COGNITION AND FUNCTIONALITY IN BREAST CANCER SURVIVORS UNDERGOING HORMONE THERAPY

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Abstract
The study aimed to describe the cognitive function and the functional capacity of breast cancer survivors who practice physical exercise. Eight women diagnosed with stages I-III breast cancer participated in this study. Cognitive tests were applied to assess overall cognitive function, processing speed, executive function, and attention. The women in the present study were 64.5 ± 4.8 years old, had a body mass index of 32.6 ± 5.4 kg.m⁻², and had 10.0 ± 3.5 years of schooling. The results showed a preserved performance in the MSSE questionnaire and verbal fluency test in older women diagnosed with breast cancer four years ago, with obesity, who have been exercising for approximately 2.5 years. On the other hand, they presented a lower performance in the cognitive Trail Making Test and the functional tests than the normative values in the literature, indicating an impaired attention, processing speed, cognitive flexibility, and low functional capacity.

Keywords: Breast Neoplasms; Cognition; Physical Functional Performance.

INTRODUCTION
Breast cancer is the most common cancer among women in Brazil, representing 29.7% of the new cancer cases yearly and the most responsible for cancer-related deaths among women (INCA, 2020). Sixty-six thousand two hundred eighty new breast cancer cases are estimated in 2020, with an estimated gross incidence rate of 81.82 per 100 thousand women in the southern region of Brazil (INCA, 2020). Advances in healthcare, improvements in diagnostic capacity, and treatment have made it possible to increase the life expectancy of women with breast cancer (CAMPBELL et al., 2019). However, the detrimental effects resulting
from the treatment negatively affect these women's physical and psychological aspects (MISHRA et al., 2012).

Breast cancer treatment can include surgery, chemotherapy, and radiotherapy. In addition, it is important to highlight that hormone receptor-positive breast cancer, estrogen receptor-positive, progesterone receptor-positive, or both is responsible for about 80% of breast cancers (NADJI et al., 2005). Hormone receptor-positive breast cancer is often treated with adjuvant hormone therapy, according to clinical practice guidelines (BURSTEIN et al., 2014). Hormone therapy reduces estrogen availability (selective estrogen receptor modulators or aromatase inhibitors) in the woman’s body. Recommendations indicate that if the women are post-menopausal and have received five years of selective estrogen receptor modulators, they should have the option to continue with the same drug or switch to an aromatase inhibitor for completing ten years of adjuvant hormone therapy (BURSTEIN et al., 2014).

Aromatase inhibitors’ most reported side effects are arthralgia, myalgia, carpal tunnel syndrome, stiffness, and paresthesia (LINTERMANS et al., 2014). Arthralgia and myalgia seem less intense among women using selective estrogen receptor modulators (WOUTERS et al., 2013). Moreover, it is important to note that most researchers and patients associate cancer-related cognitive impairment with chemotherapy treatment (BIGLIA et al., 2012). Although the literature on the effects of long-term use of hormone therapy on cognitive function is scarce compared to chemotherapy, studies investigating this issue reported a negative influence of hormone therapy on the cognition of breast cancer patients (CHEN et al., 2017; COLLINS et al., 2009; SHILLING et al., 2003).

Among the psychological aspects, cognitive problems are common in breast cancer survivors, with estimates suggesting that up to 35% of patients experience impairments that can last for years after the end of treatments (JANELSINS et al., 2014). Furthermore, impaired functional fitness is also observed in breast cancer survivors (SWEENEY et al., 2006). These associated problems can contribute to perform activities of daily living independently.

Exercise is an established and effective non-pharmacological complementary therapy in patients with cancer (MISHRA et al., 2012). At least 150 weekly minutes of moderate-intensity physical activity or 75 minutes of vigorous-intensity, including resistance training for at least two days per week, are recommended for cancer survivors (ROCK et al., 2012). Participation in physical exercise programs benefits breast cancer survivors’ physical and psychological spheres (CAMPBELL et al., 2019; MISHRA et al., 2012). However, a recent systematic review emphasizes
that there is still no clear evidence of the benefits of physical exercise in breast cancer survivors who use aromatase inhibitors and present musculoskeletal symptoms induced by such hormone therapy (ROBERTS et al., 2020).

Therefore, considering the benefits of physical exercise practice in this population, it is relevant to investigate women’s cognitive and functional profiles undergoing hormone therapy for breast cancer who are engaged in a structured physical exercise program. Thus, the study aimed to describe breast cancer survivors’ cognitive function and functional capacity who participate in a physical exercise program.

METHODS

Participants

A descriptive, cross-sectional study was conducted with breast cancer survivors participating in an Extension Project, “Exercise Research in Cancer” (ERICA), held at the Higher School of Physical Education of Universidade Federal de Pelotas. ERICA Project is a resistance and aerobic exercise program (combined training) performed twice a week. The session duration is approximately 60 minutes. To participate in ERICA, the women should have completed the primary treatment for breast cancer (surgery, chemotherapy, or radiotherapy) at least six months ago and could be under hormone treatment. ERICA participants were diagnosed with early-stage breast cancer (i.e., I to III). Eleven women were being attended for more than 20 months in the project during the performance of the study, and all were invited to participate. Of these, three did not participate for the following reasons: diagnosis of bipolar disorder, ankle sprain, and lack of compatibility with the dates for data collection. Therefore, eight women voluntarily participated in the study, and after being informed about the objective and procedures of the research, they read and signed a free and informed consent form. The research project was submitted and approved by the Research Ethics Committee of the Universidade Federal de Pelotas, under number 2.795.330 and CAAE number 94774618.7.0000.5313.

Procedures

According to the availability of the participants and the research team, visits to the Research Laboratory were scheduled so that the data collection phase could begin. Initially,
Sample characterization variables were assessed, such as age, time of diagnosis, disease stage, type of treatment, schooling, body mass, stature, and body mass index (BMI). After that, cognitive and functional tests were scheduled and applied on distinct days, always by the same evaluator. The data collection session of the cognitive tests lasted approximately 40 min, and the functional tests lasted 10-15 min for each participant.

The first test session corresponded to the cognitive function assessment. The Mini-mental state examination (MMSE) was first applied for the overall screening of cognitive function. MMSE consists of two parts: orientation, memory, and attention, with a maximum score of 21 points, and another that addresses skills such as naming and understanding, with a maximum score of nine points, totaling a maximum score of 30 points. In addition, cognitive function was evaluated in different domains, which are the following: processing speed, memory, and executive function.

For assessing attention, information processing speed, and cognitive flexibility, Trail Making Test (TMT) A and B were applied (STRAUSS et al., 2006). TMT-A consists of numbers (1 to 13), and the purpose is to draw, with a pencil or pen, a line that increasingly connects the numbers. TMT-B consists of letters and numbers whose purpose is to draw, with a pencil or pen, a line connecting the letters (A to L) and the numbers (1 to 13) inside circles in alternating sequence and increasing. Correction of tests is performed by counting the time, in seconds, that the participant took to complete each task correctly.

For the assessment of executive function (flexibility, response inhibition, attention regulation, and working memory), the adapted Controlled Oral Word Association Test (COWAT) (SENHORINI et al., 2006) was applied, in which the subject is required to produce as many words as possible with the letter indicated (A) by the researcher, for 60 seconds, wherein neither proper names nor numbers are allowed. For evaluation, the number of words mentioned by the participant was considered.

Moreover, FACT-Cognitive Function (Version 3) (WAGNER et al., 2009) was applied, a self-reported cognitive function questionnaire used to assess cognitive complaints in patients with cancer. It consists of four blocks of questions that must be interpreted, indicating answers from 0 (never) to 4 (several times a day) for the last seven days. The score is presented in subscales referring to perceived cognitive deficits, comments from other people, perceived cognitive skills, impact on quality of life, and total. The higher the score, the better the cognitive function.
The second test session corresponded to functional assessment, in which aerobic endurance, muscular endurance of lower and upper limbs tests, and agility and dynamic balance test were applied, which are part of the Rikli and Jones (1999) test battery. Firstly, aerobic endurance was determined through the 6-minute Walk Test. The test measures the maximum distance covered in six minutes along a 45.7 m course, with marked segments of 45.7 m. Participants walked through the marked course for 6 minutes to cover the greatest possible distance. At the “start” signal, the participants were instructed to walk as fast as possible (without running) over the marked distance around the cones. Participants received information on the time spent every minute. At the end of the time, the distance covered by each participant was measured.

Then, lower limb muscular endurance was determined through the 30-second chair stand test. The test started with the participant sitting in a chair, with her back supported and her feet shoulder-width apart and fully supported on the floor. The upper limbs were crossed and against the chest. At the “start” signal, the participant performed knee and hip extension movements to stay standing and return to the initial sitting position. The evaluator demonstrated the task, and the participant carried out one or two attempts before performing the test. The participant was instructed to complete the maximum repetitions in the 30s interval. The test score was obtained considering the number of times the participant correctly performed the task in the determined period.

Upper limb muscular endurance was determined through the arm curl test. The test was carried out with the participant sitting in a chair, with her feet fully supported on the floor and the trunk fully leaning against the chair. A 2 kg dumbbell was held with the dominant arm. The test started with the elbow fully extended beside the chair (perpendicular to the floor). At the “start” signal, the participant performed the radioulnar supination concomitant to the elbow flexion and then returned to the initial position. The participant was instructed to perform as many flexions as possible within 30 s, always with controlled movements in both flexion and extension phases. Every complete movement correctly performed was counted. The evaluator demonstrated the task, and the participant carried out one or two attempts before performing the test. The score was obtained by the total number of repetitions performed in the 30 s interval.

Finally, agility and dynamic balance were determined using the 8-foot up-and-go test. The test measures the time required to get up from the chair, cover 2.44 m, go around the
cone, and return to sitting. The test started with the participant fully seated in the chair, hands on her thighs, and feet fully supported on the floor. At the “start” signal, the participant rose from the chair, walked around the cone (on either side) as fast as possible, and returned to the chair. The participant was informed that it was a “for time” test, in which the objective was to walk as fast as possible (without running) around the cone and return to the chair. The evaluator started the timer at the “start” signal and interrupted at the exact moment when the participant sat in the chair.

**Statistical Analysis**

Descriptive statistics with mean and standard deviation were used to describe the results.

**RESULTS**

Eight physical exercise practitioner women with breast cancer in stages I-III were evaluated. These women participated in ERICA for 30.5 ± 3.5 months (minimum 23 months; maximum 35 months). Their characteristics are presented in Table 1. Six were older than 60 years (75%), and two were between 55 and 60 (25%). For BMI, six presented values ≥30 kg.m$^{-2}$ (75%) and two between 25-<30 kg.m$^{-2}$ (25%). For schooling, three had up to 8 years (38%), three had 11 years (38%), and two had 14 years of study (25%). Concerning the characteristics associated with breast cancer, two had been diagnosed in stage I (25%), five in stage II (62.5%), and one in stage III (12.5%). Surgery treatment was used in all cases. In addition, of the eight women, five underwent radiotherapy and chemotherapy (62.5%), and three underwent only chemotherapy (37.5%) complementary to surgery. Seven women used hormone therapy, two used tamoxifen citrate, and five used aromatase inhibitors.

**Table 1** – Sample characterization presented as mean and standard deviation values

<table>
<thead>
<tr>
<th>Variables</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>64.5 ± 4.8</td>
</tr>
<tr>
<td>Body mass (kg)</td>
<td>77.8 ± 9.9</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>155.0 ± 10.2</td>
</tr>
<tr>
<td>Body mass index (kg.m$^{-2}$)</td>
<td>32.6 ± 5.4</td>
</tr>
<tr>
<td>Schooling (years)</td>
<td>10.0 ± 3.5</td>
</tr>
<tr>
<td>Time of diagnosis (years)</td>
<td>4.4 ± 1.2</td>
</tr>
</tbody>
</table>

Note: SD = Standard deviation.
Source: authors’ construction.
Performance in the cognitive tests evaluating processing speed (Trail Making Test A and B), executive function (Controlled Oral Word Association Test), as well as the values verified in the screening (Mini-mental State Examination) and cognitive function perception (FACT-Cognitive Function) instruments are shown in Table 2.

Table 2 – Mean and standard deviation values of cognitive tests performance of breast cancer survivors who practice physical exercise

<table>
<thead>
<tr>
<th>Variables</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMSE (0-30)</td>
<td>28.63 ± 1.30</td>
</tr>
<tr>
<td>TMTA (s)</td>
<td>61.88 ± 19.52</td>
</tr>
<tr>
<td>TMTB (s)</td>
<td>279.63 ± 240.35</td>
</tr>
<tr>
<td>COWAT (number of words with the letter “A”)</td>
<td>11.25 ± 5.68</td>
</tr>
<tr>
<td>Fact-Cog (0-148)</td>
<td>72.41 ± 29.86</td>
</tr>
<tr>
<td>Perceived cognitive deficits</td>
<td>40.79 ± 20.26</td>
</tr>
<tr>
<td>Comments from other people</td>
<td>10.25 ± 5.04</td>
</tr>
<tr>
<td>Perceived cognitive skills</td>
<td>13.00 ± 4.34</td>
</tr>
<tr>
<td>Impact on quality of life</td>
<td>8.38 ± 4.41</td>
</tr>
</tbody>
</table>

Note: SD = Standard deviation; MMSE = Mini-mental State Evaluation; TMTA = Trail Making Test A; TMTB = Trail Making Test B; COWAT = Controlled Oral Word Association Test; Fact-Cog = FACT-Cognitive Function.

Source: authors’ construction.

Performance in the functional tests assessing cardiorespiratory capacity (6-minute walk), agility and dynamic balance (8-foot up-and-go), muscular endurance of upper (arm curl), and lower limbs (30-second chair stand) are presented in Table 3.

Table 3 – Mean and standard deviation values of functional tests performance of breast cancer survivors who practice physical exercise

<table>
<thead>
<tr>
<th>Variables</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-minute walk (m)</td>
<td>463.17 ± 81.75</td>
</tr>
<tr>
<td>8-foot up-and-go (s)</td>
<td>7.06 ± 1.65</td>
</tr>
<tr>
<td>Arm curl (rep)</td>
<td>15.75 ± 3.41</td>
</tr>
<tr>
<td>30-second chair stand (rep)</td>
<td>11.75 ± 1.04</td>
</tr>
</tbody>
</table>

Note: SD = Standard deviation; rep = repetitions.

Source: authors’ construction.

DISCUSSION

The present study showed that the women evaluated were diagnosed with breast cancer four years ago, and they were older, obese, and are exercising for approximately 2.5
years. The main results indicated that they seem to have impaired attention, processing speed, and cognitive flexibility, in addition to low functional capacity.

The MMSE result corresponded to 28.6 points for older women (64.5 years) diagnosed with breast cancer for 4.4 years who have been practicing physical exercise for 30.5 months. This result corroborates those observed in the study of Liu and collaborators (2018), in which women receiving chemotherapy presented a mean score of 25.6 points (n = 120; 52.0 years old and 11.3 years of schooling), while healthy women revealed a mean score of 27.9 points (n = 120; 52.4 years old and 10.8 years of schooling). Moreover, this finding agrees with the study by Brucki and collaborators (2003), which presented normative values by schooling in women from 16 to 92 years without a cancer diagnosis. Considering the range from 9 to 11 years of schooling, which comprises the mean of the present study, the median was 28 points. Therefore, our sample did not reveal impaired results in the MSSE questionnaire.

Regarding the results observed in the Trail Making Test, the women of the present study presented mean values of 61.9 s in the TMT-A and 279.6 s in the TMT-B, which were greater than those observed in other studies, i.e., indicating a worse performance (CAMPANHOLO et al., 2014; EHLERS et al., 2018). The study by Ehlers and collaborators (2018) was conducted with active women who also were breast cancer survivors (57.8 years old with complete higher education) and demonstrated a better performance in both tests (TMT-A: 54.0 s; TMT-B: 67.7 s) compared to the present study. However, the lower mean age and the higher education level of the participants in the latter study compared to the present one may be highlighted as two factors of significant influence on the performance of cognitive tests. In addition, the study of Campanholo and collaborators (2014) observed that, for healthy individuals aged 60-69 years with 9-12 years of schooling, the score for TMT-A was 44.2 s and for TMT-B was 100.8 s. The worst performance observed in the present study’s participants is possibly related to the adverse effects of breast cancer treatment. Still, the slow performance in TMT-B compared to TMT-A may indicate an impaired ability to modify an action plan and maintain two lines of thought simultaneously (ARBUTHNOTT et al., 2000). Moreover, studies indicate normative values as 29 s and 35 s for TMT-A and TMT-B, respectively, as well as cut point values corresponding to 78 s and 273 s for a deficient classification (CORRIGAN and HINKELDEY, 1987; GAUDINO et al., 1995; LEZAK et al., 2004). Thus, the women evaluated in the present study presented impaired processing speed and cognitive flexibility, although they are not considered deficient.
For the adapted COWAT test, 11 words were spoken with “A” in 60 s. No studies were found with cancer survivors performing the verbal fluency test with only the letter “A”. However, studies with adults found a mean of 14 words (OPASSO et al., 2016) and 12 words (SENHORINI et al., 2006) produced with the letter “A.” These study results seem to present relatively similar values to those found in the present study. Moreover, the systematic review by Villalobos and collaborators (2022) was carried out to present studies that provide normative data for verbal fluency tests in different languages with individuals without cancer diagnoses. Results showed ten studies with normative values performed in the Portuguese language; seven of these were performed with the Brazilian population, all categorized by age and schooling. Considering the age of the present sample and involving the letter “A”, three studies showed normative values. In the studies by Machado and collaborators (2009) and Esteves and collaborators (2015), the range of 60-69 years old was presented, stratified by schooling. However, verbal fluency was tested with the letters “F”, “A” and “S” pooled, a fact that makes it impossible the comparison with the present study. On the other hand, the study by Carvalho and Caramelli (2020) revealed a median value corresponding to 10 for the verbal fluency test with only the letter “A”, considering the age range of 55-64 years (the highest assessed in the study) and 8-11 years of schooling, like the present sample. Therefore, our sample did not reveal impaired results in the verbal fluency test.

Regarding the results observed in the FACT-Cognitive Function questionnaire, the data found in the present study are similar to those reported in the literature with the same population (BRAY et al., 2017; CAMPBELL et al., 2018). Bray and collaborators (2017) evaluated 121 cancer survivors (108 breast cancer survivors) who had already undergone at least three cycles of chemotherapy (54 years old and 12 years of schooling). Using the same evaluation instrument, they found 38.6 points in the subscale of perceived cognitive deficits, 3.0 points in the subscale of comments from other people, 12.0 points in the subscale of perceived cognitive skills, and 7.5 points in the subscale of impact on quality of life. The study of Campbell and collaborators (2018), which also evaluated breast cancer survivors (53.2 years old) who practiced physical exercise, presented scores of 40.2 points in the subscale of perceived cognitive deficits, 13.8 points in the subscale of comments from other people, 16.4 points in the subscale of perceived cognitive skills and 11.4 points in the subscale of impact on quality of life, similar to the present study. To the best of the authors' knowledge, no studies in the literature showed normative values for this questionnaire.
Increasing age (PARK et al., 2001) and low educational level (AVILA et al., 2009) are related to worse cognitive functioning in the older population. In addition, breast cancer treatment negatively impacts the quality of life of pre and postmenopausal patients in the first two years of diagnosis (FERREIRA et al., 2019). It seems that the cancer-related cognitive deficit is not just due to chemotherapy or other treatments (AHLES et al., 2012); i.e., it may result from common risk factors for cancer development and also age-related cognitive decline (JANELSINS et al., 2014). Such deficit can be a symptom of accelerated aging caused by cancer treatments and associated with psychological stress (MANDELBLATT et al., 2013). Moreover, there is evidence that estrogen modulates cognitive functioning (SHILLING et al., 2001) and that several brain regions that mediate cognition and memory are affluent in estrogen receptors (SHILLING et al., 2005).

Concerning functional capacity, the results in the present sample were lower than those of healthy women of the same age group (MAZO et al., 2015). The 6-minute Walk Test demonstrated lower mean values (463.2 m) than the normative values showed in the literature for Brazilian older women aged between 60 and 64 years (541.0 m) and between 65 and 69 years (530.0 m) (MAZO et al., 2015). Such observed value is within the 10th and 15th percentile for this age range (MAZO et al., 2015). For agility and dynamic balance test, the mean results of the present study were also lower (7.1 s) than those of Brazilian older women aged between 60-64 years (5.4 s) and between 65-69 years (5.5 s), i.e., they are in the 5th percentile (MAZO et al., 2015). Upper limb muscular endurance, assessed by arm curl test, showed lower mean values (16 repetitions) than those presented in the literature (MAZO et al., 2015) for Brazilian older women aged between 60-69 years (18 repetitions), corresponding to a score below the 40th percentile. Lastly, lower limb muscular endurance, evaluated through a 30-second chair stand, presented lower values (12 repetitions) in comparison to the same age group of Brazilian older women (60-64 years old: 15 repetitions; 65-69 years old: 16 repetitions), representing values below the 10th percentile (MAZO et al., 2015). The decline of aerobic capacity and muscular strength during breast cancer treatment is probably explained by combining the primary treatment adverse effects (MISHRA et al., 2012). Aromatase inhibitors are also associated with musculoskeletal symptoms such as pain, which can also reduce physical activity levels, contributing to muscle fitness reduction of muscle fitness (BROWN et al., 2014).

In the study of Bail and collaborators (2018), conducted with breast cancer survivors that had participated in an intervention of planning, planting, and maintenance of horticultural
gardens over a year, a performance superior to those demonstrated in the present study was observed in the arm curl (19 vs. 16 repetitions, respectively) and 30-second chair stand (14 vs. 12 repetitions, respectively) tests. In the 8-foot up-and-go test, this study showed a similar performance to that observed in the present study (7.0 vs. 7.1 s, respectively), which is lower than older women without breast cancer diagnosis (5.4 s). It is important to emphasize that this study (BAIL et al., 2018) was carried out with women aged 60 years, who had the diagnosis for 5.4 years, and 23 (out of a sample of 44) were obese (BMI>30 kg.m-2), which are similar characteristics to the participants of the present study (64.5 years old, 4.38 years of diagnosis and BMI of 32.6 kg.m-2). For the 6-minute Walk Test performance, the study of Serra and collaborators (2018) demonstrated that 11 breast cancer survivors (mean age: 60 years and mean BMI: 30 kg.m-2), who had carried out resistance training for 16 weeks, presented a mean result of 555 m, greater than the mean observed in the present study (463.2 m). However, it should be highlighted that the average time of diagnosis of these participants was ten years, whereas, in the present study, it was four years.

Our observation that older breast cancer survivors have impaired functional performance is in line with the fact that older women who developed breast cancer have a higher prevalence of reporting functional impairments than older women who did not have cancer (SWEENY et al., 2006). Nevertheless, it is essential to note that, even with a combined training period of 31 months, the functional capacity of these women is lower than the mean values presented by women of the same age. Such results can indicate that the adverse treatment effects, in combination with the aging process, influence the functional capacity of these women. Thus, the crucial role of physical exercise in this population must be highlighted to minimize such adverse effects since, depending on the functional capacity before treatment, their levels may remain much lower or perhaps be more impaired than in women who have a regular level of physical and functional pre-treatment conditioning. Nevertheless, such a statement remains speculation since information on the physical condition before treatment was not investigated in the present study.

As the limitation of the study, we highlight the absence of a control group of women without a diagnosis of breast cancer for comparison and the limited sample size since it was a convenience sample. In addition, future studies are suggested to compare inactive women who were or were not diagnosed with breast cancer. However, it is noteworthy that these are innovative data regarding the cognitive and functional characterization of breast
cancer survivors who practiced physical exercise for a constant period (from 23 to 35 months). Our results can be of great importance for clinical practice and the prescription of different exercise programs for this population, which involves a simultaneous focus on cognitive and functional function.

CONCLUSION

Thus, the present sample of older breast cancer survivors analyzed in the present study have obesity, mean schooling of 10 years, and have been practicing physical exercise for approximately 2.5 years. Considering these characteristics, they presented a preserved cognitive function, assessed by the MSSE questionnaire, and verbal fluency, evaluated by COWAT. On the other hand, they revealed impaired attention, information processing speed, and cognitive flexibility, assessed by TMT-A and TMT-B, than the normative values. Moreover, they showed a lower functional capacity than the normative values for older Brazilian women in the same age range.

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