

Menopause related hormonal and inflammatory regulation of BCL2-mediated apoptosis in cervical cancer: A Systematic review

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ABSTRACT

Introduction: Menopause is characterized by a decline in estrogen levels that may alter inflammatory signaling and apoptotic regulation. Dysregulation of apoptosis, particularly involving B-cell lymphoma-2 (Bcl2), plays a critical role in cervical cancer progression. This systematic review aimed to synthesize current evidence on menopause-related hormonal changes and inflammatory mechanisms in regulating Bcl2-mediated apoptosis in cervical cancer.

Research Methodology: This systematic review followed PRISMA 2020 guidelines. Literature searches were conducted in October 2025 using PubMed and ScienceDirect. Eligible studies included human and animal research examining menopause-related hormonal status, inflammation, and Bcl2-associated apoptotic pathways in cervical cancer. Risk of bias was assessed using the Cochrane RoB 2 tool for human studies and the SYRCLE tool for animal studies. Due to heterogeneity, data were synthesized narratively.

Results: Six studies (2 human, 4 animal) published between 2019 and 2024 were included. Human studies demonstrated menopause-associated inflammatory changes, including elevated cytokines (IL-1 α , IL-6, CRP), suggesting a pro-inflammatory environment relevant to apoptosis regulation. Animal studies consistently showed downregulation of Bcl2 and upregulation of pro-apoptotic markers (BAX, caspase-3), indicating mitochondrial apoptosis activation under estrogen-deprived conditions. Quantitative effect measures (e.g., OR, RR) were not consistently reported due to the predominance of mechanistic and preclinical designs.

Conclusion: Menopause-related hormonal decline is associated with increased inflammation and modulation of Bcl2-dependent apoptotic pathways in cervical cancer. While preclinical evidence strongly supports a mechanistic link, clinical evidence remains limited. Future translational studies integrating molecular, hormonal, and inflammatory biomarkers are needed to establish clinical relevance.

Keywords: apoptosis; BCL2 protein; cervical cancer; inflammation; menopause.



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INTRODUCTION

Cervical cancer remains a major public health burden, particularly in low- and middle-income countries, where incidence and mortality rates continue to be disproportionately high (Abdullah et al., 2026). While persistent infection with high-risk human papillomavirus (HPV) is recognized as the primary etiological factor, HPV infection alone is insufficient to drive malignant transformation (Akolkar et al., 2025). Increasing evidence indicates that host-related biological processes, especially those regulating apoptosis, inflammation, and hormonal signaling, play a decisive role in determining disease progression, therapeutic response, and clinical outcomes (Aljabali et al., 2025).

One of the key hallmarks of cancer is the ability of malignant cells to evade apoptosis, allowing uncontrolled proliferation and resistance to therapy (Asseffa et al., 2026). The B-cell lymphoma-2 (Bcl2) family of proteins is central to the regulation of intrinsic (mitochondrial) apoptotic pathways, controlling mitochondrial membrane permeability and cell survival signaling (Bates et al., 2024). Overexpression of anti-apoptotic Bcl2 has been consistently associated with tumor persistence, chemoresistance, and poor prognosis in cervical cancer (Berezowitz & Givens, 2025). Conversely, suppression of Bcl2, accompanied by activation of pro-apoptotic proteins such as BAX and caspase-3, promotes programmed cell death and limits tumor progression (Biswas et al., 2024). Despite its critical role, the upstream modulators of Bcl2 signaling in cervical cancer, particularly those related to hormonal and inflammatory changes, remain incompletely understood (Chen et al., 2025).

Menopause represents a biologically significant transition characterized by a marked decline in circulating estrogen and progesterone levels (De Oliveira, 2025). This hormonal shift has systemic consequences, including increased oxidative stress, immune dysregulation, and activation of pro-inflammatory pathways (Dedios Sanguineti et al., 2025). Estrogen is known to exert anti-inflammatory and cytoprotective effects by modulating transcription factors, such as nuclear factor kappa B (NF- κ B), and signaling pathways, including PI3K/AKT and MAPK (Dey Bhowmik et al., 2025). Therefore, estrogen deficiency during menopause may create a pro-inflammatory microenvironment that alters cellular homeostasis and apoptotic susceptibility (Edo et al., 2025). In the context of cervical cancer, this hormonal inflammatory interaction is particularly relevant, as it may influence tumor behavior, progression, and response to treatment in postmenopausal women (Forsman, 2025).

The existing literature provides fragmented insights into the relationships among menopause, inflammation, and apoptosis (He et al., 2024). Epidemiological studies suggest that earlier menopause is associated with an increased risk of gynecologic malignancies, including cervical cancer, indicating a potential role of hormonal aging in cancer susceptibility (Herrara et al., 2025). Clinical studies in postmenopausal populations have also demonstrated elevated levels of inflammatory markers such as interleukins and C-reactive protein, reflecting a chronic low-grade inflammatory state (Hietajärvi et al., 2026). However, these studies largely provide indirect evidence and do not directly assess the molecular regulators of apoptosis, such as Bcl-2, in cervical tissue (Hushmandi et al., 2024).

In contrast, preclinical studies using animal models offer more direct mechanistic evidence. Ovariectomized models, which simulate menopausal estrogen deprivation, consistently demonstrate downregulation of Bcl2 expression and upregulation of pro-apoptotic markers, including BAX and caspase-3. These findings indicate activation of the mitochondrial apoptotic pathway under conditions of hormonal deficiency. Additionally, experimental modulation of inflammatory pathways further influences apoptotic signaling, suggesting that inflammation acts

as a key intermediary linking hormonal changes to cellular survival mechanisms. While these findings are biologically plausible and internally consistent, their translational applicability to human populations remains uncertain due to differences in study design, biological complexity, and clinical context.

Despite growing interest in the interplay between hormonal status, inflammation, and apoptosis in cancer biology, a critical gap persists in the literature. Specifically, there is a lack of integrative synthesis that systematically examines how menopause-related hormonal decline and inflammatory signaling converge to regulate Bcl2-mediated apoptosis in cervical cancer. Existing studies are heterogeneous, spanning epidemiological analyses, clinical observations, and preclinical experiments, and lack a unified framework for interpreting their collective implications. Moreover, direct clinical evidence linking menopausal status to Bcl2 expression and apoptotic activity in cervical cancer remains scarce, limiting the ability to translate mechanistic insights into clinical practice.

This gap underscores the need for a comprehensive synthesis that bridges molecular mechanisms and clinical relevance. The novelty of this study lies in its integrative approach, combining evidence from human and animal studies to elucidate the hormone inflammation apoptosis axis, with a specific focus on Bcl2 signaling pathways in cervical cancer. By situating menopause as a biological modifier of apoptotic regulation, this review advances current understanding beyond isolated mechanistic or epidemiological perspectives and provides a more cohesive interpretation of disease processes. Therefore, this systematic review aims to synthesize available evidence on menopause-related hormonal and inflammatory regulation of Bcl2-mediated apoptosis in cervical cancer. Specifically, it seeks to (1) evaluate the role of hormonal decline in modulating inflammatory and apoptotic pathways, (2) examine mechanistic evidence linking Bcl2 regulation to menopause-related changes, and (3) identify critical gaps for future translational and clinical research. Through this approach, the study intends to contribute to a more precise understanding of cervical cancer biology in the context of hormonal aging and to inform the development of targeted therapeutic and preventive strategies.

RESEARCH METHODOLOGY

Study Design

This study was designed as a systematic review to comprehensively synthesize evidence on menopause-related hormonal and inflammatory regulation of Bcl2-mediated apoptosis in cervical cancer. The systematic review approach was selected to integrate heterogeneous findings from both clinical and preclinical studies in a structured and reproducible manner. The methodology adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines, which provide a standardized framework to enhance transparency, methodological rigor, and reproducibility in evidence synthesis.

Search Strategy

A comprehensive literature search was conducted in October 2025 using electronic databases including PubMed, ScienceDirect, Scopus, Web of Science, and Google Scholar to ensure broad coverage of biomedical and interdisciplinary literature. Search terms were developed using a combination of controlled vocabulary and free-text keywords related to the core concepts. The Boolean search strategy included: (“BCL2” OR “Bcl-2” OR “BCL2L1” OR “BCL2L2”) AND (“cervical cancer” OR “cervical neoplasia”) AND (“menopause” OR “postmenopause” OR “estrogen deficiency” OR “ovariectomy”) AND (“inflammation” OR “inflammatory” OR “cytokine” OR “NF-κB” OR “COX-2” OR “apoptosis”). The search was

limited to studies published between 2015 and 2025 to capture recent evidence. Only articles published in English and available in full-text format were included.

Eligibility Criteria

Studies were included if they met the following criteria: (i) original research articles (randomized controlled trials, observational studies, or preclinical animal experiments); (ii) populations involving women with cervical cancer or animal models simulating menopausal conditions; (iii) studies examining hormonal status (e.g., menopause, estrogen deficiency) and/or inflammatory pathways; and (iv) studies reporting outcomes related to Bcl2-mediated apoptosis, including Bcl2 expression, BAX, caspase-3, or related molecular markers. Studies were excluded if they were: (i) review articles, editorials, or conference abstracts; (ii) not relevant to hormonal or inflammatory mechanisms; (iii) lacking apoptosis-related outcomes; or (iv) not accessible in full text.

Study Selection Process

Study selection was conducted in two stages. First, titles and abstracts were screened to remove irrelevant studies. Second, full-text articles were assessed for eligibility based on predefined criteria. Two independent reviewers conducted the screening. Discrepancies between reviewers were resolved through discussion and consensus. When necessary, a third reviewer was consulted to ensure objectivity and minimize selection bias.

Data Extraction

Data were extracted using a standardized and pre-piloted extraction form. The extracted variables included author, year of publication, study design, sample size, study population, menopausal context, intervention and comparator (if applicable), outcome measures, and key findings related to hormonal regulation, inflammation, and apoptosis. To ensure consistency and accuracy, data extraction was performed independently by two reviewers and subsequently cross-checked.

Quality Assessment

The methodological quality of the included studies was assessed using validated tools appropriate to the study designs. The Cochrane Risk of Bias 2 (RoB 2) tool was used for randomized controlled trials, while the SYRCLE Risk of Bias tool was applied to animal studies. Each study was evaluated across relevant domains of bias, and judgments were categorized as low risk, some concerns, or high risk. This process ensured critical appraisal of internal validity and strengthened the reliability of the synthesized evidence.

Data Synthesis

Due to heterogeneity in study designs, interventions, and outcome measures, a meta-analysis was not feasible. Therefore, findings were synthesized using a narrative approach. Data synthesis was conducted by grouping studies into thematic domains: hormonal regulation, inflammatory signaling pathways, and Bcl2-mediated apoptosis. Comparative interpretation was used to identify patterns, consistencies, and discrepancies across studies, enabling an integrated understanding of the underlying mechanisms.

Ethical Considerations

Ethical approval was not required for this study because it was based exclusively on secondary data obtained from previously published studies. No direct involvement of human or animal subjects occurred; therefore, informed consent was not applicable.

RESULT

The study selection process yielded a total of 607 records identified from database searches. After removing duplicates and screening titles and abstracts, a subset of articles was assessed for full-text eligibility. Ultimately, six studies met the predefined inclusion criteria and were included in this systematic review. The included studies comprised two human clinical studies and four preclinical animal studies, reflecting both contextual and mechanistic perspectives. The results are presented according to key thematic domains, including hormonal status, inflammatory signaling, and Bcl2-mediated apoptotic pathways in cervical cancer.

A total of 607 article records were identified from two major databases based on the predefined search strategy. The records were obtained from PubMed (n = 343) and ScienceDirect (n = 264). After removing 160 duplicate records, 447 studies remained and were screened based on titles and abstracts. Of these, 375 articles were excluded, consisting of review articles (n = 281) and studies that were not relevant to the research question (n = 94). A total of 72 articles were assessed for full-text eligibility; 13 were not retrieved. Subsequently, 59 full-text articles were reviewed in detail. Based on the eligibility assessment, 53 studies were excluded due to inappropriate population (n = 16), intervention (n = 11), outcome (n = 14), or study design (n = 12). After the final screening process, six studies met the inclusion criteria and were included in the systematic review. The overall study selection process and reasons for exclusion at each stage are summarized in Figure 1.

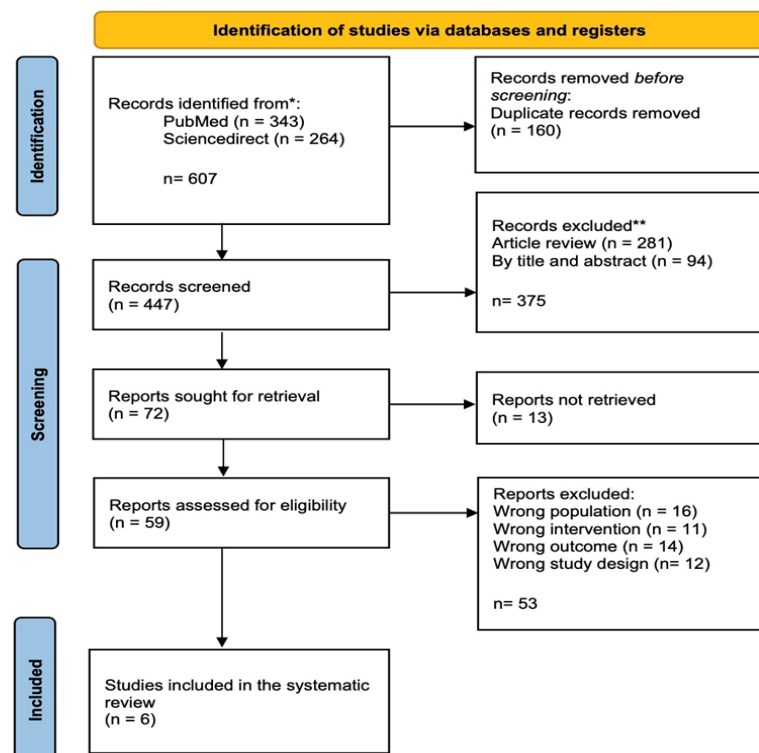


Figure 1. PRISMA flow diagram

No	Author (Year)	Study Design	Population / Model	Menopausal Context	Intervention / Exposure	Comparator	Outcomes Measured	Key Findings	Study Type
1	Irmawati S et al., (2025)	Randomized Controlled Trial	230 postmenopausal women (50–69 years)	Natural menopause	Dietary intervention ± physical activity	Usual lifestyle	IL-1α, IL-6, CRP	Increased inflammatory markers in postmenopausal women	Human
2	Jomova et al., (2025)	Secondary analysis of RCT	1,977 postmenopausal women (≥55 years)	Postmenopause	Dietary inflammatory index changes	Less inflammatory diet	Cancer incidence risk	A pro-inflammatory diet is associated with increased cancer risk	Human
3	Kotia et al., (2026)	Experimental animal study	Ovariectomized (OVX) rat, cervical cancer model	OVX-induced menopause	Phytoestrogen-based compound	Untreated OVX	Bcl-2, Bax	Bcl-2 ↓, Bax ↑ → increased apoptosis	Animal
4	D. Kumar & Sharma, (2024)	Experimental animal study	OVX rat (non-tumor model)	OVX-induced menopause	Resistance training ± vitamin D/Ca nanoparticles	Control OVX	BCL-2, BAX, Caspase-3	BCL-2 ↑, BAX ↓, Caspase-3 ↓ (reversal effect)	Animal
5	G. Kumar et al., (2024)	Experimental animal study	Mouse xenograft cervical cancer	No OVX	Natural compound	Control group	Bcl-2, apoptosis markers	Bcl-2 ↓, apoptosis ↑	Animal
6	Li et al., (2024)	Experimental animal study	C57BL/6 mice (TC-1 cervical cancer)	Non-OVX	Clostridium novyi-NT ± cisplatin	Control group	Bcl-2, Bax, Caspase-3	Bcl-2 ↓, Bax ↑, Caspase-3 ↑ → mitochondrial apoptosis	Animal

Risk of Bias
Human studies

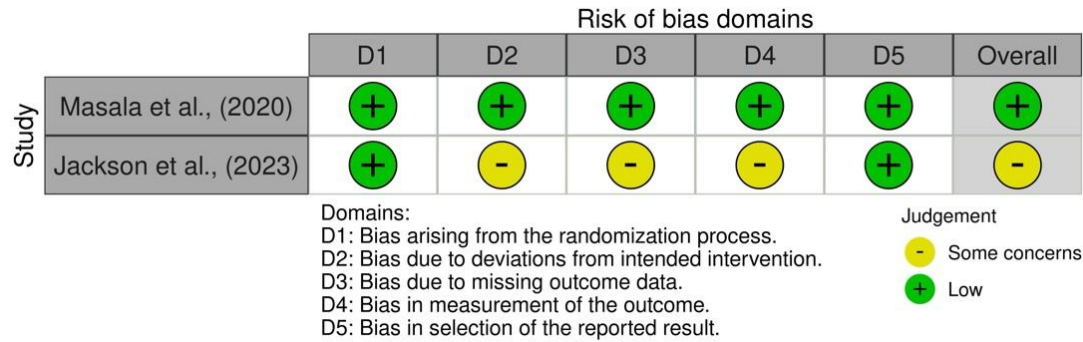


Figure 2. Risk of bias in traffic-light human studies

Figure 2 presents the traffic-light plot of risk of bias assessment for the included randomized controlled trials using the Cochrane RoB 2 tool. Overall, the methodological quality of the human studies was acceptable. One trial, Masala et al. (1), was judged to have a low risk of bias across all domains, reflecting robust randomization procedures, minimal missing outcome data, objective outcome measurements, and prespecified reporting of results. In contrast, Jackson et al (8) were rated as having some concerns, primarily due to potential deviations from intended interventions, missing outcome data, and outcome measurement bias related to self-reported dietary exposure in a secondary analysis context. Importantly, no study was judged to be at high risk of bias in any domain. These findings indicate that the human evidence included in this review is generally reliable, while acknowledging methodological limitations inherent to long-term lifestyle intervention studies.

Animal studies

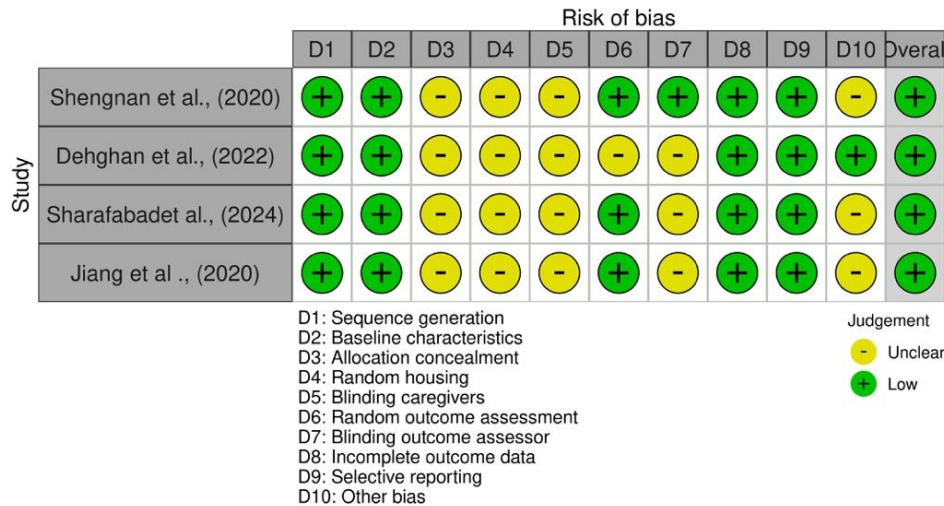


Figure 3. Risk of bias in traffic-light animal studies

Figure 3 shows the traffic-light plot of the risk of bias assessment for the included animal studies evaluated using the SYRCLE Risk of Bias tool. The studies conducted by Shengnan et al. (9), Dehghan et al. (10), Sharafabad et al. (11), and Jiang et al. (2) demonstrated a predominantly low risk of bias across most domains, particularly in sequence generation, baseline characteristics, random outcome assessment, completeness of outcome data, and selective outcome reporting. Several domains, including allocation concealment, randomization, blinding of caregivers, blinding of outcome assessors, and other sources of bias, were judged unclear, primarily due to insufficient reporting in the original articles rather than evidence of systematic methodological

flaws. Importantly, none of the included animal studies were assessed as having a high risk of bias in any domain, supporting the overall methodological acceptability of the preclinical evidence included in this review.

Molecular parameters

Across the included animal studies, a consistent molecular pattern was observed linking menopausal hormonal deprivation and experimental interventions to activation of intrinsic apoptotic pathways in cervical cancer models. All four studies demonstrated downregulation of the anti-apoptotic protein Bcl2, accompanied by upregulation of the pro-apoptotic protein BAX, resulting in an increased BAX/Bcl2 ratio, a key indicator of mitochondrial apoptosis. These upstream mitochondrial changes were further supported by increased caspase-3 activation, confirming progression to the execution phase of apoptosis. Notably, studies using ovariectomized (OVX) models showed that menopause-like hormonal deprivation enhanced susceptibility to apoptosis, suggesting that reduced estrogen signaling may sensitize cervical tumor cells to Bcl-2-mediated apoptosis. In parallel, modulation of inflammation-related signaling pathways was reported, indicating that hormonal and inflammatory alterations jointly contribute to suppression of pro-survival signaling. Collectively, these molecular findings support a mechanistic framework in which menopausal hormonal deprivation facilitates cervical cancer cell apoptosis through coordinated downregulation of Bcl2-dependent survival pathways and activation of mitochondrial apoptotic signaling.

This systematic review synthesizes preclinical evidence from four animal studies examining the molecular effects of hormonal and experimental modulation on cervical cancer. Across studies, a consistent pattern emerged showing suppression of anti-apoptotic signaling, characterized by downregulation of Bcl2, alongside upregulation of pro-apoptotic markers, including BAX and an increased BAX/Bcl2 ratio. These upstream mitochondrial alterations were accompanied by increased caspase-3 activation, indicating progression to the execution phase of apoptosis. Studies employing ovariectomized (OVX) models further demonstrated that menopause-like hormonal deprivation increased apoptotic susceptibility, suggesting a modulatory role of hormonal status in Bcl2 survival pathways. Collectively, the findings indicate that hormonal and related molecular modulation converges on the mitochondrial apoptotic pathway, providing coherent mechanistic evidence that reduced Bcl2-dependent survival signaling facilitates apoptosis in cervical cancer models.

DISCUSSION

This systematic review provides an integrated perspective on how menopause-related hormonal decline interacts with inflammatory signaling to influence Bcl2-mediated apoptosis in cervical cancer. Across the included studies, a consistent pattern emerges in which estrogen deficiency is associated with suppression of anti-apoptotic Bcl2 expression and activation of mitochondrial apoptotic pathways, reflected by increased levels of pro-apoptotic markers such as BAX and caspase-3. These findings were particularly evident in preclinical models, where hormonal manipulation could be directly controlled. Taken together, the evidence supports a biologically plausible pathway in which hormonal changes are not merely background characteristics, but active modulators of tumor cell survival and death.

This relationship can be understood within a broader conceptual framework that links hormonal decline, inflammatory activation, and regulation of apoptosis (Liu et al., 2025). Estrogen withdrawal during menopause appears to shift the systemic environment toward a pro-inflammatory state, mediated by signaling pathways such as NF- κ B, PI3K/AKT, and MAPK.

These pathways are known to influence the balance between pro-survival and pro-apoptotic signals, particularly by regulating Bcl-2 family proteins (Pandita et al., 2025). As this balance shifts, cells may become more susceptible to apoptosis, especially under conditions of hormonal deprivation. This interpretation suggests that menopausal status plays a dynamic biological role in shaping tumor behavior rather than acting as a passive demographic variable (Reddy et al., 2025).

At the same time, the findings highlight the complex and sometimes paradoxical role of estrogen in cancer biology. While estrogen is commonly associated with proliferative effects, it also exerts anti-inflammatory and cytoprotective functions that may support cell survival through Bcl2-dependent mechanisms (Reiter et al., 2024). In this context, estrogen deficiency may remove these protective signals, thereby increasing apoptotic susceptibility. This dual role underscores the importance of considering hormonal effects within specific biological and pathological contexts, rather than applying generalized assumptions about their function (Suprpto, 2026).

Compared with the existing literature, this review's findings align with well-established evidence that dysregulation of apoptosis is a hallmark of cancer progression (Tang et al., 2025). Prior studies have consistently shown that Bcl2 overexpression contributes to resistance to programmed cell death and is associated with poor clinical outcomes (Tanim et al., 2024). The present review extends this understanding by situating Bcl2 regulation within the context of menopausal hormonal changes and inflammation, thereby offering a more integrated explanation of how systemic biological processes may influence tumor dynamics (Yadav et al., 2024).

In addition, epidemiological research has suggested that earlier menopause is associated with increased risk of gynecologic cancers. The findings synthesized in this review provide a potential mechanistic basis for this association, suggesting that prolonged estrogen deficiency may alter inflammatory and apoptotic pathways, thereby influencing cancer susceptibility and progression. Similarly, experimental studies demonstrating increased BAX and caspase-3 expression under estrogen-deprived conditions are consistent with broader evidence on mitochondrial apoptosis activation in response to cellular stress. By bringing together these strands of evidence, the review contributes to a more cohesive understanding of the interplay between hormonal aging and cancer biology.

Despite these consistencies, differences between preclinical and clinical findings should be interpreted carefully. Animal studies provide controlled environments that allow direct observation of molecular mechanisms, whereas human studies are inherently more complex and often rely on indirect measures such as inflammatory biomarkers. As a result, clinical evidence remains less definitive, and translating mechanistic insights into real-world contexts requires cautious interpretation. Factors such as immune status, comorbid conditions, lifestyle, and viral oncogenesis may further modify these relationships in human populations.

Several limitations of this review should be acknowledged. The number of included studies, particularly those involving human participants, was relatively limited, which may restrict the generalizability of the findings. In addition, substantial heterogeneity in study design, populations, and outcome measures prevented quantitative synthesis and necessitated a narrative approach. While this allowed for thematic integration, it may introduce a degree of interpretive subjectivity.

Another important consideration is the reliance on preclinical models to derive mechanistic insights. Although these models are valuable for understanding biological processes, they may not fully capture the complexity of human disease, particularly in hormonal regulation and immune interactions. Furthermore, most human studies did not directly assess Bcl2 expression in

cervical tissue, instead relying on surrogate indicators. This limits the ability to draw firm conclusions regarding the clinical relevance of the proposed mechanisms. Potential publication and language biases should also be considered, as only English-language studies published in peer-reviewed journals were included. Variability in reporting quality across studies may have further influenced the assessment of methodological rigor. These factors highlight the need for cautious interpretation and reinforce the importance of further research.

Recommendations for Future Research

Looking ahead, future studies should aim to bridge the gap between mechanistic and clinical evidence. There is a clear need for well-designed translational research that directly examines the relationship between menopausal status, inflammatory pathways, and Bcl2-mediated apoptosis in cervical cancer. Integrating molecular biomarkers, hormonal profiling, and clinical outcomes within a single analytical framework would yield more robust, clinically relevant insights. Advances in high-throughput technologies, including transcriptomics and proteomics, offer promising opportunities to explore these interactions in greater depth. Such approaches could help elucidate how hormonal and inflammatory signals converge at the molecular level to regulate apoptosis. In parallel, clinical studies should consider broader systemic factors, including metabolic health, lifestyle, and healthcare access, which may influence both hormonal status and cancer outcomes. From a therapeutic perspective, the findings suggest potential value in targeting the hormone inflammation apoptosis axis. Modulation of inflammatory signaling or Bcl2-related pathways may enhance treatment responsiveness, particularly in postmenopausal populations. However, these possibilities remain speculative and require rigorous clinical validation.

CONCLUSION

This systematic review demonstrates that menopause-related hormonal decline and inflammatory modulation play a significant role in the regulation of Bcl2-mediated apoptosis in cervical cancer. The evidence consistently indicates that estrogen deficiency is associated with suppression of anti-apoptotic Bcl2 expression and activation of mitochondrial apoptotic pathways, as reflected by increased expression of pro-apoptotic markers such as BAX and caspase-3. While preclinical studies strongly support these mechanistic relationships, human evidence remains indirect and largely contextual, highlighting a gap between biological plausibility and clinical validation. These findings directly address the objective of this review by confirming that hormonal and inflammatory changes during menopause contribute to altered apoptotic regulation in cervical cancer. The integration of evidence suggests that menopause should be considered a biologically relevant factor in cancer progression, rather than merely a demographic characteristic.

From a policy and clinical perspective, the results support the need for integrating hormonal and inflammatory assessments into cervical cancer risk stratification and management, particularly among postmenopausal women. Future interventions should explore targeted modulation of inflammatory pathways and Bcl2-related signaling as potential therapeutic strategies. In addition, strengthening translational research that links molecular biomarkers to clinical outcomes is essential to inform evidence-based interventions and improve patient care.

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Conflict of Interest

The authors declare that there are no conflicts of interest related to this study.

Authors' Contributions (CRediT Taxonomy)

Amanda Fransisca Rhevytasari: Conceptualization, Methodology, Data Curation, Formal Analysis, Writing – Original Draft.

Arini Widya Risanti: Supervision, Validation, Writing – Review & Editing.

Tatit Nurseta: Conceptualization, Methodology, Supervision, Writing – Review & Editing.

Safrina Dewi Ratnaningrum: Data Curation, Investigation, Writing – Review & Editing.

Sutrisno: Validation, Resources, Writing – Review & Editing.

Agustina Tri Endarti: Formal Analysis, Visualization, Writing – Review & Editing.

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Declaration of Generative AI Use

Generative artificial intelligence tools were used to support language refinement and improve clarity of expression during manuscript preparation. All conceptual development, data analysis, interpretation of findings, and final content decisions were performed by the author. The author takes full responsibility for the accuracy and integrity of the work.

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