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# High levels of sphingolipids in human breast cancer

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ABSTRACT

*Background:* Sphingolipids, including sphingosine-1-phosphate (S1P) and ceramide, have emerged as key regulatory molecules that control various aspects of cell growth and proliferation in cancer. Although important roles of sphingolipids in breast cancer progression have been reported in experimental models, their roles in human patients have yet to be determined. The aims of this study were to determine the levels of sphingolipids including S1P, ceramides, and other sphingolipids, in breast cancer and normal breast tissue and to compare the difference in levels of each sphingolipid between the two tissues.

*Materials and methods:* Tumor and noncancerous breast tissue were obtained from 12 patients with breast cancer. Sphingolipids including S1P, ceramides, and their metabolites of sphingosine, sphingomyelin, and monohexosylceramide were measured by liquid chromatography–electrospray ionization–tandem mass spectrometry.

*Results:* The levels of S1P, ceramides, and other sphingolipids in the tumor were significantly higher than those in normal breast tissue. There was a relatively strong correlation in the levels of S1P between the tumor and those of normal breast tissue from the same person. On the other hand, there was no correlation in the levels of most of the ceramide species between the tumor and those of normal breast tissue from the same person.

*Conclusions:* To our knowledge, this is the first study to reveal that levels of sphingolipids in cancer tissue are generally higher than those of normal breast tissue in patients with breast cancer. The correlation of S1P levels in these tissues implicates the role of S1P in interaction between cancer and the tumor microenvironment.



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## Introduction

Recent advances in molecular biology have provided new treatment strategies for breast cancer patients with molecular-based targeted therapies. These have the capacity to regulate critical molecular mechanisms of breast cancer growth such as cell cycle, cell survival, DNA double-strand breaks repair, or tumor immunology.[1-4] Despite these advances in breast cancer therapy, approximately 40,000 women still die from breast cancer every year in the United States, and breast cancer remains the leading cause of cancer-related death for women aged 20 to 59 years in the world.[5] Deepening our understanding of the biology of breast cancer progression is key to developing better treatment strategies and achieving long-lasting therapeutic efficacies against breast cancer.[6]

There has been increasing evidence that lipid mediators play pivotal roles in cancer biology and the disease process.[7-9] Cancer progression requires the capacity for cell growth, invasion, angiogenesis, and metastasis.[10-12] Bioactive sphingolipids, such as sphingosine-1-phosphate (S1P) and ceramides, have been emerging as important signaling molecules that regulate these critical processes.[7-9] Despite the importance of these lipid mediators in cancer biology, it often had been "overlooked", because proteins, but not lipids, have been considered the primary signaling molecules involved in cancer progression. Moreover, unlike protein, it had been difficult to measure the absolute amount of sphingolipids in tissue samples owing to a lack of technology until recently. Because of these reasons, the importance of lipid mediators on cancer biology in human has not been fully evaluated.

S1P is generated from sphingosine (Sph) by sphingosine kinases inside the cell and transported to the extracellular space by dedicated proteins in the cell membrane.[13,14] Once outside, it exerts many biological functions by stimulating its specific G protein–coupled receptors (S1PR1-5).[15] S1P is involved in numerous cellular functions such as cell proliferation, migration, survival, immune cell trafficking, angiogenesis, and lymphangiogenesis, all of which are related to cancer progression and metastasis.[16-19]

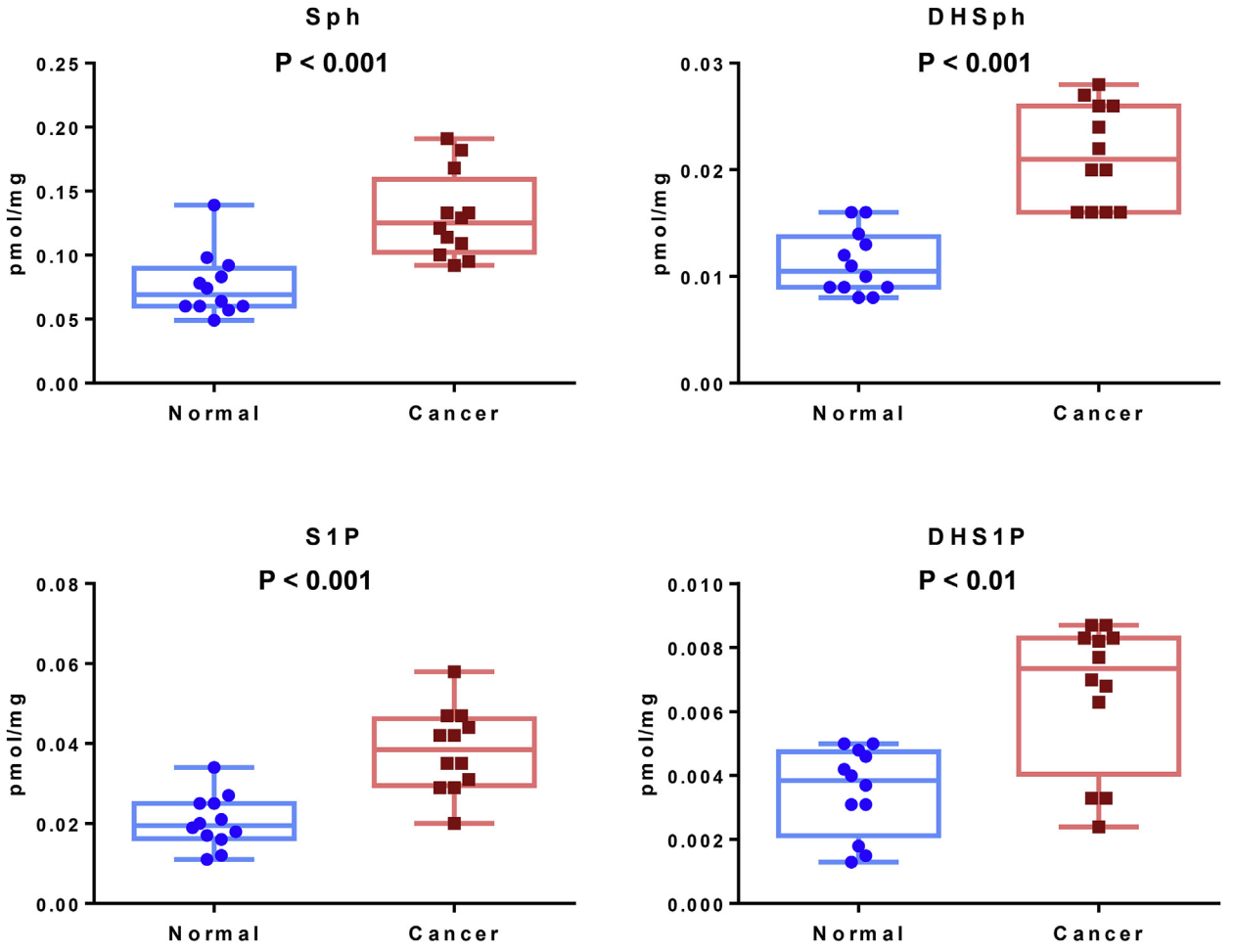


**Fig. 1 – Levels of S1P and other sphingolipids in breast cancer and normal breast tissue. The levels of the sphingolipids including sphingosine (Sph), dihydro-Sph (DHSph), S1P, DHS1P were determined by liquid chromatography–electrospray ionization–tandem mass spectrometry. Mean values are shown by horizontal lines. (Color version of figure is available online.)**