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Spatial vision in the treatment of breast cancer: Case report

Visão espacial no tratamento do câncer da mama: Relato de caso

Visión espacial en el tratamiento del cáncer de mama: reporte de caso

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RESUMO
Apresentamos o caso de uma brasileira de 48 anos com câncer de mama submetida ao tratamento antineoplásico, que foi avaliada para visão de contraste e de cor: (1) após a quimioterapia; (2) seis meses após a quimioterapia, sob uso diário de hormonioterapia. Algumas frequências espaciais e eixos cromáticos apresentaram melhores limiares seis meses após o fim do tratamento quimioterápico. O estudo avaliou o processamento visual de uma mulher com câncer de mama, controlando o efeito da interação entre os medicamentos antineoplásicos. Estudos adicionais são necessários para compreender melhor como a sensibilidade visual é afetada pelo tratamento antineoplásico.

PALAVRAS-CHAVE:
Neoplasias mamárias; Tratamento antineoplásico; Processamento visual; Visão.

ABSTRACT
We present the case of a 48-year-old Brazilian woman with breast cancer undergoing antineoplastic treatment, who was assessed for contrast and color vision: (1) after chemotherapy; (2) six months after chemotherapy, under daily hormone therapy. Some spatial frequencies and chromatic axes showed better thresholds six months after the end of chemotherapy treatment. The study assessed the visual processing of a woman with breast cancer, controlling for the effect of the interaction between antineoplastic drugs. Further studies are needed to better understand how visual sensitivity is affected by antineoplastic treatment.

KEYWORDS:
Breast neoplasms; Antineoplastic treatment; Visual processing; Vision.

RESUMEN
Presentamos el caso de una mujer brasileña de 48 años con cáncer de mama en tratamiento antineoplásico, a quien se le evaluó contraste y visión de colores: (1) después de la quimioterapia; (2) seis meses después de la quimioterapia, bajo el uso diario de hormonoterapia. Algunas frecuencias espaciales y ejes cromáticos mostraron mejores umbrales seis meses después del final del tratamiento quimioterápico. El estudio evaluó el procesamiento visual de una mujer con cáncer de mama, controlando el efecto de la interacción entre los medicamentos antineoplásicos. Se requieren estudios adicionales para comprender mejor cómo la sensibilidad visual se ve afectada por el tratamiento antineoplásico.

PALABRAS CLAVE:
Neoplasias mamarias; Tratamiento antineoplásico; Procesamiento visual; Visión.

Breast cancer is the most prevalent neoplasm in the world population and especially affects women (World Health Organization, 2020). Chemotherapy and hormone therapy are among the primary antineoplastic treatments available, contributing to the survival of women affected by breast cancer (American Cancer Society, 2019).

Previous findings have shown that breast cancer treatments are linked to visual processing (Enzsoly et al., 2015; Giralt et al., 2012; Gorin et al., 1998; Kuznetcova et al., 2012; Lee et al., 2016; Therssen et al., 1995). However, most studies did not control for the interactive effect of other antineoplastic treatments, as the participants were evaluated after undergoing

concomitant treatments (Chelala et al., 2017; Kuznetcova et al., 2012; Noureddin et al., 1999; O'Brien et al., 2019; Pavlidis et al., 1992).

In addition to cancer cells, antineoplastic drugs can impair cellular metabolism and tissue structure in non-cancerous regions, triggering physiological, cognitive, and neuronal changes (Saligan et al., 2015; You et al., 2019). Anatomical and physiological changes in the Central Nervous System (CNS) have also been noticed, especially in regions such as the hippocampus and the frontal and occipital lobes (Huang et al., 2017; Winocur et al., 2018).

Doxorubicin, a chemotherapeutic drug used in breast cancer treatment, can induce systemic inflammation and oxidative stress in various organs, including the brain (Cardoso et al., 2020). These inflammatory and oxidative processes are believed to contribute to the observed alterations in spatial memory, suggesting a potential relationship with hippocampal dysfunction (Ferroni et al., 2023).

Paclitaxel is a chemotherapeutic drug that can be administered together with doxorubicin (Mandapati & Lukong, 2023). Adverse ocular reactions such as ocular surface discomfort and corneal nerve dysfunction have been observed in women with breast cancer undergoing treatment with paclitaxel (Chiang et al., 2021). Changes in visual acuity were also present, suggesting an involvement of the drug with the retina (Chiang et al., 2021).

Tamoxifen is considered one of the main hormone therapy drugs used in the treatment of breast cancer (Chan et al., 2020). Ocular effects from its use have been reported, such as white refractive opacities of the retina, subepithelial opacities in the cornea, and optic neuritis (Bolukbasi et al., 2020; Szabelska et al., 2023). Changes in visual function involving short wavelength sensitive cone responses have also been presented (Eisner, 2004). However, the results regarding tamoxifen-induced ocular toxicity, as well as the dosage of drug that would induce these effects, are still inconsistent (Eisner & Incognito, 2006; Tang et al., 1997).

Evidence shows that antineoplastic treatment can affect visual processing (Anderson et al., 2020). However, there are still aspects of visual processing that have not been evaluated using robust and controlled tools, especially due to the difficulty of assessing these measures without the influence of other antineoplastic drugs used (Oliveira et al., 2023).

Here we present the case of a 48-year-old woman diagnosed with breast cancer who had no comorbidities (e.g., alcohol abuse). The participant underwent evaluation before and after chemotherapy, and also six months post-chemotherapy, while receiving daily hormone therapy. To the best of our knowledge, this is the first case study to prospectively evaluate the acute effects of antineoplastic treatment on visual function. Our main hypothesis was that the participant would exhibit higher thresholds (i.e., worse discrimination) on visual tests at the two evaluated time points. We hope this report provides useful information on the neurotoxic effects of some antineoplastic drugs and offers a new perspective for further investigation.

Case Report

A 48-year-old Brazilian woman (level of education = 7 years) was diagnosed with grade III invasive ductal carcinoma of the breast, involving lymph nodes. Her K-67 index, a marker indicating the percentage of tumor cells in the active phase of the cell cycle, was measured at 15%, reflecting a moderately high level of proliferation. The tumor was classified as estrogen receptor-positive (ER+) and progesterone receptor-positive (PR+), but negative for Human Epidermal growth factor Receptor-type 2 (HER2-), suggesting it might respond well to hormone therapy. She had no evidence of metastasis, indicating the disease was localized, and she had no history of previous cancer (Ibrahim et al., 2023; Wolff et al., 2023).

The participant had no history of neurological disorders, cardiovascular disease, head trauma, solvent exposure, or caffeine dependency/withdrawal that could affect visual processing or cognition. The participant was assessed for anxiety and depression symptoms at

both time points using the Beck Depression Inventory (BDI-II) and the Beck Anxiety Inventory (BAI). The BDI-II is known for its high internal consistency, with a Cronbach's alpha value typically between 0.86 and 0.91 (Beck et al., 1996). The BAI similarly shows excellent internal consistency, with a Cronbach's alpha value ranging from 0.92 to 0.94 (Beck & Steer, 1990). The results suggested mild severity levels for depression and anxiety at both time points. Assessing depression and anxiety during cancer treatment is important because these psychological conditions can significantly affect overall well-being, treatment adherence, and even recovery outcomes (Abdelhadi, 2023; Almeida et al., 2023).

Laboratory tests were also evaluated before and after the antineoplastic treatments. The tests were performed by a reliable laboratory. When compared to the normative values for women (i.e., between 0.7 mg/d; Delanaye et al., 2023), only the creatinine values showed a slight alteration (i.e., 0.2 mg/dL) right after the chemotherapy treatment. Changes in creatinine levels after chemotherapy are typically reversible and usually do not have clinical implications if other indicators of renal function remain stable. Evidence suggests that these levels tend to normalize once treatment is completed and the patient has had time to recover (Jagieła et al., 2021). This result was reversed in the evaluation performed six months after the hormone therapy treatment (Table 1).

The participant had no eye disease, according to self-reports and examinations performed in recent years. She was also screened for color blindness using Ishihara's pseudo-isochromatic plates (Ishihara, 1964) and did not have more than three errors (failure criterion) in the test (Fernandes et al., 2020). Finally, the participant had normal visual acuity (20/20), assessed using Raskin's E-optotypes.

Table 1

Laboratory and Psychological Assessments Across Chemotherapy and Hormone Therapy Interventions

Variable	Before Chemotherapy	After Chemotherapy	After Hormone Therapy
BDI-II score		18	17
BAI score		14	14
Glucose (mg/dL)	86	79	80
Creatinine (mg/dL)	0.5	0.2	0.5
AST/TGO (U/mL)	14	16	13
ALT/TGP (U/mL)	12	27	11
Red blood cells (millions/mm³)	4.0	3.4	4.0
Hemoglobin (g/dL)	12.5	11.6	12.5
Hematocrit (%)	37.2	33.3	37.4
Mean corpuscular volume (fL)	92.5	97.4	93.5
Mean corpuscular hemoglobin (pg)	31.1	33.9	31.3
Mean corpuscular hemoglobin concentration (g/dL)	33.6	34.8	33.4
Red cell distribution width (%)	12.7	12.9	12.4
Total leukocytes (cells/mm³)	6,600	4,800	5,800
Platelet count (cells/mm³)	224,000	244,000	173,000

Note. ALT = alanine aminotransferase; AST = aspartate aminotransferase; BAI = Beck Anxiety Inventory; BDI-II = Beck Depression Inventory-II; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; RDW = red cell distribution width.

The participant was mastectomized and initially submitted to chemotherapy treatment under intravenous administration of doxorubimycin 60mg/m², every 3 weeks, for 4 cycles. Subsequently, paclitaxel 80mg/m² was started once a week for 12 cycles. The first evaluation occurred one week after the administration of the last cycle of chemotherapy treatment. One month after the end of chemotherapy treatment, the participant started hormone therapy. The

second evaluation occurred after six consecutive months of administration of tamoxifen 20 mg/day.

Visual Evaluation

Visual assessments were performed using the Metropsis, specifically for the Contrast Sensitivity Function (CSF; Metropsis, Cambridge Research Systems Ltd., Rochester, UK); and the Trivector subtest of the Cambridge Color Test (CCT), specifically for chromatic discrimination.

CSF is an important measure of both optical and neural aspects of visual processing. Metropsis is considered a reliable tool for assessing subtle differences or deficiencies in visual processing (Fernandes et al., 2017; 2019). All measurements were performed under binocular vision conditions. Monitor luminance and chromatic calibrations were performed using a ColorCAL MKII photometer (Cambridge Research Systems). The frequencies used were 0.2; 0.6; 1.0; 3.1; 6.1; 8.0, 13.2 and 15.6 cycles per degree (cpd). The stimuli comprised equiluminant gratings, with dimensions of 5º visual angle, and were presented on the monitor with a spatial displacement of 2.5º from the central fixation point in the form of a cross (Fernandes et al., 2018).

The CCT stimulus is a colored Landolt ring displayed on a different colored background. The opening position of the ring is presented randomly in one of four positions: (top, bottom, left, and right). The chromatic contrast of the ring is varied until a threshold is obtained. In our scenario, the "ring" presented an aperture of 1.25° visual angle at 3m viewing distance. To ensure that the break in the ring was identified only through chromatic information, luminance noise was added by subdividing the background and the stimulus into small circles that varied randomly in size (between 2.8°arcmin and 5.7°arcmin in diameter) and in luminance (between 8 and 18 cd/m2, in 2 cd/m2 increments). Three different stimuli

were used to measure thresholds along the Protan (red), Deutan (green), and Tritan (blue) vectors across the background. Details on the use of CCT are widely reported in previous studies (Fernandes et al., 2020; Paramei & Oakley, 2014; Silva et al., 2021).

Procedures

The participant performed the chromatic and achromatic visual sensitivity measurements at two time points: (1) at the end of chemotherapy sessions; (6) six months after the end of chemotherapy treatment, under daily administration of hormone therapy. The tests were applied in the afternoon at both time points.

Detailed instructions of the tasks performed were provided before the tests began. A training session prior to each test was applied for the participant to acquire familiarity with the task. Accuracy over speed was emphasized. Each session lasted about 40 to 50 minutes and the participant was encouraged to take breaks between each block to avoid demotivation.

Contrast Sensitivity

Measurements were taken binocularly at a distance of 150 cm from the monitor. The participant was asked to identify on which side (left or right) the grating was displayed on the computer screen. She was instructed to respond randomly when she was unsure of her answer. Several catch trials, commonly used in perceptual studies to determine if the participant understood the task, were presented randomly to avoid possible test bias. Higher CSF values indicate better discrimination. For details of the task, see (Fernandes et al., 2020).

Chromatic Discrimination

The four-alternative forced choice method (4-AFC) was used to evaluate chromatic discrimination. The task required identifying the direction of the opening in the Landolt C stimulus (right, left, bottom, or top). The participant was instructed to respond even if she could not identify the opening of the stimulus (Paramei & Oakley, 2014). The CCT uses the

psychophysical staircase method to measure thresholds, calculated as the arithmetic mean of the reversals, considering changes in stimulus intensity. For each of the three vectors, Protan, Deutan, and Tritan, the CCT algorithm implemented two interleaved staircases presented randomly. The weighted rule of one up/one down was used, with a ratio to converge on the 85% accuracy. Lower thresholds indicate better discrimination. For details of the task, see Fernandes et al. (2020).

Ethics Statement. The present study followed the ethical principles of the Declaration of Helsinki and was approved by the Ethics Committee (no. 4,564,010 and CAAE: 42983821.6.0000.5188) of the Universidade Federal da Paraíba. Written informed consent was obtained from the research participant.

Discussion

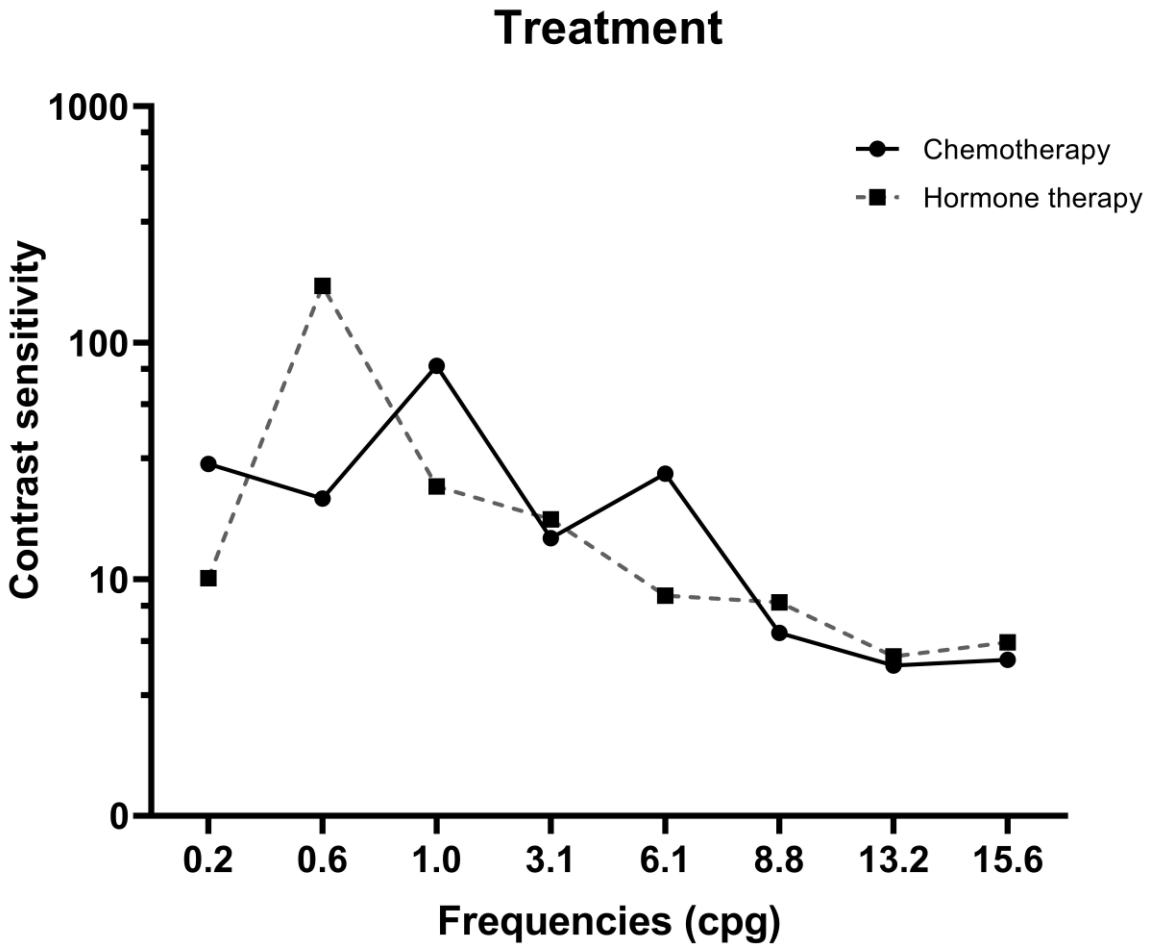
We present a case report of a woman with breast cancer indicating changes in visual processing after antineoplastic treatment. Figure 1 shows the spatial contrast sensitivity function for the research participant after receiving chemotherapy and after six months of daily treatment with hormone therapy. The solid line represents the test values for chemotherapy and the dotted line represents the test values for hormone therapy. Each data point represents the participant's contrast threshold. The acronym cpg stands for cycles per degree of visual angle.

The participant demonstrated a change in the sensitivity curve in both test conditions, compared to normative values suggested in the literature (Fernandes et al., 2019). However, we can see a slight improvement in some spatial frequencies (0.6; 3.1; 8.8; 13.2; 15.6) at the second time point, even under daily administration of hormone therapy, suggesting better test performance at the second time point.

The results presented suggest a change in contrast sensitivity for all spatial frequencies at both time points when compared to the normative data presented in the literature (Fernandes et al., 2019). In addition, the results disagree with the CSF presented in previous studies, where at photopic luminance levels maximum contrast sensitivity occurs at medium frequencies, with reduced sensitivity at the extremes of the curves (Adams & Courage, 2002).

Figure 1

Spatial Contrast Sensitivity for the Same Participant Treated with Chemotherapy and Hormone Therapy



Evidence suggests that worsening sensitivity at medium and high spatial frequencies can occur in individuals subjected to diseases or medications that can interfere with brain function (Campbell & Maffei, 1974; Roudaia et al., 2010; Sekuler & Tynan, 1977). Despite the slight improvement shown in some spatial frequencies six months after chemotherapy, the results are still incipient and controversial, and this may be due to the short comparison time between the two results. Therefore, it is important that these results be interpreted with caution.

The bar graphs present the results obtained for the three vectors, Protan, Deutan, and Tritan, for the participant who underwent chemotherapy treatment and then, six months later, received hormone therapy treatment (Figure 2). In the graph, the bars represent the test values for chemotherapy and hormone therapy. The top of the bar represents the participant's color discrimination threshold at these time points.

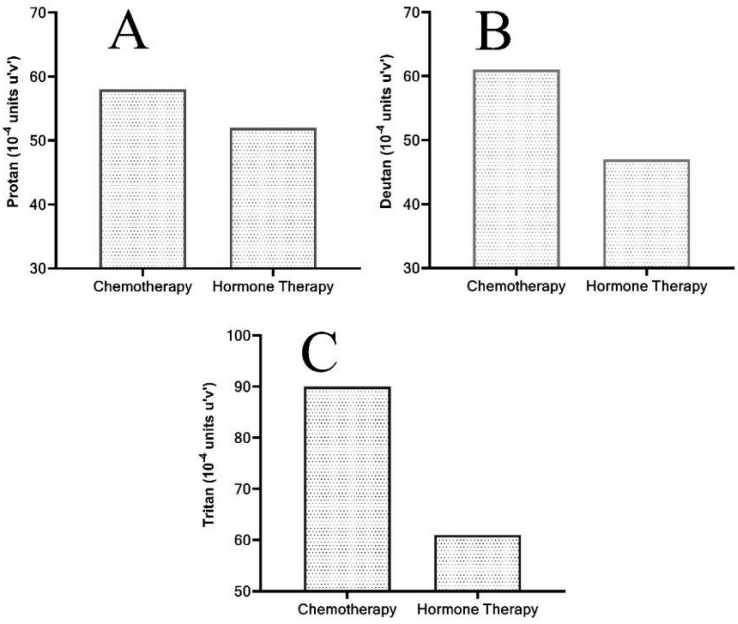
The results suggest greater sensitivity to protan, deutan, and tritan axes in the research participant six months after completion of chemotherapy treatment, with daily administration of hormone therapy. Studies investigating the sensitivity to chromatic contrast in women with breast cancer are still scarce. However, changes in color perception have been suggested in breast cancer patients undergoing FAC (5-fluorouracil, adriamycin and cyclophosphamide) chemotherapy regimen. Chromatic sensitivity improved four months after the evaluation (Giralt et al., 2012).

Regarding achromatic contrast vision, the participant showed less sensitivity to distinguish objects in low contrast for low, medium, and high spatial frequencies. Women with breast cancer being treated with doxorubicin and paclitaxel may have alterations in the M and P pathways, or in retinal receptor cells (Lee et al., 2000). Similar results have been presented in the literature in women who had received chemotherapy using the FAC system (Santos et al., 2011).

There is evidence that chemotherapy can trigger changes in nerve cells present in the primary visual cortex (Jansen et al., 2005). In addition, ocular toxicity associated with chemotherapy treatment has been reported in the literature (Anderson et al., 2020; Raffa & Tallarida, 2010). Alterations in normal brain physiology induced by drugs such as doxorubimicin and paclitaxel can occur through pro-inflammatory cytokines, which are considered immune cells that are activated in response to inflammation, stress, or direct damage to neurons (Maier & Watkins, 2003). Studies suggest that chemotherapy is related to mitochondrial dysfunction and increased levels of pro-inflammatory cytokines (IL-1b, IL-6, TNF-a, IL-10), leading to peripheral neuropathy as well as impairment of functions involving the frontal lobe (Lomeli et al., 2017; Lyon et al., 2016; Polomano et al., 2001).

Figure 2

Color Vision Axis Curve for The Same Participant Treated with Chemotherapy and Hormone Therapy.



Note. The Abbreviations A, B, And C Correspond to The Results of The Protan, Deutan, And Tritan Vectors

Glial cells synthesize and release IL-1, IL-6 and TNF-D (Hopkins & Rothwell, 1995). The interaction between neurons and glial cells in the CNS can facilitate regeneration or neuronal damage, triggering deficiencies in neurotransmitters such as acetylcholine or dopamine, thus contributing to cognitive changes (Ahles & Saykin, 2007; Wilson & Humanski, 1993). Dopaminergic amacrine cells present in the retina are sensitive to luminance contrast (Burkhardt & Fahey, 1999). Therefore, deficits in dopamine neurotransmitters can generate changes in contrast sensitivity.

The relationship between tamoxifen uses and the occurrence of retinopathy and keratopathy is well established in the literature (Noureddin et al., 1999; Pavlidis et al., 1992). However, the length of time of drug use necessary to generate ocular toxic effects is still a source of disagreement (Eisner & Incognito, 2006; Kaiser-Kupfer & Lippman, 1978; Noureddin et al., 1999; Salomão et al., 2007). While some studies suggest that the short time of tamoxifen use (< 2 years) is sufficient to generate ocular toxicity, other studies suggest the importance of higher cumulative doses for evidence of retinal abnormality (Eisner & Incognito, 2006; Salomão et al., 2007). This is because sustained administration of endocrine medications has the potential to increase the risk or severity of several age-related eye diseases or conditions, including among breast cancer survivors undergoing treatment (Oliveira et al., 2023).

Studies have been conducted to determine whether standard doses of hormone therapy drugs affect wavelength-mediated visual sensations via cones. Some cases of loss of color vision suggest that the drug may cause functional damage to the inner layers of the retina (Salomão et al., 2007). Thus, it is considered that the use of tamoxifen may affect some neural functions of the visual system (Eisner, 2004; Salomão et al., 2007).

Evidence indicates that estrogenic activity directly influences physiological functions (Burstein et al., 2019). Estrogen receptors (ERs) are distributed throughout the human body, including ocular structures like the bulbar conjunctiva, tarsal plates, lacrimal glands, lens, and cornea (Spelsberg et al., 2004). Additionally, ERs are present in the CNS (Morissette et al., 2008). Thus, changes in estrogenic activity may affect both central and ocular visual processing (Eisner & Luoh, 2011).

This study presents some limitations. The fact that the evaluation was carried out with only one participant diminishes the power of the results presented, making it impossible to stratify the results for other realities. However, the importance of the study in the search for controlling intervening variables presented in the population of interest should be considered. One of the difficulties found in previous studies was the lack of control by type of cancer and by medication used, since several drugs are administered during the antineoplastic treatment. In this regard, we sought to control for the interaction between the drugs used.

An improvement in the sensitivity curves was shown six months after the end of chemotherapy treatment (Figure 1, Figure 2). In this regard, it is important to consider that the functional measures improved somewhat, although we cannot draw any conclusions about this, especially since the period between the administration of chemotherapy and hormone therapy was very close (6 months).

The results presented suggest further research on how different cortical areas involved in spatial vision may be adversely affected by these clinical conditions. The tests used are considered very rigorous and useful clinical tools for assessing basic visual functions, as well as visual pathways from the retina to the visual cortex. Therefore, this finding may assist research in the fields of oncology and neuroscience.

Further investigations, especially with a larger sample size, are needed to elucidate the pathophysiological mechanisms that are involved in the changes presented. Such investigations would also help to determine to what extent chromatic and achromatic contrast sensitivity can serve as a biomarker of important aspects of breast cancer and its treatments.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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