E-ISSN: 3062-3731

# SABUNCUOGLU SEREFEDDIN HEALTH SCIENCES

2026 | Volume 8 | Issue 1

AMASYA UNIVERSITY

Sabuncuoglu Serefeddin Health Sciences

Open Access

e-ISSN: 3062-3731 2026, 8(1) 1-67

**e-ISSN**
3062-3731

**Volume**
8

**Issue**
1

**Publication Date**
29/04/2026

**Publication Language**
English

**Publication Period**
Three issues per year
(April & August & December)

**Scope**
Health Research

**PUBLICATION MANAGEMENT PLACE**
Amasya University, Sabuncuoğlu Şerefeddin Health Services Vocational School
Amasya/Türkiye

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Sabuncuoglu Serefeddin Health Sciences

Open Access

e-ISSN: 3062-3731 2026, 8(1) 1-67

Sabuncuoglu Serefeddin Health Sciences

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e-ISSN: 3062-3731 2026, 8(1) 1-67

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Sabuncuoglu Serefeddin Health Sciences

Open Access

e-ISSN: 3062-3731 2026, 8(1) 1-67

Sabuncuoglu Serefeddin Health Sciences

Open Access

e-ISSN: 3062-3731 2026, 8(1) 1-67


Sabuncuoğlu Serefeddin Health Sciences
Volume 8 / Issue: 1 (April 29, 2026)

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Sabuncuoglu Serefeddin Health Sciences

Open Access

e-ISSN: 3062-3731 2026, 8(1), 1-6 https://doi.org/10.55895/sshs.1747653

# NETWORK-BASED ANALYSIS OF PROTAC COMPOUNDS TARGETING CDK4/6 IN BREAST CANCER: IDENTIFICATION OF GENE INTERACTIONS AND THERAPEUTIC INSIGHTS

# (MEME KANSERİNDE CDK4/6'YI HEDEFLEYEN PROTAC BİLEŞENLERİNİN AĞ TABANLI ANALİZİ: GEN ETKİLEŞİMLERİNİN BELİRLENMESİ VE TERAPÖTİK ÖNGÖRÜLER)

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**Research Article**
**Received:** 21.07.2025, **Accepted:** 23.01.2026
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**Abstract**
Cancer is a major disease characterized by rapid and uncontrolled cell growth and proliferation, affecting a large population worldwide. A significant portion of cancer research today involves network analysis. In this study, the gene targets of 8-Cyclopentyl-2-(4-piperazin-1-ylanilino) pteridin-7-one (CPPP-7-one) and the PROTAC CDK4/6 degrader (PROTAC-CDK4/6i) were identified, and their shared targets with breast cancer-related genes were examined. Additionally, protein-protein interactions (PPI) involving the gene targets of these compounds were mapped. The analysis revealed that CDK4 is a common gene target between breast cancer and the CPPP-7-one compound. In contrast, GRM2, the sole gene target of the PROTAC CDK4/6 degrader, did not overlap with any breast cancer-related genes. These findings suggest that CPPP-7-one may play a significant role in cyclin and cyclin-dependent kinase activities, particularly in regulating cell cycle checkpoints, and therefore warrants further investigation. Furthermore, the isolated nature of PROTAC CDK4/6i's target from core cell cycle proteins indicates that it may influence distinct intracellular mechanisms.

**Keywords:** Breast Cancer, CDK, PPI network analysis, PROTAC

**Öz**
Kanser hızlı ve kontrolsüz hücre büyümesi ve çoğalması olarak tanımlanan ve çok geniş kitleleri etkileyen önemli bir hastalıktır. Kanser üzerinde yapılan araştırmaların önemli bir bölümünü network analizleri oluşturmaktadır. Yapılan bu çalışmada 8-Cyclopentyl-2-(4-piperazin-1-ylanilino) pteridin-7-one (CPPP-7-one) ve PROTAC CDK4/6 degrader (PROTAC-CDK4/6i) bileşenlerinin gen hedefleri bulunmuş, meme kanseri hedefleri ile ortak genleri tespit edilmiştir. Ayrıca bileşenlerin gen hedeflerini protein-protein (PPI) etkileşimleri bulunmuştur. Yapılan bu analizlerin sonucunda meme kanseri ile CPPP-7-one bileşiğinin CDK4 geni ortak olarak bulunmuştur. PROTAC CDK4/6 degrader bileşiğinin GRM2 gen tek gen hedefi meme kanseri ile ortak gen içermemektedir. Sonuç olarak CPPP-7-one bileşiğinin özellikle siklinler ve siklin bağımlı kinaz aktivitelerinde etkili olduğu, hücre döngüsü kontrol noktalarını etkilediği için daha geniş çapta araştırılmasına ihityaç vardır. PROTAC CDK4/6 degrader bileşiğinin de hücre döngüsü proteinlerinden izole olması hücre içinde daha farklı mekanizmaları etkilediğini göstermektedir.

**Anahtar Kelimeler:** Meme kanseri, CDK, PPI network analizleri, PROTAC

## 1. Introduction

Cancer represents a complex group of diseases marked by the uncontrolled growth and proliferation of abnormal cells. Globally, it stands as the second leading cause of death, with nearly 20 million new cases and around 10 million deaths reported in 2020 alone (Sung et al., 2021; Wu et al., 2024).

In this context, network analyses have recently become frequently utilized methods for making sense of the complex interactions in cancer biology and for deriving useful insights prior to clinical applications. Today, genomic data is being interpreted not only through individual mutations

but also through the interaction networks formed by these mutations. (Oztürk et al., 2018). For instance, protein-protein interaction (PPI) analyses have been employed to identify subnetworks and functional targets in glioblastoma multiforme (GBM), as well as in breast, colon, rectal, and ovarian cancers. (Zhang et al., 2016; Das et al., 2015; Patel et al., 2013). Moreover, these analyses have been utilized to identify gene targets of miRNAs and to elucidate the survival mechanisms of glioblastoma multiforme (GBM) and ovarian cancer. (Zhang et al., 2016; Joung et al., 2014). Network-based approaches are more powerful than other methods in identifying tumor-specific molecular mechanisms, therapeutic targets, and drugs tailored for personalized treatments. (Zhang et al., 2022; Zhang et al., 2017). Therefore, it can be said that network analyses have increasingly become a central approach in understanding cancer biology and developing personalized therapies.

PROTACs (PROteolysis TArgeting Chimeras) are a prominent class of chemical compounds that induce the selective degradation of target proteins by harnessing the ubiquitin-proteasome system. Compared to traditional protein inhibitors, PROTAC-based drugs offer several advantages and are considered significant in the discovery of anticancer therapeutics. Notably, over the past two decades, numerous PROTAC molecules have been developed for cancer research and have undergone clinical evaluation. (Li et al., 2022).

PROTACs operate as heterobifunctional molecules comprising three essential components: a ligand that binds the target protein (substrate), a ligand that recruits an E3 ubiquitin ligase, and a chemical linker that connects these two entities. By concurrently engaging the target protein and the E3 ligase, PROTACs facilitate the formation of a ternary complex (E3 ligase–PROTAC–target protein), which promotes the ubiquitination of the target protein. The polyubiquitinated protein is then recognized and degraded by the 26S proteasome, resulting in the efficient and selective elimination of the target protein rather than merely inhibiting its activity. This event-driven pharmacological mechanism enables catalytic protein degradation, sustained target suppression, and the capacity to circumvent resistance mechanisms associated with traditional occupancy-driven inhibitors (Sakamoto et al., 2001; Bondeson et al., 2015; Burslem and Crews, 2020).

In this context, the molecule 8-Cyclopentyl-2-(4-piperazin-1-ylanilino) pteridin-7-one and the PROTAC CDK4/6 degrader were subjected to network analysis, and their network associations across various cancer types were identified. Discovering the network connections of a molecule frequently used in cancer research across different cancer types can provide valuable insights for future cancer studies.

## 2. Materials and Methods

The two- and three-dimensional structures of 8-Cyclopentyl-2-(4-piperazin-1-ylanilino) pteridin-7-one and the PROTAC CDK4/6 degrader were obtained from the online data repository PubChem (https://pubchem.ncbi.nlm.nih.gov/). (Kim et al., 2025; Bolton et al., 2011). The target genes of 8-Cyclopentyl-2-(4-piperazin-1-ylanilino) pteridin-7-one and the PROTAC CDK4/6 degrader were predicted using the Swiss Target Prediction online tool (http://www.swisstargetprediction.ch/). (Daina, A., & Zoete, 2024; Gfeller et al.,2013). During the identification of SwissTarget-predicted gene targets for 8-Cyclopentyl-2-(4-piperazin-1-ylanilino) pteridin-7-one and the PROTAC CDK4/6 degrader, only genes with an interaction probability greater than zero were included. Genes associated with breast cancer were selected from the GeneCards online database (https://www.genecards.org/) (Stelzer et al., 2016; Safran et al., 2021), with only those having a relevance score of 70 or higher being included. Gene interaction networks were constructed using Cytoscape software. (Shannon et al.,2003; Ono et al.,2025). Protein-protein interactions (PPI) were identified using the STRING 12.0 database (https://string-db.org/). (Szklarczyk et al.,2023) Protein–protein interaction (PPI) analysis was conducted utilizing the STRING database, employing a high-confidence interaction score cutoff of 0.7 to guarantee dependable protein interaction networks. Target proteins linked to CPPP-7-one and PROTAC-CDK4/6i were obtained from publically accessible databases and pertinent literature. Genes associated with breast cancer were aggregated from disease-related gene databases. The intersection between compound-associated targets and breast cancer-related genes was illustrated using Venny 2.1. Fisher's exact test was employed to statistically evaluate whether the observed overlaps surpassed random expectation. Statistical significance was established at $p < 0.05$. Due to the exploration nature of the investigation and the restricted amount of compound-specific target sets, the Venn diagram was utilized mainly to offer a qualitative summary of shared and distinct targets, whereas subsequent analyses concentrated on functional and network-based interpretations. The overlapping genes between 8-Cyclopentyl-2-(4-piperazin-1-ylanilino) pteridin-7-one, the PROTAC CDK4/6 degrader, and breast cancer-associated genes were analyzed using the Venny 2.1 online tool (https://bioinfogp.cnb.csic.es/tools/venny/) for

Venn diagram construction. (Oliveros, 2015). Gene enrichment analyses were performed using the Metascape (https://metascape.org/) and Enrichr (https://maayanlab.cloud/Enrichr/) online platforms. (Zhou et al., 2019). Data used for disease associations were obtained from the DisGeNET database (https://disgenet.com/). (Piñero et al., 2017).

## 3. Results and Discussion

The schematic representation of the genes associated with breast cancer, 8-Cyclopentyl-2-(4-piperazin-1-ylanilino) pteridin-7-one, and the PROTAC CDK4/6 degrader is presented in Figure 1. As shown in the figure, CDK4 appears as the common gene between 8-Cyclopentyl-2-(4-piperazin-1-ylanilino) pteridin-7-one and breast cancer. In contrast, GRM2, the gene associated with the PROTAC CDK4/6 degrader, does not overlap with either 8-Cyclopentyl-2-(4-piperazin-1-ylanilino) pteridin-7-one or breast cancer.

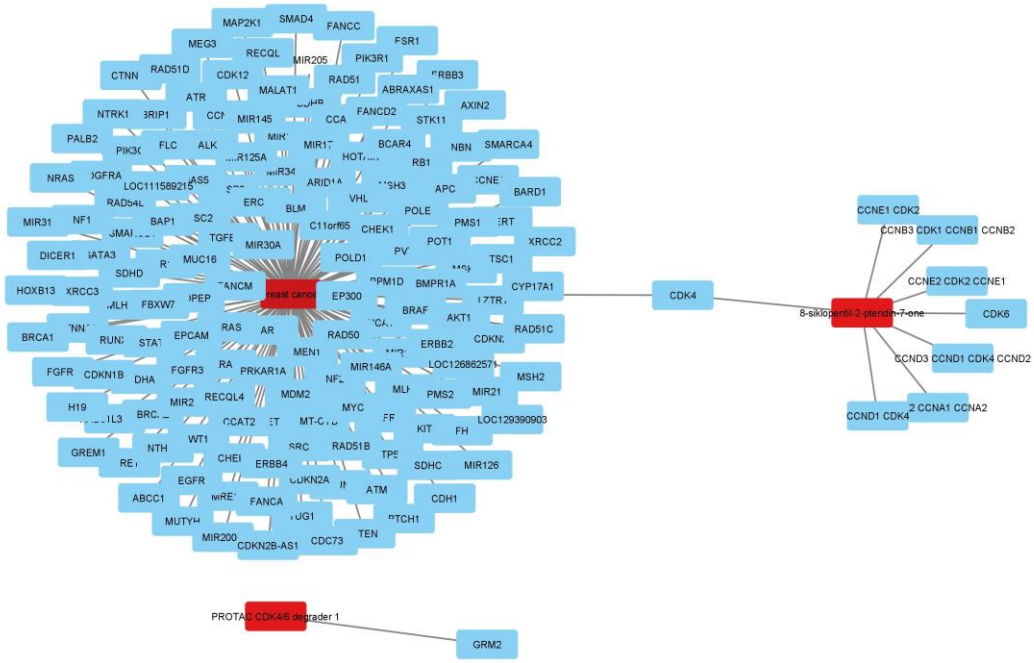


**Figure 1.** Integrated network of target genes related to 8-Cyclopentyl-2-(4-piperazin-1-ylanilino) pteridin-7-one, the PROTAC CDK4/6 degrader, and breast cancer. The network depicts interactions between the predicted gene targets of the compound, the PROTAC CDK4/6 degrader, and breast cancer–associated genes, as analyzed using Cytoscape. Red nodes indicate the compounds and breast cancer, whereas blue nodes represent associated genes.

According to the presented network diagram, the CDK4/6 genes appear to be important targets for both breast cancer and the CPPP-7-one compound. The fact that CPPP-7-one targets CDK1, CDK2, CDK4, and CDK6 suggests that it may serve as a potent CDK inhibitor. These findings support the inference that PROTAC compounds targeting CDK4/6 proteins may significantly reduce the progression of breast cancer. (Murphy, 2019). The success of CDK4/6-degrading compounds such as LPM3770277 in inhibiting tumor development highlights the significance of this study. (Qiu et al., 2022). Moreover, the cyclin D/cyclin-dependent kinase CDK4/6–retinoblastoma (Rb) protein pathway plays a critical role at cell cycle checkpoints that are frequently disrupted in cancer progression. Selective CDK4/6 inhibitors act during the G1 phase of the cell cycle by preventing the phosphorylation of the retinoblastoma protein, thereby offering an effective therapeutic strategy. (Hu et al., 2021). Therefore, further investigation of CDK4/6 inhibitors such as PROTAC-CDK4/6i is warranted. In particular, the identification of less well-characterized targets such as GRM2 holds promise for future biomarker discovery and target-based therapeutic approaches.

Figure 2 illustrates the protein–protein interactions among the target genes of 8-

Cyclopentyl-2-(4-piperazin-1-ylanilino) pteridin-7-one (CPPP-7-one) and the PROTAC-based CDK4/6 degrader (PROTAC-CDK4/6i) compounds. Notably, the CDK4 protein emerges as a shared node associated with breast cancer. An important observation is the lack of interaction between GRM2, the target protein of the PROTAC-based CDK4/6 degrader compound, and other proteins within the network, which may warrant further investigation. The PPI network presented in the figure clearly demonstrates the dense interactions between cyclins (CCND1, CCND2, CCND3) and cyclin-dependent kinases (CDKs). These proteins are known to play crucial roles in the G1/S and G2/M transitions of the cell cycle (Malumbres and Barbacid, 2009). The isolated positioning of the GRM2 protein from the core cell cycle proteins suggests that it may possess distinct functional roles.

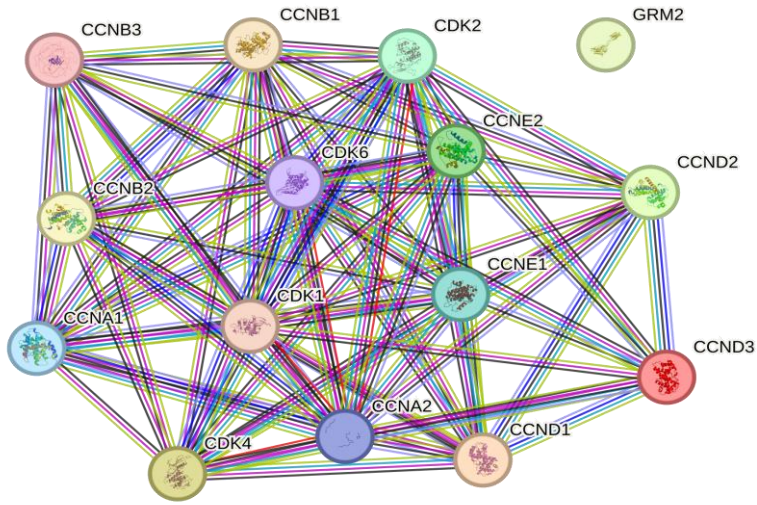


**Figure 2.** The diagram highlights shared molecular pathways targeted by 8-Cyclopentyl-2-(4-piperazin-1-ylanilino) pteridin-7-one and PROTAC-based CDK4/6 degraders. Notably, CDK4 emerges as a central cell cycle regulator influenced by these compounds and as a key biomarker in breast cancer. Overall, the presented gene interaction network offers insight into the potential therapeutic relevance of these agents in cancer biology.

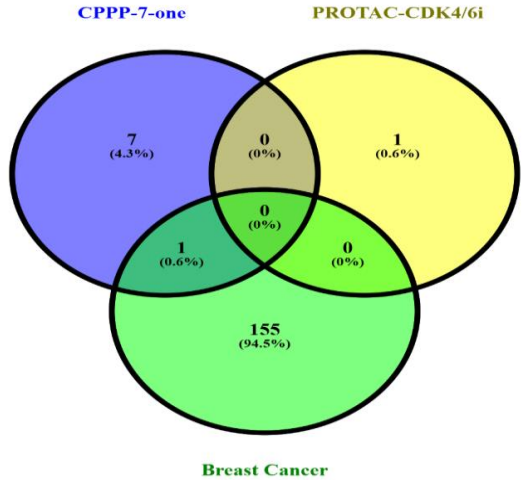


**Figure 3.** Shared genes among CPPP-7-one, PROTAC-CDK4/6i compounds, and breast cancer–associated genes. The Venn diagram displays gene sets corresponding to CPPP-7-one, PROTAC-CDK4/6i, and breast cancer. CDK4 is identified as a common gene between the CPPP-7-one and breast cancer groups, whereas no overlap is observed with the PROTAC-CDK4/6i set. In contrast, GRM2, a target of the PROTAC-CDK4/6i compound, shows no association with the other gene sets, indicating the need for further evaluation of its therapeutic significance.

The shared genes between the target genes of CPPP-7-one and PROTAC-CDK4/6i compounds and breast cancer-associated genes are presented in Figure 3. According to the presented diagram, while one shared gene was identified between breast cancer and the CPPP-7-one compound, no common gene was found with the PROTAC-CDK4/6i. This finding further supports the notion that these compounds warrant more extensive investigation, particularly in the context of cancer research.

The Venn diagram analysis indicated minimal intersection between compound-associated targets and genes connected to breast cancer. CPPP-7-one was linked to a limited number of targets, with one gene coinciding with the breast cancer gene set, but no overlapping targets were found for PROTAC-CDK4/6i. The bulk of genes associated with breast cancer were exclusive to the disease-specific dataset. Statistical analysis utilizing Fisher's exact test revealed no statistically significant enrichment of overlapping genes between CPPP-7-one–associated targets and breast cancer–related genes ($p > 0,05$). This result is likely due to the restricted size of the compound-specific target sets, which automatically diminishes statistical power. The lack of substantial enrichment does not diminish biological significance, as small-molecule and PROTAC-based approaches aim to influence cancer-related processes via unique and non-redundant molecular mechanisms. Consequently, later analyses concentrated on pathway-level and network-based methodologies to clarify the possible anticancer mechanisms of the examined drugs.

## 4. Conclusion

In this study, the target genes and protein-protein interactions of the CPPP-7-one and PROTAC-CDK4/6i compounds in breast cancer were identified. The involvement of the CPPP-7-one compound in cyclin-dependent kinase activities related to breast cancer presents promising implications for personalized therapies. Additionally, the intracellular functions and roles of GRM2—a target of PROTAC-CDK4/6i that appears isolated from core cell cycle proteins warrant further investigation, particularly in the context of different cancer types.

## Author Contributions

Idea and design: E.T., S.Y.,
Data collection and processing: E.T., S.Y.
Analysis and interpretation of data: E.T., S.Y.
Writing of significant part of the article: E.T., S.Y.

## Conflicts of interest

None.

## Funding Statement

No external funding was received for this research.

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Sabuncuoglu Serefeddin Health Sciences

Open Access

e-ISSN: 3062-3731 2026, 8(1), 7-15 https://doi.org/10.55895/sshs.1833375

# CLINICAL COURSE AND EPIDEMIOLOGY OF NON-MELANOMA SKIN CANCERS IN AMASYA: A 1.5-YEAR SINGLE PHYSICIAN EXPERIENCE

# AMASYA'DA NON-MELANOM DERİ KANSERLERİNİN KLİNİK SEYRİ VE EPİDEMİYOLOJİSİ:1.5 YILLIK TEK HEKİM DENEYİMİ

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**Research Article**
**Received:** 12.12. 2025, **Accepted:** 09.01.2026
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**Abstract**
Non-melanoma skin cancers (NMSC) are malignancies that are common especially in the elderly population and are closely associated with sun exposure, and they represent an important public health problem with an increasing incidence in our country. This retrospective study aimed to evaluate the demographic and clinical characteristics of NMSC cases diagnosed in the region and to compare the findings with the literature. The clinical data from 70 patients diagnosed with NMSC in the Dermatology outpatient clinic between March 2024 and November 2025 were reviewed. Age, sex, tumor type, lesion localization and number, clinical subtype, lesion development duration, history of previous skin cancer, and immunosuppression status were evaluated. Of the 70 patients, 49 (70%) were diagnosed with basal cell carcinoma, 19 (27.1%) with squamous cell carcinoma, and 2 (2.9%) with basosquamous carcinoma. The mean age of the patients was 72.8 years, and cases were most frequently observed in the 70–79 age group with male predominance. Most of the lesions were in the head and neck region, and the most frequent site was the face, particularly the nose. The most common clinical subtype was the nodulo-ulcerative form in basal cell carcinoma, whereas hyperkeratotic and eroded/ulcerative nodular subtypes were predominant in squamous cell carcinoma. The mean lesion development duration was 9 months, and the median was 6 months. Immunosuppression was detected in only 2 patients. This study is the first to present epidemiological data on NMSC in the Amasya region, and the findings are consistent with the literature.

**Keywords**: Basal cell carcinoma, Basosquamous carcinoma, Epidemiology, Non-melanoma skin cancers, Squamous cell carcinoma

**Öz**
Non-melanom deri kanserleri (NMDK), özellikle ileri yaş grubunda sık görülen ve güneş maruziyetiyle yakından ilişkili maligniteler olup ülkemizde insidansı giderek artan önemli bir halk sağlığı sorunu olarak kabul edilmektedir.Bu retrospektif çalışma ile bölgede tanı alan NMDK olgularının demografik ve klinik özelliklerinin değerlendirilmesi, elde edilen bulguların ulusal ve uluslararası literatürle karşılaştırılması ve böylece bölgeye özgü epidemiyolojik özelliklerin ortaya konması amaçlanmıştır. Hastanemiz Dermatoloji polikliniğine Mart 2024–Kasım 2025 tarihleri arasında NMDK tanısı alan 70 hastanın geriye dönük klinik verileri incelenmiştir. Hastaların yaş, cinsiyet, tümör tipi, lezyon lokalizasyonu ve sayısı, klinik alt tip ve hasta beyanına göre lezyonun gelişim süresi, önceki deri kanseri öyküsü ve immünsüpresyon durumu değerlendirilmiştir. Çalışmaya dâhil edilen 70 hastanın 49'u (%70) bazal hücreli karsinom (BCC), 19'u (%27,1) skuamöz hücreli karsinom (SCC) ve 2'si (%2,9) bazoskuamöz karsinom olarak sınıflandırılmıştır. Hastaların yaş ortalaması 72,8 olup olguların en sık 70–79 yaş aralığında yoğunlaştığı görülmüştür. Cinsiyet dağılımı incelendiğinde erkek cinsiyetin baskın olduğu saptanmıştır. Lezyonların %82,8'inin baş-boyun bölgesinde yerleşim göstermesi dikkat çekici olup, en sık tutulum alanı yüzde (%61,4) ve özellikle burun bölgesinde yoğunlaşmıştır. BCC olgularında en yaygın klinik alt tip nodülo-ülseratif form iken, SCC olgularında hiperkeratotik ve erode/ülseratif

nodüler alt tiplerin ön planda olduğu belirlenmiştir. Hasta beyanına göre lezyon gelişim süresi 1–48 ay arasında değişmekte olup ortalama 9 ay, medyan 6 ay olarak hesaplanmıştır. Ayrıca çalışma popülasyonunda sadece 2 hastada immünsüpresyon varlığı tespit edilmiştir. Bu çalışma, Amasya bölgesinde melanom dışı deri kanserlerine ilişkin epidemiyolojik verileri ortaya koyan ilk araştırmadır ve elde edilen bulgular hem ulusal hem de uluslararası literatürle genel olarak uyumludur.

**Anahtar Kelimeler:** Bazal hücreli karsinom, Bazoskuamöz karsinom, Epidemiyoloji, Non-melanom deri kanseri, Skuamöz hücreli karsinom

## 1. Introduction

Non-melanoma skin cancers are keratinocyte-derived malignant tumors that are the most common malignancies among Caucasians and whose incidence is progressively increasing worldwide (Lomas et al., 2012; Rogers et al., 2015). Non-melanoma skin cancers mainly consist of basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), and the most common type of skin cancer is BCC, which accounts for approximately 80% of all non-melanoma skin cancer cases (Gandhi & Kampp, 2015). Ultraviolet radiation is the primary risk factor for non-melanoma skin cancers through mutations that cause direct DNA damage; intermittent intense sun exposure associated with sunburn is particularly related to the development of BCC, whereas cumulative exposure is associated with the development of both BCC and SCC (Mona & Kurban, 2004; Harrison & Bergfeld, 2009). In addition, age, skin type (particularly Fitzpatrick type I–II), genetic diseases (such as albinism, Gorlin syndrome, xeroderma pigmentosum, etc.), environmental factors (such as construction work, agricultural work, etc.), immunosuppression, medications, chronic inflammation and irritation, premalignant skin lesions, and ionizing radiation constitute other risk factors (Baş et al., 2020; Slavinsky et al., 2024). While BCC is generally a tumor characterized by a slow growth pattern and local invasion, SCC may exhibit more aggressive behavior and demonstrate both local invasion and metastatic potential. The cancer-specific mortality rates for BCC and SCC are 1.15% and 2.17%, respectively, and they are cancers with relatively low mortality rates (Barton et al., 2017).

Since there are no previously published data on non-melanoma skin cancers in the Amasya region in the literature, this retrospective analysis aimed to contribute the clinical and epidemiological data of non-melanoma skin cancers in the region to the literature and to increase sun protection measures.

## 2. Material and Methods

### *2.1. Ethical Approval*

Prior to the initiation of the study, written approval was obtained from the Amasya University Non-Interventional Clinical Research Ethics Committee (Date: 12/12/2025, Decision No: 2025/231).

### *2.2. Study Design and Study Population*

This study was retrospective, observational, and cross-sectional in nature. Between 21 March 2024 and 15 November 2025, data were collected from patients aged over 18 years who were clinically and pathologically diagnosed with non-melanoma skin cancer (basal cell carcinoma, squamous cell carcinoma, or basosquamous carcinoma) and who presented to the Dermatology Outpatient Clinic, in accordance with the inclusion criteria.

Recorded variables included age, sex, date of admission, lesion type and clinical characteristics, number of lesions, lesion localization, mean lesion duration, presence of immunosuppression, and history of previous non-melanoma skin cancer.

### *2.3. Data Collection*

The patients were screened from patient records between 21.03.2024 and 15.11.2025 using the "International Classification of Diseases, 10th Revision (ICD-10)" diagnostic code 'C44.9'.

### *2.4. Statistical Analysis*

Statistical analysis was performed in a descriptive manner using SPSS version 26 and Microsoft Excel

## 3. Results

A total of 70 patients were included in the study. Of the patients, 60% were male (n = 42) and 40% were female (n = 28).

The ages of the 70 patients included in the study ranged from 43 to 93 years, and the mean age was calculated as approximately 72.8 ± 10.6 years. The most frequently recorded age among the cases was 85 years, representing 7.1% of the total sample. The vast majority of the participants consisted of individuals aged 60 years and older (88.6%).

Most of the patients were in the 70–79 age group, accounting for 34.3% of the total sample. This was followed by the 60–69 age group (27.1%) and the 80–89 age group (21.4%) (Table 1).

An evaluation of the distribution of non-melanoma skin cancer types among the 70 patients demonstrated that the majority of the cases were diagnosed with BCC (n = 49; 70.0%). The rate of SCC was 27.1% (n = 19), ranking second. A diagnosis of BSC was detected in only 2 patients (2.9%) (Figure 1).

**Table 1.** Age group distribution

| Age group (years) | n | % |
|---|---|---|
| 40–49 | 3 | 4.3 |
| 50–59 | 7 | 10.0 |
| 60–69 | 19 | 27.1 |
| 70–79 | 24 | 34.3 |
| 80–89 | 15 | 21.4 |
| ≥ 90 | 2 | 2.9 |

n: number of the patients

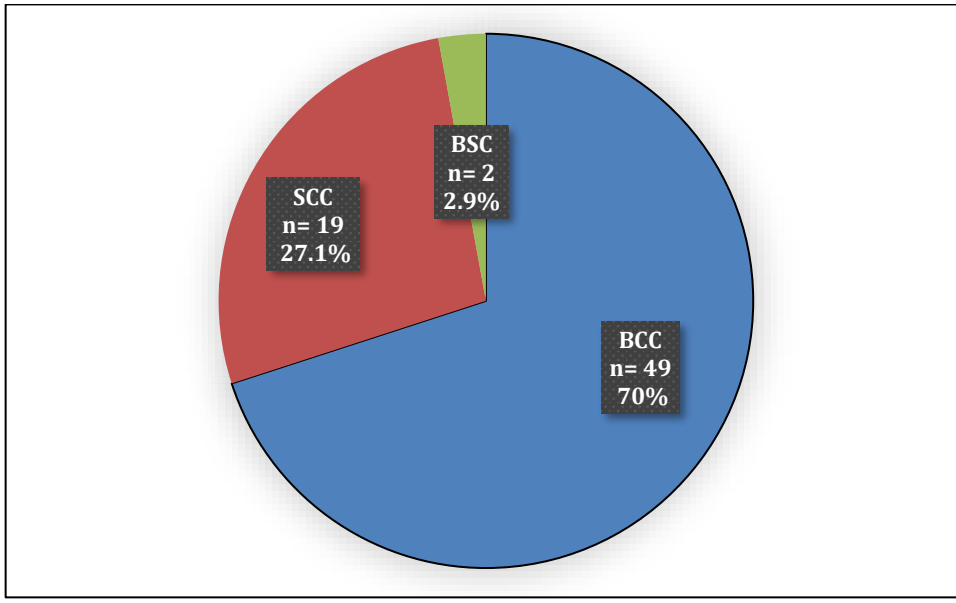


**Figure 1.** Tumor type distribution among the patients
*BCC: basal cell carcinoma; SCC: squamous cell carcinoma; BSC: basosquamous carcinoma; n: number of patients

Among the BCC cases, 53.1% were male (n = 26) and 46.9% were female (n = 23). Among the SCC cases, 84.2% of the patients were male (n = 16), whereas only 15.8% were female (n = 3). In addition, both BSC cases consisted of female patients (n = 2) (Table 2). The mean age of patients with BCC was 72.6 ± 12.1 years (43–93 years), whereas the mean age of patients with SCC was 69.3 ± 10.5 years (51–86 years). The ages of the two patients diagnosed with BSC were 85 and 93 years, and the mean age was calculated as 89 years.

The clinical subtypes of BCC were evaluated, and the most common form was determined to be the noduloulcerative type (n = 20; 28.6%). This was followed by the nodular type (n = 15; 21.4%) and the pigmented nodular type (n = 8; 11.4%). The pigmented noduloulcerative type (n = 3; 4.3%) and the superficial type (n = 3; 4.3%) were observed at lower rates (Table 3).

**Table 2.** Cancer type and gender

| Cancer type | Male | Female | Total |
|---|---|---|---|
| BCC | 26 | 23 | 49 |
| SCC | 16 | 3 | 19 |
| BSC | 0 | 2 | 2 |

*BCC: basal cell carcinoma, SCC: squamous cell carcinoma, BSC: basosquamous cell carcinoma

**Table 3.** BCC clinical subtypes

| Subtype | n | % |
|---|---|---|
| Noduloulcerative | 20 | 28.6 |
| Nodular | 15 | 21.4 |
| Pigmented nodular | 8 | 11.4 |
| Pigmented noduloulcerative | 3 | 4.3 |
| Superficial | 3 | 4.3 |

*n: number of the lesions, BCC: basal cell carcinoma

An evaluation of SCC cases showed that nodular types constituted the most common subtype group (n = 17; 89.5%). Plaque types were detected at lower rates (n = 2; 10.5%) (Table 4). In the subgroup analysis of nodular-type SCC cases, hyperkeratotic and eroded/ulcerative nodular subtypes were observed with equal frequency (each n = 7; 41.2%). The classic nodular type was observed less frequently (n = 3; 17.6%).

**Table 4.** SCC clinical subtypes

| Subtype | n | % |
|---|---|---|
| Nodular | 17 | 89.5 |
| Plaque | 2 | 10.5 |

*n: number of the lesions, SCC: squamous cell carcinoma

An evaluation of plaque-type SCC cases revealed that all cases exhibited eroded/ulcerative plaque morphology (n = 2; 100%).

In the evaluation of BSC cases, both cases were found to have nodular morphology, and one of these demonstrated ulcerative features (each n = 1; 50.0%) (Table 5).

**Table 5.** BSC clinical subtypes

| Subtype | n | % |
|---|---|---|
| Nodular | 1 | 50.0 |
| Ulcerated nodular | 1 | 50.0 |

*n: number of the lesions, BSC: basosquamous cell carcinoma

With respect to the number of lesions, solitary lesions were detected in the vast majority of patients (n = 66; 94.3%), whereas multiple lesions were detected in 4 patients (n = 4; 5.7%).

Regarding the major localizations of the lesions, the most common site was the head–neck region (90.0%; n = 63). This was followed by the extremities (5.7%; n = 4) and the trunk (4.3%; n = 3) (Figure 2).

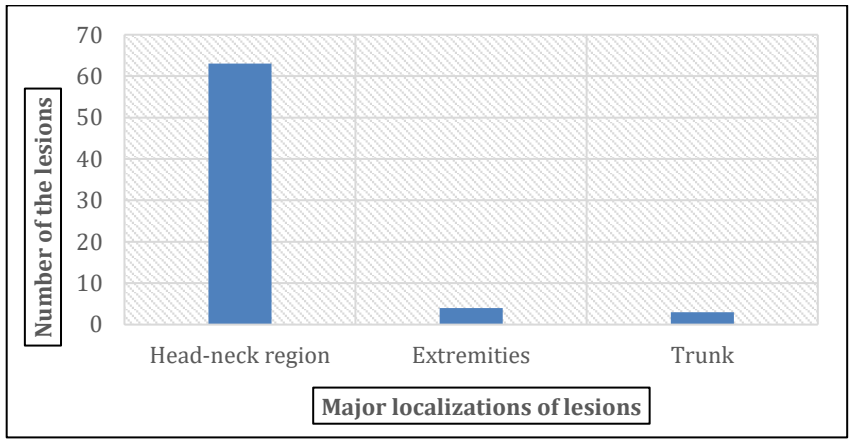


**Figure 2.** Major localizations of lesions

A detailed evaluation of all lesion localizations demonstrated that the most frequent involvement was in the nasal region (n = 16; 22.9%). This was followed by the cheek (n = 10; 14.3%), periorbital region (n = 9; 12.9%), zygoma (n = 7; 10.0%), lip (n = 6; 8.6%), forehead (n = 5; 7.1%), and upper extremity (n = 5; 7.1%). Lower frequencies were observed in the temporal region (n = 4; 5.7%), neck (n = 2; 2.9%), back (n = 2; 2.9%), and scalp (n = 2; 2.9%), whereas the ear (n = 1; 1.4%) and the nasolabial region (n = 1; 1.4%) were the rarest sites of involvement (Figure 3).

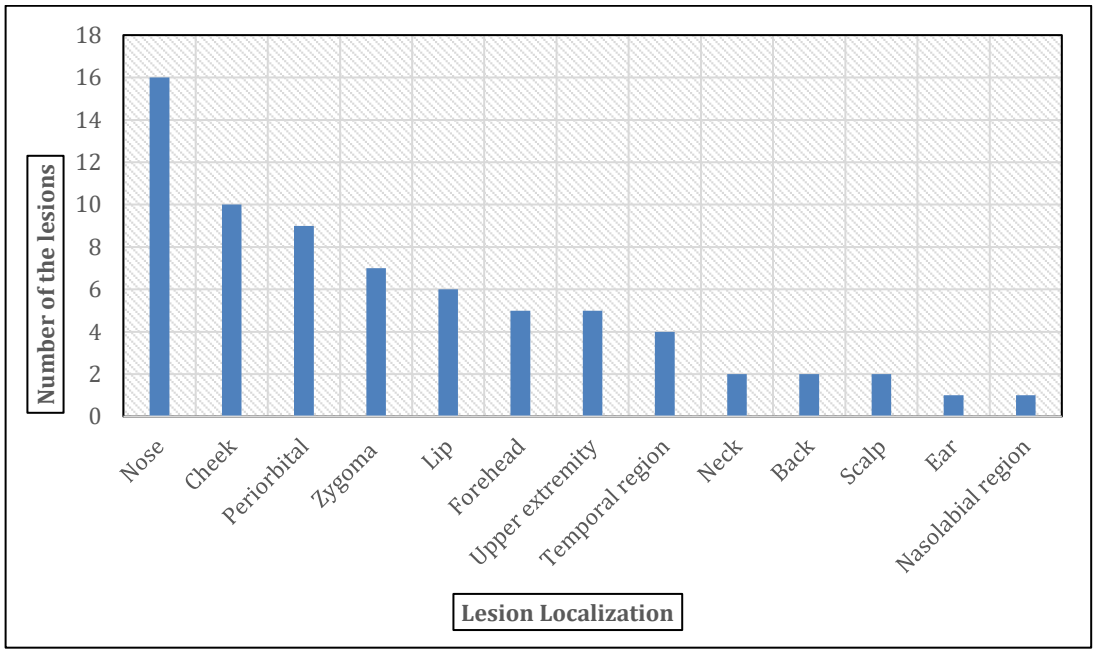


**Figure 3.** Distribution of detailed lesion localizations in patients

According to the medical history reported by the patients, the duration of lesion development ranged from 1 to 48 months. The mean duration was 9 months, and the median value was 6 months.

Among the 70 patients included in the study, 97.1% (n = 68) did not have immunosuppression, whereas immunosuppression was present in only 2.9% (n = 2).

Of the two patients with immunosuppression, one was receiving systemic immunosuppressive therapy due to liver transplantation, and the other due to kidney transplantation. The patient with a history of liver transplantation had one pigmented nodular-type BCC on the lip philtrum, whereas the patient with a history of kidney transplantation had a total of two pigmented nodular-type BCC lesions in the temporal and back regions. A history of previously diagnosed skin cancer was present in 7 of the 70 patients (10.0%), whereas no such history was detected in 63 patients (90.0%).

Among the patients with a history of previously diagnosed skin cancer, the majority consisted of those with a history of BCC (71.4%; n = 5), one of whom was evaluated as a recurrent case. In addition, a history of SCC was detected in one patient (14.3%; n = 1), and a history of sebaceous carcinoma was detected in another patient (14.3%; n = 1).

## 4. Discussion

Non-melanoma skin cancers originating from keratinocytes constitute the most common group of malignancies among Caucasians, and their incidence continues to increase steadily on a global scale (Lomas et al., 2012; Rogers et al., 2015). The mean age of the 70 patients included in the present study was approximately 72.8 ± 10.6 years. The mean age of patients with BCC was 72.6 ± 12.1 years (43–93 years), the mean age of patients with SCC was 69.3 ± 10.5 years (51–86 years), and the mean age of the two patients diagnosed with BSC was 89 years. Non-melanoma skin cancers are more frequently observed in advanced age (Baş et al., 2020). In the study conducted by Lukowiak et al., the mean age was reported as 69.82 years; in the study by Ülgen Altay et al. conducted in our country, the mean age was 65.62 ± 12.87 years; in the study by Gürsel Ürün et al., it was 67.13 ± 12.58 years; and in the study by

Baş et al., 95% of the cases were over 50 years of age and the mean age was found to be 67 ± 11 years (Lukowiak et al., 2020; Ülgen Altay et al., 2021; Ürün et al., 2023; Baş et al., 2014). The data of the present study, in agreement with the national and international literature, support that the frequency of non-melanoma skin cancers increases with age. Cumulative UV radiation exposure is considered to be the main reason for this condition.

Of the 70 patients constituting the study population, 60% were male (n = 42) and 40% were female (n = 28). Of the BCC cases, 53.1% were male (n = 26) and 46.9% were female (n = 23). In SCC cases, the male ratio was markedly higher, with 84.2% of the patients being male (n = 16) and only 15.8% being female (n = 3). In studies conducted in our country, the male patient ratio was reported as 60% by Baş et al., 58.02% by Ülgen Altay et al., 62.3% by Hayran et al., and 56.1% by Kaya et al. (Ülgen Altay et al., 2021; Baş et al., 2014; Hayran et al., 2020; Kaya et al., 2025). In a large cohort study conducted in the United Kingdom, the male/female ratio was found to be 1.2/1 for BCC and 1.7/1 for SCC (Venables et al., 2019). In the study by Katkat Çelik et al., the male patient ratio was reported as 54.5% in BCC and 67.8% in SCC (Katkat Çelik et al., 2023). The data of the present study are consistent with national and international literature findings, and male predominance is remarkable in both BCC and SCC cases. The markedly higher male predominance observed in SCC cases in the present study was attributed to occupational factors (such as agriculture and construction) leading to prolonged outdoor working among men in our region, and to lower sun exposure among women due to clothing habits. These findings emphasize the importance of cumulative UV radiation exposure in the development of SCC.

In the present study, 49 patients (70.0%) were diagnosed with basal cell carcinoma (BCC), 19 patients (27.1%) with squamous cell carcinoma (SCC), and 2 patients (2.9%) with BSC. The BCC/SCC ratio was determined to be 2.57. In the literature, the BCC/SCC ratio was reported as 2 in the study by Muzic et al., 2 in the study by Leiter et al., 2.5 in the study by Baş et al., and 3.01 in the study by Ülgen Altay et al. (Baş et al., 2020; Ülgen Altay et al., 2021; Muzic et al., 2017; Leiter & Garbe, 2008). While Baş et al. reported 66.2% BCC and 31.3% SCC, Emiroğlu et al. reported 73.6% BCC and 26.4% SCC (Baş et al., 2014; Emiroğlu & Cengiz, 2015). The findings of the present study support that BCC constitutes the majority of non-melanoma skin cancers, in agreement with the literature. Factors such as geographical region, sun exposure, skin type, age, and sociocultural structure may lead to regional differences. The evaluation of BCC clinical subtypes demonstrated that the most frequently observed forms were noduloulcerative, nodular, and pigmented nodular morphologies. The findings of the present study support the literature in that the most common BCC subtype is the noduloulcerative form. When all nodular morphologies with and without ulceration were evaluated together, the most frequently observed type was the nodular morphology. Noduloulcerative lesions may be described by patients as non-healing wounds or acne-like lesions, which may lead to more frequent outpatient visits. Therefore, noduloulcerative BCC should be kept in mind in elderly individuals presenting with such lesions.

The evaluation of SCC cases revealed that nodular types constituted the most common subtype group, and hyperkeratotic and eroded/ulcerative nodular subtypes were observed at equal frequencies. In the literature, SCC has been reported to present with nodular, papillomatous, exophytic masses accompanied by central ulceration. In long-term sun-exposed individuals, eroded or ulcerated elevated lesions should always raise suspicion for SCC, and biopsy should be performed. A limitation of the present study is the lack of histopathological differentiation grading of ulcerated and hyperkeratotic forms.

In the evaluation of BSC cases, nodular and noduloulcerative forms were observed in accordance with the literature. BSC generally presents with non-specific clinical features and is difficult to differentiate clinically from other keratinocyte-derived tumors.

With respect to lesion number, solitary lesions were detected in the vast majority of patients, consistent with the existing literature. The head–neck region was identified as the most common localization of lesions, followed by the extremities and the trunk. The higher frequency of non-melanoma skin cancers in the head–neck region is primarily attributed to increased ultraviolet radiation exposure.

Detailed localization analysis demonstrated that the nasal region was the most common site of involvement, followed by the cheek and the periorbital region. These findings are consistent with previous reports evaluating head–neck non-melanoma skin cancers.

The reported duration of lesion development ranged from 1 to 48 months, with a mean duration of 9 months and a median of 6 months. The prolonged interval between lesion onset and hospital admission may be related to low malignancy perception, attempts at treatment with topical agents, and negative bias against biopsy.

Immunosuppression was present in only two patients, both of whom had a history of organ transplantation. Non-melanoma skin cancer is increasingly common among immunosuppressed

individuals. Systemic immunosuppressive therapies significantly increase the risk of BCC and SCC in transplant recipients. Preventive measures such as sun protection, regular dermatological examinations, and early treatment of precancerous lesions are of critical importance in these patients.

A history of previously diagnosed skin cancer was present in seven patients, most commonly BCC. Only one case was evaluated as recurrent. This rate is lower than that reported in the literature. However, the lack of long-term follow-up data constitutes an important limitation of the present study with regard to secondary tumor risk.

## 5. Conclusion

Non-melanoma skin cancers are malignant tumors with a steadily increasing incidence worldwide. The present study is the first to examine the epidemiological data of skin cancers in the Amasya region. The findings of the study are generally consistent with both national studies conducted in our country and the international literature. In the Amasya region, the high prevalence of agricultural activities leads to chronic ultraviolet exposure, thereby increasing the tendency toward skin cancer development. Therefore, the enhancement of sun protection measures and the improvement of skin cancer awareness are of great importance.

The results of the present study reflect the experience of a single physician and a single center over a 1.5-year period. In order to obtain more comprehensive and generalizable results, multicenter studies should be conducted, data contributions from surgical specialties should be ensured to increase patient numbers, and data obtained from relevant disciplines should be evaluated in an integrated manner. In this context, there is a need for large-scale epidemiological studies with broader sample sizes.

## Author Contributions

Hüseyin Emre Korkmaz contributed to the conception and design of the study, data collection, analysis and interpretation of the data, drafting and critical revision of the manuscript, and approved the final version of the manuscript.

## Conflicts of interest

The author declares no conflict of interest.

## Funding Statement

This research received no specific grant from any funding agency, commercial, or not-for-profit sectors.

## Acknowledgement

The author thanks all healthcare personnel and patients who contributed to this study.

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Sabuncuoglu Serefeddin Health Sciences

Open Access

e-ISSN: 3062-3731 2026, 8(1), 16-24 https://doi.org/10.55895/sshs.1808169

# BIBLIOMETRIC ANALYSIS OF SCIENTIFIC PUBLICATIONS ON ENDOMETRIOSIS, CHRONIC PELVIC PAIN, PAIN MANAGEMENT, AND QUALITY OF LIFE (2014–2024)

# ENDOMETRİYOZİS, KRONİK PELVİK AĞRI, AĞRI YÖNETİMİ VE YAŞAM KALİTESİ ÜZERİNE YAYINLANAN BİLİMSEL ÇALIŞMALARIN BİBLİYOMETRİK ANALİZİ (2014–2024)

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**Research Article**
**Received:** 21.10.2025, **Accepted:** 12.12.2025
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**Abstract**
Endometriosis is a chronic inflammatory disease affecting reproductive-age women and is closely linked to pelvic pain, reduced quality of life, and complex care needs. As interest in this condition increases within nursing, understanding the scientific landscape is essential for guiding evidence-based practice and research. This study evaluates the literature on endometriosis, chronic pelvic pain, pain management, and quality of life through a bibliometric approach to identify research trends, collaboration patterns, and thematic concentrations relevant to nursing. A total of 297 publications published between January 1, 2014, and December 31, 2024, were retrieved from the Web of Science Core Collection. VOSviewer 1.6.20 was used to generate keyword co-occurrence maps, citation networks, author collaboration patterns, document clusters, and international research cooperation visualizations. The most frequently studied themes were "endometriosis," "pelvic pain," and "quality of life." Psychosocial factors including pain, depression, and emotional burden emerged as central topics. The most highly cited works were by Dunselman et al. (2014) and Chapron et al. (2019). The United States, the United Kingdom, and Canada produced the highest research output, while contributions from Türkiye have shown a marked increase in recent years. The findings indicate a growing shift toward a holistic biopsychosocial perspective in endometriosis research, accompanied by expanding interdisciplinary collaboration. Themes related to psychosocial support and symptom management highlight areas of direct relevance to nursing. This bibliometric overview offers insights for shaping nursing research priorities and strengthening patient-centered clinical and educational strategies in women's health nursing.

**Keywords:** Bibliometric analysis, Chronic pelvic pain, Endometriosis, Pain management, Quality of life

**Öz**
Endometriozis, üreme çağındaki kadınları etkileyen, kronik inflamatuar bir hastalıktır ve pelvik ağrı, azalmış yaşam kalitesi ve karmaşık bakım gereksinimleri ile yakından ilişkilidir. Hemşirelik alanında bu duruma yönelik ilginin artmasıyla birlikte, bilimsel literatürün yapısının anlaşılması kanıta dayalı uygulama ve araştırmaların yönlendirilmesi açısından önem taşımaktadır. Bu çalışma, hemşirelik alanıyla ilişkili araştırma eğilimlerini, iş birliği örüntülerini ve tematik yoğunlukları belirlemek amacıyla endometriozis, kronik pelvik ağrı, ağrı yönetimi ve yaşam kalitesi konularına ilişkin literatürü bibliyometrik bir yaklaşımla değerlendirmektedir. Web of Science Core Collection veri tabanından 1 Ocak 2014-31 Aralık 2024 tarihleri arasında yayımlanan toplam 297 yayın elde edilmiştir. VOSviewer 1.6.20 programı kullanılarak anahtar kelime eş-oluşum haritaları, atıf ağları, yazar iş birliği örüntüleri, doküman kümeleri ve uluslararası araştırma iş birliği görselleştirmeleri oluşturulmuştur. En sık çalışılan temaların "endometriozis", "pelvik ağrı" ve "yaşam kalitesi" olduğu görülmüştür. Ağrı, depresyon ve duygusal yük gibi psikososyal faktörler literatürün merkezinde yer alan konulardır. En yüksek atıf alan çalışmalar Dunselman ve ark. (2014) ile Chapron ve ark. (2019) olmuştur. En fazla araştırma çıktısı Amerika

Birleşik Devletleri, Birleşik Krallık ve Kanada tarafından üretilmiş olup, Türkiye'nin katkılarının son yıllarda belirgin şekilde arttığı saptanmıştır. Bulgular, endometriozis araştırmalarında bütüncül bir biyopsikososyal yaklaşıma doğru artan bir yönelimi ve disiplinler arası iş birliğinin genişlediğini göstermektedir. Psikososyal destek ve semptom yönetimiyle ilgili temalar hemşirelik açısından doğrudan önem taşımaktadır. Bu bibliyometrik değerlendirme, hemşirelik araştırma önceliklerinin belirlenmesine ve kadın sağlığı hemşireliğinde hasta merkezli klinik ve eğitim stratejilerinin güçlendirilmesine katkı sağlamaktadır.

**Anahtar Kelimeler:** Bibliyometrik analiz, Kronik pelvik ağrı, Endometriozis, Ağrı yönetimi, Yaşam kalitesi

## 1. Introduction

Endometriosis is a chronic inflammatory condition characterized by the presence of endometrial-like tissue outside the uterine cavity and is commonly observed among women of reproductive age. The condition presents symptoms such as dyspareunia, dysmenorrhea, chronic pelvic pain, infertility, and gastrointestinal or urinary complaints. Its prevalence is estimated at 6-10% in the general population, increasing to 30-50% among women experiencing infertility (Agarwal et al., 2019; Zondervan et al., 2020; Chapron et al., 2019). A substantial portion of the clinical burden arises from chronic pelvic pain, which significantly affects psychological well-being, social functioning, and overall quality of life (Facchin et al., 2015).

Recent literature demonstrates that the impact of endometriosis is shaped not only by physical symptoms but also by psychological processes such as anxiety, depression, and catastrophizing. These findings underscore the need for holistic care models that incorporate psychosocial support (Breton et al., 2025; Kalfas et al., 2022; Merlot et al., 2022). Women with endometriosis have been shown to experience challenges including impaired emotion regulation, negative body image, and limited social support, all of which hinder functional capacity and engagement with healthcare services (Farenga et al., 2024). Evidence-based interventions such as cognitive behavioral therapy, mindfulness-based approaches, and progressive muscle relaxation have proven effective in reducing pain and psychological symptoms, with systematic reviews confirming improvements in dyspareunia, dyschezia, and associated psychological outcomes (del Pino-Sedeño et al., 2024). Digital self-management programs have also been shown to improve quality of life and psychological well-being (Breton et al., 2025). The widespread use of self-care strategies further highlights the need for comprehensive and tailored support (Norman et al., 2021).

However, studies examining broader research trends, knowledge gaps, and international collaborations in the field of endometriosis remain limited. Bibliometric analyses provide an objective means to evaluate publication volume, citation patterns, and thematic structures, thereby clarifying the developmental trajectory of the field and strengthening the visibility of nursing contributions (Donthu et al., 2021).

Therefore, this study aims to analyze the scientific literature on endometriosis, chronic pelvic pain, pain management, and quality of life through a bibliometric approach, and to identify current research trends and scholarly interactions within the field.

## 2. Materials and Methods

This study employed a bibliometric analysis to examine scientific publications on endometriosis, chronic pelvic pain, pain management, and quality of life, published between January 1, 2014, and December 31, 2024. The literature search was conducted using the Web of Science (WoS) Core Collection database. To ensure transparency and reproducibility, the following exact search string and Boolean structure were used:

TS= ("endometriosis") AND TS= ("chronic pelvic pain") AND TS= ("pain management") AND TS= ("quality of life")

The exclusive use of the "AND" operator was chosen to intentionally narrow the scope and focus on studies simultaneously addressing all four key concepts. This approach allowed for a more targeted dataset aligned with the study's aim of identifying integrated research themes. However, this strategy may have excluded broader or tangentially related publications; therefore, it is acknowledged as a methodological limitation.

Based on predefined inclusion criteria, only original research articles and review papers were selected. Conference abstracts, proceedings, letters, and book chapters were excluded from the analysis. As a result, a total of 297 publications (197 original research articles and 100 reviews) were included.

Bibliometric mapping and visualization were performed using VOSviewer version 1.6.20. The analysis employed full counting for co-authorship and citation networks, and a minimum occurrence threshold of five keywords for the co-occurrence map. These parameters were selected to ensure analytic clarity and to enhance the reproducibility of the findings (Figure 1).

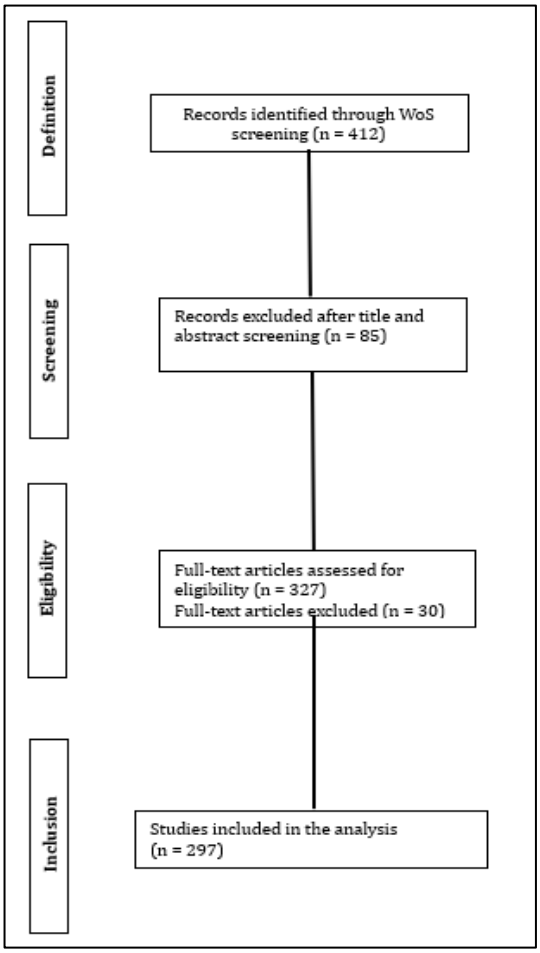


**Figure 1.** Flow diagram

*2.1. Data analysis process*

All records were exported from the Web of Science database in .txt format and analyzed using VOSviewer version 1.6.20. Bibliometric mapping and network visualizations were performed to identify structural, thematic, and collaborative patterns within the literature. Graphical outputs and clustering algorithms were applied to address the study's research questions and reveal the multidimensional characteristics of scientific production.

Five bibliometric techniques were employed:

Co-authorship analysis: Conducted to examine collaboration structures and author productivity within the field (Figure 2).

Keyword co-occurrence analysis: Used to identify major thematic domains and conceptual relationships among frequently occurring terms (Figure 3).

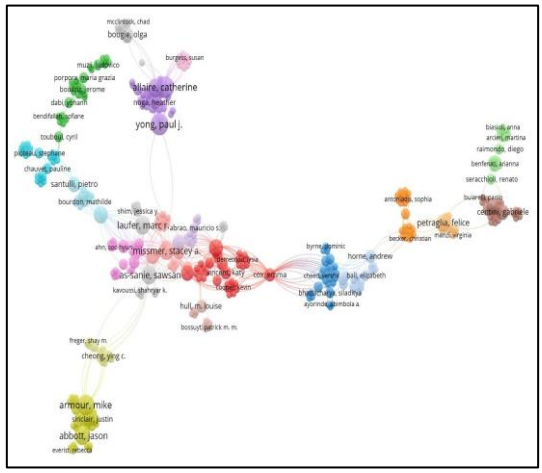


**Figure 2.** Co-authorship network map

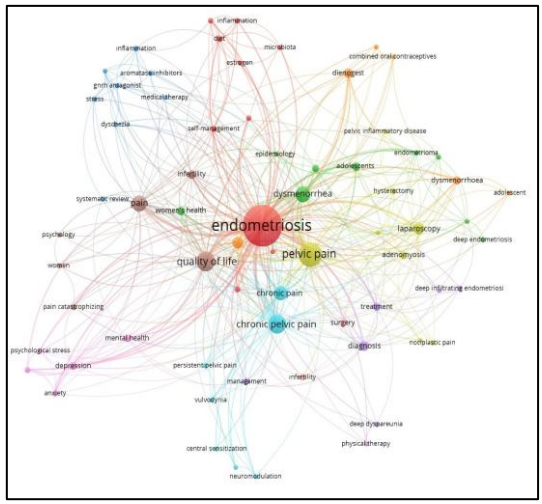


**Figure 3.** Keyword co-occurrence map

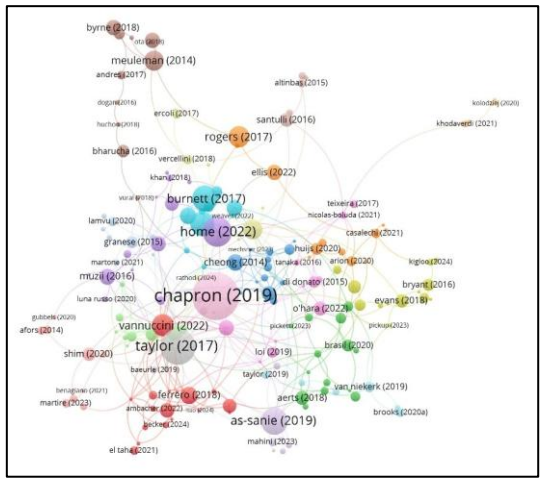


**Figure 4.** Citation network map

Citation network analysis: Applied to determine the most influential publications and to map the intellectual linkages formed through citation patterns (Figure 4).

Document clustering analysis: Publications were grouped based on content similarity and co-citation patterns, allowing the identification of core research themes and developmental directions (Figure 5).

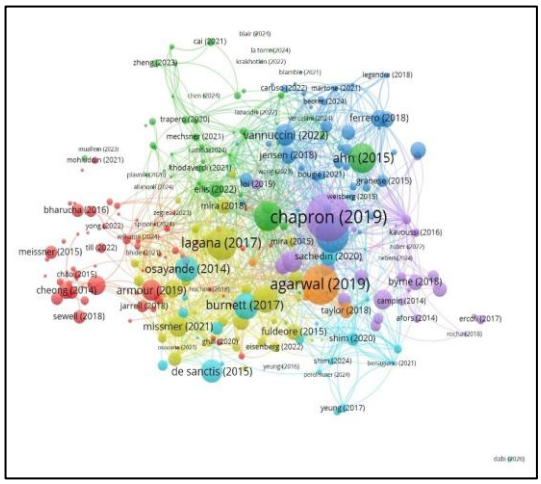


**Figure 5.** Document clustering analysis map

Country collaboration analysis: Performed to visualize international co-authorship networks and assess the global distribution of research collaborations (Figure 6).

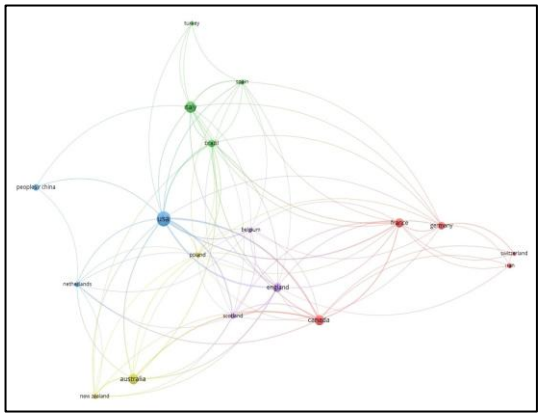


**Figure 6.** Country collaboration network map

*2.2. Data evaluation*

All analyses were performed independently by two researchers using a double-blind control procedure. Graphical outputs were interpreted using cluster colors, link strengths, and node centrality indices. Data was evaluated through qualitative indicators (thematic structure, conceptual density) and quantitative metrics (publication counts, citation frequencies, and network connections). This approach enabled a rigorous and systematic examination of structural characteristics, developmental trends, and existing research gaps within the endometriosis literature.

*2.3. The ethical dimension of the research*

This study is based on bibliometric analysis and does not involve any direct research on human or animal subjects. All data used were obtained from publicly accessible databases. Therefore, ethical approval was not required. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

## 3. Results and Discussion

*3.1. Co-authorship*

The co-authorship network presented in Figure 2 illustrates collaborative relationships among researchers, organized into distinct color-coded clusters that reflect thematic orientations within the field. The red cluster, which includes prominent authors such as Stacey A. Missmer, Sawsan As-Sanie, Marc R. Laufer, and M. Louise Hull, is primarily based in the United States and focuses on endometriosis pathophysiology, pain phenotyping, and patient-centered management. The blue cluster comprises mainly European researchers, including Dominic Byrne, Elizabeth Ball, and Christian Becker, and concentrates on clinical epidemiology and quality-of-life outcomes. The orange and brown clusters, led by Italian researchers such as Felice Petraglia and Gabriele Centini, emphasize hormonal therapies, surgical results, and women's health service delivery. The green cluster, represented by Ludovico Muzii, Sofiane Bendifallah, and Jerome Bouaziz, centers on pain management strategies and minimally invasive surgical techniques. The purple cluster, with contributors such as Catherine Allaire and Paul J. Yong from Canada, focuses on patient-centered care models and interdisciplinary approaches. The yellow cluster, formed by Australian researchers including Mike Armour, Justin Sinclair, and Jason Abbott, explores complementary and alternative methods for pain management.

Interconnections between clusters indicate co-authorship links and the circulation of expertise across research groups. The central positioning of the Missmer–As-Sanie–Vincent–Cooper network demonstrates its substantial influence on shaping the field's scientific output. The presence of researchers who appear across multiple clusters, such as Stacey Missmer and Marc Laufer, suggests their function as bridges connecting interdisciplinary collaborations. The country-based structure of clusters further indicates the continued predominance of nationally organized research networks in the field.

*3.2. Keyword co-occurrence*

The keyword co-occurrence map (Figure 3) illustrates the conceptual structure of endometriosis research between 2014 and 2024 and reveals several interconnected thematic clusters. "Endometriosis" occupies the central position in the network and shows strong associations with "pelvic pain," "dysmenorrhea," "chronic pelvic pain," and "quality of life," emphasizing the dominance of symptom-focused and patient-reported outcomes research. The presence of terms such as "chronic pain," "nociplastic pain," "central sensitization," and "pain catastrophizing" indicates growing attention to neurophysiological mechanisms, although the comparatively weak connections of "neuromodulation" and "physical therapy" reflect the early development of multimodal pain management research. Psychosocial concepts including "depression," "anxiety," "stress," and "mental health" cluster around pain outcomes, highlighting the psychological impact of the disease; however, their limited linkage to structured psychological interventions such as cognitive behavioral therapy, mindfulness, or acceptance and commitment therapy suggests that the long-term effectiveness of these approaches remains underexplored. Reproductive health–related terms such as "infertility," "adolescents," "laparoscopy," "deep infiltrating endometriosis," and "adenomyosis" demonstrate the clinical heterogeneity of the condition, yet the weak association between surgical approaches and long-term quality-of-life outcomes indicates an ongoing need for patient-centered comparative studies. Pharmacological keywords including "GnRH antagonist," "aromatase inhibitors," "dienogest," and "combined oral contraceptives" confirm the importance of medical therapy, but their minimal connection with "biomarkers," "precision treatment," or "personalized medicine" points to an emerging but underdeveloped direction in individualized pharmacotherapy. Lifestyle and coping-related concepts such as "self-management," "diet," "stress," and "psychology" reflect a shift toward empowerment-based care, although digital health tools, mobile applications, and telehealth models remain insufficiently represented in the network. Overall, the structure of the map conceptualizes endometriosis as a biopsychosocial condition and clearly identifies several research gaps, including the need for longitudinal studies integrating biological, psychological, and behavioral variables, the development and evaluation of digital and AI-supported self-management strategies, the expansion of biomarker-guided precision treatments, the creation of interdisciplinary models bridging gynecology, pain science, physiotherapy, psychology, and lifestyle medicine, and strengthened research on adolescent endometriosis, early diagnosis pathways, and the comparative effectiveness of surgical, medical, and psychosocial interventions.

These findings indicate that while existing literature has expanded significantly, opportunities remain for more integrated, multi-domain research that addresses the complex and multifactorial nature of endometriosis (Figure 3).

*3.3. Citation network*

The citation network analysis (Figure 4) maps influential scientific publications on endometriosis and chronic pelvic pain from 2014 to 2024 and visualizes how these studies are interconnected. Node sizes reflect citation frequency, while colored clusters represent thematic groupings. The primary purpose of this map is to reveal the intellectual foundations of the field by showing which studies exert the greatest scientific influence and how knowledge circulates between them; this structure helps researchers identify dominant concepts, conceptual turning points, and areas requiring further theoretical or clinical development.

At the center of the network is Chapron's 2019 publication, which addresses pain mechanisms and diagnostic challenges and appears as a major reference point due to both its centrality and high citation count. Studies by Taylor (2017), Burnett (2017), and Home (2022) also occupy prominent positions, contributing substantially to clinical assessment and treatment approaches. Research by As-Sanie (2019), Ferrero (2018), and Meuleman (2014) further enriches the network by emphasizing quality of life and multidisciplinary care.

The pink–purple cluster, containing authors such as Chapron, Vannuccini, Taylor, and Ferrero, centers on pathophysiology, diagnostic processes, and pain management. The green cluster includes contributions by Evans (2018), Brooks (2020), and Brasil (2020), focusing on adolescent endometriosis, laparoscopy, and surgical treatments. The orange and yellow clusters, represented by Nicolas-Boluda (2021), Teixeira (2017), and Ellis (2022), highlight biomarkers, imaging techniques, and emerging therapeutic protocols. The blue cluster features studies by Lavu (2020), Cheong (2014), and Granese (2015) addressing pain physiology, psychological effects, and nursing perspectives.

Overall, the citation network demonstrates that endometriosis research is becoming increasingly structured, with several publications serving as foundational anchors for both theoretical and clinical advancements. By showing how scientific influence flows between studies, the network provides a clear representation of the field's intellectual architecture and supports a deeper

understanding of evolving research priorities and remaining gaps. The presence of internationally distributed publications also reflects the global and collaborative nature of endometriosis research.

*3.4. Document clustering*

The document clustering analysis (Figure 5) groups influential publications on endometriosis, chronic pelvic pain, pain management, and quality of life according to their co-citation patterns, revealing distinct thematic bodies of literature. Chapron's 2019 study appears at the center of the network, maintaining both methodological and thematic dominance. Strong co-citation links with Agarwal (2019), Burnett (2017), and Laganà (2017) indicate a shared focus on clinical management, disease phenotyping, and treatment protocols.

The red cluster includes work by Chao (2015), Meissner (2015), Cheong (2014), and Bharucha (2016), emphasizing gastrointestinal-related pelvic pain, functional disorders, and psychophysiological aspects of pain. The green cluster, formed by more recent publications such as Cai (2021), Zheng (2023), and Ellis (2022), highlights advance in genetic markers, epigenetic pathways, and personalized therapeutic strategies. The yellow cluster contains studies by Laganà (2017), Armour (2019), and Osayande (2014), focusing on complementary medicine, psychological support, and holistic care approaches. The blue cluster comprises research by Ahn (2015), Ferrero (2018), Granese (2015), and Bougie (2021), representing surgical perspectives including laparoscopy, minimally invasive techniques, and treatment of deep infiltrating endometriosis. The purple cluster features technically oriented publications such as Ercoli (2017) and Rocha (2018), concentrating on imaging modalities, pelvic anatomy, and postoperative considerations.

Overall, the clustering map illustrates both the thematic distribution and organizational structure of endometriosis research. The patterns shaped through co-citation relationships demonstrate how specialized areas of inquiry emerge while simultaneously converging around core publications that anchor the field's scientific development.

*3.5. Country collaboration network*

The country collaboration network (Figure 6) illustrates the global distribution of scientific activity on endometriosis, chronic pelvic pain, pain management, and quality of life between 2014 and 2024. The United States appears at the center of the map with the highest publication volume and the most extensive international partnerships, showing strong collaborative links with Canada, the United Kingdom, Australia, China, Italy, and the Netherlands. The United Kingdom and Canada also occupy prominent positions, maintaining intensive co-authorship ties not only with the United States but also with Germany, France, and Australia, reflecting the interdisciplinary nature of research within Anglo-Saxon academic systems. Italy and Germany represent major European contributors with dense intra-European connections and continued collaboration with the United States. China demonstrates high scientific output and substantial partnerships with the United States and Australia, although its collaboration with European countries remains more limited. Türkiye has developed moderate but steadily increasing collaborations, particularly with Italy, Spain, and the United States, indicating a growing integration into international research networks.

Overall, the map shows that endometriosis research is strongly shaped by international partnerships, with multicenter studies playing a central role in comparative diagnostic and treatment research. A core group of countries the United States, United Kingdom, Canada, Italy, and Australia dominates global scientific output, while emerging contributors such as Türkiye, Iran, and Poland are becoming increasingly visible within these collaborative structures.

This study systematically analyzed scientific publications on endometriosis, chronic pelvic pain, pain management, and quality of life from 2014 to 2024 and demonstrated that the field has evolved into a multidimensional structure integrating clinical, psychosocial, and epidemiological perspectives within an increasingly international research environment. The co-authorship patterns highlight clear multidisciplinary clustering: groups led by Missmer, As-Sanie, Laufer, and Hull focus on pathophysiology, pain phenotypes, and patient-centered clinical care, while clusters including Armour, Sinclair, and Abbott emphasize complementary, lifestyle-based, and holistic approaches. These findings reinforce earlier evidence that contemporary endometriosis research encompasses not only biomedical management but also psychosocial and behavioral dimensions (Donthu et al., 2021; Moreira et al., 2022; Vincent et al., 2023).

The geographical alignment of thematic clusters suggests the emergence of region-specific scientific specializations. Research teams in the United States, Canada, and Australia commonly target patient experience and psychoeducational interventions, whereas Italian and French groups remain concentrated on surgical and pharmacological treatments, consistent with the "geographic scientific specialization clustering" noted by Barrow et al. (2021). The keyword co-occurrence network further confirms that endometriosis functions as a biopsychosocial condition: terms such as pelvic pain, depression, pain catastrophizing, and

neuromodulation appear centrally connected, demonstrating the integration of biopsychosocial models in pain science (Armour et al., 2019; Facchin et al., 2017). The prominence of mental health, psychological stress, and self-management also aligns with literature showing that psychological factors significantly influence pain severity and treatment response (Farshi et al., 2020; Moradi et al., 2014).

The citation network indicates that knowledge production in this field is anchored by a set of highly influential publications, including clinical guidelines (Dunselman et al., 2014), diagnostic frameworks (Chapron et al., 2019), and epidemiological studies (Zondervan et al., 2020). These works serve both as central reference points and as connectors across subfields, reflecting the close interaction between clinical practice and research. Document clustering results further demonstrate that studies by Chapron (2019), Agarwal (2019), and Burnett (2017) influence multiple thematic areas, while clusters involving Chao (2015) and Bharucha (2016) highlight the broadening of endometriosis research into interdisciplinary domains such as gastrointestinal pain, neuroscience, psychology, and public health.

The country collaboration analysis shows that the United States, United Kingdom, Canada, Italy, and Australia lead global contributions, with Türkiye gaining increasing visibility through collaborations with Italy and the United States, consistent with the recent rise in SCI-E indexed publications from Türkiye (TÜBİTAK, 2023). China, despite high publication output, exhibits more limited integration into global networks, supporting the argument that scientific impact depends not only on productivity but also on collaboration capacity and knowledge exchange (Wang et al., 2021).

Overall, the findings illustrate that endometriosis research has shifted from a primarily disease-centered framework to a holistic paradigm encompassing mental health, patient experience, access to care, and self-management strategies an evolution that aligns nursing, gynecology, psychology, public health, and pain science within a shared research agenda. Future studies should strengthen interdisciplinary and international partnerships, particularly in nursing-led psychosocial research. Systematic reviews and meta-analyses could contribute to the consolidation of core evidence identified in the citation network. Greater support for researchers from emerging economies is essential to reduce the centralization of knowledge production. Patient-reported outcome measures and personalized approaches should be prioritized, while the effectiveness of complementary and alternative therapies requires rigorous evaluation through randomized controlled trials. Finally, capacity-building initiatives for early-career researchers, including mentorship and project funding, will be critical for sustaining the field's scientific growth.

**Limitations**

The literature search was limited to the WoS Core Collection database. Other major databases (e.g., Scopus, PubMed) were not included in the analysis. The time frame of the study was restricted to the years 2014-2024.

## 4. Conclusion

This bibliometric analysis indicates that research on endometriosis has increasingly adopted a biopsychosocial and interdisciplinary perspective over the past decade. The literature is primarily concentrated on pelvic pain mechanisms, quality-of-life outcomes, psychosocial burden, and both surgical and pharmacological treatment modalities. The United States, the United Kingdom, Canada, and Italy remain the leading contributors to global scientific output, while Türkiye has demonstrated a significant rise in international collaboration. Influential publications such as Chapron (2019) and Dunselman (2014) continue to shape diagnostic practices, treatment standards, and scientific priorities in the field.

Future research should further develop multidisciplinary care models, digital health solutions, and psychosocial interventions. Strengthening early diagnostic pathways, advancing patient-centered care, and integrating complementary and technology-supported management strategies are also recommended. For emerging contributors such as Türkiye, expanding international partnerships and addressing diagnostic delays through coordinated policy efforts will be critical. Finally, increasing both clinical and community-based longitudinal studies will be essential for generating high-quality evidence and enhancing the broader scientific and public health impact.

**Author Contributions**

Conceptualization: NA, NKY; Study design: NA, NKY; Data acquisition: NA, NKY; Data analysis: NA, NKY; Interpretation of findings: NA, NKY; Manuscript drafting: NA, NKY.

**Conflicts of interest**

None.

**Funding Statement**

This research received no specific grant from any funding agency, commercial or not-for-profit sectors.

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Sabuncuoglu Serefeddin Health Sciences

Open Access

e-ISSN: 3062-3731 2026, 8(1), 25-33 https://doi.org/10.55895/sshs.1850392

# ANALYSIS OF INFORMATION ON COSMETIC RECALLS IN TÜRKİYE

# TÜRKİYE'DEKİ KOZMETİK ÜRÜN GERİ ÇAĞIRMALARINA İLİŞKİN BİLGİLERİN ANALİZİ

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**Research Article**
**Received:** 29.12.2025, **Accepted:** 30.03.2026
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**Abstract**
Cosmetics used to enhance personal appearance can pose risks to human health due to toxic substances they may contain. Therefore, monitoring the quality and safety of cosmetics after marketing is essential. Unsafe cosmetics are recalled from the market, and regulatory authorities worldwide apply standards and sanctions to ensure product safety. This study retrospectively analyzed cosmetic recalls between 2014 and 2024, as reported on the Turkish Medicines and Medical Devices Agency website. A total of 460 products from 18 different countries were recalled in Türkiye during this period. Hair care products, particularly soap and shampoo products, were the most frequently recalled, representing 46.15% of all recalls. Other notable categories included hand-body lotions (13.25%), perfumes and deodorants (7.69%), and nail care products (7.05%). The main reasons for recalls were non-compliance with regulations, poor product quality, presence of substances above legal limits, and safety concerns. Commonly applied sanctions included administrative fines, prohibition of market supply, product destruction, and mandatory recalls. This study highlights the importance of continuous monitoring and strict regulatory enforcement to ensure the safety of cosmetics in Türkiye.

**Keywords:** Cosmetic recalls, Cosmetic safety, Cosmetics, Post-marketing surveillance, Regulatory control

**Öz**
Kişisel görünümü iyileştirmek amacıyla kullanılan kozmetik ürünler, içerdikleri toksik maddeler nedeniyle insan sağlığı açısından risk oluşturabilir. Bu nedenle, kozmetiklerin pazarlama sonrası kalite ve güvenliğinin izlenmesi önemlidir. Güvensiz kozmetik ürünler piyasadan geri çağrılmakta ve dünya genelinde düzenleyici otoriteler, ürün güvenliğini sağlamak amacıyla standartlar ve yaptırımlar uygulamaktadır. Bu çalışmada, 2014–2024 yılları arasında Türkiye İlaç ve Tıbbi Cihaz Kurumu web sitesinde bildirilen kozmetik geri çağırmaları retrospektif olarak analiz edilmiştir. Bu dönemde Türkiye'de toplam 460 ürün, 18 farklı menşe ülkeden geri çağrılmıştır. En sık geri çağrılan ürünler saç bakım-sabun, şampuan ürünleri olup, tüm geri çağırmaların %46,15'ini oluşturmaktadır. Diğer öne çıkan ürün grupları el-vücut losyonları %13,25, parfüm ve deodorantlar %7,69, tırnak bakım ürünleri %7,05 şeklindedir. Geri çağırma nedenleri arasında mevzuata aykırılık, düşük ürün kalitesi, yasal sınırların üzerindeki maddeler ve güvenlik sorunları öne çıkmaktadır. Uygulanan yaptırımlar genellikle idari para cezası, ürünün piyasaya arzının yasaklanması, uygunsuz ürünlerin imhası ve geri çağırma şeklinde olmuştur. Bu çalışma, Türkiye'de kozmetik güvenliğinin sağlanmasında sürekli denetim ve sıkı düzenleyici uygulamaların önemini vurgulamaktadır.

**Anahtar Kelimeler:** Kozmetik ürün geri çağırmaları, Kozmetik güvenliği, Kozmetik ürünler, Piyasa sonrası gözetim, Mevzuat denetimi

## 1. Introduction

The skin has a multifactorial aging process caused by both internal and external factors (Ratanapokasatit et al., 2022). Aging, deterioration in physiological functions and increased disease susceptibility particularly affect the skin (Hussein et al., 2025). Cosmetic products are widely used to

rejuvenate aging and damaged skin and to reduce the visible effects of skin aging, thereby enhancing the skin's appearance (Califf et al., 2017; Reilly & Lozano, 2021).

For centuries, both women and men have sought to alter their appearance through cosmetics in pursuit of beauty ideals (Gunn, 1973). Cosmetic products intended to enhance appearance may cause serious adverse effects, ranging from skin irritation to death, due to the toxic substances they contain (Briefel, 2009; Nasa, 2014).

Thallium acetate, a toxic substance identified in the cream product known as Koremlu, caused serious adverse effects in women (Greenbaum, 1931). Serious eye injuries were observed in women using the eye makeup material called Lash-Lure (Harner, 1933; FDA, 2023). 105 people lost their lives as a result of the use of diethylene glycol, which was used as a solvent or excipient, in the content of Elixir Sulfanilamide (Wax, 1995). These events, especially in the 20th century, led to the fact that existing regulations around the world did not require toxicity testing of products before marketing (Sarkar et al., 2023; Chandran et al., 2024), and the Food, Drug and Cosmetic (FD&C) law was enacted in the United States in 1938 (Kleinfeld, 1965). This act, which included regulatory studies on cosmetics, expanded the control of cosmetic safety for the first time (FDA, 2023). It has become important for cosmetic products to have a proven efficacy to ensure consumer safety along with a comprehensive toxicological evaluation (Barthe et al., 2021). According to Regulation (EC) No 1223/2009, a cosmetic product is considered safe if it does not harm human health under normal conditions of use, contains clearly identified ingredients subjected to toxicological assessment, maintains an adequate safety margin, contains no prohibited substances, complies with relevant legislation, and is supported by a Cosmetic Product Safety Report approved by a qualified assessor (European Union, 2009).

Today, regulatory bodies worldwide set strict standards for product safety, while cosmetic manufacturers employ state-of-the-art processes to maximize safety, incorporating the latest scientific advances and good manufacturing practices (Engasser et al., 2007). Despite this, the widespread use of cosmetics imported from countries with inadequate safety regulations and lack of ideal conditions for production (Al-Saleh et al., 2009) can lead to the constant emergence of adverse post-marketing effects due to the presence of chemical substances (Di Giovanni et al., 2006; Balwierz et al., 2023). Therefore, post-marketing surveillance is important to monitor and verify that licensed medical products meet appropriate quality requirements (Neves et al., 2022).

Chemical substances used against microbial contamination to ensure consumer safety and extend shelf life in cosmetic products pose potential harm to consumers' health (Halla et al., 2018; Abrar et al., 2022). Chemical substances are added for two reasons: first, to prevent microbial spoilage and thus extend the shelf life of the product; second, to protect the consumer from possible infection (Varvaresou et al., 2009). Chemical substances found in cosmetics such as preservatives, stabilizers, fragrances and colorants accumulate in the body over time, causing reproductive, developmental disorders, dermatitis, hair loss, aging, skin reactions, eye, allergy and nail damage (Malik & Claoué, 2012; Okereke et al., 2015; Rana et al., 2025; Zhu et al., 2025). Cosmetic side effects, which are the most common reason for hospitalization, are usually mild or temporary allergic reactions (Nigam, 2009). However, these chemicals can cause serious health problems in pregnant women and children (Lindberg et al., 2004; Kokura et al., 2010; Kaushik et al., 2023).

Despite global cosmetic regulations aimed at ensuring consumer safety, stricter regulatory measures are needed to better protect human health (Vieira et al., 2024). In Türkiye, the safety of cosmetic products is regulated under the Cosmetic Products Regulation issued by the Turkish Medicines and Medical Devices Agency (TITCK) (Official Gazette, 2023). This regulation, which entered into force in 2023 under Cosmetics Law No. 5324, sets out restrictions on certain substances, provisions on animal testing, consumer information requirements, company responsibilities, safety assessments, market surveillance and control, and administrative sanctions. According to the regulation, the institution may request a recall from the relevant company regarding a risky product or may take all necessary measures to ensure that it is recalled or access to the product is restricted (TITCK, 2023). Among the measures taken as a result of adverse effects caused by risky products, 45% product change and 39.6% product recall were stated (Di Giovanni et al., 2006).

The cosmetics and personal care industry in Türkiye adheres to global standards in product manufacturing. The cosmetics and personal care products market in Türkiye grows by an average of 10% every year. Hair care products have the largest share in the sector's products. Shampoos constitute approximately 59% of hair care products (Türkiye Cumhuriyeti Ticaret Bakanlığı, 2023).

Despite the widespread use of cosmetic products, inadequate data on the type, number, and severity

of reactions can hinder the collection of both positive and negative feedback, as adverse reactions are often mild and spontaneous (Sautebin, 2007).

This study is the first systematic analysis of cosmetic products recalled after marketing in Türkiye, based on the evaluation of TITCK recall reports. In this context, it makes a unique contribution to the literature by addressing the lack of Türkiye-focused data, enabling international comparisons, and raising awareness about cosmetic safety.

## 2. Materials and Methods

In Türkiye, cosmetic products are inspected and regulated by the TITCK, which also publishes the Cosmetics Regulation. The purpose of the regulation is to regulate the procedures and principles regarding cosmetic products placed on the market to ensure a high level of protection for human health. According to the regulation, the TITCK is the institution responsible for determining all types of cosmetic safety, cosmetic inspection, market control, and administrative sanctions in Türkiye.

In this context, a retrospective descriptive analysis of TITCK recall report information regarding cosmetic products between 2014 and 2024 was conducted. The collected data were organized into tables and graphs using Microsoft Excel for quantitative analysis and visualization purposes and categorized and classified by the researcher. Data on all recall reports related to cosmetics and personal care products between 2014 and 2024 were obtained from the TITCK website and analyzed. The dataset included the number of recalled products by country, product type, and year, as well as the reasons for recalls and the sanctions applied. Because the research only included publicly available data, ethics committee approval was not required (TITCK, 2024).

## 3. Results

Table 1 shows that, according to TITCK reports, a total of 460 products from 18 different countries were recalled. Of the recalled cosmetic products, 58 were from foreign countries, 362 were of domestic origin, and the origin of 40 is unknown. The highest number of product recalls was in Türkiye with 362 products, followed by China with 23 products and India with 7 products (TITCK, 2024).

**Table 1.** Number of recalled cosmetics by country of origin and unknown origin

| Country of Origin / Origin Status | Number of Recalled Products | Percentage (%) |
|---|---|---|
| Türkiye | 362 | 79 |
| Origin Unknown | 40 | 8,6 |
| China | 23 | 5 |
| India | 7 | 1,5 |
| France | 6 | 1,3 |
| South Korea | 5 | 1,1 |
| United States | 4 | 0,9 |
| Italy | 2 | 0,4 |
| United Kingdom | 2 | 0,4 |
| Greece | 2 | 0,4 |
| Belgium | 1 | 0,2 |
| Netherlands | 1 | 0,2 |
| Spain | 1 | 0,2 |
| Lebanon | 1 | 0,2 |
| Luxembourg | 1 | 0,2 |
| Syria | 1 | 0,2 |
| Taiwan | 1 | 0,2 |
| **Total** | **460** | **100** |

Source: TITCK, 2024

According to the data in Table 2, 460 products from 202 companies were recalled. The highest number of recalls occurred in 2023, while the lowest number occurred in 2021 with only 9 applications (TITCK, 2024).

The main reasons for product recalls and the sanctions applied are shown in Table 3.

The data includes non-compliance with regulations, safety-related analytical findings, unauthorized or excessive use of substances, microbiological contamination, lack of documentation, and decisions made by competent authorities (TITCK, 2024).

**Table 2.** Number of recalled products by year

| Year | Number of recalled products | Number of companies | Min Recalled Products per Company | Max Recalled Products per Company |
|---|---|---|---|---|
| **2014** | 62 | 43 | 1 | 5 |
| **2015** | 50 | 38 | 1 | 5 |
| **2016** | 23 | 15 | 1 | 4 |
| **2017** | 26 | 20 | 1 | 3 |
| **2018** | 15 | 4 | 1 | 6 |
| **2019** | 36 | 23 | 1 | 6 |
| **2020** | 32 | 21 | 1 | 5 |
| **2021** | 9 | 8 | 1 | 2 |
| **2022** | 30 | 17 | 1 | 10 |
| **2023** | 151 | 4 | 1 | 147 |
| **2024** | 26 | 9 | 1 | 10 |
| **Total** | **460** | **202** | **-** | **-** |

Source: TITCK, 2024

**Table 3.** Reasons for product recalls and applied sanctions

| **Reasons for product recalls and applied sanctions** |
|---|
| Deterioration in product packaging quality |
| As a result of complaints and inspections, the gendarmerie, the Customs Protection Anti-Smuggling and Intelligence Directorate, the governor's office and the Supreme Court Penal Chamber decided to ban fake, illegal and unsafe products. |
| Türkiye Bilimsel ve Teknolojik Araştırma Konseyi (TUBITAK) analysis and Medical Devices Science Commission decision. |
| Lack of Technical File for the Product |
| Placing products on the market whose certification process has not been completed |
| Incompatibility of protection factor (SPF) as a result of analysis |
| As a result of the analysis, microbial growth in the product |
| As a result of the analysis, the active substance called "Minoxidil" was found to be contrary to the Cosmetics Legislation. |
| As a result of the analysis, the substance called "Trichloroacetic acid" was found to be contrary to the cosmetics legislation. |
| As a result of the analysis, the substance called "Diaminobenzene" was found to be above the limit, contrary to the Cosmetics Legislation. |
| As a result of the analysis, the substance called "Methylcloroisothiazolinone" was found to be above the limit, contrary to the Cosmetics Legislation. |
| As a result of the analysis, it was found that it contained the active ingredient called "Diclofenac sodium", contrary to the Cosmetics Legislation. |
| As a result of the analysis, the amount of "lead" in the content is above the limit, contrary to the Cosmetics Legislation. |
| As a result of the analysis, the substance called "Arsenic" was found to be contrary to the Cosmetics Legislation. |
| As a result of the analysis, the substance called "Thioglycolic acid" was found to be above the limit, contrary to the Cosmetics Legislation. |
| As a result of the analysis, the substance called "Hydrogen Peroxide" was found to be above the limit, contrary to the Cosmetics Legislation. |
| As a result of the analysis, the substances named "Methylisothiazolinone" and "Methylchloroisothiazolinone" were found to be above the limit, contrary to the Cosmetics Legislation. |
| "Methyldibromo glutaronitrile" substance contrary to Cosmetics Legislation. |
| The product contains a substance called "Ethyl Tosylamide" |
| Cosmetics Regulation: Presence of the substance called "phenylenediamine" in the product content. |

Source: TITCK, 2024

According to the percentage classification in Table 4, when looking at the ranking of recalled products, it is seen that hair care soap/shampoo products are the most frequently recalled. Anti-cellulite gel and ant egg oil are the least frequently recalled products (TITCK, 2024).

When the 460 cosmetic products analyzed were examined, the distribution of different types of findings is summarized in Table 5.

The findings were divided into four main categories: non-compliance with regulations, Unsafety, Counterfeit/Imitation products, and Judicial/Court decisions. According to Table 5, the most frequently encountered type of finding in the

products was "Ingredient violating cosmetic regulations," accounting for 45.1% of the total findings (n = 215). This was followed by "Non-compliance with regulations in the product content as a result of analysis" (12.4%; n = 59) and "Unsafety according to the analysis result" (19.5%; n = 93), respectively. Other types of detection included "Non-compliance with regulations" (10.1%; n = 48), "Unsafe product" (2.1%; n = 10), "Counterfeit/imitation product" (4.4%; n = 21), and "Court decision" (2.9%; n = 14) (TITCK, 2024).

**Table 4.** Distribution of recalled products by type (%)

| Classification of recall products | Percentage (%) |
|---|---|
| Hair care & Soap-shampoo | 46.15 |
| Hand-body lotion and cream-oil | 13.25 |
| Perfume, deodorant | 7.69 |
| Nail care product | 7.05 |
| Clay and mask | 5.56 |
| Skin care mesotherapy, stem cell, chemical peeling, serum and vitamin | 5.56 |
| Lip care product | 2.99 |
| Depilatory cream-spray | 2.56 |
| Wet wipes-towels | 2.35 |
| Foundation, blush, mascara | 2.14 |
| Powder | 1.50 |
| Sunscreen | 1.07 |
| Liquid disinfectant | 1.07 |
| Ant egg oil | 0.85 |
| Anti-cellulite gel | 0.21 |

Source: TITCK, 2024

**Tablo 5.** Reasons for the Unsafe Nature of Cosmetic Products

| Category | Type of Detection | Number | Percentage (%) |
|---|---|---|---|
| Violation of Regulations | Component contrary to cosmetic regulations | 215 | 45.10 |
| Violation of Regulations | Analysis result: Non-compliance with regulations in the product content | 59 | 12.40 |
| Lack of Security | Unsafe according to analysis result | 93 | 19.50 |
| Violation of Regulations | Non-compliance with regulations | 48 | 10.10 |
| Lack of Security | Unsafe product | 10 | 2.10 |
| Counterfeit/Imitation Product | Counterfeit/imitation product | 21 | 4.40 |
| Judiciary/Court | Court decision | 14 | 2.90 |

## 4. Discussion

Cosmetics, as an indispensable part of human life, have been used for thousands of years to enhance beauty and protect the skin from environmental damage. People are exposed to potentially harmful substances due to the use of cosmetics. Ensuring the safety of cosmetic products is one of the most important priorities of the beauty care sector.

Consumers, regulatory bodies and manufacturers want cosmetic products to be safe, that is, to pose no or negligible health risks to the consumer (Nohynek et al., 2010; Panico et al., 2019).

Cosmetics that pose a health risk or are not suitable around the world are recalled and their use is restricted in order to prevent harm to human health.

Cosmetic recall is the process by which cosmetics are removed from the market due to failures in quality control. A recall is the orderly and systematic removal of a cosmetic that has been found to be defective or potentially hazardous after marketing (Yaros & Wood, 1979).

An analysis of cosmetic product recall reports issued by TITCK between 2014 and 2024 to protect consumer health in Türkiye identified a total of 460 recalls. Of these, 362 products were of Turkish origin. Analysis of recall trends over the years shows that approximately 42 cosmetic products are recalled annually. In 2023, a total of 151 product recall incidents were reported in Türkiye, reaching the highest number recorded.

Globally, cosmetic recalls in 2023 are reported to be at a high rate. In this context, the findings demonstrate that the data from Türkiye align with global trends (AboutLawsuits, 2023; European Union, 2024).

Cosmetic product recalls, particularly due to safety concerns, are often prompted by non-compliance with regulations, safety concerns, counterfeit/imitation products, and court/judicial

decisions. In this context, the most common finding appears to be violations of regulations.

Hair care and shampoo products account for the highest share (46.15%) of recalled cosmetics, which is a significant finding. International RAPEX data similarly shows that hair care products are frequently recalled due to microbiological contamination and high preservative content (Neza & Centini, 2016; Shaqra et al., 2012). This indicates that hair care products are a high-risk category both in Türkiye and internationally. This is followed by cream, hand and body lotion products 13.25%. It can be said that TITCK monitors almost all products and detects unsafe products and carries out the application.

In Türkiye, approximately 170,000 cosmetic products are distributed in the domestic market, of which 46,000 are domestically produced. There are 3,250 companies registered in the Ministry of Health's electronic notification system (Republic of Türkiye Ministry of Trade, 2023). A low recall rate does not necessarily indicate high product safety. Literature shows that recall numbers are related not only to product quality but also to factors such as regulatory oversight intensity, market surveillance capacity, the efficiency of notification systems, and a widespread notification culture. In this context, the low recall rates observed in Türkiye should not be interpreted as a direct indicator of high product safety. An examination of the European Union's Safety Gateway (RAPEX) system and FDA recall data clearly shows that the number of reported recalls varies between countries and years depending on differences in inspection and notification mechanisms. For example, the EU Safety Gateway platform enables the rapid dissemination of information among member states regarding products identified as hazardous. Similarly, the FDA conducts frequent audits to closely monitor recall processes. Furthermore, a lack of data and inadequacies in voluntary recall practices may contribute to low recall rates. Corporate governance culture and leadership factors can also influence recall decisions; long-serving CEOs or homogenous boards of directors may conceal minor quality issues, thereby reducing recall numbers without reflecting the true product safety situation (Ball et al., 2022; FDA, 2026; European Commission, 2026). In this context, updating cosmetic product recall data in Türkiye by comparing it with international systems may be important.

Cosmetics also still have serious deficiencies in good manufacturing practices and adverse event reporting requirements (Turnbull, 2018), so it may be safer for consumers to use branded products that they trust.

This study focuses on examining cosmetic products recalled in Türkiye. The research is limited to official recall records only. Furthermore, information such as the prevalence of recalled products in the market, usage rates, observed side effects, and completion dates of recall procedures is not available. Due to the use of retrospective data analysis, cause-and-effect relationships can only be assessed to a limited extent.

## 5. Conclusion

This study systematically analyzed cosmetic product recall reports published by the TITCK between 2014 and 2024, evaluating safety at both the product and company levels. A total of 460 products were recalled, the vast majority (78.7%) of which were domestically produced, with the highest recall rate observed in hair care and soap-shampoo products (46.15%). Reasons for recalls included factors such as incompatible ingredients, missing technical files, microbial growth, and packaging deterioration. The unique contribution of this study is the systematic analysis of concrete recall data in Türkiye, the identification of high-risk product categories, and the demonstration of the effectiveness of TITCK's post-market inspections in protecting consumer health.

To ensure more controlled post-market safety monitoring of cosmetic products, a Cosmetovigilance system similar to the pharmacovigilance systems used in the pharmaceutical sector can be established. This system can enable real-time tracking of adverse effects, incompatibilities, and recall events with the active participation of consumers. Furthermore, companies can be encouraged to adopt internal monitoring systems and transparent reporting mechanisms, thus ensuring that producer responsibility and regulatory oversight work synergistically. Increasing public and media awareness can also improve the effectiveness of recall processes and support consumer safety.

**Funding Statement**

This research received no specific grant from any funding agency, commercial or not-for-profit sectors.

In conclusion, this study presents a systematic analysis of recall data specific to Türkiye and can serve as an important reference for policymakers and industry stakeholders in mitigating risks associated with high-risk product categories.

**Author Contributions**

T.E. contributed to the conception and design of the study, data collection, data analysis, manuscript writing, and final approval of the manuscript.

**Conflicts of interest**

None.

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Sabuncuoglu Serefeddin Health Sciences

Open Access

e-ISSN: 3062-3731 2026, 8(1), 34-42 https://doi.org/10.55895/sshs.1856624

# POSTPARTUM QUALITY OF SEXUAL LIFE: A STUDY ON RELATED FACTORS

# POSTPARTUM CİNSEL YAŞAM KALİTESİ: İLİŞKİLİ FAKTÖRLER ÜZERİNE BİR ÇALIŞMA

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**Research Article**
**Received:** 05.01.2026, **Accepted:** 31.03.2026
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**Abstract**

This study aimed to determine the quality of sexual life and the biopsychosocial factors affecting it in the postpartum period. This descriptive and cross-sectional study was conducted in a province with predominantly rural sociocultural characteristics, at a university hospital and a state hospital. The sample consisted of 149 women in the fourth month postpartum. Data were collected using a Personal Information Form, the Postpartum Fourth-Month Personal and Sexual Life History Form, and the Sexual Quality of Life–Female (SQOL-F) scale. Descriptive statistics and appropriate parametric and non-parametric tests were used for data analysis. The mean SQOL-F score of the participants was 69.69±1.88. Significant associations were found between sexual quality of life and educational level, employment status, income level, partner's educational level, place of residence, type of marriage, body mass index, satisfaction with physical appearance, pre-pregnancy sexual intercourse frequency, and the presence of postpartum sexual problems ($p<0.05$). No significant relationship was observed between sexual quality of life and mode of delivery or breastfeeding status. In conclusion, sexual quality of life in the postpartum period appears to be associated with the interaction of biological, psychological, and social factors. These findings highlight the importance of addressing sexuality as an integral component of postpartum care and providing women-centered, holistic counseling services tailored to individual needs.

**Keywords:** Postpartum care, Postpartum period, Sexual health, Sexual quality of life, Women's health

**Öz**

Bu çalışma, postpartum dönemde kadınların cinsel yaşam kalitesini ve ilişkili biyopsikososyal faktörleri belirlemek amacıyla yapılmıştır. Tanımlayıcı ve kesitsel tipteki araştırma, taşrada bir üniversite hastanesi ve bir devlet hastanesinde yürütülmüştür. Araştırmanın örneklemini belirtilen hastanelerde doğum yapan 149 kadın oluşturmuştur. Veriler, Kişisel Bilgi Formu, Postpartum 4. Ayda Kişisel ve Cinsel Yaşam Öykü Formu ve Cinsel Yaşam Kalitesi Ölçeği–Kadın (SQOL-F) kullanılarak toplanmıştır. Verilerin analizinde tanımlayıcı istatistikler ile uygun parametrik ve non-parametrik testler kullanılmıştır. Kadınların SQOL-F puan ortalaması 69.69±1.88 olarak bulunmuştur. Kadınların eğitim ve gelir düzeyi, çalışma durumu, eşin eğitim düzeyi, evlilik şekli, yaşanılan yer, beden kitle indeksi, fiziksel görünümden memnuniyet, gebelik öncesi cinsel ilişki sıklığı ve postpartum dönemde cinsel sorun yaşama durumuna göre SQOL-F puan ortalaması arasında istatistiksel olarak anlamlı bir fark saptanmıştır ($p<0.05$). Doğum şekli ve emzirme durumuna göre kadınların SQOL-F puan ortalamaları karşılaştırıldığında anlamlı bir fark bulunmamıştır ($p>0.05$). Sonuç olarak postpartum dönemde cinsel yaşam kalitesi; biyolojik, psikolojik ve sosyal faktörlerin etkileşimiyle şekillenmektedir. Bu bulgular, postpartum bakım hizmetlerinde cinselliğin bütüncül bir yaklaşımla ele alınması ve kadınların bireysel gereksinimlerine duyarlı danışmanlık hizmetlerinin sunulmasının önemini ortaya koymaktadır.

**Anahtar Kelimeler:** Postpartum bakım, Postpartum dönem, Cinsel sağlık, Cinsel yaşam kalitesi, Kadın sağlığı

## 1. Introduction

The postpartum period is a critical stage in a woman's life, marked by physiological, psychological, hormonal, and social changes. During this time, sexual life is affected by perineal trauma related to the mode of delivery, hormonal changes, breastfeeding, fatigue, anxiety, and changes in relationship dynamics. The literature reports that 40–90% of women experience decreased sexual desire, dyspareunia, vaginal dryness, and decreased sexual satisfaction in the first year postpartum (Eryılmaz & Şentürk Erenel, 2023; Güler & Erbil, 2022; Koç & Oskay, 2015; Türk & Erkaya, 2019). Hormonal changes, particularly high prolactin and decreased estrogen levels due to breastfeeding, cause sexual dysfunction such as vaginal dryness, difficulty arousing, and decreased libido (Gutzeit et al., 2020; O'Malley et al., 2018). In addition to hormonal changes, episiotomy, perineal tears, or pelvic floor muscle weakness during the physical healing process can also cause pain during sexual intercourse (Atlıhan et al., 2025; Rodaki et al., 2022; Serati et al., 2010).

Psychosocial factors are also determinants of postpartum sexual life quality. During this period, adaptation to the parenting role, fatigue, changes in body image, relational satisfaction, spousal support, and mental health problems such as postpartum depression and anxiety are variables that strongly affect the quality of sexual life (Aksu & Çevik, 2023; Gutzeit et al., 2020). Therefore, sexuality in the postpartum period is a multidimensional phenomenon that should be addressed holistically, not only physiologically but also within a biopsychosocial framework (Hajimirzaie et al., 2021).

Sexual life quality; Sexual life is a broad concept encompassing a woman's sexual functions, feelings about sex, satisfaction, and relationship with her partner. Identifying changes in these areas during the postpartum period is crucial for meeting women's holistic health needs. While numerous studies in the literature examine different dimensions of postpartum sexual life, the majority have focused on sexual function and sexual dysfunction and have been conducted in urban areas. Research addressing the quality of sexual life in rural areas, where cultural norms, traditional family structures, and attitudes towards sexuality are more pronounced, remains limited. This study was conducted to determine the quality of women's sexual life in the postpartum period and the biological, psychological, and social factors that may be associated with it.

## 2. Materials and Methods

*2.1. Studying Type*

This study was conducted as a descriptive and cross-sectional study.

*2.2. Population and Sample*

The study was conducted in the maternity units of a provincial University Hospital and a State Hospital after obtaining the necessary ethical and institutional permissions. The population of the study consisted of postpartum women who gave birth at the aforementioned hospitals during the study period (1 December 2011 – 30 March 2012). The sample comprised women who delivered in these two hospitals between the specified dates, met the research criteria, and voluntarily agreed to participate in the study (N=149). According to the post hoc power analysis conducted at the end of the study, using the correlation model between the two scales (Exact test) and Cohen's recommendation for a medium effect size (p H1=0.3), a statistical power of 0.96 (1−β=0.96) was achieved with 149 participants (Lower/Upper Critical r = −0.16/0.16). The inclusion criteria were having given birth at the specified hospitals, being between 18 and 49 years of age, living with their spouse, and having no diagnosed sexual dysfunction. The exclusion criteria were the presence of a diagnosed sexual dysfunction, any serious obstetric or systemic health condition that could affect sexual life during the postpartum period, a diagnosed psychiatric disorder, not living with a spouse, reporting a significant life event affecting sexual life, and the presence of communication difficulties that could prevent participation in the data collection process.

*Data Collection Instruments*

The study data were collected using the Personal Information Form, the Postpartum 4th-Month Personal Characteristics and Sexual Life History Form, and the Sexual Quality of Life–Female (SQOL-F) questionnaire.

*Personal Information Form*

Developed in line with the literature and administered during the first interview, this form consisted of open- and closed-ended questions addressing participants' sociodemographic characteristics, obstetric history, general health status, and sexual life history (Serati vd., 2010; Symonds vd., 2005; Tuğut & Gölbaşı, 2010).

*Postpartum 4th-Month Personal Characteristics and Sexual Life History Form*

This form was developed by the researchers based on an extensive literature review and expert opinions in the field of women's health and midwifery. The form included 20 items evaluating postpartum personal characteristics, sexual life patterns, timing of resumption of sexual activity,

sexual frequency, sexual problems, partner-related factors, and other variables affecting sexual life. The form consisted predominantly of structured and semi-structured questions and was administered during the second face-to-face interview conducted at the fourth month postpartum (Serati vd., 2010; Symonds vd., 2005; Tuğut & Gölbaşı, 2010).

*Sexual Quality of Life–Female (SQOL-F)*
The SQOL-F scale was developed by Symonds et al. (2005), and its Turkish validity and reliability study was conducted by Tuğut and Gölbaşı (2010). The scale consists of 18 items rated on a 6-point Likert scale, with each item evaluated based on the previous four weeks. Higher scores indicate a better quality of sexual life (Symonds et al., 2005; Tuğut & Gölbaşı, 2010). In this study, the scale's Cronbach's alpha value was calculated as 0.86.

*2.3. Data Collection Procedure*
The Personal Information Form was administered face-to-face at the hospital to women who had given birth and voluntarily agreed to participate in the study. Contact information was obtained from participants who consented to a follow-up interview at four months postpartum, and appointments were scheduled via telephone. An appointment was scheduled for the second visit, during which the Postpartum 4th-Month Personal Characteristics and Sexual Life History Form and the SQOL-F were administered face-to-face; the interviews were conducted either in the participants' homes or at family health centers. The postpartum follow-up was conducted at four months after delivery, as this time frame was considered sufficiently distant from childbirth to allow women to have resumed sexual activity, while also being close enough to reduce recall bias.

*2.4. Data Analysis*
Data analysis was performed using the SPSS statistical software package. Descriptive statistics (number, percentage, mean, and standard deviation) were used for data evaluation. The normality of continuous variables was assessed using the Kolmogorov–Smirnov test, skewness–kurtosis values, and histogram plots. Variables demonstrating normal distribution were analyzed using parametric tests, whereas non-normally distributed variables were evaluated with non-parametric methods. Accordingly, one-way analysis of variance (ANOVA) was applied when comparing SQOL-F scores across more than two groups of independent variables, and the Tukey HSD test was used to identify the source of significant differences. For non-parametric analyses, the Kruskal–Wallis and Mann–Whitney U tests were employed. Pearson's chi-square test was used for categorical variables. Correlation analysis was conducted to examine the relationships between selected characteristics of women and SQOL-F scores. A $p$ value of $<0.05$ was considered statistically significant.

*2.5. Limitations of the study*
This article is derived from the author's master's thesis, entitled "Quality of Sexual Life in Postpartum Women and Factors Affecting It," accepted at Sivas Cumhuriyet University, Institute of Health Sciences in 2012 with thesis number 336761. It was limited to women who could be reached within a specific time frame. The study was conducted in a single region and included two hospitals predominantly serving populations with rural/provincial sociocultural characteristics; therefore, the findings cannot be generalized to other regions of Türkiye or populations with different cultural backgrounds. Additionally, due to the sensitive nature of sexuality, some participants may not have responded to the questions fully or honestly, which may have led to reporting bias.

## 3. Results
The mean total score on the Sexual Life Quality Scale for women participating in the study at the fourth postpartum month was 69.69±1.88, and it was determined that the scores obtained from the scale ranged from 22-100 (Table 1).
The average age of the participants was 28.26±5.29, and the average age of their spouses was 31.83±5.44. 44.3% of the women had completed primary education, 66.4% were unemployed, and 74.5% lived in the city center. Regarding income, it was determined that 64.4% of the participants had income equal to their expenses. 40.3% of the women had been married for 4–9 years, and 55.7% had married through arranged marriages (Table 2)

**Table 1.** Mean SQOL-F scores of women at the fourth postpartum month

| | Mean | SD | Min. | Max. |
|---|---|---|---|---|
| SQOL-F | 69.69 | 11.88 | 22.0 | 100.0 |

SD: Standart Deviation

**Table 2.** Distribution of women according to their sociodemographic characteristics

| Variable | n % | SQOL-F Mean ± SD | Statistical Value | Significant Difference |
|---|---|---|---|---|
| **Education level** | | | | |
| Primary school[a] | 66 (44.3) | 65.53±17.43 | F = 5.849 | a<c |
| High school[b] | 39 (26.2) | 68.04±21.51 | p = 0.004 | |
| University and above[c] | 44 (29.5) | 77.38±15.77 | | |
| **Employment status** | | | | |
| Employed[a] | 50 (33.6) | 77.65±15.39 | t = 14.875 | a>b |
| Not employed[b] | 99 (66.4) | 65.66±19.03 | p < 0.001 | |
| **Spouse's education level** | | | | |
| Primary school[a] | 51 (34.2) | 64.53±16.90 | F = 11.622 | a<c |
| High school[b] | 51 (34.2) | 65.46±20.79 | p < 0.001 | b<c |
| University and above[c] | 47 (31.6) | 79.86±13.88 | | |
| **Place of residence** | | | | |
| Rural[a] | 8 (25.5) | 50.13±16.81 | t =18,093 | a<b |
| City center[b] | 111(74.5) | 73.30±18.02 | p < 0,001 | |
| **Income Status** | | | | |
| Income less than expenses[a] | 35 (23.5) | 62.49±20.01 | KW=6.863 | a<c |
| Income equal to expenses[b] | 96 (64.4) | 71.48±17.48 | p=0.032 | b<c |
| Income more than expenses[c] | 18 (12.1) | 74.10±18.08 | | |
| **Method of Marriage** | | | | |
| Arranged Marriage[a] | 66 (44.3) | 63.85±17.24 | t=12.413 | a<b |
| By Meeting and Agreeing[b] | 83 (55.7) | 74.33±18.65 | p=0.001 | |
| **Age Mean ± SD:** 28.26±5.29 | | | | |
| **Spouse's age Mean ± SD:** 31.83±5.44 | | | | |

F: One Way ANOVA (The Tukey test was used in the posthoc analysis), t: Independent Sample t test, KW: Kruskal Wallis H test, NOTE: In posthoc analysis, letters (a, b, c) were used to indicate differences between groups.

Table 2 presents the mean SQOL-F scores according to women's sociodemographic characteristics. As shown in the table, a statistically significant difference was found between groups according to educational level ($F = 5.849$; $p = 0.004$). Women with a university degree or higher had significantly higher mean SQOL-F scores (77.38 ± 15.77) compared with women who had completed primary education (65.53 ± 17.43).

In addition, the mean SQOL-F score of employed women (77.65 ± 15.39) was significantly higher than that of unemployed women (65.66 ± 19.03) ($p < 0.001$). Similarly, women whose spouses had a university-level education or higher had significantly higher SQOL-F scores (79.86 ± 13.88) compared with those whose spouses had completed high school (65.46 ± 20.79) or primary education (64.53 ± 16.90) ($p < 0.001$).

A statistically significant difference was also observed between women living in urban areas and those residing in rural areas. Women living in city centers had higher mean SQOL-F scores (73.30 ± 18.02) than women living in rural areas (59.13 ± 16.81) ($p < 0.001$).

When SQOL-F scores were examined according to income status, women whose income exceeded their expenses had significantly higher scores (74.10 ± 18.08) compared with the other income groups ($p = 0.032$). Furthermore, women who married by mutual acquaintance and consent had significantly higher mean SQOL-F scores (74.33 ± 18.65) than those who married through arranged marriage (63.85±17.24) ($p=0.001$) (Table 2).

When women's pre-pregnancy sexual life characteristics were examined, those who reported having sexual intercourse more than 10 times per month before pregnancy had a mean SQOL-F score of 81.30±13.57, whereas women who reported having sexual intercourse fewer than four times per month had a mean score of 56.41±18.69. The difference between the groups was statistically significant ($F = 15.861$; $p < 0.001$).

Additionally, women who reported no sexual problems prior to pregnancy had significantly higher mean SQOL-F scores (75.23±17.81) compared with those who reported experiencing sexual problems (63.25±17.78) ($p<0.001$). However, no statistically significant differences were found in SQOL-F scores according to changes in sexual intercourse frequency during pregnancy or the presence of sexual problems during pregnancy ($p > 0.05$) (Table 3).

**Table 3.** Distribution of women according to their sexual life characteristics before and during pregnancy

| Variable | n % | SQOL-F Mean ± SD | Statistical Value | Significant Difference |
|---|---|---|---|---|
| **Frequency of sexual intercourse before pregnancy:** | | | | |
| More than 10 times a month[a] | 32 (21.5) | 81.30±13.57 | F=15.861 p=0.000 | a>c a>d b>d |
| 7-10 times a month[b] | 45 (30.2) | 74.98±13.92 | | |
| 5-6 times a month[c] | 32 (21.5) | 67.23±19.00 | | |
| Less than 4 times a month[d] | 40 (26.8) | 56.41±18.69 | | |
| **Sexual problems before pregnancy** | | | | |
| Yes[a] | 69 (46.3) | 63.25±17.78 | t=16.771 p<0.001 | a<b |
| No[b] | 80 (53.7) | 75.23±17.81 | | |
| **Frequency of sexual intercourse during pregnancy:** | | | | |
| Decreased compared to pre-pregnancy | 124(83.2) | 69.60±17.61 | KW=3.769 p=0.152 | - |
| No change compared to pre-pregnancy | 22 (14.8) | 67.57±24.35 | | |
| Increased compared to pre-pregnancy | 3 (2.0) | 88.86±6.17 | | |
| **Sexual problems during pregnancy (n=131)*** | | | | |
| Yes (decreased libido, pain, etc.) | 72 (55.0) | 69.60±17.61 | KW=3.769 p=0.152 | - |
| No | 41 (32.9) | 67.57±24.35 | | |
| Did not have intercourse during pregnancy | 18 (12.1) | 88.86±6.17 | | |

*This is the number of women who had sexual intercourse during pregnancy. Percentages are evaluated on a scale of 'n'. **This is the number of women who experienced sexual problems during pregnancy. Percentages are evaluated on a scale of 'n'. F: One Way ANOVA (The Tukey test was used in the posthoc analysis), t: Independent Sample t test, KW: Kruskal Wallis H test, NOTE: In posthoc analysis, letters (a, b, c, d) were used to indicate differences between groups.

In the evaluation based on birth and postpartum characteristics, the mean SQOL-F score of women who gave birth between 38–42 weeks of gestation (71.67±17.08) was significantly different from those who gave birth between 35–37 weeks (p=0.004). No significant difference was found between the type of birth and sexual life quality scores (p=0.838). Among women who underwent episiotomy, those who experienced problems at the suture site had a statistically significant mean SQOL-F score (48.60±20.55) compared to those who did not experience problems (73.49±15.59) (p=0.000). However, no significant relationship was found between experiencing problems at the cesarean section incision site and sexual life quality (p=0.993) (Table 4).

**Table 4.** Mean SQOL-F Score of women according to certain characteristics of birth and postpartum

| Variable | n (%) | SQOL-F Mean ± SD | Statistical Value | Significant Difference |
|---|---|---|---|---|
| **Birth Week** | | | | |
| 35-37th week[a] | 43 (29.0) | 64.93±21.76 | t=3.972 p=0.048 | a<b |
| 38-42nd week[b] | 106 (71.0) | 71.67±17.08 | | |
| **Type of delivery** | | | | |
| Normal vaginal | 22 (14.8) | 67.55±4.65 | F=10.177 p=0.838 | - |
| Assisted vaginal | 58 (38.9) | 69.78±18.46 | | |
| Cesarean section | 69 (46.3) | 70.29±18.11 | | |
| **Episiotomy suture problems (n=49)*** | | | | |
| Yes[a] | 8 (16.4) | 48.60±20.55 | t=15.365 p<0.001 | a<b |
| No[b] | 41 (83.6) | 73.49±15.59 | | |
| **Cesarean section incision site problem (n=69)**** | | | | |
| Yes | 6 (8.7) | 70.23±16.17 | t=0.000 p=0.993 | - |
| No | 63 (91.3) | 70.29±18.41 | | |

*This is the number of women who underwent episiotomy; percentages are calculated based on 'n'.
**This is the number of women who had a cesarean section; percentages are calculated based on 'n'.
F: One Way ANOVA, t: Independent Sample t test

When some characteristics were examined in the fourth month postpartum, a statistically significant difference was observed between body mass index and sexual life quality scores (p<0.001). There was a statistically significant difference between the mean SQOL-F score of women with

underweight/normal BMI (76.25±17.01) and the mean SQOL-F score of obese/morbidly obese women. A statistically significant difference was found between the SQOL-F scores of women who were satisfied with their physical appearance (76.99±16.15), those who were moderately satisfied (70.94±15.40), and those who were dissatisfied (53.66±17.96) (p<0.001). No statistically significant relationship was found between breastfeeding status, use of family planning methods, and time of initiation of sexual intercourse and sexual life quality (p>0.05).

A statistically significant difference was found between the mean SQOL-F score of women who reported a decrease in the frequency of sexual intercourse compared to pre-pregnancy (47.46±17.93) and those who reported an increase in frequency (79.61±13.97) (p=0.005). A statistically significant difference was determined between satisfaction with sexual life and SQOL-F scores (p=0.05). A statistically significant difference was found between the mean SQOL-F score of women who reported experiencing sexual problems in the postpartum period (65.50±19.22) and those who did not experience problems (78.57±13.89) (p=0.000) (Table 5)

**Table 5.** Mean SQOL-F scores of women according to some characteristics in the fourth month postpartum

| Variable | n (%) | SQOL-F Mean ± SD | Statistical Value | Significant Difference |
|---|---|---|---|---|
| **BMI (Body Mass Index)** | | | | |
| Underweight/Normal[a] | 77 (51.6) | 76.25±17.01 | F = 25.364 | a>b |
| Overweight[b] | 50 (33.6) | 64.87±18.93 | p < 0.001 | a>c |
| Obese/Morbidly Obese[c] | 22 (14.8) | 57.67±14.86 | | |
| **Satisfied with physical appearance** | | | | |
| Satisfied[a] | | | | a>b |
| Moderately satisfied[b] | 69 (46.4) | 76.99±16.15 | F = 23.746 | a>c |
| Not satisfied[c] | 45 (30.2) | 70.94±15.40 | p < 0.001 | b>c |
| | 35 (23.4) | 53.66±17.96 | | |
| **Breastfeeding status** | | | | |
| Breastfeeding | 126 (84.6) | 70.65±18.54 | KW = 1.896 | - |
| Not breastfeeding | 23 (15.4) | 64.38±19.24 | p = 0.169 | |
| **Using family planning methods** | | | | |
| Not using | 44 (29.6) | 69.21±19.01 | t = 0.039 | - |
| Using | 105 (60.4) | 69.88±18.69 | p = 0.843 | |
| **Timing to start sexual intercourse:** | | | | |
| Weeks 3-5 | | | | |
| Weeks 6-8 | 45 (30.2) | 73.63±19.12 | KW = 3.744 | - |
| Weeks 9 and later | 79 (53.0) | 68.09±17.13 | p = 0.154 | |
| | 25 (16.8) | 66.97±21.94 | | |
| **Frequency of sexual intercourse compared to before pregnancy:** | | | | a>b |
| Decreased[a] | 71 (62.4) | 47.46±17.93 | KW=50.599 | a>c |
| Unchanged[b] | 14 (26.2) | 66.01±14.48 | p=0.005 | b>c |
| Increased[c] | 12 (11.4) | 79.61±13.97 | | |
| **Sexual life satisfaction** | | | | a>b |
| Satisfied[a] | 73 (49.0) | 79.61±13.97 | KW=50.599 | a>c |
| Moderately satisfied[b] | 52 (34.9) | 66.01±14.48 | p=0.005 | b>c |
| Not satisfied[c] | 24 (16.1) | 47.46±17.93 | | |
| **Sexual problem** | | | | |
| Yes[a] | 96 (64.4) | 65.50±19.22 | t=18.032 | |
| No[b] | 53 (35.6) | 78.57±13.89 | p<0.001 | a<b |

*This is the number of women who underwent episiotomy; percentages are calculated based on 'n'
**This is the number of women who had a cesarean section; percentages are calculated based on 'n'
Average time to resumption of sexual intercourse: 40.93±1.27 days
F: One Way ANOVA (The Tukey test was used in the posthoc analysis), t: Independent Sample t test, KW: Kruskal Wallis H test (The Dunn test was used in the posthoc analysis), NOTE: In posthoc analysis, letters (a, b, c) were used to indicate differences between groups.

## 4. Discussion

In this study, women's sexual quality of life was found to be at a moderate level in the fourth month postpartum, and the factors associated with sexual quality of life were associated with biological, psychological, and sociodemographic variables. These findings are consistent with the existing literature emphasizing that sexuality in the postpartum period is not limited to physiological recovery alone but is also strongly influenced by psychosocial and relational factors (Aksu & Çevik, 2023; Gutzeit et al., 2020).

The study demonstrated that as women's educational level and their spouses' educational level increased, sexual quality of life scores significantly improved. Higher educational attainment may be associated with greater access to sexual health information, enhanced body awareness, and improved communication skills. Previous studies have similarly reported that women with higher educational levels are more likely to express sexual concerns during the postpartum period and report higher levels of sexual satisfaction (Güler & Erbil, 2022; Türk & Erkaya, 2019). Likewise, higher educational levels among spouses have been shown to positively influence sexual quality of life by enhancing partner support and relational harmony (Gutzeit et al., 2020).

The finding that employed women and those with better income status had higher sexual quality of life scores suggests that economic independence and social participation may be associated with higher self-esteem and better sexual life outcomes. The literature also highlights that reduced economic stress during the postpartum period has beneficial effects on psychological well-being and couple relationships (Aksu & Çevik, 2023; Zaręba et al., 2025). The higher sexual quality of life observed among women living in urban areas compared with those residing in rural settings may be related to differences in cultural norms, perceptions of privacy, and access to health services. In rural and provincial contexts, sexuality is often a more restricted topic of discussion, which may hinder the expression of sexual concerns (Türk & Erkaya, 2019).

When the relationship between type of marriage and sexual quality of life was examined, women who married by mutual acquaintance and consent demonstrated higher sexual quality of life compared with those who entered into arranged marriages. This finding suggests that premarital emotional closeness and communication may be associated with sexual harmony and satisfaction in the postpartum period. The literature consistently identifies relationship satisfaction and spousal communication as among the strongest predictors of postpartum sexuality (Gutzeit et al., 2020; O'Malley et al., 2018)

Evaluation of pre-pregnancy sexual life characteristics revealed that women who reported more frequent sexual intercourse and no sexual problems prior to pregnancy had higher sexual quality of life during the postpartum period. This finding indicates that may be associated with better postpartum sexual well-being on postpartum sexual well-being. Similarly, previous studies have reported that a history of sexual problems prior to pregnancy is associated with postpartum sexual dysfunction (Arampatzi et al., 2025; Güler & Erbil, 2022). The absence of a significant association between mode of delivery and sexual quality of life suggests that mode of delivery alone does not determine postpartum sexuality. Consistent with this finding, the literature reports inconsistent results regarding postpartum sexual outcomes following vaginal versus cesarean delivery (Rodaki et al., 2022; Serati et al., 2010). Some studies have indicated that cesarean delivery is associated with higher sexual function scores three months postpartum compared with vaginal delivery (Bağlar et al., 2025). However, evidence suggests that beyond the first six months postpartum, sexual quality of life is more closely related to obstetric interventions rather than mode of delivery itself (Hajimirzaie et al., 2021). For example, women experiencing complications related to episiotomy sutures have been shown to report significantly lower sexual quality of life, suggesting an association between perineal trauma and lower sexual quality of life (Demir et al., 2021). Numerous studies have emphasized that episiotomy-related pain and delayed healing contribute to dyspareunia in the postpartum period (Atlıhan et al., 2025; Serati et al., 2010).

An increase in body mass index and dissatisfaction with physical appearance during the postpartum period were associated with lower sexual quality of life. Disturbances in body image may be associated with reduced feelings of attractiveness, thereby diminishing sexual desire and satisfaction (Gillen et al., 2025). This finding aligns with previous studies demonstrating a significant relationship between postpartum body image and sexual satisfaction (Aksu & Çevik, 2023; Gutzeit et al., 2020).

The lack of a significant association between breastfeeding status and sexual quality of life suggests that hormonal changes do not result in sexual dysfunction to the same extent in all women. Although increased prolactin levels and decreased estrogen during lactation have been associated with vaginal dryness and reduced libido, these effects appear to be shaped by individual differences and psychosocial factors (Gutzeit et al., 2020; O'Malley et al., 2018). One study reported decreased sexual

quality of life among women in the second to fifth postpartum months, attributing this decline to hormonal changes and variations in breastfeeding frequency (Topaloğlu Ören & Yaşar, 2023). Dyspareunia, decreased sexual desire, and reduced sexual satisfaction are widely reported in the literature as common postpartum concerns associated with lower sexual quality of life (Eryılmaz & Şentürk Erenel, 2023; Koç & Oskay, 2015; Üstgörül & Yanikkerem, 2021). However, some studies have also suggested that breastfeeding may strengthen emotional bonding between partners and enhance sexual satisfaction among women (Adeli et al., 2025).

The findings of this study indicate that sexual quality of life appears to be associated with a complex interaction of biological, psychological, and social factors. These results highlight the necessity of addressing sexuality as an integral component of postpartum care rather than limiting follow-up to physical recovery alone. In this context, individualized, holistic, and midwife-led counseling approaches that are responsive to women's specific needs may play a critical role in supporting postpartum sexual well-being.

## 5. Conclusion

This study determined that women's sexual quality of life during the postpartum period was at a moderate level and was significantly associated with sociodemographic characteristics, pregnancy- and birth-related factors, body image, and postpartum sexual problems. Educational and income levels, employment status, type of marriage, episiotomy-related complications, and sexual problems experienced during the postpartum period emerged as key factors associated with sexual quality of life. In addition, the association between pre-pregnancy sexual life characteristics and postpartum sexual quality of life highlights the importance of preconception care in supporting women's sexual well-being across the reproductive continuum. Incorporating sexual health counseling into preconception care may contribute to strengthening postpartum sexual adjustment and overall well-being. These findings suggest that systematic assessment and counseling related to sexual health should be incorporated into routine postpartum care services. Integrating sexuality into standard postpartum follow-up by healthcare professionals may facilitate early identification of sexual difficulties and enable timely referral and intervention. Additionally, longitudinal studies involving populations with diverse sociocultural backgrounds are recommended to provide a more comprehensive understanding of postpartum sexual quality of life and its determinants.

## Ethics Committee Approval

Ethical guidelines were followed in the research, and the principles of the Helsinki Declaration were adhered to. Prior to the study, permission was obtained from the Provincial Health Directorate where the study was to be conducted, under number B10.4.1SM.4.60.00.09.774/391.15676 and dated 17.12.2010. However, since ethical committee approval was not mandatory at the time the study was conducted, ethical committee approval is not available.

## Author Contributions

Concept: ZG; Design and Supervision: ZG; Resources: VE; Data Collection and/or Processing: VE; Analysis and/or Interpretation: ZG, VE; Literature Search: VE; Writing – Original Draft: VE; Critical Review: ZG.

## Acknowledgement

The authors would like to thank all women who voluntarily participated in this study.

## Conflicts of interest

The authors declare that there is no conflict of interest.

## Funding Statement

No external funding was received for this research. This article was developed from a Master's thesis.

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Sabuncuoglu Serefeddin Health Sciences

Open Access

e-ISSN: 3062-3731 2026, 8(1), 43-48 https://doi.org/10.55895/sshs.1836277

# WHAT IS THE NEW BIOMARKER CALLED ZONULIN?

# YENİ BİYOBELİRTEÇ ZONULİN NEDİR?

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**Review Article**
**Received:** 04.12.2025, **Accepted:** 31.12.2025
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**Abstract**
The human intestine, one of the body's largest barriers against potential external factors, performs this function through the tight junction elements between intestinal epithelial cells. Although more than 150 molecular components are known to form these tight connections, "zonulin" is the only identified endogenous molecule. Zonulin levels have been observed to increase in situations where intestinal permeability rises, as well as in conditions such as intense bacterial exposure, gluten enteropathy, various autoimmune diseases, and neurodevelopmental disorders. Zonulin, which appears to be a molecule that can be used in the diagnosis and monitoring of many such diseases, is considered a promising biomarker that may change the course of clinical practice in the follow-up of numerous disorders in the future.

**Keywords:** Autoimmunity, Biomarker, Tight junction, Zonulin

**Öz**
İnsan bağırsağı; vücudumuzun olası dış etkenlere yönelik en büyük bariyerlerinden olmakla beraber, bu görevi intestinal epitel hücreleri arasındaki "tight junction" (sıkı bağlantı) elemanlarıyla gerçekleştirmektedir. Bu sıkı bağlantıyı oluşturan 150'nin üstünde moleküler komponent bulunmakla beraber, saptanmış tek endojen molekül zonulindir. Barsak permeabilitesinin arttığı durumda arttığı görülen zonulin molekülünün; yoğun bakteri maruziyeti, gluten enteropatisi, birçok otoimmün hastalık ve nörogelişimsel bozuklukla birlikte yükseldiği görülmüştür. Bu ve benzeri birçok hastalığın tanı ve takibinde kullanılabilecek bir molekül olduğu görülen zonulinin; gelecekteki kullanımıyla, klinik pratikte birçok hastalığın takibi için rutin izlemi değiştirebilecek bir molekül olduğu düşünülmektedir.

**Anahtar Kelimeler:** Otoimmünite, Biyobelirteç, Sıkı bağlantı, Zonulin

## 1. Introduction

The length of human intestine is approximately 8–9 meters, representing the largest interface between the body and the external environment. The intestinal mucosa, composed of a single layer of tightly connected epithelial cells, serves as the primary barrier against environmental exposure. Covering an extensive surface area of roughly 200 $m^2$, this mucosa is continuously exposed to and interacts with external microorganisms, dietary components, metabolites, and other environmental factors (Chieppa M et al., 2006).

Tight junctions between intestinal epithelial cells are essential structures that regulate intercellular antigen trafficking (Arrieta MC et al.,2006). These junctions play a critical role in maintaining epithelial integrity under both physiological and pathological conditions (Nov, Turner JR., 2009). Initially considered static and impermeable, the understanding of tight junctions was revised following the identification of zonula occludens-1 (ZO-1) in 1993 (Itoh M et al., 1993).

Subsequent research has revealed that over 150 molecular components, including occludin (Furuse M. et al.,1993), claudins, junctional adhesion molecules (JAMs) (Martìn-Padura et al., 1998), tricellulin (Ikenouchi J et al., 2005), and angulins (Higashi T et al., 2013), contribute to the tight junction complex. Despite this extensive molecular characterization, the functional mechanisms governing intercellular tight junctions remain understoodincompletely.

Recognition of the significance of intestinal permeability in human health led to one of the

most notable discoveries in this field: zonulin, which is currently regarded as the only identified endogenous protein that physiologically modulates intestinal permeability (Fasano A et al., 2000).

## 2. Materials and Methods

Zonulin is a member of the protein family identified approximately 20 years ago and serves as the precursor of haptoglobin-2 (HP-2), known as prehaptoglobin-2 (Tripathi A et al., 2009; Rittirsch D et al., 2013). Haptoglobins initially evolved from proteins associated with the complement system and have been found to have additional functions over time, including the regulation of intercellular tight junctions (Fasano A et al., 2011).

Various luminal factors can trigger zonulin release. Among these, intestinal bacterial overgrowth and gluten exposure have been identified as the most potent inducers (El Asmar R et al., 2002; Drago S et al., 2006). Furthermore, intestinal infections have been shown to disrupt barrier integrity, contributing to the pathogenesis of allergic, autoimmune and inflammatory diseases (Fasano A et al., 2012).

Zonulin release has been demonstrated to be MyD88-dependent (Thomas KE et al., 2006). MyD88 is an adaptor protein that mediates innate immune responses. Upon activation, ZO-1 dissociates from the tight junction complex, resulting in increased intestinal permeability (Clemente MG et al., 2003).

Gliadin binds to CXCR3 receptors on intestinal epithelial cells and stimulates zonulin release via MyD88 signalling. This process suggests that gluten may be mistakenly perceived as a harmful protein through the zonulin pathway (Lammers KM et al., 2008).

These findings indicate that activation of the zonulin pathway may serve as a defense mechanism, facilitating the clearance of harmful microbes while modulating innate immune responses to changes in the intestinal microbiota. This response appears particularly relevant in conditions of increased bacterial colonization or dysbiosis in the small intestine (Fasano A et al., 2020).

All these observations suggest that alterations in the intestinal microbiota can influence intestinal permeability, and enhanced antigen translocation may contribute to the development of chronic inflammatory diseases in genetically susceptible individuals (Falszewska A et al., 2018).

Zonulin, as a precursor of HP-2, protects against hemoglobin-mediated oxidative tissue damage. It exists as a single-chain protein comprising alpha (α) and beta (β) subunits (Nelson, 2020). Zonulin can indirectly activate the epidermal growth factor receptor (EGFR) either directly or via proteaseactivated receptor 2 (PAR2). This activation modulates trans-epithelial electrical resistance (TEER) and regulates intestinal permeability.

Upon cleavage by proteolytic enzymes, zonulin becomes a double-chain molecule that loses its ability to bind EGFR, thereby functioning as an inflammatory biomarker (Fasano A et al., 2011). Zonulin and occludin molecules have molecular weights ranging from 45,000 to 65,000 Daltons (Da) (Vanuytsel T et al., 2013, Furuse M et al., 1993).

Molecules larger than 5,000 Da are immunogenic and can activate immune cells, which explains the rapid fluctuations in zonulin levels over minutes or hours (Sapone A et al., 2006; Yao Z et al., 2016). Once in circulation, these molecules are cleared by macrophages or Kupffer cells in the liver. The half-life of circulating zonulin ranges from 4 minutes to 4 hours (Vojdani A et al., 2017). Inpatients with sepsis in intensive care units, serum zonulin levels were reported to fluctuate 2- to 10-fold over a six-day period (Klaus DA et al., 2013).

### *2.1. Zonulin-Associated Diseases*

Increased intestinal permeability has been implicated in the pathogenesis of numerous inflammatory and autoimmune diseases. Disruption of the intestinal barrier allows antigens to penetrate the submucosa, which, in genetically susceptible individuals, can trigger autoimmune responses through molecular mimicry. Depending on this issue, serum zonulin levels serve as an important biomarker in these conditions (Fasano A et al., 2011).

#### *2.1.1. Celiac Disease*

Celiac disease (CD) is an autoimmune enteropathy triggered by the ingestion of gluten-containing cereals in genetically susceptible individuals, and it can be reversed by dietary gluten withdrawal. Gluten peptides that are incompletely digested bind to CXCR3 receptors, inducing zonulin release. Due to the well-characterized role of zonulin in the pathogenesis of CD, this condition has been widely used as a model to study zonulin-mediated effects (Gorelick MH et al., 1997).

Although gluten stimulates zonulin release in both healthy individuals and CD patients, the magnitude and duration of zonulin secretion are significantly higher in affected patients, pointing a marked increase in intestinal permeability (Gopalakrishnan S et al.,2012).

#### *2.1.2. Type 1 Diabetes Mellitus*

Type 1 diabetes mellitus (T1DM) is a chronic autoimmune disorder resulting from the destruction of pancreatic insulin-producing β-cells. Although its pathogenesis is not fully elucidated, studies in both animal models and humans have

demonstrated that intestinal permeability increases prior to T1DM onset (Carratù R et al., 1999).

Pre-diabetic assessments have shown that approximately 50% of T1DM patients exhibit elevated serum zonulin levels. Interestingly, about 25% of first-degree healthy relatives of patients also demonstrate increased zonulin levels (Sapone A et al., 2006). These findings suggest that zonulin may serve as an early biomarker and potential contributing factor in T1DM development.

*2.1.3. Inflammatory Bowel Diseases*

Elevated intestinal permeability has been shown to play a key role in the pathogenesis of inflammatory bowel diseases (IBD) (Buhner S et al, 2006). Clinical studies indicate that patients with active Crohn's disease exhibit increased serum and fecal zonulin levels, whereas this elevation is less pronounced in ulcerative colitis patients (Malíčková K et al., 2017).

More recent research has reported that zonulin levels are significantly higher in both IBD subtypes compared to healthy controls, and serum zonulin concentrations negatively correlate with disease duration (Caviglia GP et al., 2019).

*2.1.4. Multiple Sclerosis*

Studies using the experimental autoimmune encephalomyelitis (EAE) model indicate that Zonulin mediated intestinal permeability increases during the early stages of multiple sclerosis (MS) development (Nouri M et al., 2014).

MS patients show enhanced permeability in both the blood-brain barrier (BBB) and intestinal barrier. Imaging studies demonstrate significantly elevated serum zonulin levels in MS patients with BBB disruption. Moreover, initial zonulin concentrations correlate with disease progression in progressive MS, relapsing-remitting MS, they reflect BBB integrity alterations (Camara-Lemarroy CR et al.,2020).

These data suggest that zonulin may modulate both intestinal and BBB permeability, contributing to the gut-brain axis in neuroinflammatory processes.

*2.1.5. Obesity*

Obesity and associated metabolic disorders-including hypercholesterolemia, type 2 diabetes (T2DM), coronary artery disease, hypertension, and stroke-are linked to chronic inflammation and often correlate with dysregulation of the zonulin pathway (Olszanecka-Glinianowicz M et al., 2011).

Multiple studies report that serum zonulin levels are significantly higher in obese individuals compared to non-obese controls (Kuzma JN et al., 2020). Correlations between zonulin concentrations and total gut bacterial load suggest that microbiotadysbiosis may drive zonulin elevation. Consequently, increased intestinal permeability to endotoxins and associated microinflammation have been implicated in obesity-related pathophysiology (Gharial J et al., 2017).

*2.1.6. Irritable Bowel Syndrome*

Irritable bowel syndrome (IBS) is another condition associated with increased intestinal permeability (Camilleri M et al., 2007). Specifically, patients with diarrhea-predominant IBS exhibit elevated serum zonulin levels and involvement of protease-activated receptor 2 (PAR2) in the process (Linsalata M et al., 2018, Singh P et al., 2019).

*2.1.7. Cancer*

Recent evidence suggests that enhanced antigen translocation may contribute to the initiation of certain cancers. Zonulin, as a biomarker of epithelial and endothelial permeability, has been associated with multiple tumor types.

Notably, gliomas and hepatocellular carcinomas have been linked with elevated zonulin levels, which are often considered alongside increased permeability in these malignancies (Díaz-Coránguez M et al., 2013, Wang X et al., 2019).

*2.1.8. Neuroinflammatory Disorders*

Compromised intestinal barrier function can be assessed via immune responses (IgG, IgA, IgM) against proteins such as occludin and zonulin. Barrier disruption increases the systemic circulation of microbiota-derived molecules, triggering immune activation and cytokine production.

This phenomenon has been reported in various neuroimmune disorders, including chronic fatigue syndrome, autism spectrum disorder, major depressive disorder, and schizophrenia (Ajamian M et al., 2019). Zonulin-mediated permeability increases are thought to contribute to neuroinflammation in these conditions.

## 3. Conclusion

Zonulin is an important molecule contributing the pathogenesis of many inflammatory processes in the human body related with intestinal permeability. Recent studies focus on the mechanisms of regulation of the relationship between the intestines and the external environment. The stability of intestinal barrier is the key of all systems of the body. Zonulin may be appreciated as a biomarker in the follow up of autoinflammatory diseaseand predicting inflammatory courses both of which are related with damaged intestinal barrier.

## Author Contributions

Idea and design: E.T., S.Y.,
Data collection and processing: E.T.,
S.Y. Analysis and interpretation of data: E.T., S.Y.
Writing of significant part of the article: E.T., S.Y.

**Conflicts of interest**
None.

**Funding Statement**
No external funding was received for this research.

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Sabuncuoglu Serefeddin Health Sciences

Open Access

e-ISSN: 3062-3731 2026, 8(1), 49-54 https://doi.org/10.55895/sshs.1848498

# SIMULATION-BASED BREASTFEEDING EDUCATION: A LITERATURE REVIEW

# SİMÜLASYON DESTEKLİ EMZİRME UYGULAMALARI: LİTERATÜR DERLEMESİ

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**Review Article**
**Received:** 24.12.2025, **Accepted:** 04.03.2026
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**Abstract**
Breastfeeding is critically important for protecting and promoting maternal and infant health; however, it is a complex process influenced by numerous individual, sociocultural, and environmental factors. The mother's level of knowledge, self-confidence, and professional support are among the key determinants in initiating and maintaining breastfeeding. In this context, breastfeeding education stands out as one of the fundamental interventions for increasing breastfeeding success. However, traditional educational approaches, which are often based on passive learning, may limit the effective acquisition of breastfeeding as a psychomotor skill. In recent years, simulation-based education methods, which have become widespread in health education, allow for the simultaneous development of cognitive, affective, and psychomotor skills by providing real-life experiences in a safe environment. The purpose of this review is to examine simulation-based applications used in breastfeeding education, evaluate their effects on breastfeeding skills and self-efficacy, and provide recommendations for healthcare professionals based on the current literature. The studies reviewed demonstrate that simulation-based breastfeeding education improves mothers' breastfeeding skills, increases their self-confidence, and is effective in translating knowledge into practice.

**Keywords:** Breastfeeding, Education, Infant, Mother, Simulation

**Öz**
Emzirme, anne ve bebek sağlığının korunması ve geliştirilmesi açısından kritik öneme sahip olmakla birlikte, çok sayıda bireysel, sosyokültürel ve çevresel faktörden etkilenen karmaşık bir süreçtir. Emzirmenin başlatılması ve sürdürülmesinde annenin bilgi düzeyi, özgüveni ve profesyonel destek alması önemli belirleyiciler arasında yer almaktadır. Bu bağlamda emzirme eğitimleri, emzirme başarısını artırmada temel müdahalelerden biri olarak öne çıkmaktadır. Ancak geleneksel eğitim yaklaşımlarının çoğunlukla pasif öğrenmeye dayanması, psikomotor bir beceri olan emzirmenin etkin biçimde kazandırılmasını sınırlayabilmektedir. Son yıllarda sağlık eğitiminde yaygınlaşan simülasyon temelli eğitim yöntemleri, gerçek yaşam deneyimlerini güvenli bir ortamda sunarak bilişsel, duyuşsal ve psikomotor becerilerin birlikte geliştirilmesine olanak tanımaktadır. Bu derlemenin amacı, emzirme eğitiminde kullanılan simülasyon temelli uygulamaları incelemek, bu uygulamaların emzirme becerileri ve öz-yeterlilik üzerindeki etkilerini değerlendirmek ve mevcut literatür doğrultusunda sağlık profesyonellerine yönelik öneriler sunmaktır. İncelenen çalışmalar, simülasyon temelli emzirme eğitimlerinin annelerin emzirme becerilerini geliştirdiğini, özgüvenlerini artırdığını ve bilgiyi uygulamaya dönüştürmede etkili olduğunu göstermektedir.

**Anahtar Kelimeler:** Emzirme, Eğitim, Bebek, Anne, Simülasyon

## 1. Introduction

Breastfeeding is the most effective method for delivering breast milk the most valuable nutrient for a newborn's healthy start in life, maintenance of health, and support of development to the infant. The World Health Organization (WHO) and the United Nations Children's Fund (UNICEF)

recommend that newborns should begin breastfeeding within the first half hour after birth, be exclusively breastfed for the first six months of life, and continue breastfeeding with the addition of nutritionally adequate and safe complementary foods from six months until at least two years of age (World Health Organization, 2023).

Globally, approximately three quarters of infants are born in hospitals and other healthcare facilities providing birth services, and the antenatal and postnatal care practices offered in these settings directly affect the breastfeeding process and maternal and infant health outcomes. Mothers need quality care and the support of trained healthcare workers to initiate and maintain breastfeeding, anticipate and prevent potential difficulties, and appropriately manage problems that arise. In response to these needs, the Ten Steps to Successful Breastfeeding were developed by WHO and UNICEF in 1989 to define best practices in perinatal maternal and newborn care, and since 1991, the Baby-Friendly Hospital Initiative has aimed to integrate these practices into health systems. Updated in 2018 in light of comprehensive evidence, the Ten Steps and the restructured Baby-Friendly Hospital Initiative stand out as an effective public health approach for protecting, supporting, and ensuring the sustainability of breastfeeding. However, current data show that in only 14% of countries do the majority of births occur in baby-friendly health facilities, and the rate of postpartum breastfeeding observation by trained healthcare workers is limited to 20%; this situation indicates that the Ten Steps need to be implemented more widely and effectively within health systems to achieve the global targets of 40% set for 2030 (UNICEF, 2025; WHO, 2025).

When examining UNICEF's 2017 and 2024 reports, Turkey is among the countries that have recorded at least a 10 percentage point increase in exclusive breastfeeding rates. The most recent estimate for exclusive breastfeeding among infants aged 0–5 months in Turkey, from 2017, is 30%, which is reported to represent an increase of over 50% compared to the value reported in the 2017 report (UNICEF, 2025). Since breast milk is considered the best source of nutrition for infants under six months, maintaining breastfeeding is extremely important. To effectively continue breastfeeding and increase breastfeeding rates, it is essential to identify the factors affecting the breastfeeding process and plan and implement appropriate interventions targeting these factors (Cohen et al., 2018).

Breastfeeding is not merely a biological process; it is a complex behavior influenced by numerous factors including the mother's individual characteristics, sociocultural and economic status, mode of delivery, health system support, previous breastfeeding experiences, and environmental conditions. These factors affecting breastfeeding success can be both inhibitory and supportive. The mother's age, education and socioeconomic level, pregnancy planning status, mode of delivery, and level of knowledge about breastfeeding are among the important determinants in initiating and maintaining breastfeeding. Additionally, conditions such as health problems in the newborn, preterm birth, low birth weight, and birth complications can make it difficult to initiate breastfeeding in the early period (Erçin & Köseoğlu, 2022; Tang et al., 2019). While some of these factors are beyond the direct control of parents, the literature emphasizes that the mother's level of knowledge, self-confidence, and professional support in breastfeeding are determinants in initiating and maintaining breastfeeding (Cohen et al., 2018; Erçin & Köseoğlu, 2022; Tang et al., 2022).

Breastfeeding education is among the most effective interventions for increasing breastfeeding success (Dantas et al., 2022). Structured breastfeeding education provided during the prenatal and postnatal periods has been shown to positively affect mothers' breastfeeding knowledge level, self-efficacy perception, and breastfeeding continuity (Iliadou et al., 2018; Piro & Ahmed, 2020; Tang et al., 2022). However, traditional educational approaches, which are often based on passive learning, may limit the effective learning of breastfeeding as a psychomotor skill (Mulcahy et al., 2022). Today, simulation-based applications stand out as an innovative field that is increasingly developing and achieving successful results in health education. Simulation-based education allows for the simultaneous development of cognitive, affective, and psychomotor skills by enabling individuals to experience real-life situations in a safe environment (Motola et al., 2013). The use of simulation in breastfeeding education has been reported to be effective in improving mothers' ability to apply correct breastfeeding positions, develop milk expression skills, and increase breastfeeding self-efficacy (Beatrice et al., 2020; Webber et al., 2021). Accordingly, this review aims to examine simulation-based breastfeeding applications.

## 2. Supportive Interventions Used to Increase Breastfeeding Success

Breastfeeding education can be provided to individuals, groups, families, or broader communities. These educational programs may utilize verbal instruction, media and mass communication tools, and demonstration and practice methods (Gavine et al., 2022). In most studies aimed at increasing breastfeeding success

rates and supporting sustainability, educational programs are directed at women, including prenatal group education, individual counseling, and peer support interventions (Gavine et al., 2022; Iliadou et al., 2018). These studies demonstrate that effective breastfeeding education can increase awareness and improve knowledge levels among participants (Iliadou et al., 2018; Piro & Ahmed, 2020). However, in these educational programs, women generally assume a passive role (Kaiza & Joho, 2023; Webber et al., 2021). Since breastfeeding is a psychomotor skill, learning through active participation in a realistic environment is essential for successful skill acquisition and achieving competency, which aligns with adult education principles emphasizing that the most effective learning occurs through direct involvement in the educational process (Motola et al., 2013). Given the limitations of traditional teaching methods in enhancing breastfeeding knowledge and practices (Kaiza & Joho, 2023), there has been a growing shift toward active learning approaches in which participants explore and experience educational content directly. Active learning techniques, such as role-playing and simulation, enable deeper engagement with the material and have been shown to be more effective than passive methods such as reading or lecture-based instruction (Beatrice et al., 2020).

*2.1. Simulation-Based Breastfeeding Education*

Simulation involves mimicking the behavior of a real situation or process, and learners respond as if they were reacting to the situation under real conditions. This is an artificially planned situation using tools or mannequins as a representation of real life (Jeffries & National League for Nursing, 2012; Motola et al., 2013). From the perspective of both learners and health educators, simulation offers distinct advantages. Learners develop skills by translating knowledge into practice and can apply what they have learned, make decisions, and solve problems when they encounter a similar situation (Kaiza & Joho, 2023). Health educators, in turn, can use simulation as an educational tool for simultaneously developing cognitive, affective, and psychomotor skills in their students. Three levels of fidelity have been identified in simulation-based education: low, moderate, and high-fidelity simulators (Motola et al., 2013; Ryall et al., 2016).

*Low-fidelity simulators:* These are generally static, cannot fully reflect real-life experience or contextual situations, and the materials used do not completely match the task being practiced. Low-fidelity simulation models are used in the first stage of skills training for acquiring and developing basic psychomotor competencies. These models include specific anatomical region models such as breast models used for practicing latch techniques and positioning, pelvis and uterus organ models, and gynecological examination mannequins (Akalın & Şahin, 2019; Amin et al., 2019). In the context of breastfeeding education, low-fidelity simulators such as knitted or fabric breast models and infant dolls are commonly used to teach mothers correct positioning and attachment techniques (Kaiza & Joho, 2023; Agrina et al., 2019).

*Moderate-fidelity simulators:* These offer a higher level of realism compared to low-fidelity simulators. These models include physiological indicators such as heart, lung, and respiratory sounds, as well as pulse beats (Amin et al., 2019).

*High-fidelity simulators:* These simulators use realistic and sophisticated materials to represent the real environment and add a high level of realism to training through the ability to adapt scenarios to physical signs and clinical situations (Amin et al., 2019). Although high-fidelity simulators are widely used in various clinical training areas, their application specifically in breastfeeding education remains limited in the literature. However, the potential of these advanced simulators to create realistic breastfeeding scenarios, including infant feeding cues and maternal-infant interaction, represents a promising area for future development (Jeffries & National League for Nursing, 2012).

In the context of breastfeeding education, simulation-based methods offer several specific advantages:

- Allowing mothers to practice correct breastfeeding positions and latch techniques in a safe, non-stressful environment,
- Enabling mothers to learn from errors without risk to the infant, viewing mistakes as a natural part of the learning process,
- Developing manual breast milk expression skills through hands-on practice with realistic breast models (Beatrice et al., 2020),
- Building maternal self-confidence and self-efficacy in breastfeeding before the actual experience (Webber et al., 2021),
- Enabling multiple mothers or healthcare students to practice simultaneously on standardized scenarios,
- Providing immediate feedback from trained instructors to correct positioning and technique errors,
- Supporting the transfer of learned skills to real breastfeeding situations, thereby improving breastfeeding initiation and duration (Agrina et al., 2019; Kaiza & Joho, 2023).

Considering these advantages of simulation, simulation-based education methods appear to have significant potential not only in developing clinical skills but also in improving the quality of

education provided during pregnancy. Traditional breastfeeding education provided during the prenatal period is often theoretical and narrowly focused, which may limit pregnant women's adequate preparation for the real experience of breastfeeding. Therefore, simulation-based approaches, which offer the opportunity to experience real-life scenarios in a safe environment, stand out as an effective educational method that supports pregnant women in starting the breastfeeding process more prepared, confident, and aware (Sayres & Visentin, 2018; Tang et al., 2022). Research findings consistently support the effectiveness of simulation in breastfeeding education. Webber et al. (2021) found that mothers who received simulation training could hold their babies to the breast correctly and guide other mothers. Agrina et al. (2019) demonstrated that simulation-supported breastfeeding counseling helped learners retain skills through repetition, while Beatrice et al. (2020) reported that 97% of mothers acquired adequate milk expression skills after simulation-based training, underscoring the importance of hands-on demonstration in skill acquisition.

In the literature, studies on breastfeeding education using simulators with particularly high-fidelity levels are not encountered; however, simulation-based training using low to moderate-fidelity simulators has been observed to be effective in improving women's breastfeeding skills (Agrina et al., 2019). Increasing variation and difficulty levels in simulations and adapting them to participants' weaknesses appear to be important areas to focus on in the future (Amin et al., 2019), and quality breastfeeding education that includes simulation-based clinical training opportunities is a critical component in improving care for breastfeeding mothers (Webber et al., 2021).

## 3. Conclusion

This review reveals that breastfeeding is a multidimensional process and that education-based interventions play a central role in increasing breastfeeding success. The literature shows that simulation-based breastfeeding education positively affects mothers' skill acquisition, self-efficacy perception, and breastfeeding practices compared to traditional approaches. Particularly, simulation-based education provided during pregnancy is observed to support mothers in starting the breastfeeding process more prepared, aware, and confident.

Simulation-based education offers significant advantages in breastfeeding training by providing a safe learning environment where mothers can practice without fear of making mistakes. Unlike traditional didactic methods that rely primarily on verbal instruction and passive learning, simulation allows mothers to actively engage with realistic scenarios, develop muscle memory for correct positioning and latch techniques, and build confidence through repeated practice. This experiential learning approach aligns with adult learning principles, which emphasize that meaningful learning occurs through active participation and hands-on experience. The findings of this review also highlight the potential role of simulation-based education in addressing common breastfeeding challenges. Many mothers discontinue breastfeeding early due to perceived insufficient milk supply, difficulties with latching, nipple pain, or lack of confidence. By providing opportunities to practice problem-solving strategies and troubleshooting techniques in a controlled environment, simulation-based training can better prepare mothers to overcome these challenges when they arise in real-life situations. Furthermore, the immediate feedback provided during simulation exercises enables mothers to correct errors and refine their techniques before encountering actual breastfeeding situations.

From a healthcare system perspective, integrating simulation-based breastfeeding education into prenatal care programs could contribute to achieving global breastfeeding targets set by WHO and UNICEF. Healthcare professionals, including nurses, midwives, and lactation consultants, can benefit from simulation training to enhance their counseling skills and ability to support breastfeeding mothers effectively. The standardization of simulation-based training protocols could ensure consistent quality of breastfeeding education across different healthcare settings.

However, the limited number of studies on the use of high-fidelity simulators in breastfeeding education indicates the need for further research in this area. Most existing studies have utilized low to moderate-fidelity simulators, and the comparative effectiveness of different fidelity levels remains unclear. Additionally, the cost-effectiveness of simulation-based breastfeeding education, particularly when using high-fidelity equipment, requires further investigation to support widespread implementation.

In the future, it is recommended to plan studies that compare different simulation levels, evaluate long-term breastfeeding outcomes, and address integration into clinical practice. Research should also explore the optimal timing, duration, and frequency of simulation-based interventions, as well as the potential of emerging technologies such as virtual reality and augmented reality in breastfeeding education. Studies examining the impact of simulation-based training on exclusive

breastfeeding rates at six months and continued breastfeeding at one and two years would provide valuable evidence for policy makers and healthcare administrators.

The widespread adoption of simulation-based breastfeeding education is considered an effective and innovative approach that can contribute to improving maternal and infant health. By empowering mothers with practical skills and confidence, simulation-based education has the potential to increase breastfeeding initiation rates, extend breastfeeding duration, and ultimately improve health outcomes for both mothers and infants. As healthcare systems continue to seek evidence-based strategies to promote breastfeeding, simulation-based education emerges as a promising intervention worthy of further investment and research.

**Ethics Committee Approval**

This study is a literature review and does not involve human or animal subjects. Therefore, ethics committee approval was not required.

**Author Contributions**

a) Concept and design: E.C., B.K., Ş.K.E.; b) Literature review: E.C., B.K.; c) Drafting the manuscript: E.C., B.K., Ş.K.E.; e) Critical revision: Ş.K.E.; f) Final approval: E.C., B.K., Ş.K.E.

**Conflicts of interest**

The author declares no potential conflicts of interest relevant to this article.

**Funding Statement**

This research received no specific grant from any funding agency, commercial or not-for-profit sectors.

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Sabuncuoglu Serefeddin Health Sciences

Open Access

e-ISSN: 3062-3731 2026, 8(1), 55-67 https://doi.org/10.55895/sshs.1744479

# THE MOLECULAR ROLE OF THE WAVE REGULATORY COMPLEX IN CANCER METASTASIS: A COMPREHENSIVE OVERVIEW

# KANSER METASTAZINDA DALGA DÜZENLEYİCİ KOMPLEKSİN MOLEKÜLER ROLÜ: KAPSAMLI BİR GENEL BAKIŞ

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**Review Article**
**Received:** 18.07.2025, **Accepted:** 06.10.2025
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**Abstract**
Cancer metastasis presents one of the most formidable obstacles in oncology, contributing significantly to cancer-related mortality. This process critically depends on the active movement of malignant cells; a phenomenon intrinsically linked to the dynamic reorganization of the actin cytoskeleton. This review comprehensively examines the molecular makeup, regulatory mechanisms, and diverse functions of the WAVE Regulatory Complex (WRC) a key mediator of cell motility within the context of cancer progression, incorporating the latest research findings. Structurally, the WRC consists of five subunits that facilitate signal transmission from small GTPases, such as Rac1, to the Arp2/3 complex, thereby initiating actin filament assembly. This intricate pathway promotes the formation of invasive cellular protrusions, including lamellipodia, which are vital for cellular migration. A growing body of evidence indicates that WRC constituents are frequently overexpressed in various aggressive cancers, showing a strong correlation with heightened invasive capacity, increased metastatic potential, and unfavorable patient outcomes. Consequently, WRC-driven signaling pathways are emerging as promising therapeutic targets, offering potential avenues for developing novel anti-metastatic interventions aimed at inhibiting tumor dissemination.

**Keywords:** Actin Cytoskeleton, Arp 2/3 complex, Cancer therapy, Cell migration, Neoplasm metastasis

**Öz**
Kanser metastazı, onkolojideki en büyük zorluklardan biridir ve kanser kaynaklı ölümlerin ana nedenidir. Metastatik süreç, kanser hücrelerinin aktif göçünü gerektirir ki bu da büyük ölçüde aktin sitoskeletonunun dinamik olarak yeniden düzenlenmesine bağlıdır. Bu derlemenin amacı, hücre göçünün kritik bir düzenleyicisi olan WAVE Düzenleyici Kompleksi (WRC)'nin moleküler yapısını, regülasyonunu ve kanser metastazındaki çok yönlü rolünü güncel literatür ışığında özetlemektir. WRC, Rac1 gibi sinyal moleküllerini Arp2/3 kompleksi aracılı aktin polimerizasyonuna bağlayan beş alt birimden oluşan bir komplekstir ve lamellipodyum gibi invazif yapıların oluşumunda merkezi bir rol oynar. Literatür, WRC bileşenlerinin birçok agresif kanser türünde aşırı eksprese edildiğini ve bu durumun artan hücre invazyonu, metastaz potansiyeli ve kötü prognoz ile güçlü bir şekilde ilişkili olduğunu göstermektedir. Sonuç olarak, WRC, kanser hücrelerinin metastatik yetenek kazanmasında temel bir moleküler mekanizma olarak öne çıkmaktadır. Bu nedenle, WRC sinyal yolağının hedeflenmesi, kanserin yayılmasını önlemeye yönelik yeni anti-metastatik tedavi stratejilerinin geliştirilmesi için umut verici bir alan oluşturmaktadır.

**Anahtar Kelimeler:** Aktin Sitoskeletonu, Arp2/3 kompleksi, Kanser terapisi, Hücre göçü, Kanser metastazı,

## 1. Introduction

Cancer is a highly prevalent disease worldwide, with its incidence steadily increasing. While it was a feared disease in the 20th century, it continues to spread in the 21st century. The situation is so

alarming that one in four individuals faces a lifelong risk of cancer (Roy & Saikia, 2016). It is a leading cause of death, causing over ten million fatalities annually (Zaimy et al., 2017). Cancer, arising from cells' inability to perform their normal functions, exhibits characteristic features such as uncontrolled proliferation, invasion of surrounding structures, and spread to distant sites (Cooper, 2016). Cancer cells show abnormal growth tendencies, disregard cell cycle checkpoints, and possess the ability to induce angiogenesis, calling blood and lymphatic vessels to themselves, allowing them to spread throughout the body via metastasis. To reach these vessels, they must possess significant mobility (Lodish et al., 2008). Metastasis remains a decisive obstacle in cancer combat, accounting for a large proportion of cancer-related deaths despite advancements in controlling primary tumors (Hanahan & Weinberg, 2011). What makes this phenomenon so lethal is the ability of cancer cells to transcend local tissue boundaries and colonize distant organs; this biological process continues to be one of oncology's most persistent puzzles. The metastatic journey comprises multiple stages, including initial local invasion, entry into the bloodstream (intravasation), survival and travel within circulation, exit into a distant site (extravasation), and finally, adaptation and growth in a new microenvironment (Frugtniet et al., 2015; Hanahan & Weinberg, 2011). Each step requires not only directional movement but also continuous reshaping of cellular morphology. At the heart of this mechanical adaptation lies the versatile network of the actin cytoskeleton, which simultaneously supports cellular architecture and locomotion (Rottner & Stricker, 2021).

A key regulator that facilitates this cellular transformation is the WAVE Regulatory Complex (WRC). Operating akin to an orchestrator that converts disparate oncogenic signals into synchronized motile behaviors, the WRC serves to integrate upstream stimuli, channeling them toward dynamic cytoskeletal reorganization (Kurisu & Takenawa, 2010; Tyler & Rosenberger, 2016; Weeks et al., 2016). Its dysregulation is increasingly correlated with unfavorable outcomes in aggressive malignancies, indicating that the WRC not only supports cellular movement but can actively drive the metastatic phenotype itself (Lane et al., 2014; Rana et al., 2021).

Cancer medicine is transforming from general treatments to a more precise, biologically focused approach. Resistance to treatment and the risk of metastasis, in particular, remain ongoing challenges. For patients worldwide, advancements in molecular biology, immunological developments, and the integration of technology into these advancements are ushering in a new era of hope (Hanahan & Weinberg, 2011b).

## 2. Materials and Methods

### *2.1. Core Mechanisms of Cell Migration: The Actin Cytoskeleton and Arp2/3 Complex*

Eukaryotic cell migration is a fundamental biological process vital for phenomena like embryogenesis, immune surveillance, and tissue repair (Pollard & Borisy, 2003). This dynamic cellular behavior is driven by the rapid polymerization and depolymerization of actin filaments, which constitute the mechanical foundation of cell motility (Rottner & Stricker, 2021). The cytoskeleton plays a crucial role here, providing both structural support and enabling movement. It comprises three primary protein filaments: microtubules, microfilaments, and intermediate filaments. Microtubules are involved in organelle transport, cell division, and the formation of cilia and flagella.

Microfilaments, in contrast, are instrumental in processes such as cell locomotion, cytokinesis, and endocytosis. Intermediate filaments contribute to organelle stabilization and nuclear lamina formation. Microfilaments are primarily composed of actin proteins. Actin monomers, known as G-actin, polymerize to form actin filaments, or F-actin. This polymerization process fundamentally requires an actin nucleation event (Lodish et al., 2008). Cells utilize F-actin formation to create structures essential for movement, including filopodia, lamellipodia, and stress fibers. The actin cytoskeleton undergoes continuous reorganization within the cell, with its dynamic rearrangement facilitating eukaryotic cellular processes like cell migration and intracellular vesicle transport. Dysregulation of actin cytoskeleton dynamics is directly implicated in various health issues, such as cancer, neurological disorders, and immune system deficiencies (Rottner & Stricker, 2021).

Actin polymerization and its regulation are governed by two main protein classes: Formins, which generate unbranched actin filaments, and the Arp2/3 complex, responsible for creating branched actin filaments. Intracellular signals dictate the locations where these filaments assemble. Formins initiate polymerization for the formation of stress fibers, contractile rings, filopodia, and muscle thin filaments. Conversely, Arp2/3 proteins drive actin growth at the cell membrane, propelling the cell forward (Cooper, 2016).

The cellular migration process commences with the development of lamellipodia at the cell's leading edge. These expansive, sheet-like extensions progress by means of actin filament branching. The

Arp2/3 complex facilitates the polymerization of this actin network, initiating actin assembly by attaching to existing filaments and promoting the formation of new branches at roughly 70-degree angles (Tyler & Rosenberger, 2016). The force resulting from actin branching propels the plasma membrane forward. Subsequently, these protrusions form robust attachments to the extracellular matrix via focal adhesions, thereby providing the necessary traction for movement (Escobar et al., 2010). The cell body then advances through contractile actions, and the trailing edge retracts, concluding the migratory cycle.

The efficiency of this process relies on precise spatiotemporal control, especially concerning the activation of the Arp2/3 complex by Nucleation Promoting Factors (NPFs). Several factors are necessary to activate Arp2/3 proteins. The Wiskott-Aldrich syndrome protein (WASP) family of proteins activates the Arp2/3 complex, thereby initiating actin nucleation (Tyler & Rosenberger, 2016). Among these, the WAVE Regulatory Complex (WRC) stands out as one of the most critical players in directing directional movement and actin nucleation.

### *2.2. The WAVE Regulatory Complex (WRC): Structure and Regulation*

Actin polymerization is crucial for forming actin-based membrane protrusions, which are vital for cell migration and invasion. In this context, the Wiskott-Aldrich syndrome (WAS) protein (WASP) and WASP-family verprolin-homologous protein (WAVE) families constitute a molecular group that bridges GTPases and the actin cytoskeleton (Lane et al., 2014). This dynamic restructuring of the cytoskeleton, driven by actin polymerization, underpins numerous cellular processes. These processes are contingent upon the actin-related protein (Arp)2/3 complex, which requires a nucleation promoting factor (NPF) for its activity. While the spontaneous assembly of pure actin is kinetically unfavorable, NPFs (including WASP and WAVE family members) induce a conformational change that brings Arp2 and Arp3 subunits together, facilitating their convergence to form an actin pseudo-dimer. This action creates a significant pre-nucleus for actin polymerization, thereby supporting primary cell migration by fostering rapid actin polymerization at the cell's leading edge (Rana et al., 2021).

The WASP and WAVE family traces its origins to the isolation of the human Wiskott-Aldrich syndrome protein (WASP) gene in 1994. This family encompasses five distinct members: WASP, N-WASP, and the WASP-family verprolin homologous proteins WAVE1/SCAR1, WAVE2, and WAVE3. Human WASP and WAVE family genes reside on different chromosomes, each displaying a unique expression profile. Specifically, WAVE1 and WAVE3 exhibit robust expression in the brain and moderate expression in certain hematopoietic lineages, whereas WAVE2 is ubiquitously expressed across all tissues. These proteins vary in length from 498 to 559 amino acids and are encoded by 9 to 12 exons (Kurisu & Takenawa, 2010).

WASP and WAVE proteins demonstrate varying specificities for small GTPases, and through these interactions, they exert most of their influence on the cytoskeleton. Notably, WAVE proteins are crucial for Rac-mediated actin dynamics (Bompard & Caron, 2004; Caron, 2003; Miki & Takenawa, 2020). When overexpressed in cells, WAVE proteins that lack the GBD (GTPase Binding Domain) domain exhibit constitutive activity. The initial protein identified as linking WAVE2 to Rac was IRSp53 (Miki & Takenawa, 2020; Suetsugu et al., 2003). Nevertheless, despite IRSp53 showing no substantial impact on WAVE2 activity in vitro, it has been implicated in Cdc42-induced, WAVE2-independent filopodia formation (Bompard & Caron, 2004; Krugmann et al., 2001).

The stability of WAVE proteins is maintained through their integration into the PIR121/Nap1/Abi/HSPC300 complex, as illustrated in Figure 1. Studies in Drosophila cells have shown that the RNAi-mediated depletion of any complex member, excluding HSPC300, results in WAVE degradation via the proteasome pathway (Bompard & Caron, 2004; Kunda et al., 2003). Similarly, in mammalian cells, knockouts of p140Sra-1, Nap1, and Abi1 lead to WAVE2 degradation (Bompard & Caron, 2004; Innocenti et al., 2004; Steffen et al., 2004). Within this pentameric complex, WAVE1 alone does not activate Arp2/3 nucleation in vitro; actin polymerization only occurs when Rac or the binding protein Nck is present. This interaction causes the dissociation of PIR121, Nap1, and Abi from a WAVE1/HSPC300 subcomplex (Eden et al., 2002). Furthermore, reduced expression of any component of the pentameric complex results in WAVE degradation (Bompard & Caron, 2004; Innocenti et al., 2004; Kunda et al., 2003; Steffen et al., 2004). Consequently, the integrity of the pentameric complex is essential for the localized activation of the Arp2/3 complex by WAVE proteins. This principle of integrity is substantiated by both the promotion of WAVE2 degradation and the knockdown of PIR121 and Nap1 alongside Abi1 (Bompard & Caron, 2004; Innocenti et al., 2004; Kunda et al., 2003; Steffen et al., 2004).

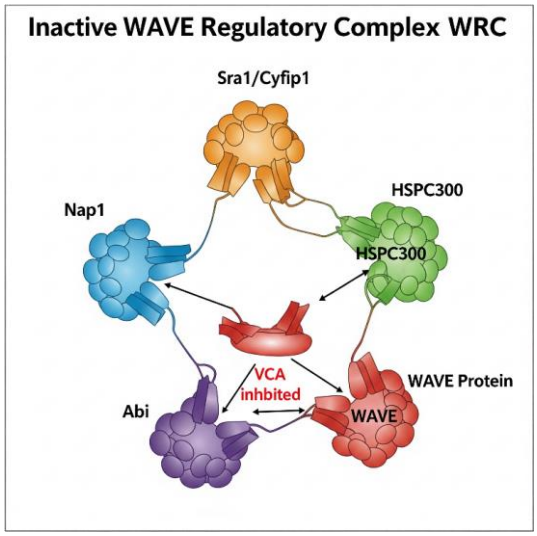


**Figure 1.** Schematic representation of the inactive WRC structure.
In this conformation, the VCA domain is sterically masked by other subunits, preventing Arp2/3 activation (This figure was created by the authors using an artificial intelligence–based graphic generation tool and was not adapted from any previously published material.)

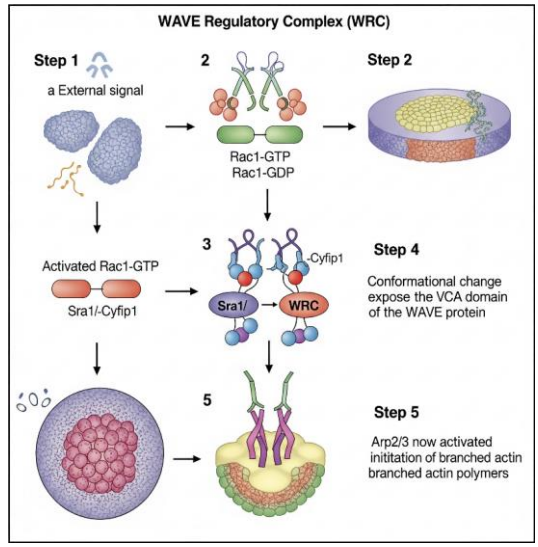


**Figure 2.** Signal transduction pathway leading to WRC activation.
Extracellular cues stimulate Rac1, which binds WRC, releasing VCA and enabling Arp2/3-mediated actin branching (This figure was created by the authors using an artificial intelligence–based graphic generation tool and was not adapted from any previously published material.)

Moreover, additional partners that interact with WAVE and might influence the regulation of WAVE activity within cells have been identified (Oikawa, 2004; Oikawa et al., 2004; Soderling et al., 2002). Among these, a WAVE-associated Rac-specific GTPase activating protein (GAP) that binds to WAVE1's proline-rich region has been discovered; it is considered a potential signal termination factor for Rac (Oikawa, 2004; Oikawa et al., 2004; Soderling et al., 2002). Furthermore, the regulatory subunit (RII) of cAMP-dependent kinase (PKA) engages with the V domain of WAVE1. Given that G-actin and RII binding are mutually exclusive, this interaction could also serve to inhibit WAVE1 activity (Oikawa, 2004; Oikawa et al., 2004; Soderling et al., 2002). More recent investigations have positioned the WRC as a central component in the signaling cascade between the cell membrane and actin cytoskeleton. Despite the WRC's auto-inhibited state, numerous ligands, including membrane receptors, phospholipids, kinases, and GTPases, possess the capacity to activate the complex, as depicted in Figure 2. Consequently, the Arp2/3 complex can initiate actin polymerization. While the precise mechanisms governing WRC function are progressively being elucidated, several mechanistic questions still require further exploration (Rottner & Stradal, 2016).

Furthermore, Table 1 provides a comprehensive overview of the intricate stages within the WAVE Regulatory Complex (WRC) signaling pathway and outlines their common dysregulation patterns observed across various cancer types.
Members of the Rho GTPase protein family, especially Rho, Rac, and Cdc42, play key roles in coordinating processes involved in invasion and cell migration through actin dynamics control. Rac activation stimulates the Arp2/3 complex via the WAVE complex, leading to the formation of branched actin filaments at the leading edge. The need for Rac to activate the Arp2/3 complex to form lamellipodia indicates that wound healing does not occur when cells cannot form this structure and migrate. Rac activity ensures the formation of focal contacts and lamellipodia, Rho ensures the formation of stress fibers and focal adhesions, and Cdc42 ensures the formation of filopodia (Pollard & Borisy, 2003).

*2.3. Multifaceted Role of WRC in Cancer Metastasis*
The migration and invasion of cancer cells are crucial processes underlying tumor progression and metastasis. It is broadly recognized that the WASP family, especially WAVE proteins, exhibit a strong association with the migratory behavior of various tumor cells and are implicated in tumor cell invasion and metastasis.

**Table1.** WAVE Regulatory Complex–Mediated Signaling Stages and their Dysregulation in Cancer

| Signaling Stage | Key Molecule/Complex | Activation Mechanism/Role | Dysregulation in Cancer (APA 7 refs) |
|---|---|---|---|
| External Stimulus | Growth factors (EGF, HGF), chemokines | Bind to cell surface receptors and initiate signaling cascades | Persistent enrichment in tumor microenvironment (Marchesin et al., 2015; Tang & Sun, 2024) |
| Receptor Activation | Receptor tyrosine kinases (RTKs) | Ligand-induced dimerization and autophosphorylation activate downstream GEFs | Overexpression or activating mutations of EGFR/HER2 (Marchesin et al., 2015; Zhang & Wang, 2023) |
| GTPase Switch | Rac1 (Rho GTPase) | Conversion from GDP-bound inactive state to GTP-bound active state via GEFs | Constitutive Rac1 activation enhances invasion (Algayadh et al., 2016; Tang & Sun, 2024) |
| Signal Integration Hub | WAVE regulatory complex (WRC) | Rac1-GTP binding releases autoinhibition and exposes VCA domain | Overexpression of WAVE2/WAVE3 increases migratory signaling (Rana et al., 2021) |
| Downstream Effector | Arp2/3 complex | Activated by WRC VCA domain to nucleate branched actin filaments | Sustained activation promotes invasion (Zhang & Wang, 2023) |
| Cellular Outcome | Actin cytoskeleton | Enhanced polymerization forms lamellipodia and invadopodia | Uncontrolled migration and metastasis (Rana et al., 2021; Zhang & Wang, 2023) |

This table was created by the authors based on current understanding in literatüre

Given their role in actin nucleation, these proteins have been connected to the aggressiveness and invasiveness of cancer cells. As the body of evidence linking WASP family proteins to the regulation of cancer cell motility expands, targeting these molecules emerges as a significant strategy to inhibit cancer cell metastasis (Lane et al., 2014). Metastasis involves cancer cells disseminating to remote locations through the lymphatic or circulatory systems and establishing secondary colonies, often signaling an unfavorable patient outcome (Lane et al., 2014). This complex metastatic cascade encompasses numerous intricate cellular interactions and signaling pathways. Initial invasion represents the foundational stage of metastasis, characterized by alterations in cellular adhesion, disruption of the local microenvironment, and, crucially, the acquisition of migratory capabilities by tumor cells, enabling their movement through tissues. During cell migration, cellular processes involve the polarization and outward extension of actin-driven structures, such as slender, finger-like filopodia and wider, sheet-like lamellipodia, oriented towards the migratory path.

Connections formed between the actin cytoskeleton of the migrating cell and either the extracellular matrix (ECM) or adjacent cells provide stability to these protrusions and establish points of traction, facilitating autonomous cellular movement. Furthermore, cancer cells can develop specialized actin-rich structures like invadopodia, which enable them to degrade the ECM and infiltrate the surrounding tissue. The genesis of protrusions at the migratory cell's leading edges is regulated by actin polymerization and various components of the actin cytoskeleton (Lane et al., 2014). The WAVE2 gene, which is central to our investigation, although not formally categorized as an oncogene, can be considered among the genes displaying oncogenic characteristics. Research has demonstrated a strong connection between WAVE2 alterations and cancer development.

Elevated expression of WAVE2 has been correlated with heightened metastasis and invasiveness across numerous cancer types, including colorectal, pancreatic, lung, liver, breast, and prostate cancers. Notably, the overexpression of the WAVE2 gene is specifically linked to an unfavorable prognosis in these malignancies (Rana et al., 2021).

Elevated WAVE2 expression has been correlated with increased metastasis and invasion in numerous cancer types, including colorectal, pancreatic, lung, liver, breast, and prostate cancers, as detailed in Table 2.

The Epidermal Growth Factor (EGF) pathway significantly influences WAVE2 gene regulation; EGF stimulation leads to WAVE2 phosphorylation, thereby enhancing cell motility. MicroRNAs represent another influential factor. For instance, MiR-29 inhibits WAVE2 expression in cancer cells, consequently regulating cell movement and dissemination (Rana et al., 2023).

**Table2.** Summary of Cancer Types and their Associated WRC Components

| Cancer type | Examined WRC component(s) | Key finding and mechanism | Reference |
|---|---|---|---|
| **Glioblastoma** | WAVE2 (WASF2) | Overexpression of WAVE2 enhances glioblastoma cell invasion and is associated with poor prognosis; functions downstream of EGFR signaling. | Ding et al., 2018 |
| **Colorectal cancer** | WAVE2, Abi1 | Increased expression of WAVE2 and Abi1 correlates with liver metastasis and advanced disease stage. | Tan et al., 2020 |
| **Malignant melanoma** | WAVE2, WAVE3 | WAVE2 and WAVE3 are highly expressed in invasive melanoma cells and regulate actin dynamics, cell motility, and invadopodia formation. | Sossey-Alaoui et al., 2007 |
| **Lung cancer** | WAVE1 (WASF1) | Reduced WAVE1 expression is associated with improved prognosis in certain lung cancer subtypes, suggesting context-dependent roles. | Iwaya et al., 2007 |
| **Pancreatic cancer** | Rac1, WAVE2 | Oncogenic KRAS-driven Rac1 activation promotes WAVE2-mediated cytoskeletal remodeling and invasion. | Ebi et al., 2013 |

This table was created by the authors based on current understanding in literatüre.

Cell migration and invasion are supported by actin polymerization at the leading edge of cells and depend on the precision of cell migration and invasion coordination. WAVE1, WAVE2, and WAVE3 protein family members function downstream of Rac-related C3 botulinum toxin substrate 1 (Rac1) for Rac-induced actin polymerization during lamellipodia formation. The WAVE2-Arp2/3 complex induces the nucleation of the actin assembly, thereby leading to the formation of cell protrusions. In this way, WAVE2 promotes protrusion formation, cell motility, and invasion. ACTN4 (Alpha-Actinin-4) is highly localized in the cytoskeleton and is also found in the nucleus in response to extracellular stimuli. Furthermore, ACTN4 levels are significantly correlated with poor prognosis after pancreatic ductal adenocarcinoma (PDAC**)** resection. Thus, the actin-related stimulation of tumor cell motility, invasion, and metastasis by the dynamic structure of ACTN4 can contribute to cancer progression. Taniuchi et al. (2018), with their studies, showed that WAVE2 induces protrusion formation in cells. This leads to an increase in cell motility and invasiveness, contributing to cancer progression. Therefore, the activity and migration of the WASP/WAVE family in cancer cell invasion have gained great interest in recent years (Taniuchi et al., 2018). The primary focus of the review by Frugtniet et al. (2015) is WAVE activity in breast cancer cell motility. With the recognition of WASP/WAVE proteins, it was noted that this family could play a role in the motility of cancer cells and their invasive and metastatic potential, inherently recognized for their involvement in cell motility through the regulation of actin polymerization. Since then, numerous studies on the role of WASP/WAVE family proteins in cancer development have been conducted. Many cell types, including breast cancer cells linked to migratory, invasive, and metastatic behavior, have been the main focus of this review. A link between WASP/WAVE activity and clinical outcomes in breast cancer patients has been identified. Recent studies suggesting that WASP/WAVEs can affect the system have begun to include their activators and pathways. Further studies are needed to fully understand the behaviors of cancer cells (Frugtniet et al., 2015). The specific factors regulating this protein family that contribute to cancer progression remain a subject of ongoing research. Nevertheless, these investigations have fostered the prospect of controlling the WASP/WAVE family or the pathways in which they participate, including their role in invasive and metastatic cellular behavior. Numerous publications have underscored the potential of targeting the WASP/WAVE family as a therapeutic approach for

cancer progression, particularly in breast cancer. Progress in elucidating the molecular mechanisms of WASP/WAVE activities and comprehending their exact contributions to various cancer stages is laying the groundwork for the development of anti-cancer drugs specifically aimed at the WASP/WAVE family (Lane et al., 2014).

*2.4. Therapeutic Targeting of the WAVE Signaling Pathway*

One of the current and increasingly important therapeutic targets to prevent metastasis is WAVE2. WAVE2 (WASP-family verprolin-homologous protein 2) is part of a protein complex that facilitates cell movement and enables the reorganization of the actin cytoskeleton. It regulates actin polymerization, allowing cells to form protrusions (lamellipodia) (Miki & Takenawa, 2020).

As detailed in Table 3, targeting different points of the WRC pathway offers distinct advantage sand challenges.

**Table 3.** Therapeutic Targeting Strategies for the WAVE Signaling Pathway

| Targeted point | Molecular target | Strategy / example inhibitor | Potential advantage | Key challenge / disadvantage | Reference |
|---|---|---|---|---|---|
| **Upstream** | Rac1 GTPase | Inhibition of Rac1–GEF interaction (e.g., NSC23766) | Potential to suppress multiple pro-invasive Rac1-dependent pathways beyond WRC signaling. | High risk of systemic toxicity due to the essential role of Rac1 in normal cells; limited pharmacokinetic properties. | Gao et al., 2004; Cardama et al., 2014 |
| **Direct complex** | WRC (protein–protein interactions) | Disruption of Rac1–Sra1 or WAVE–Abi interactions (discovery phase) | Highest specificity by selectively targeting the WRC without broadly affecting actin dynamics. | Significant technical challenges in developing effective PPI inhibitors; no clinically approved candidates to date. | Chen et al., 2010; Rana et al., 2021 |
| **Downstream** | Arp2/3 complex | Allosteric inhibition (e.g., CK-666) | Direct inhibition of actin polymerization at the terminal step of the pathway. | Very high toxicity risk due to the indispensable role of Arp2/3 in fundamental physiological processes (e.g., immune responses). | Nolen et al., 2009 |

This table was created by the authors based on current understanding in literatüre.

The involvement of the WAVE2 gene in cancer dissemination and progression positions it as a promising candidate for therapeutic intervention. Preclinical investigations have demonstrated that small interfering RNAs (siRNAs) designed to target WAVE2 result in diminished metastasis (Sossey-Alaoui et al., 2014). These observations imply that suppressing WAVE2 can mitigate both the motility and invasiveness of cancer cells, thereby impeding metastasis through this specific mechanism. Figure 3 illustrates the hyperactive WRC pathway and its associated therapeutic targets.

Furthermore, small molecule inhibitors, such as Rac1 inhibitors (e.g., NSC23766), can be employed to suppress cytoskeletal remodeling facilitated by WAVE2. Nevertheless, these inhibitors are not yet approved for clinical use, indicating a need for additional research and development before they can be applied in a clinical setting. Despite this, WAVE2 can be indirectly inhibited by compounds that target both the Arp2/3 complex and the Rac1-WAVE pathways (Machesky & Insall, 1998). Thus, a strategic approach to targeting the WAVE2 gene presents a hopeful avenue for cancer therapy (Rana et al., 2022).

*2.5. Advanced Cancer Therapies: Beyond Conventional Approaches*

Historically, cancer therapy predominantly centered on three core approaches: surgical intervention, chemotherapy, and radiation. Currently, surgical procedures remain a vital treatment for localized malignancies, frequently complemented by radiation therapy. Conversely, chemotherapy, a non-targeted approach, works by retarding cellular proliferation but is often

associated with numerous considerable side effects. Despite these drawbacks, these conventional modalities have proven life-saving for a substantial number of patients. However, their efficacy is frequently limited when confronting genetically intricate cancers, particularly those that have metastasized (DeVita et al., 2001).

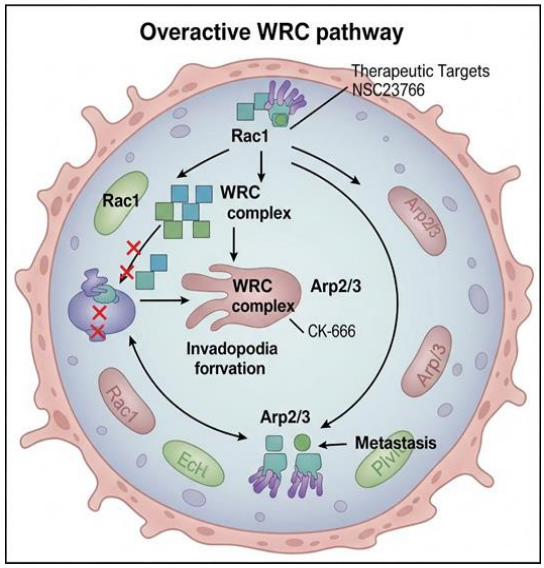


**Figure 3.** WRC Signaling in Metastatic Cancer Cells: A Pathway Overview.

This figüre elucidates the pathways that promote invasion and pinpoints potential therapeutic intervention points at the Rac1, WRC, and ARP2/3levels (This figure was created by the authors using an artificial intelligence–based graphic generation tool and was not adapted from any previously published material.)

Oncology has been propelled to a very different point in recent years by revolutionary advancements in molecular biology and genomic technologies. In response to the limitations of traditional approaches, more precise and targeted strategies have been developed in cancer treatment. For example, targeted therapies like Trastuzumab and Imatinib are designed to directly act on specific molecular pathways that are highly deregulated in cancer cells. Trastuzumab targets the HER2 gene in HER2-positive breast cancer cells, while Imatinib inhibits the BCR-ABL fusion gene in chronic myeloid leukemia. Such targeted therapies generally have fewer side effects and offer more definitive results compared to conventional treatments (Druker et al., 2001).

Genomic technologies have empowered clinicians to sequence tumor genes, facilitating the identification of mutations in genes like BRCA1/2, EGFR, or KRAS. This information is crucial for guiding treatment decisions and understanding disease progression (Collins & Varmus, 2015). Furthermore, the development of biomarkers and techniques that modulate the expression of specific genes has substantially advanced oncology. Liquid biopsies, for instance, are highly effective for both early detection and continuous monitoring, providing valuable insights through the identification of tumor DNA in the bloodstream (Wan et al., 2017).

Another turning point contributing to oncology is immunotherapy. Immunotherapy has introduced a new paradigm in cancer treatment. This approach eliminates cancer cells by using inhibitors (e.g., Nivolumab and Pembrolizumab) that block immune-suppressive pathways (e.g., PD-1/PD-L1) during the process of T lymphocytes recognizing and destroying cancer cells (Topalian et al., 2012). Another exciting study on T cells is the CAR-T cell therapy method. In this method, T cells are specifically designed to attack tumor cells, and this approach has yielded highly successful results in hematological malignancies (Maude et al., 2014).

Many research and technological advancements hold promise for the future of cancer treatment. For example, artificial intelligence (AI) is being used for data analysis and treatment method determination (Esteva et al., 2019). Nanotechnological studies have brought a new dimension with nanomedical methods promising the potential for drug delivery directly to tumors, minimizing toxic effects. Epigenetic therapies under development hold promise for incurable cancers. Furthermore, personalized cancer vaccines targeting specific mutations such as TET2, DNMT3A, and IDH1/2 are another source of hope.

### *2.6. Renal Cell Carcinoma: A Specific Context for Metastasis Research*

This section will explore the dynamics of metastasis and associated treatment challenges, particularly within the context of renal cell carcinoma (RCC), which is the primary focus of this doctoral thesis. It aims to establish a foundation for understanding the potential involvement of mechanisms such as the WAVE complex in this specific cancer type. Annually, kidney cancer impacts thousands globally and contributes substantially to mortality rates. Despite considerable advancements in immunological therapies for this disease, an effective treatment remains elusive for the majority of patients suffering from advanced RCC. Over the past two decades, genetic and clinical investigations have revealed that kidney cancer is not a singular entity but rather comprises several distinct cancer types originating within this organ. Each subtype can exhibit unique histological characteristics, follow a varied clinical trajectory, respond dissimilarly to treatment, and stem from alterations in different

genes. Similar to other malignancies like prostate, colon, and breast cancer, kidney cancer manifests in both sporadic (non-hereditary) and inherited forms. Investigations into families afflicted with specific hereditary kidney cancer types have resulted in the discovery of four highly penetrant susceptibility genes for kidney cancer, thereby establishing a foundation for developing therapies that target these particular cancer gene pathways (Linehan et al., 2004).

While advancements in early diagnosis and treatment of RCC continue to lead to excellent oncological outcomes, preservation of kidney function in kidney cancer patients has emerged as an increasingly important clinical goal. Given that diabetes, hypertension, obesity, smoking, and aging are independent risk factors for RCC, corresponding non-neoplastic kidney diseases are frequently present but often undiagnosed (Henriksen & Chang, 2020). First-line treatments for metastatic RCC have evolved rapidly in recent years. With increasing relapse rates after first-line treatment, it has become increasingly important not only to adopt a personalized treatment plan with minimal side effects but also to develop predictive biomarkers for response (Chowdhury & Drake, 2020). RCC treatment represents one of the great success stories in translational cancer research, with the development of new treatments targeting key oncogenic pathways. These include drugs targeting the VEGF and mTOR pathways, as well as new immuno-oncology agents. With a range of highly effective therapies available across multiple lines, it will become increasingly important to develop a more specific approach to treatment selection (Graham et al., 2018).

RCC, as of today, accounts for approximately 2% of all cancers, placing it in an intermediate position between rare and common cancers. Globally, RCC incidence is increasing and varies worldwide; the highest levels are observed in North America and Scandinavia. RCC originates from renal tubules, and many researchers believe that the characteristics of different types of RCC are a reflection of the histological and cellular diversity of the renal nephron.

A notable characteristic of this cancer is the growing body of evidence suggesting that the majority of RCC cases serve as pathobiological illustrations of disruptions in fundamental aspects of cellular metabolism. The most striking instance of this is clear cell RCC (CCRCC), which constitutes about 80% of all RCC diagnoses. Studies indicate that in most of these tumors, a malfunction in the von Hippel–Lindau (VHL) protein uncovers the primary initiating factor as a disturbance in the tubular cells' hypoxia-sensing mechanism. (It is worth noting that Arvid Lindau, who was born in the same town where this article was authored, later became a pathology professor at Lund University. His doctoral research focused on hemangiomas in the central nervous system, linking them to retinal lesions previously described by the German pathologist Eugen von Hippel.)

Devoting this issue of Seminars in Cancer Biology to RCC would be an extremely appropriate choice for many reasons. A clear and pathogenetically valid classification of renal neoplasms was only established in 1997. In the opening article, Professor Holger Moch summarizes the molecular-genetic and phenotypic characteristics of the main types of RCC. What is clearly understood from this general review is that the definition of RCC subtypes is still ongoing, and many new RCC subtypes have recently been identified. Significant progress in understanding the genetic and epigenetic structure of tumors has occurred with advancements in genome-wide examination methods. While the importance of the VHL gene in CCRCC has been emphasized in RCC research, recent studies have shown that chromatin regulatory genes such as PBRM-1 and SETD2 are also critical. Professor Eamonn Maher provides a review covering the current knowledge about the genetic makeup of various sporadic and hereditary kidney cancers.

Research conducted over the past two decades indicates that the pVHL tumor suppressor protein plays a crucial role as the substrate recognition component of a ubiquitin ligase, directing HIF-alpha transcription factors for oxygen-dependent degradation. In healthy cells, this system becomes active when oxygen concentrations fall below a specific threshold, leading HIF transcription factors to upregulate the expression of genes involved in glucose transport, glycolysis, and angiogenesis. Given that hypoxia is nearly universally observed in solid tumors once their growth surpasses angiogenic supply, elucidating this mechanism has become a central focus, not solely for comprehending CCRCC but also across all domains of cancer research. Shen and Kaelin (2010) provide a comprehensive overview of the current scientific understanding of the VHL/HIF axis in their work.

VHL syndrome is an uncommon and autosomal dominantly inherited neoplastic condition stemming from a germline mutation within the VHL gene. Individuals with VHL are frequently prone to developing multiple tumors, with clear cell renal cell carcinoma (CCRCC) representing one of the most substantial clinical hurdles among them. Richard et al. (2010), in their publication, not only categorize the various types of these tumors but also detail the clinical strategies implemented to manage these life-threatening malignancies.

CCRCC is considered a relatively homogeneous type of cancer, as it carries a distinct starting point in terms of cancer worsening potential. Unfortunately, however, CCRCC is resistant to cytotoxic therapies and radiotherapy, and metastatic disease is almost always fatal. Surgical intervention has been the only treatment option offering permanent survival to date. However, 40% of patients who benefit from curative surgery subsequently develop metastasis, and an additional 30% present with metastatic disease, often leading to palliative care without intervention.

Kidney cancer exhibits a notable recurrence rate when compared to other malignancies. While mortality is not universally observed among all affected individuals, the disease significantly impairs their quality of life. If left unaddressed, there is a substantial risk of metastatic dissemination to vital organs, including the lungs, bones, brain, and chest.

## 3. Results

The WAVE Regulatory Complex (WRC) plays a pivotal role in orchestrating the actin cytoskeleton dynamics essential for cell migration and, consequently, cancer metastasis. This review has highlighted the intricate molecular structure and regulatory mechanisms of the WRC, emphasizing its critical function in promoting invasive cellular protrusions like lamellipodia.

The WRC functions as a critical junction between small GTPases (especially Rac1) and the actin cytoskeleton. The complex, composed of five subunits, transmits incoming signals to the Arp2/3 complex, triggering actin polymerization and enabling the formation of invasive structures like lamellipodia at the leading edges of cells. These actin-based protrusions directly support cell motility and their ability to penetrate surrounding tissues.

## 4. Discussion

Current literature clearly indicates that WRC components, particularly WAVE2, are highly expressed in many aggressive cancer types (such as breast, colorectal, pancreatic, lung, liver, prostate cancers, and renal cell carcinoma (RCC)). This high expression shows a strong correlation with increased cell invasion, metastatic potential, and unfortunately, a worse clinical prognosis for patients. On the other hand, there are also findings suggesting that the WAVE complex may play a tumor-suppressive role in some cases (e.g., BRK1 deletion in kidney cancers associated with VHL syndrome), indicating that WRC's role in cancer is highly complex and context-dependent.

Given the challenges traditional cancer therapies face in controlling metastatic disease, targeting the WRC emerges as a promising new therapeutic strategy. Preclinical studies suggest that inhibiting WAVE2 directly or indirectly (e.g., via small interfering RNAs (siRNAs) or Rac1 inhibitors) can reduce cancer cell motility and invasiveness, thereby preventing metastasis.

## 5. Conclusion

Future investigations ought to concentrate on gaining a more profound comprehension of the molecular mechanisms underlying WRC activity and its exact involvement in various stages of cancer progression. This accumulated knowledge holds the potential to facilitate the creation of novel, individualized anti-metastatic pharmaceuticals that specifically target the WRC or modulate signaling pathways connected to it. Particularly for malignancies with a high propensity for metastasis, such as RCC, further clarification of the role played by actin cytoskeleton regulators like WAVE2 will establish the foundation for innovative therapeutic strategies aimed at early detection, preventing disease advancement, and ultimately, enhancing patient survival.

## Author Contributions

Study design: ÖH; Data collection: ÖH; Draft preparation: ÖH; Critical review for content: AHÖ; Final approval of the version to be published: AHÖ

## Conflicts of interest

The authors declare no conflicts of interest.

## Funding Statement

This research received no specific grant from any funding agency, commercial, or not-for-profit sectors.

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