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THE IMPACT OF RAD6 EXPRESSION ON CHEMORESISTANT OVARIAN CANCER: A SYSTEMATIC REVIEW

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ABSTRAK

Kemoterapi merupakan salah satu modalitas mengobati kanker ovarium (KO) yang sejatinya merupakan salah satu kanker organ reproduktif wanita terbanyak di dunia. Overekspresi RAD6 telah diidentifikasi sebagai faktor penting dalam kemoresisten pada pasien kanker ovarium. Studi sistematik ini bertujuan untuk mengevaluasi hubungan antara overekspresi RAD6 dan kemoresisten pada kanker ovarium. *Database* yang digunakan berupa PubMed, ProQuest, Science Direct, dan *Google Scholar* menggunakan artikel dalam 10 tahun terakhir dan dari total 162 artikel yang didapatkan, hanya 4 artikel yang lolos seleksi dan digunakan dalam analisis. Hasil analisis menunjukkan bahwa overekspresi RAD6 berhubungan erat dengan peningkatan resistensi terhadap agen kemoterapi, terutama platinum. Mekanisme yang mendasari meliputi peningkatan toleransi kerusakan DNA, peningkatan proliferasi, invasi, dan kemampuan sel kanker untuk mengembangkan fenotipe mirip sel punca. Temuan ini menjadi salah satu inovasi bahwa RAD6 merupakan target terapi potensial dalam mencegah kemoresisten pada KO. Penelitian lebih lanjut diperlukan untuk mengembangkan inhibitor spesifik RAD6 yang dapat digunakan dalam kombinasi dengan kemoterapi konvensional untuk meningkatkan respons pengobatan dan prognosis pasien.

ABSTRACT

The Impact of RAD6 Expression on Chemoresistant Ovarian Cancer: A Systematic Review. Chemotherapy is one of the modalities for treating ovarian cancer (OC), which is one of the most common reproductive organ cancers in women worldwide. Overexpression of RAD6 has been identified as a significant factor in chemoresistance in ovarian cancer patients. This systematic review aims to evaluate the relationship between RAD6 overexpression and chemoresistance in ovarian cancer. The databases used include PubMed, ProQuest, Science Direct, and Google Scholar, focusing on articles from the last 10 years. Out of 162 articles retrieved, only 4 met the selection criteria and were used in the analysis. The analysis results indicate that RAD6 overexpression is closely associated with increased resistance to chemotherapeutic agents, particularly platinum. The underlying mechanisms include enhanced DNA damage tolerance, increased proliferation, invasion, and the ability of cancer cells to develop stem-like phenotypes. These findings highlight RAD6 as a potential therapeutic target in preventing chemoresistance in OC. Further research is needed to develop specific RAD6 inhibitors that can be used in combination with conventional chemotherapy to improve treatment response and patient prognosis.

INTRODUCTION

Ovarian cancer (OC) is characterized by the proliferation of abnormal cells within the ovaries, which can extend beyond their normal boundaries and invade adjacent tissues.[1] The ovaries comprise three distinct cell types, each capable of giving rise to various tumor forms. Approximately 90% of OC cases originate from the epithelial cells, encompassing high- and low-grade serous carcinomas, clear cell carcinomas, endometrioid carcinomas, and mucinous carcinomas.[2,3]. In contrast, stromal cell tumors account for about 7% of OC cases, while germ cell tumors are relatively rare.[3]

Ovarian cancer (OC) represents the predominant malignancy within the female reproductive system and ranks as the eighth most frequently diagnosed cancer worldwide.[4,5] Due to its concealed anatomical location and the absence of reliable early screening methods, coupled with nonspecific early symptoms, the majority of patients are diagnosed at an advanced stage.[5,6] OC is clinically staged through surgical intervention using the International Federation of Gynecology and Obstetrics (FIGO) classification, which is based on the tumor, node, metastasis (TNM) assessment system.[7] Following initial primary debulking surgery or staging biopsy, the subsequent therapeutic objective is cytoreduction.[8] Therapeutic modalities for cytoreduction include chemotherapy, immunotherapy, and targeted therapies such as poly-ADP ribose polymerase (PARP) inhibitors and anti-angiogenic agents.[9] Chemotherapy is particularly advantageous for OC cases with a high risk of recurrence, including stage I grade 3, stage IC and II, high-grade, and clear cell carcinomas.[4,10]

Ovarian cancer (OC) frequently exhibits drug resistance, rendering treatment particularly challenging and limiting the 5-year survival rate to approximately 30–35%.[5,11] Chemoresistance in OC can arise from genetic and epigenetic alterations that enable cancer cells to withstand chemotherapy agents. Recent research indicates that the expression of specific proteins, such as RAD6, may contribute to this resistance mechanism.[12] RAD6 is a ubiquitin-conjugating enzyme that interacts with various ubiquitin ligase partners to regulate multiple DNA repair pathways and damage tolerance mechanisms. The overexpression of RAD6 promotes tumorigenesis, proliferation, invasion, and chemoresistance in both normal and immortalized cells.[13] Consequently, this systematic literature review aims to elucidate the mechanisms of chemoresistance associated with RAD6 expression, thereby facilitating the development of more effective therapies and personalized treatment strategies for OC, and reducing the risk of chemoresistance in OC patients.

METHODS

Study design

The study employed a systematic literature review design, focusing on the impact of RAD6 expression on the propensity for chemoresistance in ovarian cancer (OC). This article adheres to the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (see Chart 1). Duplicates and irrelevant articles will be manually screened and excluded by LV and PA.

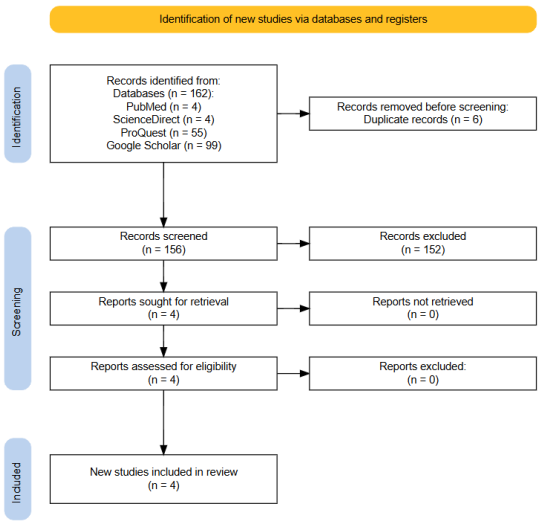

Chart 1. Literature Selection Flow based on PRISMA 2020.

Search strategy

The literature search was conducted across four electronic databases: ProQuest, PubMed, Google Scholar, and ScienceDirect, utilizing the search terms “(RAD6) AND (ovarian cancer) AND (chemotherapy response OR chemotherapy OR chemoresistance OR chemoresistant)." The search was restricted to original research articles, excluding literature reviews, systematic reviews, and meta-analyses. The selected articles were limited to those published in English between January 1, 2015, and September 24, 2024.

Reference selection, inclusion criteria, and exclusion criteria

The references for this systematic literature review include all English-language articles published in the last ten years that are freely accessible and examine the impact of RAD6 expression on the likelihood of chemo resistant ovarian cancer, utilizing Cohort, case series, and in vitro study designs. Articles in the form of case-control studies, protocols, conference papers, news articles, editorials, posters, literature reviews, and presentations were excluded.

LV and PA independently evaluated the titles and abstracts of the compiled articles to prevent the inclusion of any duplicates.

In cases of disagreement during the selection process, discussions were held to reach a consensus. The researchers selected the articles and independently performed data analysis and extraction.

Data extraction

Data extraction was conducted by two reviewers (LV, PA). The extracted information from each study encompassed general characteristics (author's name, year of publication, country, study design), characteristics of the research subjects (age group), number of research subjects, and outcomes. The primary outcome of interest was the effect of RAD6 expression on the determination of chemoresistance in ovarian cancer (OC).

Risk of bias analysis

After reviewing articles that satisfied the inclusion criteria, the Quality of Assessment Risk of Bias Tool (RoB 2) was employed to evaluate the risk of bias in four studies. Two authors (LV and PA) independently conducted this evaluation. The assessments were subsequently compared. Discussion was employed to resolve any discrepancies in the quality assessment. A moderator (NH) served as a neutral party to impartially assess the article in question as part of the quality review procedure if consensus could not be achieved. Figure 1 illustrates the results of the quality assessment

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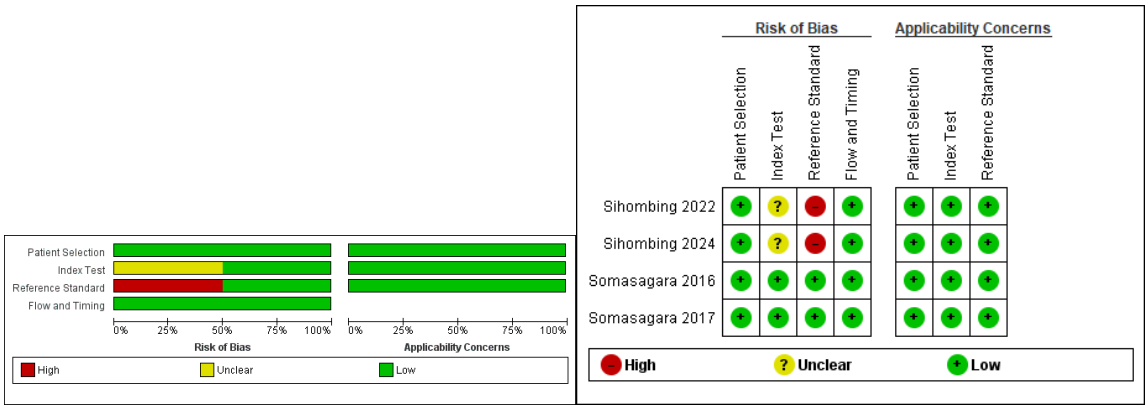

Figure 1. Results of bias risk assessment of included articles

RESULT

The search across four electronic databases using the specified keywords identified 162 articles (PubMed:4, ScienceDirect:4, ProQuest:55, Google Scholar:99) published in the last ten years, with six identified as duplicates. After removing duplicates, 156 articles remained. These were further screened based on their titles and abstracts and the inclusion and exclusion criteria. A total of 152 articles were excluded due to needing to be original studies, having inappropriate research designs, or containing irrelevant research data. This rigorous screening process ultimately included four articles in this systematic literature review (Table 1)

Two were in vitro investigations, while the other two were cohort studies. Among the cohort studies, one was a prospective cohort, and the other was an ambispective cohort (encompassing both prospective and retrospective elements). The bias assessment of the prognostic model study, conducted using the RoB 2, indicated good article quality. However, the risk of author bias could not be entirely excluded, as the in vitro and cohort studies were authored by the same researcher. In an *in vitro* study utilizing the clonogenic survival assay technique, RAD6 overexpression was observed in OC cell lines compared to immortalized cell lines derived from normal fallopian tube epithelium. This overexpression was associated with OC progression, with stage IV exhibiting a sevenfold increase in RAD6 intensity compared to stage I, a statistically significant difference ($P<0.001$). Additionally, RAD6 overexpression was identified in A2780/CP70 carboplatin-resistant cells, which displayed more invasive characteristics than their carboplatin-sensitive isogenic counterparts. Similarly, carboplatin-resistant cells derived from serous-type ovarian tumors (SKOV3/CP20) were reported to have elevated RAD6 expression, correlating with a reduced survival rate of up to 50% in clonogenic survival assays.[14]

Somasagara et al. extended their analysis to investigate the impact of RAD6 upregulation and downregulation on chemoresistance potential, focusing on cancer stem cell gene expression. Upregulation of RAD6 is linked to enhanced DNA repair and gene expression signaling in cancer stem cells post-chemotherapy, fostering chemoresistance and contributing to treatment relapse and disease recurrence.[15] The findings from in vitro studies, which demonstrated the effect of RAD6 overexpression on chemoresistance, were corroborated by cohort studies using flow cytometry and using immunohistochemistry.[12,16] Flow cytometry studies revealed a statistically significant increase in RAD6 protein levels in chemoresistant patients ($p < 0.05$). However, the Receiver Operating Characteristic (ROC) curve and Area Under the Curve (AUC) results were not statistically significant ($p > 0.05$), indicating weak accuracy (AUC 0.5-0.6) with a sensitivity of 84% and a specificity of 46%.[16] Conversely, immunohistochemical studies reported a higher AUC of 0.875, indicating good accuracy, with statistically significant results, and improved specificity (84%) and sensitivity (90%).[12]

DISCUSSION

This systematic literature review aims to evaluate the impact of RAD6 protein expression on the heightened risk of chemoresistance in ovarian cancer (OC) patients. The analysis of four studies, encompassing both in vitro investigations using clonogenic survival assays and cohort studies employing flow cytometry and immunohistochemistry, indicates that RAD6 overexpression is associated with the development of chemoresistance in OC patients. However, no studies have examined the mortality rates among chemoresistant OC patients.

Human RAD6 is encoded by two genes, RAD6A and RAD6B, which produce highly homologous and functionally similar proteins.[17] RAD6 is an enzyme involved in the ubiquitin conjugation system, which plays a central role in various biological processes, including protein degradation, cell cycle regulation, and apoptosis.[18,19] RAD6 expression is elevated in several human cancers, such as breast cancer and melanoma, by stimulating *the β*-catenin pathway.[14] This enzyme facilitates the covalent attachment of ubiquitin to target proteins and is crucial for DNA repair pathways. Evidence suggests that RAD6 enhances DNA damage tolerance and repair mechanisms in response to cytotoxic stimuli like chemotherapy.[20] The function of RAD6 is associated with disease progression, the development of stem-like cell phenotypes, and resistance to platinum-based chemotherapy, commonly used in ovarian cancer treatment.[12,15]

The DNA repair capability of RAD6 was further investigated by Somasagara et al. (2017), who demonstrated that knockdown or inhibition of RAD6 in OC cells induces replication stress and diminishes the activation of DNA repair pathways and damage tolerance in response to carboplatin therapy. Consequently, they recommend further research into therapies targeting RAD6 in OC patients to prevent acquired chemoresistance.[15] Similar recommendations were made based on findings of significant RAD6 overexpression in chemoresistant OC patients using flow cytometry and immunohistochemical methods.[12] Immunohistochemical methods were reported to have superior sensitivity and specificity for assessing RAD6 levels as a predictor of chemoresistance.[12]

RAD6 overexpression is also reported to enhance proteins that induce cancer stem cell-like properties. Although the exact pathway remains unclear, levels of H2B monoubiquitination, a marker in cancer stem cell genes, decrease with RAD6 depletion or inhibition. In contrast, control regions in gene promoters not regulated by RAD6 remain unchanged. The RAD6 expression in OC amplifies RAD6-mediated ubiquitin signaling, leading to the stabilization of β-catenin and an increase in Wnt signaling. Additionally, this upregulation enhances Gli1 expression, boosting

Hedgehog (Hh) signaling. The intensified activity of these pathways, combined with RAD6-driven chromatin remodeling, results in the elevated expression of proteins that promote stem cell-like characteristics, ultimately contributing to chemoresistance.[13]

This systematic literature review has several limitations. The analysis is restricted to English-language articles published in the last ten years due to the limited number of experimental or Cohort studies available. Other limitations include the small sample size, the continuation of previous studies, and the heterogeneity of study models, which precluded quantitative analysis. Future studies should aim to increase the sample size, consider and control for other risk factors influencing chemoresistance in OC patients, investigate additional proteins involved in chemoresistance, and explore RAD6 inhibition-based therapies to prevent chemoresistance in OC patients.

Table 1. Main results and findings in the included articles

Author, Study Design, Location, Year	Title	Sample (N)	Key Results and Findings	Limitations
Somasagara *et al.,* *In Vitro study,* USA, 2016[14]	*Rad6 upregulation promotes stem cell-like characteristics and platinum resistance in ovarian cancer*	500	● RAD6 expression is positively correlated with the progression and invasiveness of ovarian cancer (OC) cells. ● Elevated RAD6 expression contributes to resistance against platinum-based chemotherapy agents. ● RAD6 promotes the acquisition of stem cell-like properties in OC cells.	● The number of tumor samples collected, particularly post-chemotherapy samples, was limited. This constraint may affect the statistical power of the findings and limit their generalizability to a broader population. ● The study's reliance on cross-sectional data limits the ability to track changes over time. ● Although the study includes in vitro experiments to assess the role of RAD6 and its inhibition, translating these findings to in vivo settings may present challenges. ● The study may not account for all potential confounding variables influencing RAD6 expression and chemoresistance, such as genetic variations, other molecular pathways involved in cancer progression, and patient-specific factors. ● The research utilized specific ovarian cancer cell lines (e.g., OV90, SKOV3), which may not fully represent the heterogeneity of ovarian cancer. Therefore, results obtained from these cell lines may not apply to all ovarian cancer subtypes.

Author, Study Design, Location, Year	Title	Sample (N)	Key Results and Findings	Limitations
Somasagara *et al, In Vitro study,* USA, 2017[15]	*RAD6 promotes DNA repair and stem cell signaling in ovarian cancer and is a promising therapeutic target to prevent and treat acquired chemoresistance*	500	● The overexpression of RAD6 is significantly higher in ovarian cancer (OC) tissue compared to normal ovarian tissue. ● RAD6 overexpression is associated with acquired chemoresistance, suggesting that RAD6 may contribute to the resistance of cancer cells to chemotherapy agents such as carboplatin and paclitaxel. ● RAD6 enhances the DNA repair processes in OC cells. ● Inhibition of RAD6 increases DNA damage and reduces cell viability in response to chemotherapy treatment. ● RAD6 is involved in the stem cell signaling pathways in OC cells, indicating that targeting RAD6 could provide novel therapeutic strategies to enhance the efficacy of existing treatments.	● Much of the evidence presented derives from in vitro experiments using cell lines. While these studies offer valuable insights, they may not fully replicate the complexity of ovarian cancer in vivo, including interactions within the tumor microenvironment and systemic factors. ● The correlation between RAD6 expression and tumor stage in ovarian cancer patient tissues may be limited by the sample size and diversity of the patient population. Expanding the range of samples could provide more robust conclusions. ● While the study underscores the role of RAD6 in promoting stemness and chemoresistance, the precise molecular mechanisms by which RAD6 influences these processes still need to be completed. Further research is required to clarify these pathways. ● The findings related to specific cell lines (e.g., A2780, SKOV3) may not be generalizable to all ovarian cancer types or to other cancers in which RAD6 may play a role. ● The study may not account for other variables that could influence stem cell characteristics and chemoresistance, such as genetic mutations, epigenetic modifications, or the presence of other signaling pathways.

Author, Study Design, Location, Year	Title	Sample (N)	Key Results and Findings	Limitations
				● The article emphasizes the need for further studies to explore RAD6 as a therapeutic target, indicating that the current findings are preliminary and require validation in clinical settings.
Sihombing *et al., Prospective Cohort,* Indonesia, 2022[16]	*Expression of CD44+/CD24-, RAD6 and DDB2 on chemotherapy response in ovarian Cancer: A prospective flow cytometry study*	64 (32 chemoresistant, 32 chemosensitive)	● RAD6 expression is significantly elevated in chemoresistant ovarian cancer (OC) patients. ● According to prospective flow cytometry studies, RAD6 has an odds ratio (OR) of 4.76 [95% CI: 1.46–15.5] and a relative risk (RR) of 2.45 [95% CI: 1.11–5.43]. ● The results of the Receiver Operating Characteristic (ROC) curve and Area Under the Curve (AUC) RAD6 analysis via flow cytometry were not statistically significant ($p > 0.05$), with low accuracy (AUC 0.5–0.6), a sensitivity of 84%, and a specificity of 46%.	● The study involved a total of 64 patients, which may limit the generalizability of the findings to a broader population. ● Despite using a consecutive sampling method, the inclusion criteria may still introduce bias, particularly if specific patient demographics or characteristics are overrepresented. ● There may need to be more than an observation period of six months to assess long-term outcomes or the durability of the treatment response. ● Conducting the study at several hospitals may limit the applicability of the results to other settings or populations. ● A control group is necessary to determine the specific impact of the identified markers on treatment outcomes.
Sihombing *et al, Cohort* ambipektif*,* Indonesia, 2024[12]	*RAD6 Overexpression and Ovarian Cancer Chemoresistance: Flow Cytometry and Immunohistochemistry*	64 (32 chemoresistant, 32 chemosensitive)	● Measurement of RAD6 expression using immunohistochemical methods yielded statistically more significant results than flow cytometry. ● Bivariate analysis indicated that RAD6 was statistically significant when assessed immunohistochemically, with an odds ratio (OR) of 52.20 [95% CI: 11.3–239] and a relative risk (RR) of 6.12 [95% CI: 3.14–20.00].	● The study involved a relatively small sample size of 32 patients in each group, which may limit the generalizability of the findings and reduce the statistical power to detect significant differences. ● While useful, The ambispective cohort design may introduce biases due to the retrospective component,

Author, Study Design, Location, Year	Title	Sample (N)	Key Results and Findings	Limitations
			● The Area Under the Curve (AUC) for RAD6 measured by immunohistochemistry was 0.875, indicating good accuracy, with statistically significant results ($p < 0.05$), and demonstrated better specificity (84%) and sensitivity (90%).	particularly in data collection and patient selection. ● The exclusion of pregnant patients and those with other types of cancer may limit the applicability of the results to a broader population of ovarian cancer patients. ● Conducting the study at a limited number of hospitals may result in findings not representative of the wider population of ovarian cancer patients. ● The follow-up period of six months may be insufficient to fully assess long-term outcomes and recurrence rates in ovarian cancer patients. ● Other variables influencing chemotherapy response, such as genetic factors, comorbidities, and variations in treatment protocols, may have yet to be fully accounted for.

CONCLUSION

The overexpression of RAD6 protein is correlated with an elevated risk of chemoresistance in ovarian cancer (OC) patients. Comprehensive research involving larger population samples is imperative to investigate RAD6 expression in OC patients further. Such studies are anticipated to identify effective therapeutic strategies, enhance survival rates, and mitigate the incidence of chemoresistance in OC patients. Targeting RAD6 represents a pivotal opportunity for therapeutic innovation, given its critical role in cancer cell survival and resistance to chemotherapy. The development of specific RAD6 inhibitors is urgently needed to exploit this potential and enhance treatment efficacy, presenting a promising avenue for advancing cancer therapeutics.

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