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PMS2 Gene Expression Analysis in Blood of Postmenopausal Women with Breast Cancer: A Comparative Study

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Abstract

Background/aim: The PMS2 gene was evaluated for its role in the pathogenesis of breast cancer by analyzing its expression in blood samples obtained from healthy postmenopausal women, newly diagnosed breast cancer patients, and the same patients following surgical and therapeutic treatment. ***Materials and Methods:*** A total of 47 blood samples were analyzed, including 7 from healthy controls, 20 from newly diagnosed breast cancer patients (disease group), and 20 from the same patients' post- treatment (cure group, 4 months' post-surgery or therapy). RNA extraction, cDNA synthesis, and RT-PCR analysis were performed on blood samples to determine the expression levels of the PMS2 gene across groups, providing insight into the genetic changes associated with breast cancer progression and the impact of clinical interventions. SPSS was used for statistical analysis, including correlation and paired-sample t-tests. ***Results:*** PMS2 expression exhibited a highly significant difference between group 1 (healthy control), which showed no expression, and group 2 (disease group), which demonstrated upregulation of the PMS2 gene ($P < 0.001$, paired sample t-test) with a 99% confidence interval. A downregulation of gene expression was observed in group 3 (cure group) after treatment, and the comparison between the disease and cure groups revealed a statistically significant difference ($P = 0.042$, paired t-test) with a 95% confidence interval. The majority of patients aged 50–60 were diagnosed with stage 2 invasive ductal carcinoma. This systematic regulation of PMS2 expression highlights its role in disease development, progression, and therapeutic response. ***Conclusion:*** The data confirmed the involvement of the PMS2 gene in breast cancer aggressiveness and progression.

Keywords: PMS2, breast cancer, invasive ductal carcinoma, gene expression, postmenopausal women.

1. INTRODUCTION

Cancer is a complex and diverse disease with many forms, all caused by the uncontrolled growth of abnormal cells, which can form tumors. These cells can spread to other body parts through the lymphatic and circulatory systems, known as metastasis, where they invade and destroy healthy tissues. In 2016, about 7,046 neuro neoplasms were reported, with 459 being benign and 6,587 malignant [1]. In 2020, around 19.3 million new cancer cases and over 10 million deaths were reported. Breast cancer, prevalent among women, affects one in eight women during their lifetime. Approximately 10% of cases are hereditary, resulting from autosomal dominant genetic mutations. Although men can develop breast cancer, women are at much higher risk, with breast cancer being 100 times more common in women than men [2]. Breast cancer in elderly women has been found in numerous studies to be less aggressive and to react well to hormone therapy. This indicates that hormones frequently impact the growth of cancer, and in many situations, managing the disease can be achieved by medicines that specifically target these hormonal pathways [3]. In low-to-middle-income countries (LMICs), including Pakistan and India, the prevalence of breast cancer is increasing, while being more common in the industrialized world. Seventy per cent of breast cancer-related mortality occurs in LMICs due to misdiagnosis, myths, cultural beliefs, lack of diagnostic methods, inadequate healthcare policy, and advancements in therapy. According to the provided data, approximately 178,388 new cases of breast cancer were registered in Pakistan in 2020. Misconceptions and myths play a part in the increase in Pakistani cases of breast cancer. False information concerning the clinical

manifestation, diagnosis, and treatment of breast cancer impedes timely detection, deteriorates the doctor-patient bond, and prevents efficient care [4]. Having a child or getting married after the age of 30, early menarche, and delayed menopause (after 50) all increase the risk of breast cancer due to hormonal changes throughout a woman's reproductive life. A study shows that women who marry at 30 or later have a 7.0% risk, compared to a 1.4% risk for those marrying younger. Early pregnancy and prolonged breastfeeding have been linked to breast cancer incidence, with most cases being either estrogen receptor (ER) positive or negative. Long-term use of hormonal contraceptives also raises the risk of breast cancer [5]. A meta-analysis carried out in 2020 found that obese women had a 41% higher overall mortality and a 33% greater chance of death from breast cancer, in addition to several studies linking obesity to poor breast cancer outcomes. This correlation is plausible because of biological components linked to obesity, including higher insulin levels, glucose, leptin, postmenopausal estrogen, and inflammatory markers. A small percentage of instances—about 5–10%—are linked to the inheritance of high-penetrance cancer susceptibility genes despite the disease's broad incidence. About 80% of occurrences of breast cancer are found in women 50 years of age or older, and it is most frequently detected in women going through the menopausal transition. The percentage of instances of breast cancer linked to hereditary abnormalities is just 5–10%, while lifestyle decisions and environmental variables are responsible for the remaining 90–95%. Despite the high incidence of the disease, only a tiny proportion of cases—roughly 5–10%—are associated with the inheritance of high-penetrance cancer susceptibility genes. Women 50 years of age or older account for about 80% of all cases of breast cancer, and women going through the menopausal transition are the ones who get it most often. Merely 5–10% of cases of breast cancer are associated with genetic disorders. However, the remaining 90–95% are caused by environmental factors and lifestyle choices. Most of the time, genetic predisposition is not the decisive element [6]. According to an alarming study, 11 million deaths from breast cancer are expected to occur by 2030. Breast cancer is the most frequently diagnosed cancer, with lung, colorectal, prostate, and stomach cancers coming a close second [7]. Postmeiotic segregation increased 2, or PMS2, is a mismatch repair gene with 38,125 base pairs, 15 exons, and an encoded protein of 862 amino acids. It is located at chromosomal segment location 22 on the short arm of chromosome 7 [8]. PMS2 is a nuclear protein with a mass of 95.8 kDa [9]. The primary function of this protein is to correct small DNA mismatches and insertions and deletions that may occur during homologous recombination and DNA replication. The MutL-alpha heterodimer is produced when the MLH1 gene product and the PMS2 protein interact to form heterodimers. When the MutL-alpha heterodimer detects mismatches and insertion/deletion loops, its endonucleolytic activity is triggered. The MutS-beta and MutS- alpha heterodimers aid in recognition. One type of Lynch syndrome (LS) is called hereditary

nonpolyposis colorectal cancer (HNPCC). It is brought on by a heterozygous mutation in the PMS2 gene. The C-terminus of the protein produced by the PMS2 gene bears the DQHA(X)2E(X)4E motif [10]. This motif is a component of the endonuclease's active site and aids in the enzymatic activity that removes mismatched DNA. The specific amino acids in this motif are likely involved in the catalytic activity of the nuclease, contributing to its ability to cleave nucleic acids during the repair process. The conservation of certain amino acids in this motif is important for maintaining the proper structure and function of the protein. Mutations in this motif could potentially affect the protein's activity and, in this case, may be associated with conditions such as hereditary Lynch syndrome and constitutional mismatch repair deficiency (CMMRD) syndrome [11]. The Lynch syndrome carries an 80% lifetime risk of developing several types of cancer, making it an autosomal dominant cancer predisposition condition, such as small bowel, pancreatic, prostate, endometrial, ovarian, urothelial, and colorectal cancers [12]. In 1994, PMS2 was discovered to be the cause of Lynch syndrome when it was cloned [13]. The DNA mismatch repair (MMR) pathway is crucial for repair, recombination, and meiosis. Inactivation of MMR increases susceptibility to cancers [14]. The PMS2 gene is one of the genes involved in mismatch repair pathways. There is a 10% cumulative risk for any cancer in both sexes among PMS2 mutation carriers when they are between the ages of 50 and 55. The risk of colorectal cancer is 5.2 times greater than in healthy individuals [15]. PMS2 deficiency is similarly linked to a higher risk of breast cancer, with a cumulative risk of 37.7% at 60 years of age [16]. According to reports, women with LS who have mutations in the PMS2 gene are more likely to develop breast cancer than those who have mutations in the MLH1, MSH2, or MSH6 genes. A different juvenile cancer syndrome is linked to biallelic mutations in the PMS2 gene, which is not the same as the common hereditary nonpolyposis colorectal cancer (HNPCC) linked to heterozygous PMS2 mutations [17]. The research involved a sizable cohort of 8,085 Chinese women with breast cancer, of whom 15 had pathogenic germline variants in MMR genes, including PMS2. Of these carriers, 40% had a history of HNPCC-related cancers in their families, with colorectal and gastric cancers being the most common. MMR variant carriers did not vary in age at diagnosis or family history of breast cancer, but they were more likely than non-carriers to have a positive family history of HNPCC-related malignancies. Patients with PMS2 gene breast cancer were more prevalent than those with other mismatch repair genes [18]. Research indicates the personal and family history of cancer in 423 women who had germline mutations in MLH1, MSH2, MSH6, or PMS2 that were pathogenic or likely pathogenic. By comparing the study population's breast cancer frequencies with those of the

general population, standard incidence ratios (SIRs) of breast cancer were determined. Accordingly, the study found no correlation between MLH1 and MSH2, while MSH6 and PMS2 were linked to a statistically significant risk for breast cancer [19]. There is currently no information on blood levels of PMS2 gene expression before and after treatment in postmenopausal women with breast cancer. The goal of the current study is to close this information gap and investigate the molecular changes brought on by surgical procedures this population of postmenopausal women with breast cancer.

2. MATERIALS AND METHODS

2.1. Sample collection

Blood samples were collected from female breast cancer patients at the Department of Oncology, Fuji Foundation Hospital, Rawalpindi. A total of 47 samples were obtained from 27 participants, consisting of 7 samples from healthy controls, 20 from patients in the disease group, and 20 from individuals in the cure group. Venipuncture was performed to collect 5 mL of peripheral blood into EDTA vacutainer tubes. All tubes were appropriately labeled and stored for subsequent analysis. The participants' ages ranged from 40 to 60 years, with a mean age of 58.5 years. All blood samples were processed at BJ Micro Lab, Rawalpindi. RNA was extracted from whole blood using the TRIzol reagent (Thermo Fisher Scientific, Waltham, MA, USA) according to the manufacturer's instructions. For each 300 µL sample, 600 µL of TRIzol reagent was added, followed by thorough homogenization and incubation at room temperature for 5 min. Then, 400 µL of chloroform was added to each sample. The mixture was incubated for 3 min and centrifuged at 12,000 rpm for 10 min at 4 °C. The aqueous phase was carefully transferred to a new tube and mixed with an equal volume of isopropanol. Following a 10-minute incubation, the samples were centrifuged at 12,000 rpm for 10 minutes. The resulting RNA pellet was washed with 70% ethanol, air-dried, and resuspended in 35 µL of RNase-free water. RNA samples were stored at −80 °C until further analysis.

2.2. Gel Electrophoresis

To evaluate RNA integrity, 1.5% agarose gel electrophoresis was performed. Agarose (0.45 g) was dissolved in 30 mL of 1× TBE buffer by heating in a microwave. After cooling, 5 µL of ethidium bromide was added. The gel was cast and solidified in a gel tray. Subsequently, 2 µL of loading dye and 5 µL of RNA sample were loaded into the wells. Electrophoresis was carried out at 100 V for 30 min. RNA bands were visualized using a UV transilluminator

2.3. cDNA synthesis

First-strand cDNA synthesis was performed using the FIREScript® Reverse Transcriptase kit (Solis BioDyne, Tartu, Estonia). The reaction mixture contained 10 µL of total RNA, 1 µL of Oligo(dT) primer, 1 µL of random primer, and 4 µL of nuclease-free water. This mixture was incubated at 65 °C for 5 min and immediately chilled on ice. Then, 2 µL of 10× RT buffer, 0.5 µL of dNTP mix, 1 µL of FIREScript® Reverse Transcriptase, and 0.5 µL of RiboGrip® RNase Inhibitor were added. The reverse transcription reaction was carried out at 25 °C for 10 min, followed by 50 °C for 30 min. The reaction was terminated by heating at 85 °C for 5 min. The quality of the synthesized cDNA was confirmed using PCR amplification of the GAPDH gene.

2.4. Quantitative real-time PCR

Quantitative real-time PCR (qRT-PCR) was conducted to determine the expression levels of the PMS2 gene, using GAPDH as the reference gene. Specific primers for the PMS2 gene were designed based on NCBI sequences.

Forward primer: 5′-AGAGGCAGTGAGTTCCAG-3′
Reverse primer: 5′-GTGTTTGGGGTTGCGAGATT-3′

Each qRT-PCR reaction included PCR-grade water, forward and reverse primers, cDNA template, and EvaGreen dye (Bio-Rad Laboratories, Hercules, CA, USA). The amplification was performed in a thermal cycler under the following conditions: initial denaturation at 95°C for 5 min, followed by 35 cycles of denaturation at 95 °C for 30 s, annealing at 56 °C for 30 s, and extension at 72 °C for 20 s. The total amplicon length for PMS2 was 223 bp. GAPDH gene expression was used as an internal control for normalization.

2.5 Statistical analysis:

The data were statistically analyzed using Microsoft Excel and SPSS version 21. A Microsoft Excel spreadsheet was used to enter and arrange the data, and SPSS was then used for statistical analysis. Using SPSS, the differences in gene expression and the impact of clinicopathological features on gene expression were determined. Various statistical tests were used. To compare expressions, the paired sample t-test between groups was used. The p-value was $P < 0.001$ between the disease group and healthy control, and $P = 0.042$ between the disease and cure group. 3.

2.6 Descriptive statistics a

The descriptive statistics for the experimental group, as shown in Table 1, indicate that the majority of participants were aged between 50 and 60 years (55%), with a slightly lower percentage aged 60 to 70 years (45%). Histological analysis revealed 55% had invasive ductal carcinoma (IDC) and 45% had invasive lobular carcinoma (ILC). Most patients were categorized as Grade 2 (75%), and Stage 2 or 3 (80%) based on the TNM classification. The treatment duration was evenly split between 4 and 6 months. Notably, all participants had a 100% survival rate both pre- and post-tumor diagnosis.

2.7 Descriptive statistics b

The demographic characteristics of the control group are summarized in Table 2. A higher percentage of

participants were aged 60 to 70 years (57.1%), compared to those aged 50 to 60 years (42.9%). All participants showed no gene expression activity and reported no family history of cancer. The control group had 100% representation in both categories.

3. RESULTS

3.1. Expression level of PMS2 gene in the disease and control groups:

The expression level of the PMS2 gene in postmenopausal women with breast cancer (disease group) and healthy controls was assessed using quantitative real-time PCR (qRT-PCR). In the healthy control group, gene expression was nearly undetectable. In contrast, the disease group showed a significantly upregulated expression of the PMS2 gene ($P < 0.001$), indicating a strong association of this gene with breast cancer pathogenesis. The observed expression difference between the groups is illustrated in Figure 1.

3.2 Expression level of PMS2 gene in the disease and cure groups:

A significant downregulation of PMS2 gene expression was observed in the cure group (post-treatment samples) compared to the disease group. The paired sample t-test revealed a statistically significant difference ($P = 0.042$) with a 95% confidence interval, suggesting that tumor removal led to reduced gene expression. The expression levels for individual samples are shown in Figure 2.

Expression variation across the groups:

Gene expression analysis demonstrated that the PMS2 gene was not expressed in the control group, whereas it was significantly upregulated in the disease group. This pattern highlights the potential role of PMS2 in breast cancer development. Following treatment, the cure group showed a marked downregulation of gene expression, indicating that clinical intervention effectively reduced PMS2 levels associated with tumor progression.as shown in figure 3.

3.4. paired sample t-test:

Statistical analysis supported the alternate hypothesis, indicating a significant difference in PMS2 gene expression among the study groups. The mean difference in expression between the control and disease groups was 2.261, with a t-value of 2.181 and a P-value < 0.001 (99.9% confidence interval; SD = 4.636). The comparison between the disease and cure groups also showed a statistically significant difference ($P = 0.042$, 95% confidence interval; SD = 1.046). These results underscore the significance of PMS2 expression in postmenopausal women with breast cancer and its modulation following treatment.

3.5. Pearson correlation coefficient in breast cancer patients:

The Pearson correlation coefficient between PMS2 expression in the disease group and the cure group was –0.161, indicating a weak negative correlation. This suggests that higher PMS2 expression in the disease state is only weakly associated with lower expression following treatment.

The Pearson correlation coefficient between PMS2 expression in the disease group and the cure group was –0.161, indicating a weak negative correlation. This suggests that higher PMS2 expression in the disease state is only weakly associated with lower expression following treatment.

1. Descriptive Statistics: Table 1 shows descriptive statistics of experimental group variables.

Table 1

Variables	Categories	F	%
Age	50 to 60 years	11	55.0%
	60 to 70 years	9	45.0%
Histological Factor	ILC	9	45.0%
	IDC	11	55.0%
Grade	2	15	75.0%
	3	5	25.0%
Stage (TNM)	Stage 1	2	10.0%
	Stage 2	6	30.0%
	Stage 2A	2	10.0%
	Stage 3A	4	20.0%
	Stage 3B	4	20.0%
	Stage 4	2	10.0%
Time Duration	4 months	10	50.0%
	6 months	10	50.0%
Survival Rate (Pre-	Survived	20	100.0%
	Not-Survived	0	0%
Survival Rate (Post-	Survived	20	100.0%
	Not-Survived	0	0%

Descriptive statistics: Table for control demographic variables.

Variables	Categories	F	%
Age	50 to 60 years	3	42.9%
	60 to 70 years	4	57.1%
Gene Expression	Nil	7	100%
Family History	YES	0	0%
	NO	7	100%

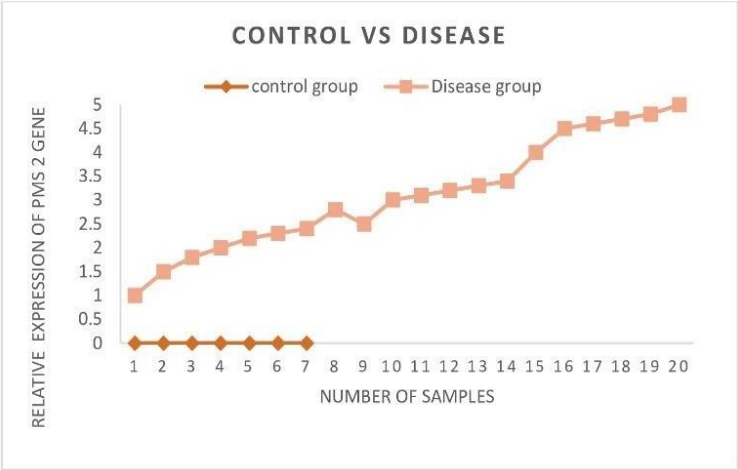

Figure 1: Shows the expression level of the PMS2 gene in the disease and control groups

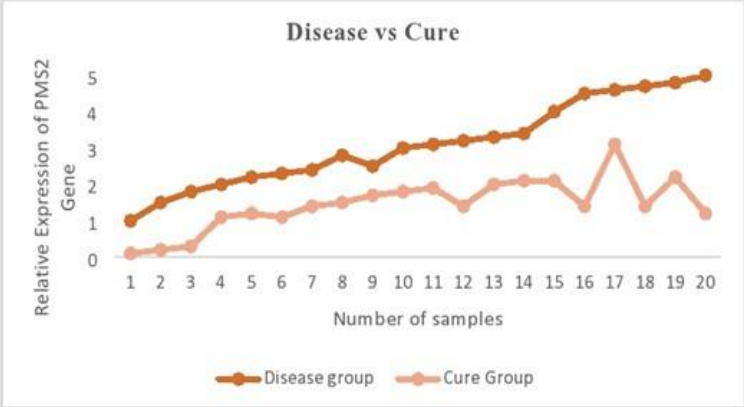

Figure 2: Shows the expression level of the PMS2 gene in the disease and cured groups

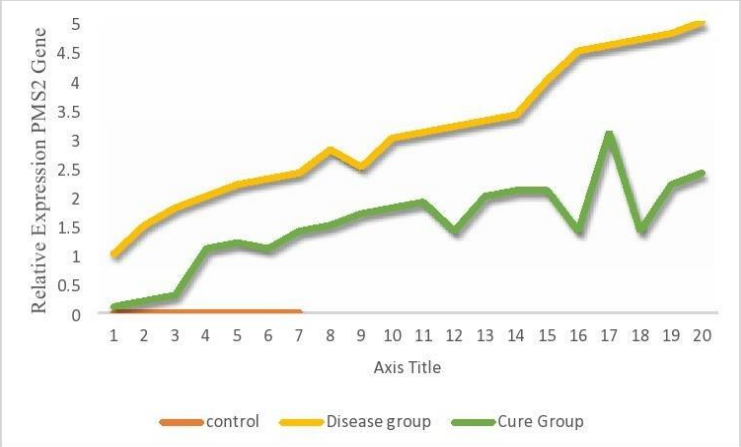

Figure 3: Shows expression variation across the groups

4. DISCUSSION

This study explored the role of PMS2 gene expression in postmenopausal women with breast cancer, comparing expression levels before and after treatment. The findings revealed a significant upregulation of PMS2 in newly diagnosed breast cancer patients and a downregulation following treatment, suggesting a dynamic regulation of this mismatch repair gene in response to tumor burden and therapeutic intervention. These results align partially with previous studies that report PMS2 overexpression in cancers such as oral squamous carcinoma and prostate cancer [2]. However, unlike colorectal or pancreatic cancers where PMS2 deficiency is more common, our findings show that in breast cancer, PMS2 may be transiently upregulated during tumor progression and reduced following surgical or chemotherapeutic interventions. This discrepancy highlights the complex role of PMS2, possibly acting differently across tissue types or cancer stages.

Importantly, this study focused specifically on postmenopausal women, a group at higher risk of breast cancer and for whom hormonal factors and gene regulation can differ significantly. The majority of our patients had stage 2 invasive ductal carcinoma, consistent with national prevalence data. The observed weak negative correlation between pre- and post-treatment gene expression suggests that PMS2 may be sensitive to therapeutic effects, though not in a strictly linear or predictable manner. These findings raise the possibility of using PMS2 expression as a biomarker to monitor treatment response. However, before clinical application, further validation is needed at the protein level, in larger multi-center cohorts, and across different molecular subtypes of breast cancer. Additionally, while PMS2 mutations are known to contribute to Lynch syndrome, their role in sporadic breast cancer—particularly in gene expression rather than mutation—is still underexplored.

This study has several strengths, including the comparison of paired pre- and post-treatment samples, and the use of real-time PCR for quantitative analysis. However, it is limited by the small sample size, lack of protein-level confirmation (e.g., Western blot), and absence of long-term survival or recurrence data. These factors may limit the generalizability of our conclusions. Future research should examine the mechanistic role of PMS2 in breast tissue, investigate whether modulating its expression can affect tumor behavior, and assess whether PMS2 could be integrated into personalized treatment planning, especially for postmenopausal patients.

5. CONCLUSION

This study highlights the potential role of PMS2 gene expression as a biomarker in postmenopausal breast cancer. The observed reduction in PMS2 levels following treatment suggests that its expression may be linked to tumor presence and could reflect therapeutic response. These findings offer preliminary insight into the molecular dynamics of PMS2 in breast cancer progression. Further research is needed to validate its diagnostic and prognostic Utility in larger and diverse patient populations.

Acknowledgment/Disclaimers/Conflict of Interest

The study was planned and carried out by Asma, who also performed all the experiments, analyzed the data, and wrote the report. Dr. Shaukat Iqbal Malik supervised the research. Mahnoor Fayyaz contributed minor assistance to the project. The authors gratefully acknowledge the Capital University of Science and Technology for providing the infrastructure and support necessary to carry out this research.

Conflicts of Interest: The authors declare that there are no conflicts of interest.

Informed Consent

This study was approved by the Institutional Review Board of Capital University of Science and Technology, Islamabad. Informed consent was obtained from all participants prior to sample collection in accordance with ethical standards

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