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REVIEW

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Emerging nanotechnologies and their role in early ovarian cancer detection, diagnosis and interventions

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Abstract

Ovarian cancer presents a significant public health challenge, often being diagnosed at advanced stages due to the limitations of current detection methods. This systematic review addresses the urgent need for innovative approaches to enhance early detection and diagnosis of ovarian cancer. We systematically evaluate recent advancements in nanotechnology, focusing specifically on their novel applications and potential in comparison to traditional diagnostic modalities. Our analysis encompasses a wide range of studies investigating nanoparticles, biosensors, advanced imaging techniques, and biomarker detection platforms, with an emphasis on evaluating key performance indicators such as detection rates, turnaround times, and the accuracy of distinguishing cancerous from non-cancerous tissues. Our findings indicate that nanotechnology-based approaches have the potential to significantly improve early detection capabilities for ovarian cancer. Notably, studies on nanoparticle-based imaging techniques and biosensors consistently demonstrate high sensitivity and specificity for identifying ovarian cancer biomarkers, with detection rates exceeding 90% reported for early-stage cancers in several instances. This review underscores the promise of emerging nanotechnologies to transform the landscape of early detection and diagnosis, offering a pathway toward earlier diagnoses, enhanced therapeutic interventions, and improved patient outcomes. We advocate for future research dedicated to the translational efforts required to move these technologies from bench to bedside, ensuring their effectiveness is validated across diverse clinical populations.

Clinical trial number

Not applicable.

Keywords Ovarian cancer, Nanocarriers, Nanoparticles, Biosensors, Biomarkers, Imaging techniques

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Introduction

Ovarian cancer remains a critical public health issue globally, given its notable mortality rates and the complexities involved in its early detection, which can impede effective treatment. With approximately 313,000 new ovarian cancer cases diagnosed worldwide in 2020 and its position as the fifth leading cause of cancer-related deaths among women, the pressing need for enhanced screening modalities is underscored. The lifetime risk of a woman developing ovarian cancer in the United States stands at roughly 1 in 78, with the incidence notably rising in older populations, particularly those aged over 63 [1]. The alarming statistics associated with ovarian cancer highlight an urgent requirement for advancements in diagnostic strategies. Furthermore, the disease is often asymptomatic during its initial stages, which frequently culminates in late-stage diagnoses where therapeutic options may be limited. Current diagnostic practices, including transvaginal ultrasound and serum CA-125 testing, exhibit insufficient sensitivity and specificity, resulting in both false positives and negatives, thereby emphasizing the need for novel methodologies to bolster early detection rates [1, 2].

The importance of early detection cannot be overstated, as it plays a pivotal role in improving survival outcomes; patients diagnosed at stage I enjoy a five-year survival rate exceeding 90%, while the prognosis declines sharply as the cancer progresses to advanced stages. Enhancing screening techniques is therefore imperative to mitigate the mortality associated with ovarian cancer [3, 4]. This calls for a multifaceted approach to ovarian cancer management that prioritizes both the development of innovative diagnostic tools and the treatment options available for patients.

Nanotechnology is at the forefront of such advancements, offering transformative potential in the realm of medicine by leveraging materials at the nanoscale (1 to 100 nanometers) to create innovative diagnostic and therapeutic solutions tailored for ovarian cancer. The application of nanotechnology in medicine encompasses multiple domains. Firstly, in targeted drug delivery, nanoparticles can be engineered to transport anticancer drugs directly to malignant cells [5, 6]. This not only minimizes damage to surrounding healthy tissues but also enhances the therapeutic efficacy of the drugs used, creating a more effective treatment paradigm for ovarian cancer patients. Secondly, nanotechnology significantly enhances imaging techniques, providing improved contrast agents that enable the earlier detection of tumors at the molecular level. This advancement in imaging modalities can facilitate more accurate and timely diagnoses, allowing for earlier interventions that are crucial for improving patient outcomes [7, 8]. Additionally, the use of nanomaterials in developing highly sensitive biosensors demonstrates another significant application in the detection of biomarkers associated with ovarian cancer. These biosensors can operate effectively with minimal sample volumes, paving the way for less invasive testing methods which could lead to earlier and more reliable detection [1].

The incorporation of nanotechnology into clinical practice thus holds the potential to revolutionize the landscape of ovarian cancer management, encompassing both diagnostic and therapeutic avenues. As research advances, the synergy between nanotechnology and current medical practices aims to foster earlier interventions, ultimately leading to enhanced treatment efficacy and patient outcomes. Therefore, the deployment of nanomedicine in the context of ovarian cancer not only highlights the critical need for innovative approaches to early detection but also encapsulates hope for transforming the overall management strategies currently utilized in treating this deadly disease.

Search strategy

This review focuses on the application of nanotechnology in the early detection, diagnosis and interventions of ovarian cancer. We conducted our literature search using multiple databases, including PubMed, Web of Science, Scopus, and Google Scholar. The search was conducted for articles published from January 2000 to October 2024 to capture a comprehensive overview of the advancements in nanotechnology and its applications in ovarian cancer. The search strategy utilized a combination of keywords including "nanotechnology," "ovarian cancer," "early detection," "diagnosis," "biomarkers," and "nanoparticles." Boolean operators (AND, OR) were strategically used to optimize search results. For example, the search string used was: ("nanotechnology" AND "ovarian cancer" AND ("early detection" OR "diagnosis") AND ("biomarkers" OR "nanoparticles")). The total number of articles identified from the search was **375**. After reviewing for duplicates, **85** articles were removed, leading to **290** articles for further evaluation. The remaining articles were assessed, and a total of **235** articles were excluded based on the following reasons:

- Language: 40 articles were not available in English.
- Accessibility: 55 articles were full articles not accessible.

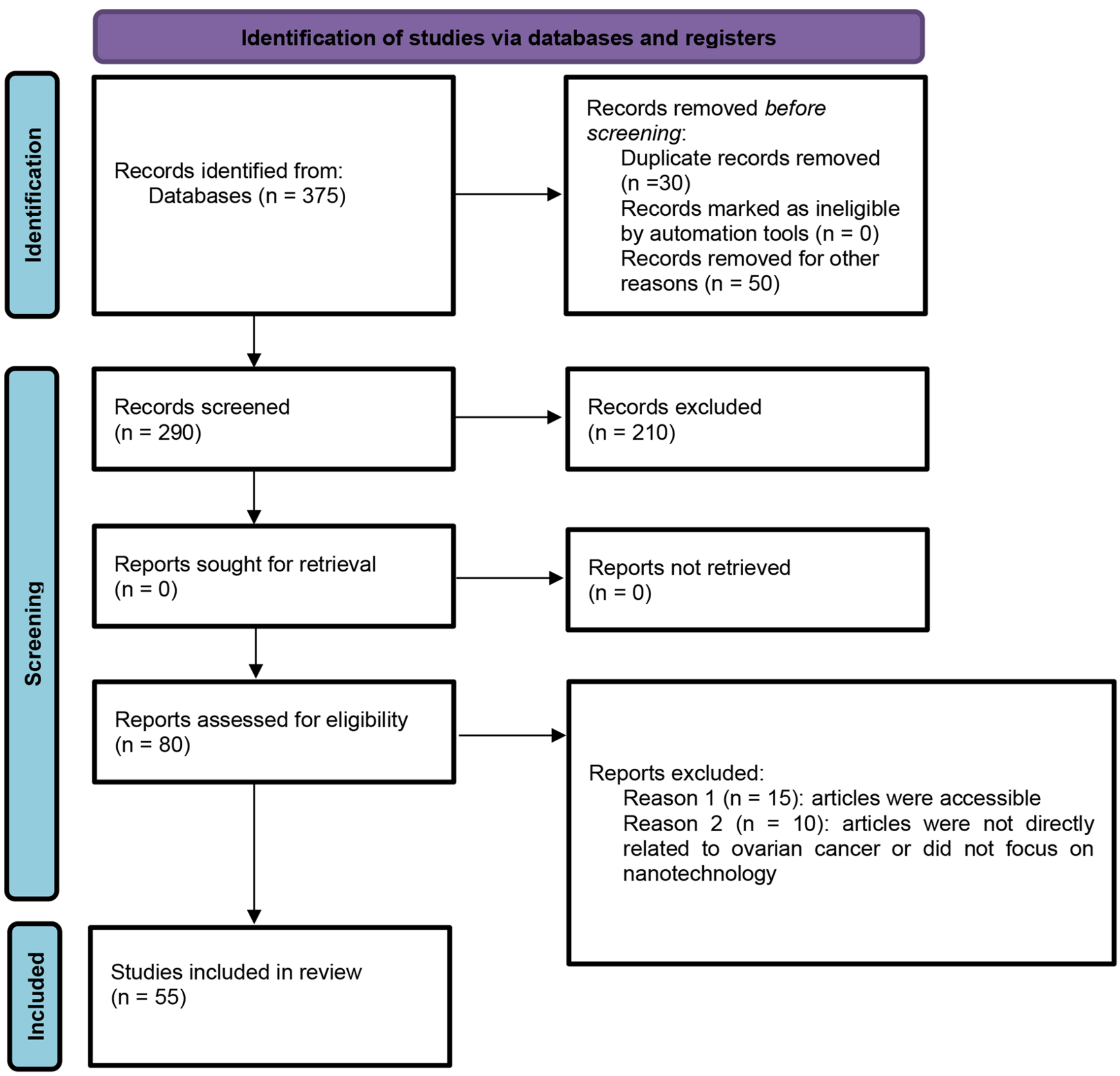
- Relevance: 140 articles were not directly related to ovarian cancer or did not focus on nanotechnology.

Thus, a total of **55** articles were retained for full-text review and final analysis.

Addressing the potential for publication bias, we conducted a qualitative review involving two independent authors. Discrepancies were resolved through discussion, ensuring a rigorous evaluation of the included studies. Statistical methods for assessing publication bias, such as funnel plots and Egger's test, were considered for the included studies to provide a clear understanding of any bias present.

The retained articles were reviewed to extract relevant data, including:

- Study design and methodologies used.
- Nanotechnologies investigated.
- Key findings related to early detection and diagnosis.
- Implications for clinical practice and future research directions.



Current approaches to ovarian cancer diagnosis

Ovarian cancer is often diagnosed at advanced stages, highlighting the need for early detection methods. Current diagnostic strategies mainly utilize image-based evaluations and biomarker assessments, each with specific advantages and limitations. Transvaginal Ultrasound (TVU) is the primary initial diagnostic tool, enabling visualization of ovarian abnormalities in size and shape. Its effectiveness is bolstered by the International Ovarian Tumor Analysis (IOTA) simple rules, which analyze key features to gauge malignancy likelihood [2, 9]. Computed Tomography (CT) scans are also used but are less favored for early-stage detection, providing broader imaging of abdominal and pelvic structures with limited efficacy for initial evaluations [2].

In diagnosing ovarian cancer, biomarker determination is vital alongside imaging. Cancer Antigen 125 (CA-125) is a well-known biomarker, often elevated in those with the disease, but it lacks specificity as high levels may also appear in benign conditions. CA-125 demonstrates approximately 77% sensitivity and about 93.8% specificity, with around 23% of patients presenting normal levels initially [9, 10]. Human Epididymis Protein 4 (HE4) complements CA-125 and improves diagnostic accuracy when combined, particularly through the Risk of Ovarian Malignancy Algorithm (ROMA) [10, 11]. Nonetheless, challenges persist regarding biomarker reliability in early detection, as HE4 may miss specific subtypes and imaging tools like transvaginal ultrasound can vary in interpretation [2, 9, 11, 12]. Additionally, the time from symptom onset to diagnosis can be extensive, often due to vague early symptoms and a lack of awareness among general practitioners, emphasizing the need for new, validated biomarkers for more effective early detection [10, 11].

Nanotechnology fundamentals

Nanotechnology is a crucial field involving the manipulation of materials at the nanoscale (1 to 100 nanometers), integrating physics, chemistry, biology, and materials science to harness unique properties that arise at this scale. These properties, including enhanced strength, reduced weight, and improved electrical characteristics, drive innovation in various sectors, particularly in medicine and cancer diagnostics. In cancer diagnostics, nanomaterials are vital, with nanoparticles being a key component. For instance, gold nanoparticles (AuNPs) are valued for their biocompatibility and enhancement of imaging techniques like Raman spectroscopy [13–15]. Quantum dots (QDs) offer distinctive optical properties for bioimaging and biomarker detection, while magnetic nanoparticles facilitate magnetic resonance imaging (MRI) and targeted drug delivery, improving precision in diagnostics and treatments [13–15].

Nanosensors also play a pivotal role, using nanomaterials for heightened sensitivity and specificity in detecting biological molecules. By integrating nanoparticles, these biosensors can identify cancer-associated proteins or nucleic acids more effectively [14–16]. Additionally, nanocarriers such as polymeric and lipid-based vehicles target and deliver therapeutic agents directly to cancer cells, enhancing drug efficacy and reducing side effects [13, 17, 18]. The interaction of nanomaterials with biological systems is influenced by mechanisms like the Enhanced Permeability and Retention (EPR) effect, which allows nanoparticles to accumulate in tumor tissues, alongside targeted binding via functionalization, thus improving diagnostic efficiency and accuracy.

Nanotechnologies in ovarian Cancer early detection and interventions

Specific nanoparticles and their roles in biomarker detection

Nanoparticles, particularly gold nanoparticles (AuNPs) and upconversion nanoparticles (UCNPs), are pivotal in cancer diagnostics, enhancing biomarker detection sensitivity and specificity (Table 1). UCNPs are used in immunoassays for significant biomarkers, achieving superior signal-to-background ratios, which aids in earlier cancer detection through blood-based biomarkers [19]. AuNPs serve as effective probes for low-abundance biomarkers in liquid biopsies, enhancing detection via techniques like surface plasmon resonance [20]. They also improve imaging in modalities such as MRI and CT, facilitating tumor visualization and personalized treatment monitoring [20]. Recent nanosensors have achieved detections at femtomolar concentrations, advancing early screening

Table 1 Summarizing the types, descriptions, applications, and detection capabilities of nanoparticles

Types of Nanoparticles	Description	Applications	Detection Capabilities
Gold Nanoparticles (AuNPs)	Nanoparticles with unique optical properties	Liquid biopsy for circulating tumor DNA (ctDNA) and circulating tumor cells (CTCs)	Effective probes for low-abundance biomarkers; enhanced detection through surface plasmon resonance and electrochemical detection [21]
Upconversion Nanoparticles (UCNPs)	Nanoparticles that convert low-energy radiation into higher energy photons	Upconversion-linked immunosorbent assays for detecting biomarkers (e.g., prostate-specific antigen, breast cancer markers)	Superior signal-to-background ratios compared to traditional fluorescent labels; capable of real-time monitoring of tumor progression [20]
Nanoplasmonic Biosensors (based on AuNPs)	Advanced sensing platforms utilizing AuNPs	Detection of multiple cancer biomarkers at femtomolar concentrations	Significant enhancement in early screening efforts for cancer [22]

[21]. For example, 8-Anilino-1-naphthalensulfonate-conjugated carbon-coated ferrite nanodots are widely used for fluoromagnetic imaging, biomolecular sensing, and drug delivery. Notably, the enrichment of 8-Anilino-1-naphthalensulfonate on carbon-decorated manganese ferrite nanodots has improved both transverse and longitudinal MRI relaxation, increased protein detection sensitivity due to higher binding efficiency and stability constants, enhanced optical imaging fluorescence [22], improved multimodal imaging capacity [23]., biocompatibility, and reduced toxicity [24].

Nanosensors for early diagnosis

Nanosensors are emerging as vital instruments for early cancer detection, leveraging advancements in nanotechnology to enhance diagnostic accuracy and speed. They work by identifying specific biomarkers associated with various cancers, including ovarian cancer, which allows for timely intervention. Electrochemical nanosensors are particularly noteworthy for their high sensitivity and specificity in detecting cancer biomarkers through electrochemical reactions, enabling monitoring of circulating tumor cells (CTCs) in blood samples [14]. Optical nanosensors utilize light-based techniques, such as fluorescent nanoparticles, for real-time imaging and have shown capabilities in identifying small tumors, underscoring their potential for early diagnosis [25]. Magnetic nanosensors further enhance detection by isolating cancer cells from complex biological samples, thereby improving the tracking of rare CTCs [14]. Focused on ovarian cancer, nanosensors facilitate non-invasive monitoring by detecting CTCs and binding to biomarkers like CA-125, which is crucial for early diagnosis. Studies using longitudinal biomarker measurements, such as CA125 and HE4, show improved detection capabilities through advanced statistical methods [26]. Additionally, combining biomarkers, including cf-DNA, can enhance sensitivity, with a combination yielding approximately 91.67% sensitivity [27]. The OVA1 test highlights the benefits of multi-biomarker approaches, detecting more cancer cases than CA125 alone, even if it may lead to false positives [28]. Overall, the integration of these technologies promises significant advancements in early ovarian cancer detection.

Nanocarriers for drug delivery and imaging

Nanocarriers, engineered nanoparticles, play a crucial role in enhancing therapeutic delivery and imaging in medicine due to their unique properties, including small size and large surface area. They enable targeted delivery of chemotherapeutics, improving efficacy and reducing side effects. Various types, such as liposomes, dendrimers, and polymeric nanoparticles, have been developed to optimize drug delivery in cancer treatment. A key mechanism is the enhanced permeability and retention (EPR) effect, which facilitates better accumulation of these carriers in tumor tissues compared to conventional drugs, thereby improving therapeutic outcomes [29, 30]. (Fig. 1).

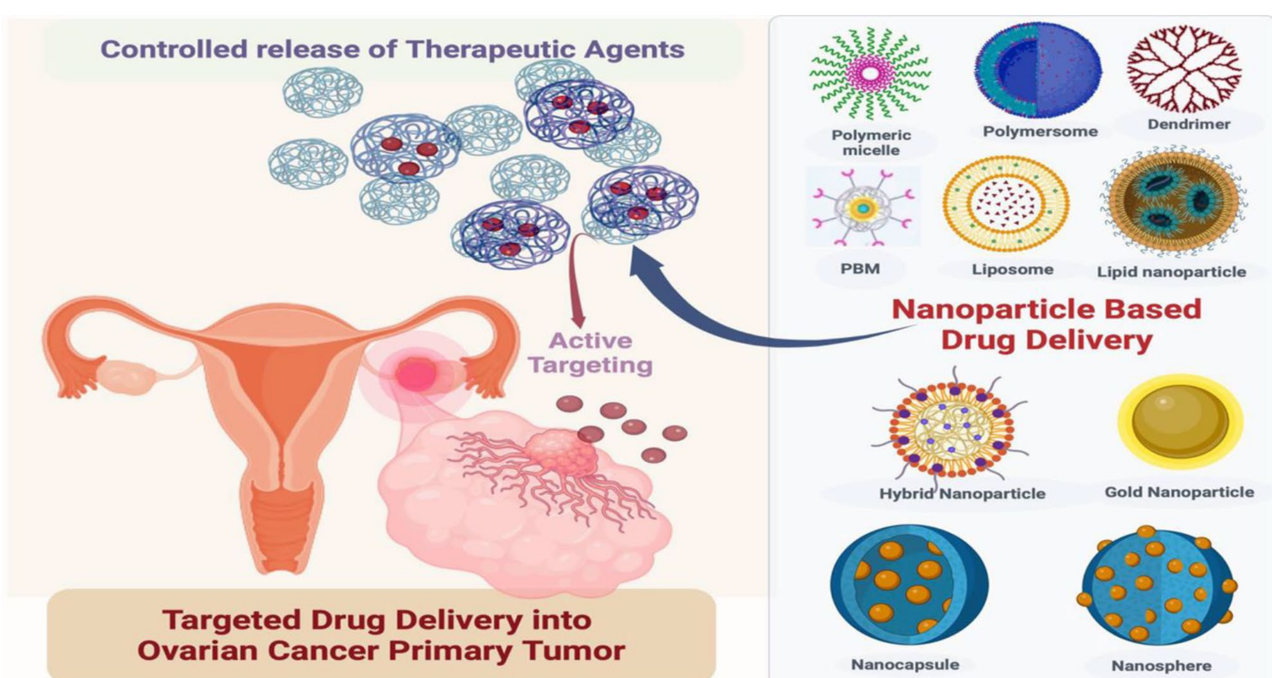


Fig. 1 Nanocarriers for targeted drug delivery in ovarian cancer

Targeted therapeutic delivery enhances the diagnosis and treatment of ovarian cancer by ensuring that therapeutics reach cancerous cells for earlier intervention and reduced disease progression. Iron oxide nanoparticles, for instance, can be linked with chemotherapeutic agents like doxorubicin (DOX) and radiolabeled for imaging, highlighting their high drug loading and pH-dependent release properties [31]. Calcium phosphate nanocarriers, noted for their biocompatibility, can also deliver anticancer drugs and imaging probes, with their ability to be functionalized improving selectivity towards tumor cells [32]. Furthermore, nanocarriers enhance imaging techniques essential for monitoring drug distribution and therapeutic effectiveness. Imaging methods such as magnetic resonance imaging (MRI) benefit from nanoparticles that improve image contrast, while positron emission tomography (PET) utilizes radiolabeled nanocarriers for real-time drug tracking (Fig. 2). Incorporating ultrasound-responsive nanocarriers optimizes ultrasound applications, releasing therapeutic payloads upon specific frequency exposure, merging effective delivery with real-time imaging capabilities [29, 33].

The clinical relevance of these imaging techniques cannot be overstated, as they provide invaluable insights into the pharmacokinetics of nanomedicines and inform personalized treatment strategies tailored to individual patients' responses. Recent studies have elucidated a correlation between the uptake of nanoparticles in tumors and the subsequent antitumor efficacy, thereby underlining the significance of image-guided drug delivery systems in modern oncology [29, 30]. As the understanding of nanocarrier technology continues to evolve, their applications in both drug delivery and imaging will likely expand, providing new possibilities for more effective and personalized cancer therapies.

Recent advances in nanotechnologies for ovarian Cancer diagnosis

Nanotechnology is emerging as a revolutionary method to tackle ovarian cancer, which is typically diagnosed at later stages with high mortality rates. Recent innovations in this field highlight the significant role of nanotechnologies in the early identification and treatment of ovarian cancer, focusing on case studies, nanomaterial design, and the integration of novel technologies with traditional diagnostics [34, 35] (Table 2). One major advancement includes nanosensors capable of detecting cancer-specific proteins at low concentrations. An initiative by Daniel Heller at the Sloan Kettering Institute is developing implantable nanosensors for continuous monitoring of key biomarkers, such as CA125 and HE4, indicative of ovarian cancer. Early trials on human tissues are currently being conducted to validate the efficacy of these sensors for clinical use [36–38].

Apart from nanosensors, various nanocarrier systems like liposomes and dendrimers are gaining attention for their potential to improve the targeted delivery of drugs to cancer cells, enhancing therapeutic outcomes while minimizing side effects [39]. The design of specialized nanoparticles, including gold nanoparticles, carbon nanotubes, and quantum dots, also plays a crucial role in elevating the sensitivity and specificity of cancer detection techniques. Carbon nanotubes, for example, are being designed to emit infrared light upon binding to cancer biomarkers, facilitating non-invasive detection [34, 35]. The development of functionalized nanoparticles that precisely target ovarian cancer cells is another significant advancement, allowing for simultaneous diagnostics and therapy—termed theranostics [34, 39].

Moreover, the synergy between nanotechnology and conventional diagnostic techniques fosters the evolution of comprehensive screening methods. Liquid biopsies analyzing circulating tumor DNA (ctDNA) are notably enhanced by nanoparticles, offering a less invasive alternative to traditional biopsies [34]. The incorporation of nanoparticles into imaging modalities like MRI and PET scans improves tumor visualization, paving the way for more effective monitoring of treatment responses [40]. Overall, the integration of these advanced technologies not only boosts diagnostic precision but also facilitates ongoing assessment of therapeutic effectiveness.

Challenges and limitations of nanotechnologies

Nanotechnology holds transformative potential across multiple sectors but faces considerable challenges that limit its wider application. These challenges fall into three main areas: regulatory issues, technical complexities, and economic limitations.

Regulatory frameworks for nanotechnology are insufficient, creating uncertainties in governance and safety standards. The unique properties of nanomaterials raise previously unrecognized health risks, highlighting the need for comprehensive risk assessments that are currently lacking [41, 42]. Additionally, ethical concerns regarding worker safety and exposure to engineered nanoparticles persist.

Technical challenges arise from the difficulty in detecting and quantifying nanomaterials, as traditional analytical methods often fall short, complicating risk assessments and regulatory development [43]. Finally, economic barriers such as high production costs and scalability limitations hinder growth, with current manufacturing often relying on inefficient batch processes [44]. Although methods like continuous-flow production could reduce costs, their adoption is limited by high initial investments and customization needs [44–46].

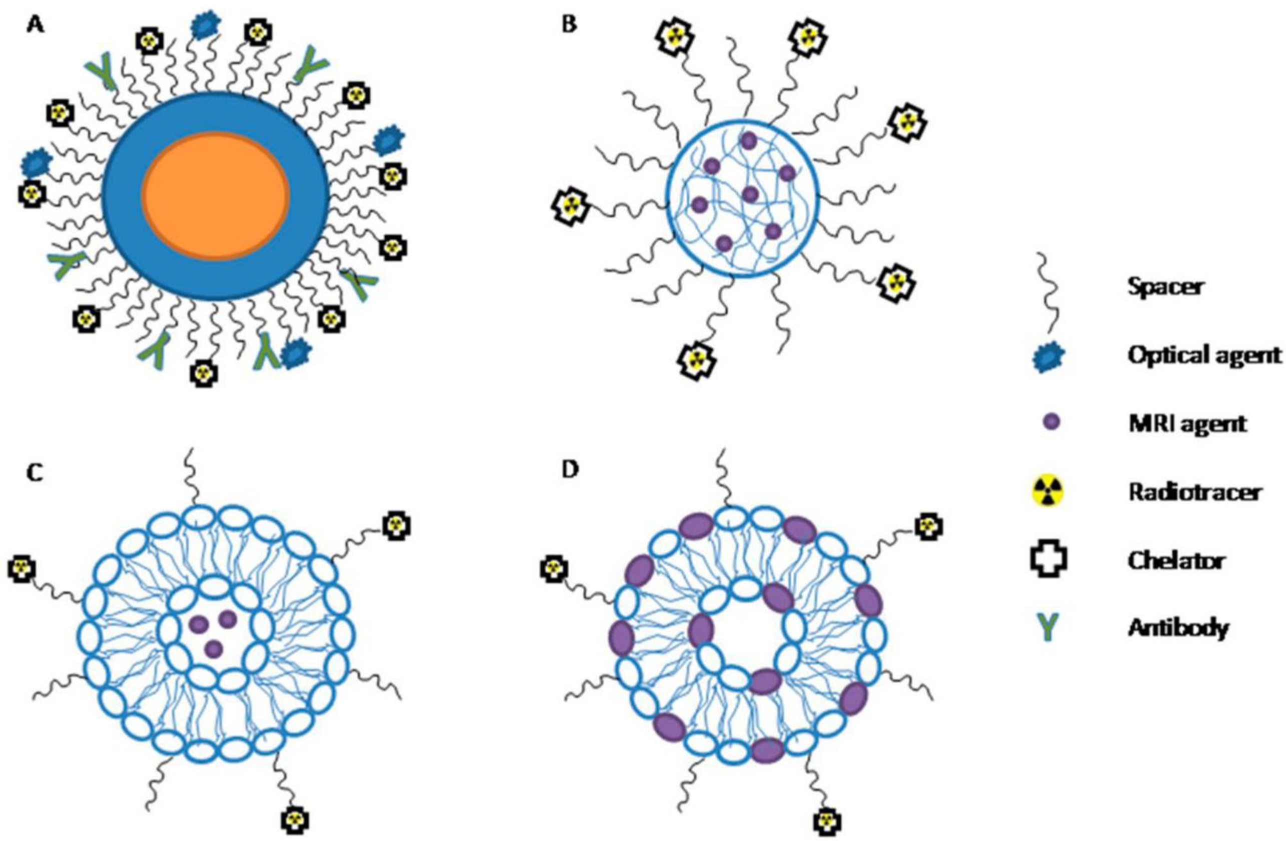


Fig. 2 Showing the innovative designs of multimodal nanoparticles with intrinsic capabilities for both imaging and targeted therapy encapsulated in nanomedicine. The exploration of multimodal nanoparticles represents a significant advancement in the field of medical imaging and therapy, demonstrating an innovative blend of various imaging techniques in a single platform, thus enhancing the diagnostic capabilities and treatment efficacy for a range of diseases, particularly cancer. The structural design of these nanoparticles typically encompasses a core-shell configuration, where the core, often composed of materials suitable for magnetic resonance imaging (MRI), works synergistically alongside a functionalized shell that harbors specific antibodies aimed at targeting particular cells or tissues (**A**). For instance, the integration of positron emission tomography (PET) capabilities into these nanoparticles is achieved by chelating the PET radiotracer and binding it to a spacer, thereby augmenting the imaging resolution and potential for therapeutic applications. In the context of polymeric nanoparticles, a sophisticated architecture is showcased through the entrapment of paramagnetic moieties, which can enhance the contrast during MRI scans (**B**). The same principle applies to the optimization of the PET component, as it remains chelated and bound to the spacer, sustaining the multipurpose functionality of the nanoparticle. Such innovative designs not only facilitate precise imaging but can also be leveraged for therapeutic interventions concurrently, representing a holistic approach to disease management. Furthermore, liposomal formulations have been explored for their promising applications in drug delivery and imaging (**C**). These structures are characterized by an aqueous inner core that can entrap various paramagnetic agents, while the PET component's covalent linkage to the spacer allows for a seamless combination of imaging modalities. This method of delivering imaging agents in an enclosed environment provides an opportunity for enhanced stability and bioavailability, which are critical for effective tracking of drug administration and target localization. Notably, the approach of inserting paramagnetic ions directly into the lipid bilayer of liposomal formulations is another innovative method demonstrated to improve imaging (**D**). This advanced method not only retains the integrity and biocompatibility of the liposomal structure but also effectively amplifies the contrast in MRI, thereby providing clearer delineation of tissues or tumor margins during diagnostic assessments. Such multifaceted designs reinforce the concept that technological advancements in nanomedicine can pave the way toward more effective and personalized therapeutic strategies, highlighting a future where treatment modalities are intricately linked with diagnosis. The adaptable nature of these multimodal nanoparticles facilitates an array of applications, including tumor imaging, targeted therapy, and monitoring therapeutic efficacy, all encapsulated within a compact platform. Their superiority over traditional imaging techniques lies in the ability to yield real-time data while simultaneously providing therapeutic agents, addressing the urgent need for efficiency in contemporary healthcare practices. As the demand for precision in medicine grows, the research and development of such nanoparticles signify a pivotal shift toward integrated diagnostic and therapeutic solutions that can cater to individual patient needs

Future directions and perspectives

The treatment landscape for ovarian cancer is increasingly shifting toward personalized medicine, focusing on tailoring therapies to the genetic features of individual tumors. Advances in genomic testing allow for the identification of specific mutations that inform therapy choices, such as in patients with BRCA mutations or homologous recombination deficiency (HRD), who significantly benefit from PARP inhibitors [47–49]. Additionally, maintenance therapies, including bevacizumab and PARP inhibitors, complement traditional chemotherapy, enhancing progression-free survival and overall

Table 2 Summarizing the key points regarding the advancements in nanotechnology for ovarian cancer diagnosis and treatment

Aspect	Description
Challenges of Ovarian Cancer	- Often detected at advanced stages - High mortality rates
Advancements in Nanotechnology	- Innovative approaches for early diagnosis and treatment - Focus on case studies and nanomaterial design - Integration with conventional methods
Nanosensors	- Designed to detect cancer-specific proteins at low concentrations - Example: Implantable nanosensors by Daniel Heller to monitor biomarkers (CA125, HE4) - Placed in uterus/under skin for ongoing surveillance - Preliminary trials on human tissues underway
Nanocarrier Systems	- Includes liposomes and dendrimers - Enhances targeted delivery of therapeutic agents to cancer cells - Improves therapeutic outcomes and reduces side effects
Nanomaterial Design	- Use of nanoparticles (gold, carbon nanotubes, quantum dots) - Carbon nanotubes emit infrared light upon binding to cancer biomarkers for non-invasive detection - Functionalized nanoparticles for targeted cancer cell treatment (theranostics)
Synergy with Diagnostic Techniques	- Integration with liquid biopsies to analyze circulating tumor DNA (ctDNA) - Nanoparticles enhance capture of biomarkers from blood samples for less invasive diagnostics
Imaging Enhancements	- Nanoparticle contrast agents used in MRI and PET scans - Improve tumor visualization, particularly at early stages - Potential for continuous monitoring of treatment responses

outcomes [48]. The integration of precision medicine facilitates higher response rates and aids in early identification for clinical trial candidates [47, 49]. Furthermore, the combination of nanotechnology with artificial intelligence (AI) and machine learning promises to revolutionize treatment methodologies. Nanoparticles improve drug delivery, targeting cancer cells more precisely, while AI helps predict patient responses based on tumor genetics, leading to more effective personalized treatment plans [50]. Collaborative efforts across academic, pharmaceutical, and healthcare sectors are essential for advancing research and development of new therapies. Such partnerships encourage knowledge sharing and expedite innovative treatments into the clinic, potentially transforming patient care through improved standards and new therapeutic strategies [48, 51].

Conclusion

In summary, the advent of nanotechnology represents a transformative leap in the field of ovarian cancer detection and diagnosis. These cutting-edge innovations, which include enhanced biomarker identification, advanced imaging techniques, non-invasive diagnostic methods, and the targeted delivery of therapeutics, are not only paving the way for earlier detection but also reshaping the landscape of personalized cancer care. As we navigate the complexities and challenges inherent to these emerging technologies, we are filled with optimism that they will soon become standard practice in oncology. By integrating these advancements into routine clinical protocols, we can aspire to improve survival rates and enhance the quality of life for ovarian cancer patients through timely intervention and tailored treatment approaches. Ultimately, our commitment to this research endeavors to make a significant impact on life-saving measures and the broader fight against cancer.

Limitations

The review discusses emerging nanotechnologies and their role in early ovarian cancer detection, diagnosis, and intervention. However, the general limitations of nanotechnology in ovarian cancer detection include a lack of clinical translation evidence. Here in our review, some of our limitations include overlooking the variability in methodologies used across studies, which could lead to confusion about the effectiveness and reliability of each approach. The review also overlooks the challenges of standardization in diagnostic devices and procedures, which can lead to discrepancies in diagnostic accuracy and reliability. The regulatory and ethical concerns and the economic implications of implementing nanotechnologies for early detection are also overlooked, with significant costs associated with development, production, and clinical use.

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Author contributions
MOO, KHB, ADA and BBA participated in concept, design, data collection, data interpretation and writing. Both authors read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Competing interests
The authors declare no competing interests.

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