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PhiΦBreast & theory of spiral cancer new diagnostic techniques for breast cancer detection

Ersilio Trapanese^{1,2*} and Giulio Tarro³

Abstract

Background: Today, breast cancer is one of the most aggressive cancers in women and new cases continue to increase worldwide. The incidence of this tumor is kept under control especially with surgery. In order to reduce mortality we need to detect this life threatening disease at an earlier stage.

For two years, we have conducted a study for the identification and characterization of suspicious breast lesions using a new diagnostic technique applied to ultrasonography and mammography called “PhiΦBreast.”

Methods: Identification and characterization of category C4-C5 lesions of the breast with high Predictive Positive PPV value, with a new innovative method called “PhiΦBreast” using the Golden Ratio (Phi, or Φ 1.618...) Fibonacci sequence and a Predictive Algorithm, applied to the ultrasonography and mammography with subsequent deepening with cytological examination using fine needle aspiration (FNAC), according to evaluation criteria of the Breast Imaging Report Data System (BI-RADS) and the American College of Radiology (ACR).

Usefulness of this research and the use of this new diagnostic technique is to detect the breast cancer in early stage. In addition to develop a classification model of the histological type identified in the section areas and the percentage of probability in relation between the golden spiral and Fibonacci sequence.

This amazing intuition and research has given contribution to the new Theory of Spiral Cancer.

Results: With the use of Golden Ratio and Fibonacci sequence, applied to ultrasonography and mammography, we have experimented and developed a diagnostic map with characteristics of high probability of identifying suspicious lesions at an early stage.

We examined 987 women, 55 lesions detected with PhiΦBreast pattern were classified according to BI-RADS descriptors for US-imaging, including morphologic features that had a high predictive value for the malignancy ($p < 0.001$).

This innovative diagnostic technique has shown a sensitivity of 95%, a specificity of 97%, a positive predictive value of 97%, and negative predictive value of 96%.

The discriminating capacity of PhiΦBreast was significantly better than normal ultrasonography ($P < 0,05$).

Furthermore with a predictive algorithm associated with malignant cytology after FNAC, we have classified different types of potentially life threatening cancers for patients.

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Conclusion: PhiΦBreast could be an important new model diagnostic technique to be applied ultrasound and mammography for detection of malignant lesions of category C4-C5.

In diagnostic imaging beyond the identification of a lesion and classification according to the BI-RADS category and the evaluation criteria of the ACR is fundamental to recognize predictively the characteristics of a potentially aggressive tumor.

Everything mentioned above, reinforces the concept that the early diagnosis is essential because it allows to remove small tumors and therefore capable of producing more limited metastases than the potential of the most voluminous neoplasm.

This way, we could plan an effective cure for the patient.

This new model (PhiΦBreast) could represent the cornerstone as an important contribution for early diagnosis of breast cancer.

Keywords: PhiΦBreast, Theory of Spiral Cancer, Predictive Algorithm, Golden Ratio, Fibonacci Sequence, Gravity, Phyllotaxis, Breast Cancer

Background

Breast cancer is the most commonly diagnosed cancer among US women. With an estimated 268,600 newly diagnosed women with invasive disease, 48,100 cases of ductal carcinoma in situ (DCIS) in 2019, accounting for approximately 15.2-30% of all new cancer cases among women, with the mortality rate of 16%.

The highest incidence is recorded in North America with 90 cases per 100,000 women [1, 2].

In Europe, every year more than 200,000 women are affected by breast cancer every year, with an incidence ranging from 5 to 10% depending on the country. In Italy the incidence is medium-high. The cases of breast cancer diagnosis are around 31,000 a year, with an increasing incidence from southern to the northern Italy [3].

In the last 6 years the incidence of breast cancer has reached 13.8%. There are several risk factors that contribute to the development of breast cancer. Most relevant non-changeable risk factors are: gender, age, genetic predisposition, mutations in the BRCA1, BRCA2 genes [4] (which carry a 60-90% risk of developing a breast cancer over the course of life), Li Fraumeni syndrome [5], mutation of the gene that codes for p53 [6], Lynch syndrome [7]. Ethnic group [8], atypical mammary hyperplasia, high breast density. Environmental factors: exposure to ionizing radiation in childhood and / or juvenile age (for example in women with previous Hodgking lymphoma). Hormonal therapies: HRT [9] estroprogestinic, which involve a minimum increased risk. The purpose of this study is to identify a mammary neoplasm in early time using this new diagnostic technique, also to develop a classification model of the histological type identified in the various areas of the Golden Ratio and the percentage of probability in relation to the Fibonacci sequence.

In our research, nodular lesions of the breast category C4-C5 with high positive predictive value (PPV), were

identified and characterized with a new method called PhiΦBreast using the Golden Ratio, Fibonacci sequence and a Predictive Algorithm, applied to ultrasonography and mammography with subsequent study with cytological examination using fine needle aspiration cytology (FNAC) in respecting the criteria of the American College of Radiology (ACR) and Breast Imaging Report Data System (BI-RADS).

Methods

From January 2016 to february 2018, 987 consecutive patients, aged between 40 and 75 years, were enrolled for the ultrasound study of echostructure alterations in the breast.

All patients underwent to two-dimensional ultrasound examination (2 DUS) with Toshiba Aplio 500 ultrasound system, using high-frequency probes of 13 -15 MHz.

High-resolution real-time ultrasonography (US) can detect characteristics of breast nodules.

Characterization of the mammary nodules was performed according to the following criteria: shape, echostructure, level of echogenicity, margins, size and topographical area.

Using the method of PhiΦBreast ultrasonographic study, on 55/987 patients were identified solid lesions markedly hypoechoic echostructure, round shape, with irregular and infiltrative margins and cuneiform shape with blurred margins (Fig. 1).

After having their consent, 55 selected patients underwent a mammography examination with subsequent diagnostic deepening Fine Needle Aspiration Cytology (FNAC) procedure under ultrasonography guidance.

PhiΦBreast imaging applied to the mammography in the craniocaudal (CC) view and mediolateral oblique (MLO) view has given rise to a mapping of neoplastic nonpalpable breast lesions (Figs. 2 and 3).

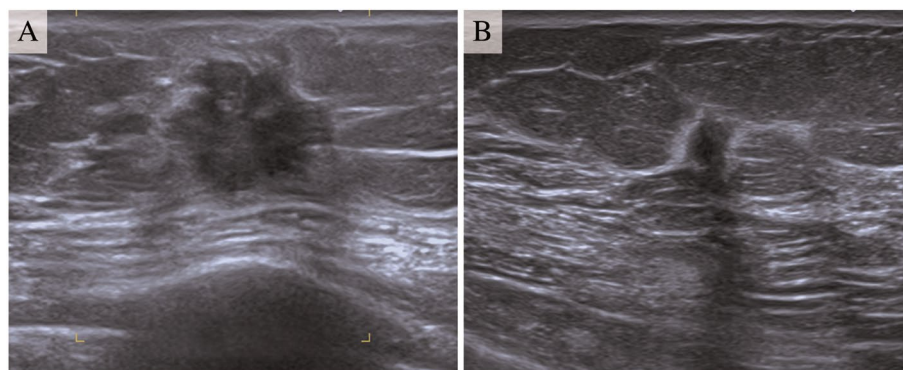


Fig. 1 Ultrasonography Image Of Suspicious Nodular Lesions Identified With PhiΦBreast Model. Solid lesion, round shape, markedly hypoechoic echostructure with irregular and infiltrative margins (A). Solid lesion, cuneiform shape, markedly hypoechoic echostructure with blurred margins (B)

PhiΦBreast produced important data for the elaboration of a Predictive Algorithm on the probability of development of various histological types of tumors and the percentage detectable in the areas of the Golden Ratio and the Fibonacci numbers, when applied in the breast (13,21,34,55,89,144) using the following nomenclature “Fibonacci-number Side” (FS1,FS2,FS3,FS4,FS5,FS6) (Table 1).

The results of cytology identified 55 tumors: 13 ductal carcinomas in situ, 10 invasive ductal carcinomas, 6 invasive lobular tumors and 26 invasive carcinomas not otherwise specified.

It has been hypothesized to develop a theory of spiral cancer cell growth, called “The Theory of Spiral Cancer.”

The surgery was established based on the type of tumor identified in patients in the preoperative phase.

The histological diagnosis confirmed the tumor nature of the cells of the analyzed tissues, performed according to the criteria established by the American College of Radiology (ACR) and Reporting Breast Imaging and Data System (BI-RADS).

Patients underwent blood chemistry controls and tumor markers. The follow up period lasted about 1 year.

Results

Theory of spiral cancer

The Golden Ratio (Phi, or Φ 1.618...) is a potentially unifying quantity of structure and function in nature, as best observed in phyllotactic patterns in plants. For centuries, Phi (Φ) has been identified in human anatomy, and in recent decades, Φ has been proved in human physiology as well with scientific studies of some authors [10, 11].

According to the intuition and in-depth studies on the Golden Ratio [12], Fibonacci Sequence [13] and Phyllotaxis [14], research from a discipline between botany and mathematics that breast cancer could have a model of

growth and evolution that combines observation and the hypothesis according to in-depth scientific studies that we have carried out.

We believe that the breast cancer growth model could have a connection with the phyllotaxis and Fibonacci sequence, under influence of the gravity (g) [15].

The spirals rise from a growth property called self-similarity or scaling, that is the tendency to grow in size but preserving the same shape. However, not all organisms grow this way.

According to the theory of the spiral growth model of cancer, it is possible that the ab-initio lesion may mimic the spiral model: the central nucleus is modified by generating dendritic striae and evolves to form spicules in an effective and anarchic way to collect a maximum quantity blood supply from the capillaries of neo-angiogenesis, necessary for growth.

Angiogenesis, the formation of new blood vessels, is a fundamental process required for the growth of primary tumors [16].

We have no definite answer, but we can cite some of the scientists.

In 1875 a botanist mathematician by the name of Julius von Wiesner [17] provided a mathematical proof that the helical arrangement of the leaves of a branch in Fibonacci proportions was an effective way to collect a maximum amount of sunlight with a few leaves, he claimed that it was the better way.

After Wiesner's pioneering work, in 1907 a famous Dutch botanist Gerrit van Iterson [18], tried to mathematically model the phyllotaxis with the so-called van Iterson model.

Let's describe our hypothetical model following the van Iterson scheme of simple reticulum: there are infinite propellers that connect successive points in serial order, the shortest of these is so-called Generating Helix

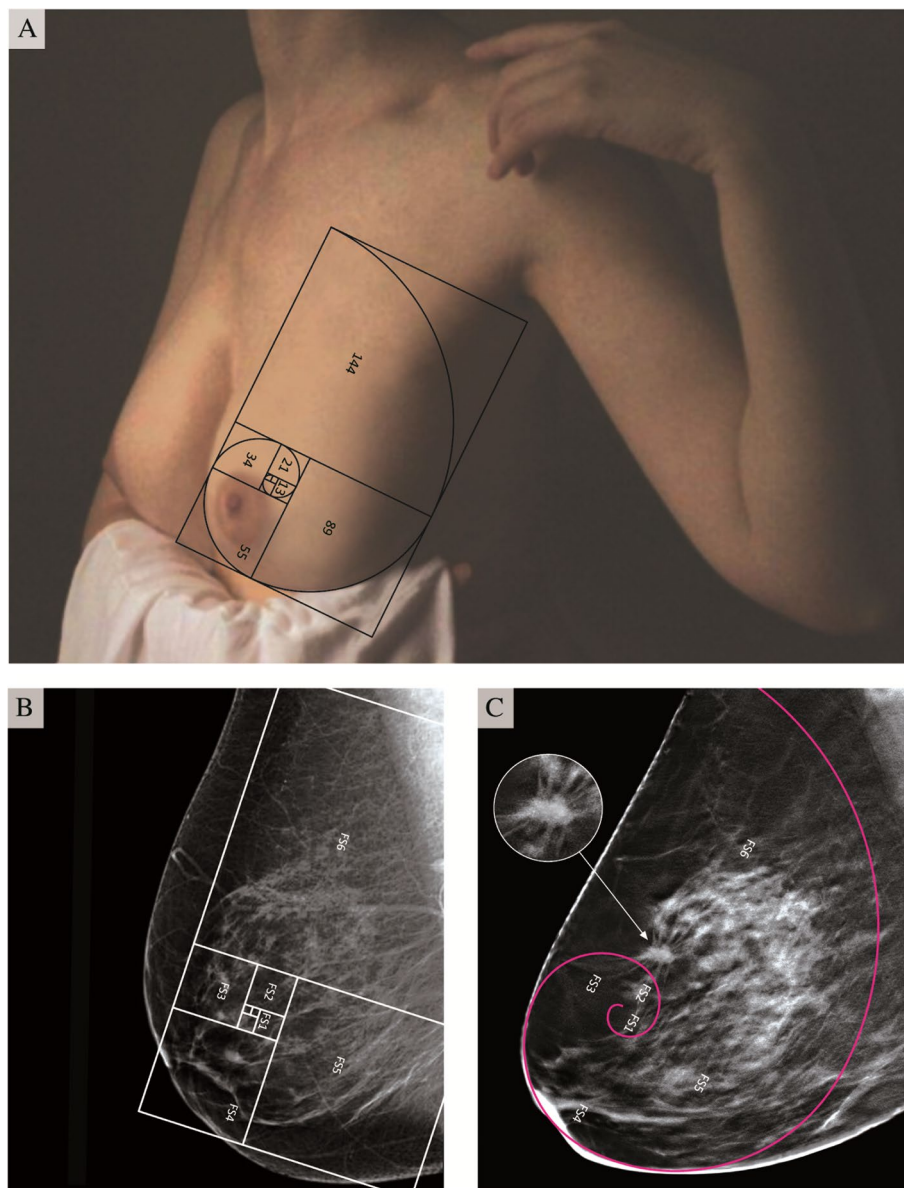


Fig. 2 PhiPhiBreast A New Diagnostic Technique For Breast Cancer Detection. **A** show the fascinating symmetry of the breast that ultimately can be represented by Golden Spiral inscribed in the regular breast anatomy. **B** show mediolateral oblique view (MLO) of the breast at mammographic X-ray with applied Golden Ratio and Fibonacci numbers of healthy individual. No nodules were detected along the Golden Ratio. **C** PhiPhiBreast imaging applied to the mammogram has provided a mapping of neoplastic lesion. White arrow highlights cancerous tumor detected in F56 side of the Golden Spiral. Cancerous mass appear as a bright and irregular image with spiky edges

highlighted in part (a) (Fig. 4), where the flat reticulum is shown on the universal coating obtained by “unrolling the cylinder”, while in part (b) the reticulum is generated from three distinct helices.

This helix is characterized by two parameters, described by botanicals: the angle α called “the angle of divergence” and their vertical distance y , called “inter-nodal distance”.

The tract of generating helix, will wrap around the cylinder a number of times, with the so-called (encyclic number) $\Delta m(x)$, thus established by van Iterson, defining the secondary divergence: $\delta m(x)$.

As observed by van Iterson’s analysis, this model can provide valuable insights on modeling on biological organisms and in this case on the hypothesis of development of breast cancer.

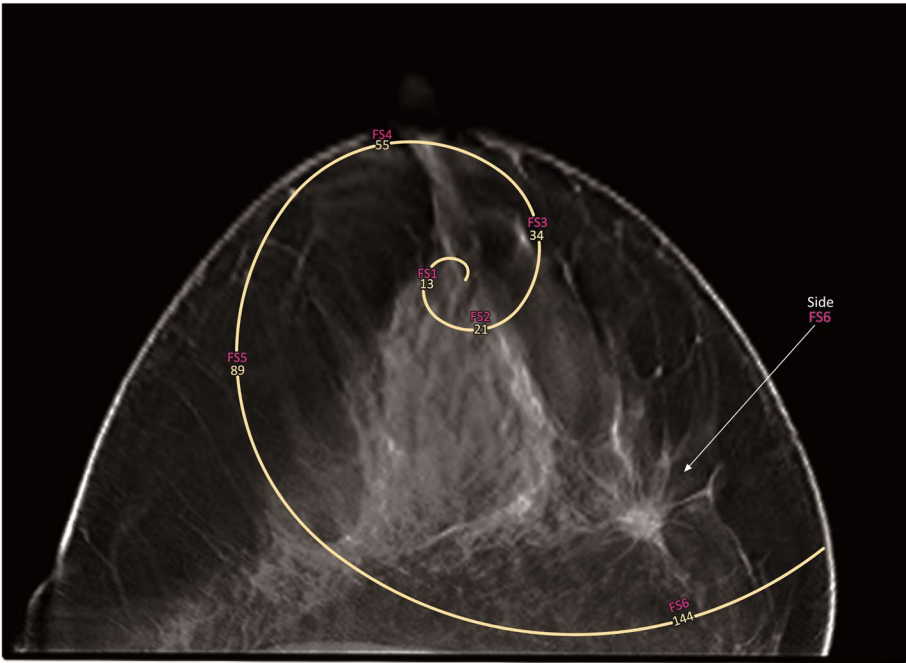


Fig. 3 Golden Ratio (Φ) Breast Cancer Detection And Fibonacci Sequence. Cranial-caudal view (CC) show Fibonacci Spiral approximates the Golden Ratio (Φ) using mammogram inscribed in squares of integer Fibonacci number side, shown for square size (13,21,34,55,89,144) making use the following nomenclature “Fibonacci-number Side” (FS1,FS2,FS3,FS4,FS5,FS6). The arrow show extraordinary X-ray vision of the cancer accurately detected in FS6 side

Table 1 Predictive algorithm breast cancer

Histological types and percentage tumors detected in the Golden Ratio (Φ) and Fibonacci sequence		
Φ Section Area 13	*FS1 Ductal Carcinomas in Situ	[3%]
Φ Section Area 21	*FS2 Ductal Carcinomas in Situ	[7%]
Φ Section Area 34	*FS3 Invasive Ductal Carcinomas	[13%]
Φ Section Area 55	*FS4 Invasive Ductal Carcinomas	[8%]
Φ Section Area 89	*FS5 Invasive Lobular Tumors	[14%]
Φ Section Area 144	*FS6 Invasive Carcinomas not Other-wise Specified	[55%]
Φ Golden Ratio	*Fibonacci-number Side	

Φ Golden Ratio And The Nomenclature

*Fibonacci-number Side

Percentage of tumors detected in the Fibonacci-number Side: FS1-FS2 10% of ductal carcinomas in situ; FS3-FS4 21% of invasive ductal carcinomas; FS5 14% invasive lobular tumors and FS6 55% invasive carcinomas not otherwise specified

Recently, 1988 a botanist from Cornell University, Karl Joseph Niklas [19] decided experiment this hypothesis in his laboratory.

He discovered that almost every reasonable arrangement of the leaves has the same radiation capacity as the sun.

The crux of the spiraling breast cancer growth model is based on extensive investigations into the influence of gravity on organisms, in particular into the knowledge of the relations between gravity and directional relationships of plants.

In fact, Julius von Wiesner published in 1902 an important research, Studien über den Einfluss der Schwerkraft auf die Richtung der Pflanzenorgane [20], a study on the influence of gravity on the direction of plant organs. We have deepened our research and therefore shaped a connection with this important study.

Response to gravity is a cellular process of mechanotransduction in both plants and animals. Interestingly, although plants and animals seem to be very genetically distant, they share common mechanisms for gravity sensing, e.g., an actin cytoskeleton and mechanosensitive ion channels combined to this skeleton [21].

Recent studies have focused on the cytoskeleton as initial gravity sensor [22, 23].

Animals evolved unique systems for gravisensing as exemplified by the transcriptional coactivator YAP/TAZ, which affects the cell fate of bones, muscles and stem cells.

Cell behaviour is strongly influenced by physical, mechanical contacts between cells and their extracellular matrix.

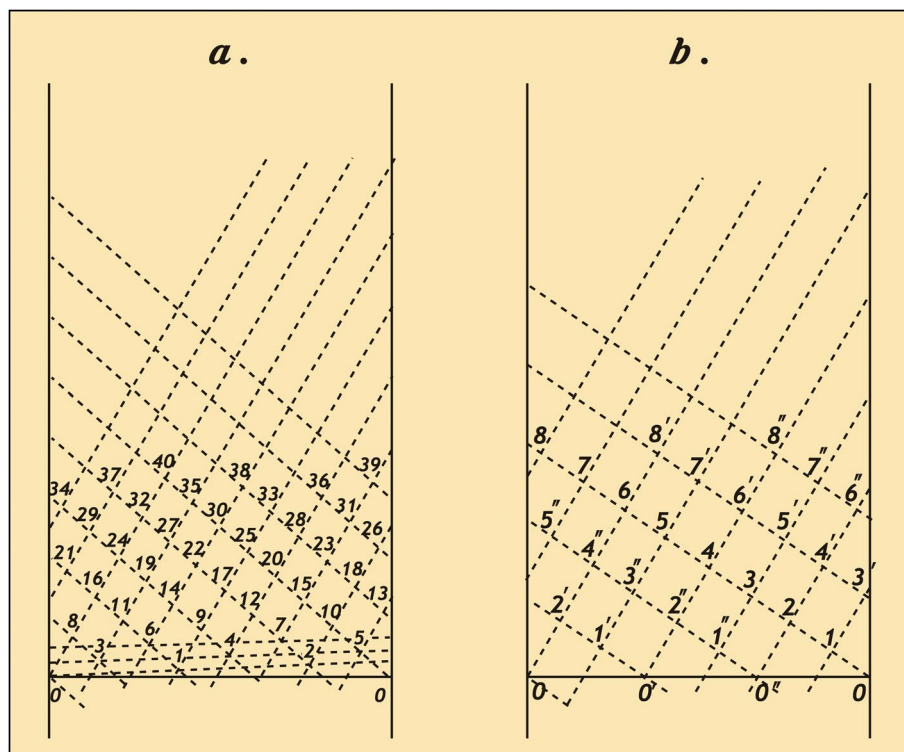


Fig. 4 The Mechanical Model Of Van Iterson

YAP/TAZ, two highly related transcriptional regulators sense how cells perceive themselves and their tissue environment and communicate with it [24].

A growing body of evidence suggests that mechanical signals emanating from the cells microenvironment are fundamental regulators of cell behaviour. Moreover, at the macroscopic scale, the influence of forces, such as the forces generated by blood flow, muscle contraction, gravity and overall tissue rigidity is central to our understanding of physiology and disease pathogenesis [25].

YAP and TAZ are highly related transcriptional regulators pervasively activated in human malignancies. Recent work indicates that, remarkably, YAP/TAZ are essential for cancer initiation or growth of most solid tumors. Their activation induces cancer stem cells attributes, proliferation, chemoresistance and metastasis. YAP/TAZ are sensors of the structural and mechanical features of the cell microenvironment [26].

We think that the force of gravity with its action can have an important role on the growth movement that produces the neoplastic spiral, through positive gravitropism and negative gravitropism [27].

Positive gravitropism allows the neoplasm to develop a complex network of blood vessels that consist very permeable arteries, veins and capillaries, developing the

“vascular system of cancer” and forming roots in deep tissues [28].

Negative gravitropism would provide the necessary input to the dynamics of growth.

The negative geotropic curvature favors the growth, which hangs towards the stronger spraying side of the new neoangiogenesis capillaries, activating in sequence many factors that regulate the proliferation and maturation of endothelial cells and vessel wall cells [29].

It is known that blood vessels change their characteristics in response to the needs of different organs. There is a “dialogue” between the cells of the perfused organ and the vascular cells that determines a high specialization of the latter that adapt to the specific functions of the organ. In cancer, things go in a similar way. Tumors not only induce the formation of new vessels, but according to our studies, they undergo the activity of a very important factor: the action of gravity (g).

The tumor vessels are altered in their structure, potentially frail and very permeable, the action of gravity could modify in an aberrant way the structure and properties, allowing cancer cells to enter the circulation and disseminate [30].

Many studies on plants state that gravity has major effects also on the reticulum of electrical activity of

plants, acting on action potentials (AP) and on the plasma membrane (PM) [31].

In 2006, a study by Stankovic [32] showed that voltage-dependent ion channels and proton pumps (electrogenic H^+ - ATPase) are involved in the generation and maintenance of these bioelectric potentials.

Hanke et al. [33] from their study found that plant's AP are sensitive to gravity in the same way they were reported for animal's AP.

We would be inclined to somehow assume this dynamic state that the gravity acts as mechanical stress on the bioelectrical and genetic processes of the cells that together with neo-angiogenesis propel this structural imbalance towards tumor growth.

In fact, every mathematical-physical model needs some assumptions about the phenomenon to be modeled.

A mathematical model is never neutral, objective: there is always a subjective component that reflects the opinions of those who put it into being. If then the predicted consequences of the mathematical-physical-botanical model agree with those that actually manifest themselves in nature, that is, if the model has a good predictive and / or descriptive capacity, somehow they confirm the hypotheses made at the outset.

Mammary gland could represent an interesting model of human fractal geometry [34] where the phyllotactic rules can be reasonably applied and where deviation from normality might give rise to dysfunctions [28].

We believe, according to theory of spiral cancer, that the neoplastic breast lesion could follow the same model of the Phyllotaxis, Golden Ratio and the Fibonacci sequence, drawing growth and expansion energy from the blood capillaries and by the imbalance of the

bioelectric activity of the cells with influenced by the gravity (g) (Fig. 5).

Using golden ratio and Fibonacci sequence, applied to ultrasonography and mammography, we have experimented a diagnostic map with characteristics of high probability of identify suspicious malignancy of C4-C5 lesions in an early stage.

We detected a different number of lesions with PhiΦBreast Imaging which were classified, according to BI-RADS descriptors for US imaging and including morphologic features as a high predictive value for the malignancy ($p < 0.001$).

The discriminating capacity of PhiΦBreast was found significantly better than normal ultrasonography ($P < 0,05$).

Furthermore with a predictive algorithm associated with malignant cytology after FNAC, we have classified different types of tumors potentially life threatening for patients.

Discussion

The story of this important research called PhiΦBreast has started in 2016.

Fascinated by botanical and mathematical laws of the phyllotaxis, golden ratio and Fibonacci sequence, we have devised a new diagnostic imaging model called PhiΦBreast applied to ultrasonography and mammography to early detection nodular lesions with echostructural features of malignancy.

The National Cancer Institute (NCI) recommends five categories for diagnosis of breast aspiration cytology [35] in order to bring a degree of uniformity to the diagnostic repoting. These categories are unsatisfactory (C1),

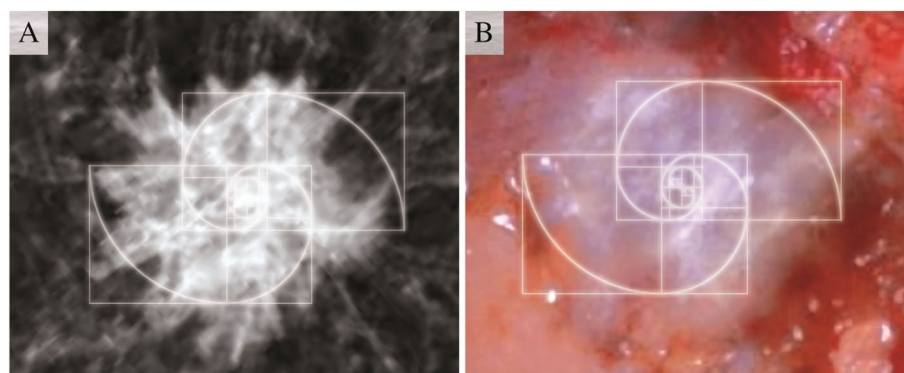


Fig. 5 Mammography Breast Cancer By PhiΦBreast Pattern & Spiral Tumor Growth Imitating The Golden Ratio Model (Φ). Mammographic X-ray seen on a closeup view large spiculated carcinoma projected over a background primarily of soft tissue parenchyma as spiral growth pattern of breast cancer in perfect configuration with the Golden Ratio (Φ) and Fibonacci Spiral (**A**). Fresh tissue specimen of the resected breast area and the tumor within. Extraordinary image showing the tumor growth imitating the Golden Ratio model (Φ) with a different fractal geometry, generating an abnormal spiral infiltrating healthy breast tissue due to the neoangiogenesis, imbalance of the bioelectric activity of the cells and the action of gravity (g) (**B**)

benign lesion (C2), atypical, probably benign (C3), suspicious, probably malignant (C4), and malignant (C5).

However, some authors believe that C3 and C4 should be categorized in the same category [36, 37].

The analyzed cytological samples were classified according to NBSBSP into the following categories: C4-C5 [38].

A modern predictive algorithm and a theoretical model of spiral cancer growth has been elaborated.

We have used a Toshiba Aplio 500 ultrasound system with high frequency probes was used, 10-15 MHz for the study of echostructural changes in the breast.

After considerable study on 987 patients, 55 nodular lesions were identified using the PhiΦBreast ultrasonography method for topographic mapping and taking into consideration the following ultrasound features: shape, echostructure, level of echogenicity, margins, size and topographical area.

Lesions detected showed two forms with an markedly hypoechoic echostructure: round shape with irregular and infiltrative margins and cuneiform shape with blurred margins. All features with high predictive value for malignancy ($p < 0.001$).

This diagnostic technique called PhiΦBreast in ultrasonography and mammography, respecting the criteria of the American College of Radiology (ACR) [39] & Breast Imaging Report Data System (BI-RADS) [40] proved to be reliable. Having compared our research with important magnetic resonance imaging (MRI) studies performed by various researchers [50–54], the early identification of malignant lesions was confirmed, with a high positive predictive value (PPV) with a sensitivity (95%) specificity (97%) value positive predictive (97%) negative predictive value (96%).

We selected 55 patients, which were subjected to a diagnostic deepening with mammography exam and used as a reading interpretation to mammogram the PhiΦBreast imaging method and subsequent FNAC [41] under ultrasound guidance with a 19 gauge needle by execution of three passages through the nodular lesion.

Suspicious lesions detected from topographic mapping were classified category C4-C5 (NCI guidelines) [42].

The surgical procedure was decided after preoperative phase based on the result of the BI-RADS cytological classification and contrast medium MRI of the breast and axillary lymph nodes (LMN).

Patients were treated with different surgical techniques.

The Veronesi quadrantectomy [43] represents a milestone in the treatment of breast cancer, currently the first scientifically validated conservative protocol.

The Nipple Sparing Mastectomy (NSM) [44], the Skin-Sparing Mastectomy that includes the Nipple-Areolar

Complex (SSM+NAC) [45] with lymphadenectomy and Intraoperative Radiation Therapy (IORT) [46].

Post-operative histological results were all classified as carcinomas.

We paid special attention to the ability of PhiΦBreast to offer an innovative topographic diagnostic imaging of suspicious lesions and using a predictive algorithm.

Different types of tumors were detected in the Golden Section areas, using Fibonacci numbers for mapping and classify the percentage of cancers identified in the different sections.

Percentage of tumors detected in the Fibonacci-number side was as follows: FS1-FS2 (10%) of ductal carcinomas in situ; FS3-FS4 (21%) of invasive ductal carcinomas; FS5 (14%) invasive lobular tumors and FS6 (55%) invasive carcinomas not otherwise specified.

These identified lesions had a high predictive value for malignancy ($p < 0.001$).

During the analysis of the model of spiral breast cancer, we hypothesized the possibility of the existence of different growth sequences, although with the same recursive structure, but due to changes in the conditions of genetic, environmental factors, to alterations of the potentials electrical cell membrane and the action of the gravity. It is possible that the development of “abnormal morphologies” in the form of a dendritic filaments allow the expansion of the tumor by recruiting nourishment and energy from the blood capillaries of neoangiogenesis and through a mechanism of tumour vascularization, termed vessel co-option [47].

Purnell et al. [48] in a recent study revealed the presence of Φ in human erythrocyte, its cell shape, growth and arrangements.

Some researchers showed that in pathological conditions these ratios depart from Φ [49] and that this angle increases in 138° (similar to the Golden Angle, $137,5^\circ$) generating abnormal growth.

A meticulous study was also performed on the echostructural characteristics of the lesions identified by this mapping. It has shown validating that the irregular and spiculated margins are associated with greater probability of malignancy, as also described by other authors.

Lieberman et al. [50] described in a study that a spicular margin was the most suspicious characteristic identified with a high PPV.

Wedegärtner et al. [51] reported an irregular margin of the lesion to be the most reliable morphological feature to indicate malignancy.

Schnall and colleagues [52] identified spiculated margins to be a highly predictive feature of the cancer image and Gutierrez et al. [53] found irregular or spiculated margins conferring the highest probability of malignancy by BI-RADS classification.

In a retrospective study, Tozaki and collaborators [54] found irregular shape (97%) and spiculated margins (100%) among the features with higher predictive value for carcinoma.

In relation to these important results, we believe that the nodular lesions identified at an early stage and using this innovative PhiΦBreast imaging method were found to be strongly associated with malignancy ($p < 0.001$) and with high PPV: 97%.

Wiesner's Law and Da Vinci Divine Proportion gave life to this research.

The theory of spiral cancer, with further insights of its mechanisms, could be useful for new technological applications such as the use of microgravity [55, 56].

Microgravity (μg) research might be an unusual method to combat the disease, but cancer biologists decided to harness the power of μg as an exceptional method to increase efficacy and precision of future breast cancer therapies

Numerous studies have indicated that μg has a great impact on cancer cells by influencing proliferation, survival and migration, it shifts breast cancer cells toward a less aggressive phenotype [57].

Conclusion

Availing Golden Ratio (Φ), Fibonacci sequence and Predictive Algorithm applied to ultrasonography and mammography, we have given rise to a new diagnostic imaging model called PhiΦBreast for the identification of category C4-C5 lesions with high PPV in respecting the criteria of the American College of Radiology (ACR) and Breast Imaging Reporting Data System (BI-RADS).

This original scientific paper could bring progress in science, an important advancement and discovery which could save more lives from despair and in the worst case scenario of the patient's death.

Early diagnosis is essential because it allows the removal of small tumors and therefore able to produce more limited metastases compared to the potential growth of larger tumors.

PhiΦBreast might be the cornerstone of important diagnostic imaging applications as a new strategic weapon against breast cancer.

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Authors' contributions

This work was carried out in collaboration among with the authors. Author ET prepared and wrote the manuscript, conceived imaging, developed concept and ideas by the Theory of Spiral Cancer and PhiΦBreast Model. Author GT contributed the supervision of the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used during the present study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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