REVIEW ARTICLE

CCNE1 Amplification as a Candidate Marker of Homologous Recombination Proficiency in High-Grade Serous Ovarian Cancer: A Scoping Review

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Abstract

BACKGROUND: Homologous recombination proficiency (HRP) high-grade serous ovarian cancer (HGSOC) is molecularly heterogeneous and lacks validated biomarkers for patient stratification. *CCNE1* amplification has been associated with molecular profiles indicative of HRP-like molecular profiles, but it is unclear whether this reflects actual functional homologous recombination (HR) repair capacity, or how consistently the association holds across different definitions of *CCNE1* and HR status. This scoping review mapped the evidence linking *CCNE1* copy-number alteration and cyclin E1 overexpression with HR-related molecular features in.

METHODS: A scoping review was following the Arksey and O'Malley framework and PRISMA-ScR. PubMed, Scopus, ProQuest, and Springer Nature were searched from inception to October 1, 2026 for original human studies examining *CCNE1* amplification, copy-number gain, or cyclin E1 overexpression in relation to HR-related features in HGSOC. *CCNE1* and HR-status definitions and the reported relationships were charted and synthesized descriptively.

RESULTS: Sixteen studies published between 2013 and 2026 were included. One amplification thresholds ranged from an average copy number above 2.0 to more than 8 copies per cell, and HR status was defined by *BRCA1/2* testing or by genomic HR deficiency (HRD) scores with differing cut-offs. Eleven studies reported a mutually exclusive between 1 amplification and *BRCA1/2* alterations or HRD-associated features, most consistently for high-level amplification versus pathogenic *BRCA1/2* variants; one reported a non-significant inverse trend. Four reported co-occurrences, mainly with low-level gain, broad alteration categories, copy-number-based HRD classifiers, or very small samples. Cyclin E1 overexpression and *CCNE1* amplification were related but non-equivalent biomarkers. Evidence from Asian populations only came from a single Japanese cohort.

CONCLUSION: High-level *CCNE1* amplification is preferentially associated with an HRP-like molecular profiles, but current evidence does not establish its validity as a candidate marker for HRP. Standardized, cross-platform validation, comparison with functional HR assays, and validation in underrepresented populations, including Asian cohorts, are needed before CCNE1 can be evaluated as a complementary pathology-based marker.

KEYWORDS: high-grade serous ovarian cancer, *CCNE1*, cyclin E1, homologous recombination status, biomarker

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Introduction

High-grade serous ovarian cancer (HGSOC) is the most common and lethal histological subtype of epithelial ovarian cancer.(1) It is characterized molecularly by near-ubiquitous TP53 mutations (96%), prevalent *BRCA1/2* mutations (22%), frequent *CCNE1* and *MYC* amplifications, extreme chromosomal instability, and recurrent somatic copy-number alterations.(2,3) Approximately 50% of HGSOCs exhibit homologous recombination deficiency (HRD), arising from germline or somatic *BRCA1/2* alterations, *BRCA1* promoter methylation, or defects in the homologous recombination repair (HRR) pathway.(2,4) HRD is associated with increased sensitivity to platinum-based chemotherapy and poly (ADP-ribose) polymerase inhibitors (PARPi). However, current HRD assays do not directly measure ongoing HRR function. Genomic scars may persist even after restoration of HRR, and available assays differ in their analytical platforms, algorithms, and classification thresholds, creating uncertainty in the classification of some tumors.(4-6) Homologous recombination proficiency (HRP) HGSOC is therefore defined largely by the absence of HRD and lacks validated positive biomarkers *CCNE1* amplification has emerged as a recurrent molecular feature in HGSOC. The *CCNE1* gene encodes cyclin E1, which activates cyclin-dependent kinase 2 (CDK2) to regulate the G1-to-S-phase transition and the initiation of DNA-replication.(7,8) Dysregulated cyclin E1-CDK2 activity can promote premature and excessive replication-origin firing, leading nucleotide depletion, replication-fork instability, DNA double-strand breaks, and chromosomal instability.(8-10) Preclinical studies suggest that *CCNE1*-amplified cells rely on intact homologous recombination (HR) to tolerate this replication stress, which may explain why *CCNE1* amplification and *BRCA1/2* loss rarely co-occur.(11,12) In this condition, *CCNE1* amplification has been proposed as a marker of HRP HGSOC.

Nevertheless, *CCNE1* amplification cannot be considered equivalent to HRP. Co-occurrence of *CCNE1* amplification with HRD-associated molecular profiles has been reported, and the strength of the association appears to depend on how both *CCNE1*, and HR status are defined.(13) Cyclin E1 protein overexpression can occur without high-level *CCNE1* amplification, adding a related but non-equivalent biomarker.(14,15) Recent reviews have described HRP HGSOC and *CCNE1* testing across gynecological carcinomas (15,16), but none has examined whether *CCNE1* amplification identifies HRP in HGSOC. Consequently, this represents an important unresolved gap in evaluating *CCNE1* as a potential biomarker of HRP specifically in HGSOC.

Clarifying this relationship has potential implications for biomarker implementation. Identifying an HRP-like status may inform potential PARPi benefit, guide the interpretation of HRD-negative, and eligibility for trials of cell-cycle-targeted agents.(15-17) Comprehensive HRD assessment typically requires sequencing, genomic-instability algorithms, and bioinformatics expertise, which limits access in resource-constrained settings (5), as reported in Vietnam (18). In contrast, *CCNE1* copy-number can be assessed through by fluorescence or chromogenic *in situ* hybridization (FISH/CISH), and cyclin E1 protein expression by immunohistochemistry (IHC), using widely available pathology infrastructure.(17,19,20) Although these methods are compatible with widely available infrastructure, *CCNE1* amplifications should be considered as a candidate complementary marker of an HRP-like status. This scoping review mapped primary human evidence examining the relationship between *CCNE1* copy number gain or cyclin E1 expression and HR status in HGSOC. Furthermore, this review also complements previous reviews of HRP HGSOC, and *CCNE1* biology and aims to define the evidence required before *CCNE1* amplification can be formally evaluated as a clinically applicable marker of HRP.

Methods

Search Strategy

This scoping review was conducted according to the methodological framework proposed (21) and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) (22).

A comprehensive literature search was performed in four databases: PubMed, Scopus, ProQuest, and Springer Nature. The searches were last updated on October 1, 2026. The search strategy was developed using controlled vocabulary, where supported by the information source, with free-text keywords representing three core concepts: HGSOC, *CCNE1*, and HR status. Search terms included combinations and variants of "high-grade serous ovarian cancer," "high-grade serous carcinoma," "ovarian neoplasm," "fallopian tube carcinoma," "primary peritoneal carcinoma," "*CCNE1*," "cyclin E1," "amplification," "copy-number gain," "homologous recombination," "homologous

recombination deficiency," "homologous recombination proficiency," "*BRCA1*," and "*BRCA2*." Boolean operators, field codes, truncation, and subject headings were adapted to the indexing structure and search functionality of each information source. Searches were limited to English-language publications, with no restrictions on publication year. The final search terms are listed in Supplementary 1.

Eligibility Criteria

Relevant articles included in this study were selected according to the Population-Concept-Context (PCC) framework. Eligible populations included patients with HGSOC originating in the ovary, fallopian tube, or primary peritoneum. Studies involving mixed high-grade ovarian carcinoma cohorts were eligible if HGSOC was the predominant histological subtype or if HGSOC-specific findings could be analyzed independently. The context was not restricted by geographic or clinical setting, encompassing primary, recurrent, platinum-resistant, and post-PARP inhibitor disease. The core concept evaluated was *CCNE1* amplification or copy-number gain and, where reported, cyclin E1 protein overexpression in relation to gene copy number. Eligible HR-related features encompassed germline or somatic pathogenic *BRCA1/2* alterations, *BRCA1* promoter methylation, genomic HRD scores, genomic-instability measures (GIM), HRD-associated mutational or copy-number signatures, and alterations in other genes directly involved in the HRR pathway. Only English articles included in this review.

Studies reporting clinical outcomes, such as overall survival, progression-free survival, platinum response, or outcomes associated with PARPi treatment, were retained when they directly contributed evidence regarding the relationship between *CCNE1* and HR status. Review articles, editorials, commentaries, conference abstracts, case reports, case series, and preclinical (cell-line or animal) studies were excluded. Studies were also excluded if they did not include an eligible HGSOC population, evaluated *CCNE1* without an eligible HR-related comparison, or reported treatment efficacy without the required molecular analysis.

Study Selection

All records retrieved from the databases were exported into a reference management software program EndNote 21 (Clarivate, London, UK), and duplicate records were removed before screening. Three reviewers (MY, AK, and PAA) independently screened the titles and abstracts against the predefined eligibility criteria. The full texts of potentially eligible articles were subsequently retrieved and assessed for inclusion by two reviewers (MY and PAA). Reasons for exclusion at the full-text stage were recorded. The selection process was presented in the PRISMA-ScR flow diagram (Figure 1).

Data Extraction

A standardized data-charting form was developed to ensure consistency across the included studies. Extracted study characteristics included first author, publication year, study location, study design, sample size, and histological type. Molecular data included the methods and thresholds used to assess *CCNE1* amplification or copy-number gain and, where applicable, cyclin E1 protein expression. Information on HR assessment was also extracted, including *BRCA1/2* status, genomic HRD measures, and other HR-related molecular features. Finally, reported relationships between *CCNE1* alterations and HR-related molecular features were charted, including evidence of mutual exclusivity, inverse associations, enrichment in HR-proficient or HRD-negative tumors, and co-occurrence with *BRCA1/2* alterations or HRD-associated profiles. Data charting was performed by MY and verified by a second reviewer PAA.

Results

Study Selection

The searches identified 711 records, across four databases: PubMed (n=109), Scopus (n=209), ProQuest (n=31), and Springer Nature (n=362). After 157 duplicate records were removed, 554 titles and abstracts were screened. Total 473 records were excluded because they did not meet the topic-based eligibility criteria and eight were excluded because they were not available in English. Of the 73 reports sought for full-text retrieval, four could not be retrieved, leaving 69 reports for full-text assessment, Fifty-three full-text reports were excluded: 9 were review articles, 16 did not include an eligible HGSOC population, 16 did not evaluate the relationship between CCNE1 status and an HR-related gene or molecular feature, 5 were clinical-trial reports without an eligible molecular analysis, and 7 were conference abstracts. Finally, 16 studies were included in this scoping review (Figure 1).

Study Characteristics of Included Studies

The 16 included studies were published between 2013 and 2026. Most of the study was conducted in Western nations and Australia, including the United Kingdom (n=3), Australia (n=3), France (n=2), the United States

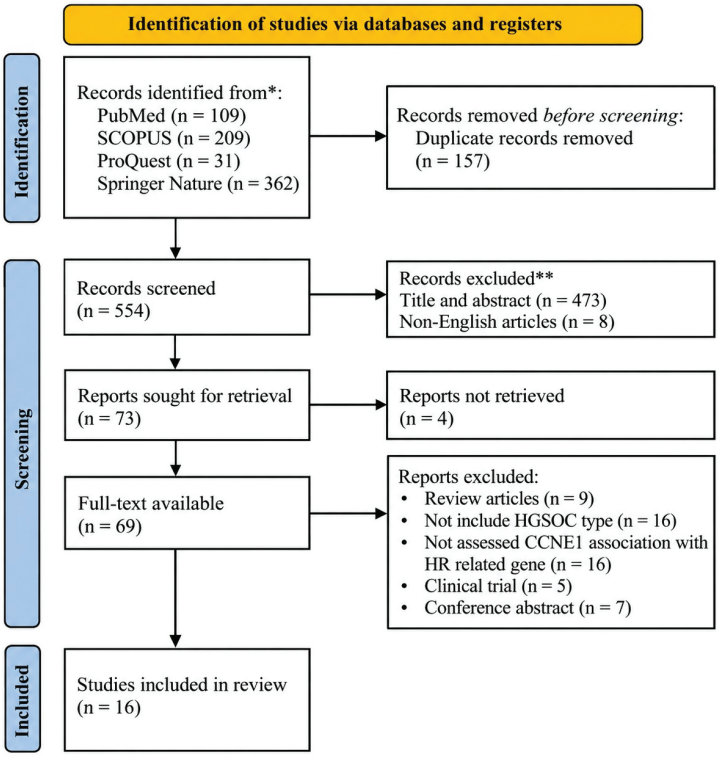


Figure 1. The PRISMA-ScR flowchart of current study.

(n=2), Canada (n=1), Italy (n=1), the Netherlands (n=1), and Brazil (n=1). In addition, two reports were derived from the same Japanese registry cohort.(23,24) Therefore, the 16 studies represented at most 15 independent cohorts. Patient-level overlap could not be excluded for several other studies, as one investigation analyzed patients from the Australian Ovarian Cancer Study (AOCS) (25), and a separate consortium study included cases from that same study as well as from the Calgary site that contributed an additional cohort (19,20). These studies were counted separately because the published reports did not allow overlapping patients to be identified. Most of studies used retrospective observational or multi-cohort designs (n=13) and three studies were employed a prospective design.

Eleven studies exclusively focused on patients with HGSOC. The remaining 5 studies analyzed mixed cohorts of high-grade ovarian, fallopian-tube, or primary peritoneal carcinomas, in which HGSOC was either the predominant subtype or analyzed as a distinct subgroup. The characteristics of the included studies were summarized in Table 1.

Methods Used to Assess *CCNE1* and HR Status

The approaches and thresholds for defining *CCNE1* status were heterogeneous across the reviewed studies (Table 1, Figure 2). There were 6 studies use combined *in situ* hybridization and IHC to assess *CCNE1* amplification and cyclin E1 overexpression (19,20,25-28), 4 studies employed sequencing-based copy-number methods, including next-generation sequencing (NGS) and whole genome sequencing (WGS) (13,29-31), 4 studies used SNP arrays (23,24,32,33), and 2 used quantitative polymerase chain reaction (qPCR) (12,34). The thresholds defining copy-number gain or amplification varied widely across platforms. SNP array-based studies applied average copy-number cutoffs of greater than 2.0 or 2.4 (32,33), whereas qPCR, FISH, and sequencing-based assays required a minimum of four, five, or six copies. To establish stringent definitions of high-level focal amplification, studies typically required more than eight copies per cell, signal clusters indicative of >8 copies, or elevated *CCNE1*-to-centromere or reference ratios. Only 2 studies explicitly adjusted copy-number cut-offs for tumor ploidy.(26,30) Several *in situ* hybridization-based studies used *CCNE1*-to-reference ratios, which partly account for chromosome 19 gain.(25,27,28)

Definitions of cyclin E1 overexpression based on IHC were varied, depending on either H-score thresholds (>100 (25), ≥120 (28), or ≥150 (27) or differing proportions of moderately-to-strongly stained positive tumor cells (>50% positive cells with moderate-to-strong nuclear staining (26); ≥ 60% positive cells with ≥5% strongly staining

Table 1. Characteristics of included studies. (cont)

Country	Study Design	Sample Size (n), Histological Type	*CCNE1* Assessment	HR Assessment	Reference No.
Australia	Retrospective observational cohort	n = 193 patients with HGSOC	qPCR (*CCNE1* amplification = relative copy number >8 copies / log2 > 2)	Germline and somatic *BRCA1/2* mutation status and *BRCA1* promoter methylation	12
France	Retrospective observational cohort	n = 105 patients with EOC - HGSOC (73.3%) - Endometrioid (10.5%) - Mucinous (7.6%) - Clear cell (5.7%)	• FISH (CCNE1 amplified = if > 6 copies for diploid and > 7 for tetraploid tumors) • IHC (Overexpression Cyclin E1 protein = >50% positive tumor cells with moderate-to-strong nuclear staining)	Large-scale state transition (LST) genomic signature (LST-high or genomic *BRCAness* = ≥15 LSTs in near-diploid or ≥20 in near-tetraploid tumors; LST-low or non-*BRCAness* = <15 LSTs in near-diploid or <20 in near-tetraploid tumors)	26
Australia	Retrospective observational cohort	n = 262 patients with HGSOC	• Dual-color ISH (*CCNE1* amplified = if 19q12/INSR ratio ≥3 and/or ≥6 copies of the 19q12 locus) • IHC (Overexpression Cyclin E1 protein = H-score > 100)	Germline *BRCA1/2* mutation status	25
UK	Retrospective	n = 178 patients with HGSOC tumors	SNP array (*CCNE1* amplified = average copy number >2.4 copies)	HRD-positive = HRD score ≥42 or tumor *BRCA1/2* mutation)	33
Brazil	Retrospective observational cohort	n = 31 total patients with platinum-resistant ovarian cancer (n = 15 patients with HGSOC evaluated by targeted NGS)	SNP array (*CCNE1* amplified = Average copy number > 2.0)	SNP array (HRD markers, if LOH > 10, CS > 42, and LST scores > 15 for near-diploid tumors or > 20 for near-tetraploid tumors)	32
Canada	Retrospective observational cohort	n = 1,292 patients with HGSOC cases	• CISH (*CCNE1* high-level amplification = > 8 copy number) • IHC (cyclin E1 overexpression = ≥60% positive tumor cells with ≥5% strongly staining cells)	Germline *BRCA1/2* mutation status	19
Netherlands	Retrospective observational cohort	n = 360 patients with advanced-stage HGSOC (n = 348 for molecular analysis)	Low-coverage WGS (*CCNE1* copy-number gain/amplification classified; assessed only in *BRCA*-non altered tumors; copy-number threshold not reported)	WGS • non-BRCA mutation HRD = Profiles with a posterior probability of > 0.5 • non-BRCA-like = profiles with a posterior probability of ≤ 0.5	13
UK	Retrospective observational cohort	n = 362 patients with HGSOC	qPCR (*CCNE1* copy number gain = ≥ 4 copies)	*BRCA1/2* mutation status	34
Australia	Retrospective observational	N = 3,029 patients with HGSOC	• CISH (High-level *CCNE1* amplification = signal clusters corresponding to >8 copies or CISH score ≥ 3) • IHC (Overexpression Cyclin E1 protein = ≥60% positive tumor cells with ≥5% strongly staining cells)	Germline *BRCA1/2* pathogenic variant status	20
UK	Prospective cohort	N = 276 patients with recurrent HGSOC	WGS (*CCNE1* amplification = CN ≥ 5 if ploidy ≤ 2.7 or CN ≥ 9 if ploidy > 2.7)	WGS (HRD-associated genomic pattern = increased exposure to CN signatures 3 and 7)	30

(cont) **Table 1. Characteristics of included studies.**

Country	Study Design	Sample Size (n), Histological Type	*CCNE1* Assessment	HR Assessment	Reference No.
USA	Retrospective cohort	n = 1,092 patients with high-grade epithelial ovarian, fallopian tube, or primary peritoneal carcinoma n = 409 for tbNGS analysis • High-grade serous: 89.0% (n = 364) • Clear cell: 4.2% (n = 17) • Endometrioid: 2.2% (n = 9) • Mixed epithelial: 2.7% (n = 11) • Adenocarcinoma NOS: 1.7% (n = 7) • Mucinous: 0.2% (n = 1)	tbNGS	tbNGS	29
Japan	Prospective	n = 274 patients with HGSOC*	SNP array (*CCNE1* amplification = focal copy number > 0.4)	NGS (HRD score = TAI + LST + LOH (TAI >11 Mb LST between adjacent ≥10-Mb regions after filtering <3-Mb segments; LOH >15 Mb but <whole chromosome)	23*
Japan	Prospective	n = 289 (274 patients with HGSOC and 15 HGEC)*	SNP array (*CCNE1* amplification = total CN ≥ 6)	SNP array (HRD score = TAI + LST + LOH (HRD High ≥ 67.	24*
Italy	Retrospective cohort study	n = 102 HGSOC patients	Oncomine Comprehensive Assay (OCA) Plus NGS (*CCNE1* amplified = > 5 gene copies), validated by FISH (*CCNE1*/CEN19 ratio > 2) and IHC (cyclin E1 overexpression = H-score ≥ 120)	OCA Plus calculating the Genomic Instability Metric (GIM) (unbalanced copy number changes in 46 HR-associated genes using genomic segmentation, HRD-positive = GIM ≥16)	28
USA	Retrospective	n = 6 patients with HGSOC	ascatNGS (*CCNE1* high amplification = Total copy number ≥ 6)	ascatNGS (HRD score = LOH + TAI + LST) • HRD High ≥ 63 • HRD low < 63	31
France	Retrospective longitudinal cohort	n = 38 patients • HGSOC: 89.5% (n = 34/38) • High-grade endometrioid carcinoma: 7.9% (n = 3/38) • OCCC: 2.6% (n = 1/38)	• IHC (Cyclin E1 overexpression = H-score ≥ 150) • FISH (CCNE1 high level amplification = ≥ 8 copies/cell and CCNE1 gain = CCNE1/CEN19 ratio ≥2 with <8 CCNE1 copies)	Targeted NGS • HRD+ / non-BRCA1/2 = GIS ≥42 • HRP or HRD-Negative = GIS < 42	27

HGSOC: high grade serous ovarian cancer; EOC: epithelial ovarian cancer; OCCC: ovarian clear cell carcinoma; FISH: fluorescence in situ hybridization; CISH: chromogenic in situ hybridization; qPCR: quantitative polymerase chain reaction; SNP: single-nucleotide polymorphism, NGS: next-generation sequencing; WGS: whole-genome sequencing; IHC: immunohistochemistry; ISH: in situ hybridization; HR: homologous recombination; HRD: homologous recombination deficiency; HRP: homologous recombination proficiency; LOH: loss of heterozygosity; TAI: telomeric allelic imbalance; LST: large-scale state transitions; GIM: genomic instability metric; GIS: genomic instability score; tbNGS: tumor-based NGS; CN: copy number; CS: composite score. *Takamatsu et al. (2023) and Takamatsu et al. (2024) are two study reports derived from a single Japanese cohort (JGOG3025-TR2) with overlapping patients (the same 274 patients with HGSOC appear in both). They therefore represent one Asian population and should not be interpreted as independent cohorts.

cells (19,20). Thus, low-level copy-number gain, high-level amplification, and cyclin E1 protein overexpression represent biologically related but non-equivalent biomarker categories within this literature.

HR status was similarly defined through diverse methodologies (Table 1). Five studies define HR-related status by *BRCA1/2* alone, assessed germline variants (19,20,25), germline and somatic variants together with

BRCA1 promoter methylation (12), or *BRCA1/2* mutation status (34). The remaining studies applied a stepwise classification combining *BRCA1/2* status with a whole genome copy-number HRD classifier (13), an large-scale state transitions (LST)-based BRCAness classification (26), composite HRD or genomic instability scores (GIS) incorporating loss of heterozygosity (LOH), telomeric allelic imbalance (TAI) and LST with heterogeneous cut-offs (23,24,27,31-33), a genomic instability metric (GIM) based on copy-number change (28), or genomic sequencing-derived copy-number signatures (29,30). Consequently, the definition of HR-proficient, non-BRCAness, and HRD-negative were not strictly equivalent across included studies.

Relationship between *CCNE1* and HR Status

The predominant pattern observed was an inverse relationship between high-level *CCNE1* amplification and *BRCA1/2* alterations or HRD-associated molecular features (Table 2). Eleven studies reported findings indicating that *CCNE1* amplification is associated with an HRP status or mutually exclusive with HR-related alterations (12,19,20,23-28,33,34) and one further study reported a lower but non-significant frequency of *CCNE1* amplification in *BRCA1/2*-mutated tumors (30). High-level *CCNE1* amplification was found to be mutually exclusive with *BRCA1/2* loss or genomic BRCAness in several cohorts.(12,26)

The inverse relationship was observed in studies incorporating cyclin E1 protein expression. One study reported that tumors exhibiting both 19q12 amplification and high cyclin E1 expression had a significantly lower frequency of germline *BRCA1/2* mutations (5.9%) compared to non-amplified tumors (24.3%).(25) Two studies, which may include overlapping patients, reported that high-level *CCNE1* amplification was mutually exclusive with pathogenic germline *BRCA1/2* variants.(19,20)

Alternative copy-number assessments yielded similar inverse associations. A study reported that *CCNE1* copy-number gain was mutually exclusive with *BRCA1* and *BRCA2* mutations.(34) *CCNE1* copy-number gain or amplification frequently correlated with a lack of *BRCA1/2* mutations, lower HRD scores, and HRD-negative status across SNP array, NGS, and WGS platforms.(23,24,28,33) In a recurrent HGSOC cohort, less frequent *CCNE1* amplification in *BRCA1/2*-mutated tumors was observed, although the difference was not statistically significant.(30) *CCNE1* amplification was also observed to be uncommon in HRD-positive post-PARP inhibitor samples.(27) These studies indicate that the inverse relationship with HRD-associated features was most consistently observed when *CCNE1* was defined as high-level amplification in relation to pathogenic *BRCA1/2* alterations. However, inverse associations were also reported in studies using lower copy-number thresholds, including mutual exclusivity with *BRCA1* and *BRCA2* mutations at a threshold of four or more copies.(34)

Co-occurrence of *CCNE1* Alterations and HRD-related Features

Four studies demonstrated that the relationship between *CCNE1* alterations and HRD- or *BRCA1/2*-related features was not consistently mutually exclusive.(13,29,31,32) In the small platinum-resistant cohort, while five of eight *CCNE1*-amplified tumors exhibited low HRD scores consistent with the HRP association), low-level *CCNE1* amplification concurrently appeared in two out of four *BRCA1*-mutated tumors.(32) This study was classified as a co-occurrence because there was no formal comparison of HRD status between amplified and non-amplified tumors, and co-occurrence with *BRCA1* mutations was observed.

Furthermore, in a cohort in which *CCNE1* and HRD status were assessed only in tumors without *BRCA1/2* alterations, 69 tumors with *CCNE1* copy-number gain exhibited a non-*BRCA* mutation HRD copy-number profile. (13) Because this category combined low-level gain with amplification and excluded *BRCA1/2*-altered tumors, the study informs co-occurrence with genomic HRD profiles but not with *BRCA1/2* alterations. Expanding the category of *CCNE1* alterations revealed co-occurrence with *BRCA1/2* alterations in up to 66.7% of *CCNE1*-altered tumors in one study, though this expanded definition limits direct comparability with stringent *in situ* hybridization-based evaluations.(29) Another study found *CCNE1* amplification co-occurring with germline *BRCA1* mutations in three out of six patients.(31) Co-occurrence was reported in studies employing low-level copy-number thresholds, broader *CCNE1* alteration criteria, non-*BRCA* copy-number-based HRD classifications, or small sample sizes.(32) Overall, mutual exclusivity was more consistently reported for high-level amplification than for broader *CCNE1*-positive classifications.

Discussion

This scoping review mapped evidence from 16 studies examining the relationship between *CCNE1* copy-number alterations and HR-related molecular features in HGSOC. The present review extends previous reviews of HRP

Table 2. Molecular association findings between *CCNE1* and HR status in the included studies.

Country	HR-related Molecular Features	Relationship between *CCNE1* and HR Status	Reference No.
Australia	• *BRCA1/2* wild-type, n = 81 • *BRCA1/2*-altered, n = 112 (germline *BRCA1* mutations [n = 52], germline *BRCA2* mutations [n = 29], somatic *BRCA1* mutations [n = 5], somatic *BRCA2* mutations [n = 4], and *BRCA1* methylation [n = 22])	High-level *CCNE1* amplification is mutually exclusive with *BRCA1/2* loss (HR-proficient).	12
France	*CCNE1* amplifications were detected in 39.4% (13/33) of non-BRCAness (HRP-like)	*CCNE1* amplification was mutually exclusive with genomic BRCAness (HRD-like)	26
Australia	Germline *BRCA1/2* status: • *BRCA1* mutation: 15.6% (n = 41/262) • *BRCA2* mutation 9.5% (n = 25/262) • *BRCA* wild type: 64.9% (n = 170/262)	• Among tumors with high cyclin E1 expression, germline *BRCA1/2* mutations were significantly less frequent in the 19q12-amplified subgroup (5.9%) than in the non-amplified subgroup (24.3%) • No mutual exclusivity observed between *CCNE1* amplification and *BRCA1/2* in non-amplified/high cyclin E1 tumors	25
UK	• *CCNE1* amplification was found in 39/178 (22%) HGSOC tumours • 30% of tumors were HRD-positive	• All *CCNE1*-amplified tumors were tumor BRCA1/2 wild-type • *CCNE1* amplification was significantly more common in HRD-negative than HRD-positive tumours	33
Brazil	HRD was found in 60% (9/15) cases	• 5 of 8 *CCNE1*-amplified cases had low HRD scores • 2 of 4 *BRCA1*-mutated cases showed low-level *CCNE1* amplification	32
Canada	*CCNE1* high-level amplification was present in 10.2% cases (n = 114/1,292)	High-level *CCNE1* amplifications and overexpression are mutually exclusive with germline *BRCA1/2* mutations	19
Netherlands	• *BRCA* mutation or *BRCA1* promoter methylation (n = 105, 30.2%) • Non-*BRCA* mutation HRD only (n = 67, 19.3%) • *CCNE1* gain/amplification only (n = 45, 12.9%; 28 gains; 17 amplification) • Double classifier (*CCNE1* amplification + non-*BRCA* mutation HRD) (n = 69, 19.8%)	• Among *BRCA*-non-altered tumors; 69 of 114 (60.5%) with *CCNE1* amplification also had a non-*BRCA* mutation HRD copy-number profile • *CCNE1* was not assessed in *BRCA*-altered tumors	13
UK	• *BRCA1* mutations: 12.7% • *BRCA2* mutations: 6.6%	*CCNE1* copy number gain is mutually exclusive with *BRCA1* and *BRCA2* mutations	34
Australia	Pathogenic germline *BRCA1/2* were present in 15.3% (n = 146)	High-level *CCNE1* amplification is mutually exclusive with germline *BRCA1/2* pathogenic variants	20
UK	Pathogenic germline mutations • *BRCA1*: 11% (n = 25) • *BRCA2*: 6% (n = 14)	*CCNE1* amplification was less frequent in *BRCA1/2*-mutated tumors than in *BRCA*-wild-type tumors, but the association was not statistically significant	30
USA	• *CCNE1* amplification was present in 7.6% of patients • Somatic *BRCA1* mutations were detected in 11/343 (3.2%), *BRCA2* mutations in 14/343 (4.1%), and CDK12 mutations in 10/278 (3.6%)	In HGSOC cases, *CCNE1* was co-altered with *BRCA1/2* alterations (*BRCA1/2* alterations occurred in 66.7% of cases with a *CCNE1* alteration *vs.* 7.3% of *CCNE1*-wild-type cases)	29
Japan	• HRD- high = 54.7% • HRD- low = 45.3%	*CCNE1* amplified tumors had relatively lower HRD scores	23
Japan	• HRD = 59.2% • Non-HRD = 40.8%	C1 (n = 41) was the *CCNE1*-amplification-enriched subtype, with significantly fewer *BRCA1/2* alterations and a lower HRD score than C2/C3 (high *BRCA1/2* alteration frequency, high HRD score, relatively higher ploidy)	24
Italy	• HRD-positive = 39.8% (37/93) • *CCNE1* amplification: 27/93 (29.03%)	*CCNE1* amplification was negatively associated with pathogenic *BRCA1/2* mutations	28
USA	High HRD score tended to be higher in tumors with germline BRCA1 mutations	*CCNE1* amplification and germline BRCA1 mutation occurred in three out of six patients	31
France	• HRD+: 72.2% (n = 26/36) - Pathogenic BRCA1/2 variants: 47.2% (n = 17) - HRD-positive without BRCA1/2 pathogenic variants: 25.0% (n = 9) • HRP: 27.8% (n = 10/36)	*CCNE1* amplification was rare in HRD+ tumors	27

HGSOC and *CCNE1* testing.(15,16) The principal finding was that high-level *CCNE1* amplification is predominantly associated with a molecular profile characterized by the absence of pathogenic *BRCA1/2* alterations and negative genomic HRD scores. However, several studies reported the co-occurrence of *CCNE1* alterations with *BRCA1/2* mutations was also reported. *CCNE1* and HR status were defined by heterogeneous platforms and thresholds and none of the included studies used a functional HRR assay as the reference standard. Our review shows that the Asian evidence comprises a single Japanese cohort.

The inverse association was the most consistently reported pattern, and it was supported by wide range of platforms. Its direction was reproduced across FISH, CISH, SNP array, targeted NGS and WGS. This also applies to germline, tumor-based, and composite comparators (12,19,20,23,25-28,32-34), which suggests that the inverse association is not rely on any single assay. Instead, magnitudes are reported in heterogeneous units that cannot be combined, namely proportions of *BRCA1/2*-altered cases, mean or median HRD scores, and subgroup frequencies within molecular classifications. The scoping design adopted here does not allow for producing a meta-analytic synthesis of estimates derived from non-equivalent constructs. Even where *CCNE1*-amplified tumors show a substantially lower prevalence of HRD-associated features, it is the residual prevalence of those features within the amplified group that will determine the degree of misclassification if amplification were used to infer HRP. The enrichment reported in this literature is thus established in direction, plausible in magnitude, and largely unquantified in precisely the metric that clinical application would require.

There are mechanisms that can explain this inverse relationship. Deregulated cyclin E1-CDK2 activity shortens G1 and drives premature S-phase entry, deregulated origin firing and replication–transcription conflicts, producing fork stalling, fork collapse and DNA damage.(8) Repair of collapsed forks is HR-dependent, and preclinical work indicates that *CCNE1*-amplified cells rely on CDK2-dependent signaling and HR to resume replication after fork collapse, while genome-wide screens show selective *BRCA1*-pathway dependency in amplified backgrounds. (11,12) This provides a plausible basis for selection against co-occurrence, but the evidence is preclinical, not uniformly reproduced, and establishes HR dependency in amplified cells. This rationale predicts an inverse relationship that strengthens with increasing amplification level, and the included studies are consistent with, but unable to isolate, such a threshold effect. Studies applying stringent criteria for high-level amplification reported an inverse relationship with pathogenic germline *BRCA1/2* variants.(19,20) In contrast, studies employing lower copy-number thresholds identified instances of co-occurrence with *BRCA1/2* mutations or HRD-associated genomic profiles.(29,32) Therefore, establishing whether the inverse relationship reflects genuine biological exclusivity requires studies that pair a focality-aspect definition of *CCNE1* amplification with both genomic and functional assessment of HRR in the same samples.

The mutual exclusivity is frequently assumed, but not an absolute finding. Co-occurrence was primarily observed in studies utilizing permissive copy-number thresholds, composite *CCNE1* alteration categories, non-*BRCA* genomic definitions of HRD, or very small exploratory cohorts. (13,29,31,32) These observations are important because the clinical utility of CCNE1 as a surrogate biomarker depends not only on its enrichment in HRP-like tumors but also on its ability to distinguish these tumors from those with HRD-associated features.

These apparently conflicting findings may partly reflect an important distinction between historical genomic instability and current HR function. Genomic scars record past DNA-repair deficiency and can persist after HR is restored, whereas *CCNE1* amplification may be acquired or selected later during tumor evolution or treatment. Co-occurrence may reflect clonal evolution, intratumoral heterogeneity, differences between historical and current HR function, or limitations of the assays used to define each state.(5,6,35) Another possibility that can be tested is the existence of partial circularity between two assessments. When both are measured on the same platform, LOH, TAI and LST scores are derived from the same copy-number profiles in which *CCNE1* amplification is detected. These scores also depend on tumor ploidy, as shown by the ploidy-specific LST thresholds used in included studies.(26,32) Cyclin E1-CDK2 activity promotes structural chromosomal instability.(8) It could therefore raise scar-based HRD scores without any loss of HR function. Thus, some studies report co-occurrence (13,32) may reflect how HRD was measured. This could be tested by comparing scar-based HRD calls with *BRCA1/2* status, HRD-associated mutational signatures, or functional *RAD51* assays in *CCNE1*-amplified tumors. Therefore, an HRD-associated genomic profile in a *CCNE1*-amplified tumor does not establish that the tumor remains functionally HR-deficient at the time of assessment.

A major finding of this review was the substantial heterogeneity in the methods and thresholds used to assess both *CCNE1* alterations and HR status. *CCNE1* was

assessed by FISH, CISH, qPCR, SNP array, NGS, WGS or IHC, with positivity defined by copy number per tumor cell, *CCNE1*-to-reference-locus ratio or signal-cluster pattern. (12,19,20,23,25-28,32-34) These definitions are non-equivalent, since *CCNE1* copy number correlates weakly with cyclin E1 protein, which is additionally regulated post-transcriptionally through phosphorylation-dependent turnover.(36) Therefore, these approaches do not identify equivalent populations, and heterogeneity on the two axes compounds.

HR status was defined by germline or tumor *BRCA1/2* testing, multigene HRR panels, or composite genomic instability scores, and these categories are not interchangeable. *BRCA1/2* wild-type status indicates only the absence of detectable pathogenic variants in two genes. Germline-restricted testing also misses somatic variants, *BRCA1* promoter hypermethylation and other HRR genes. (37) HRD-negative status is an assay-level assessment that uses platform-specific thresholds calibrated to PARP inhibitors and platinum benefit.(38,39) HRP is a biological claim about an intact pathway and, when assigned from either preceding result.(38) HRP, in contrast, requires functional confirmation such as *RAD51* focus formation.(39-41) Genomic and functional measures may be inconsistent, such as genomic scars persisting after HR is restored (40), while some *BRCA1/2*-mutant tumours retain *RAD51* focus (41). The relationship described here is between *CCNE1* alteration and assay-defined surrogates of HR status because no included study assessed functional HR capacity. Therefore, establishing whether the inverse relationship reflects genuine biological exclusivity requires studies that combine the definition of the focal aspect of *CCNE1* amplification with genomic and functional assessment of HRR in the same samples.

CCNE1 amplification and cyclin E1 overexpression are related but biologically distinct events. Increased *CCNE1* copy number can promote cyclin E1 expression, but protein abundance also reflects transcriptional regulation, protein stability, and alterations in other cell-cycle components.(8,14,15) Consequently, overexpression does not necessarily indicate high-level amplification. Consistent with this, the included studies showed that cyclin E1 overexpression can occur without detectable high-level amplification. They also showed that its relationship with HRD-associated features depends on amplification status. Tumors harboring both amplification and high cyclin E1 expression had a lower frequency of germline *BRCA1/2* mutations than non-amplified tumors. (25) Studies incorporated ISH and IHC to assess *CCNE1* alongside cyclin E1 overexpression (19,20,25-28), but formal evaluation of diagnostic performance was limited. Of the 16 included studies, only one reported accuracy for an ROC-derived IHC cut-off, with 81.6% sensitivity and 77.4% specificity for predicting high-level amplification (19), and one study derived ROC-based cut-offs without reporting accuracy (25). In addition, correlations between IHC and *CCNE1* copy number were moderate.(27,28) Therefore, cyclin E1 IHC cannot yet substitute for copy-number testing. Given their widespread availability, these methods are an interesting screening approach in settings with limited access to molecular testing, with positive cases confirmed by FISH, CISH, or another validated method. Standardized scoring, reproducibility, and concordance with copy-number status also remain to be established.(15) Future studies should determine whether combining cyclin E1 protein expression with *CCNE1* amplification improves the identification of an HRP-like molecular phenotype compared with either assessment alone, particularly when evaluated against functional HRR measures.

A notable finding of this review was the scarcity of evidence from Asian populations. Only two of the 16 included studies came from Japan (23,24) and both were derived from a single registry with overlapping patients, thereby representing one independent Asian cohort. Evidence from a single Japanese cohort cannot establish generalizability across the diverse populations of Asia. The spectrum of germline *BRCA1/2* variants differs between breast and ovarian cancer in Chinese and non-Chinese populations (42) and the histological composition of ovarian carcinomas also varied by region (43). These differences are important to note when comparing mixed-histology cohorts but do not establish molecular differences within histologically confirmed HGSOC. Therefore, these findings support careful characterization of study populations and validation across geographical settings.

This gap is particularly relevant to the rationale for pathology-based *CCNE1* assessment, which has been proposed for settings with limited access to comprehensive genomic testing. A Vietnamese study evaluating targeted *BRCA1/2* sequencing combined with shallow whole-genome sequencing in ovarian cancer identified cost and technical complexity as barriers to HRD testing (18), it did not evaluate *CCNE1* amplification relative to HR status, leaving its validity as an HRP marker unverified in Southeast Asia. Future validation should prioritize multicenter HGSOC cohorts from underrepresented Asian settings. Studies should use prespecified criteria that distinguish low-level copy-number gain from high-

level *CCNE1* amplification, evaluate cyclin E1 expression as a separate biomarker, and compare these findings with standard genomic HRD assessments. Comprehensive evaluations should encompass diagnostic performance, predictive values, inter-observer reproducibility, specimen failure rates, turnaround time, and overall costs. These data are needed to determine whether *CCNE1* assessment can provide clinically useful complementary insights in resource-constrained environments.

CCNE1 amplification can be assessed with established pathology techniques (FISH or CISH), and cyclin E1 expression with IHC. These methods could support more accessible testing strategies. However, their feasibility should be measured through formal implementation outcomes, including assay failure rates, interobserver agreement, turnaround time, cost, equipment requirements and the proportion of patients successfully classified. Validating *CCNE1* amplification as a surrogate biomarker also require prespecified thresholds to distinguish low-level *CCNE1* copy-number gain from high-level focal amplification, with cross-platform analytical concordance evaluated in matched specimens. HR status should be assessed by combining *BRCA1/2* status, genomic instability signatures and functional HRR assays, to show whether amplification on its own identifies a functionally HRP state. Adequate powered diagnostic-accuracy studies should then test high-level amplification, alone and with cyclin E1 expression, against a prespecified functional HRR reference standard. These studies should include Asian and other underrepresented populations.

This review includes only 16 studies, which differed in analytical platform, *CCNE1* copy-number threshold and HR comparator. *CCNE1* status was assessed by FISH, CISH, qPCR, SNP array, targeted NGS or WGS, and cyclin E1 overexpression by IHC with various cut-offs. HR status was defined by germline or tumor *BRCA1/2* testing, multigene HRR panels or composite genomic instability scores. A study comparing low-level copy-number gain against a genomic instability score does not address the same question as one comparing high-level focal amplification with pathogenic *BRCA1/2* variants. Quantitative meta-analysis was not possible, and the synthesis is limited to the direction and consistency of associations because the studies did not estimate the same quantity. The number of independent observations is also smaller than the number of studies, because two studies came from a single Japanese registry (23,24) and patient overlap could not be ruled out among studies using Australian Ovarian Cancer Study (AOCS) and Ovarian Tumor Tissue Analysis (OTTA) resources (19,20,25). Moreover, no included study measured functional HRR capacity. All relationships mapped here are therefore between *CCNE1* alteration and assay-defined surrogates of HR status, such as the *BRCA1/2* wild-type genotype or a genomic instability score below the threshold. The recurrent claim in the literature that *CCNE1*-amplified tumors are HR-proficient must be cautiously interpreted as an association with surrogate test results.

Conclusion

Current evidence from 16 studies indicates that high-level *CCNE1* amplification is associated with an HRP-like molecular profile in HGSOC, characterized by the absence of pathogenic *BRCA1/2* variants and HRD-negative scores. Co-occurrence of *CCNE1* alterations with *BRCA1/2* variants or HRD-associated signatures was reported, particularly where *CCNE1* was defined by broad alteration categories or when HRD was inferred from historical genomic scars. Gene amplification and cyclin E1 protein overexpression also represent distinct biomarker states whose concordance has not been formally quantified. In addition, evidence from Asian populations is currently limited to a single Japanese cohort. Therefore, standardized thresholds, cross-platform analytical validation, comparison with functional HRR measures, and prospective evaluation of treatment outcomes are required are required to determine whether *CCNE1* can reliably identify HR-proficient tumors.

Authors Contribution

MY was involved in the review conceptualization, search strategy design, abstract and full text review, data abstraction, data synthesis, manuscript drafting, final manuscript approval. DP was involved in supervision, re-review conceptualization, data synthesis, manuscript drafting, abstract and full text review, final manuscript approval. AK was involved in the data abstraction, data synthesis, abstract and full text review, final manuscript approval. PAA was involved in search strategy design, search and database management; abstract and full text review, data abstraction, manuscript drafting, final manuscript approval.

Conflict of Interest

The authors declare that they have no conflict of interest.

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