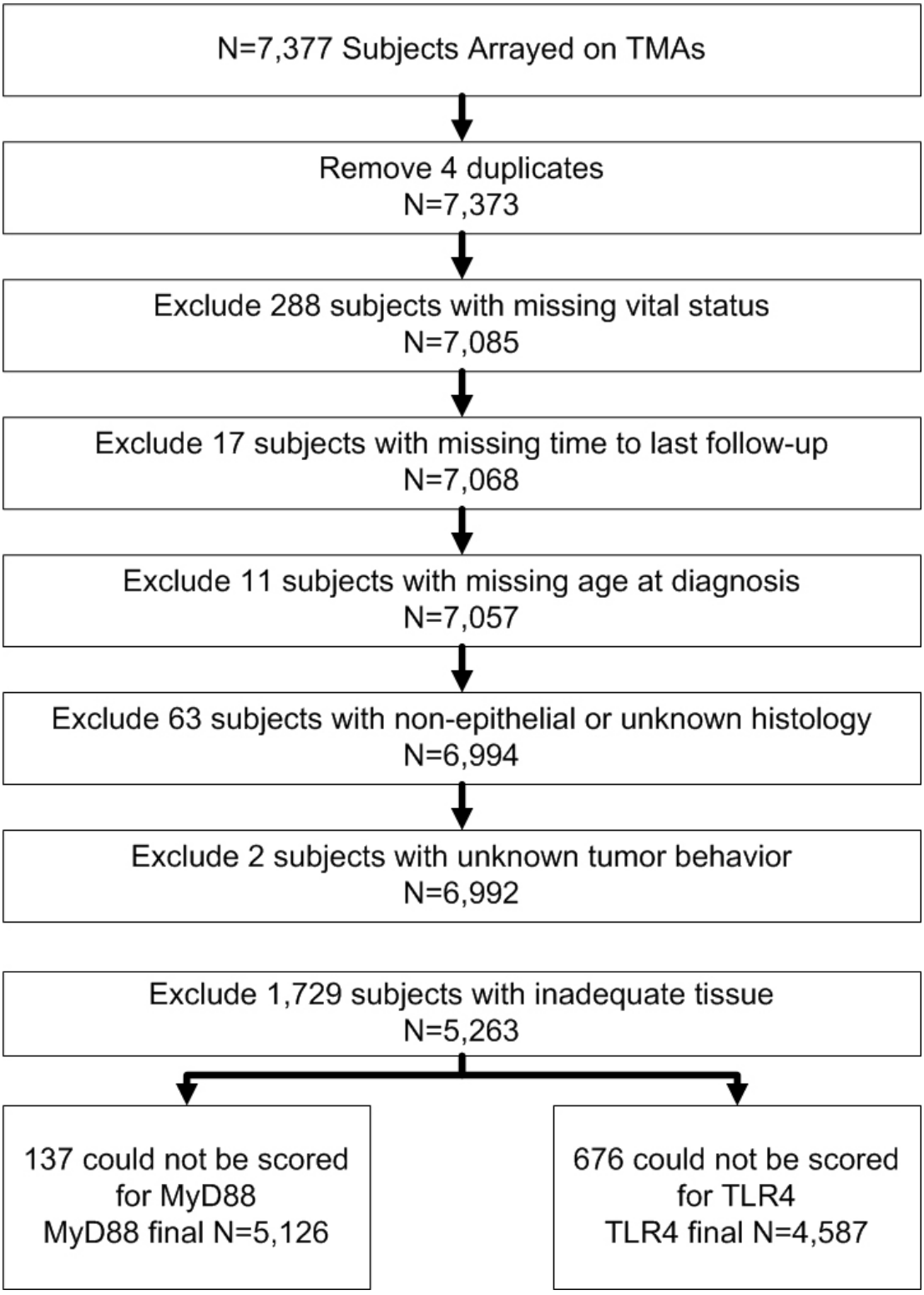
Block MS, Vierkant RA, Rambau PF, et al. MyD88 and TLR4 Expression in Epithelial Ovarian Cancer.

Supplemental Methods

We used analyses of variance and chi-square tests as appropriate to compare expression levels with clinical and prognostic variables. Our primary outcome variable was overall survival, defined as time from diagnosis to death from any cause, censoring follow-up at 10 years to minimize competing causes of mortality and accounting for possible left truncation due to delayed study enrollment. Kaplan-Meier curves and corresponding log-rank (Mantel-Cox) tests were used to visually compare survival across levels of expression. We used Cox proportional hazards regression to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for association of expression categories with survival. We ran unadjusted and adjusted analyses, with the latter including age at diagnosis (continuous), stage (I/II, III/IV, unknown), and study site as adjustment terms in order to minimize potential confounding effects. Separate analyses were carried out by histotype and among selected histological groupings. The secondary outcome of interest was progression-free survival defined as time from diagnosis to first disease progression, again censoring follow-up at 10 years and accounting for possible left truncation. We tested the proportional hazards assumption for all primary analyses. On subsets of HGSOCs with additional clinical details, we also conducted analysis by extent of residual disease following initial debulking surgery (available for 66% of patients), germline pathogenic *BRCA1* and *BRCA2* mutation status (available for 28% of patients), and confirmed use of standard first-line chemotherapy (available for 12% of patients). *P* value reporting adheres to journal requirements; more detail on statistical significance is available upon request.

Supplemental Figure 1. Patient exclusions



Supplemental Table 1. Participating epithelial ovarian cancer studies

Study	Name	Ref-erence	Location	Years	Ascertainment of Patients and Clinical Data	Pathology Data and Review	N (%)	High-grade serous N (%)
VAN	Vancouver Ovarian Cancer Study	(1, 2)	Canada	1984-2000	Ovarian Cancer Registry serving British Columbia and the Cheryl Brown Outcomes Unit	Central review of pathology reports and histological slides by University of British Columbia pathologists	1,021 (19%)	595 (21%)
AOV	Alberta Ovarian Tumor Types Study	(3)	Canada	1978-2010	Population-based Alberta Cancer Registry; annual updates are performed for vital statistics	Pathology reports and histological slides review by the study pathologist	580 (11%)	77 (3%)
SEA	Study of Epidemiology and Risk Factors in Cancer Heredity	(4)	UK	1998-2008	Eastern Region Cancer Intelligence Unit, West Midlands Cancer Intelligence Unit, and multiple cancer networks	Pathology reports and histological slides reviewed by study pathologist	537 (10%)	260 (9%)
NOT	Nottingham Study	(5)	UK	1991-2011	Hospital records and Trent cancer registry	Pathology reports reviewed by gynecologic pathologist	451 (9%)	261 (9%)
STA	Genetic Epidemiology of Ovarian Cancer Study	(6)	US	1997-2001	Greater Bay Area Cancer Registry	Pathology reports and histological slides reviewed by study pathologist	411 (8%)	169 (6%)
MAY	Mayo Clinic Ovarian Cancer Study	(7)	US	2009-2013	Mayo Clinic medical records and death certificates	Pathology reports and histologic slides reviewed by Mayo Clinic gynecologic pathologists	315 (6%)	250 (9%)
LAX	Women's Cancer Research Program - Cedars-Sinai Medical Center	(8)	US	1989-2009	Women's Cancer Program Biorepository	Pathology reports and histological slides reviewed by the Department of Pathology and Laboratory Medicine at Cedars-Sinai Medical Center	246 (5%)	243 (8%)
BAV	Bavarian Ovarian Cancer Study	(9)	Germany	2002-2006	Gynecologic Oncology Center at the Comprehensive Cancer Center Erlangen-Nuremberg	Centralized review of pathology reports and histological slides for all patients by study pathologists	230 (4%)	137 (5 %)
WMH	Westmead Hospital, Gynaecological Oncology Biobank (GynBiobank)	(10)	Australia	1992-2014	The Crown Princess Mary Cancer Centre and affiliated hospitals	Pathology reports and diagnostic slides reviewed by panel of gynecologic pathologists	199 (4%)	133 (5%)
TUE	Tuebingen University Hospital	-	Germany	1999-2008	Department of Obstetrics and Gynaecology, Eberhard Karls Universitats Tübingen, Tübingen Germany	Pathology reports and histologic slides reviewed by gynecologic pathologist	192 (4%)	151 (5%)
POC	Polish Ovarian Cancer Study	(11)	Poland	2000-2003	Hospital records and cancer registries serving Warsaw and Lodz	Histological slides reviewed by study pathologist	142 (3%)	83 (3%)
HAW	Hawaii Ovarian Cancer Study	(12, 13)	US	1993-2008	Hawaii Tumor Registry and medical records	Pathology reports and histological slides reviewed by study pathologist	129 (2%)	60 (2%)
CNI	CNIO Ovarian Cancer Study	(14)	Spain	2006-2013	Hospitals in Madrid in Medical Oncology Divisions	Pathology information was obtained from medical charts of the patients used in the Medical Oncology Units	127 (2%)	57 (2%)
BRZ	Ribeirao Preto Ovarian Cancer Study	-	Brazil	1987-2010	University Hospital of Ribeirao Preto School of Medicine (HCRP), case series with prospective follow up	Pathology reports and histologic slides reviewed by HCRP gynecologic pathologists	115 (2%)	59 (2%)
UKO	United Kingdom	(15)	UK	2006-2010	Ten major Gynecologic Oncology NHS	Central review of pathology reports by	105 (2%)	58 (2%)

Study	Name	Ref-erence	Location	Years	Ascertainment of Patients and Clinical Data	Pathology Data and Review	N (%)	High-grade serous N (%)
	Ovarian Cancer Population study				centers in England, Wales and Northern Ireland; cancer registries; NHS Information Centre for Health and Social Care (England and Wales) and Central Services Agency (Northern Ireland)	gynecologic oncologist		
CAL	Calgary Serous Carcinoma Study	(16)	Canada	2003-2007	Hospital based retrospective observational study	Histological review of all slides by study pathologist supported by centralized biomarker analysis	106 (2%)	76 (3%)
AOC	Australian Ovarian Cancer Study	(17)	Australia	2002-2006	Treatment centers throughout Australia; cancer registries serving Queensland, South and West Australia; regular follow-up by medical record review	Pathology reports and diagnostic slides reviewed by panel of gynecologic pathologists	95 (2%)	91 (3%)
GER	Germany Ovarian Cancer Study	(18)	Germany	1993-1996	26 hospitals in the study regions	Pathology reports were requested from the respective pathology institutes. Tissue samples were provided by the tissue bank of the National Center for Tumor Diseases (NCT, Heidelberg, Germany) in accordance with the regulations of the tissue bank and the approval of the ethics committee of Heidelberg University and by other pathology institutes. Histological slides were reviewed by gynecologic pathologist at the University of Heidelberg	85 (2%)	41 (1%)
MAL	Malignant Ovarian Cancer Study	(19, 20)	Denmark	1994-1999	Gynecological departments in Copenhagen, Frederiksberg and 7 surrounding counties	Review of pathology reports for all patients and histological slides for 30% by gynecologic pathologist	66 (1%)	7 (1%)
SOC	Southampton Ovarian Cancer Study	(21)	UK	1993-1998	Hospitals in the Wessex region of southern England	Original pathology report	68 (1%)	31 (1%)
HOP	Hormones and Ovarian Cancer PrEdiction	(22)	US	2003-2009	Hospital registries and active surveillance of medical practices in Western PA, Northeastern OH, and Western NY	Medical chart review for all cases	43 (1%)	26 (1%)
							5,263	2,865

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Supplemental Table 2. Clinical characteristics of 5,263 epithelial ovarian cancer patients

	Mean (range)
Age at diagnosis, years	58.0 (16-95)
Time to study entry, months	4.9 (0-118.7)
Time to last follow-up, months	58.4 (0.1-119.9
	N (%)
Tumor behavior	
Invasive	4,995 (95%)
Borderline (atypical proliferative)	268 (5%)
Histology	
High-grade serous	2,865 (54%)
Endometrioid	670 (13%)
Clear cell	616 (12%)
Mucinous	355 (7%)
Low-grade serous	188 (4%)
Mucinous borderline	129 (2%)
Serous borderline	127 (2%)
Mixed histology	114 (2%)
Serous, unknown-grade	7 (<1%)
Endometrioid borderline	10 (<1%)
Clear cell borderline	1 (<1%)
Undifferentiated/poorly differentiated epithelial	67 (<1%)
Unknown, but known to be epithelial	65 (1%)
Other specified epithelial	48 (1%)
Other specified epithelial borderline	1 (<1%)
Stage	
FIGO I, II	2,222 (44%)
FIGO III, IV	2,837 (56%)
Unknown	204
Grade	
High	4,001 (76%)
Low	703 (24%)
Not Applicable/Unknown	559
Race	
White	2,262 (76%)
Presumed white	375 (13%)
Asian	177 (6%)
Black	32 (1%)
Other	113 (4%)
Unknown	2,304
Ethnicity	
Not Hispanic	2,883 (98%)
Hispanic	54 (2%)
Unknown	2,326
Vital status at last follow-up	
Living	2,494 (47%)
Deceased	2,769 (53%)

FIGO, International Federation of Gynecologic Oncologists

Supplemental Table 3. Distributions of MyD88 and TLR4 expression by histopathological group, N (row %)

	MYD88 Expression		TLR4 Expression		
	Weak	Strong	Weak	Strong	Total
All invasive	1,414 (29%)	3,450 (71%)	1,456 (33%)	2,960 (67%)	4,995
Serous	763 (26%)	2,201 (74%)	779 (29%)	1,894 (71%)	3,060
High-grade serous	712 (26%)	2,064 (74%)	734 (29%)	1,788 (71%)	2,865
Low-grade serous	49 (27%)	133 (73%)	42 (29%)	103 (71%)	188
Endometrioid	213 (32%)	447 (68%)	169 (28%)	443 (72%)	670
Grade 1 endometrioid	108 (33%)	219 (67%)	62 (20%)	252 (80%)	329
Grade 2/3 endometrioid	101 (31%)	220 (69%)	105 (37%)	182 (63%)	328
Clear cell	250 (41%)	358 (59%)	335 (60%)	226 (40%)	616
Mucinous	95 (28%)	249 (72%)	79 (26%)	224 (74%)	355
All borderline	67 (26%)	195 (74%)	45 (26%)	126 (74%)	268
Serous borderline	40 (33%)	82 (67%)	12 (30%)	28 (70%)	127
Mucinous borderline	22 (17%)	106 (83%)	29 (24%)	90 (76%)	129
Serous borderline or invasive	803 (26%)	2,283 (74%)	792 (29%)	1,922 (71%)	3,187
Mucinous borderline or invasive	118 (25%)	355 (75%)	108 (26%)	314 (74%)	484
Low-grade serous or serous borderline	89 (29%)	215 (71%)	55 (30%)	131 (70%)	315
Overall	1,481 (29%)	3,645 (71%)	1,501 (33%)	3,086 (67%)	5,263

Numbers do not sum to total due to inclusion in sub-groups indicated by indentation as well as inclusion of patients with missing MYD88 or TLR4 expression or with tumors of unknown grade, histotype, or tumor behavior where appropriate.

Supplemental Table 4. Associations of MyD88 and TLR4 expression with clinical features of HGSOC

	MyD88			TLR4		
	Weak	**Strong**	***P***	**Weak**	**Strong**	***P***
Age, mean (SD)	60.5 (11.0)	60.7 (11.2)	0.65	60.0 (11.4)	60.6 (11.2)	0.16
Tumor stage			2.7×10^{-4}			0.75
I-II	172 (25%)	373 (18%)		141 (20%)	336 (19%)	
III-IV	517 (75%)	1,651 (82%)		572 (80%)	1,422 (81%)	
Extent of residual disease						
Macroscopic disease	274 (60%)	800 (59%)	0.77	292 (59%)	687 (59%)	0.88
No macroscopic disease	185 (40%)	561 (41%)		207 (41%)	476 (41%)	
Pathogenic mutation status						
Tested negative	152 (81%)	485 (81%)	0.78	147 (79%)	444 (81%)	0.84
Pathogenic *BRCA1* mutation	23 (12%)	82 (14%)		27 (15%)	71 (13%)	
Pathogenic *BRCA2* mutation	13 (7%)	35 (6%)		11 (6%)	31 (6%)	
First line chemotherapy treatment						
Standard treatment	59 (8%))	280 (14%)	2.6×10^{-4}	102 (14%)	231 (13%)	0.55
Unknown treatment	653 (92%)	1,784 (86%)		632 (86%)	2,189 (87%)	

HGSOC, high-grade serous ovarian cancer; adjusted for study, age (continuous), and stage (I/II, III/IV, unknown); mutation status reflects results of germline testing; standard treatment includes patients receiving ≥ four cycles of intra-venous carboplatin AUC 5 or 6 and paclitaxel 135 mg/m² or 175 mg/m² every three weeks and patients receiving ≥ four cycles of intra-venous carboplatin and paclitaxel every three weeks with dose presumed to be carboplatin AUC 5 or 6 and paclitaxel 135 mg/m² or 175 mg/m²; HR, hazard ratio, CI, confidence interval; N (%) unless otherwise specified; *P* from analysis of variance or chi-square testing, as appropriate.

Supplemental Table 5. Multivariate-adjusted association of combined MyD88 and TLR4 expression and overall survival among HGSOC cases by extent of residual disease, by pathogenic mutation status, and by first line chemotherapy

	MyD88	TLR4	N	N events	HR (95% CI)	*P*
Extent of Residual Disease						
Macroscopic disease	Weak	Weak	105	69	ref	0.13
		Strong	115	92	1.35 (0.96,1.89)	
	Strong	Weak	180	144	1.32 (0.98,1.78)	
		Strong	561	475	1.40 (1.06,1.85)	
No macroscopic disease	Weak	Weak	64	32	ref	0.11
		Strong	76	41	0.81 (0.50,1.31)	
	Strong	Weak	121	68	1.30 (0.84,2.01)	
		Strong	373	177	0.92 (0.61,1.40)	
Pathogenic Mutation Status						
Tested negative	Weak	Weak	44	25	ref	0.22
		Strong	82	54	1.34 (0.81,2.22)	
	Strong	Weak	96	69	1.40 (0.87,2.26)	
		Strong	345	253	1.56 (1.00,2.44)	
Pathogenic *BRCA1* mutation	Weak	Weak	7	3	ref	0.052
		Strong	12	5	0.69 (0.15,3.18)	
	Strong	Weak	16	5	0.27 (0.05,1.62)	
		Strong	55	35	1.12 (0.25,5.05)	
Pathogenic *BRCA2* mutation	Weak	Weak	2	0	ref	0.19
		Strong	8	3	Not estimated	
	Strong	Weak	6	4	Not estimated	
		Strong	21	8	Not estimated	
First Line Chemotherapy Treatment						
Standard treatment	Weak	Weak	23	13	ref	0.77
		Strong	29	19	0.76 (0.35,1.62)	
	Strong	Weak	70	43	1.02 (0.54,1.95)	
		Strong	185	119	1.00 (0.54,1.88)	

HGSOC, high-grade serous ovarian cancer; adjusted for study, age (continuous), and stage (I/II, III/IV, unknown); mutation status reflects results of germline testing; standard treatment includes patients receiving ≥ four cycles of intra-venous carboplatin AUC 5 or 6 and paclitaxel 135 mg/m² or 175 mg/m² every three weeks and patients receiving ≥ four cycles of intra-venous carboplatin and paclitaxel every three weeks with dose presumed to be carboplatin AUC 5 or 6 and paclitaxel 135 mg/m² or 175 mg/m²; HR, hazard ratio, CI, confidence interval.

Supplemental Table 6. Associations of MyD88 and TLR4 expression with overall survival by histopathological groups

		MyD88				TLR4			
Histotype	**Level**	**N Subjects**	**N Events**	**HR (95% CI)**	***P***	**N Subjects**	**N Events**	**HR (95% CI)**	***P***
Grade 1 endometrioid	Weak	108	25	ref	0.70	62	13	ref	0.14
	Strong	219	34	0.90 (0.52,1.55)		252	42	0.59 (0.30,1.19)	
Grade 2/3 endometrioid	Weak	101	31	ref	0.97	105	34	ref	0.70
	Strong	220	72	0.99 (0.63,1.55)		182	59	1.10 (0.67,1.82)	
Serous invasive	Weak	763	477	ref	0.21	779	513	ref	0.49
	Strong	2201	1492	1.07 (0.96,1.19)		1894	1303	1.04 (0.93,1.16)	
All borderline	Weak	67	5	ref	0.83	45	4	ref	0.47
	Strong	195	16	0.88 (0.29,2.69)		126	12	1.63 (0.44,6.09)	
All invasive	Weak	1414	717	ref	0.31	1456	790	ref	0.99
	Strong	3450	1947	1.05 (0.96,1.15)		2960	1654	1.00 (0.91,1.10)	
Serous borderline or invasive	Weak	803	480	ref	0.21	792	514	ref	0.39
	Strong	2283	1497	1.07 (0.96,1.19)		1922	1306	1.05 (0.94,1.17)	
Mucinous borderline or Invasive	Weak	118	38	ref	0.56	108	43	ref	0.14
	Strong	355	107	1.14 (0.73,1.79)		314	80	1.43 (0.89,2.29)	
Low-grade serous or serous borderline	Weak	89	29	ref	0.01	55	22	ref	0.20
	Strong	215	69	0.54 (0.33,0.88)		131	57	0.65 (0.34,1.24)	
Serous borderline	Weak	40	3	ref	0.23	13	1	ref	NA
	Strong	82	5	0.35 (0.06,1.94)		28	3	Not estimated	
Mucinous borderline	Weak	22	2	ref	0.67	29	3	ref	0.91
	Strong	106	11	1.43 (0.27,7.45)		90	9	1.08 (0.27,4.41)	

Adjusted for study, age, and stage; HR, hazard ratio, CI, confidence interval.

Supplemental Table 7. Associations of combinations of MyD88 and TLR4 expression with overall survival by histopathological groups

Histotype	MyD88	TLR4	N Subjects	N events	HR (95% CI)	*P*
Grade 1 endometrioid	Weak	Weak	33	9	ref	0.47
		Strong	69	14	0.53 (0.21,1.29)	
	Strong	Weak	27	4	0.84 (0.25,2.88)	
		Strong	183	28	0.56 (0.25,1.27)	
Grade 2/3 endometrioid	Weak	Weak	52	13	ref	0.53
		Strong	32	11	1.65 (0.70,3.84)	
	Strong	Weak	47	18	1.71 (0.78,3.75)	
		Strong	149	48	1.35 (0.70,2.62)	
Serous invasive	Weak	Weak	265	160	ref	0.32
		Strong	337	225	1.12 (0.91,1.38)	
	Strong	Weak	475	324	1.17 (0.96,1.42)	
		Strong	1,500	1,037	1.18 (0.99,1.41)	
All borderline	Weak	Weak	12	0	ref	NA
		Strong	27	3	Not estimated	
	Strong	Weak	31	4	Not estimated	
		Strong	95	9	Not estimated	
All invasive	Weak	Weak	586	283	ref	0.11
		Strong	581	305	1.10 (0.93,1.30)	
	Strong	Weak	809	470	1.21 (1.04,1.41)	
		Strong	2,309	1,302	1.13 (0.98,1.30)	
Serous borderline or invasive	Weak	Weak	271	160	ref	0.27
		Strong	344	227	1.14 (0.92,1.40)	
	Strong	Weak	480	325	1.18 (0.97,1.43)	
		Strong	1,518	1,038	1.19 (1.00,1.42)	
Mucinous borderline or invasive	Weak	Weak	33	14	ref	0.63
		Strong	59	14	1.57 (0.67,3.71)	
	Strong	Weak	68	26	1.14 (0.52,2.49)	
		Strong	251	65	1.47 (0.69,3.14)	
Low-grade serous or Serous borderline	Weak	Weak	23	10	ref	0.18
		Strong	21	10	1.06 (0.38,3.02)	
	Strong	Weak	29	12	0.78 (0.28,2.18)	
		Strong	102	46	0.54 (0.22,1.28)	
Serous borderline	Weak	Weak	6	0	ref	NA
		Strong	7	2	Not estimated	
	Strong	Weak	5	1	Not estimated	
		Strong	18	1	Not estimated	
Mucinous borderline	Weak	Weak	5	0	ref	NA
		Strong	16	1	Not estimated	
	Strong	Weak	24	3	Not estimated	
		Strong	73	8	Not estimated	

Adjusted for study, age (continuous), and stage (I/II, III/IV, unknown); HR, hazard ratio; CI, confidence interval; p value from unordered three degree-of-freedom test.

Supplemental Table 8. Associations of MyD88 and TLR4 expression with progression-free survival among cases with the five most common invasive epithelial ovarian cancer histotypes

		MyD88				TLR4			
Histotype	**Expression**	**N Subjects**	**N Events**	**HR (95% CI)**	***P***	**N Subjects**	**N Events**	**HR (95% CI)**	***P***
High-grade serous	Weak	319	214	ref	0.28	396	269	ref	0.61
	Strong	1,030	714	1.10 (0.93,1.29)		849	599	1.04 (0.89,1.23)	
Endometrioid	Weak	80	18	ref	0.61	63	13	ref	0.18
	Strong	216	47	1.17 (0.65,2.11)		227	48	1.70 (0.78,3.71)	
Clear cell	Weak	96	38	ref	0.29	170	80	ref	0.46
	Strong	185	98	1.25 (0.83,1.90)		99	48	1.16 (0.78,1.72)	
Mucinous	Weak	35	16	ref	0.27	42	23	ref	0.21
	Strong	119	43	1.49 (0.74,3.00)		101	27	1.84 (0.71,4.78)	
Low-grade serous	Weak	18	11	ref	0.06	20	13	ref	0.05
	Strong	48	27	0.41 (0.16,1.05)		43	25	0.32 (0.10,0.99)	

Adjusted for study, age (continuous), and stage (I/II, III/IV, unknown); HR, hazard ratio; CI, confidence interval.

Supplemental Table 9. Associations of combinations of MyD88 and TLR4 expression with progression-free survival among cases with the five most common invasive epithelial ovarian cancer histotypes

Histotype	MyD88	TLR4	N Subjects	N events	HR (95% CI)	*P*
High-grade serous	Weak	Weak	122	80	ref	0.60
		Strong	123	87	0.95 (0.68,1.31)	
	Strong	Weak	256	176	1.03 (0.78,1.36)	
		Strong	700	492	1.10 (0.84,1.43)	
Endometrioid	Weak	Weak	30	6	ref	0.49
		Strong	47	9	2.32 (0.71,7.51)	
	Strong	Weak	32	7	1.80 (0.54,5.99)	
		Strong	180	39	2.19 (0.80,5.94)	
Clear cell	Weak	Weak	77	30	ref	0.20
		Strong	13	3	0.98 (0.29,3.31)	
	Strong	Weak	93	50	1.65 (0.98,2.78)	
		Strong	86	45	1.71 (0.98,2.97)	
Mucinous	Weak	Weak	16	10	ref	0.45
		Strong	15	4	2.85 (0.63,13.0)	
	Strong	Weak	26	13	1.75 (0.59,5.12)	
		Strong	86	23	2.69 (0.78,9.28)	
Low-grade serous	Weak	Weak	11	8	ref	0.14
		Strong	6	3	0.67 (0.12,3.71)	
	Strong	Weak	9	5	0.84 (0.18,3.83)	
		Strong	36	22	0.25 (0.07,0.90)	

Adjusted for study, age (continuous), and stage (I/II, III/IV, unknown); HR, hazard ratio; CI, confidence interval; p value from unordered three degree-of-freedom test.