

ASSOCIATION BETWEEN MUSCLE MASS AND ADVERSE EVENTS OF CHEMOTHERAPY FOR OVARIAN CANCER

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ABSTRACT

Objective: to identify whether there is an association between muscle mass and adverse events of chemotherapy treatment in women with ovarian cancer. **Methods:** retrospective cohort from 2014 to 2019 composed of 111 women. Socio-demographic data, disease and chemotherapy treatment data, adverse events, and body mass index (BMI) were collected. Body composition was analyzed using computed tomography performed at diagnosis and analyzed with the aid of Slice-O-matic V4.3 (Tomovision) software. **Results:** The participants' ages ranged from 21 to 88 years. Before starting treatment, 14.4% were underweight, 53.9% were normal weight, and 6.1% were overweight, which at the end of treatment was 31.3%. The body composition of muscle mass of 72.2% of women was in the range of 21 to 30%. The most frequent adverse events were nausea, vomiting, and muscle fatigue, which were not significantly related to body composition, except for muscle fatigue after the first cycle of chemotherapy. **Conclusion:** The decrease in muscle mass was significantly associated with muscle fatigue at the beginning of chemotherapy, highlighting the importance of monitoring body composition to optimize the management of women with ovarian cancer.

Keywords: Ovarian Neoplasms. Side Effects and Adverse Reactions Related to Medications. Antineoplastic agents. Body Composition. Women's Health.

INTRODUCTION

Among the various types of cancer, ovarian cancer is among the most lethal gynecological cancers worldwide⁽¹⁾, ranking 18th among all cancers in incidence among women and accounting for 2.1% of deaths in this group⁽²⁾. In developed countries, the mean risk of dying from ovarian cancer before age 75 is twice that in less developed countries, exceeding an incidence of 7.5 per 100,000 inhabitants. In 2020, more than 319,000 women worldwide were diagnosed with ovarian cancer, and approximately 207,000 died^(1,2).

Ovarian cancer often presents no specific symptoms or obvious signs of the disease until it is advanced, which limits available treatments and the chances of therapeutic success⁽³⁾. It is worth noting that ovarian cancer treatment aims to improve patient life expectancy and quality of life. include radiotherapy. and may chemotherapy, and cytoreductive surgery, with or chemotherapy. Furthermore, treatment plan will depend on the staging and histological type, and may be curative or palliative. Chemotherapy represents an aggressive therapeutic approach in the treatment of this neoplasm. Although its primary goal is to destroy the tumor, it also attacks healthy cells, causing adverse events^(3, 4).

Whether due to the cancer itself and its staging or because of treatments, weight loss is one of the most prevalent symptoms identified in women with ovarian cancer⁽⁵⁾. Sarcopenia, defined as the progressive loss of skeletal muscle mass, is a prognostic factor in several types of cancer⁽⁶⁾. Studies show that muscle mass loss brings with it various adverse consequences, such as an increased risk of disease-related complications, reduced responsiveness and tolerance to cancer treatment, deterioration in quality of life, and decreased functional capacity and survival. In short, the patient's nutritional status plays a crucial role in the success of cancer treatment⁽⁶⁾.

Muscle is the primary component of the fatfree mass (FFM) compartment, where most chemotherapy drugs are metabolized, and has a weak association with body surface area in cancer patients. Therefore, there is a risk of overestimating the dosage of these drugs, a fact

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that corroborates the fact that muscle mass measurement represents a determining factor in chemotherapy dosage, especially in individuals with increased adiposity and decreased muscle mass⁽⁷⁻⁹⁾. Unfortunately, individualization of chemotherapy based on body composition has not yet been integrated into clinical practice. Future studies investigating dose reductions in patients with cachexia or sarcopenia, as well as dose adjustment studies based on pre-treatment assessment, are needed to shift cancer treatment paradigms. Despite the importance of this topic, there is a lack of literature on body composition and the toxicity of chemotherapy agents in with gynecological patients tumors, demonstrating the response to adjuvant and neoadjuvant treatments (9-10).

Given the above, the present investigation sought to identify whether there is an association between muscle mass and adverse events of chemotherapy treatment in women with ovarian cancer.

METHOD

This is a retrospective cohort study of women diagnosed with ovarian cancer who underwent chemotherapy treatment at a university hospital in the countryside of the state of São Paulo. The institution is a public tertiary care hospital and a referral center in the region.

Data collection took place from July 2021 to July 2023. To identify cases, the medical data section was consulted, searching for women with ovarian cancer who underwent chemotherapy between January 2014 and December 2019. The cutoff was established so that each participant had two years of monitoring recorded in her medical records. One hundred and seventy-four (174) cases were identified, and 111 women over the age of 18 with a diagnosis of ovarian cancer who underwent chemotherapy were included. Of the 63 excluded, 10 were due to incomplete data in the medical records; two women were under the age of 18, and 51 had other types of primary cancer.

All information was obtained through analysis of the women's electronic medical records. The data collected included socio-demographic data, such as age, marital status, and education level; ovarian cancer data, such as diagnosis, clinical

staging, and treatment plan; chemotherapy treatment data, such as the protocol used and drug dosages; measurement of adverse events, measurement of body composition, and body mass index (BMI) also were included.

Adverse events of chemotherapy were classified using the scale of adverse events during antineoplastic treatment called Common Terminology Criteria for Adverse Events (CTCAE) – version 5.0, developed by the US National Cancer Institute (NCI) and National Institutes of Health (NIH)⁽¹¹⁾.

Body Mass Index was calculated based on the patient's weight and height, as recorded in the medical records at the time of diagnosis, immediately before and at the end of chemotherapy, and at the end of cancer treatment. The World Health Organization classification for the general population was adopted as the reference values⁽¹²⁾.

Body composition analysis was performed based on the results of the computed tomography scan that the woman underwent at the time of her ovarian cancer diagnosis. This method has been gaining prominence in oncology, as it has proven to be effective in measuring an individual's percentage of fat-free mass (FFM)(13-16). From the tomographic images, the third lumbar vertebra (L3) was identified, chosen as a landmark because it shows the highest correlation with the skeletal muscle mass of the entire body (17), and four consecutive slices from L3 to the iliac crests, which were evaluated to measure the crosssectional area of muscle and adipose tissue, with the mean value of these slices calculated for each participant. The images were then analyzed using Slice-O-matic V4.3 (Tomovision) software. Using pre-established Hounsfield unit (HU) thresholds, specific tissues were identified and quantified: -29 to 150 for musculoskeletal, -190 to -30 for subcutaneous intermuscular adipose tissue⁽¹⁸⁾, and -50 to 150 for visceral adipose tissue(19). Muscle mass was categorized into ranges: low, 11 to 20%; medium, 21 to 30%; and good, 31 to 40%.

Total fat area (TFA) and visceral fat area (VFA) were assessed by measuring pixels with densities between -190 and -30 HU, which allowed excluding bones, muscles, and other intra-abdominal organs to compute the area of each. Subcutaneous fat area was calculated by

subtracting VFA from TFA; the cutoff value for VFA was 80.1 cm^2 . Low muscle mass (LMM) and appendicular muscle mass (AMM) were defined according to sex- and BMI-specific threshold values associated with poor survival. LMM was defined as <41 HU for patients with a BMI <25 and <33 HU for patients with a BMI = 25, using previously published cutoff points associated with survival after stratification in patients with solid malignancies. Sarcopenic obesity was defined as the combination of LMM and BMI = $30^{(20)}$.

The collected data were entered into a Microsoft Excel® spreadsheet and analyzed using SPSS version 27 software, adopting a significance level of 5% (0.05). Frequencies were used for categorical variables, and measures of central tendency (mean, median) and dispersion (standard deviation, minimum, and maximum) were used for quantitative variables. The chisquare or Fisher's exact test were used to correlate muscle mass percentage with adverse events.

The study was approved by the Research Ethics Committee of the University of São Paulo at Ribeirão Preto School of Nursing (Opinion number 4.826.225; CAAE: 38476720.7.3001.5440).

RESULTS

The age group of the 111 participants ranged from 21 to 88 years, with a mean age of 58 years (SD = \pm 14 years), 71.2% were Caucasian, 46.8% were married, 73% were from cities other than Ribeirão Preto and 60.4% had elementary education. When analyzing the data on the disease, it was observed that 45.9% of the participants had histological type ovarian adenocarcinoma, 51.4% did not present distant metastasis, and however, among those who did, 29.7% had peritoneal metastasis and 9.9% liver metastasis. The treatment received by 100% of the women was chemotherapy, with 7.2% undergoing neoadjuvant chemotherapy and 92.8% cytoreductive surgery followed by chemotherapy, 2.7% underwent radiotherapy. Regarding chemotherapy treatment, it was observed that 42.3% required a change in the initial protocol, 27% had the dose adjusted and 40.5% needed to suspend treatment (Table 1).

Table 1. Distribution of women undergoing chemotherapy for ovarian cancer, according to sociodemographic data and disease and treatment information. Ribeirão Preto, 2024 (n=111)

Variable	Category	N	%
Age*		58 ± 14	(21-88)
	Caucasian	79	71.2
Race	Non-Caucasian	32	28.8
	Single	29	26.1
Marital status	Married	52	46.8
Marital status	Widowed	17	15.3
	Divorced	13	11.7
Origin	Ribeirão Preto	30	27
	Other cities	81	73
	Did not attend	6	5.4
	Elementary School	67	60.4
Education	High School	23	20.7
	University Education	6	5.4
	Not provided	9	8.1
	Ovarian Adenocarcinoma	51	45.9
Diagnosis	Serous Ovarian Carcinoma	35	31.5
	Grade 3 Clear Cell Ovarian Carcinoma	15	13.5
	Adnexal Mass with Malignant Iota	10	9
Matastania	Yes	54	48.6
Metastasis	No	57	51.4
	Peritoneum	33	29.7
Site of metastasis	Liver	11	9.9
Site of illetastasis	Lung	3	2.7
	Others	7	6.3

Discosso progression	Yes	69	60
Disease progression	No	46	40
	Pelvic	37	33.3
Site of progression	Hepatic	14	12.6
Site of progression	Abdominal	6	5.4
	Others ¹	8	7.2
Neoadjuvant chemotherapy		8	7,2
Radiotherapy		3	2.7
Surgery		103	92.8
Chemotherapy		111	100
	15-15	6	5.4
	21-21	78	70.3
Cycle frequency	28-28	27	24.3
Scheme change was made		47	42.3
patients had dose adjustment		30	27
Suspension of chemotherapy		45	40.5

Legend: * Result expressed as mean; standard deviation (minimum: maximum). 1.Others: Renal, pulmonary, and uterine.

Source: Original research results.

It was observed that, before starting treatment, 13.5% of women had lost weight, with 12.6% losing >8%. At diagnosis, 55.9% had a BMI classified as normal weight and 5.4% were considered underweight. At the end of treatment,

50.5% were normal weight and 23.4% were underweight (31.3%). Computed tomography showed that 72% of women had 21-30% muscle mass (Table 2).

Table 2. Distribution of women undergoing chemotherapy for ovarian cancer, according to body composition data. Ribeirão Preto, 2024 (n=111)

Variable	Category	n	% 13.5	
Pre-treatment weight loss		15		
0/ Wainh4 I and	>8%	14	12.6	
% Weight Loss	<8%	1	0.9	
	Low Weight	6	5.4	
BMI Diagnosis	Eutrophy	62	55.9	
-	Overweight	43	38.7	
	Underweight	26	23.4	
BMI Final cancer treatment	Eutrophy	56	50.5	
	Overweight	29	26.1	
	Underweight	20	18	
Pre-immediate BMI CHT	Eutrophy	64	57.7	
	Overweight	27	24.3	
	Underweight	35	31.5	
Post-CHT BMI	Eutrophy	51	45.9	
	Overweight	24	21.6	
	11 to 20%	27	24.3	
Muscle mass diagnosis	21 to 30%	80	72	
J	31 to 40%	4	3.7	

Legend: BMI: Body Mass Index; CHT: Chemotherapy

Regarding adverse events related to chemotherapy, recorded in the medical records, it was observed that nausea and vomiting were the most frequent since cycle 1 (61.3% and 45.9% respectively), and remained in cycles 2 (52.3% and

43.2%) and cycle 3 (42.3% and 36%). No records were identified in the medical records regarding mucositis, hypoalbuminemia, dysgeusia and anorexia (Table 3).

Table 3. Distribution of women undergoing chemotherapy for ovarian cancer, according to adverse events in each chemotherapy cycle. Ribeirão Preto, 2024 (n=111)

Adverse events*		Cycle 1		Cycle 2	Cycle 3		
	n	%	n	%	n	%	
Nausea	68	61.3	58	52.3	47	42.3	
Vomiting	51	45.9	48	43.2	40	36.0	
Ascites	22	19.8	21	18.9	16	14.4	
Muscle fatigue	20	18.0	20	18.0	23	20.7	
Neutropenia	17	15.3	18	16.2	16	14.4	
Fatigue	15	13.5	14	12.6	12	10.8	
Diarrhea	10	9.0	3	2.7	2	1.8	
Other	18	16.2	10	9	5	4.5	
No events	20	18.0	32	28.8	42	37.8	
1 event	30	27.0	24	21.6	22	19.8	
2 events	24	21.6	16	14.4	17	15.3	
3 or more events	37	33.3	39	35.1	30	27.0	

^{*} The same woman may have experienced more than one adverse event.

Adverse events data were correlated with the percentage of muscle mass determined through CT scan analysis and other variables such as BMI. A correlation was observed between the percentage

of muscle mass and muscle fatigue (p=0.045) in cycle 1 of chemotherapy. No association with any adverse event was found in the remaining cycles (Table 5).

Table 5. Association of adverse events with muscle mass percentage in cycle 1 of chemotherapy. Ribeirão Preto, 2024 (n=111)

				% Musc	ele mass			
Events		11 to 20%		21 to 30%		31 to 40%		1
		n	%	n	%	n	%	p-value*
Nausea	Yes	0	0	0	0	0	0	0.937
	No	27	100	80	100	4	100	
Vomiting	Yes	13	48.1	37	46.2	1	25.0	0.764
, and the second	No	14	51.9	43	53.8	3	75.0	
Ascites	Yes	4	14.8	18	22.5	0	0	0.582
	No	23	85.2	62	77.5	4	100	
Weight Loss	Yes	3	11.1	3	3.8	0	0	0.335
O .	No	24	88.9	77	96.2	4	100	
Diarrhea	Yes	4	14.8	6	7.5	0	0	0.501
	No	23	85.2	74	92.5	4	100	
Fatigue	Yes	2	7.4	13	16.2	0	0	0.462
J	No	25	92.6	677	83.8	4	100	
Muscle Fatigue	Yes	1	3.7	19	23.8	0	0	0.045
8	No	26	96.3	61	76.2	4	100	
Neutropenia	Yes	5	18.5	12	15.0	0	0	0.879
*	No	22	81.5	68	85.0	4	100	

^{*} Chi-Square or Fisher's Exact Test.

DISCUSSION

Cancer treatment and cancer itself cause several changes in individuals' body composition. Weight loss and muscle depletion are worrying factors and have been associated with decreased functional capacity, increased chemotherapy toxicity, increased hospital stays, and increased incidence of infections^(7,9). These changes have been demonstrated in the literature as predictors of poor disease prognosis and have been observed in patients with lung⁽²¹⁾, colon⁽¹⁰⁾, breast⁽²²⁾, and renal cell cancer. However, few studies on ovarian cancer have been identified⁽²³⁾.

Ovarian cancer cases are more prevalent in women over 60 years of age⁽²³⁾, ranging from 56.3

years (±11.4 years) to 65 years (±11.4 years)⁽¹³⁻¹⁵⁾. This data are corroborated in the present study, which found a mean age of 58 years (±14 years). It was also observed that, before starting chemotherapy treatment, 14.4% of the women experienced weight loss, and at the end of treatment, 31.3% were underweight. These findings are corroborated by a retrospective cohort study conducted in Switzerland from 2011 to 2020 when 69 ovarian cancer patients were recruited. Of these, 7.69% were underweight, 35.38% were normal weight, and 56.93% were overweight before starting cancer treatment⁽¹⁴⁾.

Regarding adverse events, nausea, vomiting, ascites, and muscle fatigue were the most common, with the latter showing a positive correlation. Data corroborated by a cohort of 2,390 women with ovarian cancer, the most common chemotherapy-related adverse events were nausea (65.7%), anemia (81.7%), leukopenia (60.5%), neutropenia (55.5%), and liver toxicity (52.2%), and showed no significant association with body composition⁽¹³⁾.

Data analysis revealed that, although a significant portion of participants had low muscle mass percentages, the statistically significant association with adverse events was limited to muscle fatigue in the first cycle of chemotherapy (p=0.045). Most of the women evaluated (72%) had between 21% and 30% muscle mass, as assessed by computed tomography, and 24.3% were in the even lower range, 11% to 20%. This finding reinforces the high rate of sarcopenia or risk of sarcopenia in this cancer population, possibly related to cancer, the catabolic impact of chemotherapy, and nutritional changes associated with the disease.

The cohort conducted in Switzerland (n=69) evaluated the association between quantitative measures of the body composition profile, derived from computed tomography, and chemotherapy-related complications, in terms of dose reduction, premature discontinuation of chemotherapy, and cycle delays in patients with ovarian cancer; and no significant associations were found. However, there was a significant association between visceral adipose tissue and delays in the chemotherapy cycle (OR = 1.01, z = 2.01, 95% CI: 1.00-1.02, p < 0.05), between skeletal muscle area and early discontinuation of chemotherapy (OR = 1.03, z = 2.10, 95% CI: 1.00-1.05, p < 0.05) and between

mean skeletal muscle density and delays in the cycle (OR = 0.92, z = -2.70, 95% CI: 0.87–0.98, p < 0.01) and concluded that body composition through computed tomography may be a good predictor of the risk of chemotherapy toxicity in women with ovarian cancer⁽¹³⁾. Data also highlighted in another study, which correlated body composition with chemotherapy-induced neuropathy in women with ovarian cancer and demonstrated that muscle mass volume can be a biomarker for predicting toxicities in this group⁽¹⁶⁾.

The correlation between muscle mass and muscle fatigue is consistent with previous findings in the literature, which indicate that sarcopenia can compromise tolerance to chemotherapy treatment, impairing the patient's physical performance and functional capacity. Although this association was statistically significant only in cycle 1, it is important to consider that the progressive loss of muscle mass during treatment can have cumulative effects that are not expressed acutely, but rather over time. A study conducted in the United States patients with ovarian 173 demonstrated a statistically significant difference between sarcopenic and non-sarcopenic women regarding completion of at least six cycles of chemotherapy. Specifically, sarcopenic women were significantly less likely to complete the recommended cycles of chemotherapy, with a completion rate of 83.9% compared to 95.5% in non-sarcopenic women (p = 0.02). However, when analyzing other important treatment-related factors, such as the occurrence of dose delays, dose reductions, or severe neutropenia between the two groups, there were no significant differences, despite the lower likelihood of completing at least six cycles in the sarcopenic group⁽²⁵⁾.

Despite the high incidence of other adverse events such as nausea, vomiting, and neutropenia, no statistically significant relationship could be established between these clinical manifestations and muscle mass levels. This finding suggests that such events may be more directly related to the pharmacological toxicity of the chemotherapy regimen used, and less to the musculoskeletal condition of the patients. Nevertheless, the high rate of chemotherapy discontinuation (40.5%), especially due to febrile neutropenia, and the need for dose adjustment (27%) reinforce the importance of evaluating predictors of treatment tolerance, including nutritional and functional

variables. Although the findings of this study did not demonstrate a significant correlation, many authors demonstrate an association between body composition and the patient's therapeutic and oncological prognosis. Furthermore, patients with lower muscle mass had a greater chance of toxicity and poor adherence to chemotherapy, highlighting the importance of individualized chemotherapy treatment assessed according to body composition⁽¹¹⁾.

The lack of records of adverse effects such as mucositis, dysgeusia, and anorexia in the medical records points to possible underreporting or limitations in the systematization of clinical records, which may have affected the analysis of associations with muscle mass. This study has limitations related to retrospective data collection and the use of medical records, in which, despite women's reports, health professionals often fail to record adverse events and their severity. However, the findings reinforce the importance of assessing body composition, especially muscle mass, as part of the comprehensive care of women with ovarian cancer. Nutritional and physical support strategies, when implemented early, can help reduce the

incidence of adverse effects and improve treatment tolerance, in addition to maintaining the functionality and quality of life of these patients. Future studies, with a prospective design and continuous assessment of muscle mass throughout chemotherapy cycles, can help further elucidate this relationship and inform more effective clinical interventions.

CONCLUSION

The most frequently reported adverse events were nausea, vomiting, and muscle fatigue. After correlating these findings with body composition, a significant correlation was found only with muscle fatigue, after the first cycle of chemotherapy. Therefore, no relationship was observed between decreased muscle mass and adverse events caused by chemotherapy.

Further studies, especially with prospective monitoring are suggested to evaluate the relationship between decreased muscle mass and adverse events caused by chemotherapy among women with ovarian cancer.

ASSOCIAÇÃO ENTRE A MASSA MUSCULAR E OS EVENTOS ADVERSOS DA QUIMIOTERAPIA PARA CÂNCER DE OVÁRIO RESUMO

Objetivo: identificar se existe associação entre a massa muscular e os eventos adversos do tratamento quimioterápico em mulheres com câncer de ovário. **Métodos:** coorte retrospectiva de 2014 a 2019, composta por 111 mulheres. Coletou-se dados sociodemográficos, da doença e do tratamento quimioterápico, eventos adversos e índice de massa corporal (IMC). A análise da composição corporal foi feita a partir da tomografia computadorizada realizada no diagnóstico e analisadas com auxílio do software Slice-O-matic V4.3 (Tomovision). **Resultados:** a idade das participantes variou de 21 a 88 anos. Antes de iniciar o tratamento, 14,4% apresentavam perda de peso, 53,9% eram eutróficas, 6,1% apresentavam baixo peso, que ao final do tratamento eram 31,3%. A composição corporal de massa muscular de 72,2% das mulheres estava na faixa de 21 a 30%. Os eventos adversos mais frequentes foram: náusea, vômito e fadiga muscular, que não apresentaram significância com a composição corporal, sendo esta observada apenas com a fadiga muscular após primeiro ciclo de quimioterapia. **Conclusão:** a diminuição da massa muscular se associou significativamente à fadiga muscular no início da quimioterapia, destacando a importância de monitorar a composição corporal para otimizar o manejo de mulheres com câncer de ovário.

Palavras-chave: Neoplasias Ovarianas. Efeitos Colaterais e Reações Adversas Relacionados a Medicamentos. Antineoplásicos. Composição Corporal. Saúde da Mulher.

ASOCIACIÓN ENTRE LA MASA MUSCULAR Y LOS EVENTOS ADVERSOS DE LA QUIMIOTERAPIA PARA CÁNCER DE OVARIO

RESUMEN

Objetivo: identificar si existe asociación entre la masa muscular y los eventos adversos del tratamiento quimioterápico en mujeres con cáncer de ovario. **Métodos**: estudio de cohorte retrospectivo de 2014 a 2019, compuesto por 111 mujeres. Se recogieron datos sociodemográficos, de la enfermedad y del tratamiento quimioterápico, eventos adversos e índice de masa corporal (IMC). El análisis de la composición corporal se realizó a partir de la tomografía computarizada realizada en el diagnóstico y analizada con ayuda del *software Slice-O-matic V4.3* (Tomovision). **Resultados**: la edad de las participantes varió de 21 a 88 años. Antes de iniciar

el tratamiento, 14,4% presentaban pérdida de peso, 53,9% eran eutróficas, 6,1% presentaban bajo peso, que al final del tratamiento eran 31,3%. La composición corporal de masa muscular del 72,2% de las mujeres se encontraba en el ámbito del 21 al 30%. Los eventos adversos más frecuentes fueron: náuseas, vómitos y fatiga muscular, que no presentaron significación con la composición corporal, siendo esta observada solo con la fatiga muscular después del primer ciclo de quimioterapia. **Conclusión**: la disminución de la masa muscular se asoció significativamente a la fatiga muscular al inicio de la quimioterapia, destacando la importancia de monitorear la composición corporal para optimizar el manejo de mujeres con cáncer de ovario.

Palabras clave: Neoplasias Ováricas. Efectos Secundarios y Reacciones Adversas Relacionados a Medicamentos. Antineoplásicos. Composición Corporal. Salud de la Mujer.

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Submitted: 14/05/2024 **Accepted:** 13/07/2025

Financial support:

This work was funded by "This study was carried out with the support of the Coordination for the Improvement of Higher Education Personnel - Brazil (CAPES) - Funding Code 001.