	4.97193	9	0.83675
	Cathepsin S			
	Inverse variance weighted	14.38201	19	0.76098
	MR Egger	13.86880	18	0.73760
	Cathepsin L2			
	Inverse variance weighted	9.25204	8	0.32148
	MR Egger	7.97875	7	0.33447
	Cathepsin Z			
	Inverse variance weighted	8.34039	10	0.59563
	MR Egger	4.70412	9	0.85930
Low grade serous ovarian cancer				
	Cathepsin B			
	Inverse variance weighted	12.40564	18	0.82560
	MR Egger	12.40562	17	0.77498
	Cathepsin E			
	Inverse variance weighted	18.62560	10	0.04528
	MR Egger	18.60161	9	0.02880
	Cathepsin F			
	Inverse variance weighted	32.41770	11	0.00065
	MR Egger	29.20733	10	0.00115

	Cathepsin G			
	Inverse variance weighted	14.34602	11	0.21443
	MR Egger	13.94174	10	0.17567
	Cathepsin H			
	Inverse variance weighted	14.12339	10	0.16744
	MR Egger	11.28096	9	0.25694
	Cathepsin O			
	Inverse variance weighted	4.99157	10	0.89174
	MR Egger	4.43980	9	0.88016
	Cathepsin S			
	Inverse variance weighted	12.85784	19	0.84577
	MR Egger	12.50228	18	0.82025
	Cathepsin L2			
	Inverse variance weighted	4.40233	8	0.81912
	MR Egger	3.40632	7	0.84505
	Cathepsin Z			
	Inverse variance weighted	7.40082	10	0.68714
	MR Egger	5.39602	9	0.79851
High grade serous ovarian cancer				
	Cathepsin B			
	Inverse variance weighted	13.79456	18	0.74238
	MR Egger	13.71396	17	0.68724
	Cathepsin E			
	Inverse variance weighted	10.30649	10	0.41403
	MR Egger	9.31972	9	0.40830
	Cathepsin F			
	Inverse variance weighted	9.63139	11	0.56382
	MR Egger	8.80097	10	0.55109
	Cathepsin G			
	Inverse variance weighted	3.59318	11	0.98035
	MR Egger	3.56612	10	0.96481
	Cathepsin H			
	Inverse variance weighted	5.61472	10	0.84653
	MR Egger	5.58734	9	0.78040
	Cathepsin O			
	Inverse variance weighted	5.95830	10	0.81875
	MR Egger	5.11562	9	0.82411
	Cathepsin S			
	Inverse variance weighted	13.65977	19	0.80315
	MR Egger	13.37310	18	0.76895
	Cathepsin L2			
	Inverse variance weighted	8.27024	8	0.40753
	MR Egger	6.91071	7	0.43824
	Cathepsin Z			
	Inverse variance weighted	10.27139	10	0.41701
	MR Egger	8.49160	9	0.48546

Clear cell ovarian cancer				
	Cathepsin B			
	Inverse variance weighted	12.31638	18	0.83048
	MR Egger	11.74121	17	0.81555
	Cathepsin E			
	Inverse variance weighted	7.35104	10	0.69194
	MR Egger	6.17060	9	0.72273
	Cathepsin F			
	Inverse variance weighted	11.30262	11	0.41827
	MR Egger	8.25662	10	0.60379
	Cathepsin G			
	Inverse variance weighted	5.81392	11	0.88549
	MR Egger	5.80982	10	0.83098
	Cathepsin H			
	Inverse variance weighted	10.59523	10	0.38991
	MR Egger	10.52474	9	0.30970
	Cathepsin O			
	Inverse variance weighted	8.85820	10	0.54561
	MR Egger	8.27194	9	0.50699
	Cathepsin S			
	Inverse variance weighted	9.88805	19	0.95565
	MR Egger	9.85515	18	0.93653
	Cathepsin L2			
	Inverse variance weighted	16.56615	8	0.03496
	MR Egger	16.14105	7	0.02386
	Cathepsin Z			
	Inverse variance weighted	9.35587	10	0.49870
	MR Egger	7.86562	9	0.54774
Mucinous ovarian cancer				
	Cathepsin B			
	Inverse variance weighted	21.85762	18	0.23837
	MR Egger	17.87970	17	0.39647
	Cathepsin E			
	Inverse variance weighted	5.79454	10	0.83222
	MR Egger	5.78709	9	0.76102
	Cathepsin F			
	Inverse variance weighted	22.32051	11	0.02200
	MR Egger	21.97851	10	0.01521
	Cathepsin G			
	Inverse variance weighted	15.09585	11	0.17815
	MR Egger	11.47075	10	0.32204
	Cathepsin H			
	Inverse variance weighted	5.49411	10	0.85583
	MR Egger	5.30369	9	0.80707
	Cathepsin O			
	Inverse variance weighted	14.37338	10	0.15663

	MR Egger	4.67767	9	0.86145
	Cathepsin S			
	Inverse variance weighted	16.92769	19	0.59477
	MR Egger	15.82479	18	0.60477
	Cathepsin L2			
	Inverse variance weighted	5.73707	8	0.67666
	MR Egger	5.73701	7	0.57077
	Cathepsin Z			
	Inverse variance weighted	9.86108	10	0.45276
	MR Egger	9.75765	9	0.37046
Endometrioid ovarian cancer				
	Cathepsin B			
	Inverse variance weighted	21.22280	18	0.26832
	MR Egger	20.95664	17	0.22824
	Cathepsin E			
	Inverse variance weighted	17.31102	10	0.06776
	MR Egger	15.83728	9	0.07036
	Cathepsin F			
	Inverse variance weighted	20.43333	11	0.03974
	MR Egger	20.14682	10	0.02789
	Cathepsin G			
	Inverse variance weighted	15.29462	11	0.16940
	MR Egger	13.43069	10	0.20058
	Cathepsin H			
	Inverse variance weighted	7.44367	10	0.68300
	MR Egger	3.44745	9	0.94389
	Cathepsin O			
	Inverse variance weighted	17.76941	10	0.05898
	MR Egger	17.28726	9	0.04440
	Cathepsin S			
	Inverse variance weighted	28.23953	19	0.07893
	MR Egger	27.07740	18	0.07756
	Cathepsin L2			
	Inverse variance weighted	12.34885	8	0.13630
	MR Egger	12.14389	7	0.09593
	Cathepsin Z			
	Inverse variance weighted	17.33317	10	0.06731
	MR Egger	14.06638	9	0.11998
Q: Cochran's Q statistic; df: degrees of freedom.				

Supplementary Table 3: Pleiotropic test of the MR-Egger intercept.

cancer	cathepsins	egger_intercept		
		egger_intercept	se	pval
Ovarian cancer				
	Cathepsin B	-0.00400	0.0138	0.7755
	Cathepsin E	-0.01203	0.0152	0.4480
	Cathepsin F	-0.00201	0.0175	0.9105
	Cathepsin G	0.00758	0.0160	0.6456
	Cathepsin H	-0.00963	0.0091	0.3174
	Cathepsin O	0.01847	0.0139	0.2158
	Cathepsin S	0.00549	0.0077	0.4830
	Cathepsin L2	-0.0179	0.0169	0.3257
	Cathepsin Z	0.01829	0.0096	0.0889
Low grade serous ovarian cancer				
	Cathepsin B	0.00014	0.0299	0.9962
	Cathepsin E	-0.00426	0.0396	0.9166
	Cathepsin F	0.05903	0.0563	0.3191
	Cathepsin G	0.02232	0.0414	0.6020
	Cathepsin H	-0.0332	0.0221	0.1664
	Cathepsin O	0.02233	0.0301	0.4765
	Cathepsin S	-0.00984	0.0165	0.5584
	Cathepsin L2	0.0338	0.0339	0.3515
	Cathepsin Z	0.02893	0.0204	0.1905
High grade serous ovarian cancer				
	Cathepsin B	-0.00466	0.0164	0.7799
	Cathepsin E	-0.01505	0.0154	0.3545
	Cathepsin F	-0.01644	0.0180	0.3836
	Cathepsin G	-0.00313	0.0190	0.8726
	Cathepsin H	-0.00179	0.0108	0.8722
	Cathepsin O	0.01516	0.0165	0.3826
	Cathepsin S	0.00487	0.0091	0.5989
	Cathepsin L2	-0.0219	0.0188	0.2818
	Cathepsin Z	0.01523	0.0114	0.2150
Clear cell ovarian cancer				
	Cathepsin B	-0.03175	0.0419	0.4586
	Cathepsin E	-0.04109	0.0378	0.3055
	Cathepsin F	0.07973	0.0457	0.1115
	Cathepsin G	0.00311	0.0486	0.9502
	Cathepsin H	0.00737	0.0300	0.8116
	Cathepsin O	0.03245	0.0424	0.4635
	Cathepsin S	-0.00421	0.0232	0.8581
	Cathepsin L2	0.03112	0.0725	0.6806
	Cathepsin Z	0.03451	0.0283	0.2532
Mucinous ovarian cancer				
	Cathepsin B	0.06254	0.0322	0.0685
	Cathepsin E	-0.00246	0.0285	0.9331
	Cathepsin F	-0.02006	0.0509	0.7015
	Cathepsin G	0.06846	0.0385	0.1058
	Cathepsin H	-0.009	0.0206	0.6728
	Cathepsin O	0.09994	0.0321	0.0124
	Cathepsin S	-0.01822	0.0173	0.3075
	Cathepsin L2	0.00026	0.0367	0.9945
	Cathepsin Z	0.00699	0.0226	0.7645
Endometrioid ovarian cancer				
	Cathepsin B	-0.01535	0.0330	0.6481
	Cathepsin E	-0.0326	0.0356	0.3840
	Cathepsin F	0.01757	0.0466	0.7140
	Cathepsin G	0.04703	0.0399	0.2661
	Cathepsin H	-0.03945	0.0197	0.0767
	Cathepsin O	0.0206	0.0411	0.6284
	Cathepsin S	0.01787	0.0203	0.3910
	Cathepsin L2	-0.01543	0.0449	0.7412
	Cathepsin Z	0.03751	0.0260	0.1822

Supplementary Table 3 |pleiotropy test between cathepsins family and ovarian cancer and their pathological subtypes

Supplementary Table 4: Inverse variance-weighted results of Multivariate analysis.

cancer	Cathepsin	bate	Inverse variance weighted		
			95%CI		p value
Ovarian cancer	Cathepsin B	0.020	-0.026	0.065	0.400
	Cathepsin E	-0.021	-0.090	0.047	0.545
	Cathepsin F	-0.001	-0.062	0.060	0.982
	Cathepsin G	0.036	-0.028	0.101	0.272
	Cathepsin H	0.030	-0.005	0.065	0.091
	Cathepsin O	0.033	-0.052	0.117	0.448
	Cathepsin S	0.012	-0.030	0.055	0.565
	Cathepsin L2	-0.042	-0.119	0.035	0.286
	Cathepsin Z	-0.054	-0.116	0.007	0.084
Low grade serous ovarian cancer					
	Cathepsin B	0.012	-0.089	0.113	0.820
	Cathepsin E	0.038	-0.114	0.189	0.624
	Cathepsin F	-0.001	-0.135	0.134	0.993
	Cathepsin G	0.075	-0.068	0.218	0.305
	Cathepsin H	0.089	0.013	0.166	0.022
	Cathepsin O	0.054	-0.132	0.240	0.569
	Cathepsin S	0.041	-0.051	0.134	0.382
	Cathepsin L2	-0.210	-0.381	-0.038	0.016
	Cathepsin Z	-0.046	-0.178	0.086	0.498
High grade serous ovarian cancer					
	Cathepsin B	0.015	-0.039	0.070	0.578
	Cathepsin E	-0.059	-0.141	0.023	0.158
	Cathepsin F	-0.029	-0.101	0.044	0.436
	Cathepsin G	0.073	-0.004	0.150	0.062
	Cathepsin H	0.010	-0.031	0.051	0.621
	Cathepsin O	0.057	-0.044	0.157	0.268
	Cathepsin S	-0.009	-0.059	0.042	0.730
	Cathepsin L2	-0.067	-0.159	0.025	0.155
	Cathepsin Z	-0.052	-0.125	0.021	0.165
Clear cell ovarian cancer					
	Cathepsin B	0.017	-0.122	0.155	0.812
	Cathepsin E	-0.004	-0.210	0.202	0.970
	Cathepsin F	0.066	-0.117	0.249	0.480
	Cathepsin G	0.104	-0.093	0.300	0.300
	Cathepsin H	0.110	0.005	0.216	0.041
	Cathepsin O	0.150	-0.106	0.406	0.251
	Cathepsin S	0.033	-0.096	0.161	0.618
	Cathepsin L2	-0.144	-0.377	0.090	0.227
	Cathepsin Z	-0.100	-0.279	0.080	0.277
Mucinous ovarian cancer					
	Cathepsin B	0.003	-0.108	0.114	0.964
	Cathepsin E	0.104	-0.061	0.269	0.217
	Cathepsin F	-0.021	-0.169	0.127	0.780
	Cathepsin G	-0.055	-0.210	0.100	0.488
	Cathepsin H	-0.042	-0.124	0.040	0.318
	Cathepsin O	0.024	-0.182	0.231	0.817
	Cathepsin S	0.005	-0.098	0.108	0.928
	Cathepsin L2	-0.047	-0.235	0.141	0.623
	Cathepsin Z	-0.049	-0.198	0.099	0.515
Endometrioid ovarian cancer					
	Cathepsin B	0.069	-0.045	0.182	0.236
	Cathepsin E	0.107	-0.062	0.276	0.214
	Cathepsin F	0.004	-0.148	0.156	0.958
	Cathepsin G	-0.049	-0.209	0.112	0.551
	Cathepsin H	0.046	-0.041	0.133	0.297
	Cathepsin O	-0.077	-0.286	0.132	0.470
	Cathepsin S	0.008	-0.098	0.114	0.886
	Cathepsin L2	0.095	-0.097	0.286	0.333
	Cathepsin Z	0.020	-0.133	0.173	0.799

Supplementary Table 4 | Inverse variance weighted analysis of Multivariate analysis to estimate the relationship between cathepsin and ovarian cancer and its histological subtypes.

Supplementary Table 5: Pleiotropic test of the MR-Egger intercept in Multivariate analysis.

Supplementary Table 5 | The multivariable MR-Egger method was used to analyze the level pleiotropy between cathepsin family and ovarian cancer and its subtypes		
	MR-Egger method	
Exposure(intercept)	Estimate	p-value
cancer		
Ovarian cancer	-0.004	0.194
Low grade serous ovarian cancer	0.008	0.199
High grade serous ovarian cancer	-0.004	0.204
Clear cell ovarian cancer	-0.001	0.899
Mucinous ovarian cancer	0.001	0.934
Endometrioid ovarian cancer	-0.007	0.341

Supplementary Table 6: Causal association estimated by reverse Mendelian Randomization (MR) analyses.

cancer	Cathepsin	nsnp	Inverse variance weighted	
			OR （95%CI)	p value
Ovarian cancer				
	Cathepsin B	40	0.924 (0.840-1.016)	0.104
	Cathepsin E	40	0.981 (0.892-1.079)	0.706
	Cathepsin F	40	1.046 (0.937-1.168)	0.416
	Cathepsin G	40	0.953 (0.866-1.048)	0.323
	Cathepsin H	40	1.007 (0.905-1.120)	0.894
	Cathepsin O	40	1.009 (0.918-1.110)	0.840
	Cathepsin S	40	0.966 (0.870-1.073)	0.528
	Cathepsin L2	40	0.992 (0.902-1.091)	0.879
	Cathepsin Z	40	1.044 (0.949-1.149)	0.366
Low grade serous ovarian cancer				
	Cathepsin B	18	0.988 (0.911-1.071)	0.779
	Cathepsin E	18	0.968 (0.898-1.044)	0.408
	Cathepsin F	18	0.982 (0.919-1.049)	0.600
	Cathepsin G	18	0.973 (0.899-1.053)	0.500
	Cathepsin H	18	0.966 (0.904-1.032)	0.310
	Cathepsin O	18	0.938 (0.865-1.016)	0.117
	Cathepsin S	18	0.974 (0.911-1.040)	0.438
	Cathepsin L2	18	0.944 (0.875-1.018)	0.135
	Cathepsin Z	18	0.964 (0.902-1.030)	0.278
High grade serous ovarian cancer				
	Cathepsin B	34	0.926 (0.856-1.001)	0.0549
	Cathepsin E	34	0.988 (0.914-1.068)	0.768
	Cathepsin F	34	1.042 (0.964-1.126)	0.298
	Cathepsin G	34	0.946 (0.873-1.026)	0.188
	Cathepsin H	34	1.004 (0.928-1.086)	0.915
	Cathepsin O	34	1.004 (0.928-1.086)	0.913
	Cathepsin S	34	1.006 (0.923-1.095)	0.889
	Cathepsin L2	34	0.975 (0.902-1.055)	0.541
	Cathepsin Z	34	1.087 (1.005-1.175)	0.0356
Clear cell ovarian cancer				
	Cathepsin B	14	1.011 (0.952-1.074)	0.701
	Cathepsin E	14	0.971 (0.920-1.024)	0.281
	Cathepsin F	14	0.991 (0.941-1.043)	0.733
	Cathepsin G	14	0.978 (0.929-1.030)	0.414
	Cathepsin H	14	0.998 (0.941-1.059)	0.973
	Cathepsin O	14	0.971 (0.911-1.034)	0.368
	Cathepsin S	14	0.996 (0.946-1.049)	0.896
	Cathepsin L2	14	0.965 (0.908-1.024)	0.243
	Cathepsin Z	14	0.992 (0.942-1.044)	0.771
Mucinous ovarian cancer				
	Cathepsin B	26	1.003 (0.932-1.078)	0.934
	Cathepsin E	26	1.024 (0.959-1.093)	0.468
	Cathepsin F	26	0.996 (0.942-1.052)	0.887
	Cathepsin G	26	1.029 (0.967-1.094)	0.366
	Cathepsin H	26	0.994 (0.931-1.062)	0.869
	Cathepsin O	26	0.999 (0.939-1.063)	0.999
	Cathepsin S	26	1.012 (0.958-1.070)	0.653
	Cathepsin L2	26	1.020 (0.952-1.092)	0.566
	Cathepsin Z	26	1.017 (0.959-1.078)	0.571
Endometrioid ovarian cancer				
	Cathepsin B	10	0.936 (0.850-1.030)	0.176
	Cathepsin E	10	1.021 (0.907-1.150)	0.718
	Cathepsin F	10	0.979 (0.885-1.084)	0.694
	Cathepsin G	10	0.994 (0.903-1.094)	0.906
	Cathepsin H	10	1.046 (0.930-1.177)	0.447
	Cathepsin O	10	1.027 (0.889-1.188)	0.710
	Cathepsin S	10	0.878 (0.798-0.966)	0.00803
	Cathepsin L2	10	1.044 (0.935-1.165)	0.437
	Cathepsin Z	10	1.022 (0.906-1.153)	0.719

Supplementary Table 6 | Causal association of cathepsins on ovarian cancer and its histological subtypes estimated by reverse MR analyses.

Supplementary Table 7: Calculated values of the statistical power.

cancer	Cathepsin	nsnp	OR （95%CI)	power
Supplementary table 7 | The calculated value of power				
Ovarian cancer	Cathepsin B	19	1.026	0.32
	Cathepsin E	11	0.919	0.84
	Cathepsin F	12	0.993	0.07
	Cathepsin G	12	1.033	0.28
	Cathepsin H	11	1.032	0.65
	Cathepsin O	11	0.993	0.06
	Cathepsin S	20	0.995	0.06
	Cathepsin L2	9	0.984	0.09
	Cathepsin Z	11	0.944	0.92
Low grade serous ovarian cancer				
	Cathepsin B	19	0.997	0.05
	Cathepsin E	11	1.026	0.18
	Cathepsin F	12	0.943	0.97
	Cathepsin G	12	1.075	0.94
	Cathepsin H	11	1.057	1
	Cathepsin O	11	1.016	0.11
	Cathepsin S	20	0.999	0.05
	Cathepsin L2	9	0.803	1
	Cathepsin Z	11	0.951	0.93
High grade serous ovarian cancer				
	Cathepsin B	19	1.017	0.12
	Cathepsin E	11	0.893	0.87
	Cathepsin F	12	0.979	0.16
	Cathepsin G	12	1.045	0.32
	Cathepsin H	11	1.015	0.14
	Cathepsin O	11	1.016	0.08
	Cathepsin S	20	0.987	0.11
	Cathepsin L2	9	0.946	0.37
	Cathepsin Z	11	0.926	0.94
Clear cell ovarian cancer				
	Cathepsin B	19	1.034	0.09
	Cathepsin E	11	0.887	0.21
	Cathepsin F	12	1.010	0.05
	Cathepsin G	12	1.133	0.36
	Cathepsin H	11	1.149	0.89
	Cathepsin O	11	0.959	0.08
	Cathepsin S	20	1.023	0.07
	Cathepsin L2	9	0.980	0.06
	Cathepsin Z	11	0.998	0.05
Mucinous ovarian cancer				
	Cathepsin B	19	1.031	0.11
	Cathepsin E	11	1.066	0.15
	Cathepsin F	12	0.937	0.29
	Cathepsin G	12	0.934	0.19
	Cathepsin H	11	0.955	0.26
	Cathepsin O	11	0.912	0.28
	Cathepsin S	20	0.956	0.21
	Cathepsin L2	9	0.957	0.1
	Cathepsin Z	11	0.960	0.15
Endometrioid ovarian cancer				
	Cathepsin B	19	1.074	0.41
	Cathepsin E	11	1.039	0.09
	Cathepsin F	12	1.037	0.14
	Cathepsin G	12	1.021	0.06
	Cathepsin H	11	1.033	0.17
	Cathepsin O	11	0.949	0.13
	Cathepsin S	20	0.997	0.05
	Cathepsin L2	9	1.082	0.24
	Cathepsin Z	11	1.008	0.05