

# THE LANCET **Oncology**

## **Supplementary appendix**

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Sieh W, Köbel M, Longacre TA, et al. Hormone-receptor expression and ovarian cancer survival: an Ovarian Tumor Tissue Analysis consortium study. *Lancet Oncol* 2013; published online July 9. [http://dx.doi.org/10.1016/S1470-2045\(13\)70253-5](http://dx.doi.org/10.1016/S1470-2045(13)70253-5).

**Supplementary Table 1. Hormone receptor expression and disease-specific survival, adjusted for extent of residual disease and other clinical covariates in seven sites<sup>a</sup>, by subtype.**

	HGSC		LGSC		MC		EC		CCC	
	HR <sup>b</sup> (95% CI)	p	HR <sup>b</sup> (95% CI)	p	HR <sup>b</sup> (95% CI)	p	HR <sup>b</sup> (95% CI)	p	HR <sup>b</sup> (95% CI)	p
<b>PR expression</b>										
Negative	Referent		Referent		Referent		Referent		Referent	
Weak	1.01 (0.85-1.20)	0.90	0.52 (0.14-1.87)	0.31	0.44 (0.07-2.61)	0.37	0.45 (0.24-0.84)	0.013	1.19 (0.45-3.11)	0.73
Strong	0.73 (0.53-1.00)	0.049	0.54 (0.18-1.61)	0.27	1.60 (0.51-5.01)	0.42	0.49 (0.26-0.92)	0.027	1.06 (0.35-3.23)	0.92
<b>ER expression</b>										
Negative	Referent		Referent		Referent		Referent		Referent	
Weak	0.91 (0.72-1.14)	0.41	2.04 (0.36-11.73)	0.42	1.00 (0.21-4.71)	1.00	0.45 (0.22-0.92)	0.028	1.39 (0.61-3.16)	0.43
Strong	0.91 (0.75-1.10)	0.33	1.11 (0.21-5.73)	0.90	0.52 (0.16-1.64)	0.26	0.45 (0.27-0.76)	0.0026	1.09 (0.57-2.07)	0.79

HGSC=high-grade serous carcinoma; LGSC=low-grade serous carcinoma; MC=mucinous carcinoma; EC=endometrioid carcinoma; CCC=clear cell carcinoma.  
a. Seven sites (AOC, HAW, MAL, MAY+MAC, NOT, TOR, VAN) provided information on extent of residual disease following primary cytoreductive surgery.  
b. Hazard ratio (HR) and 95% confidence interval (CI) estimated using Cox regression stratified by site, and adjusted for age, age-squared, stage (localized, regional, advanced), and macroscopic residual disease (no, yes, unknown). We also adjusted for grade in models for HGSC (moderately, poorly differentiated), MC and EC (well, moderately, poorly differentiated).

**Supplementary Table 2. Progesterone receptor expression and high-grade serous carcinoma survival, unadjusted or adjusted for clinical covariates.**

Covariate	All study sites		All study sites		Subset of 7 sites	
	HR <sup>a</sup> (95% CI)	p	HR <sup>b</sup> (95% CI)	p	HR <sup>c</sup> (95% CI)	p
<b>PR expression</b>						
Negative or weak	Referent		Referent		Referent	
Strong	0.65 (0.51-0.83)	0.0006	0.71 (0.55-0.91)	0.0061	0.73 (0.53-0.99)	0.044
<b>Age (years)</b>			0.95 (0.92-0.99)	0.022	0.93 (0.88-0.97)	0.0025
<b>Age-squared</b>			1.0005 (1.0002-1.0008)	0.0022	1.0007 (1.0003-1.0012)	0.0003
<b>Stage</b>						
Localized			Referent		Referent	
Regional			1.79 (1.17-2.76)	0.0079	1.02 (0.60-1.74)	0.94
Distant			4.78 (3.17-7.20)	<0.0001	2.22 (1.35-3.67)	0.0018
<b>Grade</b>						
Moderately differentiated			Referent		Referent	
Poorly differentiated			0.92 (0.80-1.06)	0.27	0.87 (0.74-1.02)	0.087
<b>Macroscopic residual disease</b>						
No					Referent	
Yes					2.19 (1.78-2.68)	<0.0001
Unknown					1.57 (1.17-2.11)	0.0025

Hazard ratio (HR) and 95% confidence interval (CI) estimated using Cox regression: (a) stratified by study site; (b) stratified by study site and adjusted for age, age-squared, stage (localized, regional, advanced) and grade (moderately, poorly differentiated) at diagnosis; (c) stratified by study site and adjusted for age, age-squared, stage (localized, regional, advanced), grade (moderately, poorly differentiated), and macroscopic residual disease (no, yes, unknown) using data from 7 sites (AOC, HAW, MAL, MAY+MAC, NOT, TOR, VAN).

**Supplementary Table 3. Hormone receptor expression and endometrioid carcinoma survival, unadjusted or adjusted for clinical covariates.**

Covariate	All study sites		All study sites		Subset of 7 sites	
	HR <sup>a</sup> (95% CI)	p	HR <sup>b</sup> (95% CI)	p	HR <sup>c</sup> (95% CI)	p
<b>Hormone receptor status</b>						
Negative for ER and PR	Referent		Referent		Referent	
Positive for ER and/or PR	0.35 (0.23-0.54)	<0.0001	0.33 (0.21-0.51)	<0.0001	0.34 (0.20-0.57)	<0.0001
<b>Age (years)</b>			0.88 (0.77-1.00)	0.055	0.88 (0.75-1.04)	0.14
<b>Age-squared</b>			1.0013 (1.0002-1.0024)	0.020	1.0013 (1.0000-1.0027)	0.054
<b>Stage</b>			Referent		Referent	
Localized						
Regional			2.66 (1.33-5.33)	0.0057	3.27 (1.29-8.28)	0.012
Distant			9.00 (4.40-18.42)	<0.0001	8.07 (3.03-21.49)	<0.0001
<b>Grade</b>			Referent		Referent	
Well differentiated						
Moderately differentiated			1.11 (0.60-2.04)	0.73	0.91 (0.43-1.91)	0.80
Poorly differentiated			2.10 (1.12-3.91)	0.020	1.89 (0.86-4.15)	0.11
<b>Macroscopic residual disease</b>					Referent	
No						
Yes					2.29 (1.16-4.52)	0.017
Unknown					0.84 (0.36-1.97)	0.69

Hazard ratio (HR) and 95% confidence interval (CI) estimated using Cox regression: (a) stratified by study site; (b) stratified by study site and adjusted for age, age-squared, stage (localized, regional, advanced) and grade (well, moderately, poorly differentiated) at diagnosis; (c) stratified by study site and adjusted for age, age-squared, stage (localized, regional, advanced), grade (well, moderately, poorly differentiated), and macroscopic residual disease (no, yes, unknown) using data from 7 sites (AOC, HAW, MAL, MAY+MAC, NOT, TOR, VAN).

**Supplementary Table 4. Sensitivity analysis of hormone receptor expression and disease-specific\* survival censoring patients with unknown cause of death, by subtype.**

	HGSC		LGSC		MC		EC		CCC	
	HR <sup>a</sup> (95% CI)	p	HR <sup>a</sup> (95% CI)	p	HR <sup>a</sup> (95% CI)	p	HR <sup>a</sup> (95% CI)	p	HR <sup>a</sup> (95% CI)	p
<b>PR expression</b>										
Negative	Referent		Referent		Referent		Referent		Referent	
Weak	0.97 (0.83-1.14)	0.75	0.48 (0.19-1.19)	0.11	0.55 (0.11-2.83)	0.47	0.47 (0.25-0.88)	0.019	0.74 (0.31-1.79)	0.50
Strong	0.71 (0.53-0.94)	0.016	0.34 (0.14-0.79)	0.012	1.17 (0.31-4.41)	0.82	0.43 (0.23-0.79)	0.0068	0.63 (0.14-2.75)	0.53
<b>ER expression</b>										
Negative	Referent		Referent		Referent		Referent		Referent	
Weak	1.20 (0.97-1.49)	0.10	1.03 (0.20-5.27)	0.97	1.30 (0.13-12.67)	0.82	0.43 (0.20-0.92)	0.029	1.75 (0.84-3.67)	0.14
Strong	1.12 (0.93-1.36)	0.24	0.75 (0.18-3.08)	0.69	0.28 (0.08-0.94)	0.039	0.42 (0.25-0.71)	0.0013	1.18 (0.63-2.23)	0.61

HGSC=high-grade serous carcinoma; LGSC=low-grade serous carcinoma; MC=mucinous carcinoma; EC=endometrioid carcinoma; CCC=clear cell carcinoma.

\* Failures were defined as deaths due to ovarian cancer, and deaths due to unknown causes were censored.

a. Hazard ratio (HR) and 95% confidence interval (CI) estimated using Cox regression stratified by site, and adjusted for age, age-squared, and stage (localized, regional, advanced) at diagnosis. We also adjusted for grade in models for HGSC (moderately, poorly differentiated), MC and EC (well, moderately, poorly differentiated).

**Supplementary Table 5. Hormone receptor expression and overall survival, by subtype.**

	HGSC		LGSC		MC		EC		CCC	
	HR <sup>a</sup> (95% CI)	p	HR <sup>a</sup> (95% CI)	p	HR <sup>a</sup> (95% CI)	p	HR <sup>a</sup> (95% CI)	p	HR <sup>a</sup> (95% CI)	p
<b>PR expression</b>										
Negative	Referent		Referent		Referent		Referent		Referent	
Weak	1.00 (0.87-1.15)	0.96	0.56 (0.24-1.26)	0.16	0.69 (0.24-2.02)	0.50	0.72 (0.46-1.13)	0.16	0.81 (0.36-1.83)	0.62
Strong	0.74 (0.58-0.94)	0.013	0.46 (0.22-0.94)	0.034	0.99 (0.40-2.46)	0.98	0.43 (0.26-0.70)	0.0008	1.24 (0.50-3.06)	0.64
<b>ER expression</b>										
Negative	Referent		Referent		Referent		Referent		Referent	
Weak	1.00 (0.83-1.21)	0.96	1.23 (0.34-4.48)	0.76	1.44 (0.41-5.01)	0.57	0.51 (0.30-0.87)	0.014	1.65 (0.84-3.25)	0.14
Strong	1.01 (0.86-1.18)	0.92	0.79 (0.24-2.58)	0.70	0.71 (0.35-1.47)	0.36	0.50 (0.33-0.75)	0.0007	1.26 (0.76-2.08)	0.38

HGSC=high-grade serous carcinoma; LGSC=low-grade serous carcinoma; MC=mucinous carcinoma; EC=endometrioid carcinoma; CCC=clear cell carcinoma.  
a. Hazard ratio (HR) and 95% confidence interval (CI) estimated using Cox regression stratified by site, and adjusted for age, age-squared, and stage (localized, regional, advanced) at diagnosis. We also adjusted for grade in models for HGSC (moderately, poorly differentiated), MC and EC (well, moderately, poorly differentiated).

**Supplementary Table 6. Association of clinical prognostic factors with hormone receptor status in endometrioid carcinoma.**

Clinical prognostic factor	Negative for ER and PR n (%)	Positive for ER and/or PR n (%)	Exact p <sup>a</sup>
<b>Grade, N</b>	83	368	0.0007
Well differentiated	17 (20.5)	148 (40.2)	
Moderately differentiated	31 (37.4)	127 (34.5)	
Poorly differentiated	35 (42.2)	93 (25.3)	
<b>Stage, N</b>	83	368	0.57
Localized	27 (32.5)	118 (32.1)	
Regional	34 (41.0)	170 (46.2)	
Distant	22 (26.5)	80 (21.7)	
<b>Macroscopic residual disease<sup>b</sup>, N</b>	62	278	0.041
No	45 (72.6)	230 (82.7)	
Yes	10 (16.1)	17 (6.1)	
Unknown	7 (11.3)	31 (11.2)	

a. Unadjusted p-value for Fisher's exact test.

b. Seven sites (AOC, HAW, MAL, MAY+MAC, NOT, TOR, VAN) provided information on extent of residual disease following primary cytoreductive surgery.

**Supplementary Table 7. Association of clinical prognostic factors with progesterone receptor status in high-grade serous carcinoma.**

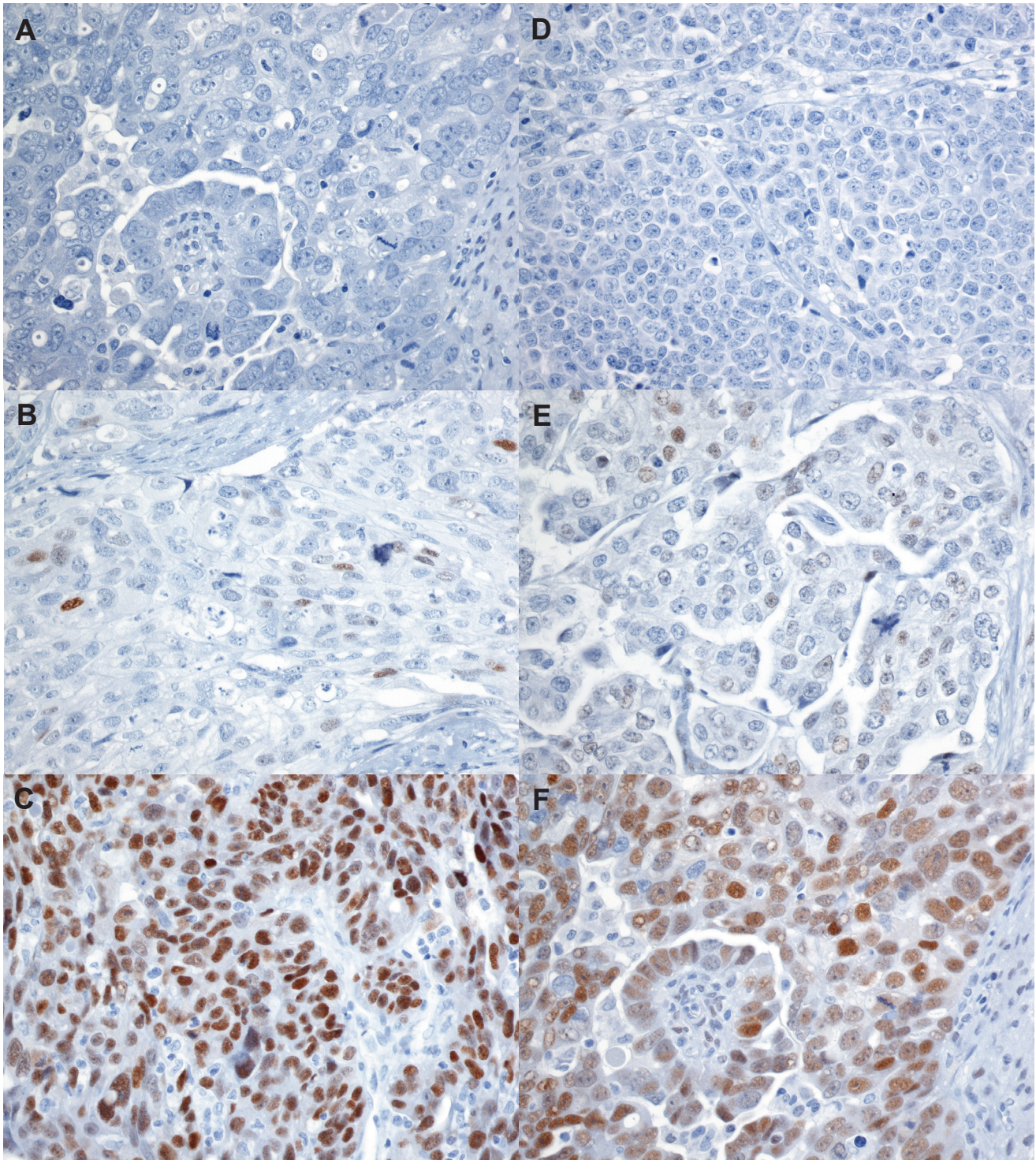
Clinical prognostic factor	Negative n (%)	PR status		Exact p <sup>a</sup>
		Weak n (%)	Strong n (%)	
<b>Stage</b>	1144	393	124	0·0029
Localized	46 (4·0)	25 (6·4)	10 (8·1)	
Regional	172 (15·0)	83 (21·1)	23 (18·6)	
Distant	926 (80·9)	285 (72·5)	91 (73·4)	
<b>Macroscopic residual disease<sup>b</sup>, N</b>	733	267	81	0·11
No	232 (31·6)	89 (33·3)	35 (43·2)	
Yes	417 (56·9)	152 (56·9)	34 (42·0)	
Unknown	84 (11·5)	26 (9·7)	12 (14·8)	
<b>BRCA1/2 mutation carrier<sup>c</sup>, N</b>	255	96	25	0·072
No	224 (87·8)	75 (78·1)	21 (84·0)	
Yes	31 (12·2)	21 (21·9)	4 (16·0)	

a. Unadjusted p-value for Fisher's exact test.

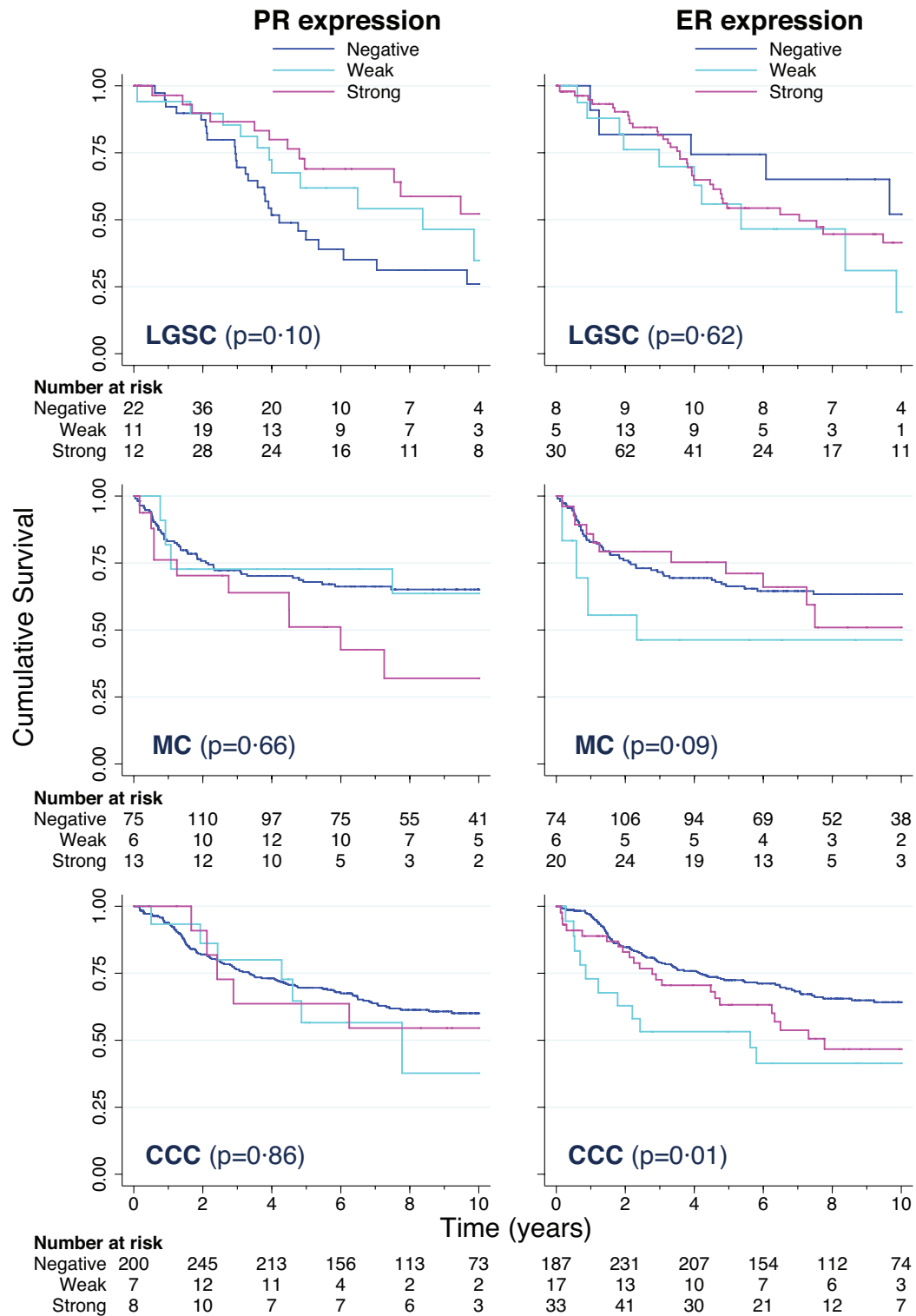
b. Seven sites (AOC, HAW, MAL, MAY+MAC, NOT, TOR, VAN) provided information on extent of residual disease following primary cytoreductive surgery.

c. Four sites (AOC, MAL, MAY+MAC, STA) provided *BRCA1* and *BRCA2* germline mutation data.





**Supplementary Figure 1. Immunohistochemical evaluation of high-grade serous ovarian carcinoma at 200× magnification.** Panels illustrate: negative (A), weakly (B) and strongly (C) positive staining for PR (Roche clone 1E2); and negative (D), weakly (E) and strongly (F) positive staining for ER (Thermo clone SP1, 1:25).



**Supplementary Figure 2. Kaplan-Meier curves of disease-specific survival for low-grade serous (LGSC), mucinous (MC), and clear cell (CCC) carcinomas, according to hormone receptor status.** The data were left truncated to avoid potential survival bias from the inclusion of patients (<10%) enrolled >1 year after diagnosis, and right censored at 10 years. P-values correspond to log-rank tests of the equality of survivor functions across hormone receptor expression levels, stratified by study site.