The Official Journal of the Hellenic Senologic Society

Mastologia

July - December 2015
Isuue 2, Volume 1
ISSN 1790 - 3963

REVIEW

CLINICAL ARTICLE

ZITA
MEDICAL MANAGEMENT

From vision to reality...

- Sponsorship
- Website & Digital Marketing
- Graphic Design
- Congress Organization
- Scientific Journals
- Financial Organization
- Media Office
- Travel Services

We' ve made it a science!

www. zita-management.com

CONTACT

Βοηθήστε να γίνουν τα φάρμακα πιο ασφαλή και
Αναφέρετε
ΟΛΕΣ τις ανεπιθύμητες ενέργειες για
ΟΛΑ τα φάρμακα
Συμπληρώνοντας την «ΚΙΤΡΙΝΗ ΚΑΡΤΑ»

JANSSEN-CILAG ΦΑΡΜΑΚΕΥΤΙΚΗ Α.Ε.Β.Ε.
Λεωφόρος Ειρήνης 56, 151 21, Πεύκη, Αθήνα, Τηλ.: 210 8090000
www.janssen.com.gr

janssen
PHARMACEUTICAL COMPANIES
OF Johnson&Johnson

Giotto Class

TOMOSYNTHESIS

Design
Technology
Ergonomy
Never seen.

ALL-IN-ONE-SYSTEM

- TOMOSYNTHESIS
- SYNTHETIC VIEW
- 2D MAMMOGRAPHY
- TOMO & STERO BIOPSY in PRONE or Up-RIGHT

TOMO & STERO BIOPSY In PRONE or Up-RIGHT

- 360° breast accessibility
- Compatible with all bioptic systems

TOMOSYNTHESIS

- **30° scan angle** and only **11 exposure**
- **Step & Shoot**
- **No Binning (85 µm)**
- **Iterative Reconstruction Software** dedicated to Tomosynthesis

Giotto Class. The new dimension in Tomosynthesis and Breast Biopsy.

Via Sagittario, 5 - 40037
Sasso Marconi - Bologna
Italy - Tel +39 051 84.68.51

IMS 50° 1965-2015

www.imsitaly.com
www.tomosynthesis-class.com
imscomm@imsitaly.com

The Official Journal of the Hellenic Senologic Society

Mastologia

The Official Journal of the Hellenic Senologic Society

Mastologia

Distributed at no charge to all members of the Hellenic Senologic Society
ISSN 1790 - 3963
Address: Kifisias Avenue 18, P.C. 11526, Athens, Greece
tel: +30 210 7470257, fax: +30 210 7716834, E-mail: eem_1979@yahoo.gr, www.mastologia.gr

Published by
ZITA MEDICAL MANAGEMENT S.A.,
ΖΙΤΑ ΔΙΑΧΕΙΡΙΣΗ ΣΥΝΔΕΣΜΩΝ ΚΑΙ ΙΑΤΡΙΚΩΝ ΟΡΓΑΝΙΣΜΩΝ Α.Ε.,
1st klm Peanias - Markopoulou Avenue, 190 02 Peania, Attica, Greece, P.O BOX 155,
tel.: +30 211 1001 777, fax: +30 210 6642116, E-mail: info@zita-management.gr

Gadovist® 1.0

Gadobutrol

There’s MORE to see

L.GR.RI.03.2015.0020

Bayer HealthCare

Ελλάδα: GADOVIST PFS: ΚΑΚ: Bayer Ελλάς ΑΒΕΕ,
Τηλ.:+ 30 210 6187500
Κύπρος:GADOVIST PFS
Κατ. Ειδ. Αδ. Κυκλ: Bayer Ελλάς ΑΒΕΕ/Τοπικός αντιπρόσωπος:
Novagem Ltd, Τηλ. +35722483858
Τμήμα Επιστημονικής Ενημέρωσης
Τηλ. +302106187742
Fax: +302106187522
Email: medinfo.gr.cy@bayer.com

Βοηθήστε να γίνουν τα φάρμακα πιο ασφαλή και Αναφέρετε ΟΛΕΣ τις ανεπιθύμητες ενέργειες για ΟΛΑ τα φάρμακα Συμπληρώνοντας την «ΚΙΤΡΙΝΗ ΚΑΡΤΑ»

Πριν τη συνταγογράφηση συμβουλευθείτε την Περίληψη Χαρακτηριστικών του Προϊόντος που διατίθεται στο εκθετήριο

CONTENTS

New edition

EDITORIAL

REVIEW

CLINICAL ARTICLE

Senographe Essential

Senographe™ Essential offers efficient workflow and high-quality images on an upgradeable platform for advanced applications.

GE Works.

gehealthcare.gr

HELLENIC SCHOOL OF SENOLOGY

FIVE (2 DAY) COUSRSES

Under the Auspices of the SIS

SOCIÉTÉ INTERNATIONALE DE SÉNOLOGIE

SENOLOGIC INTERNATIONAL SOCIETY

2016 Dates

- 19-20/02
- 15-16/04
- 1-2/07
- 23-24/09
- 25-26/11

Filling the educational gap in Senology

Information:
Tel: 210 7470257, e-mail: eem_1979@yahoo.gr

Place: Amphitheater "Epaminontas Megapanos",
LITO Maternity Hospital, 7-13 Mouson str., Athens

Welcome note

Editor in Chief
Ass Pr Lydia Ioannidou - Mouzaka

Gynecologist-Surgeon-Breast Specialist, National Representative of Greece to the Guidelines Development Group of ECIBC (European Commission Initiative on Breast Cancer), Member of the UEMS Training Group for Breast Cancer Surgery, Studies Director of the Hellenic School of Senology, President of the Hellenic Senologic Society

The reception you showed to our 1st issue with your comments and positive remarks for this important effort of the Hellenic Senologic Society (HSS) was a very nice surprise.

The Journal "Mastologia" is an edition which aims to become a basic vehicle for communication between Senologists (Mastologists). Further- more, it can become an additional useful tool full of information -especially presenting the work performed in Greece-, of the scientific evolutions all around the world and giving the opportunity of sharing scientific knowledge.

The effort of this edition is a collective one. I would like to thank very much all the Members of the Editorial Board. They managed an important volume of information, articles and notices in order to compose the material which has been included in the previous issue.

A huge thanks belongs to our Colleagues who have submitted scientific papers. I would welcome all of you to submit papers and reports in order the Journal to be accessed in the international scientific data bases such as PubMed and Scopus. It is also a good opportunity to express here our willingness to participate and to be involved in multi-centric studies and also in International or European projects. For example the participation in the Guidelines Development Group (GDG) of the European Commission Initiative on Breast Cancer (ECIBC).

Looking back on the 2015 events, we see events that really made us sad, but also events that are giving hope and an optimistic outlook for the future. Among the sad events we count the loss of Professor of Surgery and former President of the Senologic International Society (SIS) Antonio Figueira Fo from Recife, Brazil, as well as the loss of Professor of Surgery and former Treasurer of the Hellenic Senologic Society (HSS) Lazaros Tsouskas from Thessaloniki, both of them were personal friends. The family of Senology became poorer, missing two distinguished colleagues.

The social activity and contribution of HSS continued in 2015 and it ended with the awareness campaign for lay people as well as breast examination, ultrasounds tests free of charge in Lefkada island (Ionian island), where 257 women were examined. The recognition from the local community was very warm, which encourages us to continue our efforts for early breast cancer detection and in other parts of the rural Greece.

In the year 2016 a dominant position among scientific conferences, holds the 19th SIS World Congress on Breast Health Care which will take place on 5-8 May 2016 in Warsaw-Poland, a Congress of high scientific level, as well as all the SIS Congresses. Warsaw is an amazing city that emerged from the ashes of World War II and it was restored with a full respect to its history. Today it is a vibrant metropolitan city that is constantly growing, thanks to the creativity of its motivated and polite inhabitants. The Greek medical community has an additional reason to participate, since this Congress, besides the importance of its scientific issues to be presented, will confirm and finalize the organization of the 21st International SIS Congress in 2020 in Greece.

The second important scientific conference for 2016, especially for the Greek Colleagues, will be the 13th National Congress on Senology which will be held between 20-23 October 2016 in Thessaloniki. The conference will address the latest developments in Senology and the useful exchange of views which will be the occasion for a creative scientific dialogue. Our massive participation in our National Congress is of big importance. Also, in the frame of the Congress we will be celebrating the Senologic International Society' s 40th Anniversary. The "Artion" PCO Congress Organisers will be at your disposal for any further information you may need.

With this opportunity I would like to thank the Pharmaceutical Companies and the Companies with Medical Equipments for supporting the edition of the Journal "Mastologia", as without their valuable contribution we would not be able to publish the Journal.

Last, but not least, I would like to thank the Zita Medical Management, which encouraged us to publish the Journal and helps us during each edition.

With my best personal regards
Lydia Ioannidou-Mouzaka MD, PhD
President of the HSS

REVIEW

Breast Cancer Treatment

An old pub, a brewery, some seafood, Noble prize for Physiology and Medicine and the treatment of breast cancer

An evolving tale

Konstantinos T. Papazisis and Loukas F. Kontovinis

"Euromedica" General Clinic of Thessaloniki, 54645, Thessaloniki, Greece
www.oncomedicare.com

ABSTRACT

Years of research in cell cycle, connected yeast scientists and cancer research. The elucidation of cell cycle control machinery led to the discovery of a new pharmacological category, cyclin-dependent kinase inhibitors (CDK inhibitors). This review is discussing the process that led yeast researchers to Nobel Prize winning and introduced a breast cancer treatment breakthrough.

Scientists, beer and seafood

Just some yards away from King's College, Cambridge, on the north side of Bene's street there is an old pub, with the familiar name "The Eagle", running since 1667. The pub was always a popular destination for a lunch break for scientists and workers nearby, as well as for a refreshing pint of beer after work. It was on such an occasion when on the 28th of February 1953 Francis Crick interrupted lunch to announce that he and James Watson had discovered "the secret of life", after they had come up with the proposed structure of DNA[1]. The instance is now commemorated with a blue plaque next to the entrance and the pub serves "Eagle's DNA" ale… Some years later, on 1962, both scientists shared with Maurice Wilkins the Nobel Prize in Physiology or Medicine "for their discoveries concerning the molecular structure of nucleic acids and its significance for information transfer in living material"[2].

Some year later, in 1970, Lee Hartwell discovered the cell division cycle (CDC) genes in baker's (or brewer's) yeast (Saccharomyces cerevisiae)[3], a system often used for studying cell division processes and for making beer. He cloned several genes, amongst them cell-division cycle gene 28 (CDC28) and he help in the introduction of the concept of "cell cycle", a carefully structured process that follows one direction, driving cells first to duplicate their genetic information (what we know as S phase) and then divide (mitosis or M phase). He later introduced the concept of cell cycle "checkpoints"[4], where DNA and the other cellular biochemistry is inspected, to

Corresponding author
Konstantinos T. Papazisis
E - mail: konstantinos.papazisis@gmail.com

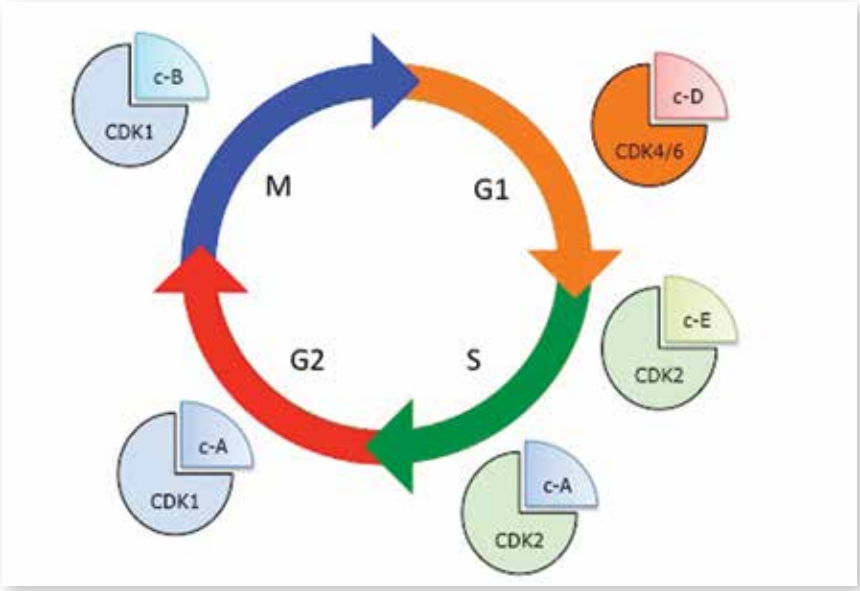


Figure 1. *Cell cycle is controlled by cyclins (c-D, c-E, c-A and c-B) and cyclin-dependent kinases (CDKs) that are associated in different phases of the cycle to orchestrate the biochemical processes for cellular proliferation*

make sure everything is in order before going onwards to the next step.

In those times of long hair, flared trousers and disco music, a young scientist from northern London, Paul Nurse, working at Murdoch Mitchinson's laboratory at the University of Edinburgh, identified the cdc2 gene in the fission yeast (Schizosaccharomyces pombe), a species used in traditional brewing[5]. As he had already spent a year working at a local Guinness brewery[6], one cannot help but notice the influence his previous work may have had in his later career. He subsequently found that cdc2 was the same as CDC28 and he discovered that it was transcribing for a serine/threonine kinase[7] and cloned a human homologue[8], later known as CDK-1 (Cyclin-Dependent Kinase-1). The discovery that elements of cell cycle machinery were highly conserved between species as yeast and humans, with evolutionary distance of millions of years, helped scientists to further explore this complex phenomenon and boomed the research that led to our understanding of cell cycle.

Meanwhile, in 1982 Tim Hunt was teaching summer courses at Woods Hole Marine Biological Laboratory (close to Massachusetts cost) and was working on the control of protein synthesis in sea urchin eggs (a delicacy in many Mediterranean cuisines), when he noticed something very unusual: A protein, that he named cyclin, was barely if at all detectable in the unfertilized egg, was expressed in cycling cells, but it was disappearing every time the cells divided[9]. He went on to clone it and he found that the same molecule could work across species in the frog eggs (Xenopus spp)[10] where Marc Kirschner had already shown that the activity of MPF (maturation or mitosis-promoting factor) was oscillating in a similar way[11]. It was finally shown that MPF is a cyclin-CDK complex where the activity and the specificity of the kinase is regulated (amongst other biological processes) by the presence of the escorting cyclin[12]. As cyclins are destroyed before mitosis, the complex is no longer active and cyclins need to be synthesized again for the whole process to re-initiate.

The Nobel Prize in Physiology or Medicine 2001 was awarded jointly to Leland H. Hartwell, Tim Hunt and Sir Paul M. Nurse *"for their discoveries of key regulators of the cell cycle"*[13]. Cell cycle research was largely expanded in the 1990s (publications with the tag "cell cycle" increased by a factor of x60 between 1980s and 1990s) and the two British scientists Paul Nurse and Tim Hunt were knighted in 1999 in 2006.

Cell cycle regulation and G1 checkpoint

In a simplified version, mammalian cell cycle is the ordered sequence of two important events: DNA synthesis and mitosis. A cell should not enter mitosis before DNA is correctly duplicated and should not be allowed

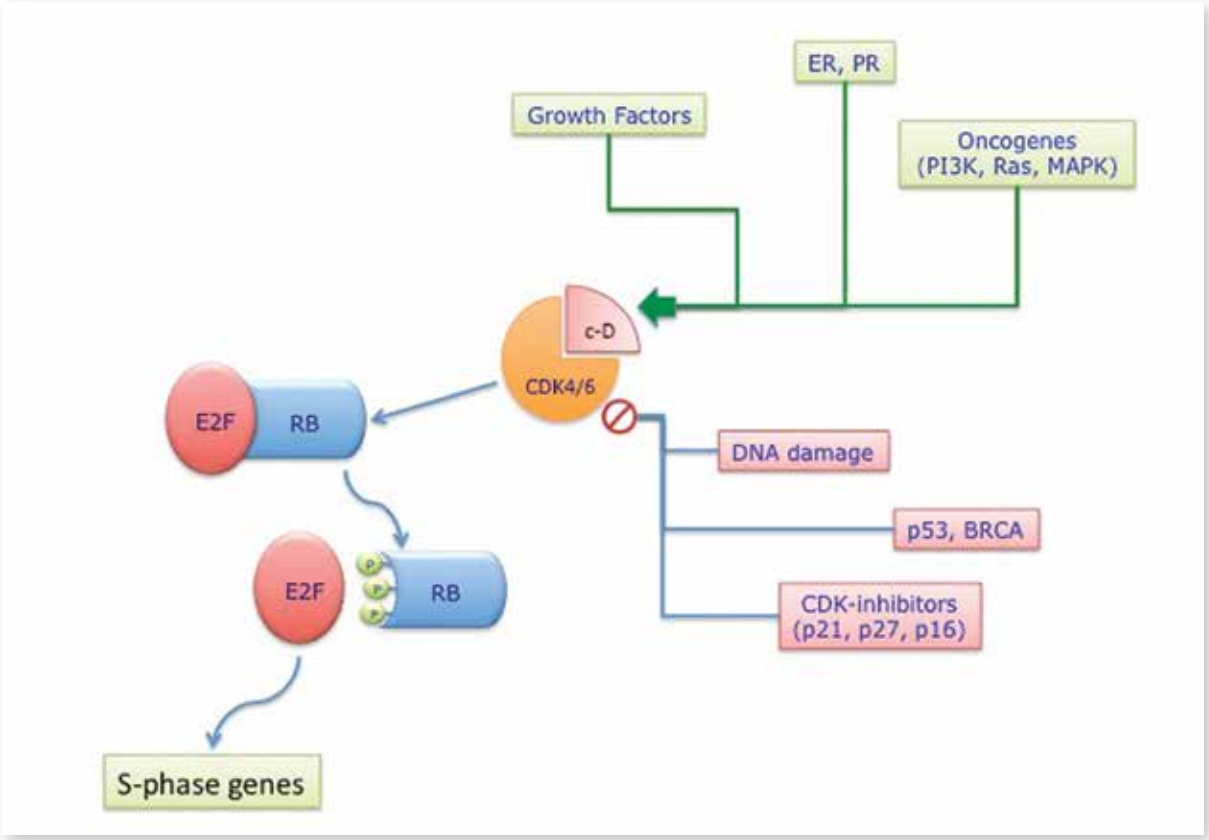


Figure 2. *G1 checkpoint. Positive and negative proliferative signals converge for the cyclin-D and CDK4/6 activation*

to duplicate its DNA before it has successfully divided. Cyclins and Cyclin-Dependent Kinases help in controlling this process. In each phase of cell cycle a different cyclin escortes the specific CDK to promote the phosphorylation of the targets that needed to be activated in order of cell cycle to progress (**Figure 1**). The picture is much more complicated as there are negative regulators of the cyclin-dependent kinases (the INK4 family p16, p15, p18 and p19[14] as well as p21, p27, etc.[15]) and enzymes (mostly kinases and phosphatases) that activate or inhibit the cyclin/CDK complexes. Finally, in metaphase, anaphase-promoting-complex (APC), an E3 ubiquitin ligase, that targets S and M-phase cyclins for degradation in the proteasome[16], thus resetting the cell cycle clock to start again in the G1 phase.Once entering the G1 phase cell faces a crucial dilemma: Should it go on and prepare for another cycle (duplicate DNA - divide, etc.) or should it rest, in what we call G0 phase (biochemically a G1 phase but with no "will to divide", a status that many of our mature differentiated cells have adopted)? What we call G1 checkpoint is all the biochemical pathways that interact to provide the signal for proliferation[17]. Growth factors, oncogenes, nutritional sufficiency, nearby cells (what we call "contact inhibition") and inhibitory signals, all converge into the G1 checkpoint and specifically into the activation of Cyclin D-CDK4/6 complex. Once activated the complex phosphorylates the tumor suppressor retinoblastoma protein (RB) that was inhibiting a crucial transcription factor E2F. E2F is then released and increases transcription of several gens involved in cDNA synthesis, cell cycle progress etc (**Figure 2**). By all means, this is a one-way decision. Once a cell passes the G1 checkpoint is destined to complete a whole cycle and divide or die. This is why G1 checkpoint is such an attractive target for cancer treatment. All cancers have lost the control of cellular proliferation (e.g. all cancers have a deficiency targeting the G1 checkpoint)[18] and restoring G1 checkpoint could lead to long-term control of cancer growth[19]. Thus, the CDK4/6 inhibitors became the Holy Grail for drug development any many pharmaceutical companies entered the race that started almost 20 years ago.

G1 checkpoint, cyclin D and breast cancer treatment

Proliferation is an indication of aggressiveness in hormone receptor-positive breast cancer. In fact, 5 out of the 16 genes analyzed by the Oncotype DX assay are proliferation genes (Ki67, Cyclin B1, Survivin, MYBL2 and STK15) are proliferation genes[20]. Cyclin D is overexpressed in breast cancer[21,22], correlates with poor progression in hormone receptor-positive disease[23] and its expression has been associated to shorter relapse-free and overall survival in women treated with tamoxifen in the adjuvant setting[24,25]. Cyclin D is therefore an attractive therapeutic target for hormone receptor-positive breast cancer[26,27]. Targeting protein-protein interactions (as cyclins interact with CDKs) is a very difficult task for drug development. Research has focused instead on the development of small molecules that mimic the ATP-binding pocket of kinases and thus inhibit the enzymatic activity of the kinase. However, CDK4/6 (the CDKs that partner cyclin D at the G1 checkpoint) has been proven a difficult target and only recently small molecules that inhibit CDK4/6 were developed.

Palbociclib (formerly PD-0332991) is an orally active potent and highly selective inhibitor of CDK4 and CDK6 kinases[28,29]. Palbociclib preferentially inhibits hormone receptor-positive human breast cancer cells and has a synergistic effect with tamoxifen in resistant cell lines[30,31]. Inhibition of CDK4/6 with palbociclib leads to suppression of a number of downstream genes required for proliferation including cyclin A and CDK1, a stable cell cycle arrest and induction of cellular senescence[32]. A randomized phase 2 study (PALOMA-1/TRIO-18), assessing the safety and efficacy of palbociclib in combination with letrozole as first-line treatment in women with advanced breast cancer, was recently reported[33]. The study showed a statistically and clinically significant prolongation of disease-free survival from 10.2 months for the letrozole alone group to 20.2 months for the palbociclib plus letrozole group (HR 0.488, 95% CI 0.319-0.748), but no difference in overall survival (from 33.3 to 37.5 months, HR 0.813, 95% CI 0.492-1.345). The successful phase 2 study was followed by a large phase 3 randomized study (PALOMA-3) in patients that had relapsed or progressed during prior endocrine therapy[34]. PALOMA-3 randomized 521 patients with advanced hormone receptor-positive (and HER2-negative) disease, in a 2:1 ratio, to receive either palbociclib and fulvestrant or placebo and fulvestrant (pre- and peri-menopausal patients received goserelin as well). Almost 60% of the patients enrolled had visceral metastases and only 25% received treatment as first line. The results showed again a statistically significant prolongation of disease-free survival from 3.8 months for the fulvestrant/placebo group to 9.2 months for the palbociclib plus fulvestrant group (HR 0.42, 95% CI 0.32-0.56, p<0.001). Palbociclib did not increase objective responses (from 6.3% with fulvestrant/placebo to 10.4% with the combination, p=0.16) and overall survival data have not yet been reported. The combination had an excellent tolerability profile, with neutropenia and leukopenia as the most common grade 3 or 4 adverse events (62.0% and 25.2%, respectively). Febrile neutropenia was extremely rare (0.6%). On February 3, 2015, the U. S. Food and Drug Administration (FDA) granted accelerated approval to palbociclib (Ibrance, Pfizer) for use in combination with letrozole for the treatment of postmenopausal women with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer as initial endocrine-based therapy for their metastatic disease[35]. The drug is currently being validated by EMA (European Medicines Agency).

Ribociclib (LEE011) is another CDK4/6 inhibitor developed by Novartis and tested in several malignancies[36]. A phase I study showed an acceptable toxicity profile and preliminary signs of clinical activity[37] and a phase Ib/II study showed similar signs in combination with letrozole for estrogen receptor-positive breast cancer patients[38]. A phase 3 study in postmenopausal women with hormone receptor-positive and HER2-negative disease and no prior therapy for advanced breast cancer has recently completed accrual. Several other studies (in the neoadjuvant setting, in premenopausal women, or in combination with PI3K or mTor inhibitors, etc.) are underway[39].

Finally, **abemaciclib** (LY2835219) another selective CDK4/6 inhibitor developed by Eli Lilly showed again acceptable safety and evidence of clinical activity in pretreated patients with multiple tumor types[40]. A Phase 2 trial, MONARCH 1, is studying abemaciclib's impact as a monotherapy in women with hormone receptor-positive, HER2-negative metastatic breast cancer. Abemaciclib is been tested in large phase 3 studies in combination with fulvestrant (MONARCH-2) or aromatase inhibitors (MONARCH-3)[41]. Recently FDA handed Lilly

the coveted "breakthrough therapy" designation for abemaciclib.

Conclusions

A fine line connecting the process of beer fermentation, the tasteful sea urchins and very hard experimental work, has elucidated the cell cycle control machinery and identified several of its important components as potential anticancer targets. Though it seems a long time, 20 years later we are able to bring the first of these drugs to fight breast cancer, the most common form of cancer in women. As we succeed in prolonging life span and quality, we cannot avoid thinking Sir Paul Nurse's comment in his biography, when he moved his research to ICRF (Imperial Cancer Research Fund) at Lincoln's Inn Fields, London: "*Perhaps, not unreasonably, some wondered what a yeast researcher was doing in a cancer research institute*"[6]...

Conflict of interests

The authors declare that they have no commercial competing interests or financial support for this study. ■

REFERENCES

1. Molecular structure of nucleic acids; A structure for deoxyribose nucleic acid. Watson JD, Crick FH. *Nature*. 1953 Apr 25; **171**(4356): 737-8.
2. http://www.nobelprize.org/nobel_prizes/medicine/laureates/1962/
3. Genetic control of the cell-division cycle in yeast. I. Detection of mutants. Hartwell LH, Culotti J, Reid B. *Proc Natl Acad Sci U S A*. 1970 Jun;**66**(2):352-9.
4. Cell cycle arrest of cdc mutants and specificity of the RAD9 checkpoint. Weinert TA, Hartwell LH. *Genetics*. 1993 May;**134**(1):63-80.
5. Genetic control of the cell division cycle in the fission yeast Schizosaccharomyces pombe. Nurse P, Thuriaux P, Nasmyth K. *Mol Gen Genet*. 1976 Jul 23;**146**(2): 167-78
6. http://www.nobelprize.org/nobel_prizes/medicine/laureates/2001/nurse-bio.html
7. Cell. 1986 Apr 25;45(2):261-8. The cell cycle control gene cdc2+ of fission yeast encodes a protein kinase potentially regulated by phosphorylation. Simanis V, Nurse P.
8. Complementation used to clone a human homologue of the fission yeast cell cycle control gene cdc2. Lee MG, Nurse P. *Nature*. 1987 May 7-13;**327**(6117):31-5
9. Cyclin: a protein specified by maternal mRNA in sea urchin eggs that is destroyed at each cleavage division. Evans T, Rosenthal ET, Youngblom J, Distel D, Hunt T. *Cell*. 1983 Jun;**33**(2):389-96.
10. Molecular cloning and characterization of the mRNA for cyclin from sea urchin eggs. Pines J, Hunt T. *EMBO J*. 1987 Oct;**6**(10):2987-95.
11. Cell cycle dynamics of an M-phase-specific cytoplasmic factor in Xenopus laevis oocytes and eggs. Gerhart J, Wu M, Kirschner M. *J Cell Biol*. 1984 Apr;**98**(4): 1247-55.
12. The role of cyclin synthesis and degradation in the control of maturation promoting factor activity. Murray AW, Solomon MJ, Kirschner MW. *Nature*. 1989 May 25;**339**(6222):280-6
13. http://www.nobelprize.org/nobel_prizes/medicine/laureates/2001/
14. INK4 proteins, a family of mammalian CDK inhibitors with novel biological functions. Cánepa ET, Scassa ME, Ceruti JM, Marazita MC, Carcagno AL, Sirkin PF, Ogara MF. IUBMB. Life. 2007 Jul;59(7):419-26.
15. 15 Control of the cell cycle and apoptosis. Lundberg AS, Weinberg RA. Eur J Cancer. 1999.Dec;35(14):1886-94
16. Identification of subunits of the anaphase-promoting complex of Saccharomyces cerevisiae. Zachariae W, Shin TH, Galova M, Obermaier B, Nasmyth K. *Science*. 1996 Nov 15;**274**(5290):1201-4
17. The G1/S cell-cycle checkpoint in eukaryotic cells. Peeper DS, van der Eb AJ, Zantema A. *Biochim Biophys Acta*. 1994 Dec 30;**1198**(2-3):215-30.
18. Cell cycle checkpoints and their inactivation in human cancer. Molinari M. *Cell Prolif*. 2000 Oct;**33**(5):261-74
19. Cell cycle regulation in the G1 phase: a promising target for the development of new chemotherapeutic anticancer agents. Owa T, Yoshino H, Yoshimatsu K, Nagasu T. *Curr Med Chem*. 2001 Oct;**8**(12):1487-503.
20. A population-based study of tumor gene expression and risk of breast cancer death among lymph node-negative patients. Habel LA, Shak S, Jacobs MK, Capra A, Alexander C, Pho M, Baker J, Walker M, Watson D, Hackett J, Blick NT, Greenberg D, Fehrenbacher L, Langholz B, Quesenberry CP. *Breast Cancer Res*. 2006;**8**(3):R25.

21. Expression and amplification of cyclin genes in human breast cancer. Buckley MF, Sweeney KJ, Hamilton JA, Sini RL, Manning DL, Nicholson RI, deFazio A, Watts CK, Musgrove EA, Sutherland RL. *Oncogene*. 1993 Aug;**8**(8):2127-33.
22. Amplification and overexpression of cyclin D1 in breast cancer detected by immunohistochemical staining. Gillett C, Fantl V, Smith R, Fisher C, Bartek J, Dickson C, Barnes D, Peters G. *Cancer Res.* 1994 Apr 1;**54**(7):1812-7
23. Overexpression of cyclin D1 messenger RNA predicts for poor prognosis in estrogen receptor-positive breast cancer. Kenny FS, Hui R, Musgrove EA, Gee JM, Blamey RW, Nicholson RI, Sutherland RL, Robertson JF. *Clin Cancer Res.* 1999 Aug;**5**(8):2069-76.
24. Cyclin D1 expression in breast cancer patients receiving adjuvant tamoxifen-based therapy. Rudas M, Lehnert M, Huynh A, Jakesz R, Singer C, Lax S, Schippinger W, Dietze O, Greil R, Stiglbauer W, Kwasny W, Grill R, Stierer M, Gnant MF, Filipits M; Austrian Breast and Colorectal Cancer Study Group. *Clin Cancer Res.* 2008 Mar 15;**14**(6):1767-74
25. Adverse effect of adjuvant tamoxifen in premenopausal breast cancer with cyclin D1 gene amplification. Jirström K, Stendahl M, Rydén L, Kronblad A, Bendahl PO, Stål O, Landberg G. *Cancer Res.* 2005 Sep 1;**65**(17):8009-16.
26. Cyclin D as a therapeutic target in cancer. Musgrove EA, Caldon CE, Barraclough J, Stone A, Sutherland RL. *Nat Rev Cancer.* 2011 Jul 7;**11**(8):558-72
27. Cyclin D1 in breast cancer pathogenesis. Arnold A, Papanikolaou A. *J Clin Oncol.* 2005 Jun 20;**23**(18):4215-24.
28. Specific inhibition of cyclin-dependent kinase 4/6 by PD 0332991 and associated antitumor activity in human tumor xenografts. Fry DW, Harvey PJ, Keller PR, Elliott WL, Meade M, Trachet E, Albassam M, Zheng X, Leopold WR, Pryer NK, Toogood PL. *Mol Cancer Ther.* 2004 Nov;**3**(11):1427-38.
29. Discovery of a potent and selective inhibitor of cyclin-dependent kinase 4/6. Toogood PL, Harvey PJ, Repine JT, Sheehan DJ, VanderWel SN, Zhou H, Keller PR, McNamara DJ, Sherry D, Zhu T, Brodfuehrer J, Choi C, Barvian MR, Fry DW. *J Med Chem*. 2005 Apr 7;**48**(7):2388-406.
30. PD 0332991, a selective cyclin D kinase 4/6 inhibitor, preferentially inhibits proliferation of luminal estrogen receptor-positive human breast cancer cell lines in vitro. Finn RS, Dering J, Conklin D, Kalous O, Cohen DJ, Desai AJ, Ginther C, Atefi M, Chen I, Fowst C, Los G, Slamon DJ. *Breast Cancer Res.* 2009;**11**(5):R77.
31. CDK inhibitors as potential breast cancer therapeutics: new evidence for enhanced efficacy in ER+ disease. Sutherland RL, Musgrove EA. *Breast Cancer Res.* 2009;**11**(6):112
32. Therapeutically activating RB: reestablishing cell cycle control in endocrine therapy-resistant breast cancer. Thangavel C, Dean JL, Ertel A, Knudsen KE, Aldaz CM, Witkiewicz AK, Clarke R, Knudsen ES. *Endocr Relat Cancer.* 2011 Apr 28;**18**(3):333-45.
33. The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): A randomised phase 2 study. Finn RS, Crown JP, Lang I, Boer K, Bondarenko IM, Kulyk SO, Ettl J, Patel R, Pinter T, Schmidt M, Shparyk Y, Thummala AR, Voytko NL, Fowst C, Huang X, Kim ST, Randolph S, Slamon DJ. *Lancet Oncol.* 2015 Jan;**16**(1):25-35.
34. Palbociclib in Hormone-Receptor-Positive Advanced Breast Cancer. Turner NC, Ro J, André F, Loi S, Verma S, Iwata H, Harbeck N, Loibl S, Huang Bartlett C, Zhang K, Giorgetti C, Randolph S, Koehler M, Cristofanilli M; PALOMA3 Study Group. *N Engl J Med.* 2015 Jul 16;**373**(3):209-19.
35. http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm432886.htm
36. Dual CDK4/CDK6 inhibition induces cell-cycle arrest and senescence in neuroblastoma. Rader J, Russell MR, Hart LS, Nakazawa MS, Belcastro LT, Martinez D, Li Y, Carpenter EL, Attiyeh EF, Diskin SJ, Kim S, Parasuraman S, Caponigro G, Schnepp RW, Wood AC, Pawel B, Cole KA, Maris JM. *Clin Cancer Res.* 2013 Nov 15;19(22):6173-82.
37. A phase I study of the single-agent CDK4/6 inhibitor LEE011 in pts with advanced solid tumors and lymphomas. Infante JR, Shapiro G, Witteveen P, Gerecitano JF, Ribrag V,Chugh R, Issa I, Chakraborty A, Matanao A, Zhao X, Parasuraman S, Cassier P. *J Clin Oncol* **32**:5s, 2014 (suppl; abstr 2528^).
38. Phase Ib/II study of LEE011 and BYL719 and letrozole in ER+, HER2– breast cancer: Safety, preliminary efficacy and molecular analysis. Juric D, Hamilton E, Estevez LG, De Boer RH, Mayer I, Campone M, Asano S, Bhansali S, Zhang V, Hewes B, Munster P. *SABCS* 2014; **abstr** P5-19-24
39. www.clinicaltrials.gov (NCT01958021, NCT02422615, NCT02278120)
40. Shapiro G, Rosen LS, Tolcher AW, et al. A first-in-human phase 1 study of the CDK4/6 inhibitor, LY2835219, for patients with advanced cancer (abstract 2500). *J Clin Oncol* 2013; **31(suppl).**
41. www.clinicaltrials.gov (NCT02102490, NCT02107703, NCT02246621).

Breast Tomosynthesis - 3D Mammography

Peter Malakasis[1] MD, Lydia Ioannidou-Mouzaka[2] MD, PhD, Apostolos Zavos[3] MD, Ioannis Papadopoulos[4] MD

[1] Breast Radiology Specialist, Director of Breast Imaging Department-Euroclinic Hospital, Board member of Hellenic Senologic Society, Athens, Greece

[2] Gynecologist-Surgeon-Breast Specialist, National Representative of Greece in the UEMS for the needs of training in Breast Cancer surgery, President of the Hellenic Senologic Society, Delegate of European Committee Initiative on Breast Cancer, in Guidelines Development Group on diagnosis and breast screening

[3] Surgeon Gynecologist Obstetrician. Subspecialty Breast Diagnostic and Surgery, Board member of Hellenic Senologic Society, Deputy Editor of Mastologia Journal. Larisa, Greece

[4] Resident Radiologist-Sismanoglio Hospital, Athens, Greece

ABSTRACT

Introduction: Digital breast tomosynthesis is a new modality for the diagnosis and screening of breast cancer. Its advantage is that it provides multiple images of the breast from different angles that are synthesized into a three-dimensional image set.
Objective: Our purpose is to describe the advantages of digital breast tomosynthesis comparatively to 2D mammography for breast cancer diagnosis and screening.
Material and methods: Many cases from our personal archive is presented in order to show the tomosynthesis advance.
Results: Mammography and screening has reduced breast cancer but not depict all types of cancers. DBT has overcome the limitations of conventional 2D mammography improving sensitivity and specificity for detection of breast cancer and breast-cancer screening.
Conclusions: Patients undergoing 2D and 3D mammography had significantly lower screening recall rates and the potential to reduce false positive recalls as a result to improves breast-cancer detection.

Mammography is specialized medical imaging (a low-dose x-ray system) to see inside the breasts that may indicate the presence of cancer, benign and malignant changes, search for abnormal areas of density, mass, architectural distortion or any calcification and helps in the early detection and diagnosis of breast diseases. The mammographic images are often not enough If a finding or spot is suspicious to determine the existence of a benign or malignant disease then radiologist will recommend further diagnostic studies.

Interpretation of mammograms is difficult because every breast looks different for each woman and an image may be

Corresponding author
Peter Malakasis
E - mail: petrosmalakasis@gmail.com

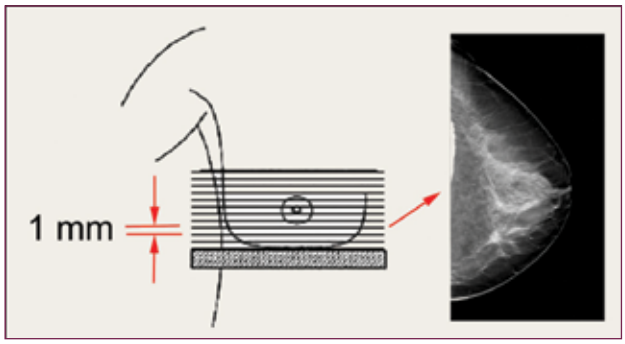


Image 1. *Breast Tomosynthesis*

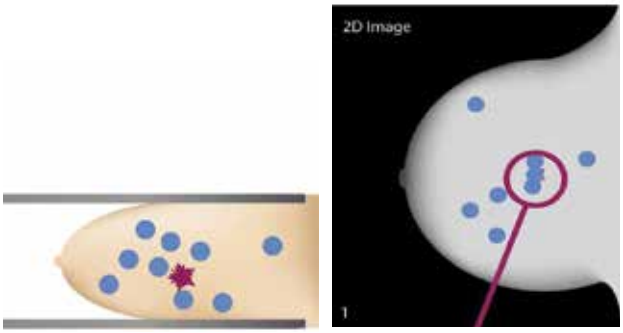


Image 2.*Tissue superimposition hides*

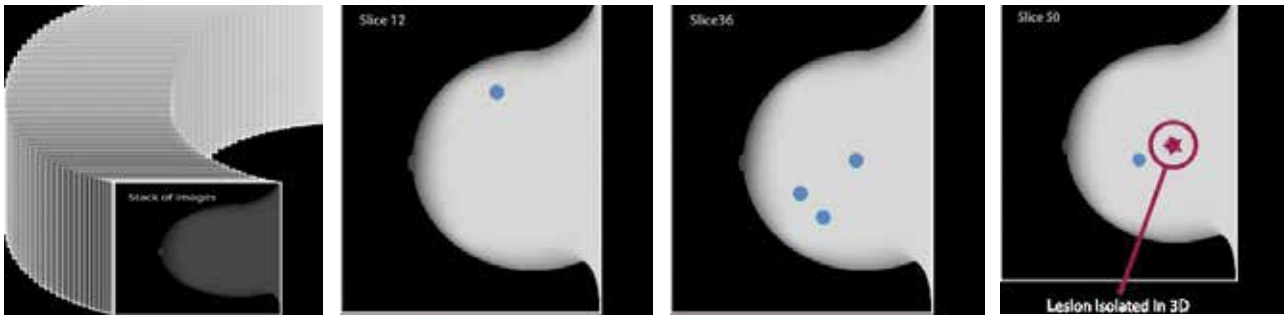


Image 3. *Tomosynthesis procedure*

compromised if there is powder or salve on the breasts or if she has undergone breast surgery. Three recent advances in mammography include digital mammography, computer-aided detection and breast tomosynthesis.

Digital mammographyor full-field digital mammography (FFDM) is a system in which the x-ray film is replaced by electronics detectors that convert x-rays into mammographic pictures of the breast, with a lower or similar radiation dose. The images are transferred to a computer for review by the radiologist.

Computer-aided detection (CAD) is a direct digitized breast imaging system for mammographic images.

Breast tomosynthesisor three-dimensional (3-D) mammography and **digital breast tomosynthesis (DBT)** is an advanced form of digital breast imaging where multiple images of the breast from different angles are synthesized (captured and reconstructed) into a three-dimensional image set.

Nomenclature
Breast Tomosynthesis

Is a relatively new approved 3-dimensional method, but

Table 1. Nomenclature

Shorthand	Definition
2D	Conventional digital mammography
3D	Tomosynthesis
2D plus 3D	A protocol where both digital mammograms and tomosynthesis images are acquired (CC & MLO for both modalities)
2D plus 3D MLO	A protocol where the two-view digital mammogram (CC & MLO) and the tomosynthesis MLO images are acquired

isn't yet considered the standard for the primary use in breast cancer screening programs, because it is available at a limited number of private clinics and hospitals.

- A method of imaging the breast in three dimensions (3D)
- Image slices are 0,5 or 1 cm thick
- Image slices high resolution: like mammograms

Is different from a standard mammogram, usually takes multiple X-rays of each breast from different angles, top to

bottom and oblique side to side. Procedure is the same for all methods, the breast is held between detector and a compression plate to ensure that the whole breast is viewed, and compressed. **(Image 1).** Imaging of the breast in three dimensions improves ability to detect small tumors, also enables the radiologist to determine the size of the lesion more precisely and therefore the woman have better treatment options. A major factor contributing to the limited performance of mammography is the tissue superimposition that is created by the overlap (can obscure a lesion making it more difficult to perceive or render and it can show completely mammographically occult) of normal breast structures in a two-dimensional mammographic projection.

Why we choose breast tomosynthesis (3D mamography)? 3D improves visibility by reducing tissue superimposition. **(Image 2)**

How Tomosynthesis does work?

Digital tomosynthesis takes multiple X-ray images of each breast from many angles in the two standard views. The X-ray tube moves in an arc around the breast while images are taken during examination. Then the information is sent to a computer, where 3-dimensional images are processed to high-resolution. **(Images 3,4, Figure 1)**

Tomosynthes is safe limit technique "combo mode" and "low dose". **(Figure 2 &Table 2)**

Clinical use of tomosynthesis

The use of screening increases the detection of small abnormal tissue, called ductal carcinoma in situ (DCIS) and also for detecting all types of breast cancer, including invasive ductal and invasive lobular cancer. (**Images 5-8**)

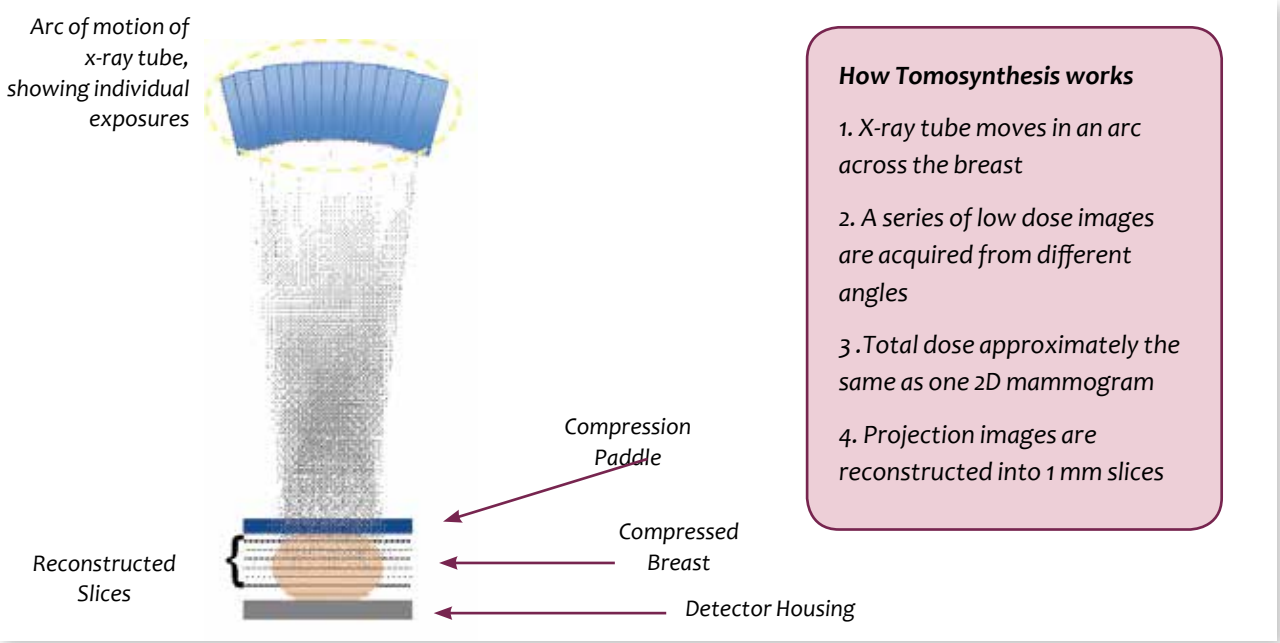


Figure 1

Combo mode dose is below MQSA "safe limit" for conventional screening exam

The increase in dose compared to conventional 2D mammography alone is more than offset by:

- *Increased cancer detection,*
- *Decreased recalls and*
- *Potential to decrease negative breast biopsies.*

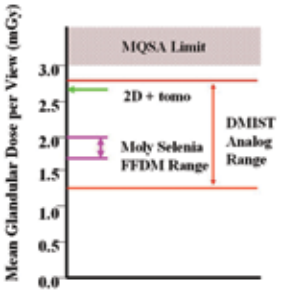


Figure 2

Table 2. Typical Mammography Dose Levels

Description	Dose per view (mGy)*
Dimensions 2D (W anode)	1.0 - 1.2
Selenia 2D (Mo anode)	1.6 - 1.8
Dimensions 2D+3D Dose mode (W anode)	1.6 - 1.8
Dimensions 2D+3D Contrast mode (W anode)	2.4 - 2.6

** Doses are measured relative to the ACR accreditation phantom, which simulates a 4.2 cm compressed breast consisting of 50% adipose tissue. Doses measured relative to 4.5 cm PMMA are approximately 20% higher*

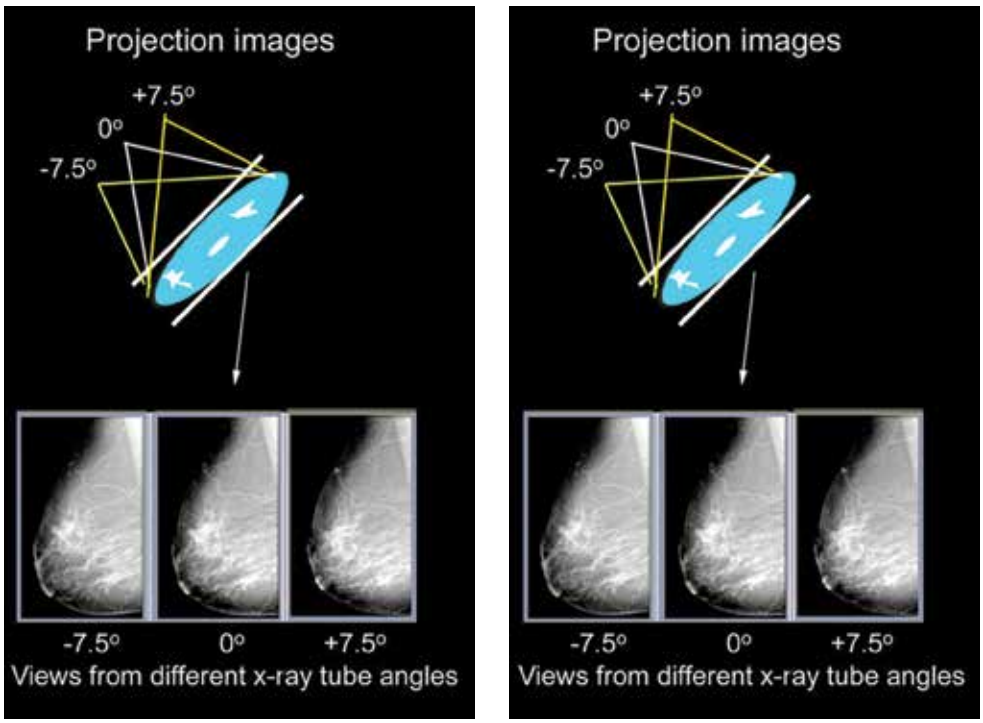
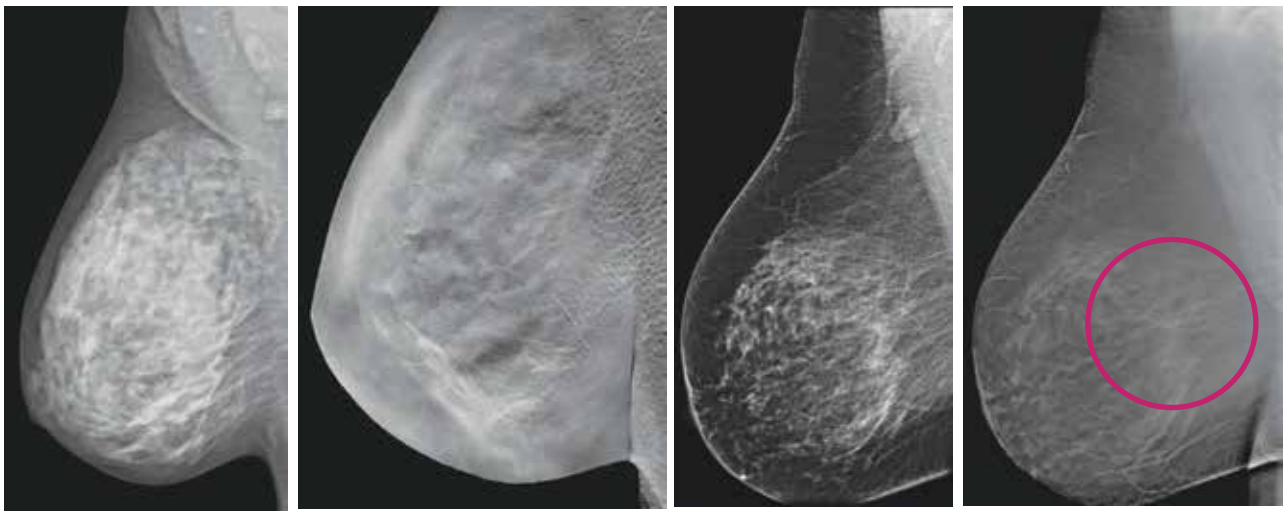
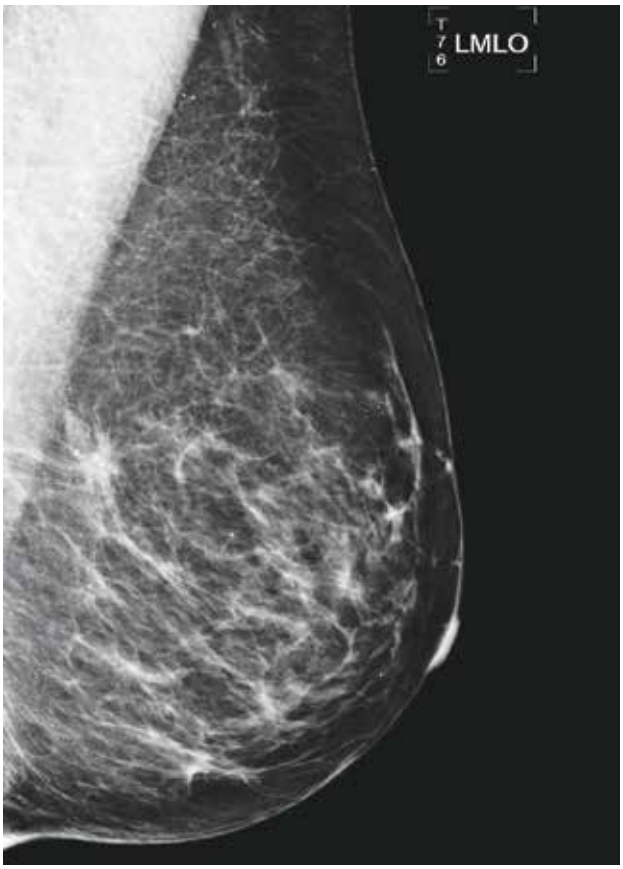
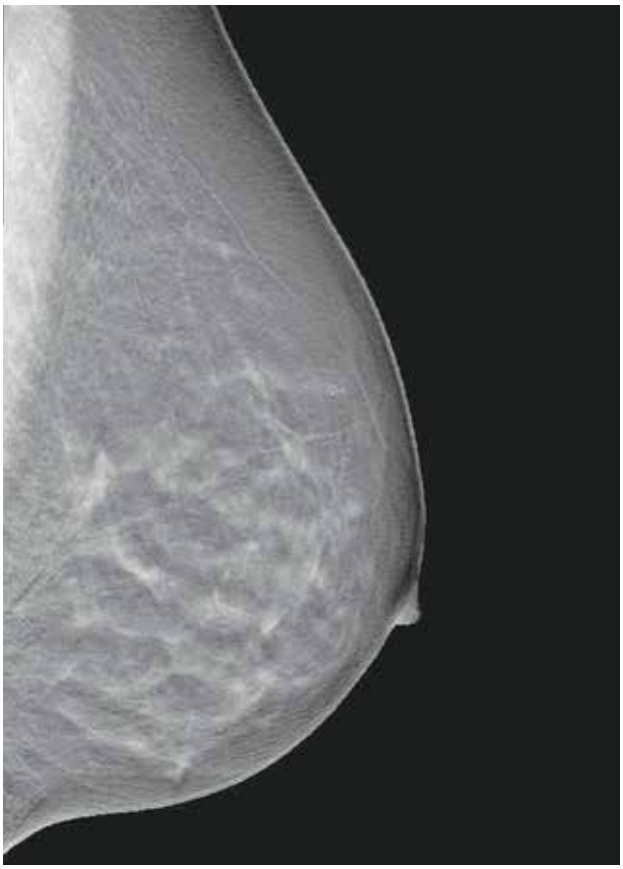


image 4. *Tomosynthesis procedure*

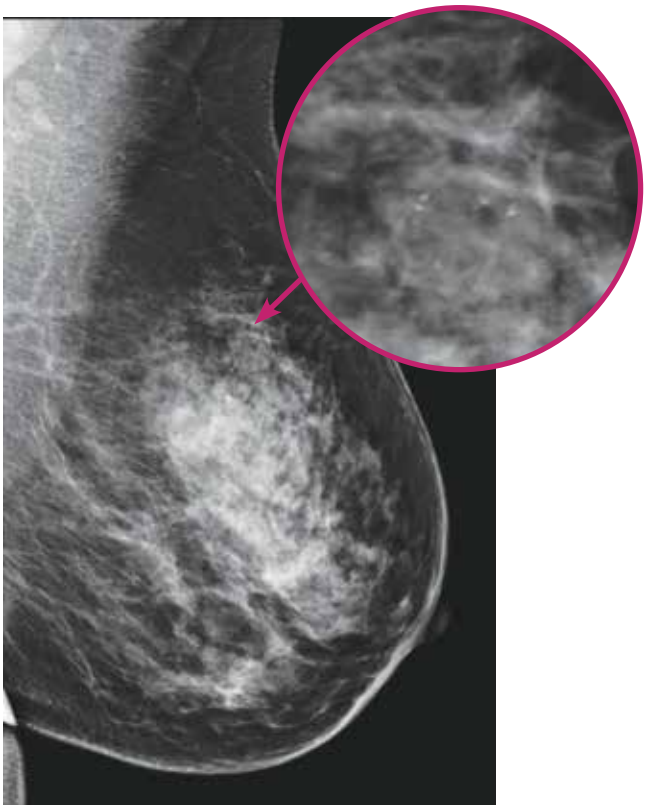


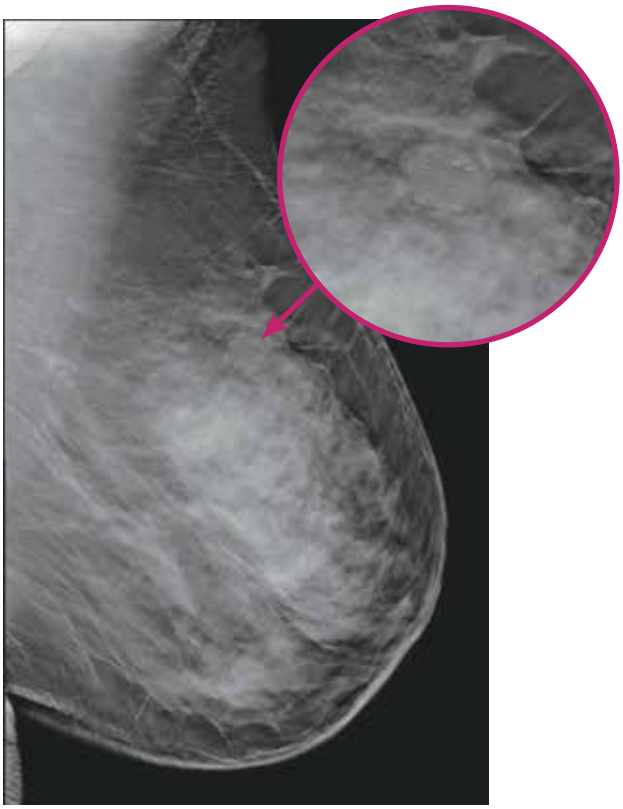
Images 5,6,7,8. *Palpable masses not shown in 2D*



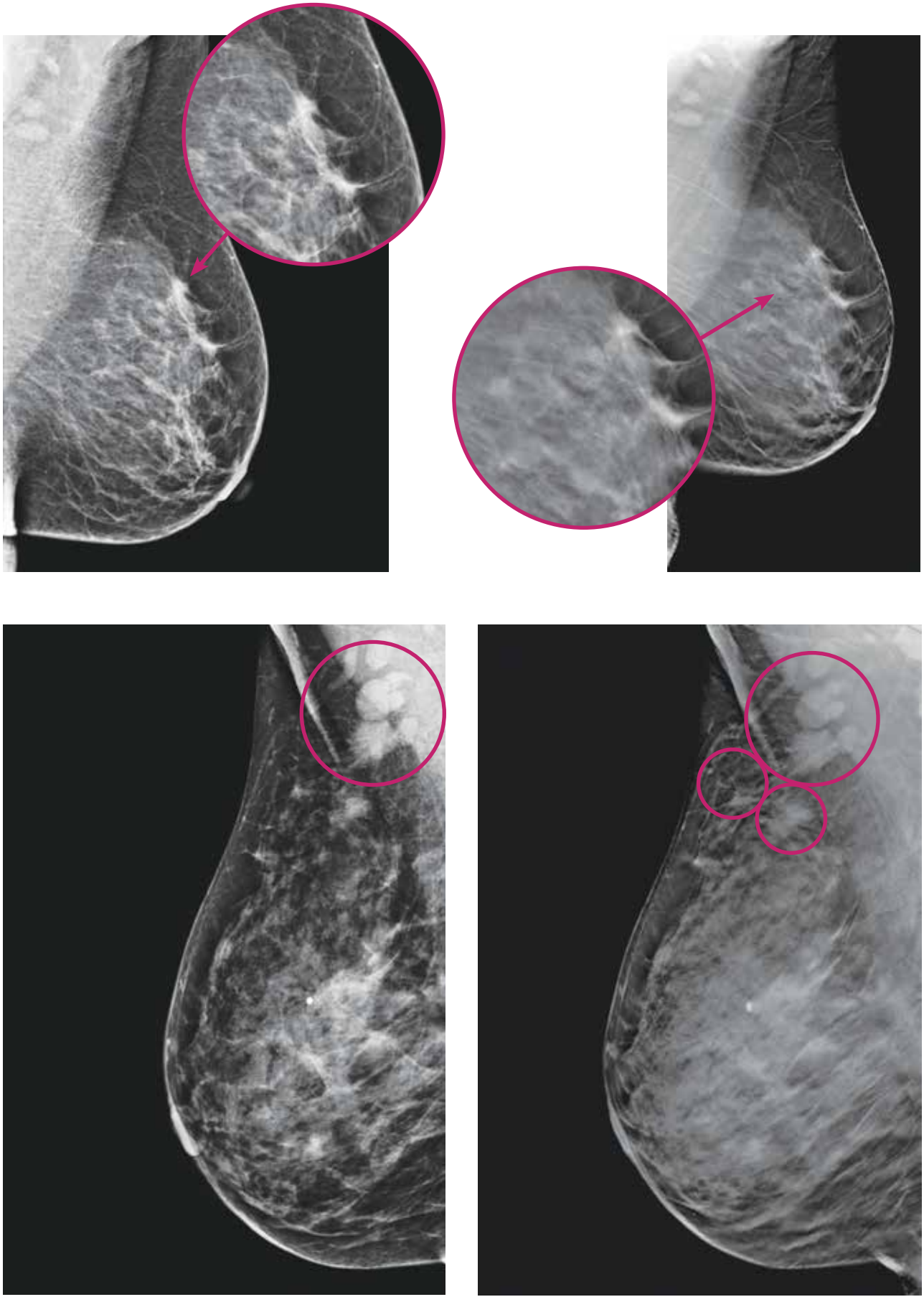


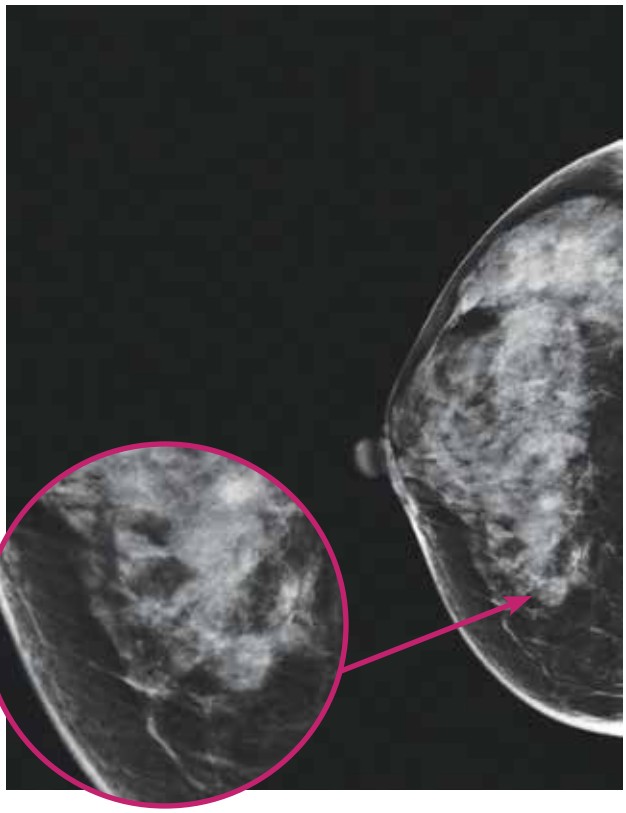
Superimposition findings

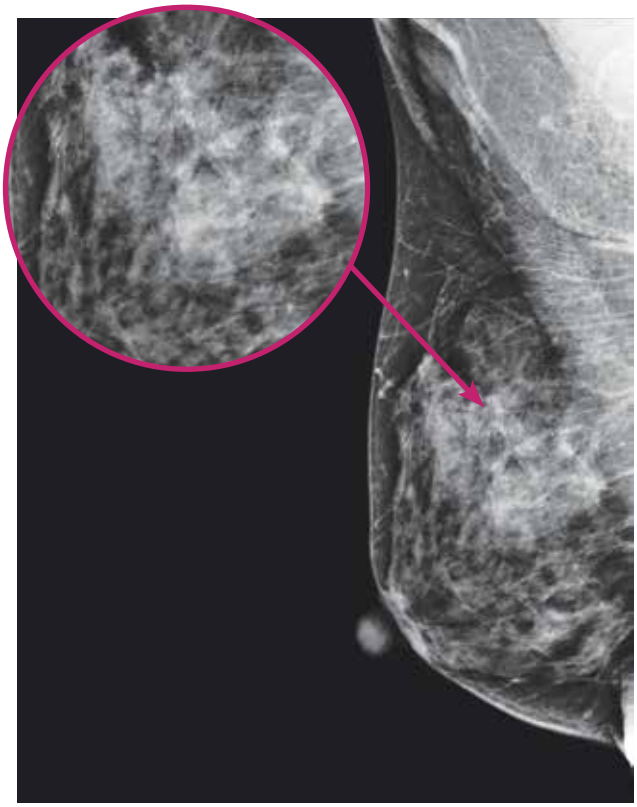


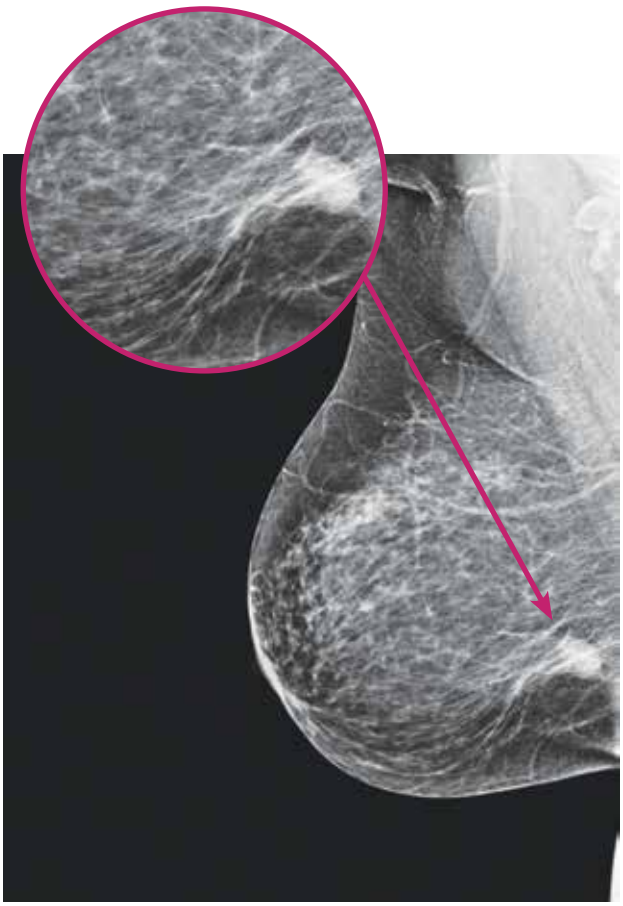


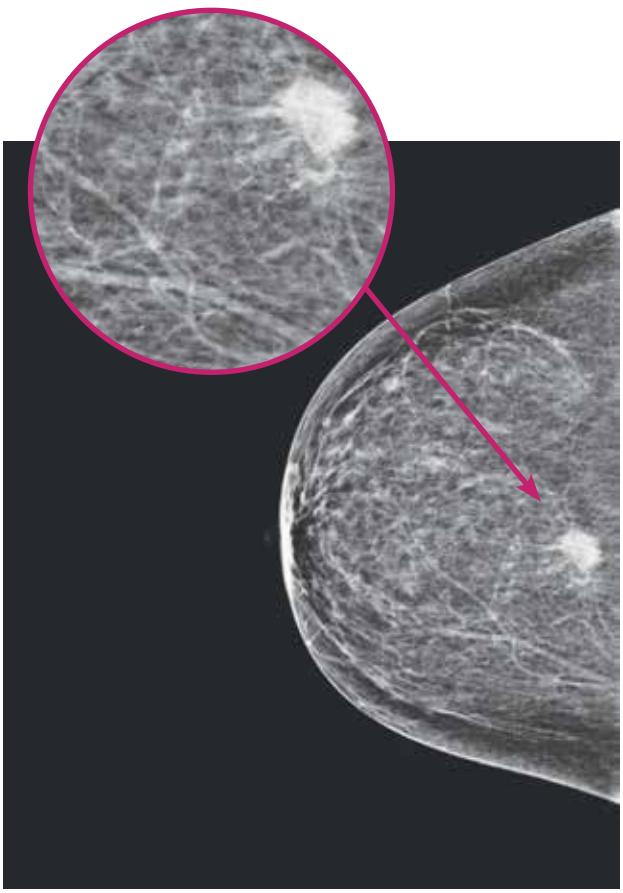
Benign or Malignant findings cases

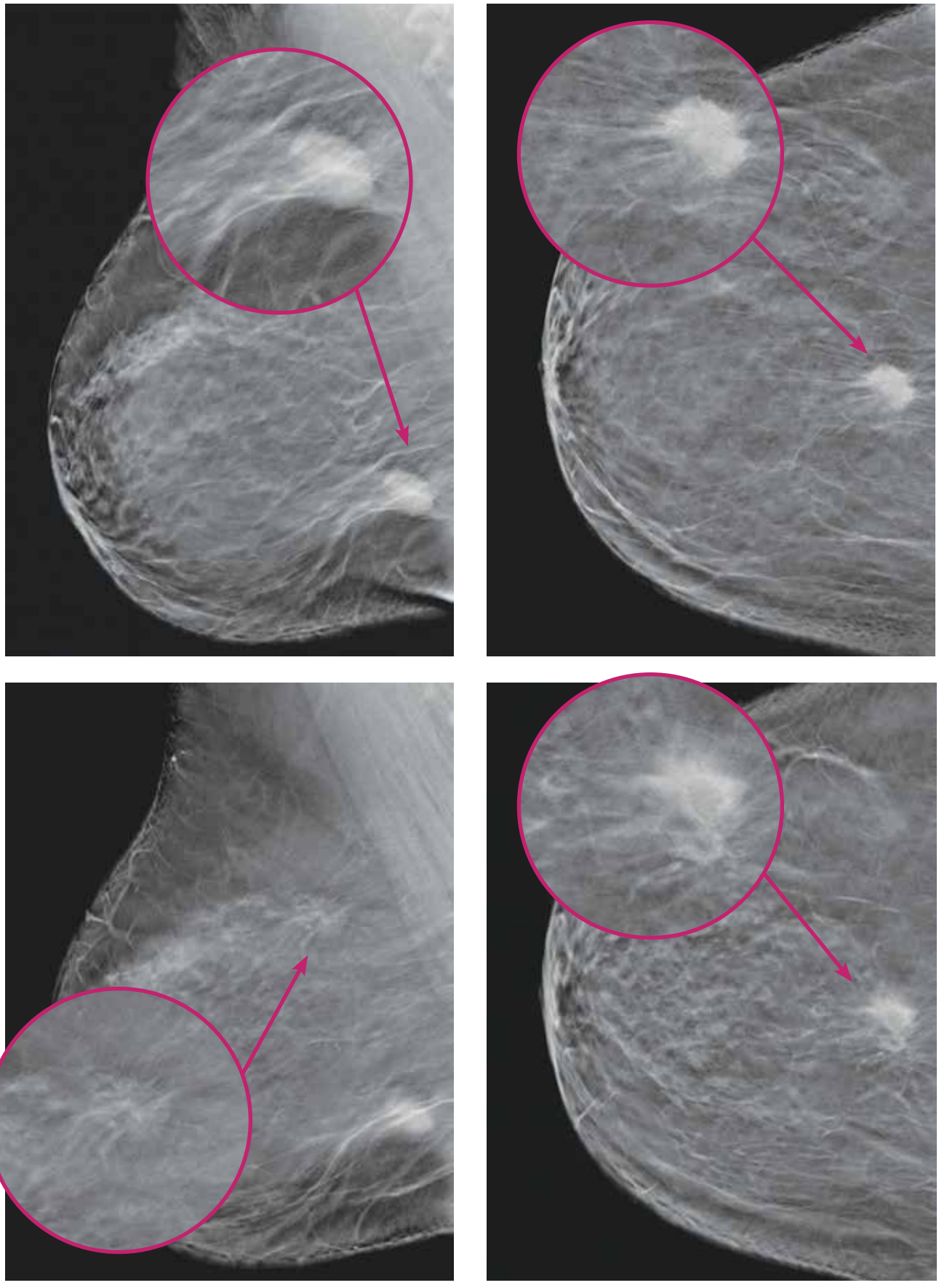


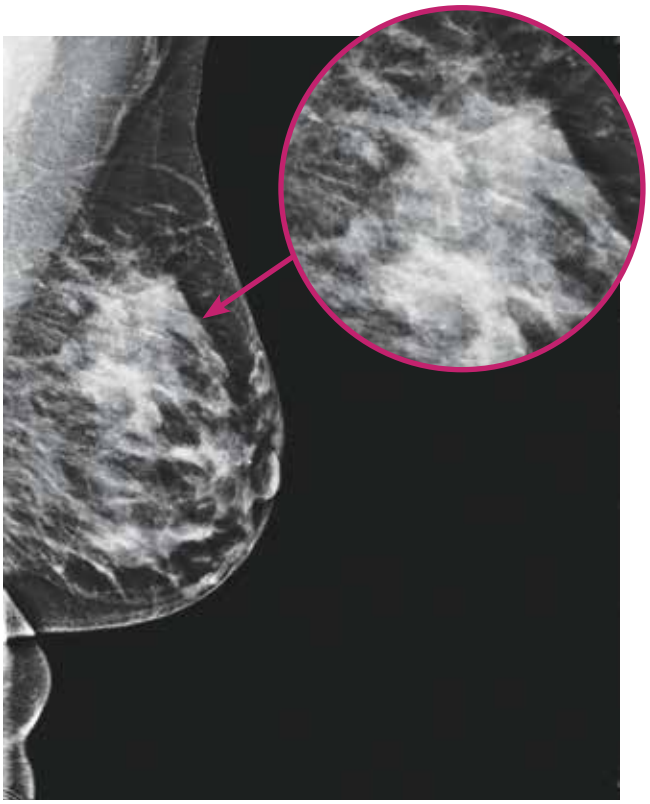


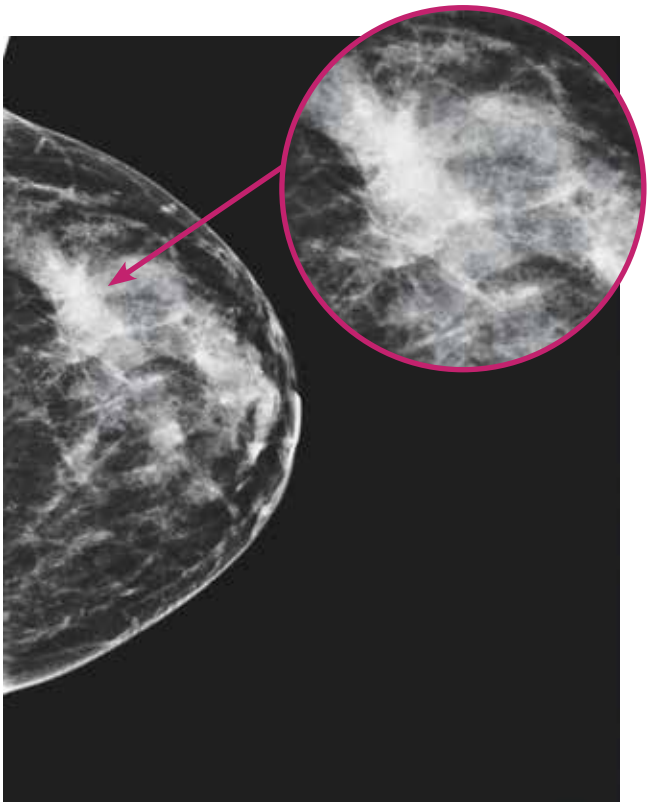




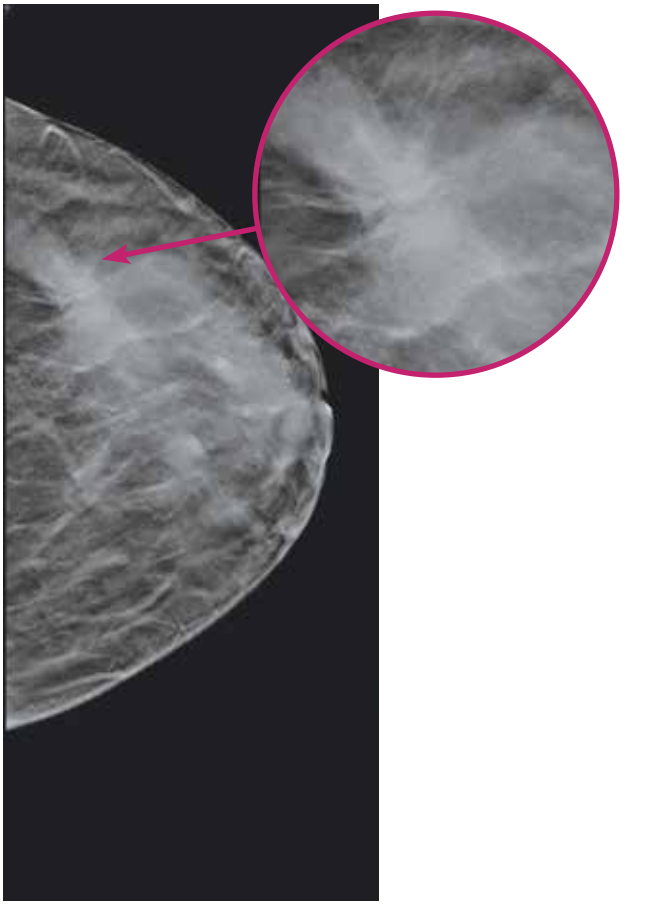








Suspicious microcalcifications with or without a mass?

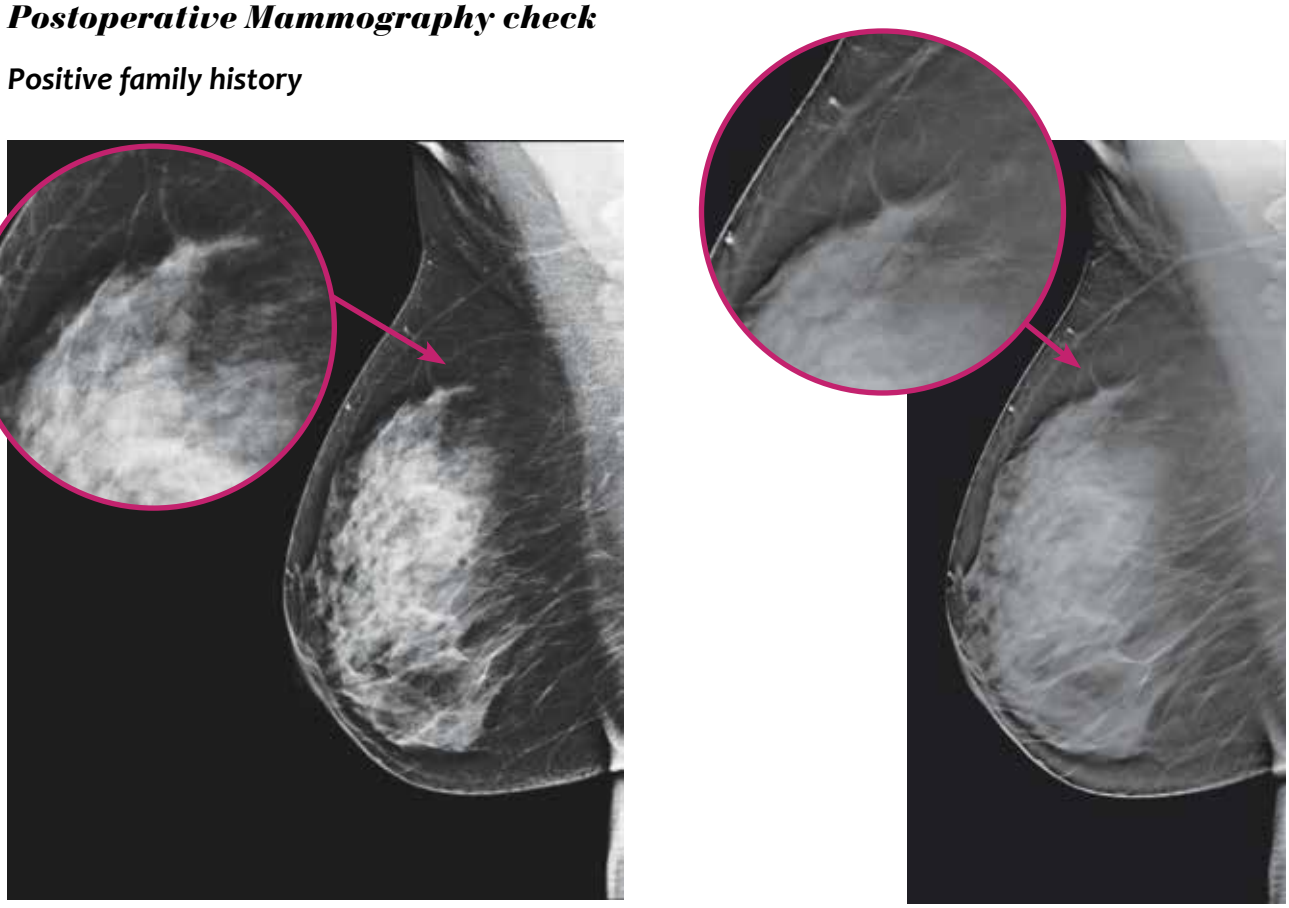


Risk cases

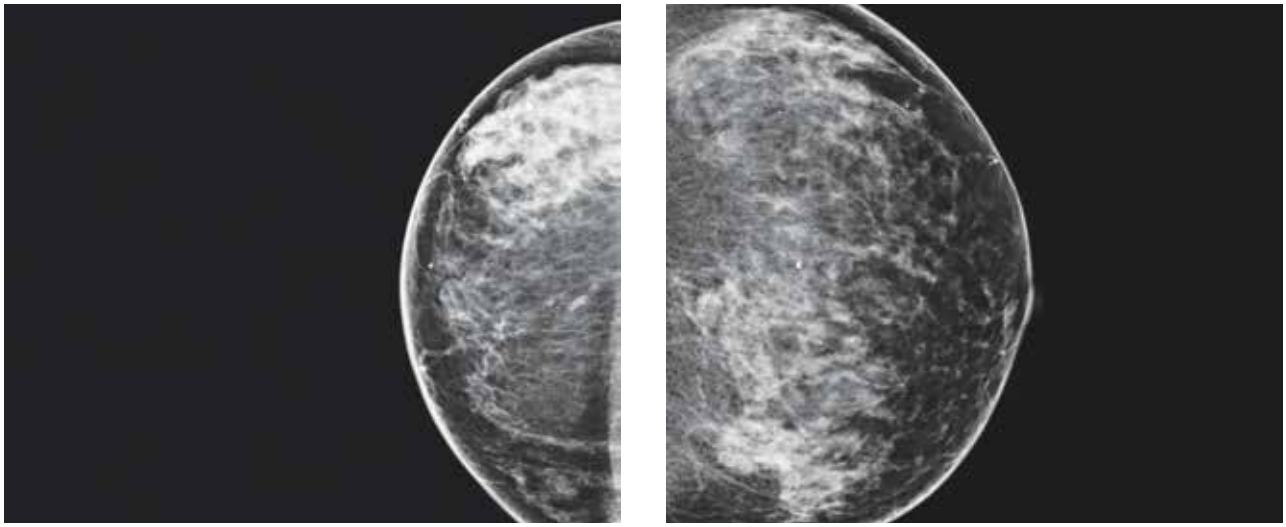
- Positive family history
- Postoperative Mammography check
- Checking the other breast in a breast cancer case.

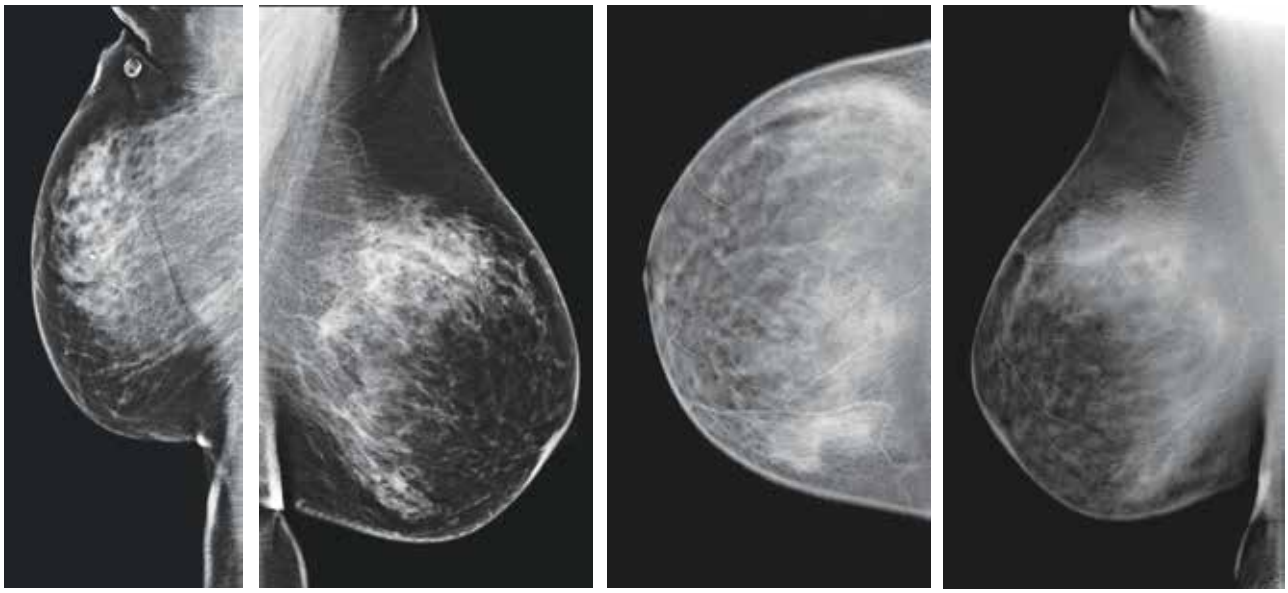
Postoperative Mammography check

Positive family history

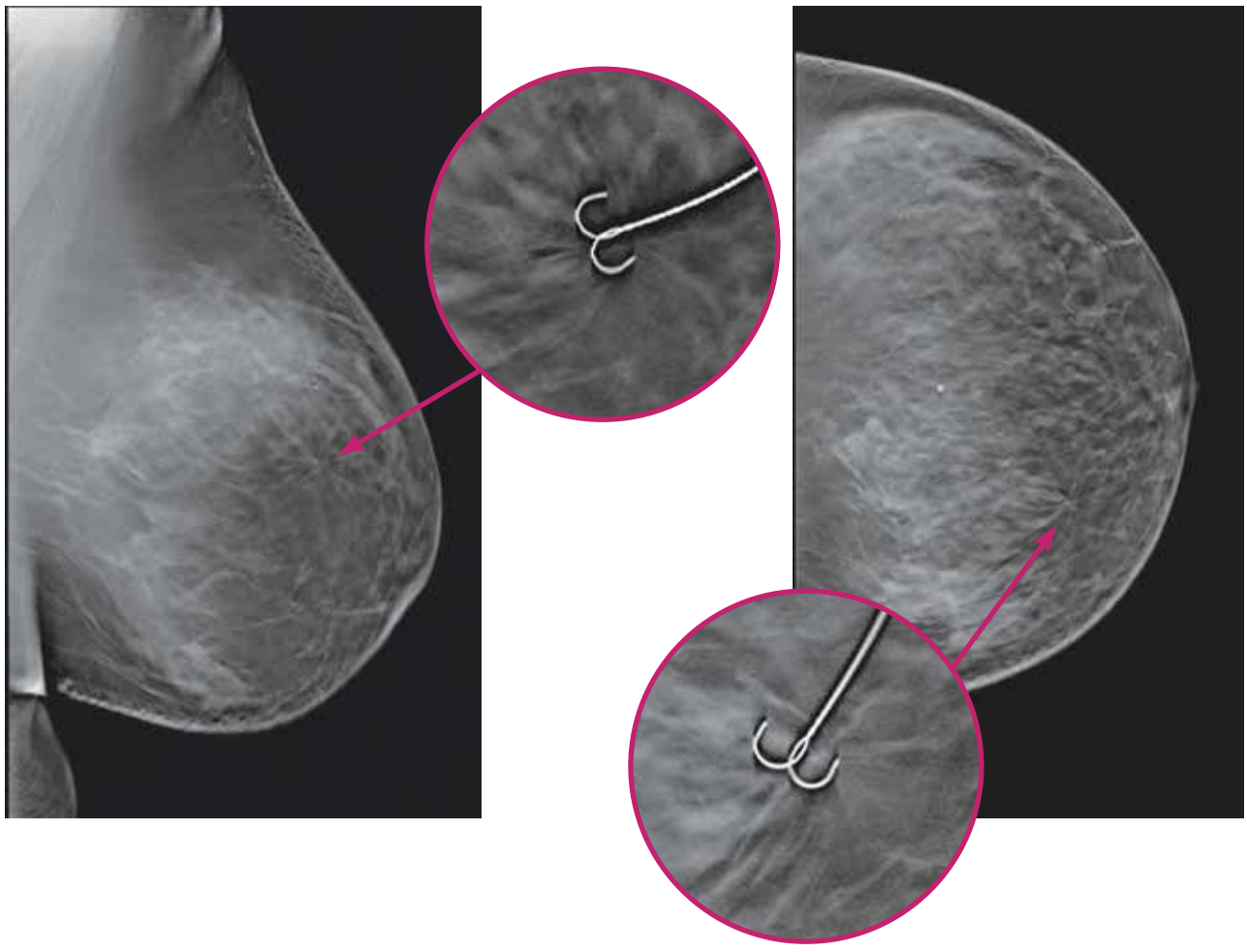


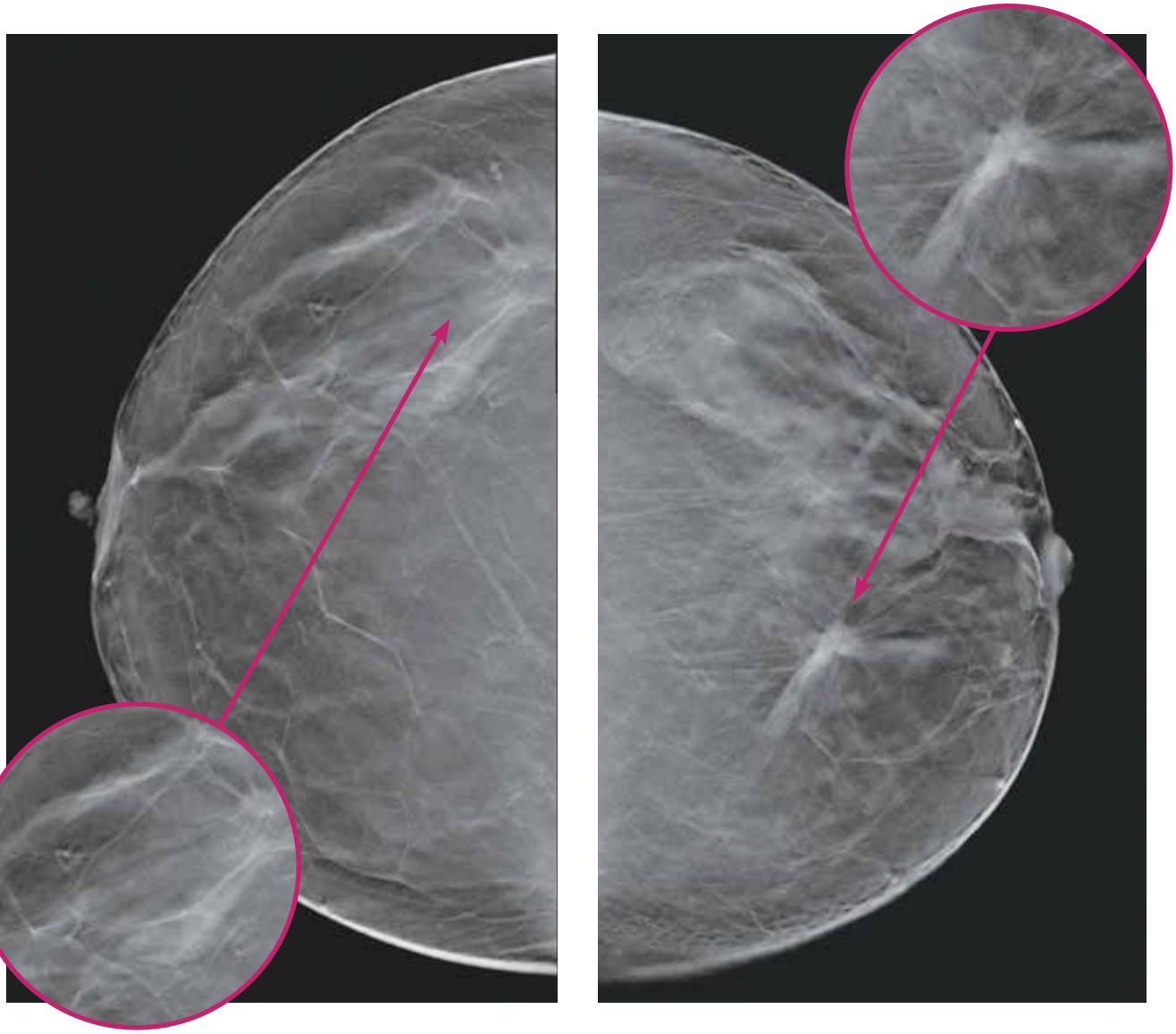
Postoperative Mammography check





Checking the other breast in a breast cancer case





Clinical advantages of tomosynthesis

- Easier B.I.R.A.D.S Classification.
- Fewer Recalls.
- Better Imaging of the Findings.
- Fewer Biopsies

RSNA 2007 E Rafferty, L Niklason, et al.

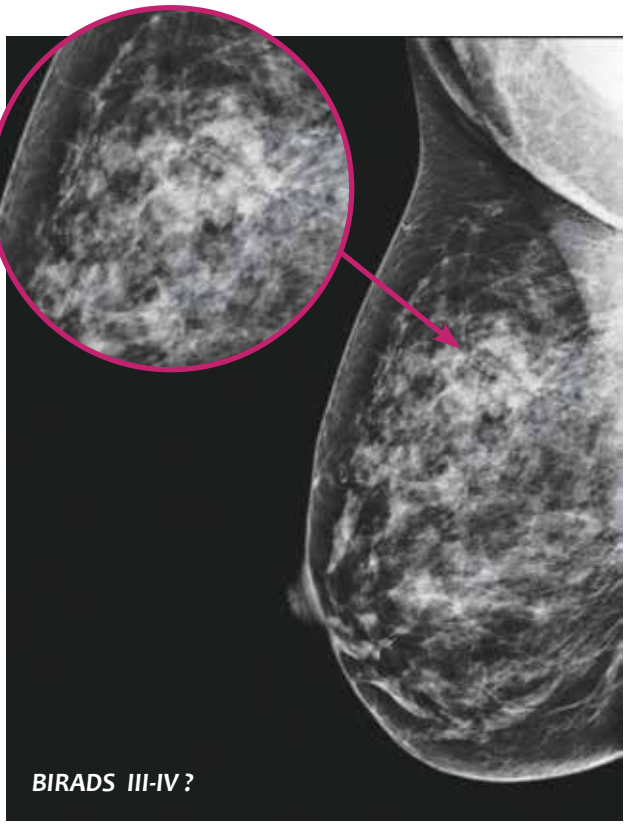
Assessing Radiologist Performance Using Combined Full-Field Digital Mammography and Breast Tomosynthesis Versus Full-Field Digital Mammography Alone: Results of a Multi-Center, Multi-Reader Trial

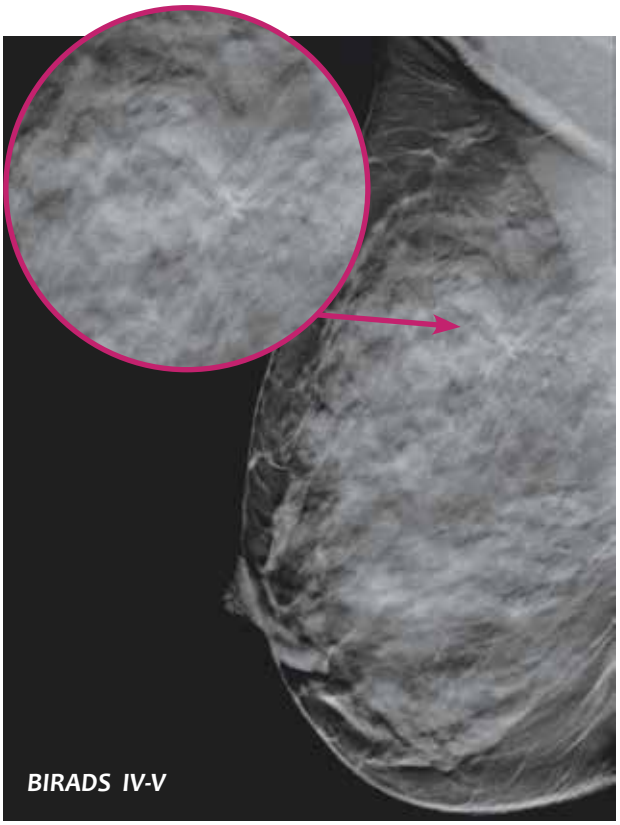
1083 women imaged

- 316 women in reader study with 12 radiologists
- Study performance 2D vs. 2D+3D

Results

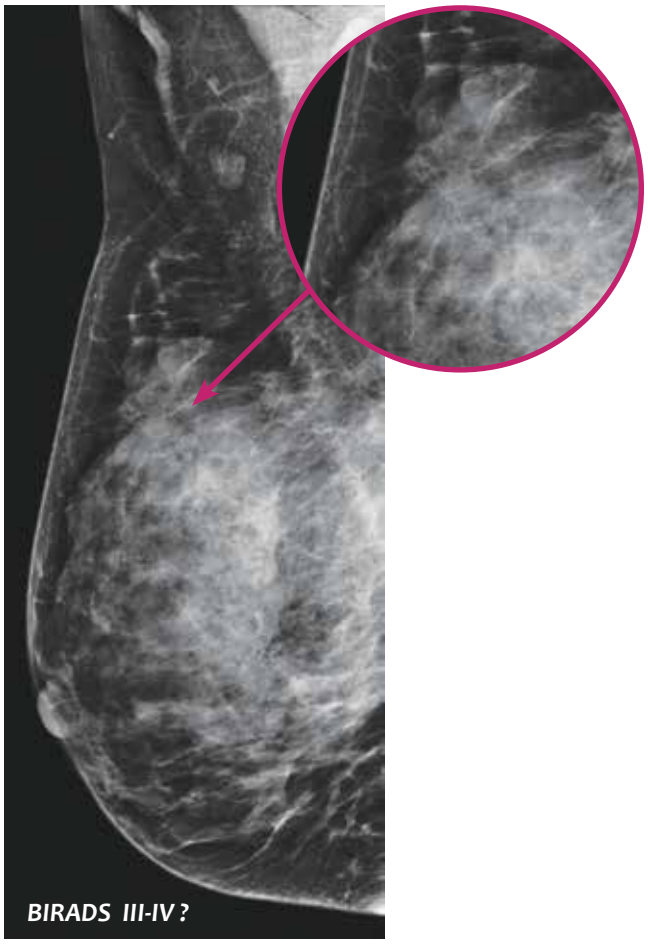
- Sensitivity (cancers with BIRADS 4&5) increased from 66% to 76%
- Specificity (normals with BIRADS 1-3) increased from 81% to 89%
- Recall rate reduced by 43%


BIRADS III-IV ?


BIRADS IV-V


BIRADS III-IV ?

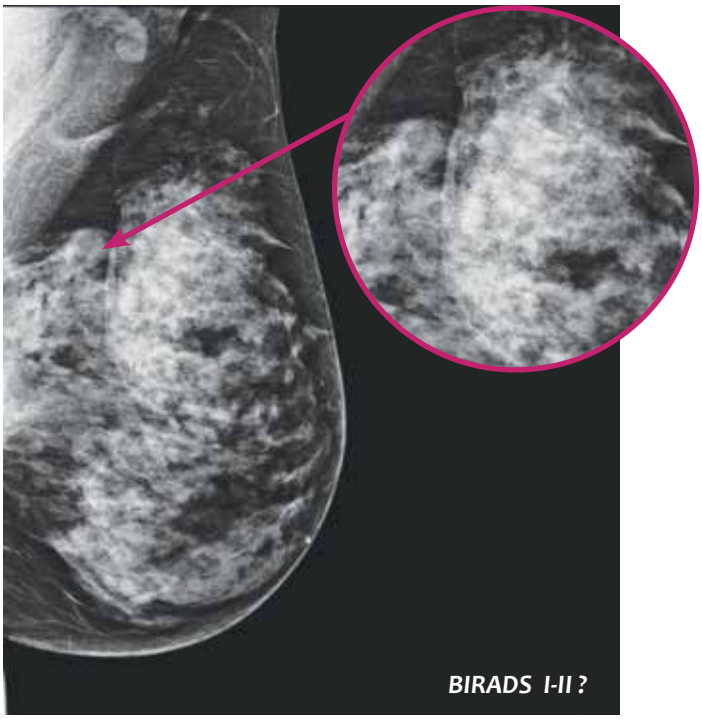

BIRADS IV-V

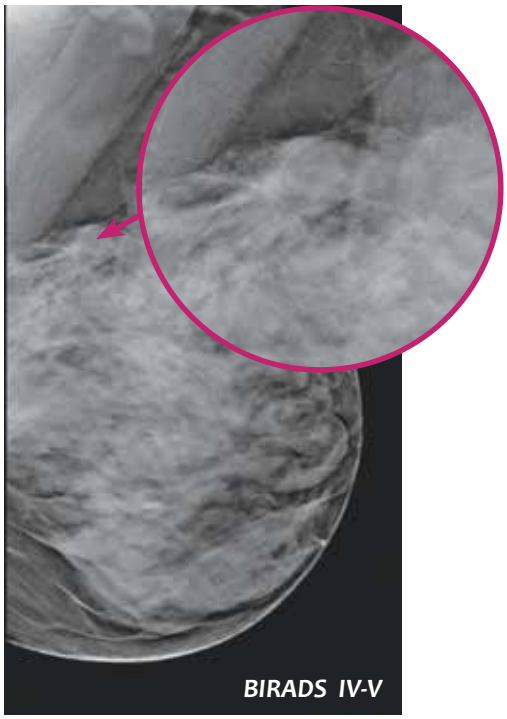

BIRADS III-IV ?

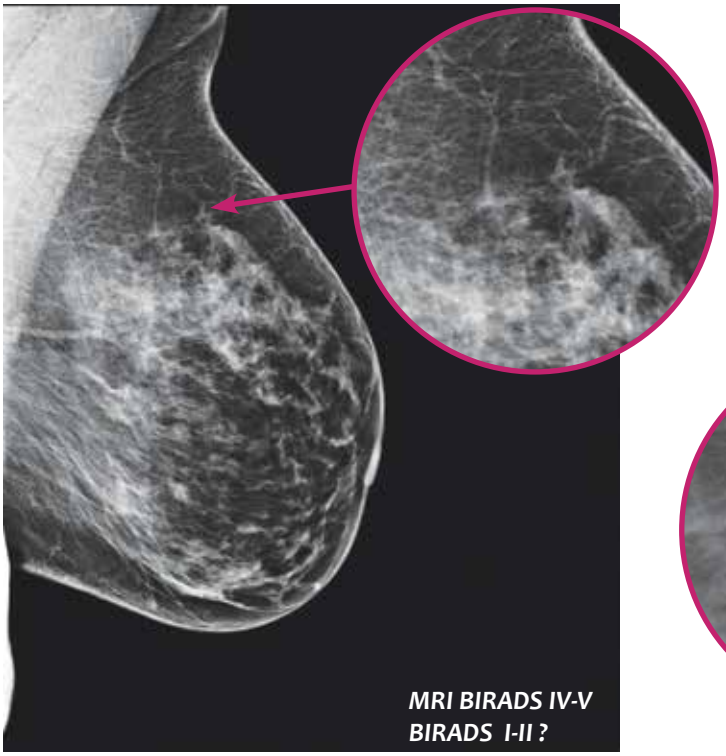

BIRADS IV-V

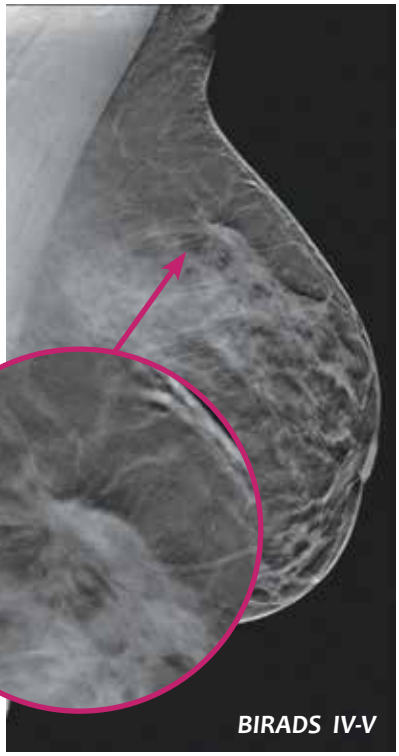

BIRADS III-IV ?


BIRADS IV-V


BIRADS I-II ?


BIRADS IV-V


MRI BIRADS IV-V
BIRADS I-II ?


BIRADS IV-V

Mammography Limitations

- Prompt annual mammography has shown the ability to reduce the mortality rate from breast cancer in a population by 15% to 50%.[1-3]
- As many as 20% of breast cancers will be missed by mammography.
- Approximately 10% of women are recalled for additional workup and a significant portion prove to have no abnormality, resulting in unnecessary anxiety and cost.

Conclusion

Early results with digital tomosynthesis are new promising breast imaging technique that will make breast cancers easier to find in dense breast tissue and will make breast screening more comfortable.

Conflict of interests

The authors declare that they have no commercial competing interests or financial support for this study.

REFERENCES

1. Smith RA, Duffy SW, Gabe R et al. The randomized trials of breast cancer screening: What have we
1. learned? *RadiolClin N Am* 2004; **42**:793 – 806.
2. Hendrick RE, Smith RA, Rutledge JH, Smart CR. Benefit of screening mammography in women ages 40-49: A new meta-analysis of randomized controlled trials. *Monogr Natl Cancer Inst* 1997;**22**:87-92.
3. Tabar L, Vitak B, Tony HH, Yen MF, Duffy SW, Smith RA. Beyond randomized controlled trials: organized mammographic screening substantially reduces breast carcinoma mortality. *Cancer* 2001;**91**:1724-31.

REVIEW

Psychology

Psychosocial support for women with breast cancer

The experience of the Elli Labeti Centre

Chronopoulou Constantina[1] MSc and Lydia Ioannidou-Mouzaka[2] MD,PhD

[1] MSc psychologist - psychotherapist , Head of the psychosocial support Centre " Elli Lambeti "

[2] Gynecologist-Surgeon-Breast Specialist, National Representative of Greece for Breast Centers and Breast Cancer in the European Union, President of the Hellenic Senologic Society,Delegate in European Initiative on Breast Cancer in Guidelines Development Group

ABSTRACT

Among other forms of the same disease, breast cancer has special differences, resulting from the target organ specific perceptions. Woman with breast cancer doesn't confront only a serious disease, but also the possible loss of a part of her body, which stands for two of the most significant aspects of her existence: motherhood and sexuality. Depression and Post Traumatic Stress Disorder are the most common psychological consequence of cancer diagnosis as also therapy. The main mechanisms used for the disease adaptation are denial, fighting, stoic acceptance, accepting with escort anxiety/grief, desperation /helpless. The Hellenic Society of Mastology, founded in 2002 the Centre for psychosocial support of women with breast cancer and their families "Elli Lambeti", providing psychosocial support, absolutely free

Although breast cancer is still the most frequent malignant tumor of the female population; unlike the older belief, it is not considered any longer as a final disease. Despite the fact that most cases nowadays are treatable, it still remains a "painful" condition for the woman at all phases, such as diagnosis, treatment but mainly rehabilitation. In this specific period in the healing process many adaptive efforts are required, both from the patient and her family, since the whole situation requires full acceptation in order to make the disease part of woman's life. Among other forms of the same disease, breast cancer has special differences, resulting from the target organ specific perceptions. Woman with breast cancer doesn't confront only a serious disease, but also the possible loss of a part of her body, which stands for two of the most significant aspects of her existence: motherhood and sexuality. The latter is particularly important, if one considers that breast cancer is most common in an age that also other factors (e.g. menopause, normal aging) adversely affect the sense of femininity and attractiveness that felt and believed by women. (Pagonidis., 2005).

Corresponding Author

Chronopoulou Constantina, Msc Psychologist-Psychotherapist

Email: k_chronopoulou@yahoo.gr

The rates of serious mental disorders (e.g. schizophrenia) are not higher in patients with cancer than the general population. Yet, many women with cancer experiencing psychological exhaustion, which manifests with symptoms of depression (Daush et al., 2004), such as insomnia, inability to concentrate, loss of appetite, increased use of alcohol and sedatives, suicidal thoughts, sexual dysfunction and disruption of daily activities. Depression is the most common psychological consequence of cancer diagnosis as also therapy (Sharippo , Gottman &Carrere, 2000). Currently, there is interest in the study of cancer diagnosis as a traumatic event, which causes symptoms nearly identical to those of post-traumatic stress disorder (PTSD).

Cancer is a life threatening, chronic disease and people who have been diagnosed with cancer, report reactions that include fear, sense of impotence or panic. Through this angle, it seems logical to be classified among the events that trigger PTSD. Patients are likely to experience stress when something reminds them of the treatment or their experience with cancer. Stress manifest very often with recurrent, intrusive memories, dreams about treatment, fear of relapse, fears of death and physical reactions (Cordova et al., 1995, Hodgkinson et al, 2007).

Extensive studies have shown that the main mechanisms used for the disease adaptation are the following:

a) Denial. The person denies vigorously any indication that argues suffer from serious disease. In breast cancer cases for example, the woman refuses emphatically the diagnosis, while labeling surgical interventions with words like: "it wasn't anything serious, they just removed the breast for prudence reasons". These women never refer to the issue and quickly change the conversation subject if something is brought up by someone else.

b) Fighting. The patient appears devoted to fight and defeat. She keeps a positive attitude, hopes for a good outcome and usually gathers by herself as much information as she can for the disease and the treatment. Usually these patients ask their doctor to learn as much details as they can about their condition, or other friends who happen to suffer from the same disease, and may feel lucky that it was "discovered on time".

c) Stoic acceptance. Those patients accept diagnosis as it is. They don't seek information about their problem unless new issues arise and generally continue to live as before without dealing with their disease.

d) Accepting with escort anxiety/grief. These patients react to the diagnosis with excessive anxiety and/or sadness. As women with stoic spirit, they actively seek to learn as much information as they can, but unlike the first group they tend to the interpratate everything with a negative and pessimistic manner. However, they are able to come through their daily ordinary activities.

e) Desperation /Helpless. These women seem to be dominated entirely by the diagnosis. They consider themselves constantly sick whether or not they have symptoms, and sometimes they act as if they are going to pass away shortly. Their daily functionality is completely effected by the disease and totally disordered.

Considering all this fact, the Hellenic Society of Mastology, founded in 2002 the Centre for psychosocial support of women with breast cancer "Elli Lambeti", aiming at improving their quality of life, as well as supporting members of their families. Since 2004 the Centre is functioning under the municipality of Athens sponsorship and is accommodated in the Kalfopouleio Central health clinic in Athens centrum, Solon 78.

The Center is referred to every woman with a recent diagnosis of Breast Cancer, who are under treatment or during recovery process, but also to people of their immediate environment e.g. family, work or community.

The facilities provided by the Center are information in relation to the disease, individual or group counselling, counselling patient's families, during or after treatment. The "Elli Lampeti center" also provides the possibility of meeting and communicating with other women experiencing the same problem, attendance at cultural events and other activities (conferences, festivities, bazaars, concerts, exhibitions etc.). An important thing to be noticed is that all the services are **absolutely free**. There is also the opportunity supporting women in the province, via telephone sessions or via skype.

Conflict of interests

The author declares that she has no commercial competing interests or financial support for this study.

REFERENCES

1. Cordova MJ, Cunningham LLC, Carison CR, & Anrykowski MA. **Posttraumatic growth following breast cancer: A controlled comparison study**. *Health Psychology*.2001;20:176-185
2. Dausch BM, Compas BE, Beckjord E, Luecken L, Anderson–Hanley C, Sherman M et al. **Rates and collatesof DSM-IV diagnoses in women newly diagnosed with breast cancer**. *J of Clin Psychol in Medical Settings*.2004;**11**:159-169
3. Shapiro AF, Guttman JM & Carrere S. **The baby and the marriage. Identifying factors that buffer against decline in marital satisfaction after the first baby arrives.** *Journal of family Psychology*. 2000;14: (1),59-70
4. Pwgwnidis Ch, Xenodochidoy E, Christodoulou E, Bagiopoylos G, Gkototsidis K, Livaditis M. **Depression and cancer of the breast-μ μ. A case Report.** Athens: 9th Congress of Psychosocial Oncology, 2005

REVIEW

Breast Cancer

Hereditary Breast and Ovarian Cancer *BRCA 1&2*

Apessos Angela, Agiannitopoulos Konstantinos, Pepe Georgia, Papadopoulou Eirini, Metaxa-Mariatou Vasiliki, Tsirigoti Angeliki, Efstathiadou Chysa, Tsaousis Georgios, Nasioulas Georgios

Genekor Medical S.A, Department of Molecular Biology, 52 Spaton Ave., 15344 Gerakas, Greece

ABSTRACT

Germline mutations in BRCA1 and BRCA2 genes are highly associated with predisposition to breast and ovarian cancer. Sensitive and accurate detection of BRCA1 and BRCA2 mutations is crucial for the prevention and clinical management of the individuals affected by breast or ovarian cancer, and for the identification of at-risk healthy relatives. Until recently, the "gold" standard method for BRCA1/2 molecular analysis was Sanger sequencing. However, advances in high throughput technologies such as Next Generation Sequencing (NGS) are changing genetic diagnosis due to its huge sequencing capacity and cost-effectiveness.

Most cases of breast cancer are sporadic. However, it is more common in some families due to their genetic background. Approximately 5-10% of all cancers are due to hereditary (genetic) damages on the DNA which is passed down from parents to offspring. These damages are called hereditary (germline) mutations.

Hereditary Breast and Ovarian Cancer syndrome is mostly due to mutations in the BRCA1 (approximately 50%) or the BRCA2 gene (approximately 35%). The lifetime risk of breast cancer in female carriers of a BRCA1 mutation is 60-80% while that of ovarian cancer is 20-40%. Male carriers of BRCA2 mutations have 8% risk of developing breast cancer and 20% risk of developing prostate cancer by the age of 80. The median age at diagnosis of breast cancer is 42 years, i.e. 20 years earlier than the median of unselected women in the U.S.A. and Western Europe.[1]

Both genes are very large and their protein products function in maintaining genomic integrity and in transcriptional regulation.[2,3] A multitude of mutations scattered throughout the coding sequence of the genes have been described. In particular, germ line mutations in BRCA1 have been identified in 15-20% of women with a family history of breast cancer and 60-80% of women with a family history of breast and ovarian cancer.[4,5] The percentage of mutations identified is strongly dependent on the population studied, with strong founder effects evident in some populations.[6-8] The vast majority of mutations described to date are point mutations and small insertions and deletions (http://www.nhgri.nih.gov/Intramural_research/Lab_transfer/Bic/).

DNA sequencing is used in order to characterize the mutations traditionally using the Sanger method and more recently Next Generation Sequencing (NGS). NGS broadly

Corresponding author

Konstantinos Agiannitopoulos, MSc,

Genekor Medical S.A, Department of Molecular Biology, 52 Spaton Ave., 15344 Gerakas, Greece

describes those technologies that share the ability to massively parallel sequence millions of DNA templates. The terms second-generation and third-generation sequencing are also used synonymously to describe the evolution of sequencing technology from the first-generation dideoxy 'Sanger' sequencing. To achieve massive parallel sequencing, second-generation platforms employ the clonal amplification of DNA templates on a solid support matrix followed by cyclic sequencing.[9, 10,11,12]

While in the early studies for mutation detection only single point or small insertion/deletion mutations were screened for, recent studies have shown that genomic rearrangements are also a common type of mutation in the two genes accounting for 10-30 % of all mutations identified in some populations.[13-16]

As a result of these observations more recent international guidelines state that analysis of the two genes should include both complete sequencing of the entire coding region, including intron-exon boundaries, and a method for the detection of large genomic rearrangements.[17,18]

Molecular diagnosis of breast and ovarian cancer syndromes is very important as it can be used to tailor the treatment of the patient. Multiple studies in families with mutations have shown that the survival probability increases rapidly with early diagnosis and adequate surgical intervention for the prevention of cancer in individuals at high risk. Furthermore, target-therapy for BRCA1/2 mutation carriers is already being used in the treatment of ovarian cancer.

Genetic testing criteria differ between countries. Widely accepted clinical criteria for referral include[19,20]:

- three or more breast and/or ovarian cancer cases
- at least one <50 years
- two breast cancer cases <40 years
- male breast cancer and ovarian cancer or early onset female breast cancer
- Ashkenazi Jewish decent with breast cancer at <60 years
- young onset bilateral breast cancer
- breast and ovarian cancer in the same patient

Less specific criteria include [19]:

- a potential benefit in the medical
- or surgical management of the individual and/or his/her relatives.
- Pathological features of breast cancer such as
  - medullary carcinoma and
  - triple negative phenotype (estrogen receptor, progesterone receptor and no overexpression of HER2neu).

In all cases, genetic testing should be performed on adults, usually >25 years old, after having received genetic counseling and informed consent. Carriers should be encouraged to advise close family members to obtain genetic counseling.[19]

In recent years, technological advances have allowed the rapid expansion of genetic analysis both in research and in clinical practice. With the advent of NGS, it has become possible to analyze multiple genes simultaneously. This is especially important in families with multiple cancer types for which mutations in different genes have been implicated and in syndromes with overlapping phenotypes. Indeed, recent bibliography indicates that 4-16% of women with breast and / or ovarian cancer carry germline pathogenic mutations in genes other than BRCA1 or BRCA2.

The data being accumulated from such studies is rapidly transferred to clinical practice and new clinical management guidelines for carriers of mutations in these genes are being issued.[20] Furthermore, continuing research on these genes is focused on the development of targeted therapy compounds for the treatment of patients from families with a hereditary cancer predisposition syndrome.[21]

Conflict of interests

The authors declare that they have no commercial competing interests or financial support for this study. ■

REFERENCES

1. Nathanson KN, Wooster R, Webber BL: **Breast cancer genetics: What we know and what we need.** *Nature Medicine* 2001, **7**:552-556
2. Venkitaraman AR: **Functions of BRCA1 and BRCA2 in the biological response to DNA damage.** *Journal of Cell Science* 2001, **114**:3591-3598
3. Deng C-X, Wang R-H: **Roles of BRCA1 in DNA damage repair: a link between development and cancer.** *Human*

Molecular Genetics 2003, **12**:R113-R123

4. Gayther SA, de Foy KA, Harrington P, Pharoah P, Dunsmuir WD, Edwards SM, Gillett C, Ardern-Jones A, Dearnaley DP, Easton DF, Ford D, Shearer RJ, Kirby RS, Dowe AL, Kelly J, Stratton MR, Ponder BA, Barnes D, Eeles RA: **The frequency of germ-line mutations in the breast cancer predisposition genes BRCA1 and BRCA2 in familial prostate cancer. The Cancer Research Campaign/British Prostate Group United Kingdom Familial Prostate Cancer Study Collaborators.** *Cancer Res*. 2000, **60**:4513-4518
5. Ford D, Easton DF, Stratton M, Narod S, Goldgar D, Devilee P, Bishop DT, Weber B, Lenoir G, Chang-Claude J, Sobol H, Teare MD, Struewing J, Arason A, Scherneck S, Peto J, Rebbeck TR, Tonin P, Neuhausen S, Barkardottir R, Eyfjord J, Lynch H, Ponder BA, Gayther SA, Zelada-Hedman M, and the Breast Cancer Linkage Consortium: **Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families. The Breast Cancer Linkage Consortium.** *Am J Hum Genet* 1998, **62**:676-689
6. Szabo CI, King MC: **Population genetics of BRCA1 and BRCA2.** *Am J Hum Genet* 1997, **60**:1013-1020
7. Neuhausen SL: Ethnic differences in cancer risk resulting from genetic variation. *Cancer* 1999, **86**:2575-2582
8. Steinberg KK, Pernarelli JM, Marcus M, Khoury MJ, Schildkraut JM, Marchbanks PA: **Increased risk for familial ovarian cancer among Jewish women: a population-based case-control study.** *Genet Epidemiol*: 1998, **15**:51-59
9. Andrulis IL, Anton-Culver H, Beck J, Bove B, Boyd J, Buys S, Godwin AK, Hopper JL, Li F, Neuhausen SL, Ozcelik H, Peel D, Santella RM, Southey MC, van Orsouw NJ, Venter DJ, Vijg J, Whittemore AS; Cooperative Family Registry for Breast Cancer studies: **Comparison of DNA- and RNA-based methods for detection of truncating BRCA1 mutations.** *Hum Mutat* 2002, **20**:65-73
10. Gross E, Arnold N, Goette J, Schwarz-Boeger U, Kiechle M: **A comparison of BRCA1 mutation analysis by direct sequencing, SSCP and DHPLC**. *Hum Genet* 1999, **105**:72-78
11. Metzker ML (2010) **Sequencing technologies - the next generation**. *Nat Rev Genet*. 11:31-46.
12. Weiss M, Van der Zwaag B, Jongbloed J, Vogel M, Brüggenwirth H, Lekanne Deprez R, Mook O, Ruivenkamp C, Marjon A. van Slegtenhorst, Arthur van den Wijngaard, Quinten Waisfisz, Marcel R. Nelen , Nienke van der Stoep. **Best Practice Guidelines for the Use of Next-Generation Sequencing Applications in Genome Diagnostics: A National Collaborative Study of Dutch Genome Diagnostic Laboratories.** *Human Mutation* 2013, **34**:1313–21.
13. Montagna M, Dalla Palma M, Menin C, Agata S, De Nicolo A, Chieco-Bianchi L, D'Andrea E. **Genomic rearrangements account for more than one-third of the BRCA1 mutations in northern Italian breast/ovarian cancer families.** *Hum Mol Genet* 2003, **12**:1055-1061
14. Barrois M, Bieche I, Mazoyer S, Champeme MH, Bressac-de Paillerets B, Lidereau R: **Real-time PCR-based gene dosage assay for detecting BRCA1 rearrangements in breast-ovarian cancer families.** *Clin Genet*. 2004, **65**:131-136
15. Casilli F, Di Rocco ZC, Gad S, Tournier I, Stoppa-Lyonnet D, Frebourg T, Tosi M: **Rapid detection of novel BRCA1 rearrangements in high-risk breast-ovarian cancer families using multiplex PCR of short fluorescent fragments.** *Hum Mutat* 2002, **20**:218-226
16. Apessos A, Papadopoulou E, Metaxa-Mariatou V, Agiannitopoulos K, Markopoulos C, Venizelos V, Xepapadakis G, Vasilaki-Antonatou M, Keramopoulos A, Bredakis N, Tsiftsoglou A, Kesisis G, Kakolyris S, Touroutoglou N, Natsiopoulos I, Papazisis K, Nasioulas G. **Different genomic rearrangements account for 17% of BRCA1/2mutations in Greece.** *Cancer Res May 1*, 2015 75; P1-03-08.
17. Unger MA, Nathanson KL, Calzone K, Antin-Ozerkis D, Shih HA, Martin AM, Lenoir GM, Mazoyer S, Weber BL: **Screening for genomic rearrangements in families with breast and ovarian cancer identifies BRCA1 mutations previously missed by conformation-sensitive gel electrophoresis or sequencing.** *Am J Hum Genet* 2000, **67**:841-850
18. Puget N, Stoppa-Lyonnet D, Sinilnikova OM, Pages S, Lynch HT, Lenoir GM, Mazoyer S: **Screening for germline rearrangements and regulatory mutations in BRCA1 led to the identification of four new deletions.** *Cancer Res* 1999, **59**:455-461.
19. J. Balmana, O. Diez, I.T. Rubio, F. Cardoso: **BRCA in breast cancer: ESMO Clinical Practice Guidelines.** *Annals of Oncology* 2011, **22 (Supplement 6)**: vi31–vi34
20. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): **Genetic/Familial High-Risk Assessment: Breast and Ovarian.** Version 3.2013.
21. Hennessy BT, Timms KM, Carey MS, Gutin A, Meyer LA, Flake DD 2nd, Abkevich V, Potter J, Pruss D, Glenn P, Li Y, Li J, Gonzalez-Angulo AM, McCune KS, Markman M, Broaddus RR, Lanchbury JS, Lu KH, Mills GB.: **Somatic mutations in BRCA1 and BRCA2 could expand the number of patients that benefit from poly (ADP ribose) polymerase inhibitors in ovarian cancer**. *J Clin Oncol*. 2010, **28**:3570-6.

An overview of in situ carcinoma of the breast. The role of ultrasound with presentation of multiple cases

Georgios Kyropoulos[1], Dora Kanavou[2], Apostolos Zavos[2]

1 Radiologist, Breast Radiologist Alexandreia Imathias

2 Breast Radiologist Larissa, Greece

3 Surgeon Gynecologist Obstetrician. Subspecialty Breast Diagnostic and Surgery, Board member of Hellenic Senologic Society, Deputy Editor of Mastologia Journal. Larisa, Greece

ABSTRACT

Although there are two types of in situ carcinoma, ductal carcinoma in situ (DCIS) and lobular carcinoma in situ (LCIS), DCIS is the most common type since LCIS is generally considered not real cancer. Nowadays, nearly 24% of all new diagnosed breast cancers are DCIS with 1 case of DCIS detected per 1300 screening mammographies. According to the WHO classification there are 3 grades of DCIS although there are also other histological based classifications including cribriform DCIS, solid DCIS, papillary DCIS, and "comedo type" DCIS. The most common appearance of DCIS in mammography is a cluster of microcalcifications with variable morphology. The role of Ultrasound of increasing importance giving a great opportunity for faster effective and cheaper solution to the diagnosis of a common problem. Even more inherently US can contribute depict cases of non-calcified DCIS that are occult in mammography.

1. Introduction

In situ carcinoma are characterized as proliferating lesions that tumor cells do not penetrate the basement membrane. There are two types of in situ carcinoma, ductal carcinoma in situ (DCIS) and lobular carcinoma in situ (LCIS). We will mainly deal with the DCIS since it is the most common type and because LCIS is generally though as an increased risk situation and not a real cancer.

Although breast cancer is a well-known disease for thousands of years, *ductal carcinoma in situ* (DCIS) is a relatively new diagnosis that was virtually unknown before the widespread use of mammography as a screening tool ("Ductal carcinoma in situ of the breast," 1988). Formerly to mammography, we could not detect much of the DCIS cases, except of these that were presented as palpable masses. Nowadays, it is possible to identify more and more cases, reaching, eventually, to a point that nearly 24% of all new diagnosed breast cancers are DCIS("Ductal carcino-

Corresponding author

Dr Apostolos Zavos MD

Surgeon Gynecologist Obstetrician. Deputy Editor of Mastologia Journal. Larisa, Greece, E - mail: zavosa@gmail.com

ma in situ of the breast," 1988). It has been evaluated that one case of DCIS is detected per 1300 screening mammographies.

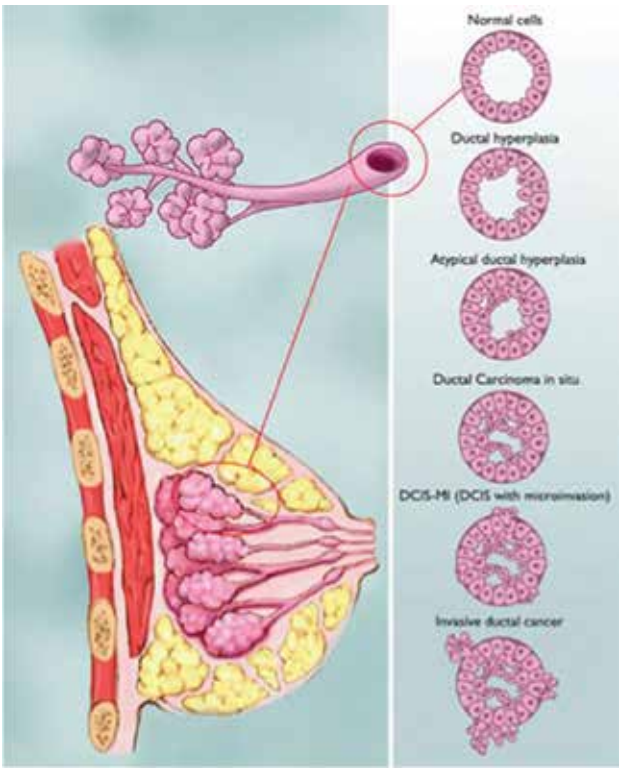
From what is known by now, breast cancers arise from cells that line the ducts and lobules of the breast. The exact mechanism is still not known but it is established that the cells start growing continuously without control. One could make a comparison with a broken copy machine that doesn't have an "OFF" button. Normal cells, "know" how many copies to make and stop when it gets to that number, on the other hand cancer cells don't.

As shown in **picture 1**, the normal duct can be presented schematically with a single layer of cells lining the duct. When cells in the ducts are growing abnormally, this is called hyperplasia. When they grow abnormally and do not appear normal under the microscope, they are called atypical hyperplasia.

In DCIS cells are growing abnormally inside the ducts and look like cancer cells microscopically. They are totally confined to the duct and do not spread into the surrounding fatty breast tissue or to any other part of the body. Invasive tumors, on the other hand, interrupt the basal membrane, invade in healthy tissue and have the ability to metastasize to other parts of the body.

So the big difference between invasive and in situ carcinoma is that DCIS cells lack the biological capability to metastasize, or spread elsewhere in the body like cancer cells of invasive tumors do.

It is a usual academic question whether DCIS falls into the category of cancer or not. The truth is that DCIS is a non-invasive type of cancer, but without treatment, the abnormal cells could turn into invasive cancer. In deed it is found that left untreated, 40 – 50% of DCIS may progress to invasive cancer. It also established that higher the DCIS grade, higher the possibility for DCIS to turn into invasive cancer if left untreated. The problem is that we cannot predict which cases of DCIS will progress to invasive breast cancer and which will not. So taking all these into account and considering our incapability to distinguee which patient's DCIS will turn into invasive cancer it seems rather unethical not to treat patients, so every case of DCIS is treated.



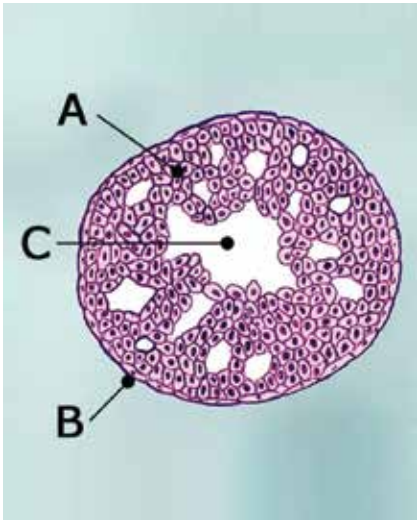
Picture 1

2. Histological categories of DCIS

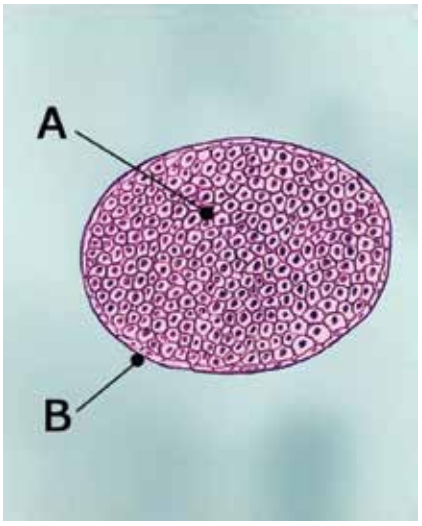
According to the WHO classification there are 3 grades of DCIS. Grade 1 or low grade, Grade 2 or moderate grade and grade 3 or high grade.

Other Histological based classifications include the cribriform DCIS where gaps exist between cancer cells in the affected breast ducts (like the pattern of holes in Swiss cheese), the solid DCIS in which cancer cells completely fill the affected breast ducts and finally the papillary DCIS, where the cancer cells are arranged in a finger-like pattern within the ducts. If the cells are very small, they are called micropapillary.

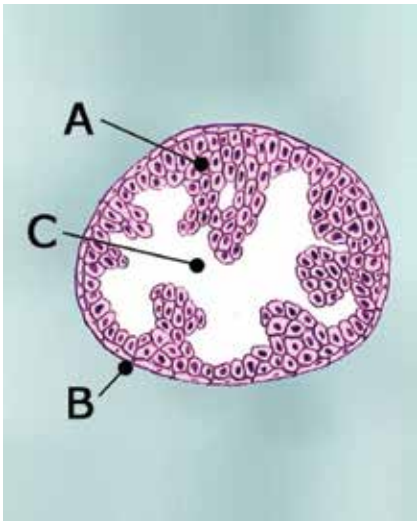
Another histological classification depends on whether there is necrosis in the tumor or not. The category of DCIS that have areas of dead (necrotic) cancer cells (comedo necrosis) are characterized as "comedo type" DCIS. It is grade 3 (high-grade) DCIS in which cancer cells grow that quickly, that some cells don't get enough nourishment and die, leaving areas of necrosis.



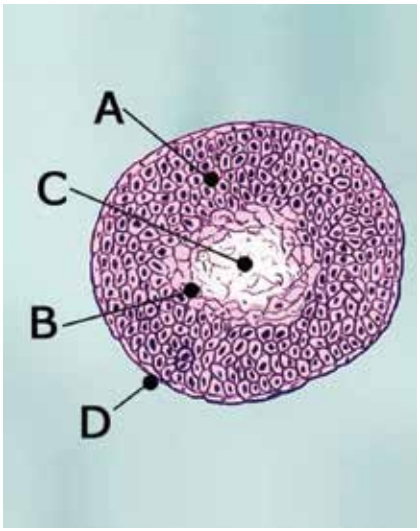
Cribriform DCIS



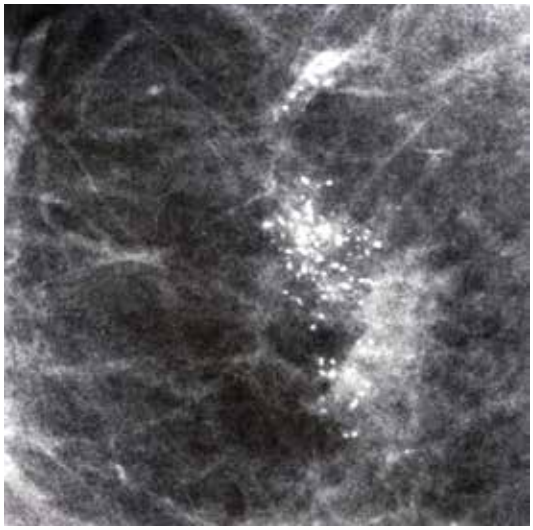
Solid DCIS



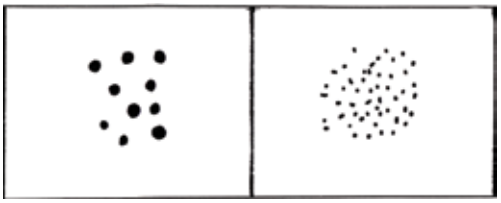
Papillary DCIS



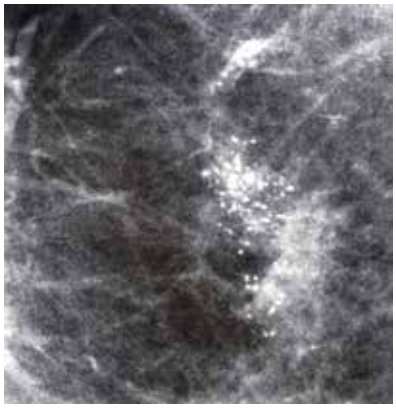
"Comedo type" DCIS

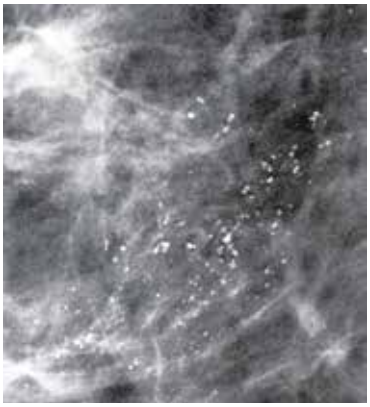


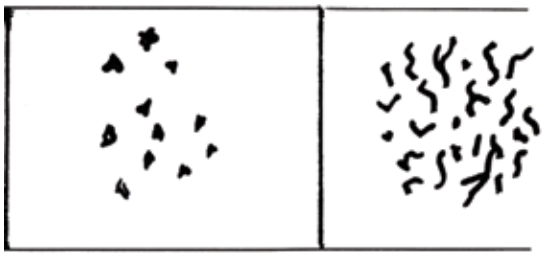
The most common appearance of DCIS in mammography



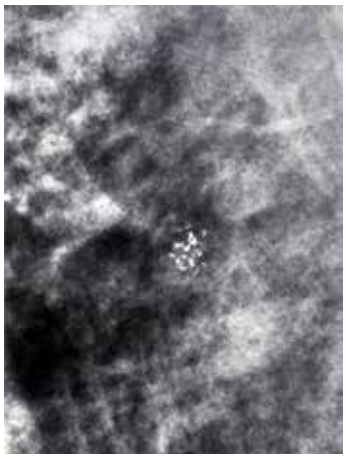
Punctuate or round calcifications

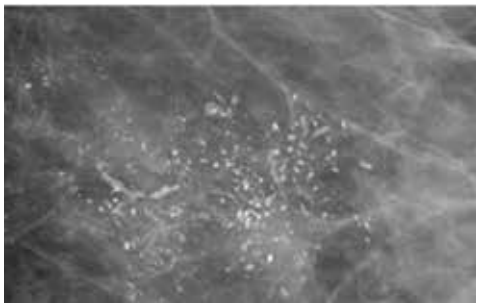


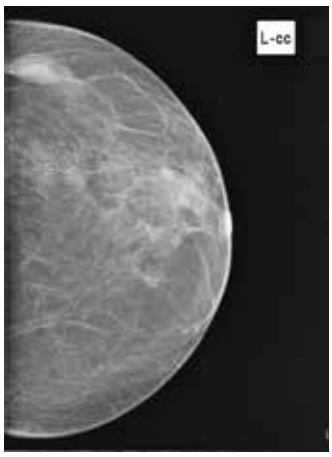


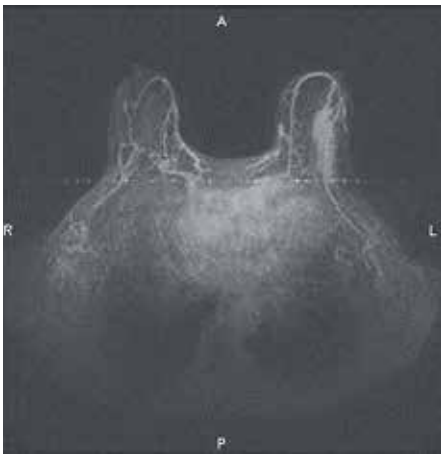


Crushed stone like or Casting type









3. Mammography appearance

The most common appearance of DCIS in mammography is a cluster of microcalcifications with variable morphology. Morphological the calcifications may appear:

- Punctuate or round
- Crushed stone like or
- Casting type

with a different probability of malignancy in each type which is 20% -Birads 4a- for round microcalcifications, 47% Birads 4a for punctuate (usually grade 1 DCIS), 67% when they present as crushed stone like -Birads 4b- (usually grade 2 DCIS) and 96% for the casting type calcifications -Birads 5- (usually grade 3 DCIS).

Malignant calcifications are more frequently visualized at US than benign calcifications. Calcifications seen at US are three times more likely to be malignant than calcifications not seen at US.

Mammography depicts the calcified DCIS but sometimes there is also non-calcified component.

MRI is the best modality to estimate the extent of DCIS.

4. The role of ultrasound in the diagnosis of DCIS

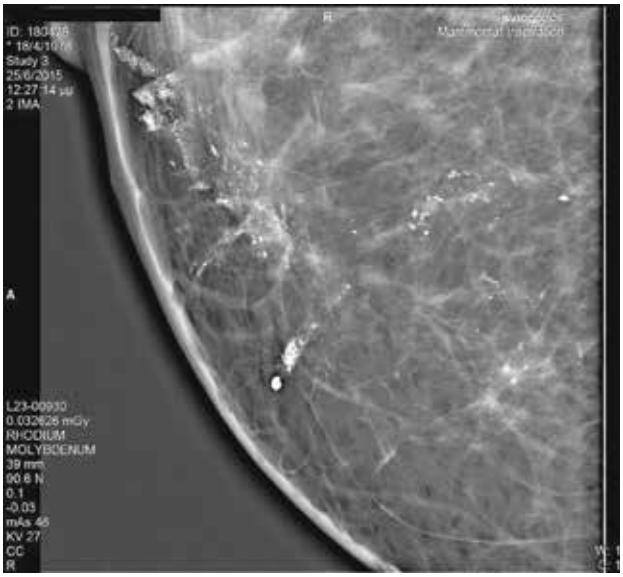
Since 80% of cases present as microcalcifications they are diagnosed by mammographic screening. The rest 20% of cases present as masses and can be diagnosed by clinical examination, mammography, tomosynthesis, ultrasound or MRI.

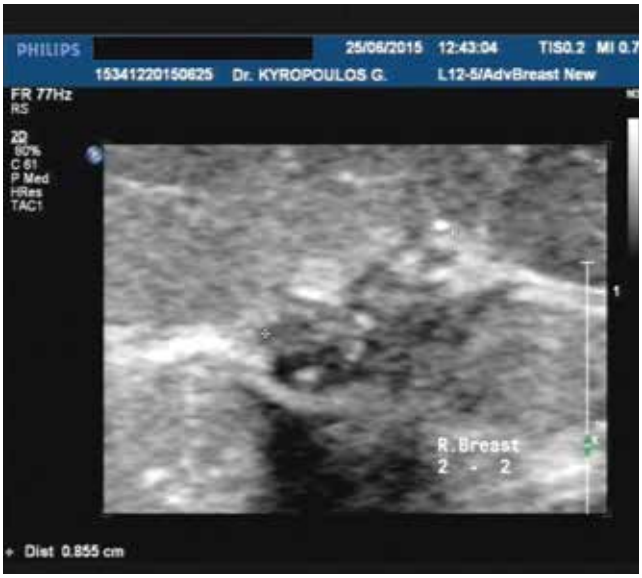
Based on that fact one could question the role of US in diagnosing DCIS. In order to answer this question, we should firstly distinguee the 2 types of DCIS, the calcified and the non calcified.

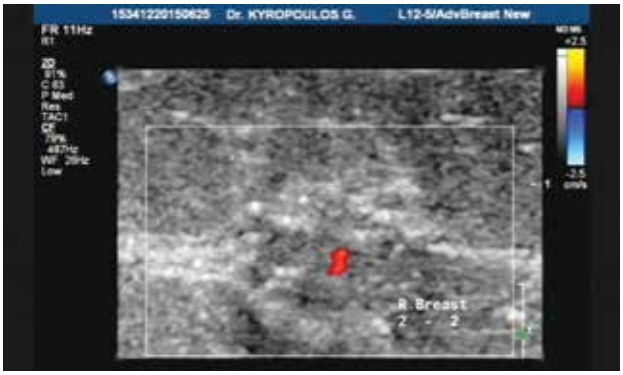
4.1 CALCIFIED DCIS

When DCIS is presented with microcalcifications visible at mammography, the role of US is to depict any invasive component mammographically occult, and in absence of invasive component to depict the microcalcifications. While mammography resolution for microcalcifications is 50-100 μm, US resolution for microcalcifications is 200-500 μm. Thus, US can identify 30%

Case presentation No 1.







of calcifications seen at mammography. Calcifications may be visualized at US as echogenic foci within a mass or a duct.

There are some methods that help the sonographer to optimize the microcalcification detection with US. Namely:

- High frequency transducers 5-12 MHz or 5-17 MHz
- Spatial compounding
- Speckle reduction algorithms
- Speed of sound correction
- Harmonic imaging
- Coronal reconstruction

Detection of invasive tumor with US that is mammographically occult as well as microcalcifications without invasive tumor allows us to perform US guided biopsy instead of stereotactic biopsy with mammography, which is best tolerated by women, has lower cost and lacks ionizing radiation. Second look US is helpful in cases of non-mass enhancement in MR mammography.

It depicts approximately 40% of DCIS and US-guided biopsy is performed instead of MR-guided biopsy that is very expensive.

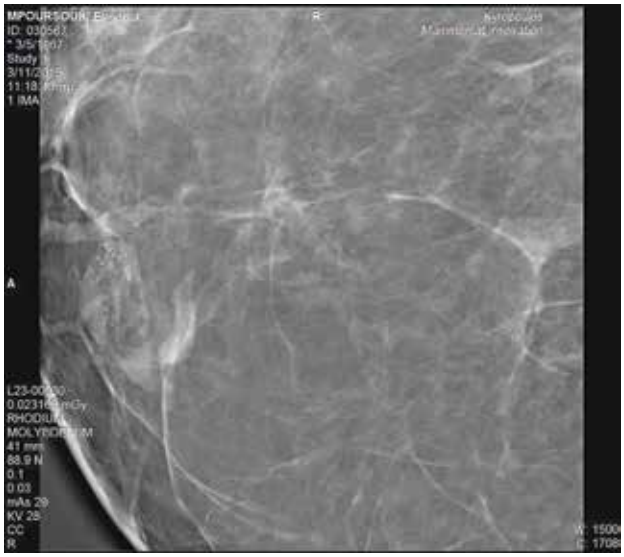
Case presentation No 1. (mammographically found, ultrasound detected-biopsied)

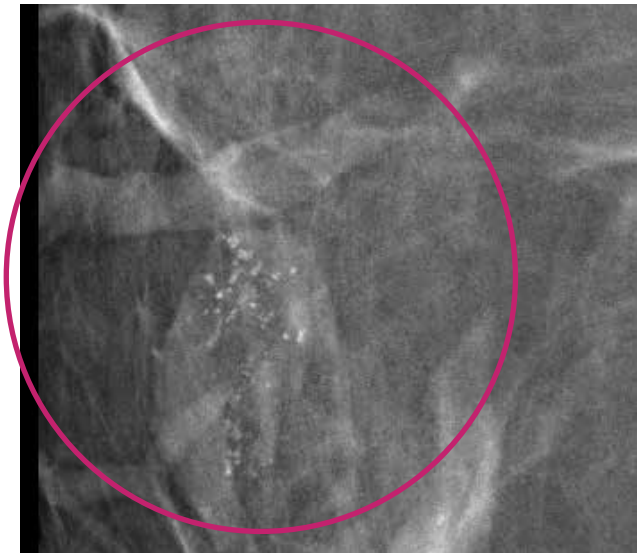
A 37 yo woman with segmental pleiomorphic microcalcifications at mammography. They were depicted in US and US-guided biopsy was performed. A DCIS grade 3 micropapillary and solid was diagnosed.

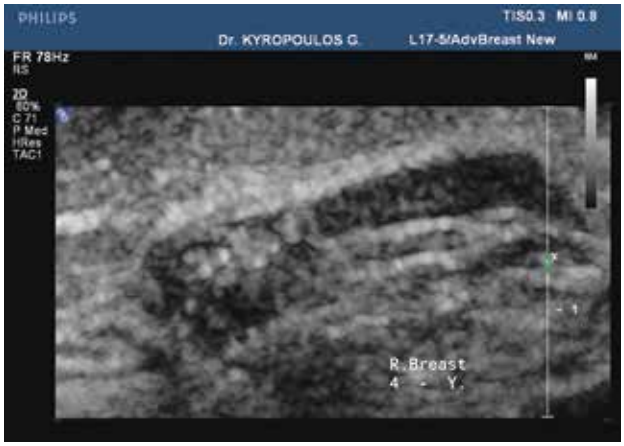
Case presentation No 2. (mammographically found, ultrasound detected-biopsied)

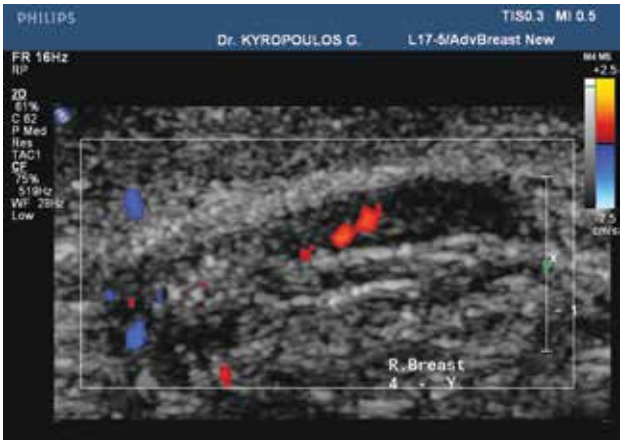
Woman 47 yo came to us the last Tuesday for stereotactic biopsy. We did an US examination and the calcifications were depicted. We scheduled an US guided core biopsy for next week.

Case presentation No 2.









4.2 NON-CALCIFIED DCIS

US findings of noncalcified DCIS are heterogeneous. They can manifest as:

- Masses
- Duct distention
- Cluster of microcysts with internal vascularity
- Area of altered echotexture
- May also arise in preexisting lesions such as papillomas, radial scars
- Nipple discharge: abnormal number of ducts from neoductgenesis and enlarged or abnormal ducts.

Case presentation No 3. (Masses)

A 28 years old woman with a palpable lesion at the right breast . At US the palpable finding corresponded to a well-defined hypoechoic mass highly vascularized. High grade DCIS papillary and solid.

Case presentation No 4. (Masses)

A 41 yo woman with a mass with indistinct margins and irregular shape, taller than wide and hypervascular. DCIS papillary and solid grade 2 and 3.

Case presentation No 5. (Duct distension)

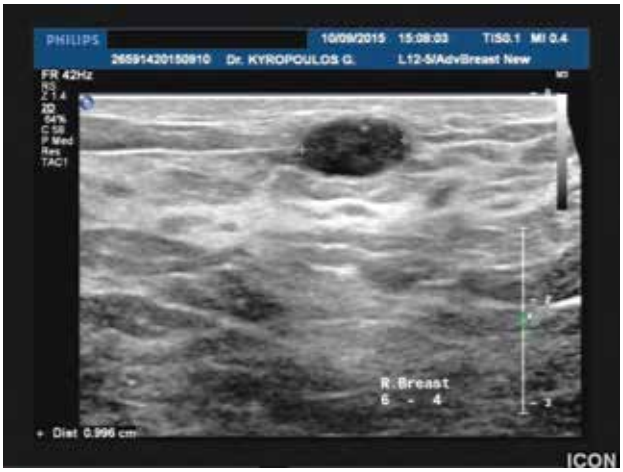
A 28 yo woman with enlarged ducts filled with echogenic hypervascular tissue. US-guided biopsy was performed. Mammography of the histological specimens verified the presence of microcalcifications. DCIS papillary and solid grade 2 and 3.

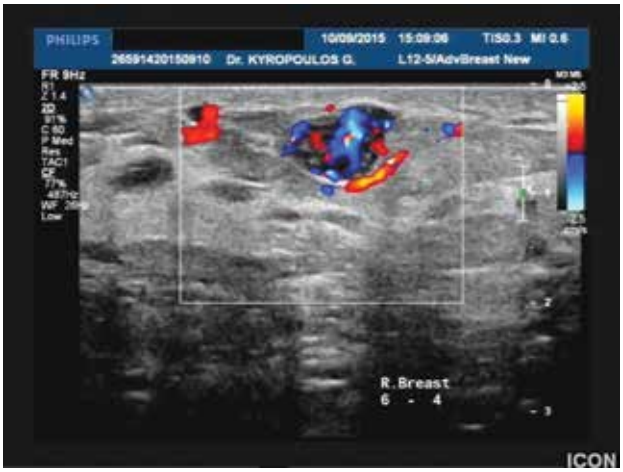
Case presentation No 6. (Cluster of microcysts)

With high visualization and Negative elastography, DCIS with microinvasion.

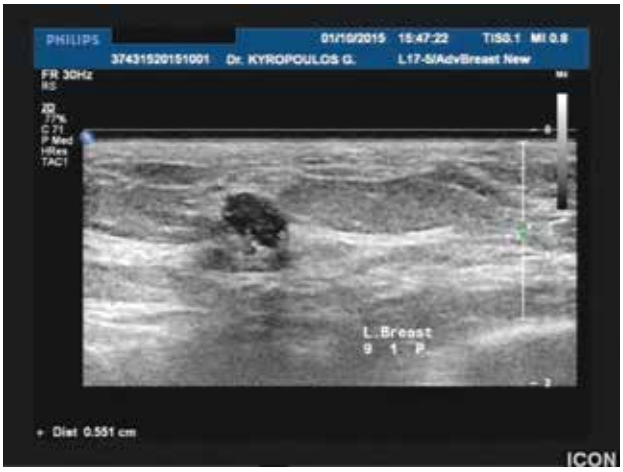
Case presentation No 7. (Area of altered echotexture)

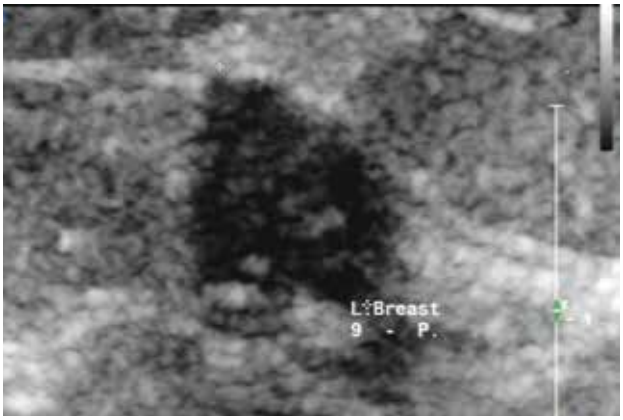
Case presentation No 3.

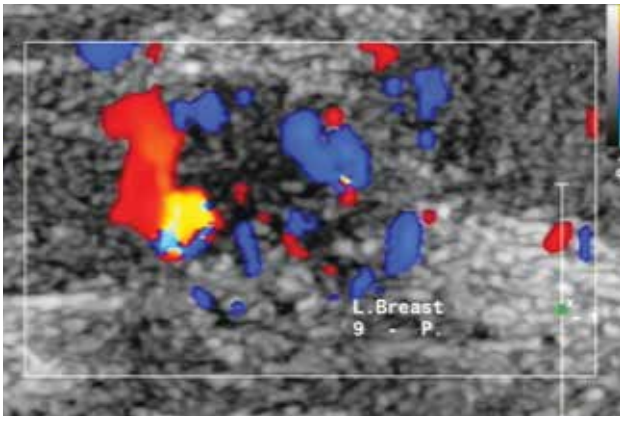




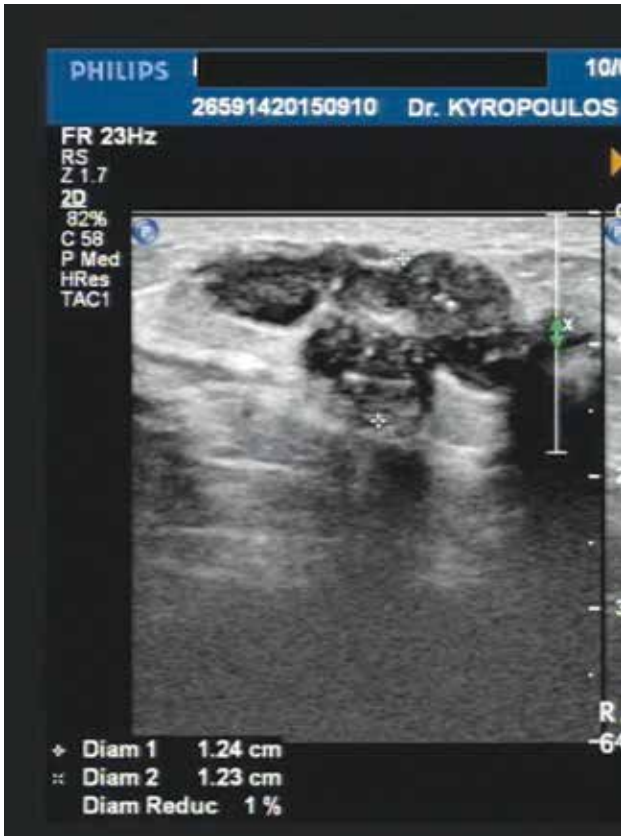
Case presentation No 4.

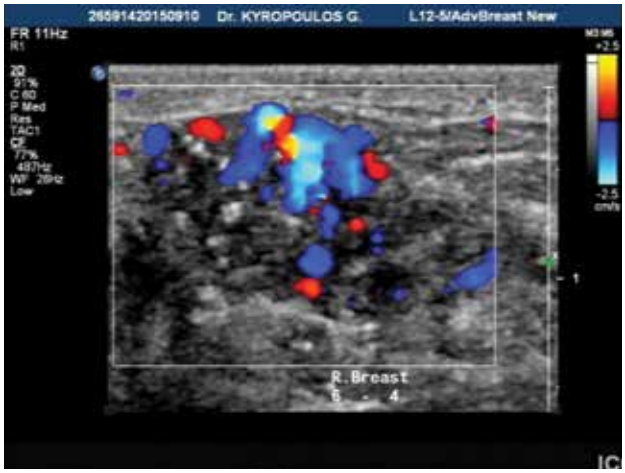




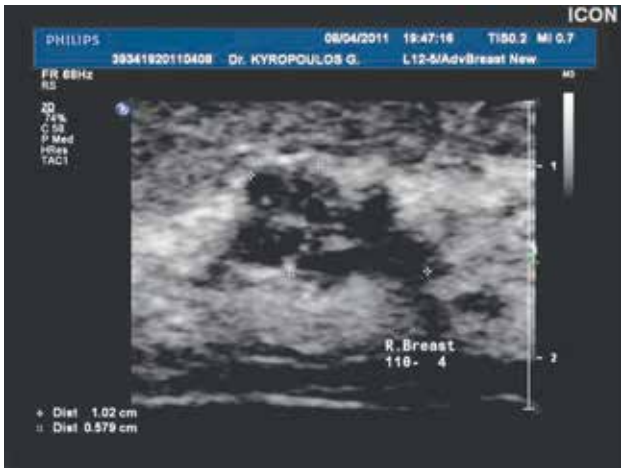


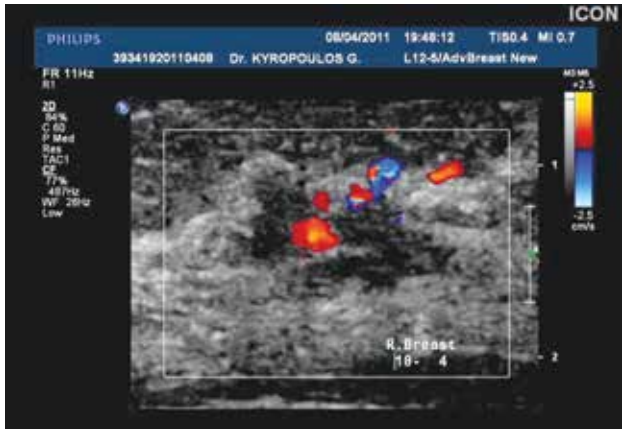
Case presentation No 5.

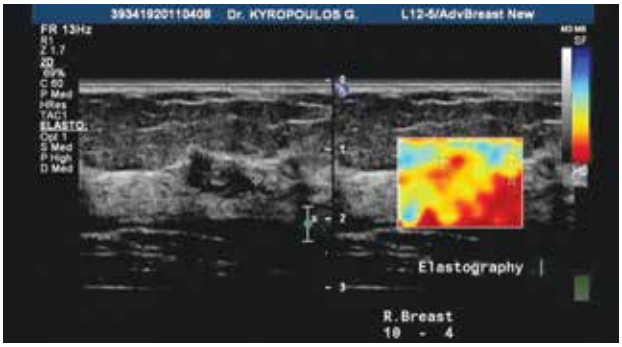




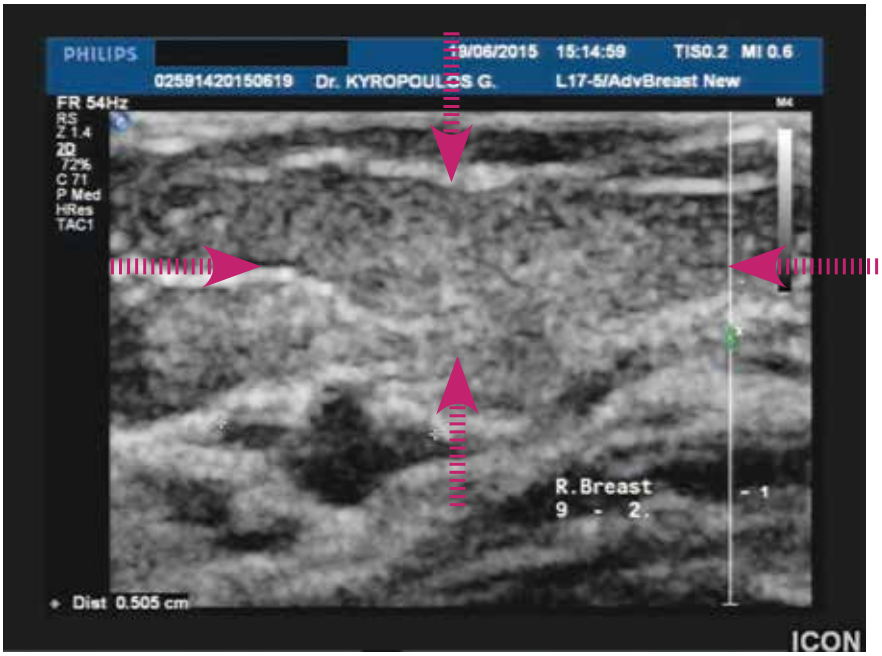
Case presentation No 6.



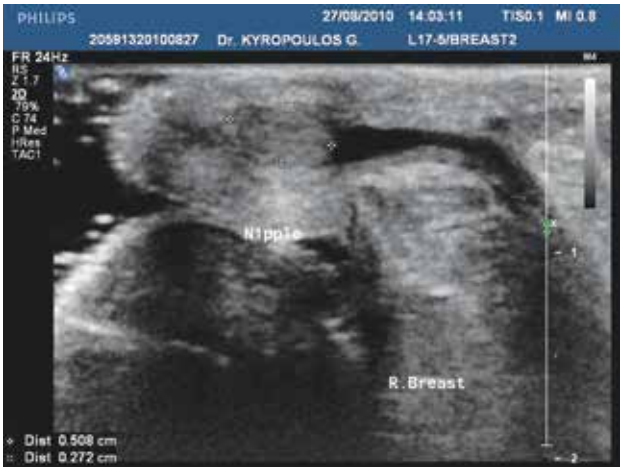


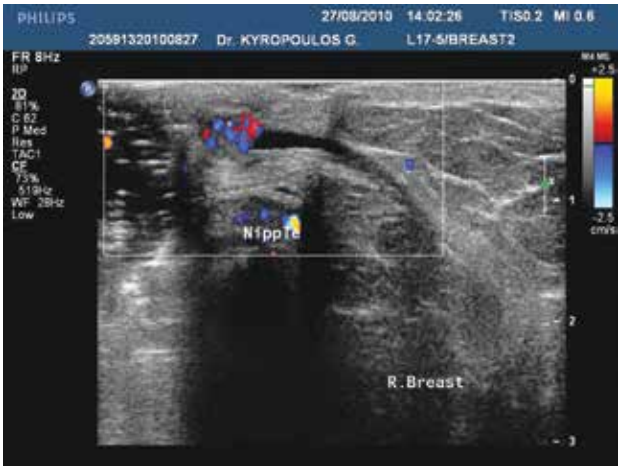


Case presentation No 7.



Case presentation No 8.





Case presentation No 8. (Nipple discharge)
A 77 yo woman with bloody nipple discharge. US revealed a papilloma and also an area of altered echotexture. DCIS grade 1. In preexisting lesions. A 65 yo woman with bloody nipple discharge. US revealed an intraductal mass in the nipple.Papilloma with DCIS.

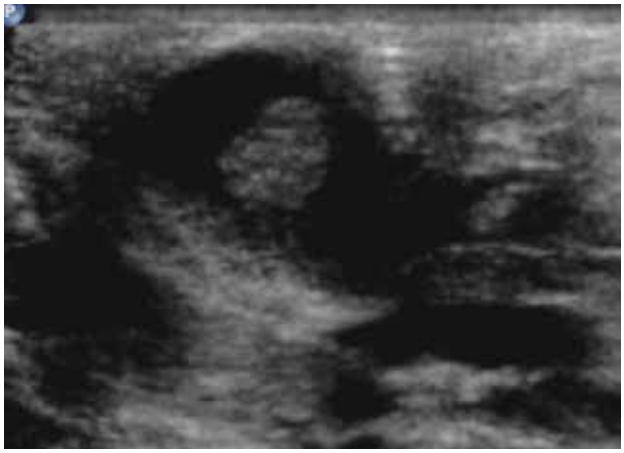
Case presentation No 9. (Papilloma)
A 62 yo woman with an intraductal central papilloma (within the duct sinus). Surgery revealed a DCIS 2,5 mm

Case presentation No 10. (Nipple discharge)
A 72 yo with bloody nipple discharge. US depicted enlarged ducts. After following the track of the dilated ducts we found an area of architectural distortion.

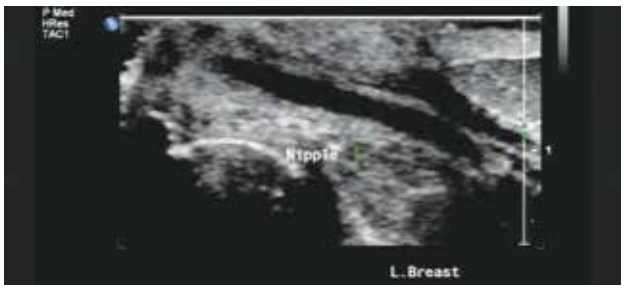
5. LCIS

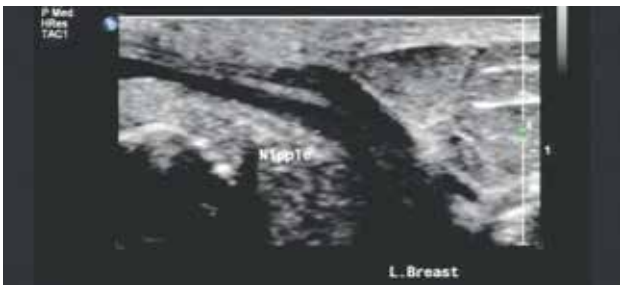
LCIS is a condition in which abnormal cells form in the lobules of milk glands in the breast. In LCIS usually more than one lobules are affected and 10-15% is bilateral. Despite the fact than its name includes the term carcino-

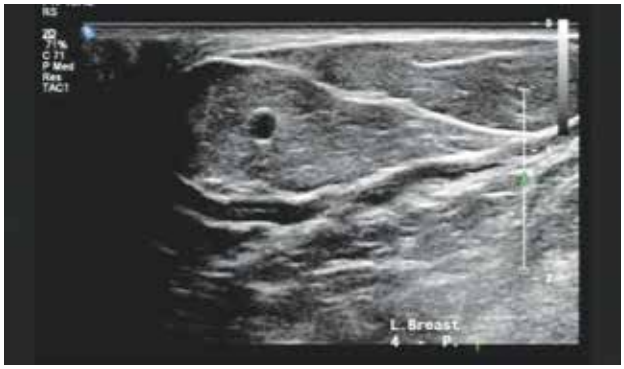
Case presentation No 9.

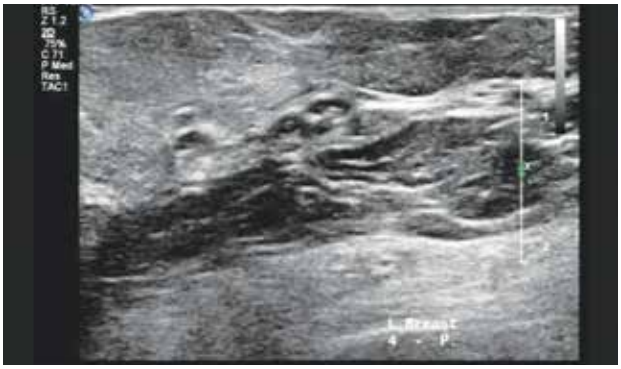


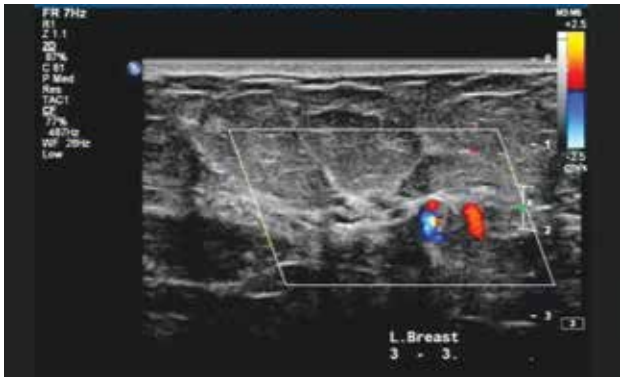
Case presentation No 10.



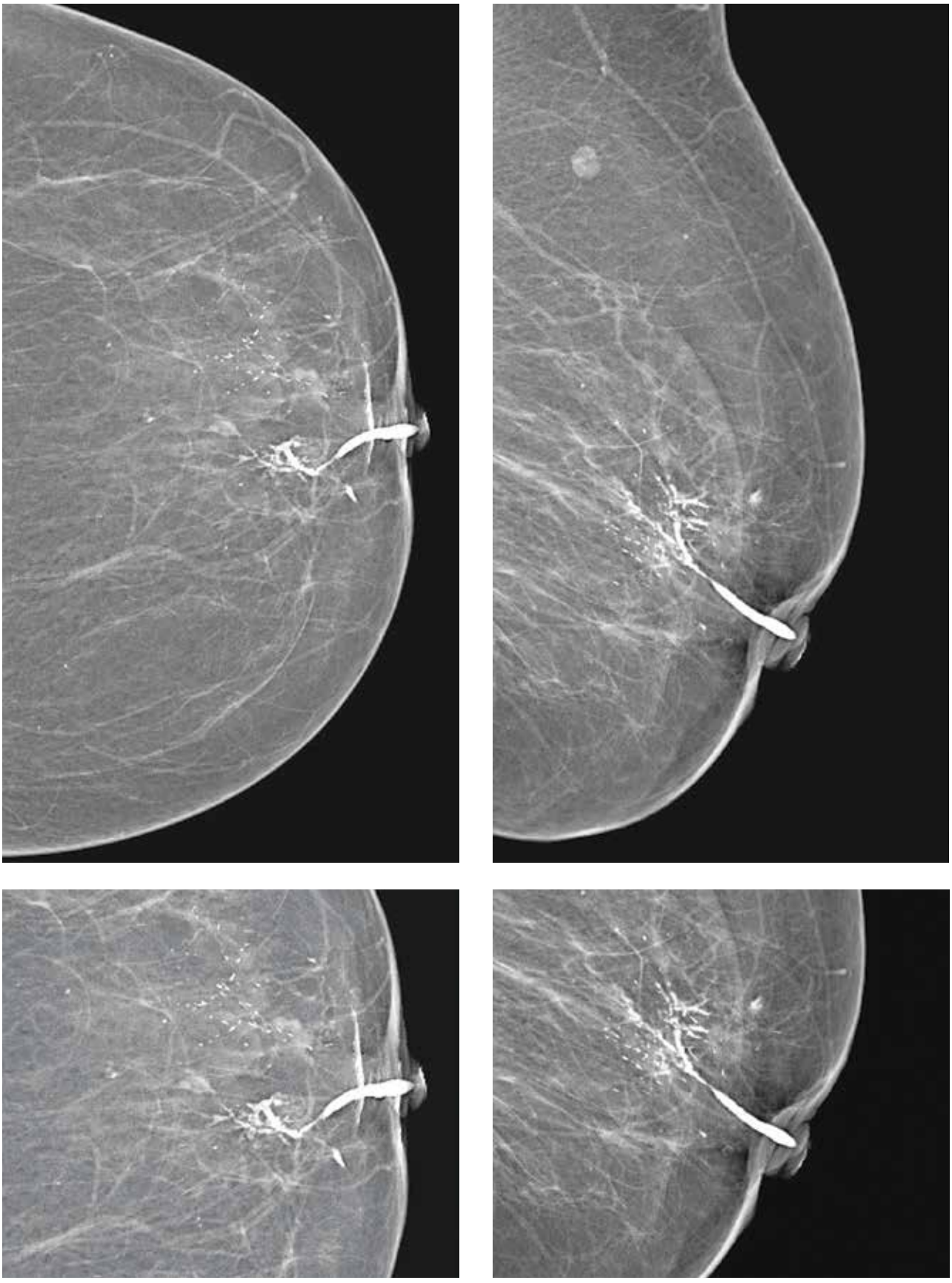




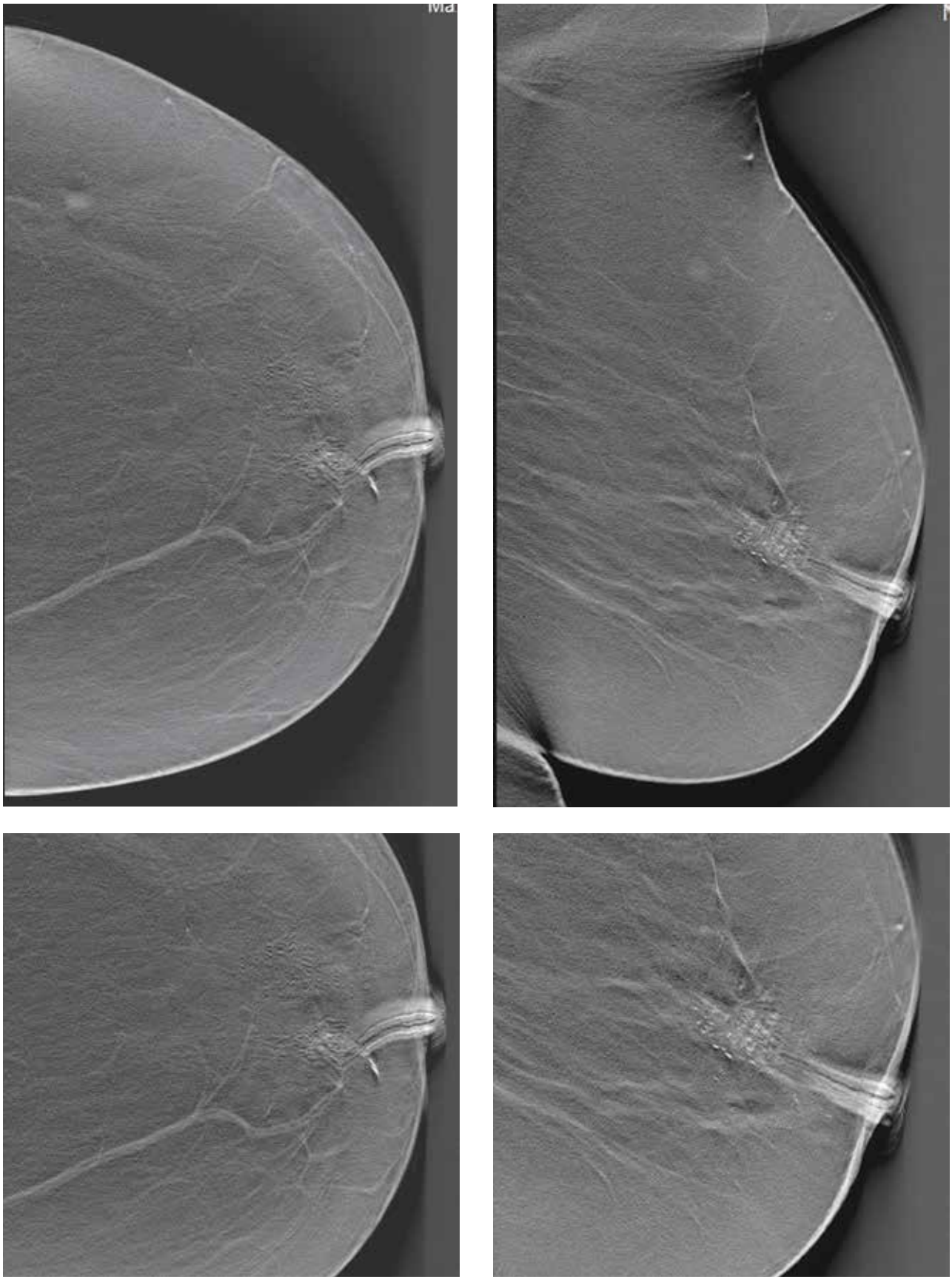




The area of architectural distortion showed marked vascularization



Ductography CC Ductography MLO Enlarged ducts with multiple filling defects



Ductography and Tomosynthesis with evidence of neoductogenesis

ma, LCIS is not true breast cancer , but LCIS is a reason for an increased risk of developing breast cancer (7-11 times higher risk of developing invasive cancer)

It differs from DCIS in that it doesn't become an invasive cancer if left untreated.

For this reason some experts prefer the term lobular neoplasia. LCIS usually doesn't show up on mammography and it is usually an incidental finding at a breast biopsy performed for an other reason.

6. Conclusion

DCIS is a very common, nowadays, finding among screening for breast cancer with mammography. The knowledge of its appearance is of great importance in order to detect and deal with these cases. The role of Ultrasound of increasing importance giving a great opportunity for faster effective and cheaper solution to the diagnosis of a common problem. Even more inherently US can contribute depict cases of non calcified DCIS that are occult in mammography.

Conflict of interests

The authors declare that they have no commercial competing interests or financial support for this study.

REFERENCES

1. Cho, K. R., Seo, B. K., Kim, C. H., Whang, K. W., Kim, Y. H., Kim, B. H., Chung, K. B. Non-calcified ductal carcinoma in situ: ultrasound and mammographic findings correlated with histological findings. *Yonsei Med J*, 2008; **49**(1), 103-110. DOI: 10.3349/ymj.2008.49.1.103.
2. Ductal carcinoma in situ of the breast. *N Engl J Med*, 1998; **319**(13), 869-870. DOI: 10.1056/NEJM198809293191313.
3. Shin, H. J., Kim, H. H., Kim, S. M., Kwon, G. Y., Gong, G., & Cho, O. K. Screening-detected and symptomatic ductal carcinoma in situ: differences in the sonographic and pathologic features. *AJR Am J Roentgenol*, 2008; **190**(2), 516-525. DOI: 10.2214/AJR.07.2206.
4. Wang, L. C., Sullivan, M., Du, H., Feldman, M. I., & Mendelson, E. B. US appearance of ductal carcinoma in situ. *Radiographics*, 2013; **33**(1), 213-228. DOI: 10.1148/rg.331125092.
5. Yang, W. T., & Tse, G. M. Sonographic, mammographic, and histopathologic correlation of symptomatic ductal carcinoma in situ. *AJR Am J Roentgenol, 2004;* **182**(1), 101-110. DOI: 10.2214/ajr.182.1.1820101.
6. Stavros AT. Ultrasound of ductal carcinoma in situ. In: Silverstein MJ, ed. Ductal carcinoma in situ of the breast. Baltimore, MD: Williams & Wilkins, 1997; 135 -158.

Educational case presentation

A case from the Department of Mammography Screening Paderborn, Germany

Regina Schwanitz-Gräwingholt and Axel Gräwingholt

Radiologists Department of Mammography Screening Paderborn, Radiologie am Theater, Paderborn

History

A 50-year old woman without any clinical symptom was invited for a first round screening appointment in our Center. No family history, no genetic predisposition for breast cancer. In Germany,women of age group 50 to 69 years are invited to the screening center of their region with a fixed appointment. The two view bilateral mammography (craniocaudal {CC} and mediolateral oblique {OBL}) is performed by radiographer and the woman returns home.

Thereafter, two radiologists, independently, read the mammograms. In case one of the radiologist, or both, find a suspicious radiological image, the finding is discussed in a Consensus Conference. It is then decided if further assessment is necessary and what is supposed to be done.

Case Report

In the case presented here, one of the two radiologists noticed a suspicious lesion in the right breast but only in the CC view. The radiological abnormality has been described as an architectural distortion with a central speculated opacity, seen only in CC view. (**Images 1-4**)

In the Consensus Conference the radiologists agreed to go further into assessment for the woman with two projections tomosynthesis of the right breast according to the rules of the German screening program for assessment.

Unilateral Tomosynthesis was performed on the same device as was the 2D mammography only with an additional device adapted. The thickness of tomosynthesis slices was 1 mm (**Images 5, 7, 9, 11**) . Tomosynthesis revealed much better the lesion in both projections and thus the lesion could be localized at the upper inner quadrant of the right breast. **(Images 5-12)**

Next, Sonography was performed and showed a 5 mm in its greater diameter hypoechoic lesion with unsharp margins and a dorsal shadowing. Typical signs of malignancy *(BIRADS V)* (**Image 13**). No pathologic finding in the ipsilateral axilla was found.

Thereafter, a sonographically guided core biopsy with a 14 gauge needle was performed and a titanium clip was placed into the tumor bed in order to find this non palpable lesion in a wire guided surgery. Three specimens were taken. The histopathology report showed a NOS (non-otherwise specified) invasive ductal carcinoma, Grade I, ER/PR positive and HER2 negative. **(Image 14)**

The case was discussed in the weekly Tumor Board of the Screening Center and the patient was referred to a Breast Clinic for a large tumorectomy sentinel lymph node biopsy and radiation therapy. The tumor was classified as: T1a, N0, M0. The postsurgical diameter proved to be also 5 mm. The postsurgical findings matched the radiological and histopathological diagnosis.

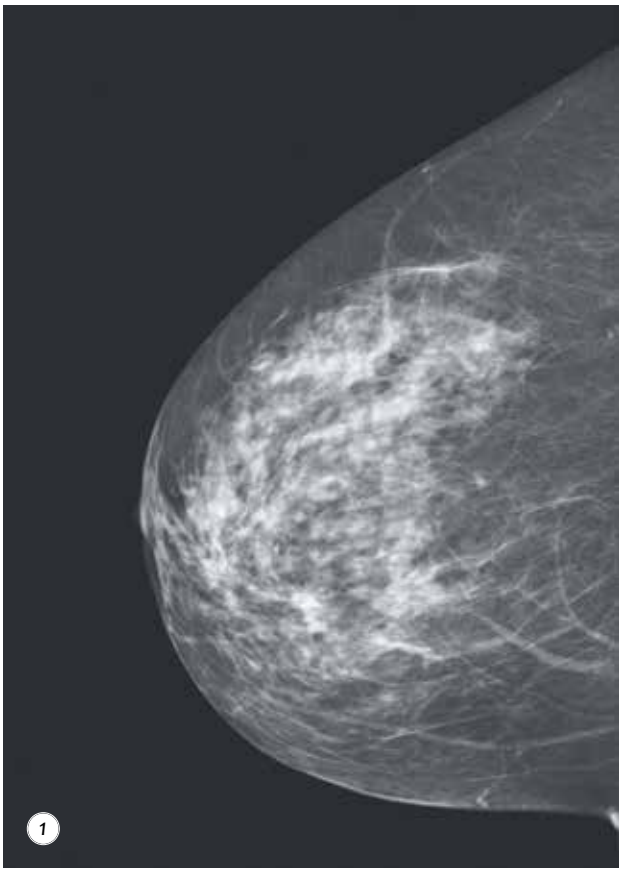
Conclusion

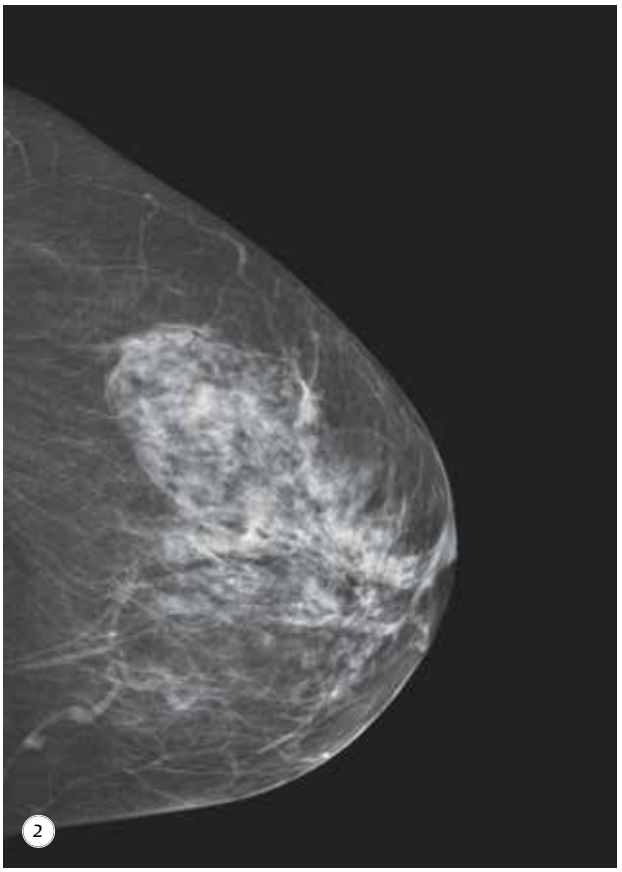
The mammogram was read by two very experienced ra-

Corresponding author

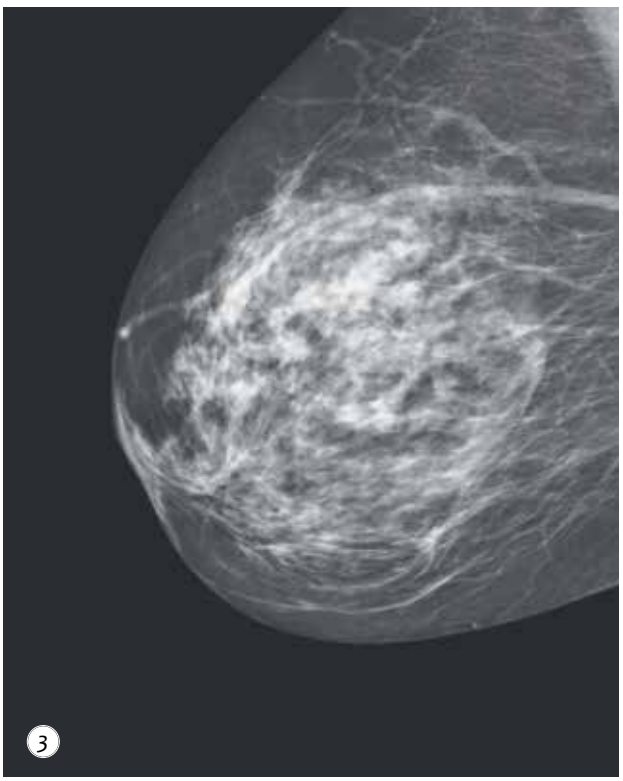
Dr. med. Axel Gräwingholt

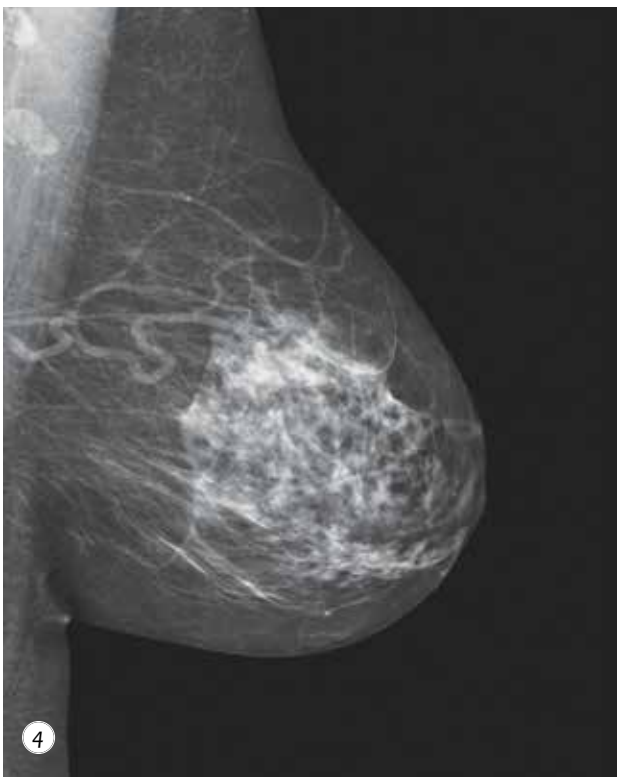
Mammographie screening Paderborn, Visiting Professor YSMU , Yerevan State Medical University, Armenia



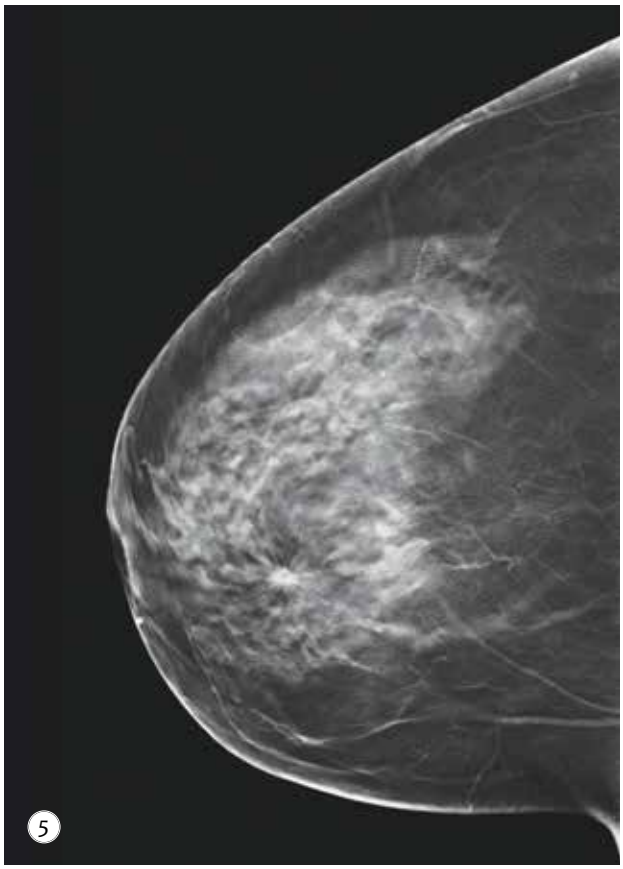


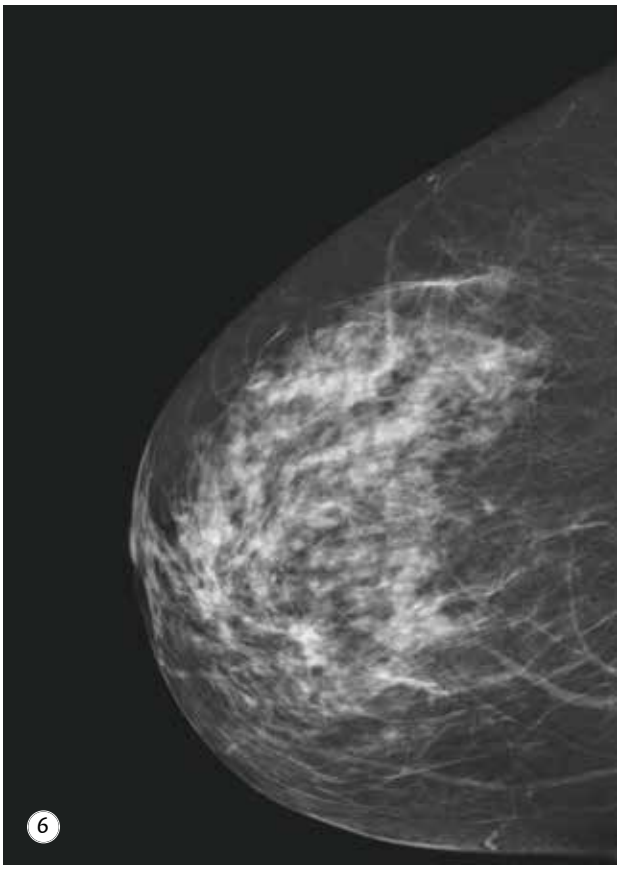
Images 1,2: *Bilateral CC projections 2D images*

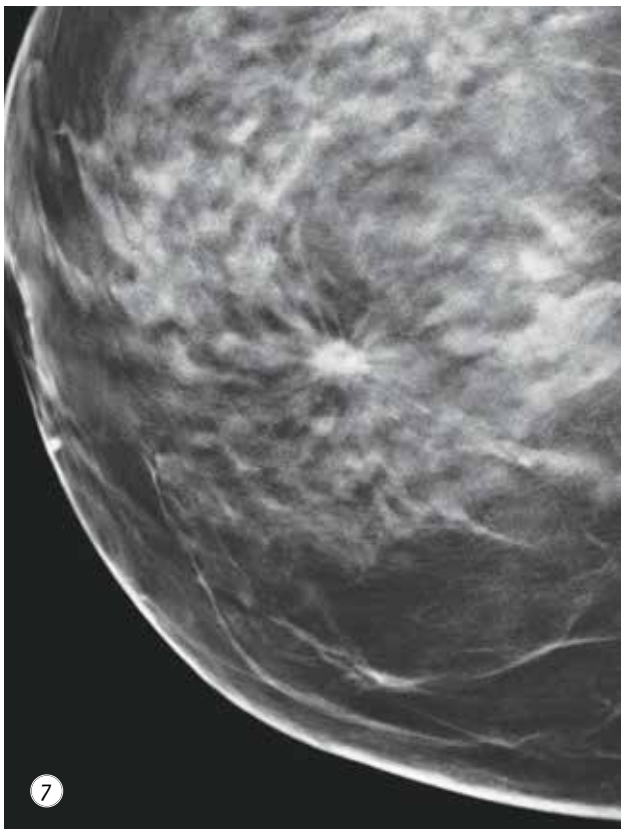


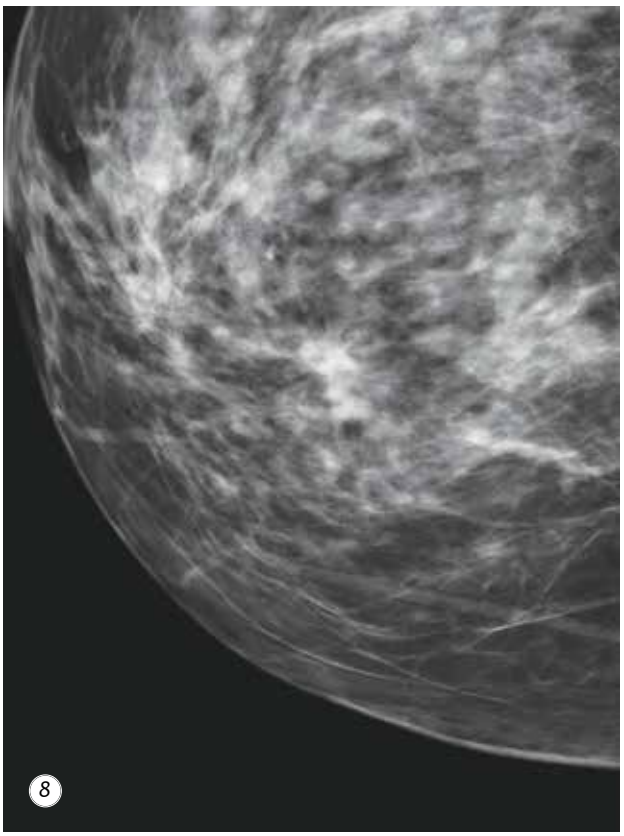


Images 3,4: *Bilateral OBL projections. 2D images*



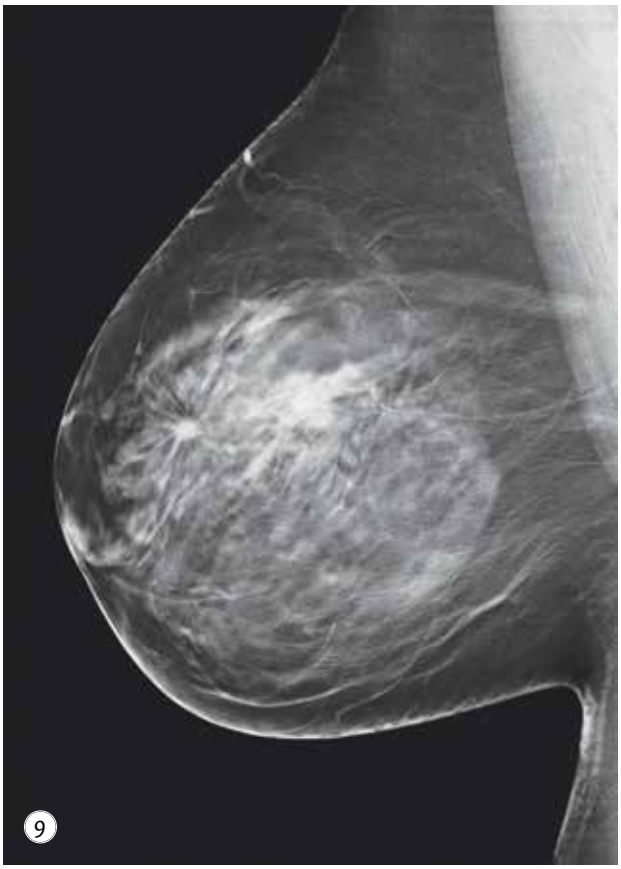


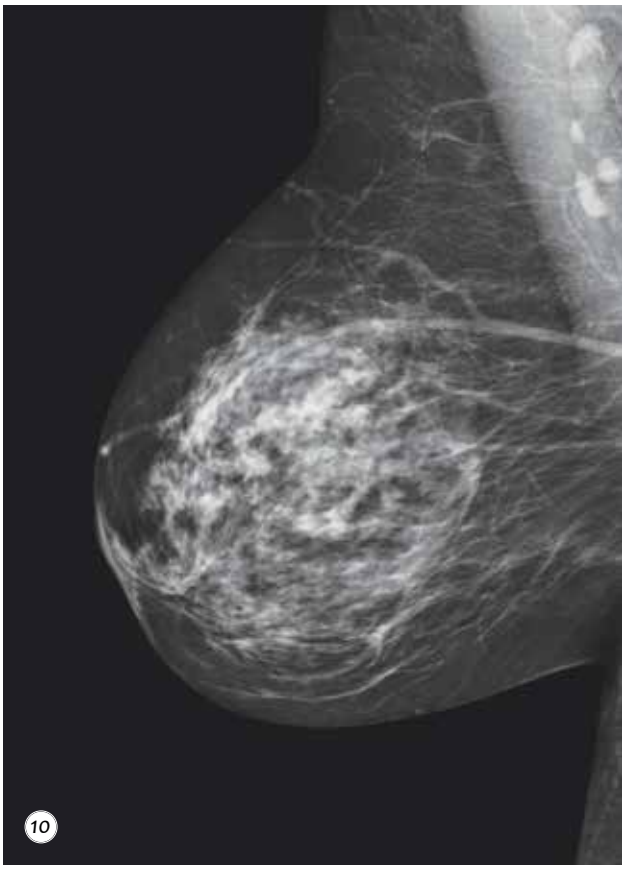


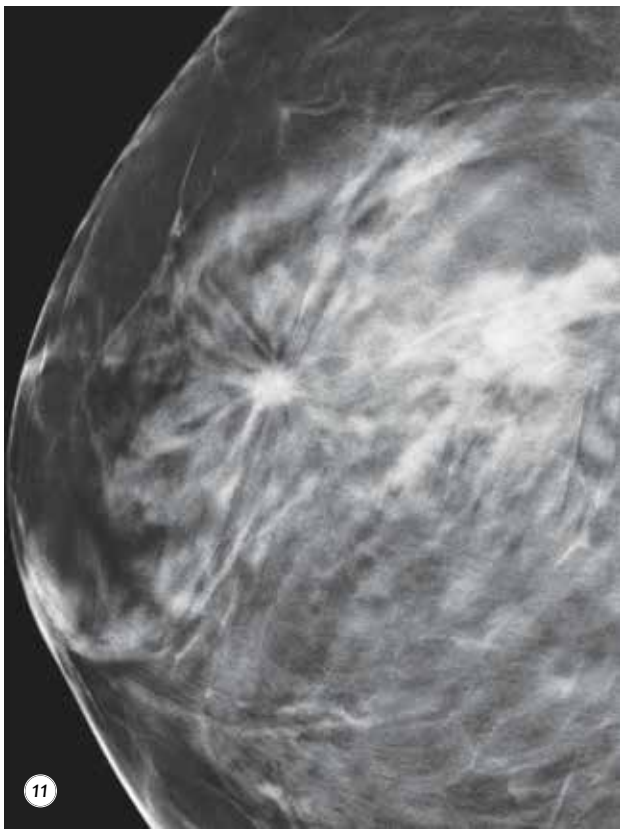


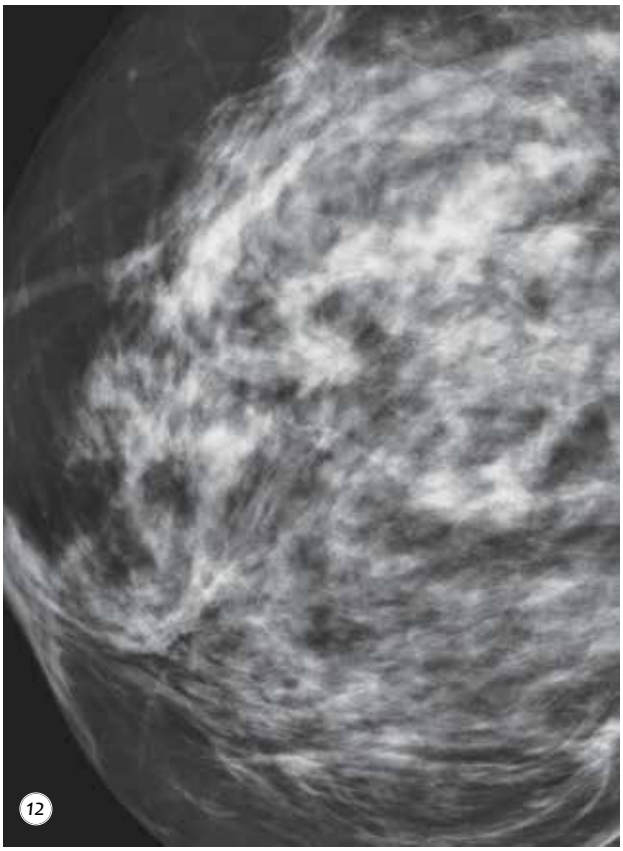
Images 5, 7: *Tomosynthesis 1 mm slice*

Images 6, 8: *Full field digital 2D image cc*









Images 9,11: *Tomosynthesis OBL 1 mm*

Images 10, 12: *, Full field digital 2D image*

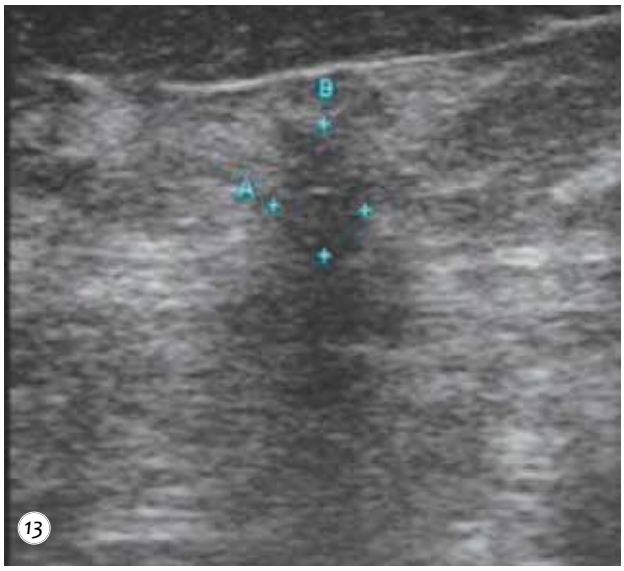


Image 13: *Sonography*

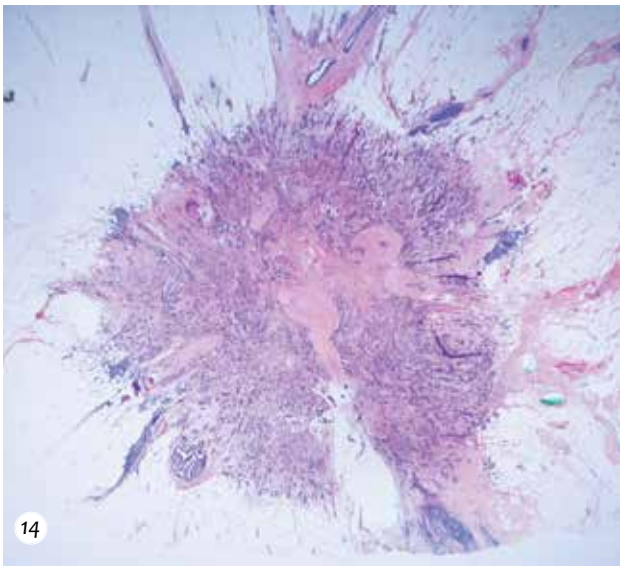


Image 14: *Histopathology exam. Courtesy of Institut für Pathologie Paderborn*

diologists already working since ten years in screening mammography. As only one of them detected the suspicious lesion, we can conclude that this shows:

- Double reading is essential for symptomless women who participate in a screening program.

Comparing the tomosynthesis to the 2D images shows, that in this case detectability of the tumor was much easier, than in the digital 2D images and certainly easier to fit into a reporting system like the BIRADS classification. If tomosynthesis would have been performed at first appointment the BIRADS would have been BIRADS 5.

We believe, that in order to achieve an even higher detection rate in screening programs it would be very helpful to include tomosynthesis as primary detection method. It would probably increase the sensitivity and specificity of the readers and therefore reduce the number of unnecessary recalls in screening programs. This should apply especially for dense breasts so we could imagine that if screening programs will once have a more personalized design there could be differing procedures in different age groups according to different average densities of the breast tissue in the age groups.

Conflict of interests

The authors declare that they have no commercial competing interests or financial support for this study.

REFERENCES

1. Skaane P , Bandos AI, Gullien R, Eben EB, Ekseth U, Haakenaasen U, Izadi M, Jebsen IN, Jahr G, Krager M, Niklason LT, Hofvind S, Gur D. Comparison of digital mammography alone and digital mammography plus tomosynthesis in a population-based screening program. *Radiology*. 2013 Apr;267(1):47-56. DOI: 10.1148/radiol. 12121373. Epub 2013 Jan 7.
2. Lång K, Andersson I, Rosso A, Tingberg A, Timberg P, Zackrisson S. Performance of one-view breast tomosynthesis as a stand-alone breast cancer screening modality: results from the Malmö Breast Tomosynthesis Screening Trial, a population-based study. *Eur Radiol*. 2016 Jan;26(1):184-90. DOI: 10.1007/s00330-015-3803-3. Epub 2015 May 1.
3. Mark A. Helvie. Digital Mammography Imaging: Breast Tomosynthesis and Advanced Applications. *Radiol Clin North Am*. 2010 Sep; 48(5): 917-929.DOI:10.1016/j.rcl.2010.06.009.

Meetings, Conferences & Congresses

5-8 May 2016	**19th SIS World Congress on Breast Healthcare** *Warsaw, Poland, Info: www.sisbreast.org/19th-sis-worldcongressonbreasthealthcare*
16-17 May 2016	**ABS Conference & AGM. 2016 Manchester Small Banner Association Of Breast Surgery Conference & Manchester Central** *www.associationofbreastsurgery.org.uk*
3-7 June 2016	**2016 ASCO Annual Meeting- American Society of Clinical Oncology** *Chicago, ILLINOIS, Tel: (571) 483-1300 E- Mail :ascoregistration@jspargo.com*
16-18 June 2016	**11th Duesseldorf Breast Cancer Conference** *Dusseldorf - Germany*
3-5 July 2016	**Symposium Mammographicum 2016, Arena & Convention Centre (ACC) Liverpool,** *Website: http://conferencesympmamm.org.uk/, Tel: + 44 (0) 20 8977 7997,* *E-Mail: sympmamm@conferencecollective.co.uk*
8-10 September 2016	**London Breast Meeting**
8-11 September 2016	**2nd World Congress on Controversies in Breast Cancer (CoBrCa)** *Barcelona, Spain*
14-16 September	**2016 ESSO36,** *Krakow, Poland*
19-21 September 2016	**2nd World Congress on Breast Cancer (OMICS International Conferences)** *Phoenix, USA*
23-24 September 2016	**International Clinical Trials Workshop** *Cluj Napoca, Romania, Romanian Breast Cancer Group*
23-24 September 2016	**EUSOBI Annual Scientific Meeting 2016,** *Paris/France*
28 Sept.-1 Oct 2016	**15th World Congress on Menopause,** *Prague, Czech Republic, www.IMSPRAGUE2016.com*
10-12 November 2016	**3rd ESO-ESMO Breast cancer in young women International Conference,** *Lugano, Switzerland. Info: fmarangoni@eso.net*
10-12 November 2016	**Breast Cancer Conference Istanbul Wyndham Grand Hotel Turkey,** *www.breastanbul.org*
10-13 November 2016	**26th Annual Interdisciplinary Breast Cancer Center Conference,** *Las Vegas, NV, NCBC*
6- 10 December 2016	**San Antonio Breast Cancer Symposium,** *San Antonio, TX*
27-30 January 2017	**ECCO2017 European Cancer Congress,** *Amsterdam, The Netherlands*
15-18 March 2017	**15th St. Gallen International Breast Cancer Conference Primary Therapy of Early Breast Cancer Evidence, Controversies, Consensus** *Austria Convention Centre in Vienna / Austria*
2-4 November 2017	**4TH ESO-ESMO International Consensus Conference.** *Lisbon- Portugal*

GE Healthcare

Look differently with Invenia ABUS

Automated Breast Ultrasound

Invenia™ ABUS is an FDA approved and CE marked screening technology that provides a view beyond mammography for women with dense breasts.

Dense tissue can mask the appearance of tumors and limit the performance of mammography. Screening with ABUS has a 55% relative increase in invasive breast cancers identified using supplemental ABUS and a 37% relative increase in cancer detection overall than mammography alone.[1]

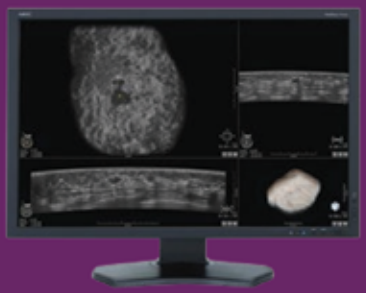
1. Brem RF, Tabár L, et.al Assessing Improvement in Detection of Breast Cancer with Three-dimensional Automated Breast US in Women with Dense Breast Tissue: The somoInsight Study. Radiology 2015 Mar; 274(3):663-73

Look differently.

Designed for the fast-paced screening environment, Invenia ABUS provides automated technology for users to quickly and comfortably create reproducible exams that can be efficiently reviewed by physicians.

The Invenia ABUS exam is easily performed by your mammography technologist or sonographer. The streamlined user interface, automated image optimization, compression, and acquisition allow complete exams to be performed in 15 minutes.[1]

1. Average acquisition time per patient measured from Invenia ABUS users



The Invenia ABUS Workstation displays 3D volumes in a patented, 2 mm thick coronal slice from the skin to the chest wall. The workstation's intelligent tools provide efficient exam reading and analysis within 3 minutes[2] - which offers remarkable time saving for Physicians compared to hand-held Ultrasound.

2. ARRS 2012 Breast Imaging: Screening/Emerging Technologies Oral/Abstract: Radiologist Interpretation Time for 3D Automated Breast Ultrasound Screening, R. Beem

imagination at work

GE Healthcare AE.
Σωρού 8-10, 151 25 Μαρούσι, Αθήνα
T 210 8930600, F 210 9625 931

Αγ. Γεωργίου 5, "COSMOS Offices"
55535 Πατριαρχικά Πυλαίας, Θεσσαλονίκη
T 2310 365138, 2310 844081, F 2310 847654

healthymagination

March 2015 |
JB27743XEa

"MASTOLOGIA" is the official scientific journal of the Hellenic Senologic Society (HSS). Its main objective is to publish original articles, reviews and case reports on breast diseases. The journal "Mastologia" is also concerned in the continuous education of the Senologists and aims at promoting the science of Senology. The journal publishes papers, which concern clinical research and scientific achievements. It also welcomes clinical investigations, basic applied laboratory research as well as new data and recent developments of senological interest. Papers published in other Journals are not accepted.

Submission of Papers

1. General Information:

The official language of "Mastologia" is English. Authors whose native language is not English will have their manuscripts proofread by a professional copyeditor offered by the editorial team. If Authors like to submit their manuscript in Greek language we can provide translation with a fee. All the authors are jointly responsible for the contents of the paper and sign together the Authorship Responsibility, Financial Disclosure and Acknowledgment form. The list of authors should not exceed six (6) otherwise the participation of those exceeding the above numbers should be justified accordingly.

In case of reports, the authors should not exceed four (4). In review articles the authors should not exceed the number of two (2). The following should be observed in the case of clinical studies:

a) The authors should state that the research was conducted according to the principles as have set forth by the Helsinki Declaration of 1975.

b) In the Studies that involve human subjects, a statement-approval from the appropriate human ethics committees should be obtained.

c) A statement-approval of the competent scientific committee of the centre in which the research work was carried out, pertaining to the protocol of the perspective studies, should be included.

In the case of the experimental studies on animals a statement should be made that the paper has adhered to the international guidelines for research involving animals, which has been recommended by the WHO, stating that "all research on animals was conducted in accordance with guidelines tendered by international law".

2. Copyright Transfer:

Papers published in "Mastologia" constitute copyright ownership of the manuscript to the Hellenic Senologic Society (HSS). Thus any reproduction and/or copying of said manuscript is allowed only after written consent of the Editorial Board of the Journal.

3. Procedure:

The corresponding author is informed for receipt of the manuscript and the number of registration. The manuscripts are first checked whether they have been written and submitted according to the instructions of the Journal (instructions to authors). Manuscripts which do not meet the requirements of correct submission are returned to the corresponding author with instructions for due corrections. The manuscript is double –blind checked by special consultants reviewers of the Journal.

The revised manuscript with an accompanying letter signed by the corresponding author, in which he declares that all corrections have been done. The final decision for acceptance of the manuscript lies on the Editorial Board that decides for approval, or return of manuscript for supplementary information, decision for re-approval or to reject the manuscript. As soon as the paper is accepted and has been allotted final publication, a proof is dispatched to the authors for final checking.

Article types

Reviews: maximum 4,000 words, 50 references, 6 tables and 10 figures, Abstract 300 words in English

Original Articles: maximum 3,000 words, 30 references, 6 tables and 10 figures, Abstract 200 words in English and 300 words in Greek

Case Reports: maximum 1,500 words, 10 references and 6 figures, Abstract 100 words in English

Letter to the editor: maximum 600 words, 6 references, 1 table and 1 figure

Article structure

Subdivision: Divide your article into clearly defined sections. Any subsection may be given a brief heading. Each heading should appear on its own separate line.

Introduction: State the objectives of the work and provide an adequate background, avoiding a detailed literature survey or a summary of the results.

Material and methods: Provide sufficient detail to allow the work to be reproduced. Methods already published should be indicated by a reference: only relevant modifications should be described. Statistical methods should be included in Material and Methods section.
Results: Results should be clear and concise.
Discussion: This should explore the significance of the results of the work, not repeat them. Avoid extensive citations and discussion of published literature.
Conclusions: The main conclusions of the study may be presented in a short conclusions section, which may stand alone or form a subsection of a Discussion section.

Title page information

Title: Concise and informative. Titles are often used in information-retrieval systems. Avoid abbreviations and formulae where possible. Author names and affiliations Where the family name may be ambiguous (e.g., a double name), please indicate this clearly. Present the authors' affiliation addresses (where the actual affiliations with a lower-case superscript letter immediately after the author's name and in front of the appropriate address. Provide the full postal address of each affiliation, including the country name and, if available, the e-mail address of each author.
Corresponding author: Clearly indicate who will handle correspondence at all stages of refereeing and publication. Ensure that phone numbers (with country and area code) are provided in addition to the e-mail address and the complete postal address. Contact details must be kept up to date by the corresponding author.
Summary: A concise and factual abstract is required. It should state briefly the purpose of the research, the principal results and major conclusions. An abstract is often presented separately from the article, so it must be able to stand alone.
For this reason, references should be avoided, but if essential, then cite the author(s) and year(s). Also, non-standard or uncommon abbreviations should be avoided, but if essential they must be defined at their first mention in the abstract. Abstracts should be structured as to include items of Objectives, Methods, Results and Conclusions.
Keywords: Immediately after the abstract, provide a maximum of 6 keywords, using American spelling and avoiding general and plural terms and multiple concepts (avoid, for example, 'and', 'of'). Be sparing with abbreviations: only abbreviations firmly established in the field may be eligible. These keywords will be used for indexing purposes.
Abbreviations: In the main text, abbreviation should be detailed at their first mention. Ensure their consistency throughout the article.
Acknowledgements: Collate acknowledgements in a separate section at the end of the article before the references. List here those individuals who provided assistance during the research.
Math formulae: Present simple formulae in the line of normal text where possible and use the solidus (/) instead of a horizontal line for small fractional terms, e.g., X/Y. In principle, variables are to be presented in italics. Powers of "e" are often more conveniently denoted by exp. Number consecutively any equations that have to be displayed separately from the text (if referred to explicitly in the text).
Footnotes: Footnotes should be used sparingly. Number them consecutively throughout the article, using superscript Arabic numbers. Many word processors build footnotes into the text, and this feature may be used. Should this not be the case, indicate the position of footnotes in the text and present the footnotes themselves separately at the end of the article. Do not include footnotes in the reference list.
Table footnotes: Indicate each footnote in a table with a superscript lowercase letter.
Artwork: Image manipulation: Whilst it is accepted that authors sometimes need to manipulate images for clarity, manipulation for purposes of deception or fraud will be seen as scientific ethical abuse and will be dealt with accordingly. For graphical images, this journal is applying the following policy: no specific feature within an image may be enhanced, obscured, moved, removed, or introduced. Adjustments of brightness, contrast, or color balance are acceptable if and as long as they do not obscure or eliminate any information present in the original.

Electronic artwork

General points: Make sure you use uniform lettering and

sizing of your original artwork. Embed the used fonts if the application provides that option.

- Aim to use the following fonts in your illustrations: Times New Roman, 12.
- Number the illustrations according to their sequence in the text.
- Use a logical naming convention for your artwork files.
- Provide captions to illustrations separately.
- Size the illustrations close to the desired dimensions of the printed version.
- Submit each illustration as a separate file.

Formats: If your electronic artwork is created in a Microsoft Office application (Word, PowerPoint, Excel) then please supply 'as is' in the native document format. Regardless of the application used other than Microsoft Office, when your electronic artwork is finalized, please 'Save as' or convert the images to one of the following formats (note the resolution requirements for line drawings, halftones, and line/halftone combinations given below): PDF or JPEG. Keep to a minimum of 300 dpi Vector drawings, embed all used fonts.

Please do not: Supply files that are optimized for screen use (e.g.,GIF, BMP, PICT, WPG); these typically have a low number of pixels and limited set of colors; Supply files that are too low in resolution. Submit graphics that are disproportionately large for the content.

Figure legends: Ensure that each illustration has a legend. Supply legends separately, not attached to the figure. A legend should comprise a brief title (not on the figure itself) and a description of the illustration. Keep text in the illustrations themselves to a minimum but explain all symbols and abbreviations used. Legends should be sent separately.

Tables: Number tables consecutively in accordance with their appearance in the text. Place footnotes to tables above the table body and indicate them with superscript lowercase letters. Avoid vertical rules. Be sparing in the use of tables and ensure that the data presented in tables do not duplicate results described elsewhere in the article.

References

Citation in text: Please ensure that every reference cited in the text is also present in the reference list. Any references cited in the abstract must be given in full. Unpublished results and personal communications are not recommended in the reference list, but may be mentioned in the text. If these references are included in the reference list they should follow the standard reference style of the journal and should include a substitution of the publication date with either 'Unpublished results' or 'Personal communication'. Citation of a reference as 'impress' implies that the item has been accepted for publication.

Web references: As a minimum, the full URL should be given and the date when the reference was last accessed. Any further information, if known (DOI, author names, dates, reference to a source publication, etc.), should also be given. Web references can be listed separately (e.g., after the reference list) under a different heading if desired, or can be included in the reference list.

Reference style

Text: Indicate references by number(s) in square brackets in line with the text. The actual authors can be referred to, but the reference number(s) must always be given. However, for more than one author, only the first should be listed followed by „et al".

List: Number the references (numbers in square brackets) in the list in the order in which they appear in the text.

Examples:

Reference to a journal publication:

1. Van der Geer J, Hanraads JAJ, Lupton RA. The art of writing a scientific article. J Sci Commun 2000;163:51–9.

Reference to a book:

2. Strunk Jr W, White EB. The elements of style. 3rd ed. New York: Macmillan; 1979.

Reference to a chapter in an edited book:

3. Mettam GR, Adams LB. How to prepare an electronic version of your article. In: Jones BS, Smith RZ, editors. Introduction to the electronic age, New York:

E-Publishing

Inc; 1999, p. 281–304.

Note shortened form for last page number. e.g., 51–9, and that for more than 6 authors the first 6 should be listed followed by «et al».

CENTRE OF PSYCHOSOCIAL SUPPORT FOR WOMEN WITH BREAST CANCER "ELLI LAMBETI"

Tel: +30 210 77 73 112, Fax: +30 210 77 16 834
E-Mail: reception@mastologia.gr

The Centre "ELLI LAMBETI" - Background:

The Centre of Psychosocial Support for Women with Breast Cancer "Elli Lambeti" was founded in April 2002 by the Hellenic Senologic Society with the aim to improve the quality of life of women with breast cancer and at the same time support the members of their families. It is an independent non-governmental Centre which is sponsored by public and private entities.

Since its creation until today, the Centre has offered its services to over 4500 people, who either visited it, or asked support via phone conversations either because they live in rural areas, or because they are not able to move, or even due to their wish to remain anonymous.

In the friendly and pleasant environment of the Centre, trained psychologists provide psychological services and social support by appointment for FREE, following the principles of medical confidentiality.

To whom the Center refers to

- All women with a recent diagnosis of breast cancer
- All women diagnosed with breast cancer and who follow medical treatment
- All women who are in the process of recovery
- All close family members as well those persons who are close to their work and social environment
- All women with carcinophobia

Services offered by the Centre.

The Center offers the following services free of charge:

- Information in relation to the disease
- Individual psychological and counseling support to women with breast cancer
- Psychological and counseling support to their family members, both during and after treatment
- Support the process of reintegration into the family and the work environment
- Ability to meet and contact other women facing the same problem
- Participation in cultural events and other activities (meetings, celebrations, bazaars, concerts,drawing exhibitions etc.)
- Group therapy
- Beauty therapeutic groups
- Dietary therapeutic groups
- Provision of specialised brochures

LIST OF EDITORIAL BOARD

AUTHOR INDEX

19th SIS World Congress On Breast Healthcare

May 5-8, 2016 | Warsaw, Poland

Founded in 1976 in Strasbourg, France

SOCIÉTÉ INTERNATIONALE DE SÉNOLOGIE

SENOLOGIC INTERNATIONAL SOCIETY

POLSKIE TOWARZYSTWO DO BADAŃ NAD RAKIEM PIERSI

"Warsaw is an amazing city that emerged from the ashes of World War II and it was restored with a full respect to its history. Today it is a vibrant metropolitan city that is constantly growing, thanks to the creativity of its motivated and polite inhabitants."

ΕΛΛΗΝΙΚΗ ΕΤΑΙΡΕΙΑ ΜΑΣΤΟΛΟΓΙΑΣ

As additionally in this Congress the final decision regarding the confirmation of the candidature of Greece for the organization of the 21st International Congress of the SIS for breast disease will be taken

ΣΤΗΝ ΠΡΟΣΠΑΘΕΙΑ ΣΑΣ ΝΑ ΕΠΙΒΡΑΔΥΝΕΤΕ ΤΗΝ ΕΞΕΛΙΞΗ ΤΟΥ HR+ ΠΡΟΧΩΡΗΜΕΝΟΥ ΚΑΡΚΙΝΟΥ ΤΟΥ ΜΑΣΤΟΥ

ΜΗΠΩΣ ΕΧΕΤΕ ΑΦΗΣΕΙ ΤΟΥΣ ΑΣΘΕΝΕΙΣ ΣΑΣ **ΕΥΑΛΩΤΟΥΣ** ΣΤΟ ΜΟΝΟΠΑΤΙ ΣΗΜΑΤΟΔΟΤΗΣΗΣ PI3K-mTOR;

Lectus adv.

Εάν παραβλεφθεί, η υπερενεργοποίηση του μονοπατιού PI3K-mTOR ενισχύει την αντίσταση στην ενδοκρινική μονοθεραπεία και την εξέλιξη του HR+ [1,2] προχωρημένου καρκίνου του μαστού

- Το **PI3K-mTOR** είναι το συνηθέστερο μονοπάτι που ενεργοποιείται με παρεκκλίνοντα τρόπο στον καρκίνο του μαστού, με εμφάνιση γενετικών διαταραχών σε ποσοστό άνω του 70% των περιπτώσεων [2,3]
- Το μονοπάτι **PI3K-mTOR** αποτελεί κύρια πηγή αντίστασης και εξέλιξης του HR+ προχωρημένου καρκίνου του μαστού [1,2]
- Η Novartis δεσμεύεται να αξιοποιήσει πλήρως τις θεραπευτικές δυνατότητες της στόχευσης του μονοπατιού **PI3K-mTOR** σε ασθενείς με HR+ προχωρημένο καρκίνο του μαστού

Το μονοπάτι **PI3K-mTOR** είναι σημαντικό στοιχείο που πρέπει να λαμβάνεται υπόψη στην προσέγγιση του HR+ προχωρημένου καρκίνου του μαστού.

Για περισσότερες πληροφορίες, ανατρέξτε στον ιστότοπο **TargetingPI3K-mTOR.com**

HR+= θετικός στους ορμονικούς υποδοχείς, mTOR = στόχος της ραπαμυκίνης στα θηλαστικά.

Παραπομπές: 1. Miller T. Endocrine resistance: what do we know? Am Soc Clin Oncol Educ Book. 2013:e37-e42. **2.** Miller TW, Rexer BN, Garrett JT, Arteaga CL. Mutations in the phosphatidylinositol 3-kinase pathway: role in tumor progression and therapeutic implications in breast cancer. Breast Cancer Res. 2011;13(6):224-235. **3.** Hosford SR, Miller TW. Clinical potential of novel therapeutic targets in breast cancer: CDK4/6, Src, JAK/STAT, PARP, HDAC, and PI3K/AKT/mTOR pathways. Pharmgenomics Pers Med. 2014;7:203-215.

NOVARTIS ONCOLOGY

Novartis (Hellas) A.E.B.E.
12ο χλμ. Εθνικής Οδού Αθηνών-Λαμίας, 144 51 Μεταμόρφωση, Τηλ. 210 2811712
Γραφείο Θεσσαλονίκης: 12ο χλμ. Θεσσαλονίκης - Ν. Μουδανιών, 570 01 Θέρμη, Τηλ. 2310 424039
ΦΑΡΜΑΚΟΕΠΑΓΡΥΠΝΗΣΗ: 210 2828812

GR1511405901