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Association of Cyclin E1 Expression With Genomic Instability in Ovarian Cancer

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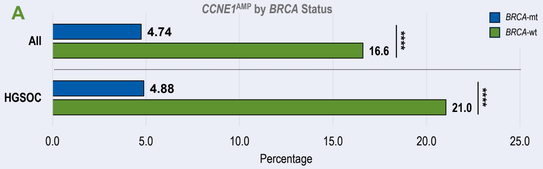
Background

- Cyclin E1 (CCNE1) expression has been associated with replicative stress and defects in double-strand break repair in multiple tumor types[1]
- An association between CCNE1 expression and genomic instability in ovarian cancer (OC) has not currently been demonstrated
- Here, we describe *CCNE1* DNA amplification (AMP), messenger RNA (mRNA) expression, and protein expression in 2 large cohorts of high-grade serous OC (HGSOC) (The Cancer Genome Atlas [TCGA] and Caris Life Sciences, Phoenix, AZ, USA)

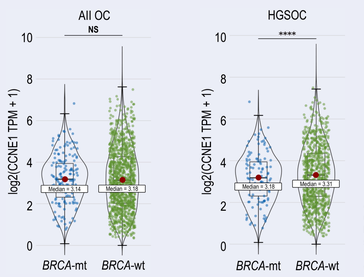
Methods

- 8,127 HGSOC samples were analyzed by next-generation sequencing (NextSeq, 592 genes or NovaSeq, whole exome sequencing) and RNA sequencing (NovaSeq, whole transcriptome sequencing [WTS]; Caris Life Sciences)
- For genomic loss of heterozygosity (LOH), 22 autosomal chromosomes were split into 552 segments and the LOH of single nucleotide polymorphisms within each segment was calculated (LOH-H ≥16%)
- Homologous repair deficient (HRD$^{+/-}$) status was determined by high genomic scar score (GSS) or *BRCA1/2* mutant (mt) [HRD^{+}], or low GSS and *BRCA1/2* wild-type (wt) [HRD^{-}], respectively
- GSS was calculated from large-scale transitions (LSTs) and LOH (GSS-H ≥46)
- 1,177 OC samples from TCGA were also included as a validation dataset which contains CCNE1 protein expression

wt-*BRCA* is Associated With *CCNE1*^{AMP} and Increased CCNE1 mRNA Expression in HGSOC Tumors



Histology	*BRCA*-mt	*BRCA*-wt	*P* value
All	78/1,645 (4.74)	1,875/11,270 (16.6)	<0.0001
HGSOC	59/1,209 (4.88)	1,431/6,800 (21.04)	<0.0001

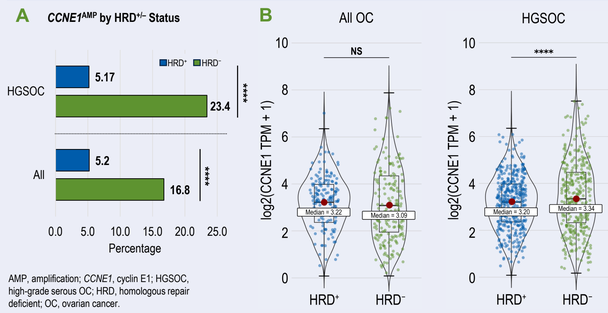


AMP, amplification; CCNE1, cyclin E1; mt, mutant; HGSOC, high-grade serous OC; NS, not significant; OC, ovarian cancer; TPM, transcripts per million; wt, wild-type.

Histology	*BRCA* Status	N	CCNE1, log2	*P* value
All OC	*BRCA*-mt	1,645	3.18 (0.08-7.21)	0.854
	BRCA-wt	11,270	3.14 (0.0-9.1)	
HGSOC	*BRCA*-mt	1,209	3.18 (0.08-7.21)	1.68E-0.5
	BRCA-wt	6,800	3.31 (0.0-9.1)	

A. *BRCA* wt samples were highly enriched for *CCNE1*^{AMP} across all OC samples, including HGSOC, vs *BRCA* mt samples
B. *BRCA* wt samples had increased CCNE1 mRNA expression vs *BRCA* mt samples in HGSOC, but not across all OC samples

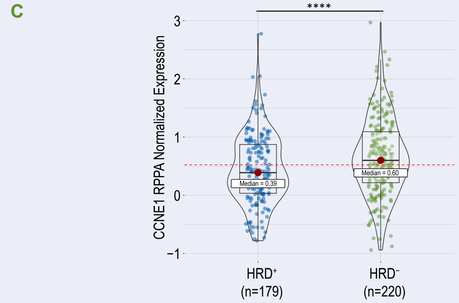
HRD^{-} Status Is Associated With *CCNE1*^{AMP} and Increased CCNE1 mRNA Expression



AMP, amplification; *CCNE1*, cyclin E1; HGSOC, high-grade serous OC; HRD, homologous repair deficient; OC, ovarian cancer.

Histology	HRD^{-}	HRD^{+}	*P* value
All	410/2,447 (16.76)	110/2,117 (5.2)	<0.0001
HGSOC	325/1,389 (23.4)	81/1,567 (5.17)	<0.0001

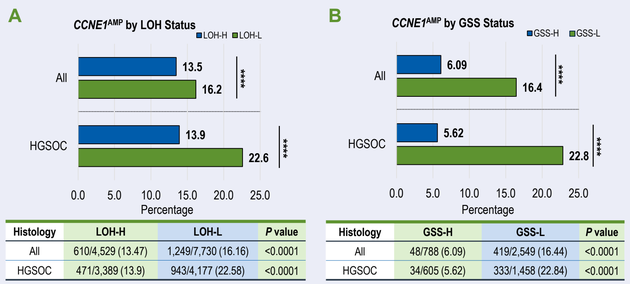
Histology	HR Status	N	CCNE1, log2	*P* value
All OC	HRD^{+}	2,117	3.22 (0.08-7.41)	0.177
	HRD^{-}	2,447	3.09 (0.09-8.38)	
HGSOC	HRD^{+}	1,567	3.2 (0.08-7.41)	2.8E-05
	HRD^{-}	1,389	3.34 (0.17-8.38)	



****P≤0.0001. *CCNE1*, cyclin E1; HRD, homologous repair deficient; RPPA, reverse phase protein array.

A. HRD^{-} samples were highly enriched for *CCNE1*^{AMP} across all OC samples, including HGSOC
B. HRD^{-} samples had increased CCNE1 mRNA expression vs HRD^{+} in HGSOC but not across all OC samples
C. HRD^{-} samples[2] also had increased CCNE1 protein expression in TCGA OC samples vs HRD^{+} samples. Red line indicates overexpression, defined by median expression of CCNE1 protein across all TCGA OC samples

CCNE1^{AMP} Is Associated With Low Global LOH and GSS Status



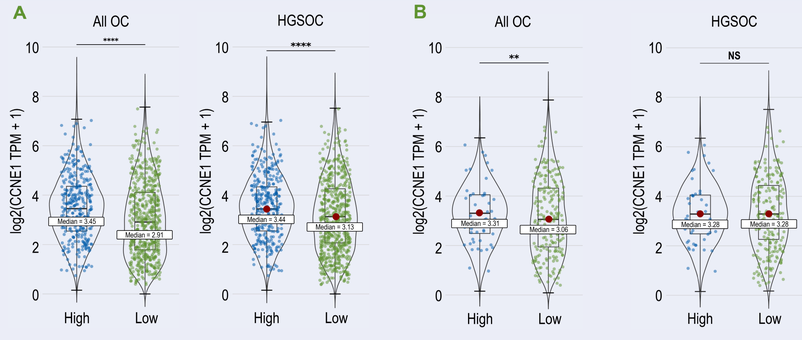
Histology	LOH-H	LOH-L	*P* value
All	610/4,529 (13.47)	1,249/7,730 (16.16)	<0.0001
HGSOC	471/3,389 (13.9)	943/4,177 (22.58)	<0.0001

Histology	GSS-H	GSS-L	*P* value
All	48/788 (6.09)	419/2,549 (16.44)	<0.0001
HGSOC	34/605 (5.62)	333/1,458 (22.84)	<0.0001

AMP, amplification; *CCNE1*, cyclin E1; GSS, genomic scar score; HGSOC, high-grade serous ovarian cancer; LOH, loss of heterozygosity.

A & B. Low global LOH and GSS status was enriched for *CCNE1*^{AMP} samples across all OC samples

Increased CCNE1 mRNA Expression Is Associated With High Global LOH Status



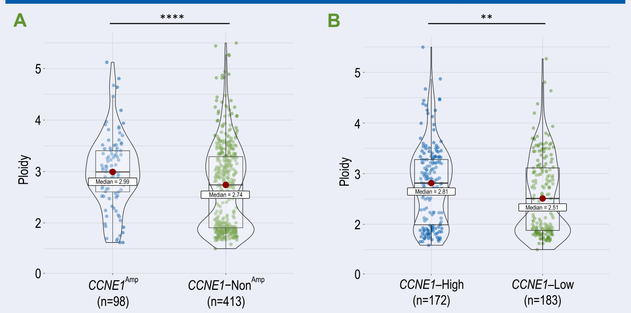
Histology	LOH Status	N	CCNE1, log2	*P* value
All OC	High	4,529	3.45 (0.15-9.1)	<0.0001
	Low	7,730	2.91 (0-8.39)	
HGSOC	High	3,389	3.44 (0.15-9.1)	<0.0001
	Low	4,177	3.13 (0-8.39)	

Histology	GSS Status	N	CCNE1, log2	*P* value
All OC	High	788	3.31 (0.15-7.41)	0.002
	Low	2,549	3.06 (0.09-8.38)	
HGSOC	High	605	3.28 (0.15-7.41)	0.322
	Low	1,458	3.28 (0.17-8.38)	

CCNE1, cyclin E1; GSS, genomic scar score; HGSOC, high-grade serous OC; NS, not significant; OC, ovarian cancer; TPM, transcripts per million.

A. Increased CCNE1 mRNA expression was observed in samples with high global LOH status vs low global LOH status across all OC samples
B. Increased CCNE1 mRNA expression was only observed in the entire OC cohort for high-GSS status vs low-GSS status. This trend was not observed in the HGSOC cohort

CCNE1^{AMP} and CCNE1 Protein Overexpression Is Associated With Aneuploidy



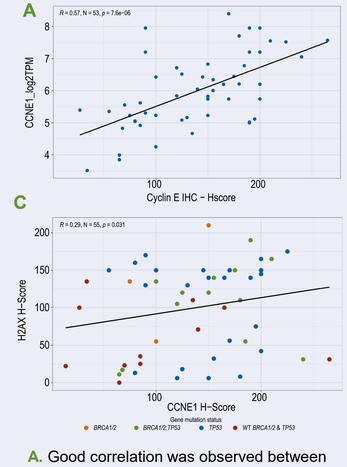
****P≤0.0001; **P≤0.01. AMP, amplification; CCNE1, cyclin E1.

A & B. Ploidy was elevated in both *CCNE1*^{AMP} and CCNE1 protein overexpressed TCGA OC samples.[2] CCNE1-High denotes samples with CCNE1 overexpression and the remainder of samples were defined as CCNE1-Low

Conclusions

- ***CCNE1*^{AMP} and increased CCNE1 mRNA expression was associated with *BRCA*-wt and HRD^{-} state**
- **While HRD^{+} was not associated with either *CCNE1*^{AMP} or higher mRNA expression, high LOH was associated with increased CCNE1 mRNA expression**
- **Surprisingly, *CCNE1*^{AMP} was associated with low global LOH status and low GSS, which may indicate different mechanisms of action for *CCNE1*^{AMP} and high CCNE1 mRNA expression in HGSOC**
- **IHC-based CCNE1 protein expression correlated with mRNA expression in HGSOC commercial samples. Increase in this protein expression was also associated with high LOH status akin to trends observed in the RWE mRNA expression dataset**
- **A weak correlation was seen in IHC based CCNE1 protein expression and pH2AX; however, *TP53* mutants were associated with increased pH2AX and CCNE1 staining. Having no prior treatments in HGSOC commercial samples could explain the lack of strong correlation**
- **Understanding the mechanism of action in CCNE1 high expression ovarian tumors that lead to DNA damage will help develop precision medicine therapies in the HRD^{-} setting**

Validation With Commercial HGSOC Samples



A. Good correlation was observed between immunohistochemistry (IHC)-based CCNE1 protein expression and WTS-based CCNE1 mRNA expression in HGSOC commercial samples
B. IHC based CCNE1 protein expression was also high in high LOH status HGSOC commercial samples, as seen with *CCNE1* mRNA expression in the Caris real-world evidence (RWE) WTS data. As expected, based on RWE WTS data, no association was seen in GSS status (data not shown)
C. A weak correlation was observed in phospho-histone H2AX (pH2AX) staining, denoting double stranded DNA breaks and CCNE1 H-Score. *TP53* mutations were associated with increased H2AX and CCNE1 H-Score

***P≤0.001; **P≤0.01; *P<0.05. CCNE1, cyclin E1; LOH, loss of heterozygosity; mt, mutant; wt, wild-type.

References

1. Kok, Yannick P, et al. *Oncogenesis*. 2020;9:88. **2**. Marquard AM, et al. *Biomark Res*. 2015;3:9.

Disclosures

Obla, **Kinder**, **Sun**, **Bullins**, **Timmers:** Employment and stock ownership – *Incyte Corporation*. **Poi, Wu:** Employment – *Caris Life Sciences*. **Missiglia, Bisig:** No disclosures to report. **Homicsko:** Advisory board – Incyte Corporation; Research Funding – *BMS, Boehringer Ingelheim, Doppl AG, MSD, Owkin, Panthera AG, Roche/Genentech, and TOLREMO AG*.

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