Selectively increased autofluorescence at certain regions of skin may become a novel diagnostic biomarker for lung cancer

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Abstract

Early diagnosis can significantly enhance the 5-year survival rates of lung cancer patients, while a large majority of lung cancer patients have advanced disease at the time of diagnosis. We tested our hypothesis that increased autofluorescence (AF) of skin may become a new diagnostic biomarker for lung cancer, which has generated the following findings: First, the AF intensity of untreated lung cancer group in certain regions of skin is significantly higher than that of the healthy group and the group of benign lung diseases; second, the percentage of the people with 3 or more regions with increased green AF is 11.1%, 47.06%, and 71.80% for the healthy group, the group of benign lung disease patients, and the group of untreated lung cancer patients, respectively; and third, the AF intensity at several regions of the skin of untreated lung cancer patients is significantly lower than that of acute ischemic stroke patients. Moreover, the AF increases in lung cancer may result from oxidative stress-induced increases in keratins' AF. Collectively, our study has indicated that lung cancer patients have significant AF increases in certain regions of their skin, which may become a novel diagnostic biomarker for the illness. This approach could be used to diagnose both lung cancer and acute ischemic stroke, since we may differentiate these diseases based on the differences in both the patterns of their AF at multiple regions and their clinical symptoms. This non-invasive diagnostic approach may significantly increase the rate of early diagnosis of lung cancer.

Keywords: Autofluorescence; lung cancer; lung diseases; non-invasive; diagnosis.

Introduction

Lung cancer is the leading cause of cancer deaths around the world (18). Approximately 85% of lung cancer are non-small cell lung cancer (NSCLC), with approximately 15% of lung cancer being small cell lung cancer (SCLC) (3). The main histological subtypes of NSCLC are adenocarcinoma and squamous cell carcinoma (3). If identified at an early stage, surgical resection of NSCLC offers a favorable prognosis, with 5-year survival rates of 70 – 90% for small, localized tumors (stage I) (5,16). However, approximately 75% patients have advanced disease at the time of diagnosis (stage III/IV) (20). As reported by the UK Office for National Statistics in 2014, patients diagnosed with distant metastatic disease (stage IV) had a 1-year survival rate of 15-19%. The majority of the patients of Adenocarcinomas - the most common subtype of lung cancer - come to clinical attention with distantly metastatic or locally advanced disease, since the disease may be asymptomatic in their early stages (17).

CT screening is a widely used diagnostic approach for lung cancer. However, in addition to the concerns of radiation exposures (1) and the cost of testing, CT screening is also associated with a high rate of falsely positive tests which may result in unneeded treatment (1). Because early diagnosis is a key factor determining the 5-year survival rates of the disease, it becomes increasingly valuable to establish approaches that can conduct diagnosis of lung cancer at patients' homes non-invasively and efficiently.

Skin autofluorescence (AF) has shown promise for non-invasive diagnosis of diabetes, which is based on detecting the AF of advanced glycation end-products (AGEs) of the collagen in dermis (10,13). The excitation wavelength of AGEs' AF (9,11) is profoundly different from that of the epidermal AF of keratins (7,15). Keratins, together with melanin, NADH and FAD, are major epidermal fluorophores (2,15). Our recent study has found that UV-induced epidermal green AF, which is originated from UV-induced keratin 1 proteolysis in the spinous cells of epidermis, can be used as a novel biomarker for predicting UV-induced skin damage (7). Since detection of AF is non-invasive and simple, it is of great significance to further investigate the potential of AF as biomarkers for diseases. Our latest study has further found that the oxidative stress induced by UVC is causative to the increased epidermal AF of mouse ears by inducing keratin 1 proteolysis (12). Since a number of studies have found increased oxidative stress in the plasma of lung cancer patients (4,6,8,14,19), it is warranted to determine if there are increases in the epidermal AF of lung cancer patients, which may become a new diagnostic biomarker for the disease.

In this study, we tested our hypothesis that lung cancer patients may have increased AF in certain regions of their skin, which may become a novel diagnostic biomarker for the disease. Our study has provided first evidence that there are selective increases in green AF intensity at certain regions of the skin of lung cancer patients, which has provided evidence supporting our hypothesis.

Methods

Human subjects

This study was conducted according to a protocol approved by the Ethics Committee of Shanghai Chest Hospital, Shanghai Jiao Tong University, and a protocol approved by the Ethics Committee of Shanghai Fifth People's Hospital, Fudan University. The human subjects in our study were divided into five groups: Group 1: The group of healthy persons; Group 2: the group of benign lung disease patients, which includes the patients of bronchiectasis, chronic obstructive pulmonary disease, and lung infection (not including tuberculosis or interstitial lung disease), who were hospitalized in the Department of Pulmonary Medicine, Shanghai Chest Hospital, Shanghai Jiao Tong University; Group 3: The group of untreated lung cancer patients, including untreated adenocarcinoma, squamous-cell carcinoma and small-cell lung carcinoma patients, who were hospitalized in the Department of Pulmonary Medicine; Group 4: The group of lung cancer patients who have received chemotherapy, who were hospitalized lung cancer patients in the Department of Pulmonary Medicine; and Group 5: The group of acute ischemic stroke patients who were diagnosed as 'ischemic stroke patients' by the neurologists of the Department of Neurology, Shanghai Fifth People's Hospital, Fudan University within 7 days from the time of the examination. The age of Group 1, Group 2, Group 3, Group 4 and Group 5 is 63.15 ± 5.46, 65.13 ± 8.40, 63.46 ± 8.80, 59.97 ± 9.92, and 67.30 ± 10.27 years of old, respectively.

Autofluorescence determination

A portable AF imaging equipment was used to detect the AF of the fingernails and certain regions of the skin of the human subjects. The excitation wavelength is 485 nm, and the emission wavelength is 500 – 550 nm. For all of the human subjects, the AF intensity in the following seven regions on both hands, i.e., fourteen regions in total, was determined, including the index fingernails, Ventroforefingers, dorsal index fingers, Centremetacarpus, Dorsal Centremetacarpus, Ventriantebrachium, and Dorsal Antebrachium.

Statistical analyses

All data are presented as mean ± SEM. Data were assessed by one-way ANOVA, followed by Student – Newman - Keuls *post hoc* test, except where noted. *P* values less than 0.05 were considered statistically significant.

Results

1. The AF intensity of certain regions of the skin of untreated lung cancer patients is significantly higher than that of the healthy persons and the benign lung disease patients

We determined the green AF intensity of two index fingernails and twelve regions of the skin of the healthy group, the group of benign lung disease patients, the group of untreated lung cancer patients, and the group of lung cancer patients with chemotherapy. We found that the AF intensity of the untreated lung cancer patients

is significantly higher than that the healthy persons and the benign lung disease patients at left and right Ventriantebrachuim (Fig. 1A) and Dorsal Antebrachium (Fig. 1B), as well as right Dorsal Centremetacarpus (Fig. 1C). The AF intensity of the untreated lung cancer patients is also significantly higher than that of the healthy persons at left and right Ventroforefinger (Fig. 1D), Index Fingernails (Fig. 1E) and Centremetacarpus (Fig. 1F), as well as the dorsal index fingers (Fig. 1G). There is no any significant difference between the AF of the untreated lung cancer patients and that of the lung cancer patients with chemotherapy at any regions examined, except at the right Dorsal Antebrachium, the AF of the untreated lung cancer patients is significantly lower than that of the lung cancer patients with chemotherapy (Fig. 1B).

2. The AF asymmetry of untreated lung cancer group is significantly higher than that of the healthy group and the benign lung diseases group at two regions of the skin

We determined the 'asymmetry of the AF intensity', which is defined as 'a significant difference between the same region at left and right side of the body'. Our study showed that the AF asymmetry of untreated lung cancer group is significantly higher than that of the healthy group only at Ventroforefinger (Fig. 2A) and Dorsal Antebrachium (Fig. 2B).

3. The healthy group, the group of benign lung disease patients, the group of untreated lung cancer patients, and the group of lung cancer patients with

chemotherapy have profound differences in the percentage of the people with three or more regions with increased AF

We found that the percentage of the people with 0, 1 or 2 regions with increased green AF is 88.9%, 47.06%, 28.2% and 31.43% for the healthy group, the group of benign lung disease patients, the group of untreated lung cancer patients, and the group of lung cancer patients with chemotherapy, respectively (Fig. 3A). We also found that the percentage of the people with 3 or more regions with increased green AF is 11.1%, 47.06%, 71.80% and 68.60% for the healthy group, the group of benign lung disease patients, the group of untreated lung cancer patients, and the group of lung cancer patients with chemotherapy, respectively (Fig. 3A). In a majority of the regions examined, a significantly higher percentage of the untreated lung cancer patients have increased AF intensity, compared with the healthy persons and the benign lung disease patients (Fig. 3B).

4. Comparisons between the AF of lung cancer group and that of acute ischemic stroke group

The AF of lung cancer group is significantly lower than that of acute ischemic stroke group at six regions examined, including left and right index fingernails, Ventroforefingers, and dorsal index fingers (Figs. 4A, 4B and 4C).

Discussion

The major findings of our study include: First, the AF intensity of untreated lung cancer group in certain regions of skin is significantly higher than that of the healthy group; second, there is AF asymmetry at two regions of the skin of untreated lung cancer group; third, the percentage of the people with 3 or more regions with increased green AF is 11.1%, 47.06%, 71.80% and 68.60% for the healthy group, the group of benign lung disease patients, the group of untreated lung cancer patients, and the group of lung cancer patients with chemotherapy, respectively; and fourth, the AF intensity at several regions of the skin of untreated lung cancer patients is significantly lower than that of acute ischemic stroke patients. Collectively, our study has indicated that lung cancer patients have selective AF increases in certain regions of their skin, which may become a new diagnostic biomarker for the disease.

Early diagnosis is crucial for the 5-year survival rates of lung cancer patients. Our current study has provided the first evidence suggesting that lung cancer patients may be diagnosed at homes by determining the AF of certain regions of their skin: The AF of lung cancer patients has shown its characteristic pattern, and the percentage of lung cancer patients with 3 or more regions with increased green AF is markedly higher than that of the healthy persons and benign lung disease patients. Based on this piece of evidence, we proposed a new criteria for lung cancer diagnosis – ‘selective AF increases in certain regions of skin’, which may be used jointly with the clinical symptom-based diagnostic criteria for diagnosis of the disease. We expect that the sensitivity and specificity of this diagnostic approach would be significantly

enhanced in the future, with both increases in the regions examined and applications of artificial intelligence and big data science in our future studies.

It is important to elucidate the mechanisms underlying the increases in green AF in lung cancer. We have found that the oxidative stress induced by UVC mediates the increase in the epidermal green AF of mouse ears by inducing keratin 1 proteolysis (7). A number of studies have shown significant increases in oxidative stress in the plasma of lung cancer patients (4,6,8,14,19). Therefore, we propose that the oxidative stress may induce increases in the epidermal AF of the lung cancer patients by inducing keratin 1 proteolysis, which may become a new biomarker for non-invasive and efficient diagnosis of the disease.

There are significant increases in green AF in both lung cancer patients and ischemic stroke patients. It is a critical challenge to differentiate lung cancer patients from ischemic stroke patients. We propose that several factors can be used to differentiate the patients of these diseases: First, clinical symptoms should be used as an important approach to enhance the specificity of the AF-based diagnostic method; 2) there are significant differences in the 'pattern of AF' between these two diseases: The AF of acute ischemic stroke group is significantly higher than that of untreated lung cancer group selectively at six regions examined; and AF asymmetry occurs in all of the regions examined in ischemic stroke, while AF asymmetry occurs only in less than 30% regions examined in lung cancer. It is reasonable to expect that with the increases in both the regions examined for AF and applications of big data science and artificial intelligence, we would discover increasingly precise

patterns of the AF of lung cancer patients, ischemic stroke patients and other groups of people. Based on these increasingly precise patterns of AF, we would achieve increasingly greater precision in diagnosis of lung cancer and ischemic stroke.

Acknowledgment

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Figure Legends:

Fig. 1. The AF intensity of certain regions of the skin of untreated lung cancer patients is significantly higher than that of the healthy persons and the benign lung disease patients. (A) The green AF intensity in the Ventriantebrachium of the right hands of untreated lung cancer patients is significantly higher than that of the healthy persons and benign lung disease patients. (B) The green AF intensity in the Dorsal Antebrachium of the right hands of untreated lung cancer patients is significantly higher than that of the healthy persons and benign lung disease patients. (C) The green AF intensity in the Dorsal Centremetacarpus of the right hands of untreated lung cancer patients is significantly higher than that of the healthy persons and benign lung disease patients. (D) The green AF intensity in the Ventroforefingers of both right and left hands of untreated lung cancer patients is significantly higher than that of the healthy persons. (E) The green AF intensity in the index fingernails of both right and left hands of untreated lung cancer patients is significantly higher than that of the healthy persons. (F) The green AF intensity in the Centremetacarpus of both right and left hands of untreated lung cancer patients is significantly higher than that of the healthy persons. (G) The green AF intensity in the dorsal index fingers of the right hands of untreated lung cancer patients is significantly higher than that of the healthy persons and benign lung disease patients. The number of subjects in the healthy group, the group of benign lung disease patients, the group of untreated lung cancer patients, and the group of lung cancer patients with chemotherapy is 27, 17, 39, and 35, respectively. *, $p < 0.05$; **, $p < 0.01$; ***, $p <$

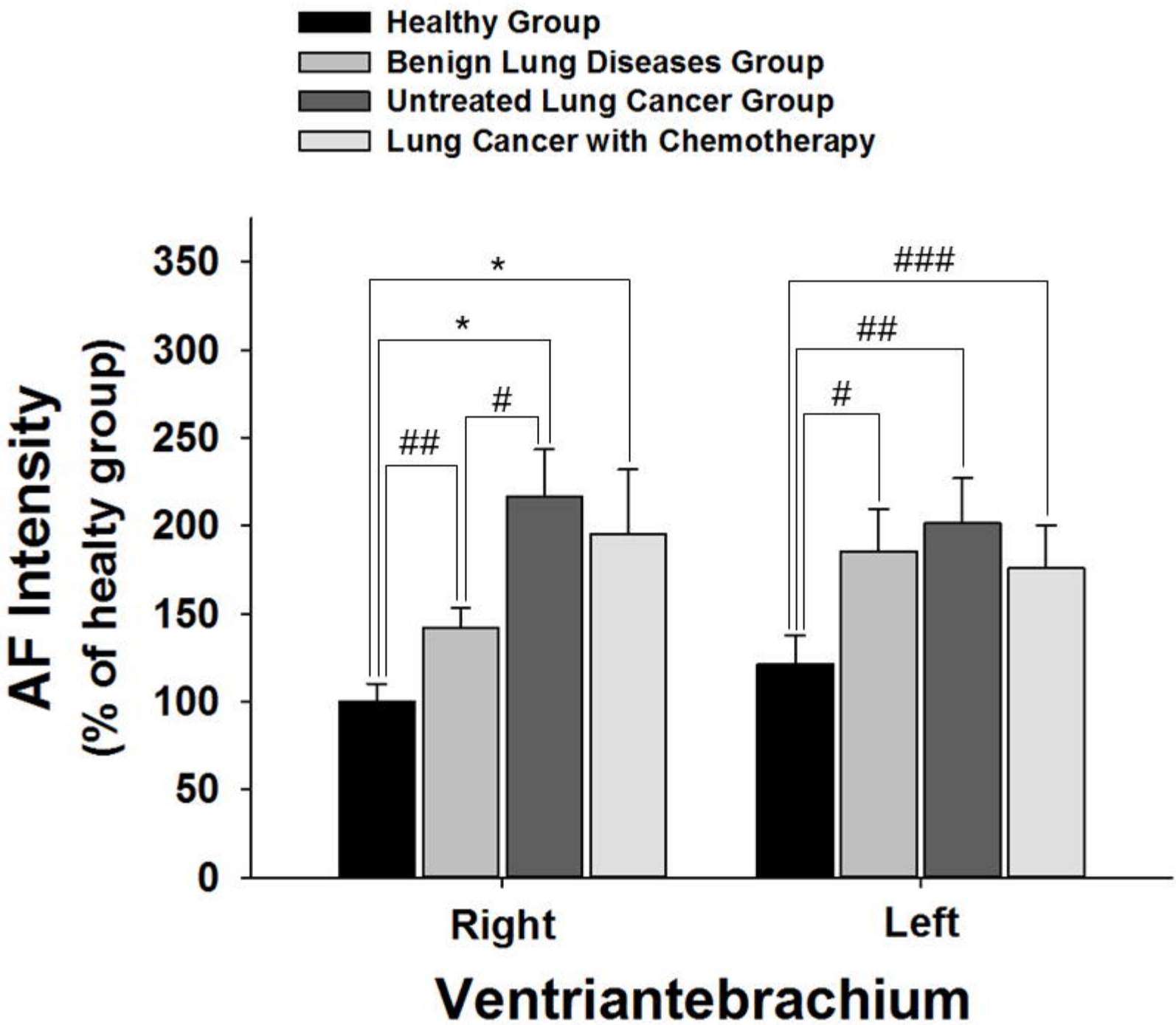
0.001; #, $p < 0.05$ (Student *t*-test); ##, $p < 0.01$ (Student *t*-test); ###, $p < 0.001$ (Student *t*-test).

Fig. 2. The AF asymmetry of untreated lung cancer group is significantly higher than that of the healthy group and the benign lung diseases group at two regions of the skin. There is no significant AF asymmetry in Ventriantebrachium (A), Centremetacarpus (B), index fingernails (D), dorsal index fingers (E), and Dorsal Centremetacarpus (F) of untreated lung cancer patients, except that the AF asymmetry of untreated lung cancer group is significantly higher than that of the healthy group at Ventroforefinger (C) and Dorsal Antebrachium (G). The number of subjects in the healthy group, the group of benign lung disease patients, the group of untreated lung cancer patients, and the group of lung cancer patients with chemotherapy is 27, 17, 39, and 35, respectively. *, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$; #, $p < 0.05$ (Student *t*-test).

Fig. 3. The healthy group, the group of benign lung disease patients, the group of untreated lung cancer patients, and the group of lung cancer patients with chemotherapy have profound differences in the percentage of the people with three or more regions with increased AF. (A) The percentage of the people with 0, 1 or 2 regions with increased green AF is 88.9%, 47.06%, 28.2% and 31.43% for the healthy group, the group of benign lung disease patients, the group of untreated lung cancer patients, and the group of lung cancer patients with chemotherapy, respectively.

The percentage of the people with 3 or more regions with increased green AF is 11.1%, 47.06%, 71.80% and 68.60% for the healthy group, the group of benign lung disease patients, the group of untreated lung cancer patients, and the group of lung cancer patients with chemotherapy, respectively. (B) In a majority of the regions examined, a significantly higher percentage of the untreated lung cancer patients have increased AF intensity, compared with the healthy persons and the benign lung disease patients. In the scale of the figure, 0.1, 0.2, 0.3, 0.4, 0.5 represents 10%, 20%, 30%, 40%, 50%. The number of subjects in the healthy group, the group of benign lung disease patients, the group of untreated lung cancer patients, and the group of lung cancer patients with chemotherapy is 27, 17, 39, and 35, respectively.

Fig. 4. Comparisons between the AF of untreated lung cancer group and that of acute ischemic stroke group. The AF of untreated lung cancer group is significantly lower than that of acute ischemic stroke group at left and right index fingernails (A), Ventroforefingers (B), and dorsal index fingers (C). There is no significant difference between the AF of untreated lung cancer group and that of acute ischemic stroke group at Dorsal Antebrachium (D), Ventriantebrachium (E) and Centremetacarpus (F). The number of the human subjects in the healthy group, the group of lung cancer patients, and the group of acute ischemic stroke patients is 39, 44-50, and 47-49, respectively. *, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$.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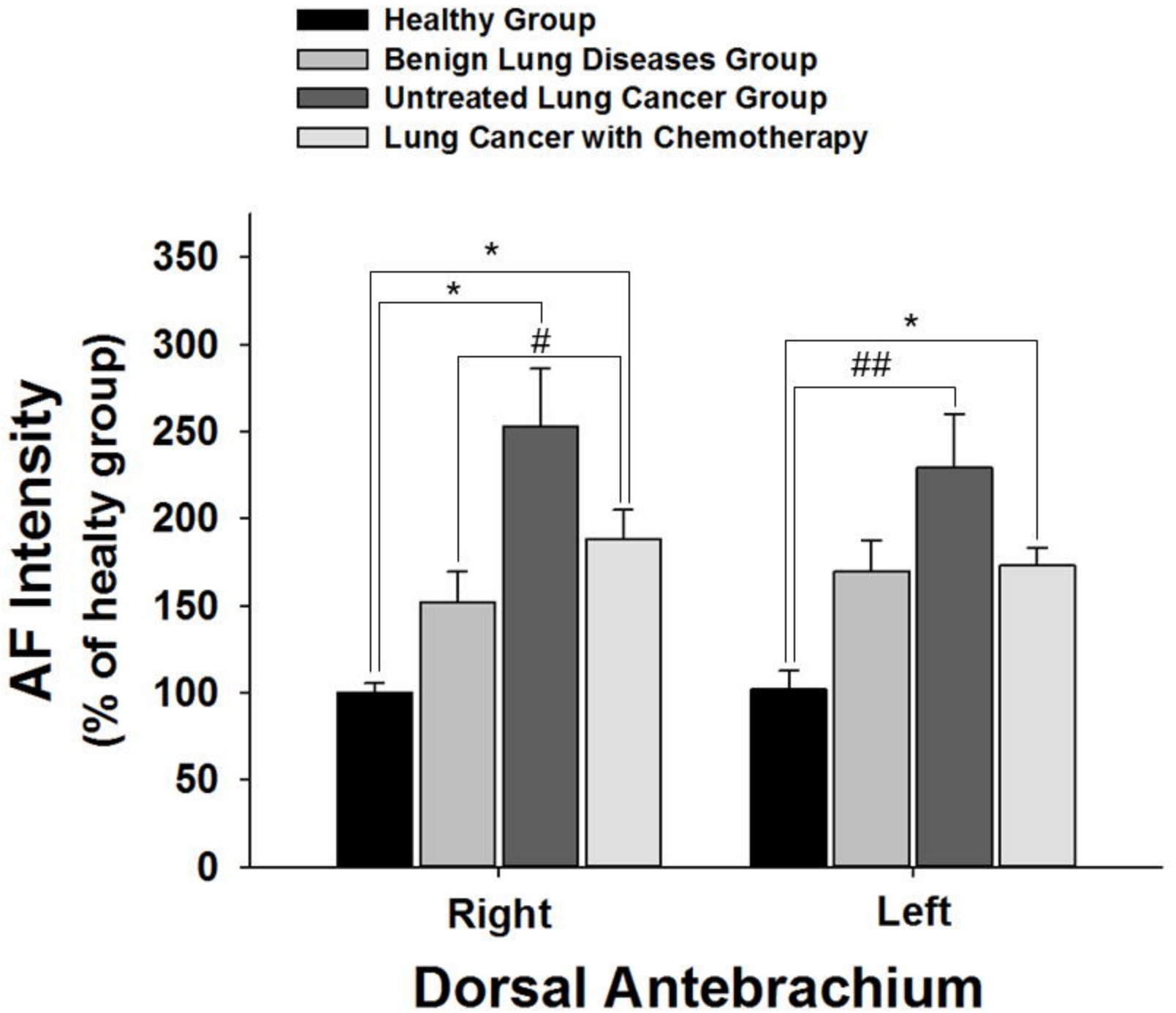
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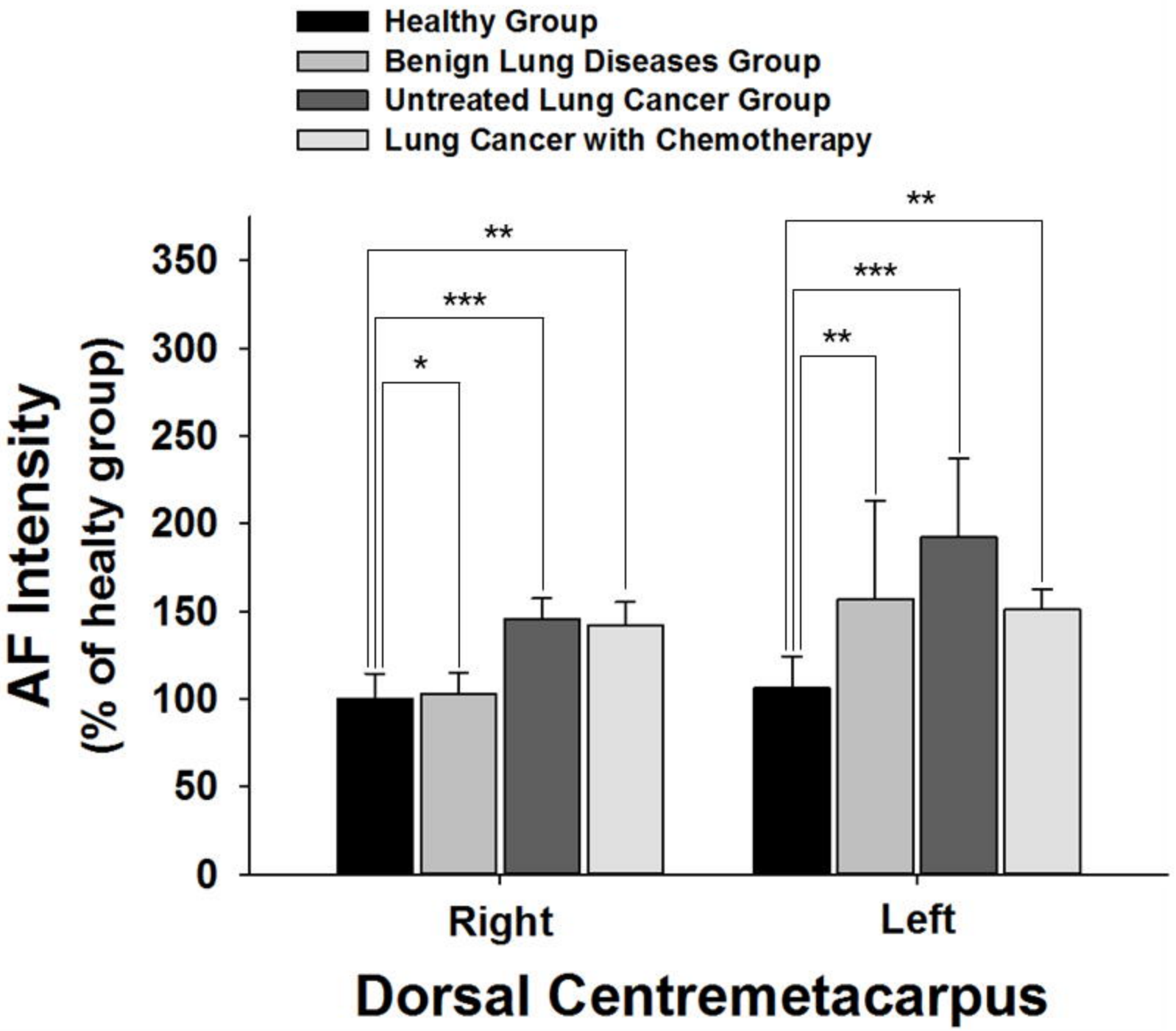
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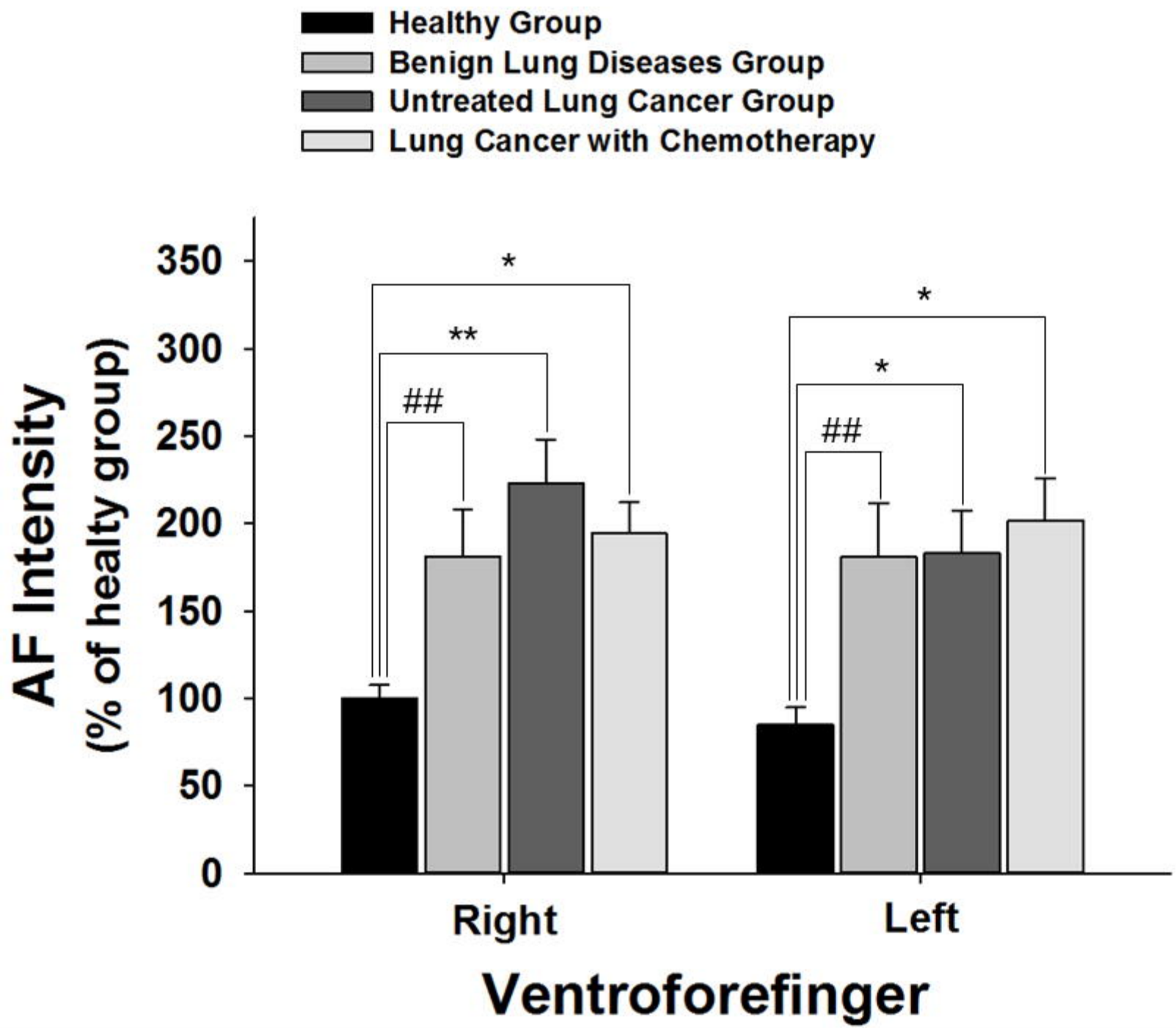
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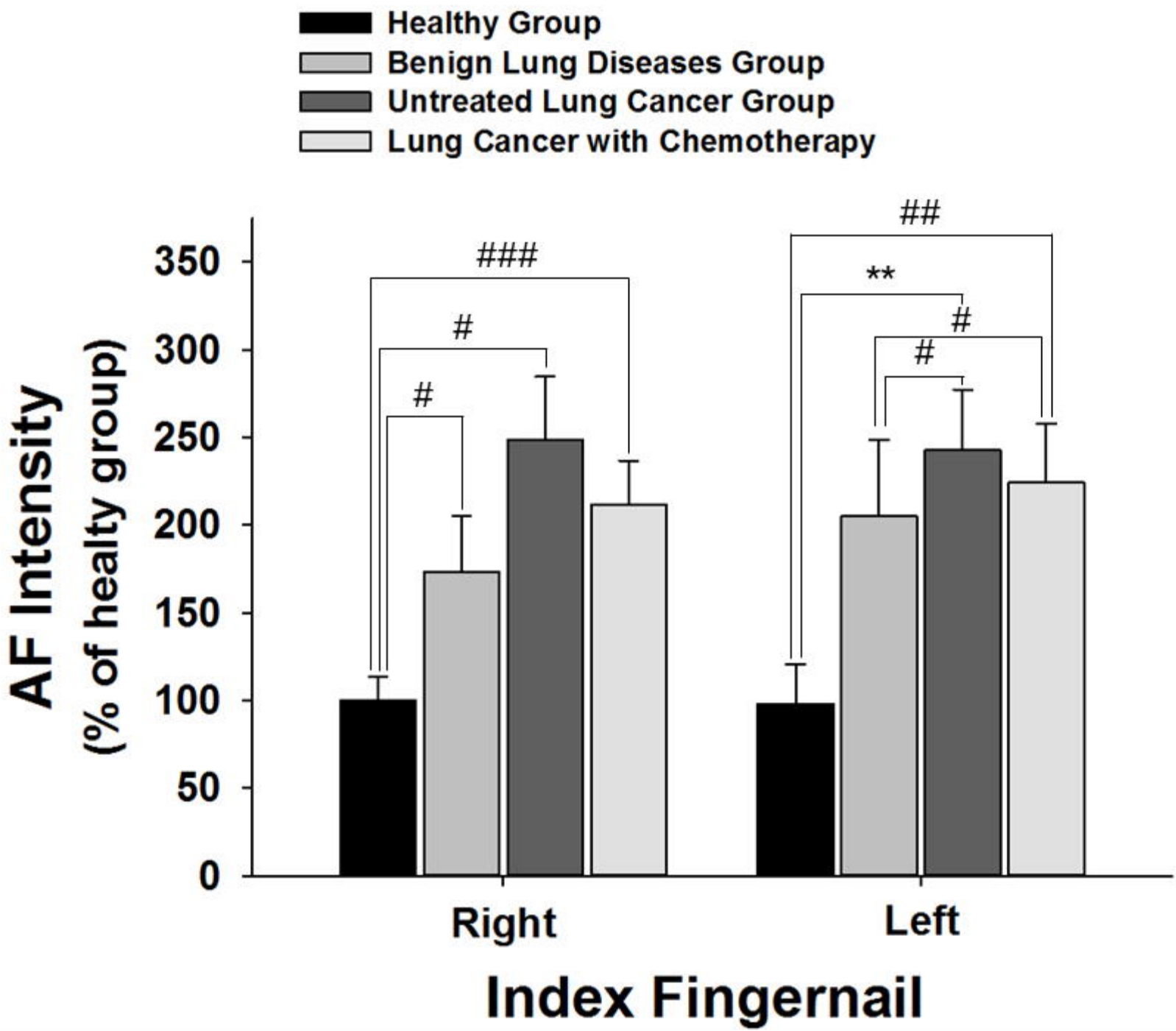
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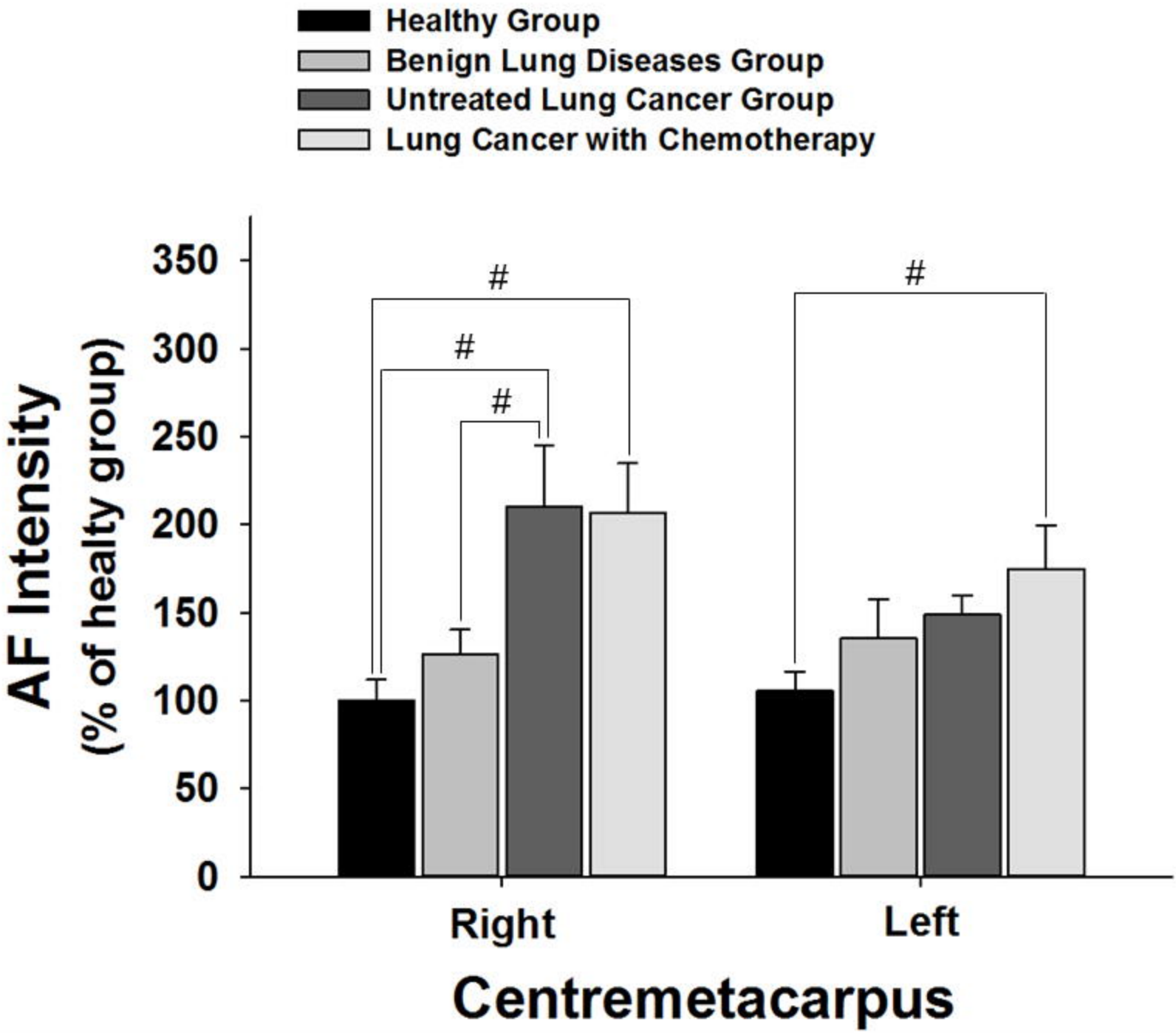
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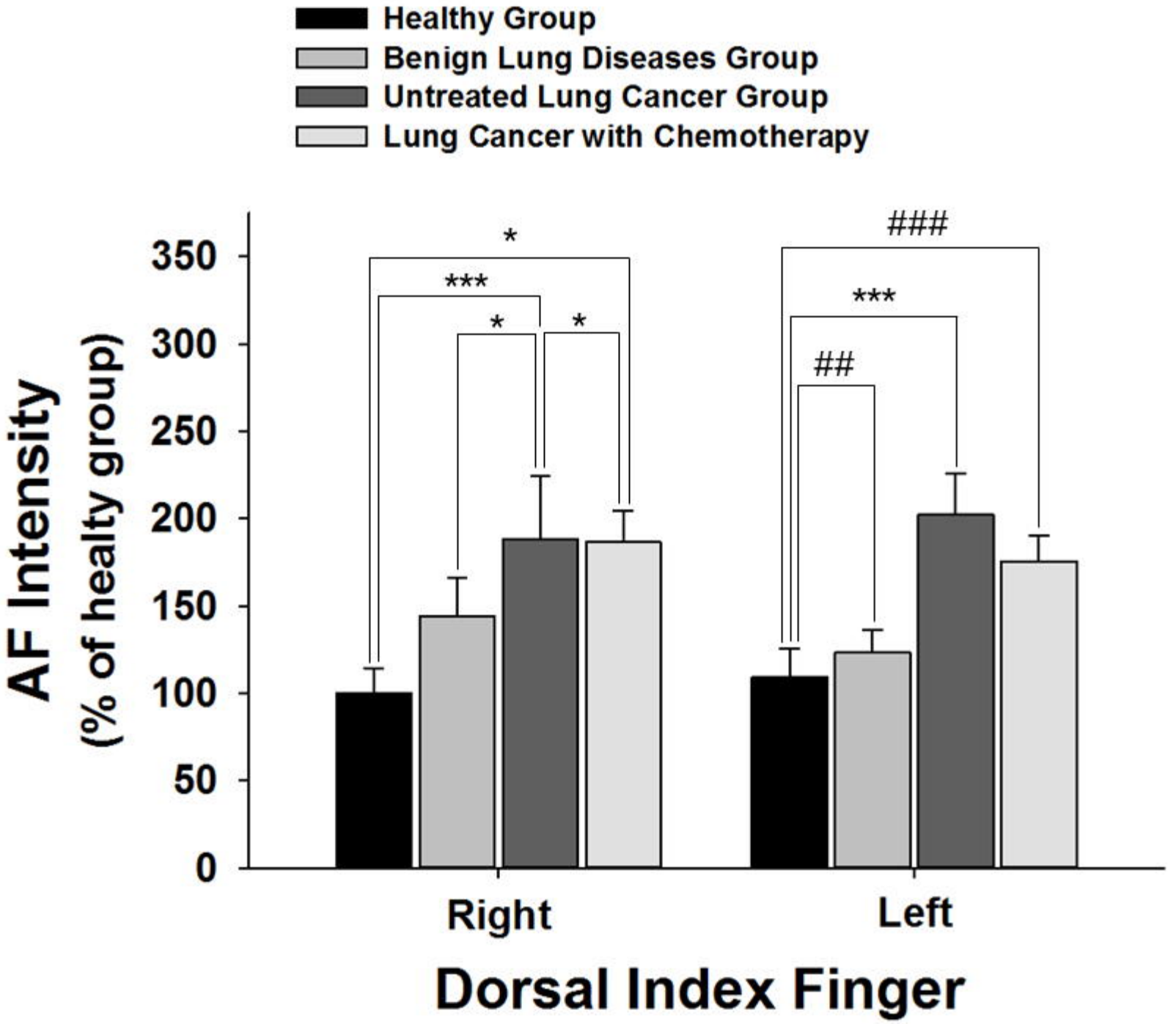
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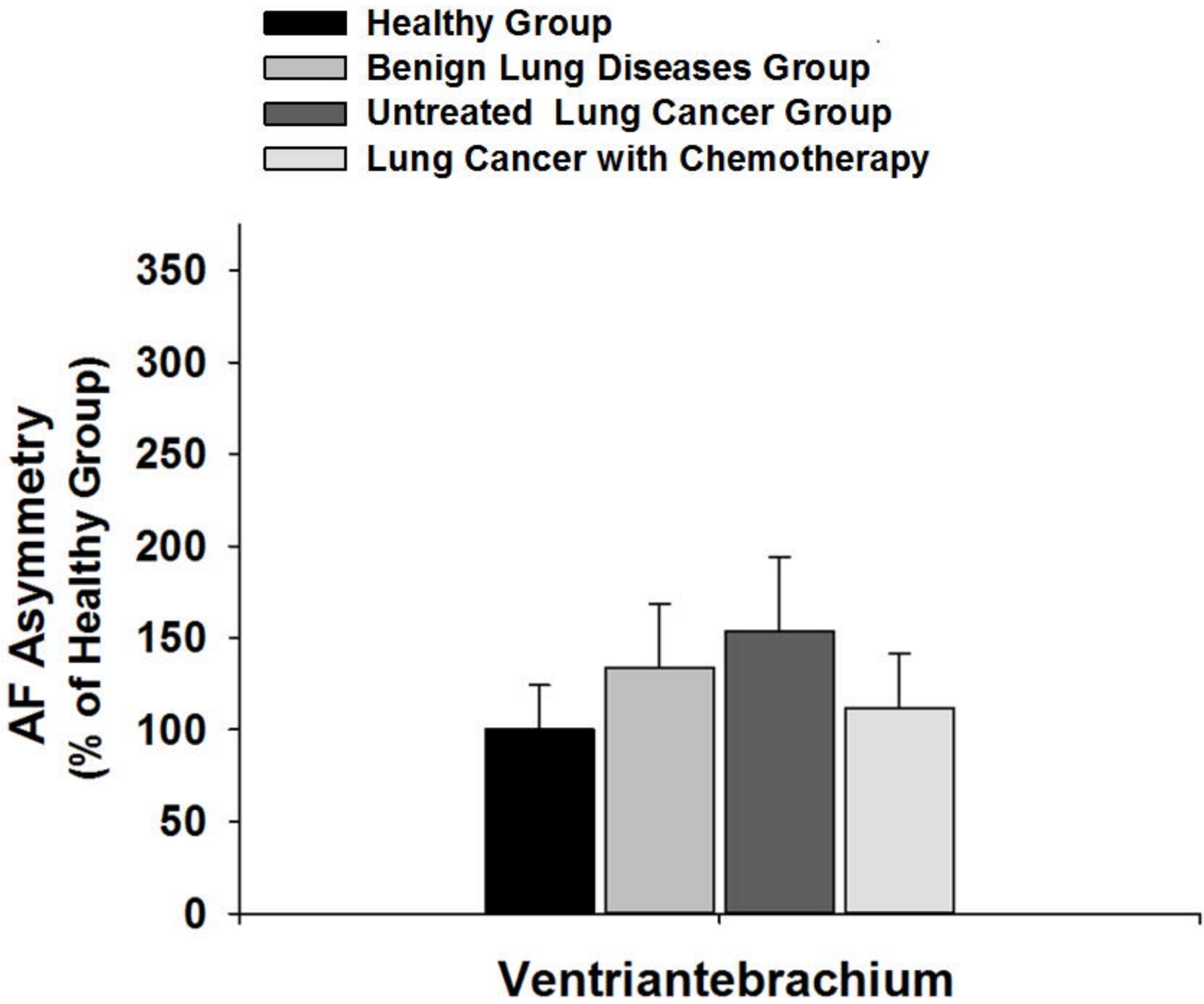
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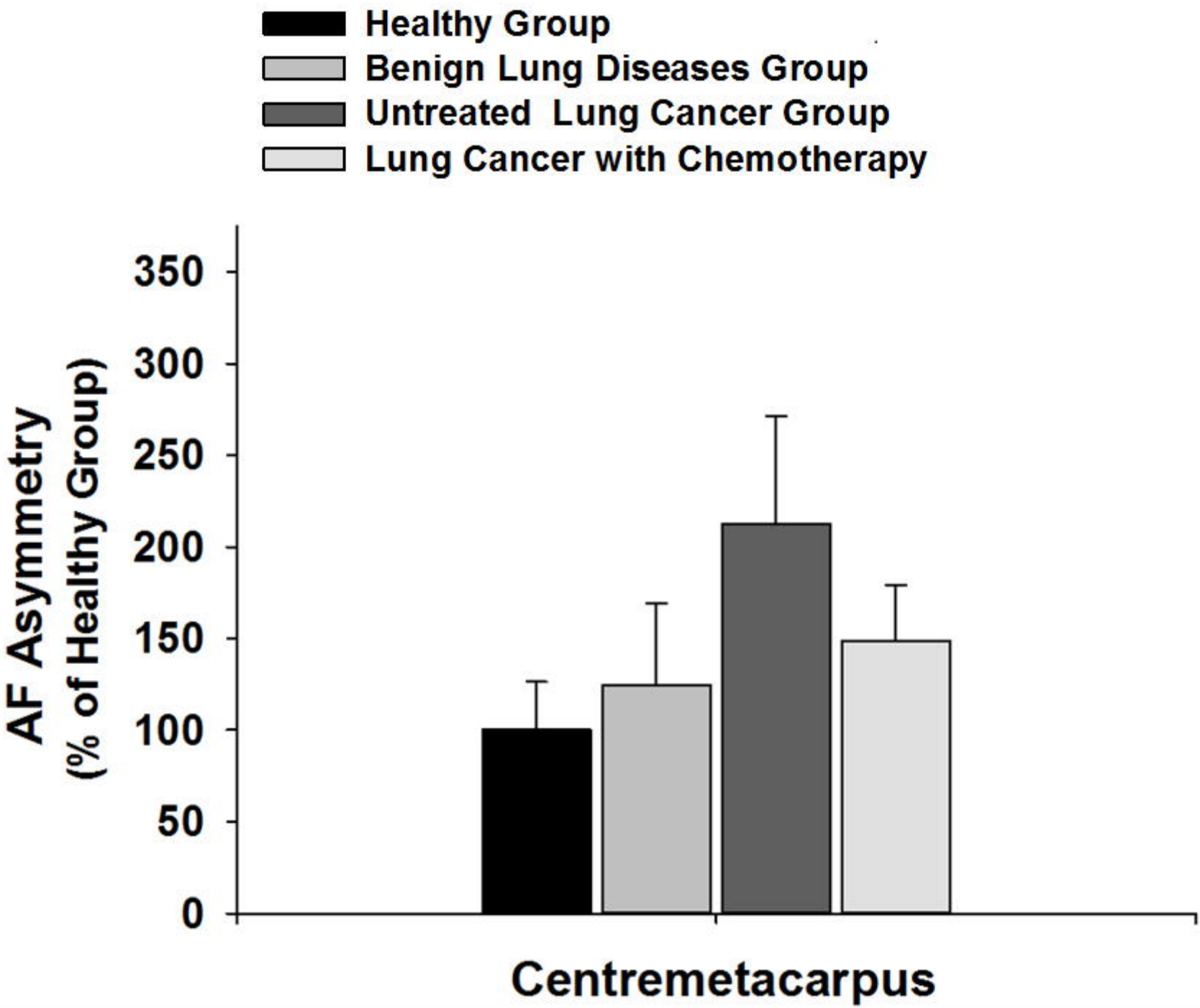
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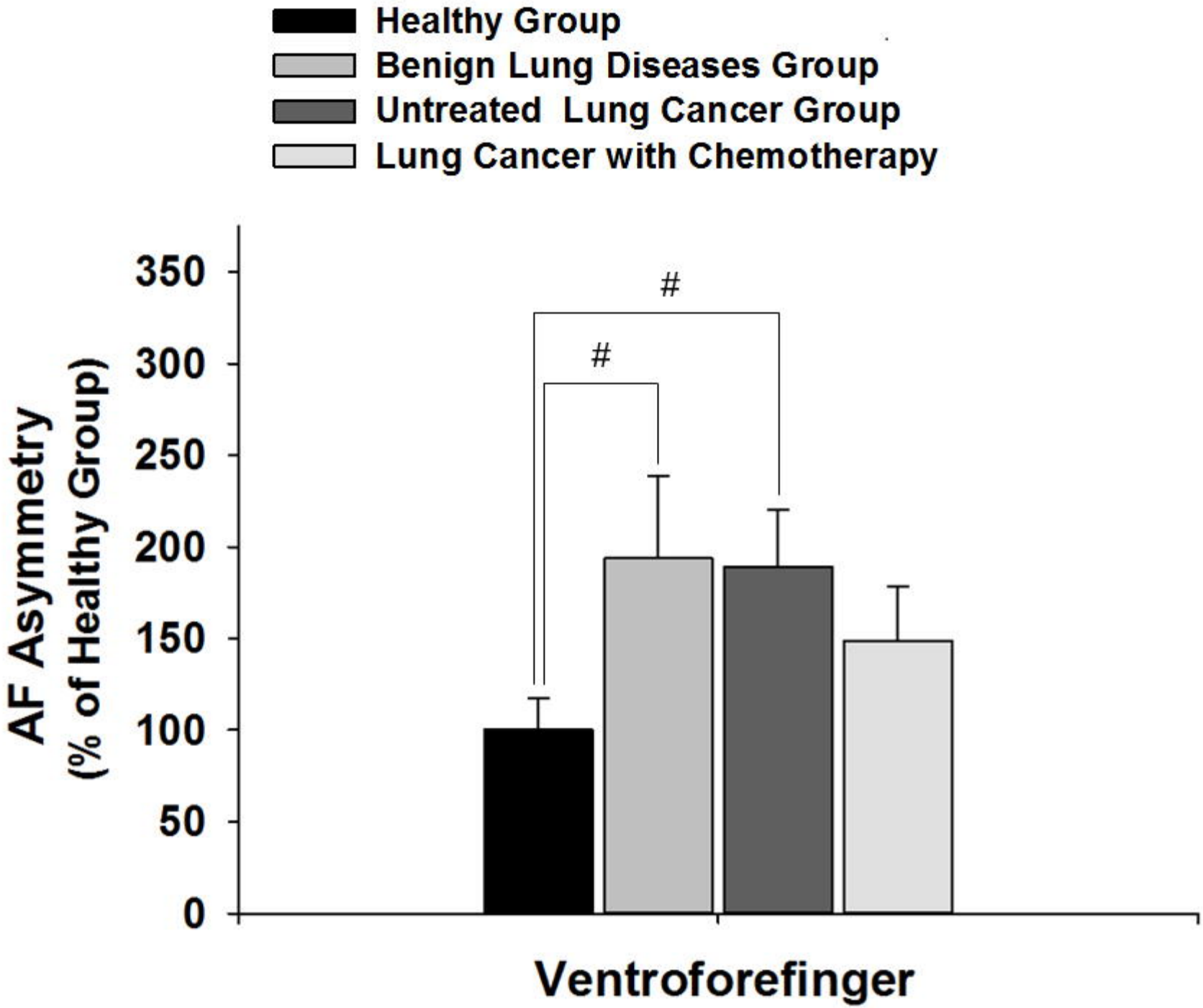
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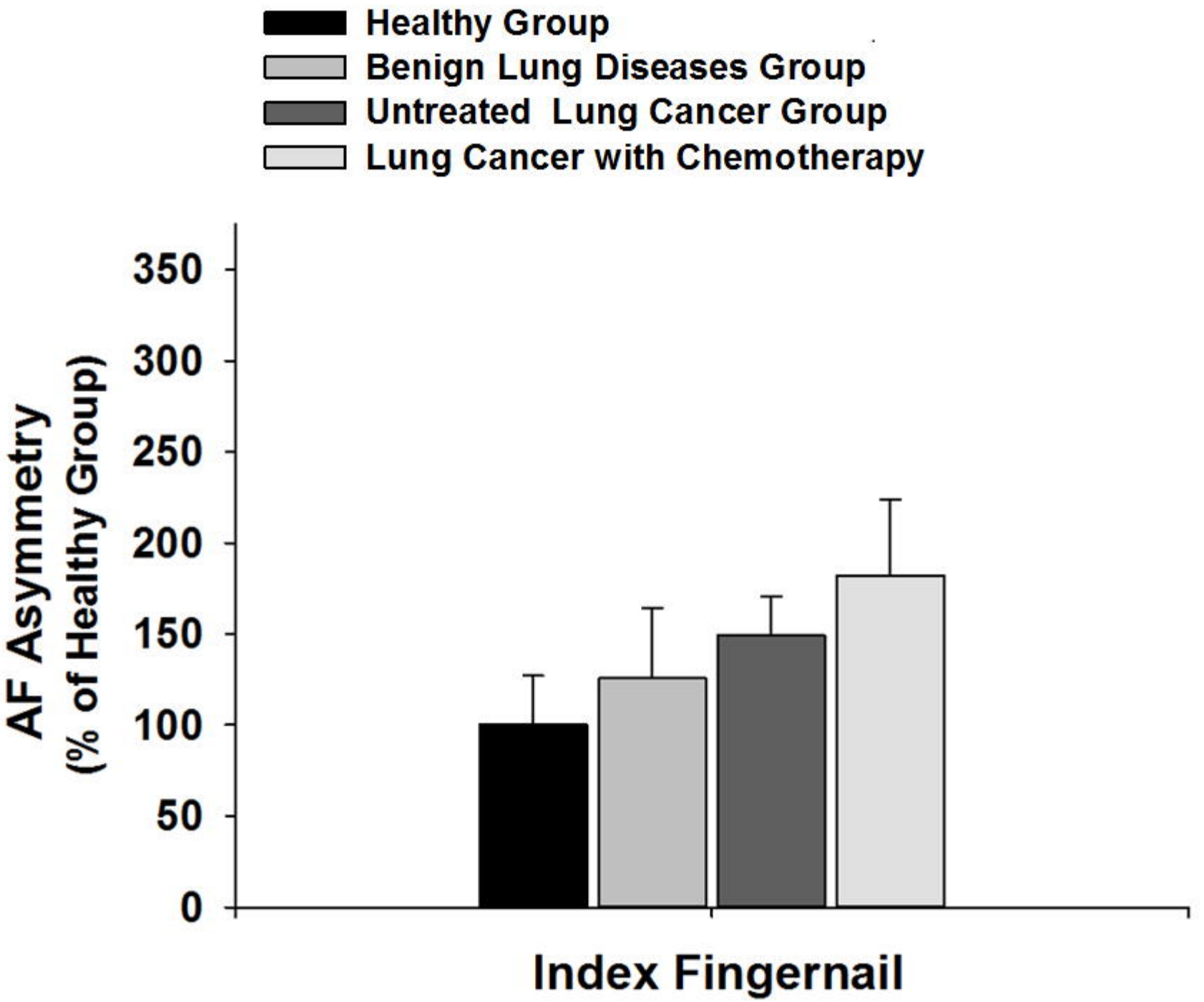
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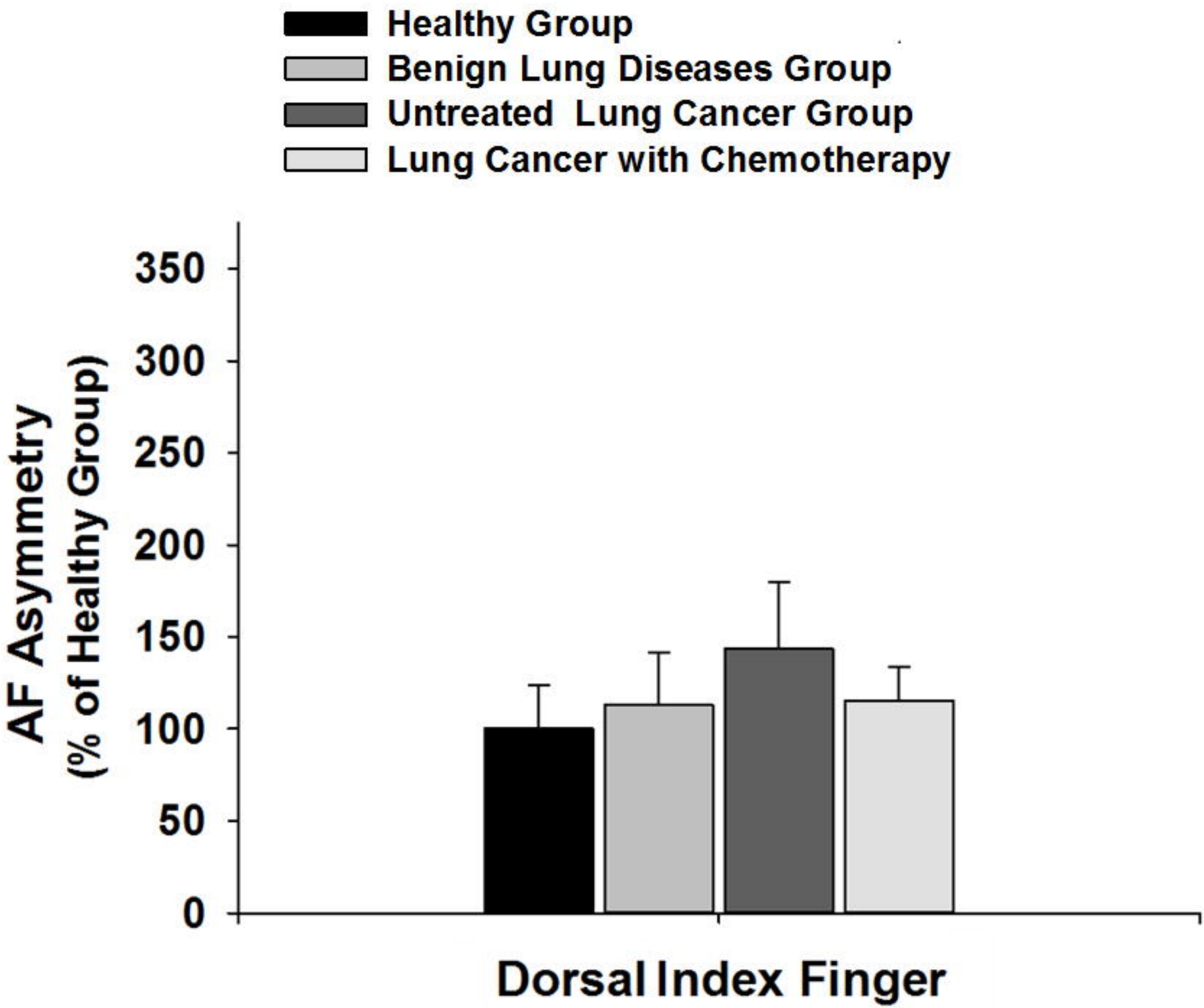
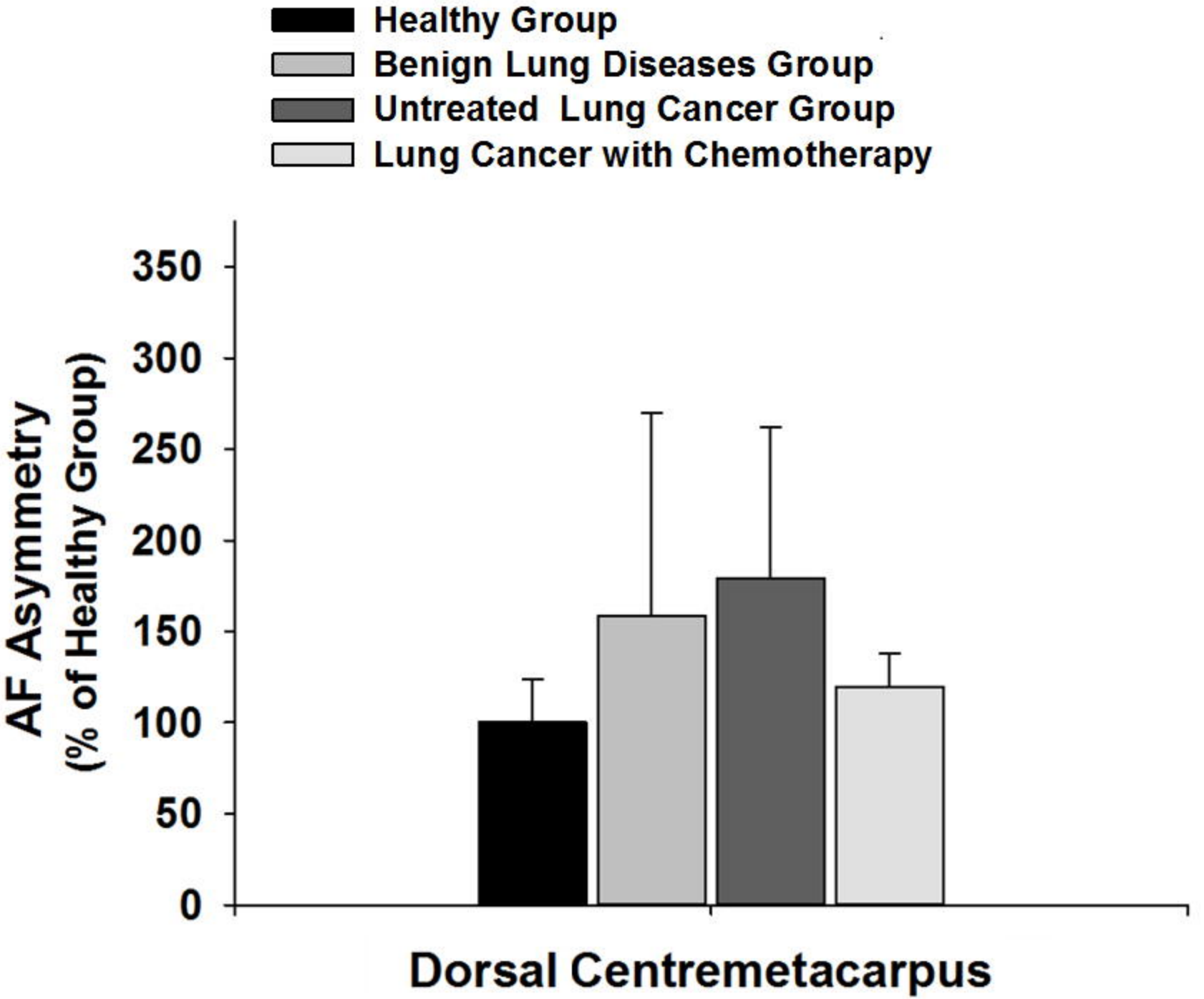
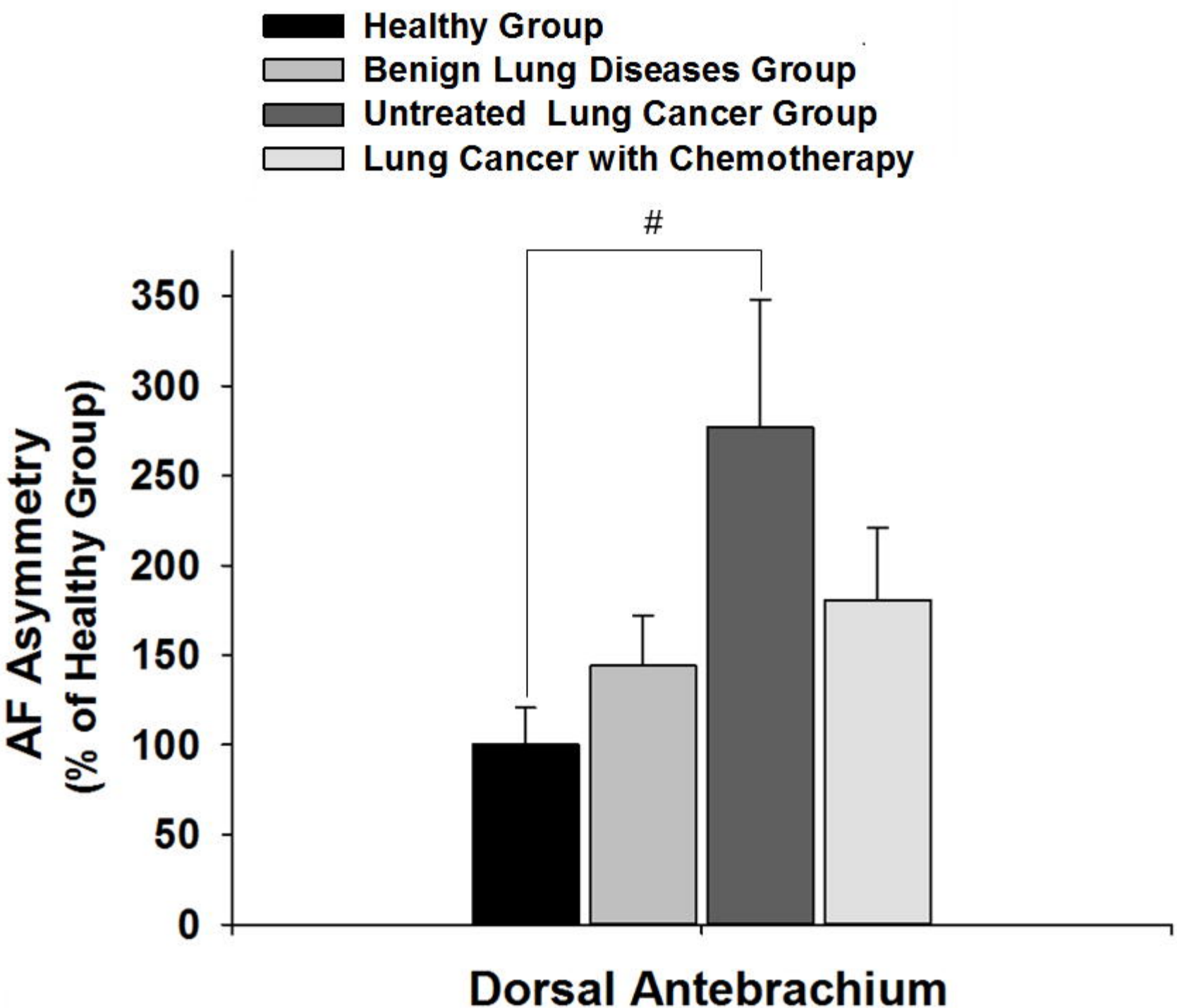
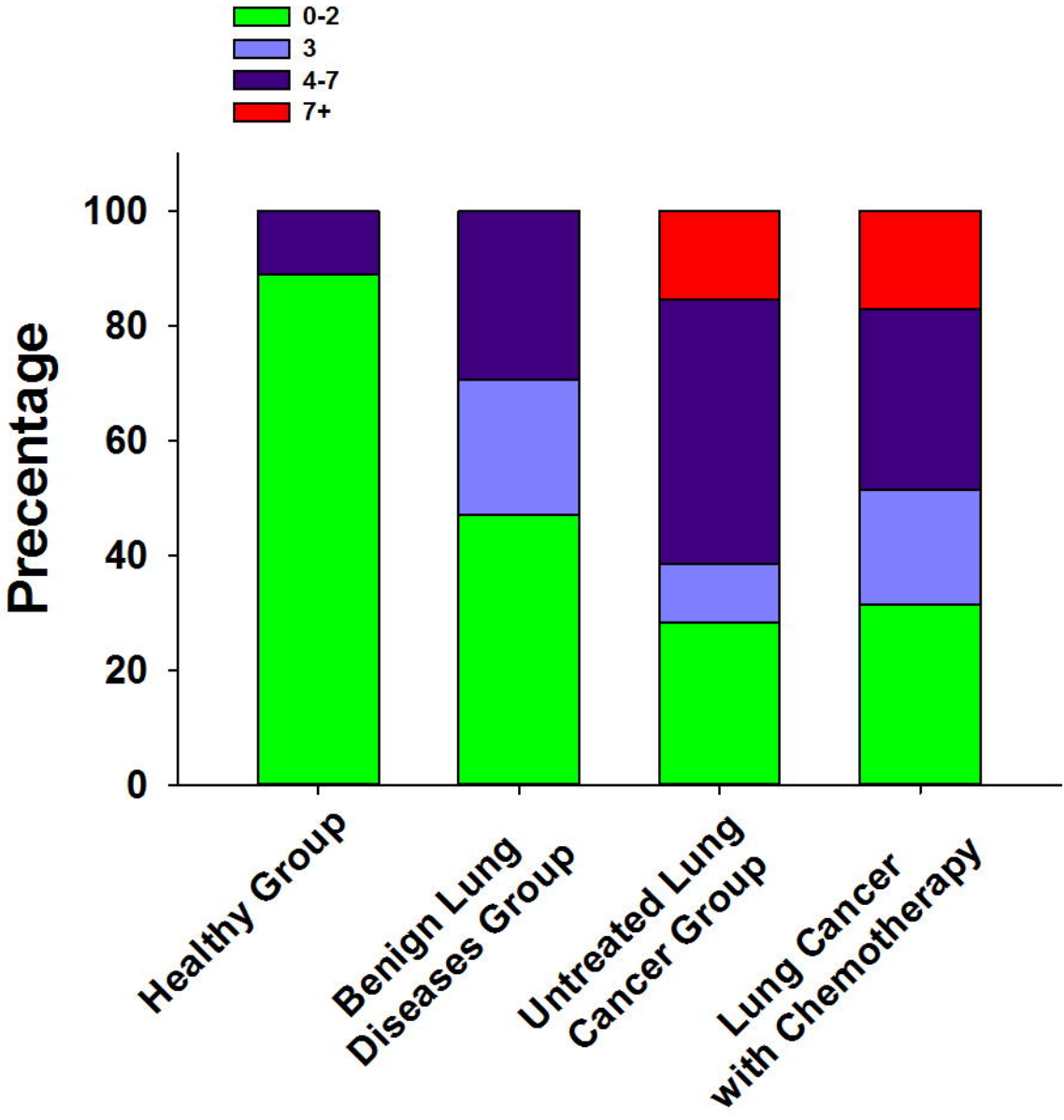
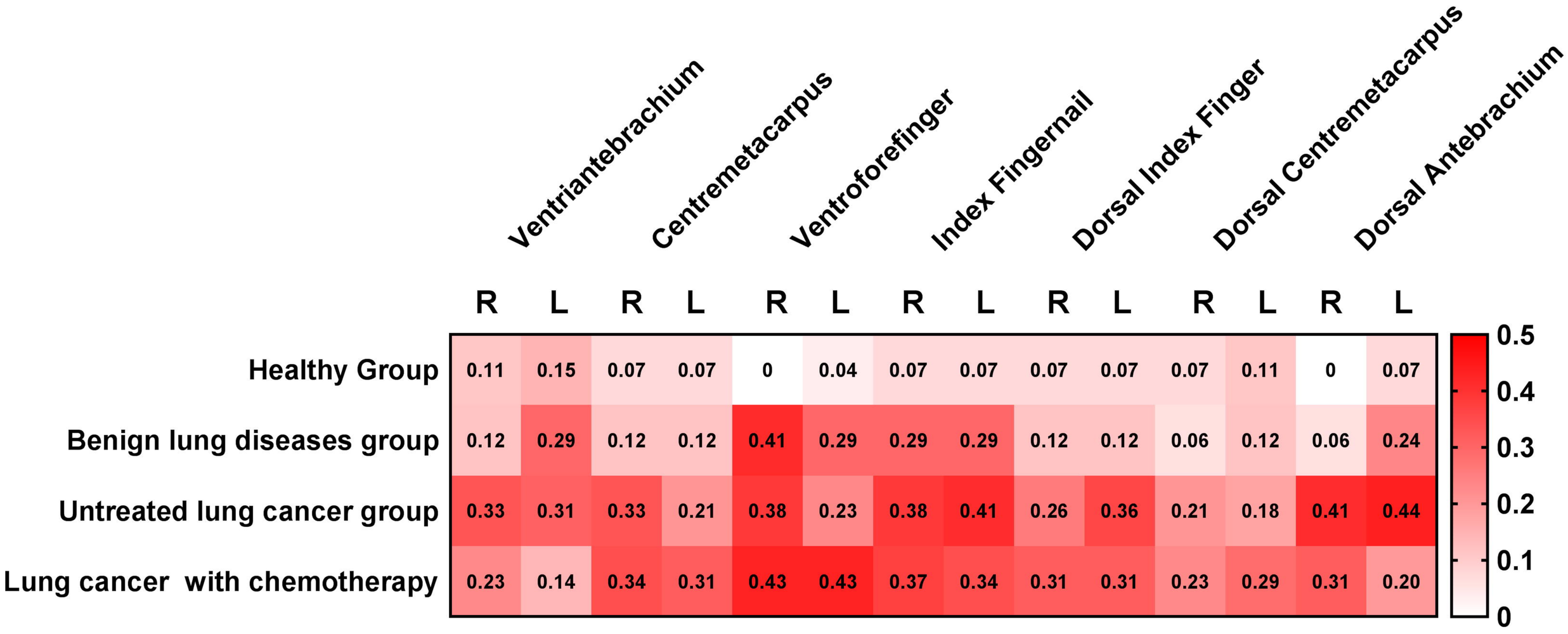
Lung Cancer with Chemotherapy
AF Asymmetry
(% of Healthy Group)
350
300
250
200
150
100
50
0
Index Fingernail

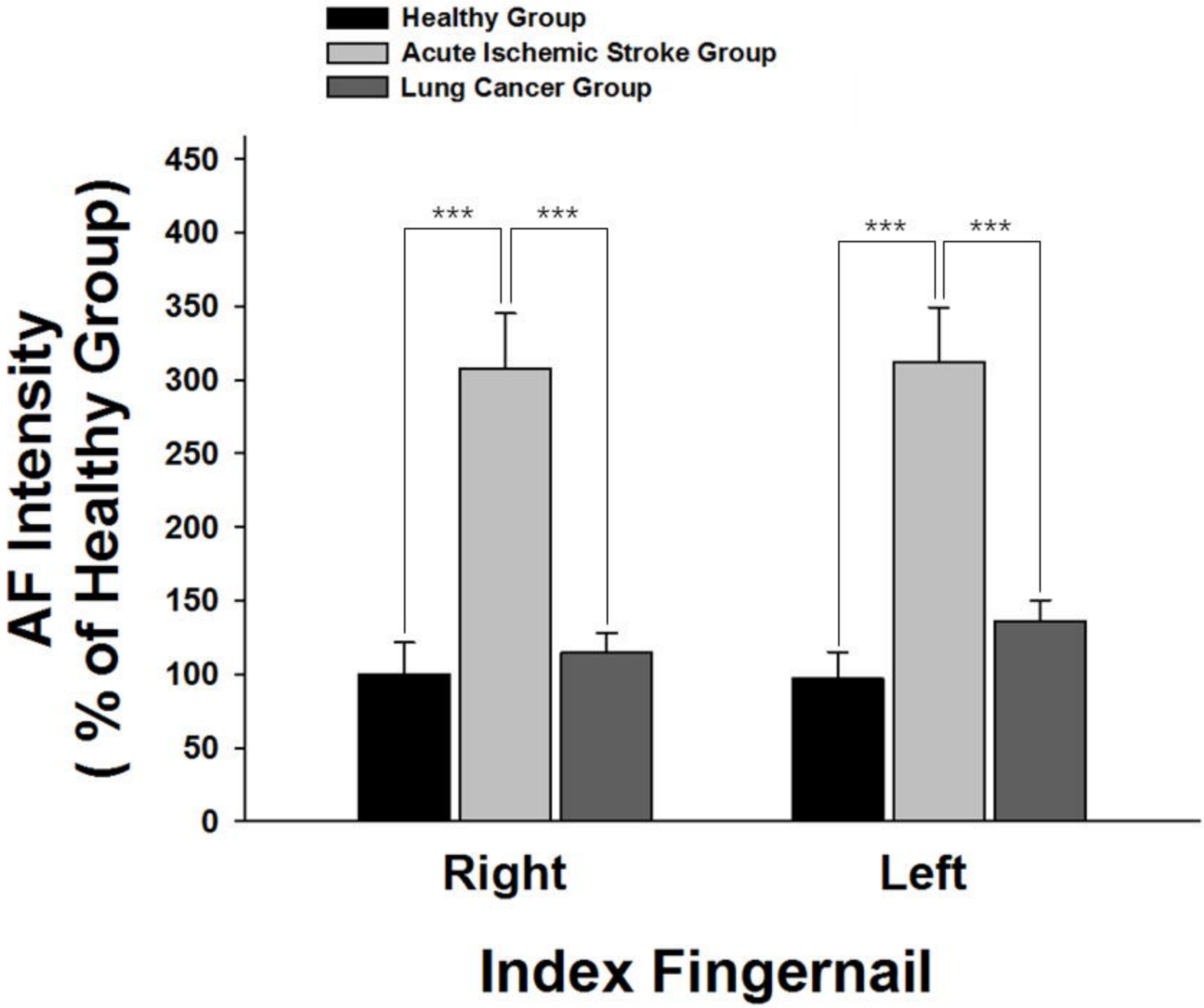

Healthy Group
Benign Lung Diseases Group
Untreated Lung Cancer Group
Lung Cancer with Chemotherapy
AF Asymmetry
(% of Healthy Group)
350
300
250
200
150
100
50
0
Dorsal Index Finger

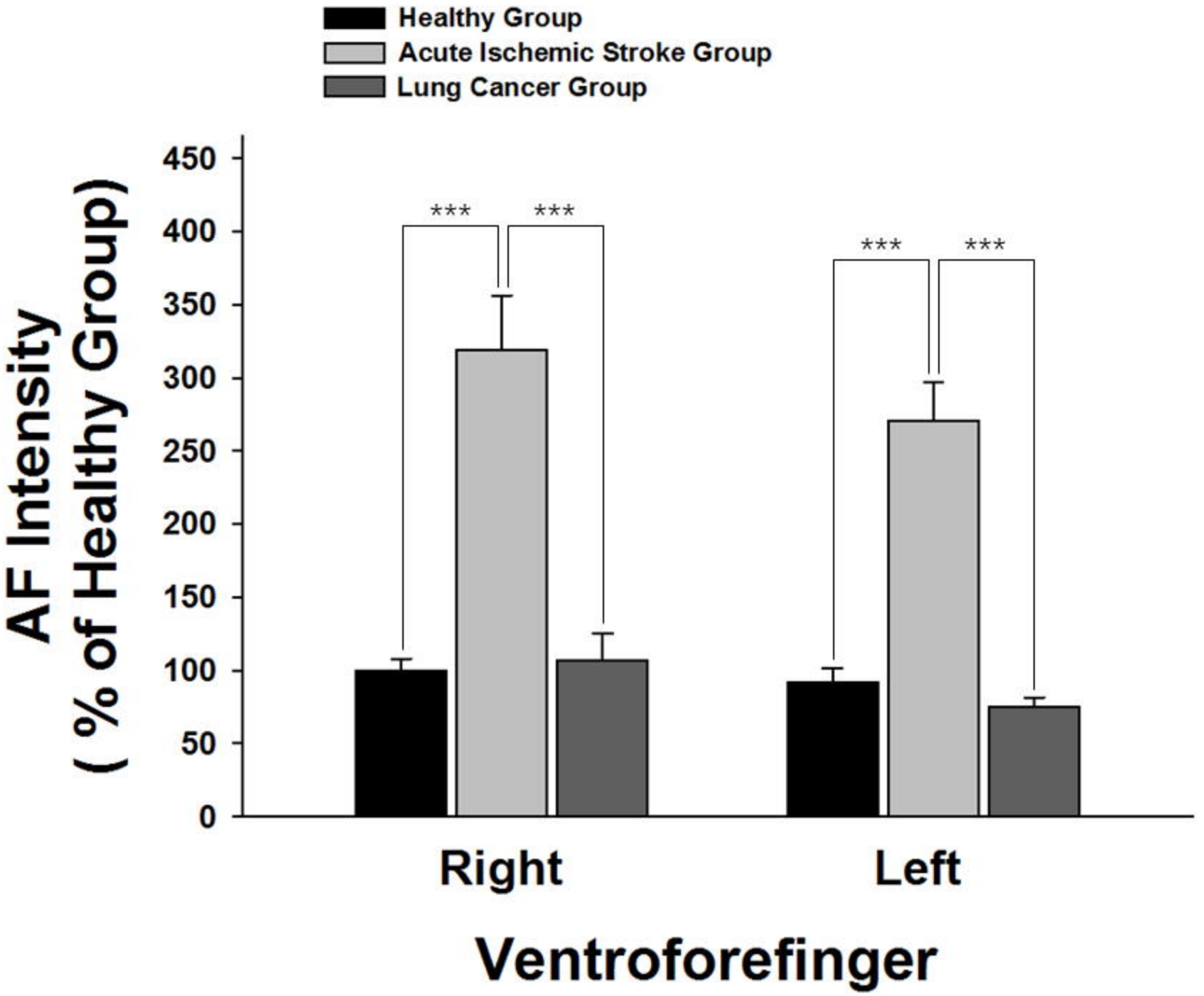

Healthy Group
Benign Lung Diseases Group
Untreated Lung Cancer Group
Lung Cancer with Chemotherapy
AF Asymmetry
(% of Healthy Group)
350
300
250
200
150
100
50
0
Dorsal Centremetacarpus

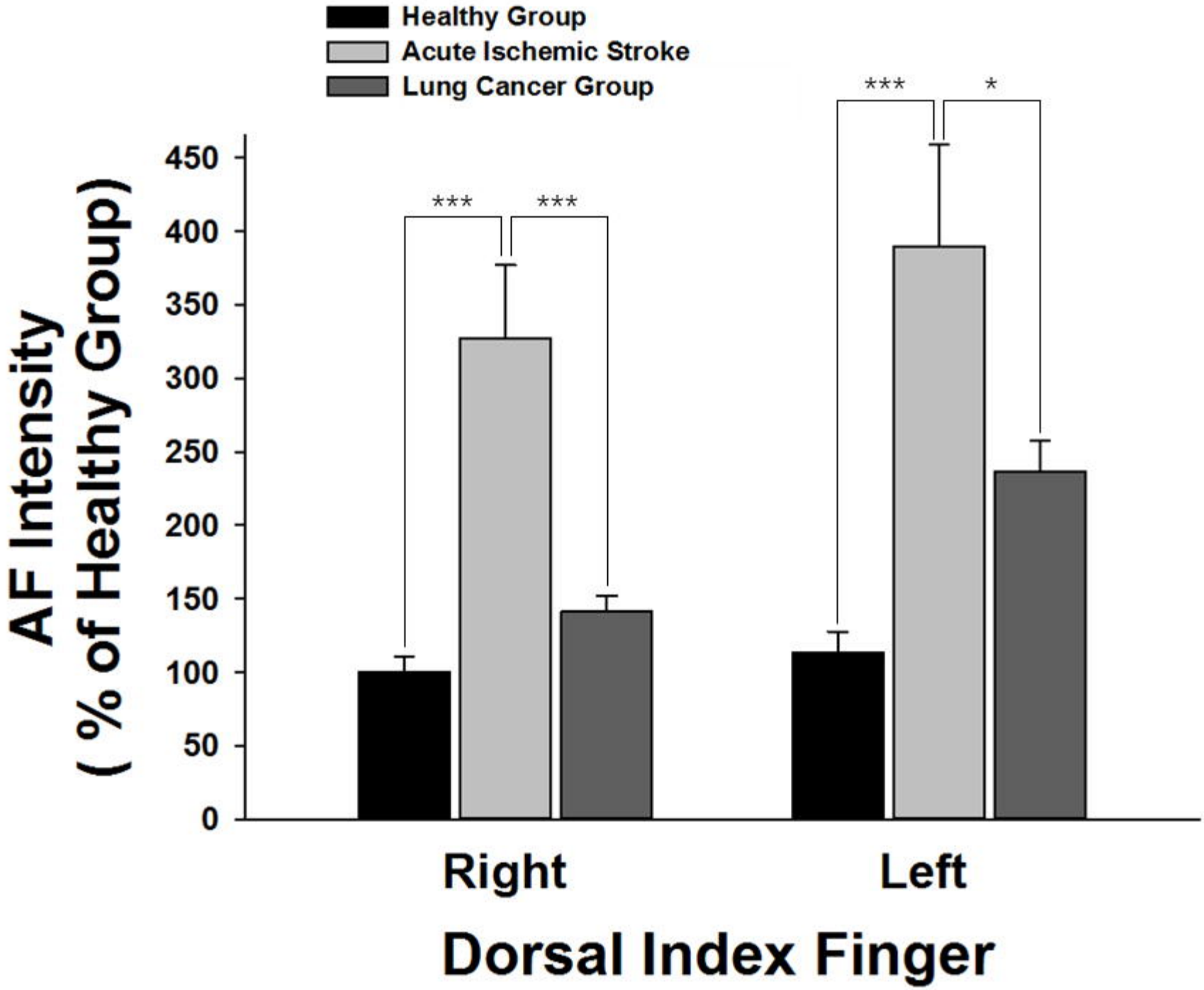

Healthy Group
Benign Lung Diseases Group
Untreated Lung Cancer Group
Lung Cancer with Chemotherapy
#
350
300
250
200
150
100
50
0
AF Asymmetry
(% of Healthy Group)
Dorsal Antebrachium

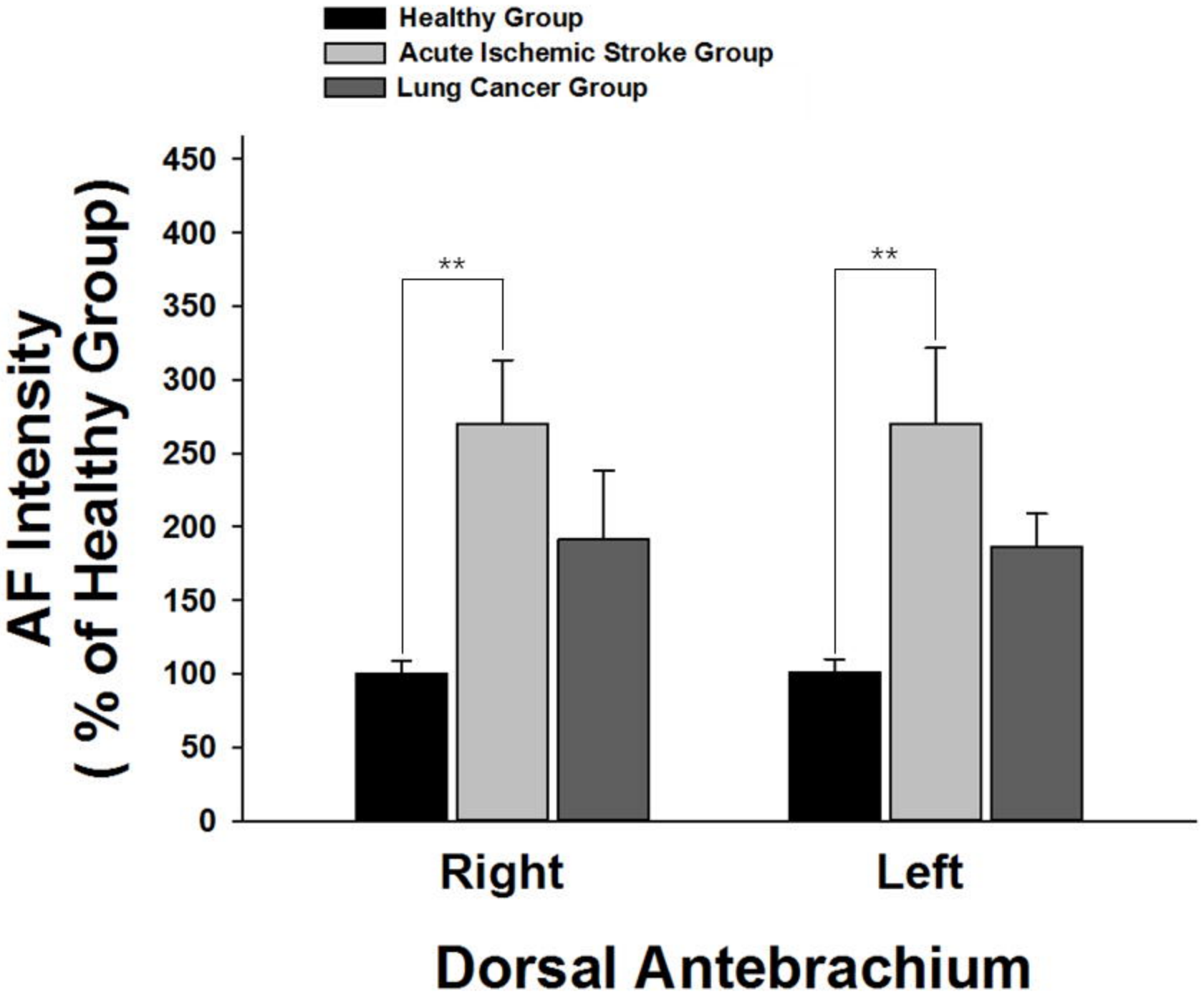

0-2
3
4-7
7+
Precentage
100
80
60
40
20
0
Healthy Group
Benign Lung Diseases Group
Untreated Lung Cancer Group
Lung Cancer with Chemotherapy

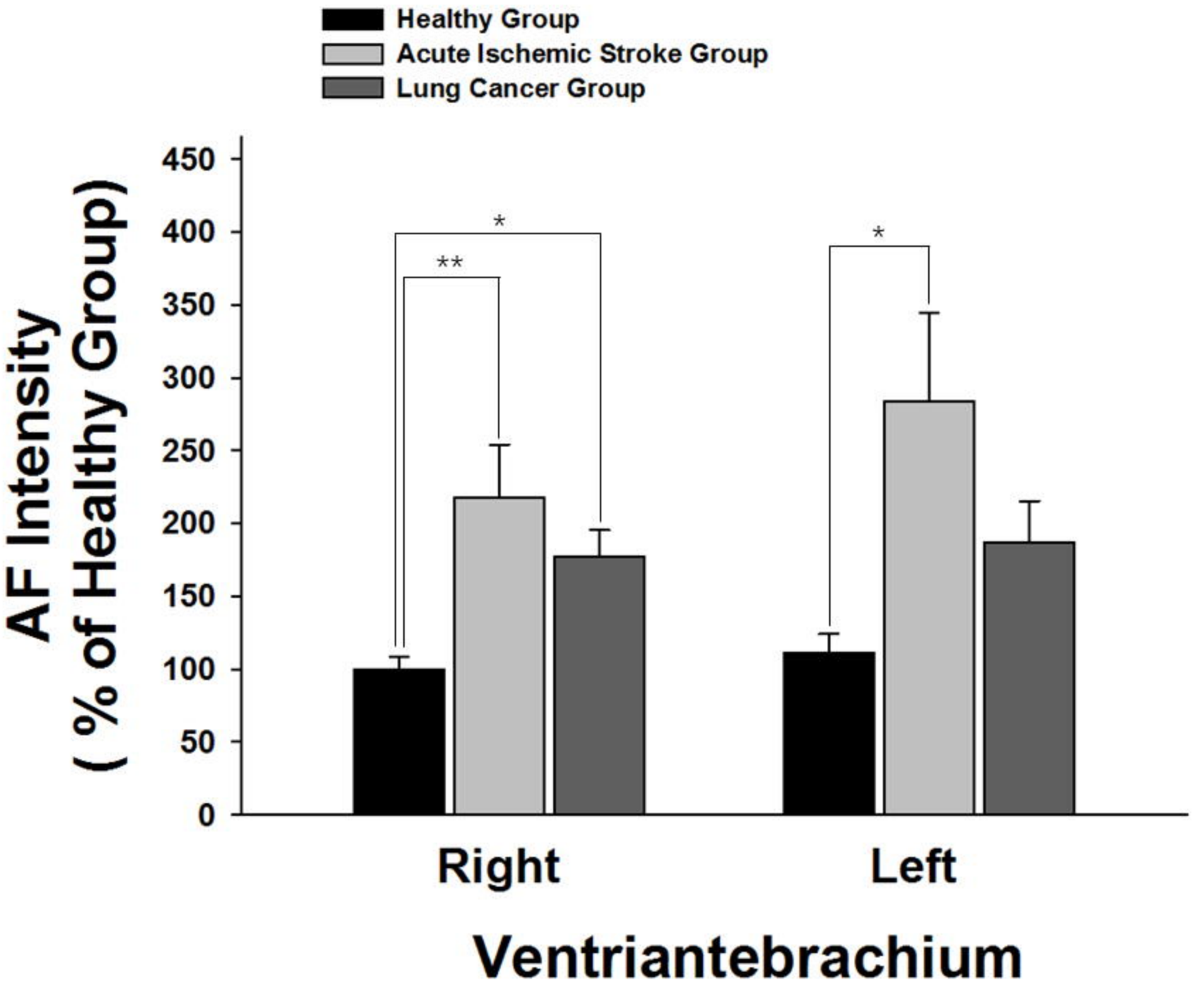

Ventriantebrachium
Centremetacarpus
Ventroforefinger
Index Fingernail
Dorsal Index Finger
Dorsal Centremetacarpus
Dorsal Antebrachium
R L R L R L R L R L R L R L
Healthy Group 0.11 0.15 0.07 0.07 0 0.04 0.07 0.07 0.07 0.07 0.07 0.11 0 0.07
Benign lung diseases group 0.12 0.29 0.12 0.12 0.41 0.29 0.29 0.29 0.12 0.12 0.06 0.12 0.06 0.24
Untreated lung cancer group 0.33 0.31 0.33 0.21 0.38 0.23 0.38 0.41 0.26 0.36 0.21 0.18 0.41 0.44
Lung cancer with chemotherapy 0.23 0.14 0.34 0.31 0.43 0.43 0.37 0.34 0.31 0.31 0.23 0.29 0.31 0.20
0.5
0.4
0.3
0.2
0.1
0


Healthy Group
Acute Ischemic Stroke Group
Lung Cancer Group
AF Intensity
(% of Healthy Group)
450
400
350
300
250
200
150
100
50
0
***
***
***
***
Right
Left
Index Fingernail


Healthy Group
Acute Ischemic Stroke Group
Lung Cancer Group
AF Intensity
(% of Healthy Group)
450
400
350
300
250
200
150
100
50
0
***
***
***
***
Right
Left
Ventroforefinger


Healthy Group
Acute Ischemic Stroke
Lung Cancer Group
AF Intensity
(% of Healthy Group)
450
400
350
300
250
200
150
100
50
0
***
***
***
*
Right
Left
Dorsal Index Finger


Healthy Group
Acute Ischemic Stroke Group
Lung Cancer Group
AF Intensity
(% of Healthy Group)
450
400
350
300
250
200
150
100
50
0
**
**
Right
Left
Dorsal Antebrachium


Healthy Group
Acute Ischemic Stroke Group
Lung Cancer Group
AF Intensity
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0
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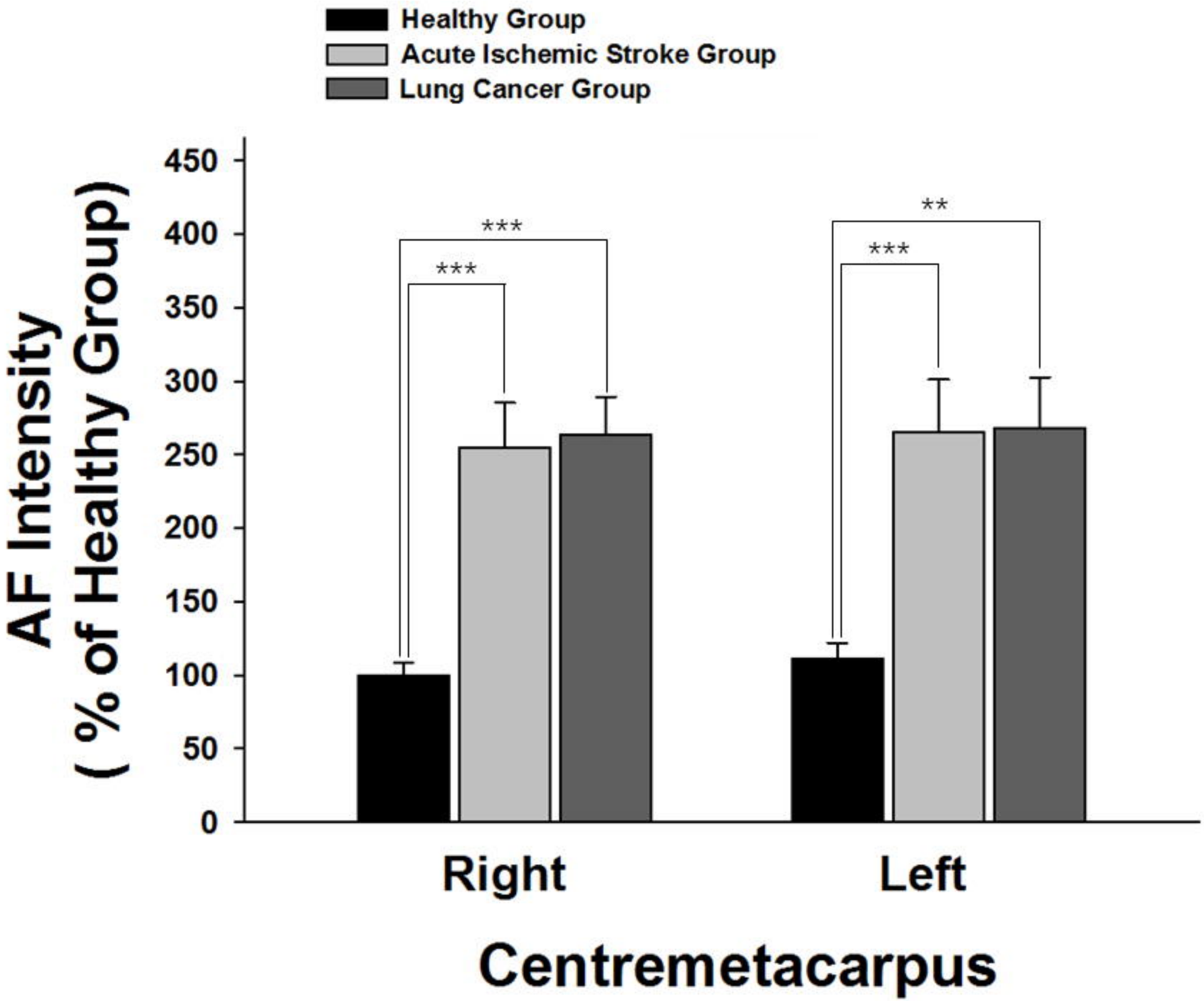
*
Right
Left
Ventriantebrachium


Healthy Group
Acute Ischemic Stroke Group
Lung Cancer Group
AF Intensity
(% of Healthy Group)
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150
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50
0
***
***
**
***
Right
Left
Centremetacarpus