REVIEW

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KI67 and MCM2 histology pattern in breast cancer: a comparative analysis for better prognostic assessment

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ABSTRACT

This review investigates **prognostic roles of Ki67 and MCM2 in breast cancer, aiming to evaluate their effectiveness as biomarkers for assessing tumor proliferation and predicting patient outcomes**. This paper was created using a literature review approach with Boolean logic operators "OR" and "AND, using keywords including "KI67," "MCM2," "breast cancer," "histology pattern," "prognostic marker," and "comparative analysis." We use several databases such as PubMed, ScienceDirect, Springer Nature, and Google Scholar. The results demonstrate that while Ki67 is extensively used and has a substantial correlation with tumor aggressiveness, it is constrained by interpretative diversity and uneven prognostic significance within subtypes. MCM2 has increased sensitivity, especially in heterogeneous cancers, and shows greater correlations with aggressive tumor characteristics and worse survival outcomes in high-risk subtypes. This review also finds deficiencies in standardized MCM2 evaluation methodologies and a lack of thorough investigation into its integration with other biomarkers and therapeutic potential. Standardized techniques, multivariate prognostic models, and more exploration of MCM2 are needed as a therapeutic target. This work deepens the knowledge of breast cancer biology and boosts the possibility for tailored treatment regimens, eventually enhancing prognostic accuracy and patient outcomes.

Keywords: Ki67, MCM2, Breast Cancer, Histology Pattern, Prognostic Biomarkers, Tumor Proliferation.
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INTRODUCTION

Breast cancer is a significant public health concern, as shown by the high incidence and fatality rates seen globally. As reported by the Global Cancer Observatory (GLOBOCAN), breast cancer ranked as the second most prevalent illness globally in 2022, with more than 2,296,840 new cases and 666,103 deaths recorded.[1] Regional disparities are evident in the data, with Asia having the greatest breast cancer prevalence at 39.1%. The recent rise in reported cases is due to changes in society that have a big effect on lifestyle factors linked to the illness and improvements in ways to find it.[2] The persistent challenge of breast cancer underscores the need for enhanced prognostic markers to facilitate individualized treatment strategies and elevate patient outcomes.

In these circumstances, histopathological markers such as Ki67 and MCM2 are critical elements in the prognosis of breast cancer. Cancer tissues widely employ the proliferation marker Ki67, a nuclear protein present in proliferating cells. Its expression is associated with the aggressiveness of the tumor and recurrence risk, which helps guide treatment strategies.[3,4] MCM2 is an important part of DNA replication and has become an intriguing biomarker because it stays active throughout the cell cycle and can show whether a tumor is growing or not.[5] Furthermore, studies have shown how important it is to look at Ki67 and MCM2 levels in relation to survival rates, especially in aggressive types like triple-negative breast cancer (TNBC), which has a bad prognosis.

Ki67 and MCM2 are signs of cell proliferation that are critical in breast cancer because of the molecular processes that make them work. Higher Ki67 expression, a sign of cell multiplication, indicates harsher treatment and is associated with worse tumor grades.[6,7] However, MCM2 is responsible for DNA replication; its detection implies that the cell has been granted permission to proliferate. Because MCM2 can show that cells might divide even if they are not in the active cell cycle currently, this functional difference provides a theoretical basis for looking at both markers at the same time.[8,9] These markers enhance the understanding of tumor biology and improve prognostic assessments beyond traditional criteria.

Although their utilization has evolved, some limitations remain surrounding Ki67 and MCM2's application for breast cancer prognostic evaluation. Labs have implicated differing marker cut values in Ki67's erratic reporting, leading to varying prognostic interpretations.[10] Similar to Ki67, MCM2 lacks standardized tests and has not been the subject of enough large-scale studies to demonstrate its clinical utility.[11] The differences found show that we need to agree on some standards and validation methods in order to make the therapeutic use of these indicators better, since they make us question how reliable they are for making treatment decisions.

Comparative studies that look at the prognostic abilities of Ki67 and MCM2 show that each marker has its own pros and cons. According to research, Ki67 works especially well in certain types of luminal breast cancer, and a high Ki67 index is often linked to bad outcomes.[12,13] Still, the unique expression patterns of MCM2 may provide extra prognostic information, especially when Ki67 levels aren't enough to accurately predict how a disease will behave.[11,12] In clinical settings where histopathological evaluation guides treatment decisions, it is important to carefully look at these biomarkers, taking into account how they affect biology and how they can help predict outcomes.

The existing research clearly indicates the need for more comparative studies of Ki67 and MCM2 in breast cancer. There aren't many large-scale studies that directly compare outcomes based on the levels of expression of these two markers in different populations and types of tumors. This information will help us for better understand how Ki67 and MCM2 work together in various treatment plans, especially when it comes to personalized treatments for certain types of breast cancer.6 Investigations are necessary into the combined use of both biomarkers to determine if they provide improved prognostic capabilities compared to their independent use, and these findings may result in advancements in specific medical practices.

The integration of these talks indicates that Ki67 and MCM2 are essential for improving prognostic assessments in breast cancer. Histopathological patterns provide vital insights into tumor behavior, therefore informing therapeutic strategies and patient care. We agree that Ki67 is an important marker for measuring proliferation, but MCM2's other biological functions also present a lot of room for more research and real-world use. It might be possible to improve these markers' ability to predict outcomes by standardizing evaluation methods and comparing them on a large scale. This would help breast cancer patients have better outcomes.

METHOD

This paper was created using a literature review approach. Using Boolean logic operators "OR" and "AND, the authors search using keywords including "KI67," "MCM2," "breast cancer," "histology pattern," "prognostic marker," and "comparative analysis." Among the terms were ("ki67," OR "MCM2"), ("breast cancer," AND "histology pattern"), and ("prognostic marker," AND "comparative analysis"). Journal searches were carried out on reliable databases like PubMed, ScienceDirect, Springer Nature, and Google Scholar to ensure the inclusion of outstanding and relevant sources.

The authors arranged the subject in line with the focus of the study and applied particular inclusion and exclusion guidelines depending on the obtained information. English reference sources based on the PICO framework. (1) Population: People with breast cancer, (2) Intervention: investigation of KI67 and MCM2 expression (3) Comparison between KI67 and MCM2: Histology pattern and prognostic value (4) Outcome: Evaluation of accuracy and predictive value in the evaluation of breast cancer. Studies published in indexed, peer-reviewed publications, and works published throughout the preceding 10 years (2015–2025).

Conversely, the exclusion criteria included studies not subject to peer review (e.g., gray literature, commentaries, or case reports without in-depth analysis), reference sources published more than 10 years ago, and papers lacking comprehensive data on KI67 and MCM2 expression or failing to address prognostic aspects of breast cancer.

These inclusion and exclusion criteria helped guarantee the quality and relevance of the selected references and minimize selection bias in literary research. This analytical approach provides a strong basis for comparing KI67 and MCM2 as prognostic markers in breast disease. It facilitates understanding their histological patterns and prognostic importance.

RESULT AND DISCUSSION

Functional Role of Ki67 and MCM2 in Breast Cancer

Ki67 and MCM2 are proteins that are essential for the regulation of the cell cycle and the promotion of cell proliferation. They play complementary functions in breast cancer. Ki67 is a nuclear protein produced throughout the active stage of the cell cycle, except G0. Ki67 levels vary across the cell cycle, peak during mitosis, and are crucial for cell division and separation of chromosomes.[14,15] In order to facilitate precise chromosome movement and separation, Ki67 also serves as a "biological surfactant," aiding in the dissolution of mitotic chromosomes.14 Furthermore crucial for the proper distribution of chromosomes during cell division is Ki67's interaction with chromatin stabilizing the mitotic spindle machinery.[14,15]

Conversely, MCM2 is a basic component of the microchromosome maintenance complex (MCM2-7), which starts DNA replication. MCM2 and other MCM proteins produce a helicase complex that releases DNA at the start of replication during the S phase.[16,17] Dbf4-dependent kinase (DDK) and cyclin-dependent kinase (CDK) control MCM2 activity by means of phosphorylation.[18,19] Apart from its function in DNA replication, MCM2 is also engaged in chromatin remodeling and serves as a histone escort thereby enabling appropriate chromatin assembly.20,21 Maintaining many stages of the cell cycle (G1, S, G2, and M), MCM2 expression indicates "licensed" cells ready for replication.[8]

Especially in relation to breast cancer, Ki67 is well known as a sign of cell proliferation. Increased Ki67 expression is often linked to poor prognosis and aggressive tumor activity. The degree of Ki67 expression is tightly connected to tumor development rate.[22–24] Ki67 also helps to classify molecular subtypes of breast cancer, like luminal A (low Ki67) and luminal B/HER2-positive (high Ki67), therefore impacting therapy plans.[23–25] Furthermore utilized in clinical recommendations, like the St. Gallen Consensus, Ki67 helps to categorize patients for further chemotherapy.24 Still, Ki67 evaluation suffers from sample bias and inter-observer variability. Digital image analysis has been advised in order to raise objectivity.[26–28] In response to neoadjuvant treatment, Ki67 also acts as a predictive agent. A drop in Ki67 levels indicates the effectiveness of the treatment. Including Ki67 into multivariate prognostic models has enhanced risk classification for managing breast cancer.[29]

MCM2 is attracted to the origin of replication during the G1 phase and activated by phosphorylation CDK once every cell cycle to ensure appropriate DNA replication.[17] MCM 2 also interacts with other proteins, including Cdc45 and GINS, to build the CMG helicase complex, which drives replication forks.30 Many forms of cancer, including breast cancer, show MCM2 overexpression and connected to unrestrained cell growth. Therefore, the inhibition of MCM2 is proposed as a therapeutic approach, as the reduction of this molecule may cause cell cycle arrest and death in tumor cells.[31,32] Furthermore, crucial in the framework of genomic instability in cancer is MCM2's involvement in the reaction to replication stress and DNA damage repair.

The aggressiveness and development of breast cancer are correlated in part with Ki67 and MCM2. While low Ki67 levels are more prevalent in luminal A (65, 66), high Ki67 expression levels are often linked with aggressive breast cancer subtypes, like luminal B and triple-negative (TNBC).[12,33] As a "licensed" cell marker for replication, MCM2 likewise significantly connects with cancer cell proliferation and poor prognosis.[7,12] Studies show that combining Ki67 and MCM2 tests can enhance responsiveness to neoadjuvant chemotherapy and prognostic prognosis.[34] The accuracy and repeatability of assessing these two indicators have been advised to be enhanced by automated image analysis.[35,36] The value of Ki67 and MCM2 as biomarkers in clinical practice has to be confirmed by further validation in many clinical environments.

Despite all of that, Ki67 and MCM2 generally help control the cell cycle and cell proliferation with separate but complementary methods. MCM2 is necessary for DNA replication, while Ki67 is a proliferation marker engaged in chromatin assembly during mitosis.

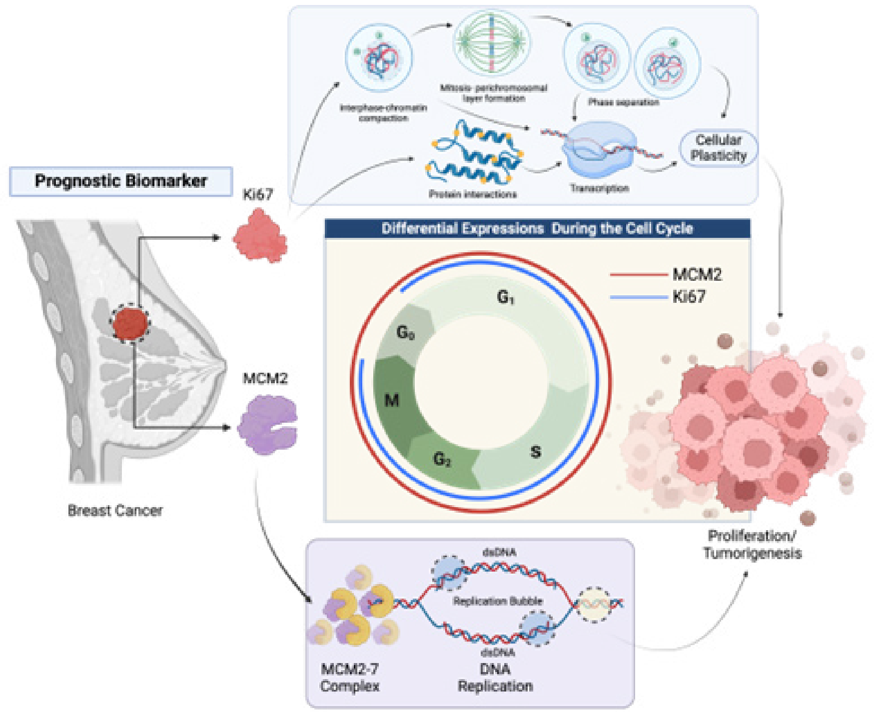

Figure 1. Function and Differential Expression of Ki67 and MCM2 During Cell Cycle in Breast Cancer

Both proteins are clinically very relevant in breast cancer as their expression levels match tumor aggressiveness and patient prognosis. To fully actualize Ki67 and MCM2 as biomarkers and targets for therapy in breast cancer care, further study and clinical validation are required. Therefore, which can have a better impact and prognostic assessment still needs to be understood.

Ki67 in Breast Cancer: Regulation, Detection, and Clinical Implications

Ki67 has widely recognized as a cellular proliferation marker that is indispensable in the study of breast cancer, particularly in the context of tumor development, aggressiveness, and therapy response. Because it is tightly regulated by a complex network of genetic, hormonal, and molecular elements cooperating, its expression is a fundamental means of predictability and tracking of therapy efficacy. The expression of Ki67 in breast cancer regulated by a multifarious system, including hormone signaling, cancer-causing pathways, and connections to cell cycle regulators. For example, since estrogen stimulates estrogen receptor (ER)-positive breast cancer cells to proliferate, estrogen is a regulator of Ki67 expression. Hormonal treatments frequently alter the expression of Ki67 to prevent tumor growth, as estrogen signaling influences its levels.[9,37] Moreover, it is associated with more aggressive tumor morphologies, oncogenic pathways, including HER2 signaling assist to increase Ki67 levels.[38,39] Ki67's involvement with cyclins and cyclin-dependent kinases (CDKs), which regulate the cell cycle, further clarifies its contribution to tumor development. For instance, CDK inhibitors may reduce Ki67 expression, inhibiting the growth of cancer cells.[40] Moreover, influencing Ki67 expression are molecular fingerprints and genetic elements. These include interactions with TOP2A and other proliferation indicators, therefore stressing the need to know breast cancer biology.[41] Particularly in hormone receptor-positive breast cancer, where raised Ki67 usually indicates less sensitivity to endocrine therapy, Ki67 levels are clinically predictive of treatment response.[42] Nevertheless, the International Ki67 in Breast Cancer Working Group is working to develop consensus rules as standardizing Ki67 evaluation techniques remains difficult.[43]

Correct Ki67 detection and quantification will help to evaluate tumor progression and guide therapeutic choices. In clinical situations, immunohistochemistry (IHC) is the best method to estimate Ki67.[43,44] Searching formalin-fixed paraffin-embedded (FFPE) tissue samples for Ki67-positive cells employs specific antibodies. However, IHC is prone to inter-observer variability, which demands consistent protocols and quality control methods. Using algorithms to make Ki67 assessment more objective and reproducible, digital image analysis (DIA) offers a fresh perspective on things that get past these challenges.[45] To increase the accuracy of hotspot identification and enable the process to run itself, more sophisticated technologies such deep learning and convolutional neural networks are also under investigation.[46] Furthermore, providing quantitative Ki67 expression data are molecular methods that include quantitative reverse transcription PCR (RT-PCR). They lack the geographical background IHC provides.[47] Notwithstanding these advancements, it is still difficult to establish optimal Ki67 cut-off values, so constant research aimed at raising thresholds for medical decision-making helps define levels.[48]

Variations in Ki67 expression across different forms of breast cancer help one understand tumor behavior and prognosis. Luminal A and luminal B are two forms of luminal breast cancer, and Ki67 distinguishes between them. For instance, luminal B tumors can display Ki67 levels exceeding 15%, which demands more severe treatment strategies.[33,49] Using HER2-targeted therapy helps one forecast outcomes because higher Ki67 levels in HER2-positive breast cancer are associated with more aggressive tumors and poorer outcomes. Usually with the highest Ki67 levels, triple-negative breast cancer (TNBC) devoid of ER, PR, or HER2 demonstrates how aggressive it is and how rapidly it spreads.[6,50–53] Usually used to project response to neoadjuvant chemotherapy, elevated Ki67 in TNBC is associated with worse clinical outcomes.[54,55] Lehmann et al. contend that Ki67's capacity for working with molecular subtyping makes it even more beneficial for tailoring TNBC therapy regimens. Comprehensive studies on Ki67 as a diagnostic and prognostic marker in breast cancer have been carried out; various clinical investigations reveal its importance in guiding therapy decisions. Particularly in ER-positive breast cancer, the International Ki67 in Breast Cancer Working Group (IKWG) has underlined its function in stratifying patients for adjuvant therapies.[24] Higher Ki67 levels in luminal subtypes predict worse results and a greater probability of recurrence, which alters the therapy choice. Ki67 may also be used to find if a HER2 breast cancer patient responds pathologically completely to neoadjuvant therapy.[6,56] Usually elevated Ki67 levels in TNBC match fast tumor growth and short survival rates.[57] It's challenging to use in clinical environments nevertheless as there are no standard evaluation techniques. Making it more dependable calls for automated, repetitive processes.[58] Combining Ki67 assessment with genetic subtyping and known procedures helps clinicians better modify treatment approaches and thereby improve patient outcomes. Constant research and attempts to standardize the assessment will help to confirm Ki67's central importance in the treatment of breast cancer.

Prognostic Significance of Ki67 in Breast Cancer

Ki67 expression has been extensively studied for prognostic relevance in patients with breast cancer. Poor overall survival (OS) and disease-free survival (DFS) across many forms of breast cancer are repeatedly linked to high Ki67 levels. A meta-analysis with 64.196 patients demonstrated that a Ki67 index higher than 25% is an independent predictive factor for OS, underscoring its therapeutic value.6,58 In luminal breast tumors, Ki67 is a significant prognostic factor. It is used for distinguishing between luminal A (low Ki67, better prognosis) and luminal B (high Ki67, more aggressive behavior), the St. Gallen International Breast Cancer Conference advises a Ki67 cut-off of 14%. Compared to luminal A cancers, luminal B tumors which are characterized by greater Ki67 levels have more recurrence risk and treatment resistance. In HER2-positive and triple-negative breast cancer (TNBC), too high Ki67 levels are also associated with aggressive tumor activity and worse clinical outcomes. For TNBC, increased Ki67 predicts a more significant initial response to neoadjuvant chemotherapy but worse long-term survival, highlighting its dual function as a predictive and prognostic marker (111).[58]

Several studies have shown that higher Ki67 levels are strongly correlated with tumor aggressiveness and metastatic potential. These are linked with greater tumor size, higher histological grade, and greater risk of lymph node metastases.[6,59] For example, high Ki67 levels are closely correlated with nodal metastases, which implies that they may be used to forecast the course of the illness (116).[4] High Ki67 levels are linked to worse general survival and a higher risk of distant metastases, particularly in aggressive subtypes like HER2-positive and TNBC.[60] Lower Ki67 levels have been related to luminal A breast cancer to improved long-term survival and therapy responsiveness. Conversely, luminal B and TNBC subtypes commonly show high Ki67 levels, which are linked to an increased risk of metastases and recurrence.[61] These results highlight the use of Ki67 in evaluating tumor aggressiveness and metastatic potential, thus assisting doctors in developing therapy plans.

In the other way, Ki67 is essential in directing treatment choices, especially in Choosing chemotherapy courses. High Ki67 levels, often defined as >20–30%, are associated with a more significant response to chemotherapy. As such, Ki67 is a valuable tool for identifying patients who may benefit from adjuvant or neoadjuvant chemotherapy.[62,63] Chen et al. showed that significant decreases in Ki67 levels demonstrate a strong response to treatment. Variations in Ki67 levels throughout neoadjuvant therapy might predict pathological complete response (pCR) and patient outcomes.[64] In HER2-positive and TNBC, high Ki67 levels are associated with a poorer prognosis. Yet, they also indicate a greater likelihood of responding to targeted treatments and chemotherapy. Still, it isn't easy to agree on the ideal cut-off values and standardize Ki67 testing techniques.[65,66] More study and consensus rules are therefore required.

Hormone receptors (ER, PR), HER2, and indicators of cell proliferation, including MCM2, MCM3, and Topoisomerase IIα (Topo IIα), have been compared to Ki67 as further indications of prognosis. Studies combining Ki67 with these markers have shown that it offers complimentary predictive information. For instance, Hashmi et al. found that reduced ER and PR expression and high Ki67 levels suggest that the tumor is behaving more aggressively.[6] Particularly in HER2-targeted treatments, high Ki67 levels indicate HER2-positive breast cancer and assist clinicians in determining therapy efficacy.59,67 Even if Ki67 assessment is helpful, standardized procedures are needed, as it suffers from many measuring techniques and interpretations.[22,68]

In the end, Ki67 offers a prognostic marker in breast cancer and can give an analysis of the tumor aggressiveness, metastatic potential, and therapy response. Particularly by separating breast cancer subtypes and guiding therapy options, its incorporation into clinical practice has dramatically improved patient care. Though standardizing and interpreting Ki67 values still presents challenges, more study and cooperation are required to make it more helpful in clinical settings. Right now, combining Ki67 with additional biomarkers and improving conventional evaluation techniques would be better, enable physicians to create individualized treatment plans even more, and assist in the betterment of breast cancer patients.

MCM2 in Breast Cancer

A protein called Minichromosome Maintenance 2 (MCM2) is involved in both cell cycle control and DNA replication. In studies on breast cancer, this feature makes a valuable biomarker. Besides Ki67, its expression is also a good indicator of tumor aggressiveness, proliferation, and patient outcomes. Therefore, it is a helpful instrument for choosing therapy or prognosis. Managers of DNA Replication MCM2-7 complex is mainly composed of MCM2, which is necessary to start DNA replication throughout the cell cycle. MCM2 overexpression drives cell proliferation and tumor aggressiveness. MCM2 levels in breast cancer tissues are more significant than in healthy tissues, indicating that the tumor has progressed. Consequently, the cancer is more significant and has a higher histological level.[12] Since MCM2 helps with DNA replication, it is an effective way to find quickly developing cells even at low Ki67 levels.11 Thus, MCM2 is a promising biomarker for Ki67, particularly in searching for collections of cancer cells that are likely to divide rapidly.[8]

Since DNA replication begins here in cancer cells, MCM2 is essential in their proliferation. Compared to luminal A, MCM2 expression is substantially greater in aggressive forms of breast cancer, including luminal B and HER2-positive tumors.[12] MCM2 supports tumor development by interacting with cell cycle regulators such as cyclins A and D1. Particularly in many forms of cancer where Ki67 expression isn't always constant, researchers believe MCM2 is a more accurate signal of proliferation than Ki67.[11,12] Significant changes in the MCM2 transcript under many types of breast cancer reveal their prognostic prediction and therapeutic-guiding ability. TNBC is linked to aggressive tumor behavior and inadequate survival outcomes in excessively high MCM2 levels.[5] Researchers have shown in HER2-positive breast cancer, high MCM2 levels correlate with poorer tumor aggressiveness and a worse prognosis.[69] In luminal B tumors, as opposed to luminal A tumors in luminal breast cancer, MCM2 expression is higher in adjuvant therapy. This defines these groups and affects the available therapeutic choices.[12] These results show how helpful MCM2 is for anticipating patient outcomes and various kinds of breast cancer classification.

Since high levels of MCM2 are associated with aggressive tumor development, more metastases, and worse odds of survival, MCM2 become another possible therapeutic target that is now being researched.[12,19] Blocking MCM2 enhances cancer cells' responsiveness to treatment and raises their sensitivity to chemotherapy.[70,71] To create more accurate prediction models in future studies, researchers want to mix MCM2 expression with other molecular indicators, like the condition of hormone receptors and HER2 expression. This will enable them to create more individualized therapy schedules. The expression of MCM2 changes based on subtypes of breast cancer, providing a fascinating study of tumor aggressiveness and treatment direction.

In order to analyze MCM2 in breast cancer tissues, MCM2 detection immunohistochemistry is the most widely employed method. Specific antibodies make MCM2 visible in formalin-fixed paraffin-embedded (FFPE) samples. This helps us see it in benign and malignant tissues.[12] Digital Image Analysis (DIA) is increasingly becoming a proper technique because it can standardizing MCM2 measurements, enhancing agreement between observers, and raising the accuracy of prognostic assessments. Moreover, tissue microarray (TMA) technology lets scientists see numerous samples simultaneously and track MCM2 expression. This helps them investigate in detail the link between MCM2 levels and clinical findings.[12] Mass spectrometry and other proteomic techniques are essential for gauging the growth of cancer, as they enable us to understand better how MCM2 molecules migrate and evolve throughout time.[72] These sophisticated detection strategies improve the therapeutic worth of MCM2 as a breast cancer prognostic marker.

Prognostic Significance of MCM2 in Breast Cancer

The prognostic significance of MCM2 in breast cancer is a crucial part of the MCM2-7 helicase complex. Its expression is closely linked to tumor development, aggressiveness, and patient prognosis, making it an essential tool for prognostic assessment. According to a study by Mamoor *et al.*, MCM2 expression is always higher in breast cancers that are more likely to spread, like TNBC and HER2-positive tumors, than in luminal A malignancies, which are less likely to spread.5 Higher MCM2 levels are linked to more metastases, a worse tumor grade, and a more enormous tumor. This study shows how vital these levels are for determining how aggressive a cancer is and how bad the treatment results will be.[5] In TNBC, higher MCM2 expression is linked to shorter overall survival, which shows how important it is for predicting outcomes in high-risk breast cancer groups.[5] MCM2 levels are much higher in luminal B breast cancer compared to luminal A, which helps find the subtype and decide on the best treatment.[12,19]

Ki67 is a commonly used marker for cell proliferation, but MCM2 is more sensitive to finding proliferating cells. This is especially true in heterogeneous malignancies, and it is a better indicator of a patient's prognosis and risk of recurrence.[11] Ki67 is very important in clinical practice, but it can be interpreted differently and isn't always helpful in predicting outcomes across subtypes.[73,74] MCM2 can include more proliferating cells than Ki67, including some that Ki67 can't see. This makes it a useful extra or alternative marker.[8,11] In addition, MCM2 controls the S-phase of the cell cycle, which connects its expression to critical pathways that help tumors grow. This gives us a better understanding of how tumors change over time.[70]

Clinical studies have validated the prognostic significance of MCM2. Issac et al. demonstrated that increased MCM2 expression correlates with aggressive tumor characteristics and worse clinical outcomes, particularly in luminal B and HER2-positive breast cancer.[12] Liu *et al.*, observed that increased MCM2 levels in estrogen receptor-positive breast cancer correlate with reduced survival, indicating their influence on therapy effectiveness and patient prognosis.[69] In TNBC, MCM2 expression is very high, and the fact that it is linked to worse survival rates shows that it could be used to find high-risk patients who might benefit from more aggressive treatment methods.[5]

Although MCM2 has considerable potential, its current understanding and use suffer due to many shortcomings. The lack of consistent procedures for assessing MCM2 limits its broad application in clinical practice.[75,76] Also, if comparison studies show that MCM2 is bigger than Ki67 in some situations, these results need to be shown again in a larger group of people and with different types of breast cancer. It is essential to learn more about how MCM2 interacts with other molecular markers, like hormone receptors and HER2 status because this information could be used to make more accurate prediction models.[70,71] In addition, further research is needed to determine MCM2's efficacy as a therapeutic target, particularly in aggressive forms such as TNBC, to determine its ability to inhibit tumor growth and overcome medication resistance.[70,71] To make the results more consistent and lessen the differences between observers, future research should focus on making MCM2 assessment methods more uniform, like digital image processing and automatic scoring systems. Extensive multicenter studies that test MCM2's effectiveness across a wide range of demographic groups and breast cancer subtypes are needed before it can be widely used in clinical settings. Furthermore, investigating MCM2's relationship with other biomarkers and its potential as a therapeutic target would improve risk categorization, change treatment methods, and increase prognosis accuracy. It might help to teach doctors and pathologists consistent ways to make diagnoses. However, long-term studies that track changes in MCM2 expression after treatment could tell us important new things about how tumors work that could help make prognosis models more accurate.

Comparing Ki67 and MCM2 in Breast Cancer: Prognostic and Clinical Implications

Despite Ki67's long-standing usage as a standard, MCM2 has emerged as a useful supplementary or alternative biomarker. Many scientists concur that Ki67 is a good gauge of cell proliferation. Greater levels of this protein usually correlate with more assertive tumors, a greater likelihood of returning, and worse survival rates.[24] It is beneficial for directing treatment choices and separating luminal A from luminal B breast cancer subtypes. MCM2 is a more reliable marker as it can identify a broader spectrum offast-developing cells, including ones Ki67 cannot identified. Comparative studies like those by Joshi *et al.*, have shown in early-stage breast cancer. MCM2 is a more reliable indicator of a patient's death. Such data indicates a more reliable method of gauging treatment response and outcomes. Issac et al. also discovered that MCM2 improves Ki67's supportive role by making it easier to tell the difference between high-grade tumors and aggressive subtypes.[8,12] Although Ki67 remains a pillar in assessing tumor development, research has shown that MCM2 may provide additional information, especially in different tumors where Ki67 might not fairly represent proliferative activity.[12] For instance, Joshi *et al.*, discovered that MCM2 takes up more cell proliferation in breast tumors than Ki67, acting as an extra-sensitive marker in specific contexts.[8] When it comes to aggressive types of breast cancer, like triple-negative and HER2-positive types (206, 207), MCM2 is an even more critical extra biomarker because it can predict bad clinical outcomes.[25,77] Moreover, MCM2 regulates the S-phase of the cell cycle, therefore connecting its expression to fundamental mechanisms driving tumor development and providing a deeper understanding of tumor evolution over time.[78]

Meta-analyses and systematic reviews have given perceptive comparisons of Ki67's relative efficiency to MCM2. A Ki67 cutoff of >25% is a consistent indication of overall survival, according to the findings of a sizable research study including 64,196 individuals. Particularly in aggressive forms of breast cancer like luminal B and triple-negative, studies have also demonstrated that MCM2 may be used alone to forecast the outcome of a cancer diagnosis.[12,27] Compared to Ki67, MCM2 may give a more complete picture of how tumors grow, especially in tumors that aren't all the same, where Ki67 may not be as accurate.[59,79] While Ki67 remains fundamental for clinical practice, MCM2's ability to enhance therapeutic decision-making precision and prognosis accuracy is becoming increasingly evident.

Ki67 has well-established immunohistochemical assessment techniques and a high correlation with the severity of tumors and how well patients perform.[75,76] Among its shortcomings is the fact that subjective grading systems might result in various interpretations and that it does not always perform as well as a predictor for some forms of breast cancer.[73,80] One good thing about MCM2 is that it is better at finding cells that are multiplying and has stronger links to aggressive tumor activity and poor survival outcomes.5 Nevertheless, it's not generally acknowledged because there are no consistent approaches to evaluating

MCM2, and it's not genuinely used in regular clinical settings.[75,76]

Regarding assessing tumor development and projecting clinical outcomes in breast cancer, Ki67 and MCM2 have particular advantages. Sensitive and able to record a larger spectrum of proliferating cells, MCM2 is a helpful complementing biomarker. Conversely, Ki67 is a standard in clinical practice, as it is effective and future-predictive. More studies are required to standardize MCM2 evaluation techniques and see how they may be combined with Ki67 and other clinical indications to generate complete prognostic models. By putting these markers together, doctors can better divide risks and change how they treat patients, which improves their outcomes when they have breast cancer.

CONCLUSION

MCM2 and Ki67 are important biomarkers in breast cancer because they can predict patient prognosis and evaluate tumor growth. Although the marker Ki67 is almost common, its prognostic value varies according to the subtype and may be understood in many ways. In the future, researchers should fill in these holes, make sure that MCM2 works for a wide range of people, and create complete models for predicting the future. By making it simpler to classify patients according to risk, develop customized treatment plans, and provide more precise prognoses, researchers looking into Ki67 and MCM2 want to enhance the effectiveness of breast cancer treatment results. It now serves as a potential complementary or alternative marker. There are still some gaps, such as the fact that there aren't any standardized methods for testing MCM2 and there haven't been any full studies on how it interacts with other biomarkers and therapeutic uses. In the future, researchers should fill in these holes, make sure that MCM2 works for a wide range of people, and create complete models for predicting the future. By making it simpler to classify patients according to risk, develop customized treatment plans, and provide more precise prognoses, researchers looking into Ki67 and MCM2 want to enhance the effectiveness of breast cancer treatment results.

SUGGESTION

Future studies should mostly concentrate on standardizing MCM2 measurement methods, including digital image processing, to reduce variation and increase repeatability. Furthermore, large-scale multicenter research should investigate MCM2 and Ki67 in many populations to ensure their greater applicability in daily life. Combining MCM2 with other indicators, such as HER2 status and hormone receptors, could result in novel therapies and improved methods of predicting individual outcomes. For forms of high-risk breast cancer, including triple-negative and HER2-positive subtypes, this information is especially crucial. Looking into MCM2's part in DNA replication as a possible therapeutic target could also lead to new ways to treat aggressive cancers. Tracking biomarker changes over time will give improved prognosis tools and signal detection, indicating therapy success. Teaching clinicians how to use consistent assessment techniques and machine learning might help us create more accurate and valuable prognostic tools. Looking into how MCM2 is involved in various types of cancer will help us understand how tumors work and make it easier to use, which will lead to more personalized cancer care and better outcomes for patients.

CONFLICT OF INTEREST

All authors declare no conflict of interest regarding this article's publication.

AUTHOR CONTRIBUTIONS

All authors contributed equally contribute to the study.

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ETHICAL CONSIDERATION

None declared.

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