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The impact of changes in breast density over time on breast cancer risk

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Mammographic density is not static; instead, it is influenced by a range of factors, including age, number of births, hormone use, and menopause. The current study aims to evaluate the association between both baseline breast density and its changes over time and the risk of breast cancer in both premenopausal and postmenopausal women. Patients over the age of 40 who presented between 2022 and 2024 for either breast cancer diagnosis or routine breast cancer screening were retrospectively reviewed. The patterns of changes in density in the mammograms were analyzed, comparing those who developed cancer with those who did not. In premenopausal patients, a statistically significant relationship was found between cancer development and both age ($p = 0.01$, OR = 0.90 [0.82–0.98]) and the rate of change in density in the mammograms ($p = 0.04$, OR = 7.46 [1.09–50.40]). In postmenopausal patients, A statistically significant relationship could not be demonstrated ($p = 0.60$, OR = 1.72 [0.24–12.30]). The rate of decrease in fibroglandular tissue density was found to be associated with breast cancer in premenopausal patients. Applying this finding and monitoring the pattern and rate of density changes in mammographic images may allow more personalized risk-reduction strategies.

Keywords Breast cancer, Breast density, Density rate of change

Abbreviations

BIRADS	Breast imaging reporting and data systems
BMI	Body mass index
HRT	Hormone replacement therapy
MRI	Magnetic resonance imaging
OR	Odds ratio

Breast cancer is the most commonly diagnosed cancer in women. Mammography is the primary screening method for the early detection of breast cancer in women and is a widely accessible, cost-effective imaging technique. Breast density reflects the amount of radio-opaque fibroglandular tissue relative to radio-lucent fatty elements observed on a mammogram. The sensitivity of mammography in detecting breast cancer varies depending on breast density; in patients with dense breast tissue, the effectiveness of mammography evaluation can be up to 30% lower. Additional imaging methods are recommended for women with dense breast tissue[1].

Breast density is one of the risk factors for breast cancer, and women with dense breast tissue have a higher risk of developing breast cancer[2]. However, mammographic density is not a static characteristic; it is influenced by various factors such as age, parity, hormone use, menopause, and genetics. Breast density is known to decrease, particularly during the perimenopausal period. In the postmenopausal period, breast density decreases at varying rates among women. It has been suggested that changes in mammographic density over time could be useful in predicting breast cancer risk[1]. If changes in breast density independently influence breast cancer risk over time, changes in breast density over time could provide additional information about individual risks[3].

In our study, the relationship between the rate of change in breast density in screening mammograms and breast cancer risk was assessed.

Materials and methods

Patients aged 40 and over who presented to Ankara Etlik City Hospital between 2022 and 2024, either with a diagnosis of breast cancer or for routine breast cancer screening, were retrospectively screened. Patients who

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had at least 5 mammograms before cancer diagnosis or during the entire screening period were included after obtaining the informed consent form. The interval between two examinations had to be at most 24 months. Patients with a diagnosis of breast cancer formed the case group, while those without a cancer diagnosis formed the control group. The pattern of density changes in mammograms of patients who developed cancer and those who did not was examined during follow-up. Breast density evaluation was performed according to the American College of Radiology's Breast Imaging Reporting and Data Systems (BIRADS). The BIRADS mammographic density classification includes four categories[4] (Table 1).

All mammographic images were reported by the same four radiologists, who specialize exclusively in breast imaging and work at the breast cancer diagnosis and screening center. Mammographic images taken at external centers were routinely reviewed by the four specified radiologists. Patients whose external center images could not be accessed, whose image quality was deemed low, or who had more than a 24-month gap between their last five mammograms were excluded from the study. Patients' age, body mass index, menopausal status, age at menopause, family history, number of children, BIRADS density category for each mammogram, time and number of mammograms, and density changes between mammograms were retrospectively reviewed and recorded.

Univariate analyses comparing the cases and controls in terms of age, body mass index (BMI), number of births, and number of months between mammograms are conducted using two-sample t-tests while those for menopause status, family history, and mammogram density categories at the first and last visits are performed using Pearson chi-square tests. Further analyses with mammogram density category changes are stratified by menopausal status. The change in density category from the first to the last visit is compared between the cases and controls using a chi-square test. A two-stage model, based on Li et al., is used to examine the relationship between the rate of change in mammogram density and breast cancer, adusting for age and BMI[5]. In stage 1, a generalized linear mixed model is used to analyze mammogram density category recordings over time and estimate their rate of change while in stage 2, a logistic regression is applied to evaluate the association between breast cancer and the rate of change in mammographic density. Significance level is set at 0.05 for all tests. In addition, statistical power for the study sample size is obtained using a Monte Carlo simulation. All the analyses are carried out using RStudio[6].

Results

A total of 643 patients were included in the study: 253 patients formed the case group (with a breast cancer diagnosis) and 390 patients formed the control group (without a breast cancer diagnosis). The average age of patients in the cancer group was 53.37 (±6.60), while the average age of patients in the control group was 53.16 (±6.51). The BMI for the cancer diagnosis group was 29.28 (SD 2.06), while for the control group it was 29.66 (±2.42). In the case group, 152 patients (60%) were postmenopausal, while in the control group, 165 patients (42%) were postmenopausal. In the case group, 68 patients (27%) had a family history of cancer in at least one first- or second-degree relative, while in the control group, 93 patients (24%) had such a history. The average number of pregnancies was 2.09 (±1.32) in the case group and 2.21 (±1.38) in the control group. The average interval between mammograms was 14.21 months (±3.41) in the case group, while it was 14.32 months (±3.24) in the control group.

In the first mammogram, 88 patients (35%) in the case group had density category C, while 165 patients (65%) had density category D. In the control group, 182 patients (47%) had density category C, and 208 patients (53%) had density category D. In the last mammogram, 133 patients (52%) in the case group had density category B, 108 patients (43%) had density category C, and 12 patients (4%) had density category D. In the control group, 310 patients (79%) had density category B, 78 patients (20%) had density category C, and 2 patients (1%) had density category D. There were no significant differences between the groups in terms of age, family history, or number of pregnancies. However, statistically significant differences were observed between the groups in terms of BMI, menopausal status, and density types (Table 2).

The p-value associated with the relationship between rate of density changes and cancer development in the premenopausal and postmenopausal periods are provided in Table 3. The rate of density change in mammography was found to be statistically significantly linked with breast cancer in premenopausal patients (OR = 7.46, 95% CI = (2.70,22.49), p-value = 0.00). However, in postmenopausal patients, the rate of density change was not associated with cancer development (OR = 1.72, 95% CI = (0.26,11.22), p-value = 0.57). In postmenopausal patients, it was observed that density remained at D and there was less transformation from D to C. In premenopausal patients, however, more patients in the case group were found to transition from D to C and remain at that level.

Statistical power of the analysis for our study size is examined using a Monte Carlo simulation and presented in Figs. 1, 2 and 3. The blue dashed line represents 80% power. Accordingly, our study has the power to detect

BIRADS density category	Breast type (Fibroglandular tissue %)
A	Almost entirely fatty (< 25%)
B	Scattered densities (25–50%)
C	Heterogeneously dense (50–75%)
D	Extremely dense (> 75%)

Table 1. BIRADS mammographic density Classification.

Variables	Case group (*n* = 253)	Control group (*n* = 390)	*p*-value
Age (mean)	53.37 (± 6.60)	53.16 (± 6.51)	0.70
BMI (mean)	29.28 (± 2.05)	29.66 (± 2.42)	**0.04**
Menopause status	152 (60%)	165 (42%)	**0.001**
Family history status	68 (27%)	93 (24%)	0.44
Number of births (mean)	2.09 (± 1.32)	2.21 (± 1.38)	0.28
Number of months between mammograms (mean)	14.21 (± 3.41)	14.32 (± 3.24)	0.39
Mammogram density type at first visit			**0.001**
B	0	0	
C	88 (35%)	182 (47%)	
D	165 (65%)	208 (53%)	
Mammogram density type at last visit			**0.001**
B	133 (52%)	310 (79%)	
C	108 (43%)	78 (20%)	
D	12 (5%)	2 (1%)	

Table 2. Univariate analyses for patient demographics and characteristics. Significant values are in bold.

Mammographic density types	Case group *n* (%)	Control group *n* (%)	*p*-value
D → D	12 (5%)	2 (1%)	
D → C	105 (41%)	75 (19%)	
D → B	48 (19%)	131 (33%)	
C → C	3 (2%)	3 (1%)	
C → B	85 (33%)	179 (46%)	
Mammographic density changes by case-control status in the premenopausal period			**0.04**
D → D	10 (10%)	2 (1%)	
D → C	51 (50%)	67 (30%)	
D → B	25 (25%)	96 (42%)	
C → B	15 (15%)	60 (27%)	
Mammographic density changes by case-control status in the postmenopausal period			0.6
D → D	2 (1%)	0 (0%)	
D → C	54 (36%)	8 (5%)	
D → B	23 (15%)	35 (21%)	
C → C	3 (2%)	3 (2%)	
C → B	70 (46%)	119 (72%)	

Table 3. Mammographic density change by case-control status.

an OR of at least 1.65 with 80% power. In other words, our study is capable of identifying a difference of at least 1.65 units in the odds of developing cancer associated with changes in mammographic density with 80% power.

Discussion

It is thought that the rate of density of mammograms change could be a determinant of cancer risk. The decrease in mammographic density with age parallels the decline in endogenous estrogen levels occurring during the menopausal period, and endogenous hormones are associated with breast cancer risk in postmenopausal women. Additionally, age-related lobular involution has been found to be associated with a reduction in breast cancer risk. Lobular involution, linked to aging, involves a decrease in the number and size of acini per lobule, as well as replacement of the extralobular stroma with fat. The same mechanism applies to the use of tamoxifen. Tamoxifen is used as an adjuvant therapy to reduce the risk of recurrence in hormone-positive breast cancer and to slow disease progression in advanced stages. It can also be used as a preventive treatment in women at risk for breast cancer. In studies examining the effect of tamoxifen on breast density, a significant reduction in density was observed compared to the group that did not use tamoxifen, starting from the first year of use[7]. In a study conducted by Wu et al., the relationship between the rate of change in breast density and hormone replacement therapy (HRT) and other hormonal interventions was examined. It was found that breast density tends to increase to a greater extent in women undergoing hormonal therapy, and this increase, depending on the rate of density change during treatment, can also elevate breast cancer risk[8]. These findings suggest that

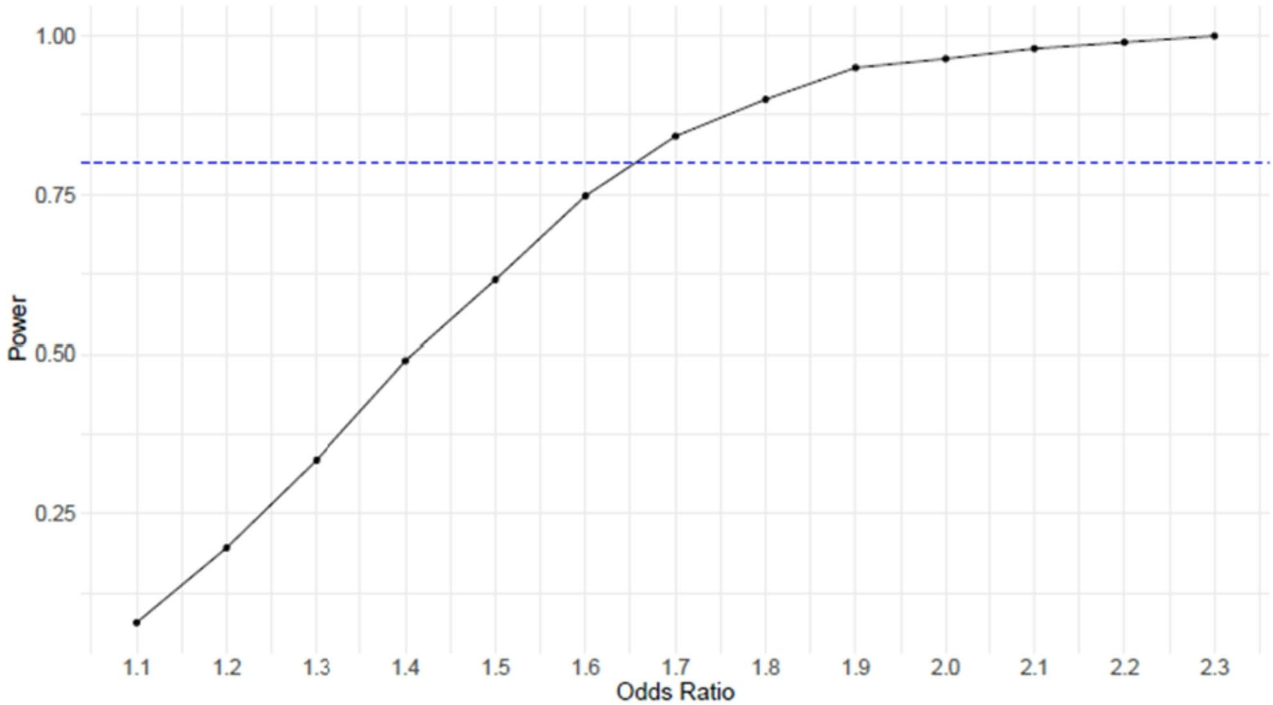

Fig. 1. Power curve for 253 cases and 390 control patients.

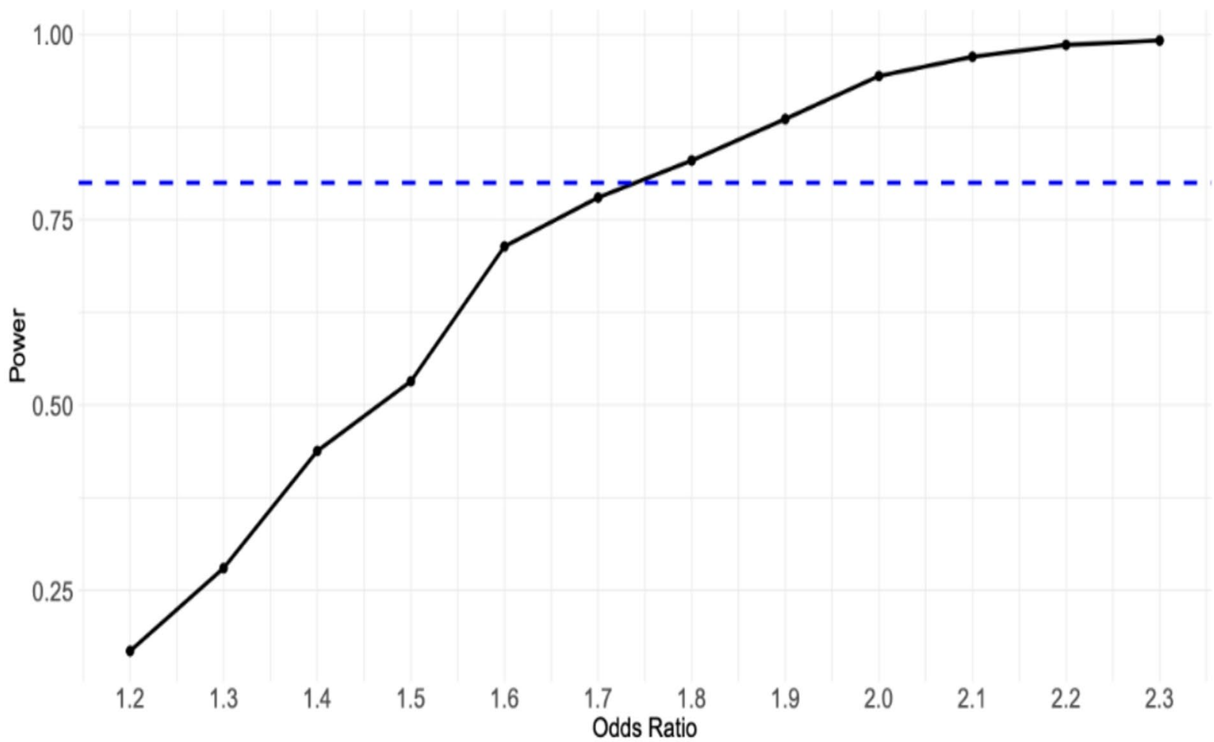

Fig. 2. Power curve for premenopausal group.

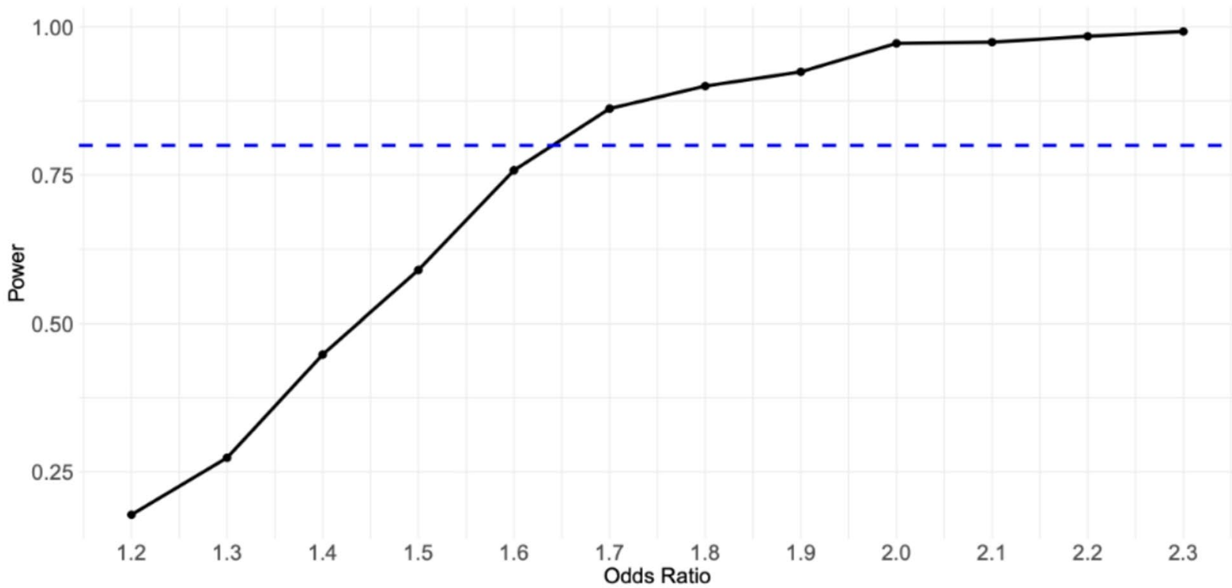

Fig. 3. Power curve for postmenopausal group.

monitoring breast density changes, particularly during hormonal therapy, could contribute significantly to risk management.

Breast density is one of the most accessible measurements from screening mammograms that can be used to assess breast cancer risk. In recent studies, it has been suggested that breast density may change over time due to various factors such as age, hormonal influences, and genetic predisposition, and there may be a positive correlation between the rate of these changes and the development of breast cancer[9,10]. In individuals with gene mutations such as BRCA1 and BRCA2, both high breast density and an increased cancer risk have been observed[11]. Breast density tends to be higher at younger ages but may decrease with aging due to hormonal changes and the effects of menopause. However, in some individuals, unexpected patterns of rapid decrease or increase in breast density may be observed, potentially opening new areas for risk assessment[12].

There are various methods for measuring breast density, including percentage density, homogeneous density percentage, and absolute density measurements. Although the BIRADS density classification aims to identify cancers obscured by dense tissue, it does not fully capture breast density. However, it is the most commonly used method for assessing density. Risk assessment based on changes in BIRADS categories can be easily implemented in a screening setting and incorporated into risk evaluation[13]. In our study, changes in breast density were assessed based on BIRADS density classification from routine screening mammograms.

There are few studies examining whether the decrease in breast density with increasing age, particularly during menopause, is associated with a reduced breast cancer risk[14]. The assessment of the rate of change in breast density can provide a more effective risk indicator than measuring static breast density levels alone. This is particularly important in specific age groups or postmenopausal periods, as it represents a key factor to consider in risk management[15]. It is known that breast density decreases in both premenopausal and postmenopausal women, which was also demonstrated in our study. In Bowles et al.'s study, the relationship between breast density change rates and cancer risk was examined in both premenopausal and postmenopausal periods. Individuals with rapid declines in breast density during the postmenopausal period were found to have a lower cancer risk[16]. In another study, breast density change rates in the postmenopausal period were not found to be associated with breast cancer, likely due to age- and hormonal-induced involution[17]. In our study, no significant relationship was observed between breast density change rates and breast cancer development in postmenopausal women. However, in premenopausal women, the rate of breast density change was found to be statistically significant and associated with breast cancer.

Obesity is closely associated with many factors that influence breast cancer risk and can directly or indirectly impact the rate of breast density change. In obese individuals, higher fat content in breast tissue typically results in lower overall breast density. However, the impact of obesity on breast density appears to have a complex effect on breast cancer risk[18]. Studies indicate that BMI has different effects on breast cancer risk in premenopausal and postmenopausal women. Some research suggests no relationship between BMI and breast cancer risk in premenopausal women, whereas in postmenopausal women, higher BMI is associated with an increased risk of breast cancer[19]. In another study examining the relationship between BMI, breast density, and breast cancer development, it was found that the average BMI was significantly higher in cancer patients (p-value = 0.027) and in postmenopausal groups (p-value = < 0.001). When examining the relationship between BMI and breast density, both premenopausal (OR = 0.289, p-value = 0.001) and postmenopausal (OR = 0.292, p-value = 0.000) groups showed a high statistically significant negative correlation between BMI and breast density[20]. In our study, no relationship was found between BMI and breast cancer risk in premenopausal and postmenopausal women.

In the meta-analysis, the biological relationship between breast density and breast cancer risk has been supported. Increased breast density is associated with higher breast cancer risk, while decreased breast density is linked to a reduced risk. Given the increased cancer risk in patients with high breast density, further studies are needed to evaluate whether enhanced screening strategies, such as ultrasound, tomosynthesis, or breast Magnetic Resonance Imaging (MRI), could lead to higher detection rates of breast cancer[21]. In another meta-analysis, the emphasis is placed on considering additional MRI screening and other intervention methods to detect and reduce breast cancer cases earlier in women with dense breast tissue. However, no data is available from these meta-analyses regarding the relationship between breast density change rates and cancer risk[22].

In a study that considered breast density as a continuous variable, no significant relationship was found between density changes and breast cancer risk[13]. Another study examining annual mammographic density found that density changes did not influence breast cancer risk and that baseline breast density also had no impact on breast cancer risk[23]. In a study examining three-year mammographic intervals, it was found that women with increasing breast density had a higher breast cancer risk, while those with decreasing breast density had a lower risk compared to those with stable breast density[24]. There is no consensus in the literature regarding the relationship between the rate of density change and breast cancer risk.

A stronger relationship between mammographic density and breast cancer risk has been noted, particularly in premenopausal women[1]. Our findings contribute to the limited existing literature on changes in breast density and breast cancer, further confirming previous findings in postmenopausal women. Racial factors also play a role in changes in breast density, and this study examines breast density changes in the Turkish population. Our findings, which demonstrate a relationship between density change rates and breast cancer risk in the premenopausal period, may contribute to preventive approaches and encourage further studies that could help develop targeted interventions.

Conclusion

In our study, we obtained clues and evidence suggesting that the rate of density change is associated with breast cancer in premenopausal patients. Clinical approaches focus on the early diagnosis of breast cancer, as it is most treatable in its early stages. Monitoring the patterns of density changes in mammographic images and utilizing this data could pave the way for more personalized approaches that guide risk reduction strategies. Therefore, we emphasize the importance of monitoring the rate of breast density changes in mammography.

Data availability

The data in this study were obtained from Ankara Etlik City Hospital database where restrictions may apply as information could compromise the privacy of research participants. Datasets may be requested from the corresponding author (M.O.K.)

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Author contributions
Kulturoglu MO: Conceptualization; formal analysis; methodology; writing—original draft; writing—review & editing. Aydın F: Methodology; writing—review & editing. Sagdic MF: Data curation; project administration. Aslan F: Data curation; project administration. Oflaz Z: Formal analysis. Danisman FB: Formal analysis. Kalaylioglu ZI: Formal analysis; resources; writing—review & editing. Dogan L: Conceptualization; methodology; writing—review & editing; supervision.

Declarations

Competing interests
The authors declare no competing interests.

Ethical approval
Ethical approval for this study was obtained from the Ethics Committee of Ankara Etlik City Hospital (approval number: AESH-BADEK-2024-328). This study was conducted in accordance with the Declaration of Helsinki with informed consent from eligible participants.

Additional information
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