COMPARATIVE PROTEOMICS BETWEEN TUMORS AND HEALTHY TISSUES FOR THE EARLY DETECTION OF AGGRESSIVE CANCERS

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Abstract

Comparative proteomics of tumor and healthy tissues has become established as a promising approach to the early detection of aggressive cancers because it enables the identification of biomarkers associated with the initial stages of carcinogenesis. This study aimed to analyze scientific evidence on the application of this strategy to the molecular differentiation of normal and neoplastic tissues, with an emphasis on its diagnostic and prognostic potential. This integrative literature review was conducted in the PubMed/MEDLINE, Scopus, SpringerLink, and DOAJ databases and considered publications in Portuguese and English issued between 2020 and 2026. The selected studies showed that proteomics enables the identification of protein signatures capable of distinguishing among different types of cancer, particularly colorectal, prostate, ovarian, and esophageal cancers. The authors agreed that multivariate proteomic panels outperform individual biomarkers, increasing diagnostic sensitivity and specificity. Furthermore, the findings indicate that protein alterations can be detected at subclinical stages, reinforcing their potential for early screening and risk stratification. It is concluded that comparative proteomics represents an innovative and promising tool in precision oncology, although clinical validation studies and methodological standardization are still required before it can be fully incorporated into clinical practice.

Keywords: Aggressive cancer, Comparative proteomics, Early diagnosis, Precision oncology, Tumor biomarkers.

INTRODUCTION

Cancer represents one of the foremost global public health challenges because of its high incidence and mortality and its impact on the population's quality of life. Aggressive tumors, in particular, progress rapidly and have a high metastatic potential, making early diagnosis a decisive factor in successful treatment. Nevertheless, many cases are still identified at advanced stages, when the prospects

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for curative treatment are limited. In this context, the search for more sensitive and specific biomarkers has driven the development of new diagnostic strategies based on molecular biology (Budnik et al., 2024).

Comparative proteomics stands out as an important tool for investigating protein alterations associated with carcinogenesis. By comparing tumor and healthy tissues, this approach makes it possible to identify differentially expressed proteins, understand the biological mechanisms involved in tumor progression, and discover biomarkers with potential clinical applications. Furthermore, advances in mass spectrometry and bioinformatics techniques have significantly increased the precision of these analyses (Qian et al., 2024).

In colorectal cancer, comparative studies of tumor cells and normal colonic mucosa cells have demonstrated marked differences in protein expression associated with malignant transformation. These results have contributed to the identification of proteins involved in cell proliferation, tumor invasion, and disease development, demonstrating the potential of proteomics for early diagnosis and the discovery of new therapeutic targets (Ludvigsen et al., 2020).

Advances in the analysis of serum and plasma samples have also broadened colorectal cancer screening possibilities. Proteomic panels comprising multiple proteins have demonstrated a strong ability to identify advanced adenomas and early-stage tumors, outperforming individual biomarkers and supporting the implementation of less invasive approaches to early diagnosis (Hua et al., 2024; Tan et al., 2024).

More recent studies reinforce these findings by identifying plasma and tissue proteins with high diagnostic potential for colorectal cancer. Integrating different biomarkers has yielded greater sensitivity and specificity in differentiating healthy individuals from patients with the disease, demonstrating the importance of comparative proteomics in building more robust diagnostic models (Jin et al., 2025; Xiao et al., 2025).

In prostate cancer, the early identification of clinically significant tumors remains challenging because of the limitations of conventional screening methods. In this context, protein biomarkers obtained from serum samples have demonstrated a strong ability to identify aggressive tumors at an early stage and support risk stratification, thereby contributing to more individualized treatment decisions (Eickelschulte et al., 2022; Wang et al., 2022).

The integration of proteomic analyses of prostate tissue and urine samples has further expanded knowledge of prostate cancer biology. Protein signatures identified in different biological matrices have enabled the recognition of biomarkers associated with both tumor onset and progression, including lesions undetectable by conventional imaging examinations, demonstrating the high sensitivity of this approach (Blanca et al., 2026).

Comparative proteomics has also produced relevant results in other aggressive cancers. In ovarian cancer, proteome mapping revealed alterations in proteins associated with proliferation, invasion, and treatment resistance, while a panel comprising eight plasma proteins demonstrated high accuracy in differentiating benign from malignant tumors, reinforcing its potential for clinical use (Qian et al., 2024; Moskov et al., 2025).

Similar findings have been observed in esophageal squamous cell carcinoma, in which comparisons among healthy tissue, tumor-adjacent tissue, and neoplastic tissue enabled the identification of progressive protein alterations associated with disease progression. Accordingly, this study aims to analyze scientific evidence on the use of comparative proteomics of tumors and healthy tissues for the early detection of these cancers, highlighting its contribution to improving cancer diagnosis.

METHODOLOGY

This descriptive, qualitative integrative literature review was undertaken to gather, analyze, and synthesize scientific evidence on the use of comparative proteomics of tumors and healthy tissues for the early detection of aggressive cancers. The integrative review method was selected because it allows

studies with different methodological designs to be incorporated, thus providing a broad understanding of the subject and identifying advances, gaps, and prospects for clinical practice and future research.

The review was conducted in six stages: formulation of the guiding question; establishment of the search strategy; definition of the inclusion and exclusion criteria; selection and reading of the studies; data extraction and organization; and critical synthesis of the findings.

The study's guiding question was formulated as follows: What scientific evidence is available on the use of comparative proteomics of tumors and healthy tissues for the early detection of aggressive cancers?

The literature search was conducted in PubMed/MEDLINE, Scopus, SpringerLink, and the Directory of Open Access Journals (DOAJ), which were selected because of their recognized and extensive coverage of studies in oncology, molecular biology, proteomics, and health sciences.

The search strategy was constructed using descriptors in Portuguese and English drawn from the Health Sciences Descriptors (Descritores em Ciências da Saúde – DeCS) and Medical Subject Headings (MeSH). The principal descriptors used were: Proteomics, Tumor Biomarkers, Early Diagnosis, and Neoplasms. The descriptors were combined using the Boolean operators AND and OR, with strategies adapted to the specific features of each database.

The inclusion criteria comprised original scientific articles published between 2020 and 2026, available in full text in Portuguese or English, addressing comparative proteomics of tumor and healthy tissues, protein biomarkers, or proteomic signatures associated with the early diagnosis of aggressive cancers. Studies investigating tissue, plasma, serum, or urine samples with potential clinical applications were also considered.

The exclusion criteria encompassed articles duplicated across the databases, literature reviews, editorials, letters to the editor, abstracts published in scientific conference proceedings, book chapters, master's dissertations, doctoral theses, experimental studies not directly related to the research objective,

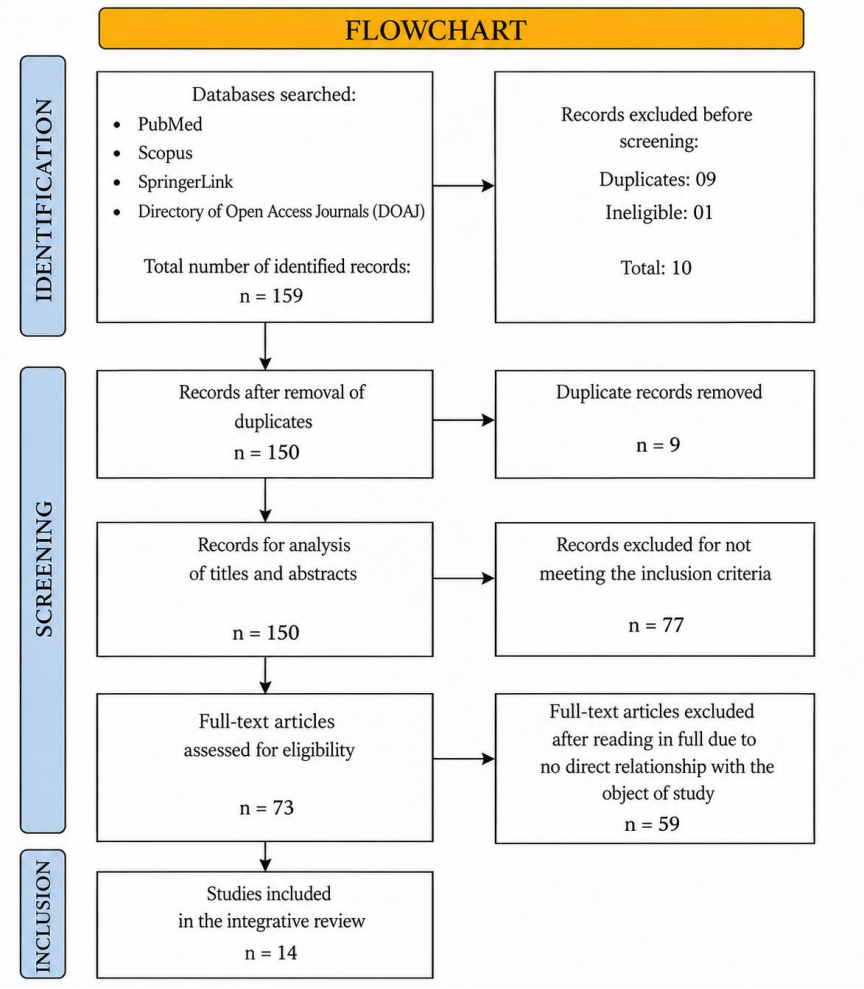
publications whose full text was unavailable, and studies reporting insufficient findings to answer the guiding question.

Study selection occurred in two stages. First, titles and abstracts were reviewed to assess their alignment with the proposed subject. Potentially eligible articles were then read in full and analyzed in terms of their objectives, methodological design, sample type, principal biomarkers identified, and contributions to the early detection of aggressive cancers.

The study identification, screening, eligibility, and inclusion process is presented in Figure 1, which was prepared according to the stages of the integrative review to enhance the transparency and reproducibility of the method used.

Figure 1

Flowchart of the study-selection process for the integrative review.



Source: Prepared by the authors (2026).

After the articles had been selected, the data were organized using a previously developed instrument containing information on the authors, year of publication, country in which the study was conducted, type of cancer investigated, study objective, methodology employed, principal protein biomarkers identified, and main findings. A descriptive analysis and narrative synthesis of the scientific evidence were then performed, making it possible to identify advances in comparative proteomics in differentiating tumor from healthy tissues and its contribution to the early diagnosis of aggressive cancers.

RESULTS AND DISCUSSION

The search strategy resulted in the selection of 14 studies that met the previously established eligibility criteria. The publications were produced between 2020 and 2026 and encompassed research conducted in different countries involving various types of aggressive cancer, particularly colorectal cancer, prostate cancer, ovarian cancer, and esophageal squamous cell carcinoma. The studies used different proteomic approaches to compare tumor and healthy tissues or related biological samples, identifying biomarkers with potential applications in early diagnosis, prognostic stratification, and the differentiation of benign and malignant lesions.

Overall, significant advances were observed in the use of mass spectrometry platforms and high-resolution proteomic techniques, reinforcing the potential of this technology as a complementary tool to conventional diagnostic methods.

The general characteristics of the studies included in the integrative review are presented in Table 1.

Table 1

Characteristics of the studies included in the integrative review

Author/year	Objective	Domain	Principal contributions
Ludvigsen et al. (2020)	To compare the proteomic profile of colorectal cancer cells with that of normal colonic mucosa cells.	Comparison of tumor and healthy tissues.	Demonstrated marked differences in protein expression between neoplastic and normal cells, identifying proteins potentially associated with colorectal carcinogenesis. The findings supported the development of diagnostic biomarkers and broadened understanding of the molecular mechanisms involved in malignant transformation.
Eickelschulte et al. (2022)	To evaluate biomarkers for detecting and stratifying the risk of aggressive prostate cancer.	Protein biomarkers.	Showed that protein biomarkers are highly capable of identifying clinically significant tumors and improving prognostic stratification, thereby contributing to more individualized treatment decisions and reducing the limitations associated with using PSA alone.
Wang et al. (2022)	To identify serum biomarkers for the early diagnosis and classification of prostate cancer aggressiveness.	Serum proteomics.	Identified serum proteins capable of distinguishing patients with prostate cancer at an early stage and differentiating more aggressive tumors, demonstrating considerable potential to improve screening and the selection of more precise clinical management strategies.
Zhu et al. (2023)	To investigate proteomic alterations in tumor-adjacent tissues in hepatocellular carcinoma.	Proteomics of tumor-adjacent tissues.	Demonstrated that tumor-adjacent tissues exhibit important molecular alterations even before evident histological involvement, revealing biological events associated with tumor progression and identifying potential biomarkers for early diagnosis and prognosis.
Budnik et al. (2024)	To develop a proteomics-based plasma test for the early screening of multiple cancers.	Plasma proteomics.	Developed a test based on plasma proteomic signatures capable of detecting different types of cancer in asymptomatic individuals, demonstrating high sensitivity for early identification and highlighting the potential of proteomics as a population-screening tool.
Hua et al. (2024)	To develop a proteomic panel for the early screening of colorectal cancer.	Proteomic panel.	Developed a proteomic classifier comprising multiple proteins that demonstrated high sensitivity and specificity in detecting early-stage colorectal cancer, outperforming individual biomarkers.

Qian et al. (2024)	To characterize the proteomic landscape of epithelial ovarian cancer.	Tumor proteome.	Extensively characterized the epithelial ovarian cancer proteome, identifying alterations in pathways associated with cell proliferation, invasion, tumor-microenvironment remodeling, and treatment resistance, thereby expanding knowledge of the disease's molecular biology.
Tan et al. (2024)	To evaluate serum proteins for the early detection of advanced adenoma and colorectal cancer.	Serum proteomics.	Identified serum proteomic profiles associated with the initial stages of colorectal carcinogenesis, demonstrating their potential to differentiate healthy individuals, individuals with advanced adenomas, and patients with cancer, thereby supporting earlier screening strategies.
Zheng et al. (2024)	To compare the proteomic composition of tumor and normal tissues using mass spectrometry.	Comparative proteomics.	Demonstrated quantitative and qualitative differences in protein composition between tumor and normal tissues, emphasizing the importance of methodological standardization and appropriate control selection to improve the reliability of clinical biomarker identification.
Jin et al. (2025)	To identify plasma biomarkers for the early diagnosis of colorectal cancer.	Plasma proteomics.	Identified high-performance plasma biomarkers capable of distinguishing patients with early-stage colorectal cancer, reinforcing the potential of proteomics for developing less invasive and more precise diagnostic methods.
Moskov et al. (2025)	To validate a protein panel for differentiating benign and malignant ovarian tumors.	Plasma biomarkers.	Validated an eight-protein plasma biomarker panel capable of differentiating benign from malignant ovarian tumors with high accuracy, contributing to greater diagnostic precision and a reduction in unnecessary invasive procedures.
Xiao et al. (2025)	To identify protein biomarkers in intestinal tissues using the Olink platform.	Tissue proteomics.	Identified differentially expressed proteins in intestinal tissues using the Olink platform, revealing new biomarkers with potential applications in the early diagnosis, prognosis, and monitoring of colorectal cancer.
Blanca et al. (2026)	To integrate urinary and tissue proteomic signatures in prostate cancer.	Integrated proteomics.	Demonstrated that integrating proteomic profiles obtained from urine and tumor tissue significantly increases the ability to identify biomarkers associated with prostate cancer development and progression, including tumors undetectable by conventional imaging examinations.

Liu et al. (2026)	To evaluate proteomic alterations among healthy, tumor-adjacent, and tumor tissues in esophageal squamous cell carcinoma.	Comparative tissue proteomics.	Demonstrated that progression from healthy tissue to tumor-adjacent and neoplastic tissue is accompanied by progressive proteomic alterations, enabling the identification of clinically relevant biological events and promising biomarkers for early diagnosis and prognostic stratification.

Source: Prepared by the authors (2026).

The studies analyzed show that comparative proteomics is becoming established as one of the most promising strategies for improving the early diagnosis of aggressive cancers. Unlike approaches based exclusively on genetic alterations, this technology makes it possible to identify functional modifications that directly reflect the biological behavior of neoplastic cells.

In this regard, Zheng et al. (2024) demonstrated that the systematic comparison of tumor and normal tissues reveals consistent differences in protein composition, providing a more robust basis for identifying clinically relevant biomarkers.

Comparisons among healthy, tumor-adjacent, and neoplastic tissues also broaden understanding of the molecular evolution of carcinogenesis. Zhu et al. (2023) observed that apparently preserved tissues already exhibit proteomic alterations associated with tumor progression, indicating that important biological modifications precede the morphological changes detectable by conventional examinations. Consistently, Liu et al. (2026) found that these changes occur progressively during the development of esophageal squamous cell carcinoma, reinforcing the importance of proteomics in identifying early carcinogenic events.

In colorectal cancer, the literature demonstrates strong convergence regarding the diagnostic potential of proteomic signatures. Ludvigsen et al. (2020) identified differentially expressed proteins in tumor tissue and normal colonic mucosa, revealing alterations directly associated with malignant transformation. These findings are corroborated by Xiao et al. (2025), who identified new biomarkers in intestinal tissues using highly sensitive proteomic platforms, broadening the possibilities for developing more specific diagnostic tests.

The use of blood samples represents another aspect extensively discussed in the selected studies. Hua et al. (2024) demonstrated that panels comprising multiple biomarkers have better diagnostic performance than individual proteins, providing greater sensitivity and specificity in the early identification of colorectal cancer. Similarly, Jin et al. (2025) found that high-performance plasma biomarkers make it possible to distinguish individuals affected by the disease while it is still at an early stage, reinforcing the potential of so-called liquid biopsies as a less invasive alternative for population screening.

Similar results were reported by Tan et al. (2024), who demonstrated the ability of serum proteomic profiles to differentiate healthy individuals, individuals with advanced adenomas, and patients with colorectal cancer. This agreement among the studies shows that integrating multiple proteins into a single diagnostic panel significantly increases clinical accuracy compared with conventional markers used individually.

In prostate cancer, the authors similarly show strong convergence regarding the limitations of the diagnostic methods currently in use. Eickelschulte et al. (2022) emphasized that protein biomarkers have greater potential to stratify patients with clinically significant tumors, reducing the risk of overdiagnosis associated with PSA. Complementing this perspective, Wang et al. (2022) identified serum proteins capable of differentiating aggressive tumors from low-risk tumors, supporting more precise therapeutic decision-making.

The simultaneous use of different biological matrices represents another important advance identified in the literature. Blanca et al. (2026) demonstrated that integrating urinary and tissue proteomic signatures increases the ability to identify biomarkers associated with both tumor development and progression, including lesions undetected by conventional imaging examinations.

Studies involving ovarian cancer reinforce this trend toward molecular integration. Qian et al. (2024) demonstrated that comprehensive tumor-proteome mapping provides insight into biological pathways associated with cell proliferation, tumor-microenvironment remodeling, and treatment

resistance. Consistently, Moskov et al. (2025) validated an eight-protein plasma biomarker panel capable of differentiating benign from malignant tumors with high accuracy, demonstrating the clinical applicability of proteomic biomarkers in different oncological contexts.

Another relevant aspect identified in the literature concerns the development of tests capable of identifying different types of cancer simultaneously. Budnik et al. (2024) demonstrated that plasma proteomic signatures have potential for multicancer screening in asymptomatic individuals, significantly broadening the prospects for population-based early-detection programs. This advance represents an important paradigm shift, as it redirects the focus from investigating a single tumor to an integrated approach based on molecular alterations shared by different cancers.

Despite the promising findings, the studies analyzed also highlight challenges to incorporating comparative proteomics into clinical practice. Biomarkers need to be externally validated in larger and more heterogeneous populations, and protocols for sample collection and processing and bioinformatic analysis must be standardized.

Taken together, the evidence demonstrates broad agreement that comparative proteomics of tumors and healthy tissues is a strategic tool for advancing precision oncology. Identifying specific protein signatures enables greater diagnostic sensitivity, better risk stratification, and a deeper understanding of tumor biology. The consolidation of these technologies may therefore contribute to the development of earlier, less invasive, and clinically more precise diagnostic methods, supporting individualized therapeutic interventions and better outcomes for patients with aggressive cancers.

CONCLUSION

This integrative review has shown that the analysis of the selected scientific literature provided a comprehensive understanding of the potential of comparative proteomics of tumors and healthy tissues for the early detection of aggressive cancers. The synthesis of the available knowledge answered the

guiding question by demonstrating that this approach represents a consistent strategy for identifying biomarkers associated with the initial stages of carcinogenesis.

Regarding the proposed objective, the review achieved its purpose by gathering and interpreting evidence on different applications of proteomics across a range of cancers. The findings indicate that comparisons among tumor tissues, non-tumor tissues, and peripheral biological samples, such as blood and urine, as well as tumor-adjacent tissues, contribute significantly to identifying protein signatures associated with tumor development and progression.

From the perspective of the principal findings, the studies converge regarding the considerable potential of comparative proteomics to identify biomarkers with applications in diagnosis, prognosis, and risk stratification. The evidence indicates that protein panels comprising multiple markers outperform individual proteins, providing greater sensitivity and specificity in detecting aggressive cancers.

With respect to early diagnosis, the evidence analyzed reinforces the ability of proteomics to identify molecular alterations during the subclinical stages of disease. This characteristic indicates that protein changes may precede structural alterations detectable by conventional methods, expanding the possibilities for early screening and timely therapeutic intervention.

Regarding limitations and challenges, despite significant advances, barriers remain to the consolidation of comparative proteomics in clinical practice. The principal obstacles include the need for external biomarker validation, methodological standardization across different studies, and expanded investigation in more heterogeneous populations to ensure greater robustness and reproducibility of the findings.

Finally, regarding future prospects, multicenter and longitudinal studies should be conducted to evaluate the clinical applicability of integrated proteomic panels across different types of cancer. The use of artificial intelligence and advanced computational approaches to analyze large volumes of proteomic data is also recommended to improve diagnostic accuracy and strengthen the development of precision medicine in oncology.

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