

The Official Journal of the Hellenic Senologic Society

Mastologia

July - December 2016
Issue 1, Volume 2
ISSN 1790 - 3963

EDITORIAL

- Welcome note

REVIEW ARTICLES

- Pathologic Features and Molecular Characteristics of BRCA Associated Breast Cancer
- Breast Cancer During Pregnancy
- Chronic Recurrent Mastitis
- Evaluation of breast microcalcification

CLINICAL CASES - EDUCATIONAL ARTICLES

- A case from the Department of Mammography Screening, Paderborn, Germany
- Pitfalls in Mammography the role of Clinical examination

MEMORIAL

To Prof Umberto Veronesi





Senographe Essential

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

GE Works.





Mastologia

Editor in Chief

Lydia Ioannidou - Mouzaka, MD, PhD

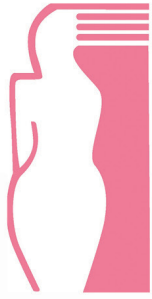
Deputy Editor

Apostolos Zavos, MD

Editorial Board Members

Niki J. Agnantis, Athens - Greece
Benjamin Anderson, Seattle - Washington - USA
Dimitrios Bafaloukos, Athens - Greece
Carol Ann Benn, Johannesburg - South Africa
Mauricio Camus, Santiago - Chile
Luigi Cattaliotti, Firenze - Italy
Eduardo Cazap, Buenos Aires - Argentina
Evanthia Diamanti - Kandaraki, Athens - Greece
Nikolaos Dimitropoulos, Athens - Greece
Ivan Drinković, Zagreb - Croatia
Enzo Durante, Ferrara - Italy
Athanasios Exadactylos, Thessaloniki - Greece
Stephen A. Feig, Orange Ca - USA
Lina Florentin, Athens - Greece
Andreas Foustanos, Athens - Greece
Rufo de Freitas Junior, Coiania - Brazil
Hans Joachim Frischbier, Hamburg - Germany
Constatin Gennatas, Athens - Greece
Pierre Alain Goumot, Paris - France
Axel Gräwingholt, Paderborn, Germany
Rahdi Hamza, Tunis, Tunisie
Dimitrios Hapsas, Athens-Greece
Nektaria Lambrinaki-Kalamata, Athens - Greece
Dimitris Kelekis, Athens - Greece
Antony Keramopoulos, Athens - Greece
David Khayat, Paris - France
Krystyna D. Kiel, Chicago ILL - USA
Michael Koutsilieris, Athens - Greece
Pagona Lagiou, Athens - Greece
Spyros Lazarou, Athens - Greece
Helmut Madjar, Freiburg - Germany

Petros Malakasis, Athens - Greece
Robert Mansel, Cardiff - U.K.
Shahla Masood, Jacksonville Florida - USA
Carole Mathelin, Strasbourg - France
Leonardo McLean, Buenos Aires - Argentina
Monica Morrow, New York - USA
Alexander Mundinger, Osnabruck - Germany
Ezio Novais Diaz, Bahia - Brazil
Ruben Orda, Tel-Aviv - Israel
Valerijus Ostapenko, Vilnius - Lithuania
Dimitrios Pektasidis, Athens - Greece
Savvas Papadopoulos, Athens - Greece
Tadeusz Pienkowski, Warsaw - Poland
Edio Pusterla, Lugano - Switzerland
Emiel Rutgers, Amsterdam - The Netherlands
Arkadios Rousakis, Athens - Greece
Ayşegül Şahin, New York - USA
Schlomo Schneebaum Tel - Aviv - Israel
Ashraf Selim, Cairo - Egypt
EfthimiosSivridis, Alexandroupoli - Greece
Kalliopi P. Siziopikou, Chicago, ILL - USA
Antony Thomas Stavros, Colorado-Denver - USA
Kyriakos Souliotis, Athens - Greece
Laszlo Tabar, Malmo-Sweden & USA
Tibor Tot, Uppsala - Sweden
Serdal Türhal, Istanbul - Turkey
Christina Tsionou, Athens - Greece
Carlos Vazquez Albaladejo, Valencia - Spain
Christopher Zielinski, Vienna - Austria
Georgios Zografos, Athens - Greece
Gustavo Zucca - Mattes, Barretos - Brazil



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

The Official Journal of the Hellenic Senologic Society



Mastologia

***Board of Directors
of the
HELLENIC SENOLOGIC SOCIETY***

President

Pr Lydia Ioannidou - Mouzaka MD, PhD

Vice President

Dr Athanasios Exadactylos

Secretary General

Aggeliki Athanasiou

Treasurer

Georgios Kokkalis

Members

Petros Malakasis

Vassiliki Malamou - Mitsi

Apostolos Zavos



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.,

ZITA 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

SOCIÉTÉ
INTERNATIONALE
DE SÉNOLOGIE



SENOLOGIC
INTERNATIONAL
SOCIETY



SENOLOGIC
HELLENIC
SOCIETY

SAVE ^{THE}
DATE

21st SIS World Congress on Breast Healthcare 2020

Official Website: www.breastsiscongress2020.com



JUNE 11-14, 2020

Athens, Greece

Under the Auspices:



ECUMENICAL
PATRIARCHATE



HELLENIC REPUBLIC
MINISTRY OF TOURISM



REGION OF
ATTICA
ATHENS



CITY OF ATHENS



PANHELLENIC
MEDICAL ASSOCIATION



MEDICAL ASSOCIATION
OF ATHENS



GLOBAL GREEK
DOCTORS' INSTITUTE



I.H.T.C.
International
Health Tourism Center



FREI S.A.
Congresses - Conventions - Exhibitions - Incentives,
3, Papanigapoulou Street, 105 61 Athens, Greece,
Tel: +30 210 3215600, web: www.frei.gr, email: info@frei.gr

New edition

EDITORIAL

Welcome note

Lydia Ioannidou - Mouzaka **p. 9**

REVIEW ARTICLES

Pathologic Features and Molecular Characteristics of BRCA Associated Breast Cancer

Kalliopi P. Siziopikou **p. 10-16**

Breast Cancer During Pregnancy

Aggeliki D. Athanasiou & Lydia Ioannidou - Mouzaka **p. 17-23**

Chronic Recurrent Mastitis

Aggeliki D. Athanasiou **p. 24-25**

Evaluation of breast microcalcification

Elisavet Soilemezi, Georgios Kyropoulos, Apostolos Zavos **p. 26-35**

CLINICAL CASES - EDUCATIONAL ARTICLES

A case from the Department of Mammography Screening, Paderborn, Germany

Regina Schwanitz - Gräwingholt and Axel Gräwingholt **p. 36-39**

Pitfalls in Mammography the role of Clinical examination

Lydia Ioannidou - Mouzaka **p. 40-41**

Memorial

To Umberto Veronesi

Lydia Ioannidou - Mouzaka **p. 42**

Upcoming congresses

p. 43-45

Instructions to Authors

p. 47-50

List of Editorial Board

p. 51-53

List of Authors

p. 54

ΕΛΛΗΝΙΚΗ ΣΧΟΛΗ ΜΑΣΤΟΛΟΓΙΑΣ



ΔΙΗΜΕΡΟΙ ΚΥΚΛΟΙ



2018

Ημερομηνίες

- 2 & 3 Μαρτίου
- 11 & 12 Μαΐου
- 22 & 23 Ιουνίου
- 5 & 6 Οκτωβρίου
- 16 & 17 Νοεμβρίου

***Συμπληρώνουμε
το κενό Εκπαίδευσης
στη Μαστολογία***

Περισσότερες Πληροφορίες:

τηλ.. 2103215600 - email: congress_events@frei.gr

Χώρος διεξαγωγής: Αμφιθέατρο "Επαμεινώνδας Μεγαπάνος"

Μαιευτήριο Λητώ, Μουσών 7-13 Αθήνα

Welcome note



Editor in Chief
Ass Pr Lydia
Ioannidou - Mouzaka

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

The third issue of our scientific Journal “Mastologia” is a reality. Everyone knows the difficult financial situation that Greece is going through.

In such situations, believe me, the attempt to edit a Journal is a difficult achievement. For this reason, from the start of my Welcome note of the present issue, I would like to address on my behalf but also on behalf of all the Members of the Board of Directors of the Hellenic Senologic Society (HSS) our heartiest thanks to all Pharmaceutical Companies which, despite the financial difficulties, they have remained and remain by our side.

As we had previously announced, the “19th World Congress on Breast Health Care” took place in May 5-8, 2016, in Warsaw, Poland. The Congress had a high scientific level. At the same time we had the opportunity to discover this vibrant city, which is constantly developing, thanks to the creativity and the motivation of its inhabitants. The Hellenic medical representation returned from Warsaw very satisfied, as the General Assembly of the Senologic International Society (SIS), elected Greece as the venue of the 21st World Congress on Breast Health Care of the year 2020. This brought enormous satisfaction to the Hellenic Senologic Society, giving us courage and energy to continue to work for the World of Senology, for women, the patients and the survivors.

On 20-23 October, we organized in Thessaloniki, the 13th National Congress on Senology with International participation. We tried to make an attractive and high level scientific program. During the Congress the attempt of the new European guidelines regarding screening and diagnosis was presented. Patient advocacy was also given a place and we encouraged the patients to participate in the decision making process.

During the Congress, as the Hellenic Senologic Society is a Society affiliated to the SIS, since its foundation, a celebration regarding the 40th anniversary of the SIS took place.

During the month of October, the European month against breast cancer, the Hellenic Senologic Society offered breast clinical examination and ultrasound examination, free of charge, in several urban places of Greece. In addition, the same kind of offer was given to the Athenian women on the 30th October and 1st November, with the collaboration of the Department of Social Services of the Municipality of Athens, at the Kalfopoulou-1st Municipal Infirmary, at 78, Solonos street in Athens. On the 31st of October, at the same place, a voluntary blood donation also took place, and the blood supplies collected were offered to the Pediatric Oncology Unit “Marianna V. Vardinogiannis- Elpida”.

Ending this editorial message I would like to invite you to save the date for the 11-14 of June of 2020, for the 21st World Congress on Breast Health Care of the SIS and I hope that God keeps us in good health and permits all of us to participate.

The International family of Senology since November 8th became poorer, as one of the most important colleagues who worked on the breast, abandoned the mundane and migrated to the Lord. The reason, for the very well known breast surgeon from Milan, Italy, Professor Umberto Veronesi. Please see the Memorial written for him on page 42 in this issue of the Journal.

With my best regards
Lydia Ioannidou-Mouzaka MD, Ph.D

Pathology - Molecular biology

Pathologic Features and Molecular Characteristics of BRCA Associated Breast Cancer

Kalliopi P. Siziopikou, MD, Ph.D

Professor of Pathology, Director of Breast Pathology, Director of Breast Pathology Fellowship Program, Department of Pathology, Breast Pathology Section, Northwestern University Feinberg School of Medicine Robert H. Lurie Comprehensive Cancer Center

ABSTRACT

Familial breast carcinomas constitute a significant percentage of all newly diagnosed breast cancer cases. A number of high penetrance susceptibility genes, such as BRCA1 and BRCA2, as well as many other moderate and low penetrance genes play a role in the development of familial breast cancer. However, to date, their exact role is still poorly understood. Recent studies show that BRCA1 associated breast carcinomas belong to the basal subtype of breast carcinomas and have distinct histologic features. The molecular biology characteristics of carcinomas associated with BRCA1 and BRCA2 genes are emerging. Our deepening understanding of the role of BRCA1 and BRCA2 in DNA repair may provide opportunities for novel therapeutic strategies in these familial breast carcinomas.

KEYWORDS: BRCA1; BRCA2; pathology; familial breast cancer; basal phenotype

Introduction

Breast cancer is the most common cancer in women with over 245,000 cases of invasive carcinoma and over 63,000 of preinvasive breast cancer diagnosed in the United States alone every year^{1,2}. The incidence is increasing with the 1 in 11 women statistic of 15 years ago, now standing at 1 in 8 women to be expected to be diagnosed with breast cancer by the age of 85¹. Half (50%) of these carcinomas arise in the upper outer quadrant and breast cancer in gen-

eral is more common in the left breast than in the right side. Our improved understanding of the molecular pathways that drive breast cancer development and progression is expected to lead to further improvements in the therapeutic management of breast cancer, especially in specific subgroups of breast cancer patients.

Familial Breast Cancer Incidence

Familial breast cancer is common; 13% of women diagnosed

Corresponding author

Kalliopi P. Siziopikou, MD, PhD

251 East Huron Street, Galter 7-132 O, Chicago, IL 60611

E-mail: p-siziopikou@northwestern.edu

with breast cancer have a family history of one affected first degree relative and 1% report multiple affected relatives from their maternal or paternal side of the family³. A full quarter (25%) of all familial breast cancers are associated with the breast cancer susceptibility genes BRCA1 and BRCA2 that confer a general lifetime breast cancer risk of 60-85%³. The presence of these genes also confer a lifetime ovarian cancer risk that is calculated to be 20-40% for BRCA1 carriers and 10-20% for BRCA2 carriers³. Although the BRCA1 and BRCA2 associated breast carcinomas account for only 3% of the total breast cancer incidence when all breast carcinomas are put together, these tumors account for a large burden of morbidity and mortality given the high overall incidence of breast cancer in the population.

Genes associated with familial breast cancer

It is now understood that the genes that confer risk for future development of breast cancer can be divided into genes that confer high risk and genes that confer small to moderate risk⁴. Better characterized are the genes that confer high risk such as the BRCA1 and BRCA2 genes, the p53 gene that is associated with the Li-Fraumeni syndrome, the PTEN gene associated with Cowden syndrome and the CDH1 gene that is associated with the familial lobular carcinoma syndrome^{4,7}. Our knowledge of the genes conferring small to moderate risk is increasing; genes such as the ATM, NBS1, RAD50, and PALB2 gene belong in that intermediate category^{4,8,9}. However, based on data from genome wide association studies (GWAS) it appears that most cases of breast cancer are associated with many yet unknown genes that by themselves appear to confer only minimal risk, while that risk becomes much higher when these genes interact with one another or with other known and unknown environmental factors⁴.

Syndromic breast cancer

Rarely breast cancer develops as part of a more general syndrome; the most well known such syndromes are the Li-Fraumeni syndrome and the Cowden syndrome. Li-Fraumeni is a cancer predisposition syndrome with an autosomal dominant inheritance. In half of the cases a mutation in the TP53 gene is detected. A number of malignancies develop in the affected individuals: breast carcinomas,

soft-tissue sarcomas, osteosarcomas, leukemias, melanomas, colonic carcinomas, pancreatic carcinomas, adrenal carcinomas, and brain carcinomas. The breast cancer risk is calculated to be about 60%⁴⁻⁶.

Cowden syndrome has an autosomal dominant inheritance as well and the mutated gene is the PTEN. It presents as a multiple hamartoma syndrome and benign and malignant tumors of the thyroid, breast and endometrium are common. The breast cancer risk is calculated to be about 25-50%⁴⁻⁶.

BRCA1 and BRCA2 genes and breast cancer

The BRCA1 gene, located on chromosome 17q21, was isolated in 1994. The following year the BRCA2 gene was isolated; BRCA2 is located on chromosome 13q12-13. The BRCA1 gene encodes for an 1863 aminoacid zinc finger protein, containing nuclear localization signals and a RAD51 binding protein³. The BRCA2 gene encodes for a 3418 aminoacid protein containing 39 aminoacid repeats and is critical to binding RAD5³. Numerous mutations of these genes are identified. Four of these mutations are most commonly found in the Ashkenazi Jewish population of eastern European decent; these mutations, such as the common 185delAG, are called founder mutations¹⁰. A number of other high frequency mutations are found in other racial/ethnic groups a fact that complicates testing^{3,11}. Methods to isolate and detect BRCA1 and BRCA2 genes were patented in the US by Myriad Genetics, which was the only company allowed to offer BRCA testing in the US for many years. The Myriad Genetics patent was invalidated in 2013 by the United States Supreme Court mainly due to the concern that exclusive patent rights prevented patients from seeking second opinion evaluation and testing of the status of their gene mutations¹².

In addition to their association with the development of breast carcinomas, BRCA1 mutations are associated with development of ovarian, uterine, cervical, peritoneal, pancreatic and colonic carcinomas, while BRCA2 mutations are associated with the development of breast, ovarian, pancreatic, stomach, gallbladder, prostate and male breast cancer³.

The mechanism of BRCA1 gene action is now understood to involve homologous DNA repair mechanisms; BRCA1 de-

cient cells are unable to repair DNA double-strand breaks by homologous recombination. In addition, the BRCA1 gene is involved in numerous other cell functions such as the regulation of estrogen (ER) expression, cell proliferation and chromosomal stability. The end result of BRCA1 mutations is genomic instability and malignant transformation³. BRCA2 deficient cells also lack homologous DNA repair mechanisms and are unable to repair DNA double-strand breaks by homologous recombination. In addition BRCA2 plays a central role in the regulation of RAD51 activity. RAD 51 is a highly conserved DNA recombinase involved in the repair of double-strand breaks and arrested replicon forks. The end result of BRCA2 mutations is once again genomic instability and malignant transformation³.

The pathology of BRCA1 and BRCA2 associated breast carcinomas

The pathology of BRCA1 associated breast carcinomas is distinct. These tumors are usually triple negative, poorly differentiated (high grade), invasive carcinomas of ductal histology, with high mitotic counts. Areas of necrosis are usually present. The tumors are usually circumscribed with pushing margins and prominent surrounding lymphocytic infiltrate, giving these carcinomas “medullary-like” features. Of interest, ductal carcinoma-in-situ (DCIS) is usually scant or completely absent^{3, 13-15}.

In contrast, BRCA2 tumors do not seem to have any special morphologic features and the frequency of estrogen (ER) and progesterone (PR) expression, as well as HER2 amplification is similar to sporadic breast tumors. Thus, pathologic features alone are not very helpful in identifying potential BRCA2 carriers^{3, 14-15}.

The Molecular Biology and Biomarkers of BRCA1 and BRCA2 Associated Breast Carcinomas

The molecular biology and biomarker expression of BRCA1 and BRCA2 associated tumors are becoming better understood. The majority (63-90%) of BRCA1 associated breast carcinomas are ER and PR negative. Even when only poorly differentiated (high grade) carcinomas are evaluated, BRCA1 associated carcinomas are 4-5x more likely to be ER negative than sporadic tumors^{3, 16-18}. Lakhani and associates reported that, in their series, 90% of BRCA1 associated tumors were ER-negative and 79% were PR-negative (versus 35% and 41% of their sporadic breast carcinoma controls). Other ER-associated gene expression such as bcl-2 and cy-

clin D1 are also negative. HER2 is overwhelmingly negative; only 0-3.7% of BRCA1 associated breast tumors are reported to be positive. Thus, the vast majority of BRCA1 associated carcinomas are triple negative and specifically of the basal phenotype, since they usually express markers of basal/myoepithelial origin such as cytokeratin CK5/6, CK5, CK14 and EGFR as well as p27 and cyclin E1. Expression of p53 is reported in 37-77% of BRCA1 associated carcinomas compared to about 20% of breast sporadic tumors; of interest, the distribution of p53 mutations in BRCA1 associated carcinomas is different than those in sporadic breast tumors^{3, 16-18}. C-myc expression is seen in 20% of the BRCA1 associated breast carcinomas. In contrast, c-myc expression is much more common in BRCA2 associated breast carcinoma (>60%); these tumors also overexpress the cell cycle proteins cyclin D1, CDK1, CDK2 and CDK4^{3, 16-18}.

The Basal Subtype of Breast Carcinomas

In the last 15 years, our classic understanding of the histologic subtypes of breast cancer was expanded to include the molecular classification of breast carcinomas. C. Perou and collaborators in their seminal work in the journal Nature in 2000, described what they called “the molecular portraits of human breast tumours”¹⁹. These investigators used recently developed techniques that examine DNA, RNA and proteins in a global way instead of a gene at a time. This analysis provided the framework for the new, molecular classification of breast carcinomas based on gene profiling as follows: Luminal A subtype consisting of ER-positive/HER2-negative breast carcinomas, comprising 40-55%, Luminal B subtype consisting of ER-positive/mostly HER2-positive breast carcinomas, comprising 15-20%, HER2-positive subtype consisting of ER-negative / HER2-positive breast carcinomas, comprising 7-12%, and the newly described basal subtype consisting of ER-negative/PR-negative/HER2-negative (triple negative) breast carcinomas, comprising 13-25% of all breast tumors and expressing basal/myoepithelial type keratins¹⁹⁻²¹.

The basal subtype of breast carcinomas is usually seen in young, premenopausal patients; the average age at presentation is 47 years. It is also more common among African-American and Hispanic women. It is characterized by rapid clinical growth and is over-represented among “interval” breast cancers, meaning breast carcinomas that appear suddenly and grow quickly between mammographic screenings. These tumors are aggressive with

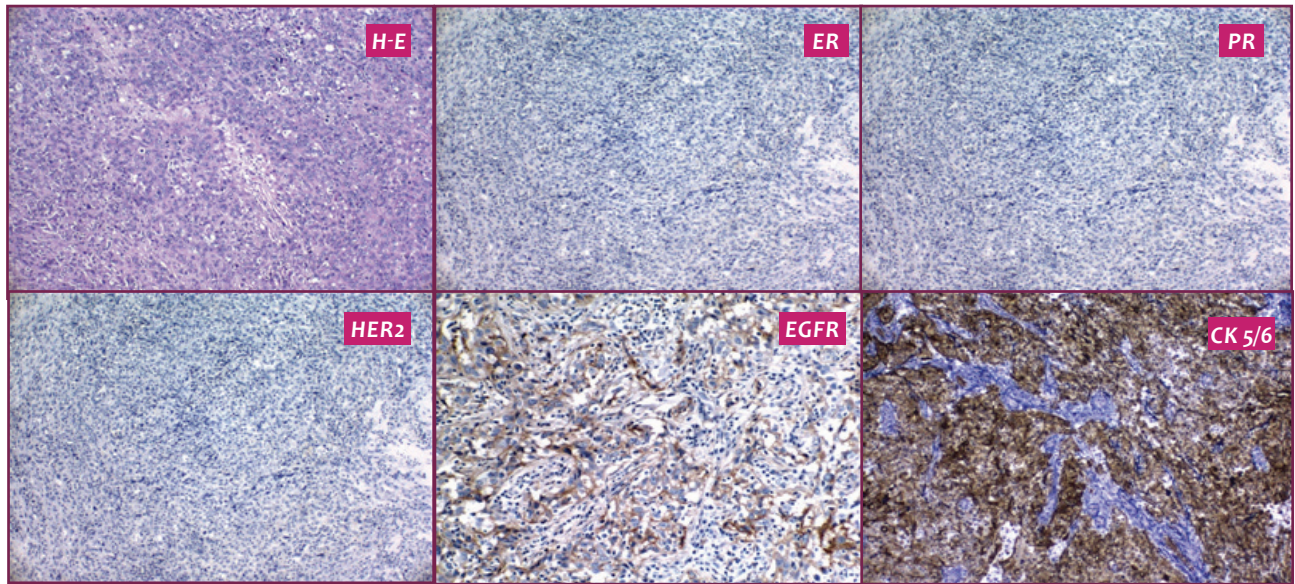


Image. Invasive poorly differentiated ductal carcinoma (grade 3), ER-negative/ PR-negative/ HER 2-negative, exhibiting EGFR and strong CK5/6 positivity (triple negative, basal subtype, BRCA1 associated breast carcinoma)

higher rates of recurrence (often in the first few years after diagnosis), higher rates of distant metastatic disease and higher overall mortality rates. Of interest, these tumors display distinct pattern of metastatic spread usually to the brain or lungs instead of lymph nodes or bone²²⁻²⁷.

Histologically most of breast carcinomas of the basal subtype are invasive ductal carcinomas (68-86%) of large size and high histologic grade; 75-100% are poorly differentiated grade III tumors. Areas of geographic necrosis are usually present. The tumors are usually circumscribed with pushing margins and prominent surrounding lymphocytic infiltrate. When they are associated with DCIS, the DCIS is of high nuclear grade and of basal subtype. By definition these tumors exhibit positivity for basal/myoepithelial keratins such as cytokeratin CK5/6, CK5, CK14 and EGFR²²⁻³¹.

The Possible BRCA1 Connection of the Basal Subtype of Breast Carcinomas

A number of preclinical studies and clinical observations have raised the intriguing possibility that BRCA1 associated breast carcinomas and basal breast carcinomas share many molecular aberrations, especially those related to defects in DNA repair mechanisms^{32, 33}. These reports raised the intriguing possibility that both types of tumors may respond to similar novel therapeutic interventions. More specifically, mouse models with BRCA1-deficient mammary glands develop mammary carcinomas

with histologic and immunohistochemical characteristics similar to those of human breast carcinomas of the basal subtype. Furthermore, although BRCA1 gene mutations are rare in sporadic breast cancers, BRCA1 mRNA and protein levels are preferentially downregulated in the basal subtype of breast carcinomas³⁴. In this subtype the BRCA1 pathway dysfunction seems to be mediated through epigenetic silencing of the BRCA1 promoter or by up-regulation of ID4, a BRCA1 negative regulator of function³⁵. On the clinical side, many of the breast tumors that arise in patients with BRCA1 mutations have similar pathologic characteristics, gene expression profile and genomic aberrations with the basal subtype of breast carcinomas. Of interest, in addition to the primary tumor characteristics, even the metastatic pathways of spread are similar, with both types of tumors preferentially metastasizing to the brain^{32, 33}.

The Use of Pathologic Features to Guide BRCA1 Testing

A number of risk assessment models are currently used for early identification of possible breast cancer mutation carriers, but these models are not very specific nor very accurate. Given the distinct pathologic features of the BRCA1 associated carcinomas, the possibility of using pathologic and immunohistological features in improving risk estimation algorithms for BRCA

status testing and screening was raised³⁶⁻³⁸. While initial such efforts with small numbers of BRCA1 carriers were disappointing³⁹, a number of other studies with larger sample sizes were very encouraging. Specifically, in a univariate analysis of 292 invasive breast carcinomas diagnosed in Ashkenazi Jewish patients, cytokeratin 5/6 expression was associated with BRCA1 mutations (odds ratio: 9)⁴⁰. In addition, Lakhani and collaborators from the International Breast Cancer Linkage Consortium reported that, in multivariate analysis expression of cytokeratin 5/6 and 14 and ER negativity were significant predictors of BRCA1 status, although no association with BRCA2 status was seen¹⁷. Furthermore, incorporation of pathology results was reported to improve the probability of detecting BRCA1 mutations in an analysis of 207 families using the BRCAPRO model⁴¹. Finally, the Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA) after analyzing 4,325 BRCA1 and 2,568 BRCA2 mutation carriers reported that pathologic characteristics of BRCA1 breast tumors were useful in improving risk prediction algorithms and informing clinical strategies for screening and prophylaxis¹⁶.

Novel Targeted Treatment for BRCA1 and BRCA2 Associated Breast Carcinomas

The understanding of the role of BRCA1 and BRCA2 genes in DNA repair by homologous recombination, raises the possibility of novel targeted therapies in BRCA1 and BRCA2 associated breast carcinomas. Some of the most promising ways of tailored treatment include:

1. Use of DNA cross-linking agents such as mitomycin-C and platinum based drugs to cause damage that in the absence of reliable repair results in apoptosis, and
2. Use of inhibitors of the poly-ADP ribose polymerase (PARP) enzyme.

PARP inhibitors result in apoptosis by blocking the additional repair mechanisms, such as base excision repair and single strand break repair, that become important when homologous recombination repair is defective, as is the case in BRCA1 and BRCA2 breast tumors⁴²⁻⁴⁶. The results of clinical trials evaluating the role of such agents in sporadic triple negative breast carcinomas of the basal subtype are awaited with intense interest, especially since early results are encouraging⁴⁷⁻⁵⁰.

Conclusion

A number of high penetrance susceptibility genes, such as BRCA1 and BRCA2, as well as many other moderate and low penetrance genes play a central role in the development of familial breast cancer. BRCA1 associated breast tumors have a distinct histology; they are often high grade invasive ductal carcinomas with a basal phenotype; these distinct pathologic parameters could be incorporated into risk assessment models resulting in improved detection of mutation carrier status. Our expanding understanding of the role of BRCA1 and BRCA2 genes in DNA repair and identification of new molecular targets for tailored treatment are currently exploited for the development of novel therapeutic strategies for improved management of these aggressive tumors that usually affect young women.

Conflicts of interest

The author declares that there are no conflict of interest regarding the publication of this paper. ■

REFERENCES

1. Cancer facts and figures, 2016. American Cancer Society, INC. www.cancer.org, last viewed 7/27/2016.
2. Special section: Breast carcinoma in situ, 2015. American Cancer Society, INC. www.cancer.org, last viewed 7/27/2016.
3. BRCA1 and BRCA2: Cancer risk and genetic testing-National Cancer Institute. www.cancer.gov/cancertopics/factsheet/Risk/BRCA, last viewed 07/27/2016.
4. Foulkes WD. Inherited susceptibility to common cancers. *New England Journal of Medicine* 2008; 359 (20): 2143-2153.
5. Campeau PM, Foulkes WD, and Tischkowitz MD. Hereditary breast cancer: New genetic develop-

- ments, new therapeutic avenues. *Human Genetics* 2008; 124 (1): 31-42.
6. Lynch HT, Silva E, Snyder C, et al. Hereditary breast cancer: Part1. Diagnosing hereditary breast cancer syndromes. *The Breast Journal* 2008; 14(1): 3-13.
7. Xie ZM, Li LS, Laquet C, et al. Germline mutations of the E-cadherin gene in families with inherited invasive lobular breast carcinoma but no diffuse gastric cancer. *Cancer* 2011; 117(14): 3112-3117.
8. Evans MK, Longo DL. PALB2 mutations and breast cancer risk. *New England Journal of Medicine* 2014; 371 (6): 566-568.
9. Antoniou AC, Casadei S, Heikkinen T, et al. Breast cancer risk in families with mutations in PALB2. *New England Journal of Medicine* 2014; 371(6): 497-506.
10. Kadouri L, Hurtert A, Rosenberg Y, et al. Cancer risks in carriers of the BRCA1/2 Ashkenasi founder mutations. *Journal of Medical Genetics* 2007; 44(7): 467-471.
11. Morris GJ, Naidu S, Topham AK, et al. Differences in breast carcinoma characteristics in newly diagnosed African-American and Caucasian patients: a single institution compilation compared with National Cancer Institute's Surveillance, Epidemiology, and End Results database. *Cancer* 2007; 110: 876-884.
12. Gold RE, Cook-Deegan R, Bubela T. AMP vs. Myriad: A surgical strike on blockbuster business models. *Science Translational Medicine* 2013; 5(192)
13. Turner NC, Reis-Filho JS. N.C. Turner, J. S. Reis-Filho. Basal-like breast cancer and the BRCA1 phenotype. *Oncogene* 2006; 25: 5846-5853.
14. Van Beers EH, Van Welsem T, Wessels LF, et al. Comparative genomic hybridization profiles in human BRCA1 and BRCA2 breast tumors highlight differential sets of genomic aberrations. *Cancer Research* 2002; 62: 7110-7117.
15. Van der Groep P, Van Diest PJ, Menko FH, et al. Molecular profile of ductal carcinoma in situ of the breast in BRCA1 and BRCA2 germline mutation carriers. *Journal of Clinical Pathology* 2009; 62 (10): 926-930.
16. Mavaddat N, Barrowdale D, Andrulis IL, et al. Pathology of breast and ovarian cancers among BRCA1 and BRCA2 mutation carriers: Results from the Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA). *Cancer Epidemiology and Biomarkers Prevention* 2012; 21(1): 134-147.
17. Lakhani SR, Reis-Filho JS, Fulford L, et al. Prediction of BRCA1 status in patients with breast cancer using estrogen receptor and basal phenotype. *Clinical Cancer Research* 2012; 11 (14): 5175-5180.
18. Foulkes WD, Stefansson IM, Chappuis PO, et al. Germline BRCA1 mutations and a basal epithelial phenotype in breast cancer. *Journal of National Cancer Institute* 2003; 95(19): 1482-1485.
19. Perou CM, Sorlie T, Eisen MB, et al. Molecular portraits of human breast tumors. *Nature* 2000; 406: 747-752.
20. Sorlie T, Tibshirani R, Parker J, et al. Repeated observation of breast tumor subtypes in independent gene expression data sets. *Proceedings of the National Academy of Sciences USA* 2003; 100: 8418-8423.
21. Nielsen TO, Perou CM. The development of breast cancer molecular subtyping. *Clinical Cancer Research* 2015; 21(8): 1779-1781.
22. Nielsen TO, Hsu FD, Jensen K, et al. Immunohistochemical and clinical characterization of the basal-like subtype of invasive breast carcinoma. *Clinical Cancer Research* 2004; 10: 5367-5374.
23. Won JR, Gao D, Chow C, et al. A survey of immunohistochemical biomarkers for basal-like breast cancer against a gene expression profile gold standard. *Modern Pathology* 2013; 26: 1438-1450.
24. Leidy J, Khan A, Kandil D. Basal-like breast cancer; update on clinicopathologic, immunohistochemical and molecular features. *Archives of Pathology and Laboratory Medicine* 2014; 138: 37-43.
25. Badve S, Dabbs DJ, Schnitt SJ, et al. Basal-like and triple-negative breast cancers: A critical review with an emphasis on the implications for pathologists and oncologists. *Modern Pathology* 2010; 24: 157-167.
26. Rakha E, Reis-Filho JS. Basal-like breast carcinoma: From expression profiling to routine practice. *Archives of Pathology and Laboratory Medicine* 2009; 133 (6): 860-868.
27. The Cancer Genome Atlas Network. Comprehensive molecular portraits of human breast tumors. *Nature* 2012; 490: 61-70.
28. Rakha EA, Reis-Filho JS, Ellis IO. Basal-like breast cancer: A critical review. *Journal of Clinical Oncology* 2008; 26: 2568-2581.

29. Rakha EA, El-Sayed ME, Reis-Filho J, et al. Pathobiological aspects of basal-like breast cancer. *Breast Cancer Research and Treatment* 2009; 113(3): 411-422.
30. Carey LA, Perou CM, Livasy CA, et al. Race, breast cancer subtypes and survival in Carolina Breast Cancer Study. *JAMA* 2006; 295: 2492-2502.
31. Mayer IA, Abramson VG, Lehmann BD, et al. New strategies for triple-negative breast cancer- deciphering the heterogeneity. *Clinical Cancer Research* 2014; 20(4): 782-790.
32. Santarosa, Maestro R. BRACing news on triple-negative/basal-like breast cancers: How BRCA1 deficiency may result in the development of a selective tumor subtype. *Cancer Metastasis Review* 2012; 31: 131-142.
33. Turner N, Tuff A, Ashworth A. Hallmarks of "BRCAness" in sporadic cancers". *National Review Cancer* 2004; 4: 814-819.
34. Esteller M, Silva JM, Dominguez G, et al. Promoter hypermethylation and BRCA1 inactivation in sporadic breast and ovarian tumors. *Journal of National Cancer Institute* 2000; 92: 564-569.
35. Beger C, Pierce LN, Kruger M, et al. Identification of Id4 as a regulator of bRCA1 expression by using a ribosome-library-based inverse genomics approach. *Proceedings of the National Academy of Sciences USA* 2001; 98: 130-135.
36. Fulford LG, Easton DF, Reis-Filho JS, et al. Specific morphological features predictive for basal phenotype in grade 3 invasive ductal carcinoma of the breast. *Histopathology* 2006; 26: 22-34.
37. Turner NC, Reis-Filho JS, Russell AM, et al. BRCA1 dysfunction in sporadic basal-like breast cancer. *Oncogene* 2007; 26: 2126-2132.
38. Bryan BB, Schnitt SJ, Collins LC. Ductal carcinoma in situ with basal-like phenotype: A possible precursor to invasive basal-like breast cancer. *Modern Pathology* 2006; 19: 617-621.
39. Collins LC, Martyniak A, Kandel MJ, et al. Basal cytokeratin and epidermal growth factor receptor expression are not predictive of BRCA1 mutation status in women with triple-negative breast cancers. *American Journal of Surgical Pathology* 2009; 33 (7): 1093-1097.
40. Foukles WD, Smith IE, Reis-Filho JS. Triple-negative breast cancer. *New England Journal of Medicine* 2010; 363(20): 1938-1948.
41. James PA, Doherty R, Harris M, et al. Optimal selection of individuals for BRCA mutation testing: A comparison of available methods. *Journal of Clinical Oncology* 2006; 24(4): 707-715.
42. Vidula N, Rugo HS. Translating the molecular message of triple-negative breast cancer into targeted therapy. *Clinical Cancer Research* 2015; 21 (7): 1511-1513.
43. Ashworth A. A synthetic lethal therapeutic approach: Poly (ADP) ribose polymerase inhibitors for the treatment of cancers deficient in DNA double-strand break repair. *Journal of Clinical Oncology* 2008; 26: 3785-3790.
44. Sirohi, Arnedos M, Popat S, et al. Platinum-based chemotherapy in triple-negative breast cancer. *Annals of Oncology* 2008; 19: 1847-1852.
45. Rottenberg S, Jaspers JE, Kersbergen A, et al. High sensitivity of BRCA1-deficient mammary tumors to the PARP inhibitor AZD2281 alone and in combination with platinum drugs. *Proceedings of the National Academy of Sciences USA* 2008; 105: 17079-17084.
46. Yap TA, Boss DS, Fong PC, et al. First in human phase I pharmacokinetic (PK) and pharmacodynamics (PD) study of KU-0059436 (Ku), a small molecular inhibitor of polyADP-ribose polymerase (PARP) in cancer patients, including BRCA1/2 mutation carriers. *Journal of Clinical Oncology* 2007; 25: 3529, 2007.
47. Iglehart D, Silver DP. Synthetic lethality-a new direction in cancer drug treatment. *New England Journal of Medicine* 2009; 361(2): 189-191.
48. Fong PC, Boss DS, Yap TA, et al. Inhibition of poly (ADP-ribose) polymerase in tumors from BRCA mutation carriers. *New England Journal of Medicine* 2009; 361(2): 123-134.
49. Rugo HS, Olopade OI, DeMichele A, et al. Adaptive randomization of verapapib-carboplatin treatment in breast cancer. *New England Journal of Medicine* 2016; 375(1): 23-34.
50. Carey A, Winer EP. I-SPY 2-Towards more rapid progress in breast cancer treatment, *New England Journal of Medicine* 2016: 375(1):83-84.

Breast cancer during pregnancy

Aggeliki D. Athanasiou¹ MD, Lydia Ioannidou-Mouzaka² MD, Ph.D

¹ Surgeon Obstetrician - Gynecologist, Specialist of Breast Diseases. Secretary General of the Hellenic Senologic Society

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

ABSTRACT

The association of breast cancer and pregnancy, defined as breast cancer that occurs during pregnancy and up to 1 year after delivery is expected to increase as more women delay childbearing over the age of 30. A better understanding of breast oncogenesis helps explain the dual epidemiological effect of pregnancy on the risk of breast cancer: Firstly, the risk of breast cancer increases transiently after delivery, but then falls after 15 years. Breast cancer diagnosed during pregnancy is a stressful situation for the patient, her family as well as for the medical team. Although the different clinical breast examinations are not contraindicated, delay in diagnosis may often be noticed: A later stage of disease at diagnosis with nodal involvement in about 70 % of cases. The management of this clinical situation should be conformed as closely as possible to standardized approach for non-pregnant women. Most treatments indicated for the management of a localised breast cancer are not contraindicated, except breast radiotherapy. The termination of pregnancy is not justified by the diagnosis of cancer as it does not improve prognosis.

The management of breast cancer during the 2nd and 3rd trimesters of pregnancy should be conformed as closely as possible to standard protocols including surgery without sentinel node procedure as first-line treatment, and anthracycline-based chemotherapy which appears to be relatively safe for the mother and the fetus according to data currently available. The use of taxanes and targeted therapies is not recommended during pregnancy given the limited data available and the need for further study. Chemotherapy is not used and contraindicated during the first trimester. As result, treatment may be delayed if pregnancy is maintained. If breast-conserving surgery is a possible option, it should be performed immediately. The date of delivery depends on when cancer has been diagnosed and should be planned after the 35th week of gestation in most cases. It should be discussed with the oncologist and the obstetrician to minimize the risks of harm to mother and fetus. Radiotherapy and hormonal therapy should be delayed until after delivery.

Corresponding author

Lydia Ioannidou-Mouzaka

Kifisias Avenue 18, P.C. 11526, Athens, Greece

E - mail: lydiamouzaka@yahoo.gr

Definition: Gestational breast cancer (or pregnancy-associated breast cancer) is defined as breast cancer that is diagnosed during pregnancy, in the first postpartum year, or any time during lactation. Gestational breast cancer presents a challenging clinical situation, since the welfare of both the mother and the fetus must be taken into account. There are limited prospective data about diagnosis, treatment, and outcome of breast cancer during pregnancy.

Epidemiology: Breast cancer is one of the most common cancers in nonpregnant and pregnant women¹. Up to 20 percent of breast cancers in women under age 30 are pregnancy-associated, but fewer than 5 percent of breast cancers diagnosed in women under age 50 are detected during pregnancy or in the postpartum period^{2,3}. Pregnancy-associated or gestational breast cancer is a relatively uncommon event. The incidence of pregnancy-associated breast cancer (for the prenatal to postpartum period) is approximately 15 to 35 per 100,000 deliveries, with fewer breast cancer cases diagnosed during pregnancy than during the first postpartum year⁴⁻⁷. The incidence of pregnancy-associated breast cancer appears to be increasing as more women delay childbearing^{6,8}. Women with a genetic predisposition to breast cancer may be overrepresented among pregnant women with cancer, although the available evidence is limited⁹⁻¹¹. In women who inherit BRCA2 (but not BRCA1) mutations, the protective effect of multiparity on breast cancer risk may be lost¹².

Diagnosis: The clinical diagnosis of breast cancer is difficult during pregnancy or breast feeding firstly because of the physiological changes occurring to the breast (increased breast density, hypervascularity, engorgement) and also because it is rarely considered by the physician or even by the patient herself¹³. Any suspicious signs including a painless lump, a cutaneous lesion or a unique duct bleeding or discharge which may occur infrequently should lead to the diagnosis of breast cancer. In retrospective case series, a painless mass is a complaint made by 82 to 95% of women presenting with breast cancer^{14,15}. Clark reported that bilateral tumors occurred in 4,6 % of cases, and multifocal tumors have also been frequently reported¹⁶. However, the incidence of inflammatory tumors is not higher (1,5 to 4%). Finally, axillary lymphadenopathies which may often be taken for accessory mammary glands, may lead to the diagnosis of breast cancer¹⁷. The diagnostic delay varies from 2 to 15 months. As a result, the risk of advanced-stage disease is 2.5 higher in PABC patients (40% of PABC) as compared to non-pregnant patients¹⁸.

KEYWORDS: breast infections; non-lactating; mastitis

All women should be encouraged to practise breast self-examination during pregnancy and lactation as 90% breast cancers are diagnosed this way¹⁹. Breast ultrasound should be the first line imaging procedure for the diagnosis of PABC. It can be performed during all trimesters of pregnancy without risks for the mother and fetus. If cancer is diagnosed, the use of a bilateral one-view mammography to rule out micro-calcifications should be discussed. The density of mammary glands in pregnant women reduces the sensitivity of mammography^{18,21}. Mammography (digital if possible) does not seem to be less sensitive or less specific during lactation^{22,23}.

Mammography should be performed with adequate abdominal shielding. Consequently, it is not contraindicated in pregnant or lactating women, but, contrarily to non-pregnant patients, it should not be used as first-line imaging procedure. If a multifocal tumor is suspected during conventional imaging procedure, MRI can be considered before choosing neo-adjuvant chemotherapy or surgery. However, it should not be systematically recommended. According to the recommendations of the European Society of Urogenital Radiology, MRI with gadolinium injection can be considered. No effect has been recorded after the administration of gadolinium-based contrast media during pregnancy²⁰.

Treatment

In general, pregnant women with breast cancer should be treated according to guidelines for non-pregnant patients, with some modifications to protect the fetus. However, the treatment should be approached with curative intent. Therefore, treatment of gestational breast cancer should not be unnecessarily delayed because of pregnancy. Informed consent is a critical component of choosing appropriate therapy. Treatment should be considered after obtaining histological results. Fine needle aspiration biopsy can be performed even though it is associated with risks of false-positive and false-negative results^{24,25}. Indeed, some authors reported technical difficulties and sampling errors because of the frequency of lobular hyperplasia with a possible hypertrophy of the nucleolus and absence of size regularity²⁶. The distribution of hyperproliferative cells of breast tissue may lead to falsepositives. A core-needle biopsy is required as this technique can diagnose lesions with high sensitivity and specificity (90%). It should at least be performed under ultrasound guidance if a palpable mass is present, which may increase the sensitivity of the procedure. Although pregnancy termination may be considered during treatment planning, pregnancy termination has not been demonstrated to improve outcomes in gestational breast cancer. Stopping breastfeeding beforehand can reduce the risks of hematoma and milk fistula. Imaging procedures, core-needle or stereotactic biopsies are not contraindicated during pregnancy or breast feeding. Importantly, all patients with gestational breast cancer should be evaluated for distant metastatic disease according to guidelines in non-pregnant patients with breast cancer. In order to protect the fetus, this can be attenuated to include: chest radiograph with fetal shielding, ultrasound of the liver, and magnetic resonance imaging (MRI) of the spine without contrast to evaluate for bone metastases^{27,28}. A complete assessment of PABC should include a chest X-ray (with abdominal lead shielding) and an abdomino-pelvic ultrasound. According to the European Association of Nuclear Medicine, a bone scan should be considered with regard to the potential benefits and risks to the mother and fetus. It exposes the fetus to only low doses (uterus dose: 0,0063 mGy, dose for a fetus at 8 weeks gestation: 0,0046 mGy, dose for a fetus at 18 weeks gestation: 0,0026 mGy). It can be performed after delivery and is only recommended during pregnancy to exclude a suspicion of bone metastases, which may alter the treatment.

Most PABC are invasive ductal carcinomas²⁹. Other histological forms have been diagnosed infrequently in pregnant and non-pregnant women. Histopathologic characteristics of PABC are reported in table 1. Most PABC are high grade and do not express hormone receptors. Amplification and/or over expression of HER2 are present in almost 40% of cases. Pregnancy-associated breast cancers are generally highly invasive cancers. The frequency of axillary node metastases seems higher in PABC. Figures reported in the literature vary from 47 % to 89 %³⁰. The widespread use of neo-adjuvant chemotherapy, responsible for axillary down staging takes us back to former series to know the node involvement rate. During pregnancy, some specific conditions including lactating adenoma and giantomastia do not generally pose any problems in terms of differential diagnosis.

Several specific questions should be discussed with the surgeon including the possibility of a breast-conserving surgery and consequently radiotherapy, as well as the sentinel lymph node biopsy.

Surgery for breast cancer is generally safe in pregnancy. Other treatments for breast cancer, such as chemotherapy, hormone therapy, targeted therapy, and radiation can harm the fetus if given during pregnancy. Although chemotherapy seems to be safe for the fetus if given later in pregnancy, it isn't safe early on. If a woman has breast cancer in early pregnancy and needs chemotherapy right away, she may be asked to think about ending the pregnancy. For some breast cancers, such as inflammatory breast cancer, a delay in treatment would likely harm the patient. Surgery to remove the cancer in the breast and nearby lymph nodes is generally safe in pregnancy. This is a major part of treatment for any woman with early breast cancer, including women who are pregnant. For many cancers, either removing the entire breast (mastectomy) or just the part containing the cancer (breast-conserving surgery - BCS) is an option. Mastectomy is used more often for pregnant women with breast cancer because women who have breast-conserving surgery need radiation therapy afterward. Pregnancy has long been considered an absolute contraindication to breast-conservation. It is no longer true although the following reservations have to be made. As a result of delayed diagnosis, pregnant women tend to have significantly more advanced disease than non-pregnant women. Mastectomy may be the preferred option in such context. Surgery is often more complex because of increased vascularity

of the breast during pregnancy. A meticulous haemostasis is required⁹. In addition, as the median maternal age of women with PABC is 34 years, the decision for a conservative treatment should be taken with regard to the high rate of local recurrences noted in this age group and the risk of multifocal disease. A thorough bilateral preoperative imaging is essential. The use of MRI has been discussed earlier. Only minimal oncoplastic surgery may be considered during pregnancy because of increased vascularity. Immediate breast reconstruction doesn't also make a lot of sense as it is difficult to achieve symmetry with the contralateral breast which continues to change as pregnancy advances. There is only limited data on the safety of sentinel node procedure in pregnant patients. Even if the procedure is technically possible, this prevalence confirms that pregnant patients should not currently undergo a sentinel node biopsy. However, the Sentinel Lymph Node procedure could be punctually considered during pregnancy following multidisciplinary decision-making to treat very small tumors or extended in situ carcinomas.

Radiation can be safely used after delivery. However, it exposes the fetus to considerable risks during pregnancy. No anomaly was reported for embryo exposure to radiation doses of less than 300mGy (0.3Gy). The American Academy of Paediatrics and the American College of Radiology do not recommend the termination of pregnancy if the fetus has been exposed to less than 5cgrays (0.05 Gy)^{31,32}, but most authors do not consider it if the fetus has been exposed to less than 0.1Gy. There are several case reports of normal children born after their mothers had received breast radiation therapy²⁷⁻²⁹. The fetal doses ranged from 0,039 Gy to 0,18 Gy. The use of lead blocks reduced the dose the fetus was exposed to. Without using any lead blocks, the fetus would have been exposed to 0,28 Gy. Breast and other radiation therapies may be considered during pregnancy, but the dosimetry should be adapted accordingly by specialist teams.

Chemotherapy

There is a paucity of information on the use of chemotherapy during pregnancy and its long-term effects. Patients should be clearly informed about these limits before making a decision concerning treatment strategy and the development of pregnancy. Cytotoxic chemotherapy causes genetic damage in exposed somatic cells including chromosomal breaks, translocations, deletions, gene mutations, aneuploidies and cell cycle disruptions^{33,34}. Cell culture and

animal data regarding the carcinogenic, teratogenic and mutagenic effects of chemotherapy on embryonic and placenta cells are not reassuring. Chemotherapy can start after the 1st trimester has been completed, at 14 weeks. A standardized protocol with anthracyclines (up to 100 mg/m² but 50 mg/m² in most studies) may be prescribed without any significant risks to the mother and fetus. However, two important elements should be considered:

- Anthracycline 50 mg/m² dose is not optimal, particularly in node-positive patients³⁵.
- Randomized trials showed that the combination of taxanes and anthracyclines increased survival rate in these patients^{36,37}. However, given the limited data available, their use is not recommended as first line treatment.

No pharmacodynamic study on the use of cytotoxic drugs in pregnant women is available. Experts recommend²⁹ to use the same cytotoxic doses as in non-pregnant patients with breast cancer. It may be recommended to use Epirubicin 100mg/m² per cycle dose.

The date of delivery should be planned according to the date when cancer was diagnosed. If diagnosis of PABC is made after 18 weeks, delivery should be planned after 35 weeks, and preferably beyond 37 weeks. It is recommended that delivery occurs 2 to 3 weeks after the last cycle of chemotherapy so as to minimize the risk of maternal and fetal neutropenia³⁸. If PABC is diagnosed before 18 weeks, delivery should be induced after 35 weeks if possible (or even earlier if cancer was diagnosed earlier in pregnancy) so as to minimize complementary therapy delay (taxanes, radiotherapy).

Hormone therapy

Should not be used during pregnancy because it can affect the fetus. It should be delayed until after the woman has given birth.

Targeted therapy

Drugs that target HER2, like trastuzumab (Herceptin®), pertuzumab (Perjeta®), ado-trastuzumab emtansine (Kadcyla™) and lapatinib (Tykerb®), are an important part of the treatment of HER2-positive breast cancers in women who aren't pregnant. Trastuzumab is used as a part of adjuvant treatment after surgery, pertuzumab can be used with trastuzumab before surgery, and all of these drugs can be useful in treating advanced cancer. But based on animal studies and reports of women who were treated during pregnancy, none of these drugs are

considered safe for the fetus if taken during pregnancy. Everolimus (Afinitor®) and bevacizumab (Avastin®) are also targeted drugs that can be used to treat advanced breast cancer. Again, neither of these drugs is safe to use during pregnancy.

In most cases, timing of delivery should be planned. Three weeks after the last cycle of chemotherapy, and depending on the obstetric conditions, the patient may have her labor induced or wait for the maturation of the fetus. Timing may be shorter if she is treated with weekly paclitaxel. Chemotherapy may start again at 10 days post-partum. There is no information to assert that syntocinon or bromocriptine is contraindicated in women with breast cancer as these molecules have an anti-proliferative effect^{39,40}. The contraceptive device to be recommended is the copper IUD which should be fitted approximately 6 weeks after delivery.

Survival rates after breast cancer during pregnancy

Pregnancy can make it harder to find, diagnose, and treat breast cancer. Most studies have found that the outcomes among pregnant and non-pregnant women with breast cancer are about the same for cancers found at the same stage, but not all studies agree. A 2013 study looked at more than 300 women diagnosed during pregnancy. During the 5-year follow-up, researchers reported comparable survival in women at the same stage whose breast cancer was found when they weren't pregnant. Disease-free survival tended to be slightly shorter in the pregnant women. Most studies have found no difference in prognosis, and the prognosis of women with PABC is believed to be similar to that in non-pregnant patients of the same age and stage of disease^{9,29,41}. The part linked to pregnancy seems very small and the amount of unfortunate elements may increase and alter prognosis: *Young age, high grade, absence of hormonal receptors, diagnosis delay and absence of standardized therapy*. A strict follow up is essential although no specific recommendations related to PABC may be set up. An individual follow-up plan should be carried out during the interdisciplinary team meeting (ITM).

Conclusion

Breast cancer associated with pregnancy is a rare clinical situation, but its prevalence keeps on increasing. The clinical diagnosis may often be delayed and difficult. Breast cancers with node involvement seem to be more frequent in pregnant women than in non-pregnant patients. Additional examinations including ultrasound, mammography and biopsy can be considered without any risks for the fetus. The treatment should conform as closely as possible to protocols for non-pregnant patients. Nonetheless, decisions and therapeutic sequences should be considered according to the gestational age, stage of disease and preferences of the patient during a multidisciplinary meeting involving gynaecologists, obstetricians, radiologists, oncologists and paediatricians. Breast-conserving surgery can be performed during pregnancy, but radiation therapy should be postponed until after delivery. Sentinel lymph node procedure is not recommended considering the only few cases reported so far. Hormonal or targeted therapy is not possible during pregnancy or breast feeding. FAC 50/FEC 100 chemotherapy can be prescribed after 14 weeks, if the tumour is not operable or not accessible for a conservative treatment, or in an adjuvant situation. The use of taxanes or targeted therapies is not recommended as routine treatment so far. The administration of taxanes, platinum agents or navelbine may be considered as a second treatment option, if anthracycline-based chemotherapy fails. The creation of a national pilot site as well as a specific registry may ultimately help in finding the optimal method to manage cancer during pregnancy. It is absolutely essential that patients and her partners obtain honest and accurate information on the potential benefits and risks of the different treatment options before the final common decision making approved during the multidisciplinary meeting.

Conflicts of interest

The authors declare that there are no conflict of interest regarding the publication of this paper. ■

REFERENCES

- Hill C, Doyon F. The frequency of cancer in France in year 2002, and trends since 1968. *Bull Cancer* 2006; 93: 7-11.
- Haas JF. Pregnancy in association with a newly diagnosed cancer: A population-based epidemiologic assessment. *Int J Cancer* 1984; 34: 229 - 235.
- Mathieu E, Merviel P, Barranger E, Antoine JM, Uzan S. Breast cancer and pregnancy: Review of the literature. *J Gynecol Obstet Biol Reprod (Paris)* 2002; 31: 233 - 242.
- Mathieu E, Merviel P, Antoine JM, Uzan S. Cancer and Pregnancy: The point of view of the obstetrician. *Bull Cancer* 2002; 89: 758 - 764.
- Pentheroudakis G, Pavlidis N. Cancer and pregnancy: Poena magna, not anymore. *Eur J Cancer* 2006; 42: 126-40.
- Mignot L. Cancer du sein et grossesse : Le point de vue du sénologue. *Bull Cancer* 2002; 89: 772 - 778.
- Waalén J. Pregnancy poses tough questions for cancer treatment. *J Natl Cancer Inst* 1991; 83: 900 - 902.
- Saunders CM, Baum M. Breast cancer and pregnancy: A review. *J R Soc Med* 1993; 86: 162 - 165.
- Petrek JA. Breast cancer during pregnancy. *Cancer* 1994; 74: 518 - 527.
- Lambe M, Hsieh C, Trichopoulos D, Ekblom A, Pavia M, Adami HO. Transient increase in the risk of breast cancer after giving birth. *N Engl J Med* 1994; 331: 5 - 9.
- Albrektsen G, Heuch I, Kvale G. The short-term and long-term effect of a pregnancy on the risk of breast cancer: A prospective study of 802,457 parous Norwegian women. *Br J Cancer* 1995; 72: 480 - 484.
- Venn A, Watson L, Bruinsma F, Giles G, Healy D. Risk of cancer after use of fertility drugs with in-vitro fertilisation. *Lancet* 1999; 354: 1586 - 1590.
- Leveque J, Giono A, Poulain P, et al. Breast cancer associated with pregnancy. Nine case reports. Review of the literature and current update. *J Gynecol Obstet Biol Reprod (Paris)* 1992; 21: 616 - 624.
- Ribeiro G, Jones DA, Jones M. Carcinoma of the breast associated with pregnancy. *Br J Surg* 1986; 73: 607 - 609.
- King RM, Welch JS, Martin JK, Coulam CB Jr. Carcinoma of the breast associated with pregnancy. *Surg Gynecol Obstet* 1985; 160: 228 - 232.
- Clark RM, Reid J. Carcinoma of the breast in pregnancy and lactation. *Int J Radiat Oncol Biol Phys* 1978; 4: 693 - 698.
- Woo JC, Yu T, Hurd TC. Breast cancer in pregnancy: A literature review. *Arch Surg* 2003; 138: 91 - 98; discussion 99.
- Moore HC, Foster RS Jr. Breast cancer and pregnancy. *Semin Oncol* 2000; 27: 646 - 653.
- Sorosky JI, Scott-Conner CE. Breast disease complicating pregnancy. *Obstet Gynecol Clin North Am* 1998; 25: 353 - 363.
- Webb JA, Thomsen HS, Morcos SK. Members of Contrast Media Safety Committee of European Society of Urogenital Radiology (ESUR). The use of iodinated and gadolinium contrast media during pregnancy and lactation. *Eur Radiol* 2005; 15: 1234 - 1240.
- Pavlidis N, Pentheroudakis G. The pregnant mother with breast cancer: Diagnostic and therapeutic management. *Cancer Treat Rev* 2005; 31: 439 - 447.
- Samuels TH, Liu FF, Yaffe M, Haider M. Gestational breast cancer. *Can Assoc Radiol J* 1998; 49: 172 - 180.
- Swinford AE, Adler DD, Garver KA. Mammographic appearance of the breasts during pregnancy and lactation: False assumptions. *Acad Radiol* 1998; 5: 467 - 472.
- Mitre BK, Kanbour AI, Mauser N. Fine needle aspiration biopsy of breast carcinoma in pregnancy and lactation. *Acta Cytol* 1997; 41: 1121 - 1130.
- Shannon J, Douglas - Jones AG, Dallimore NS. Conversion to core biopsy in preoperative diagnosis of breast lesions: Is it justified by results? *J Clin Pathol* 2001; 54: 762 - 765.
- Bottles K, Taylor RN. Diagnosis of breast masses in pregnant and lactating women by aspiration cytology. *Obstet Gynecol* 1985; 66: 765 - 78S.
- Amant F, Deckers S, Van Calsteren K, et al. Breast cancer in pregnancy: Recommendations of an international consensus meeting. *Eur J Cancer* 2010; 46: 3158.
- Hahn KM, Johnson PH, Gordon N, et al. Treatment

- of pregnant breast cancer patients and outcomes of children exposed to chemotherapy in utero. *Cancer* 2006; 107: 1219.
29. Loibl S, von Minckwitz G, Gwyn K, et al. Breast carcinoma during pregnancy. International recommendations from an expert meeting. *Cancer* 2006; 106: 237 - 246.
 30. Dequanter D, Hertens D, Veys I, Nogaret JM. Breast cancer and pregnancy. Review of the literature. *Gynecol Obstet Fertil* 2001; 29: 9 - 14.
 31. Greer BE, Goff BA, Koh W. Cancer in the pregnant patient. In: Hoskins WJ, Perez CA, Young RC, eds. *Principles & Practice of Gynecologic Oncology*. 2nd ed. New York: Lippincott Raven, 1997.
 32. Brent RL. The effects of embryonic and fetal exposure to X-ray, microwaves, and Ultrasound. *Clin Obstet Gynecol* 1983; 26: 484 - 510.
 33. Cardonick E, Iacobucci A. Use of chemotherapy during human pregnancy. *Lancet Oncol* 2004; 5: 283 - 291.
 34. Witt KL, Bishop JB. Mutagenicity of anticancer drugs in mammalian germ cells. *Mutat Res* 1996; 355: 209 - 234.
 35. Bonnetterre J, Roche H, Kerbrat P, et al. Epirubicin increases long-term survival in adjuvant chemotherapy of patients with poor-prognosis, node-positive, early breast cancer: 10-year follow-up results of the French Adjuvant Study Group 05 randomized trial. *J Clin Oncol* 2005; 23: 2686 - 2693.
 36. Trudeau M, Charbonneau F, Gelmon K, et al. Selection of adjuvant chemotherapy for treatment of node - positive breast cancer. *Lancet Oncol* 2005; 6: 886 - 898.
 37. Campone M, Fumoleau P, Bourbouloux E, Kerbrat P, Roche H. Taxanes in adjuvant breast cancer setting: Which standard in Europe? *Crit Rev Oncol Hematol* 2005; 55: 167 - 175.
 38. Zemlickis D, Lishner M, Degendorfer P, et al. Maternal and fetal outcome after breast cancer in pregnancy. *Am J Obstet Gynecol* 1992; 166: 781 - 787.
 39. Cassoni P, Sapino A, Marrocco T, Chini B, Bussoleti G. Oxytocin and oxytocin receptors in cancer cells and proliferation. *J Neuroendocrinol* 2004; 16: 362 - 364.
 40. Lissoni P, Bucovec R, Malugani F, Ardizzoia A, Villa S, Gardani GS, et al. A clinical study of taxotere versus taxotere plus the antiprolactinemic agent bromocriptine in metastatic breast cancer pretreated with anthracyclines. *Anticancer Res* 2002; 22: 1131 - 1134.
 41. Petrek JA, Dukoff R, Rogatko A. Prognosis of pregnancy-associated breast cancer. *Cancer* 1991; 67: 869 - 872.

Non malignant breast pathology

Chronic Recurrent Mastitis

Aggeliki D. Athanasiou

Surgeon Obstetrician-Gynecologist, Specialist of Breast Diseases Secretary General of the Hellenic Senologic Society

ABSTRACT

Breast infection in non-lactating women is an infrequent but recognized clinical entity that deserves special attention. An underlying clinical condition should always be sought and treated. Indeed, in addition to cultures, radiological modalities such as ultrasonographic imaging may provide specific diagnosis and aid the management.

KEYWORDS: breast infection; non-lactating mastitis

Definition

The term chronic mastitis describes inflammatory lesions of the breast tissue that occur unrelated to pregnancy or breastfeeding. When the situation and symptoms frequently appear then mastitis is called recurrent.

Under the surface of the nipple, the lactiferous ducts are expanded and they are forming the lactiferous sinuses who act like milk tanks during breastfeeding. When the inner layer of the lactiferous duct suffers epidermalization, the production of keratin could lead to ductal obstruction and the formation of an abscess. That explains the high rates (39-50%), of breast abscesses in patients treated with incision and drainage.

The recurrent mastitis, that is the result of non-breastfeeding is divided into two categories: **Central or peri-areolar and peripheral**. The first category is essentially an active inflammation around non-dilated lactiferous ducts, a pathological entity called periductal mastitis. Sub-areolar abscess is a subcutaneous abscess of the breast tissue beneath the areola of the nipple. It is also called

Zuska's disease (only nonpuerperal case) and it is a frequently aseptic inflammation and has been associated with squamous metaplasia of lactiferous ducts. 90% of cases are smokers, however only a very small fraction of smokers appear to develop this lesion. It has been speculated that either the direct toxic effect or hormonal changes related to smoking could cause squamous metaplasia of lactiferous ducts. It is not well established whether the lesion regresses after smoking cessation. The second category is less frequent and it is associated with an underlying pathological condition like Diabetes Mellitus, chronic illness, HIV-infection, Rheumatoid Arthritis, steroid therapy, granulomatous mastitis etc. Mastitis can also be caused by direct trauma to the breast tissue (for example during sport activities or due to seat belt), or after nipple piercing.

Causes

Infectious pathogens commonly associated with chronic mastitis are: Staphylococcus Aureus and Streptococci. In the case of periductal mastitis, the most frequent cause

Corresponding author

Aggeliki D. Athanasiou

E - mail: louelath@yahoo.gr

is *Staphylococcus Aureus*. Streptococci, *Staphylococcus Epidermalis*, Enterococci, Peptostreptococci and Enterobacterie such as *Escherichia Coli* and *Salmonella* are less often causes.

Diagnosis

The diagnosis of mastitis can usually be based on physical examination. The signs and symptoms of the condition are:

- Breast tenderness or warmth
- General fatigue
- Breast swelling
- Pain or a burning sensation
- Skin redness
- Nipple retraction
- Fever.

However if it is not certain whether the mass is an abscess or a tumor, a breast ultrasound should be performed. The ultrasound provides a clear image of the breast tissue and may be helpful in distinguishing between simple mastitis, abscess and its depth or breast cancer.

The microbiological cultures are needed in order to determine the type of the microorganism which is causing the infection and also can be helpful in deciding the specific antibiotics which will be used. These cultures should be taken from the abscess or from the nipple discharge.

Mammograms, breast biopsies or/and cytological examination can be used to exclude the possibility of a rare and very serious type of breast cancer called inflammatory

breast cancer. Its symptoms are similar to mastitis. It must be noted that this type is the most aggressive type of breast cancer with the highest mortality rate.

Treatment

The treatment is divided in two categories depending on the form of inflammation.

A. In cases of acute inflammation and abscesses below 3cm in diameter, the treatment is with antibiotics. The most common used antibiotics are:

- Clindamycin (600mg i.v. or 300mg /6h per os) for 14 days or
- Amoxicillin with clavulanic acid (375mg/8h) plus Clarithromycin 500mg/12h for 14 days and Metronidazole 500mg/8h for 10 days.

However it is quite often the disease to reappear after the end of the antibiotic treatment. In these cases we should proceed with the excision of the affected tissue along with the lactiferous ducts and chronic abscesses.

B. In cases of subareolar abscess or abscesses with a diameter above 3cm, the first step is the incision and drainage followed by antibiotics treatment. Unfortunately it is often and in this category the situation to recur, especially in smokers. As a result the final solution is a radical or circumareolar incision or preventive mastectomy.

Conflict of interests

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

REFERENCES

1. Versluijs FNL, Roumen RMH, Goris RJA. Chronic recurrent subareolar breast abscess: Incidence and treatment. *British Journal of Surgery* 2000; 87(7): 931-964.
2. Rizzo M, Gabram S, Staley C, Peng L, Frisch A, Jurado M, et al. Management of breast abscesses in nonlactating women. *The American Surgeon* 2010; 76(3): 292-295.
3. Dixon JM. ABC of breast diseases. Breast infection. *BMJ* 1994; 309(6959): 946-949.
4. Dixon JM. Outpatient treatment of non-lactation breast abscesses. *Br J Surg* 1992; 79:56-57.
5. Schafer P, Furrer C, Mermmild B. An association of cigarette smoking with recurrent subareolar breast abscess. *Int J Epidemiol* 1988; 17: 810-813.
6. Krause A, Gerber B, Rhode E. Puerperal and non-puerperal mastitis, 1994.

Evaluation of breast microcalcification

Elisavvet Soilemezi¹ MD, Georgios Kyropoulos² MD, Apostolos Zavos³ MD, Ph.D

¹ Radiologist, Breast Radiologist - Larissa Greece

² Radiologist, Breast Radiologist Alexandra Imathias

³ MD Surgeon Gynecologist Senologist. Board member of Hellenic Senologic Society.
Member of the UEMS Breast Cancer Group. Larisa - Greece

ABSTRACT

Breast microcalcifications diagnosis and management are crucial for the treatment of breast cancers. Calcifications are a quite frequent finding in mammographies. The proper analysis of calcifications based on morphology, size, number, distribution, density and stability can help distinguish malignant from benign calcifications. The correct analysis and categorization according to BIRADS Lexicon is of great importance for the suitable management of every case.

KEYWORDS: Breast cancer; microcalcification; mammography; diagnosis; management

Introduction

Identification of breast microcalcifications, differential diagnosis and proper management, are of great importance for the appropriate treatment of subclinical cases of breast cancers. In 1913, a German surgeon, Solomon, mentioned the presence of microcalcifications in a mammography after mastectomy. In 1949 Ledorgne, an Uruguayan radiologist mentioned that the presence of microcalcifications might be the only mammographic indication for cancer.

Calcifications are a quite frequent finding in mammographies and could be depicted in nearly 85% of them. The frequency of depiction increases with age. They could be consisted of phosphate calcium or calcium oxale deposits. Microcalcifications can be perfectly depicted in mam-

Table 1. Manifestation of subclinical breast-cancers in Mammography

Speculated or Round Masses without Calcifications	64%
Calcifications only	19%
Speculated or Round Masses with Calcifications	17%

mographies even if they are as small as 50µm. Calcium absorbs radiation and as a result, white, light spots are created and furthermore absorbs radiation more than the parenchyma of the breast (even more than the dense parenchyma).

The identification of microcalcifications of the breast,

Corresponding author

Elisavvet Soilemezi

E-mail: esoilemezi@yahoo.com

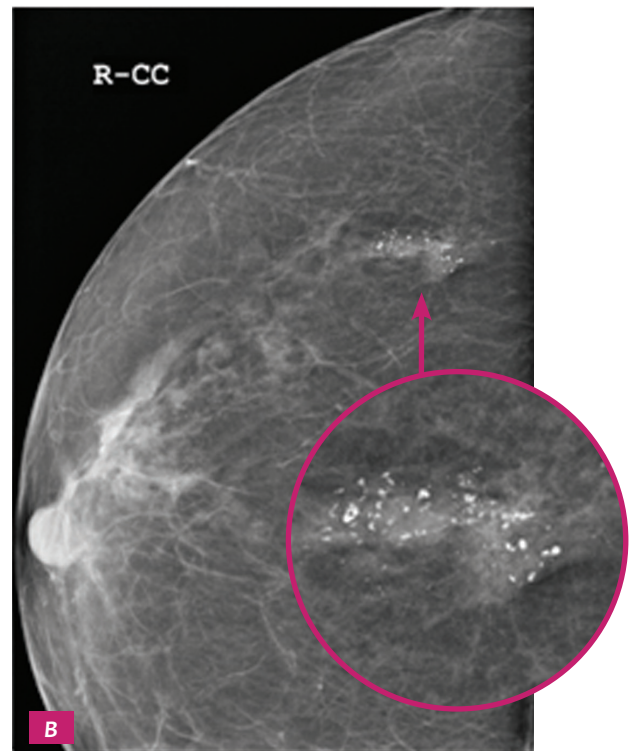
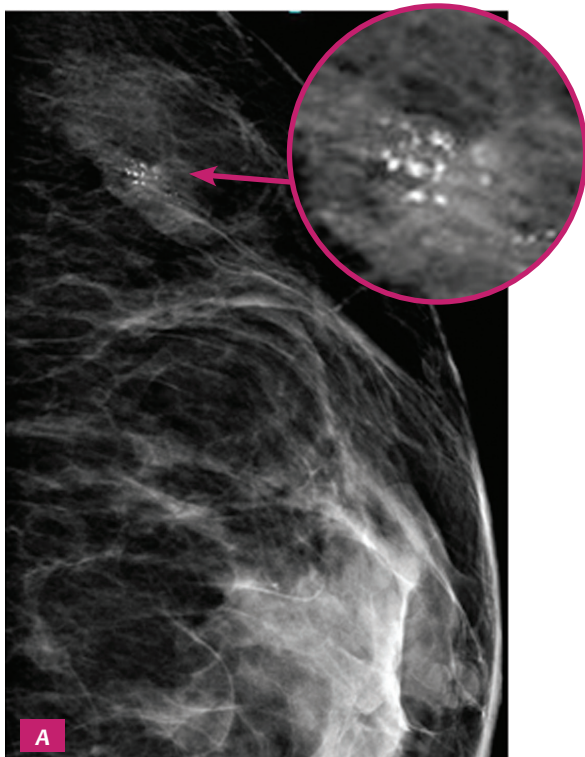


Image 1. A. Calcifications only. B. Mass with Calcifications

that are depicted in a mammography, is one of the most important processes, since a vast percentage of subclinical cancers (35-40%) occurs with microcalcifications as the only manifestation (**Table 1**).

Calcifications can present as the only sign of a cancer or can be together with a mass or an asymmetric density (**Image 1**). Moreover, the identification, the differential diagnosis and the management of calcifications are of great importance so that neither would a malignancy be unidentified nor would a patient undergo unnecessary biopsies and recalls.

When suspicious calcifications are depicted in a mammography, magnification should be applied in two views with a 90° angle difference, where existing calcifications are better depicted and there is the possibility for others to be identified that cannot be with the single views (**Image 2**).

Formation of calcifications

Calcifications could be formed:

- Intraductal, where they take the shape of the duct. They are deposits of calcium on debris or in secre-

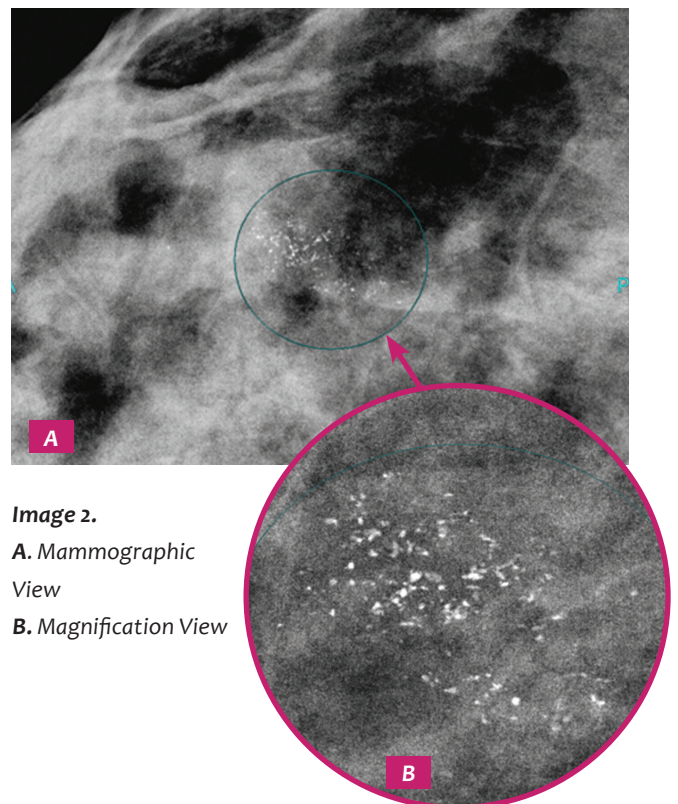


Image 2.
A. Mammographic View
B. Magnification View

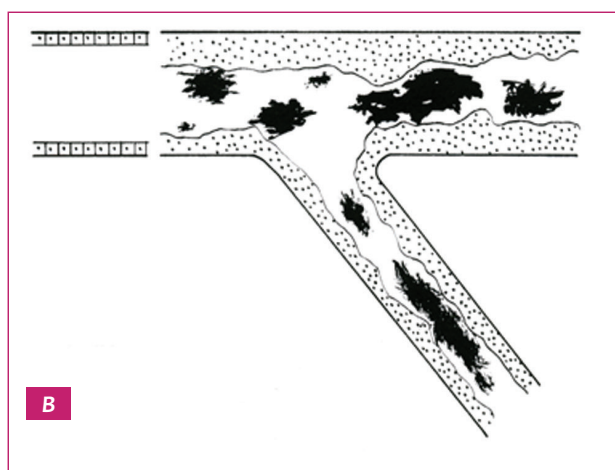
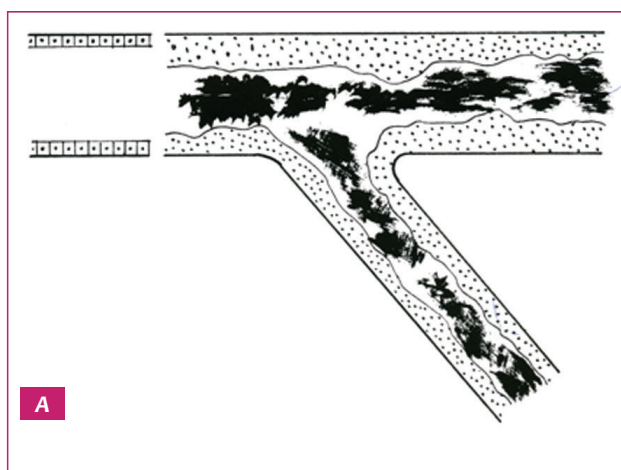


Image 3. **A.** Intraductal formed calcifications. **B.** Intraductal punctate calcifications

tions within ducts. The unequal decalcification of these materials has as a result the shattered like depiction and the irregular outline of these calcifications, which are linear, branch or punctate (**Image 3**).

■ In the terminal lobular units (TDLU), where they are formed. This has as a result consistent, homogeneous and well defined calcifications that could be spot like, punctate or crashed-stone. If the TDLU augment (like in cystic hyperplasia), cavities are filled with Milk of Calcium. If there is enough fibrosis in the surrounding stroma (like in sclerosing adenosis) calcifications are smaller and less consistent (**Image 4**).

■ Out of the parenchyma, like the vascular wall, the backing stroma of the breast, the skin and in or around mass lesions (cysts or oil cysts).

Analysis of calcifications

Analysis of calcifications could be obtained by taking in to consideration the morphology, size, number, distribution, density, stability.

Based on morphology

- Punctate (malignancy percentage 20%, usually Grade I)
- Spotlike (malignancy percentage 47%, usually Grade I)
- Crashed stone (malignancy percentage 61%, usually Grade II)
- Sependicular (malignancy percentage 96%, usually Grade III) (**Image 5**).

When various types of calcifications co-exist they are called pleomorphic (**Image 6**).

Amorphous calcifications are those with uncertain

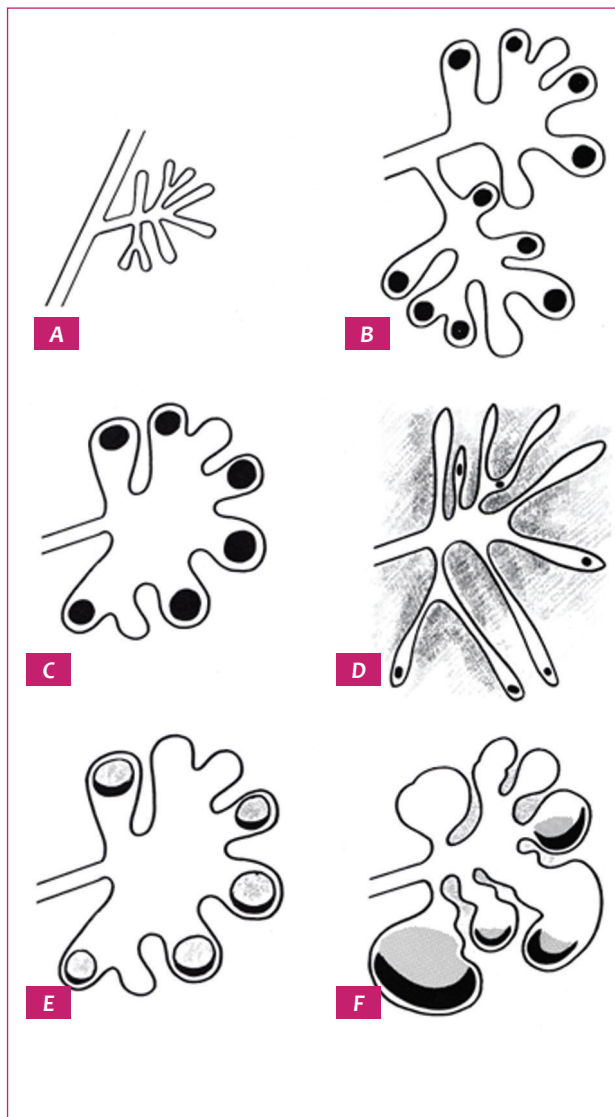


Image 4. **A.** Normal TDLU **B,C.** Adenosis **D.** Sclerosing adenosis **E,F.** Cystic hyperplasia

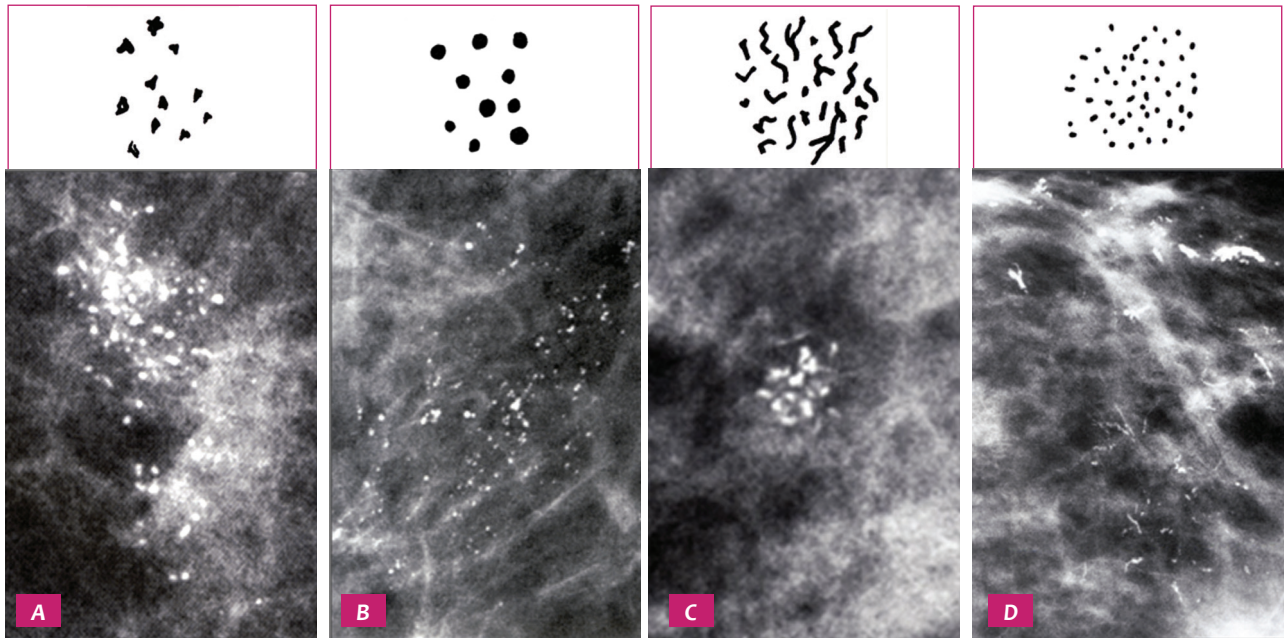


Image 5. A. Punctate Punctate B. Spot like C. Crashed Stone D. Serpentine

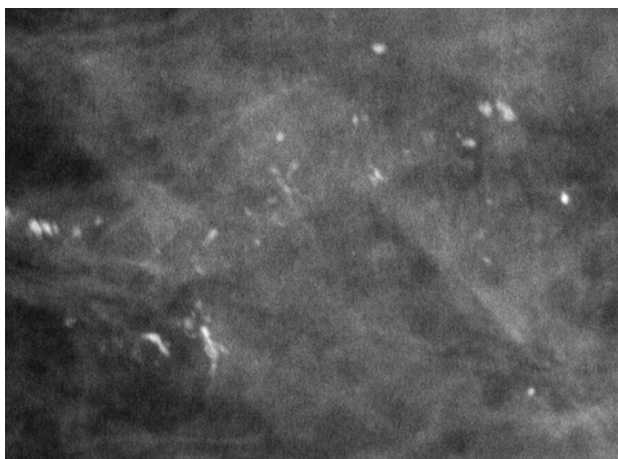


Image 6. Pleomorphic calcifications Coexist Punctate, Spot like, Serpentine, Branched calcifications

Amorphous calcifications	
60% benign	especially when diffuse and bilateral or multiple bilateral clustered - usually FCC (fibrocystic changes) - associated mass suggests papilloma, fibroadenoma or sclerosing adenosis
20% high risk	Atypical duct hyperplasia Atypical lobular dysplasia Lobular carcinoma in situ
20% malignant	Low grade DCIS 10% IDC (invasive ductal carcinoma) usually with associated mass

Image 7.

shape or form. They are usually so small or undefined that cannot be categorized based on their morphology. Many benign or malignant situations could be presented with amorphous calcifications (**Image 7**). Amorphous calcifications represent in 20% of the cases malignancy (usually low grade DCIS).

Based on Size

■ Calcifications of the same size tend to be benign whereas those of various sizes tend to be malignant. Calcifications over 1mm in size rarely harbor malignancy. Most calcifications that are malignant are less than 0,5mm in size.

Based on Number

■ In clustered calcifications the more numerous they are, the higher possibility of malignancy they have. Nonetheless there is not a certain number which could be critical for malignancy, as the proximity among clusters and the shape are more indicative than number. One or two serpentine calcifications of the form of the duct are far more suspicious than a cluster of ten rimlike calcifications (**Image 8**).

Based on Distribution

■ Defused or scattered calcifications: these are numerous calcifications scattered through the whole area of

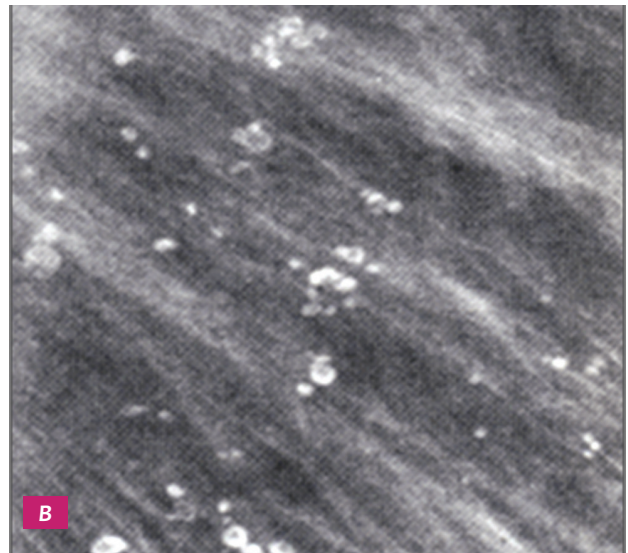
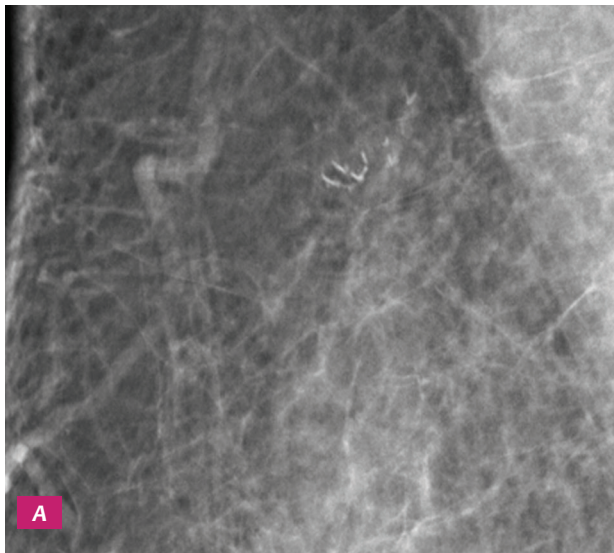


Image 8. A. Two Serpenticular calcifications: Malignancy Grade III B. Multiple Rim like: Benign

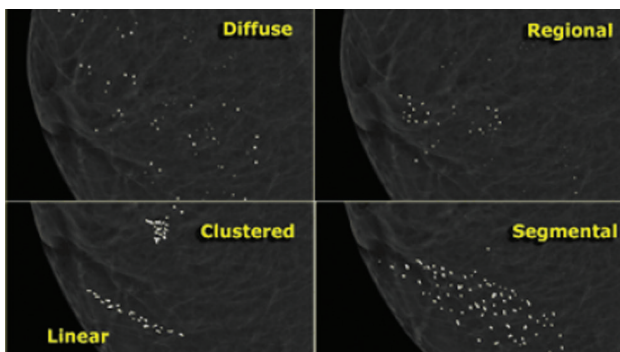


Image 9.

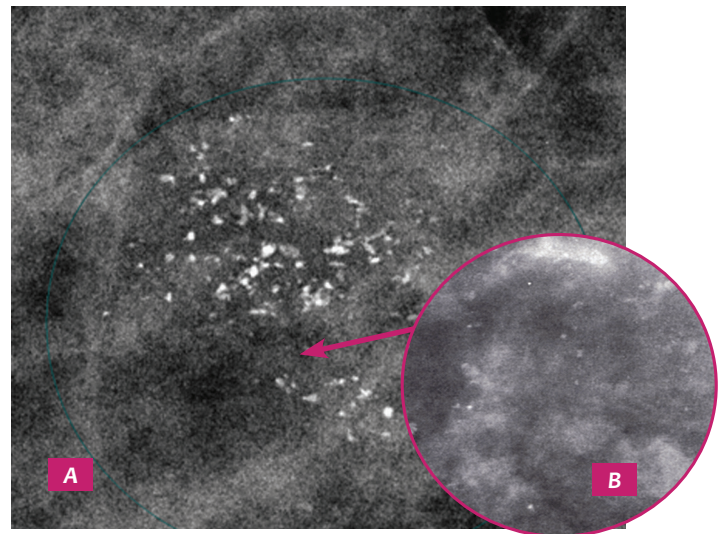


Image 10. A. Clustered. B. Scattered

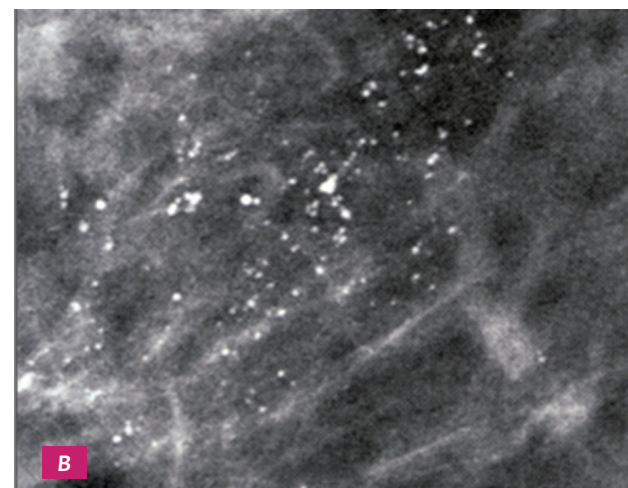
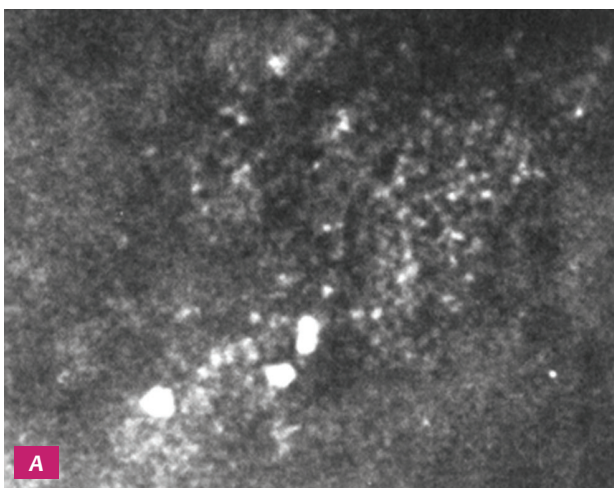


Image 11. A. Heterogeneous Density B. Homogeneous Density

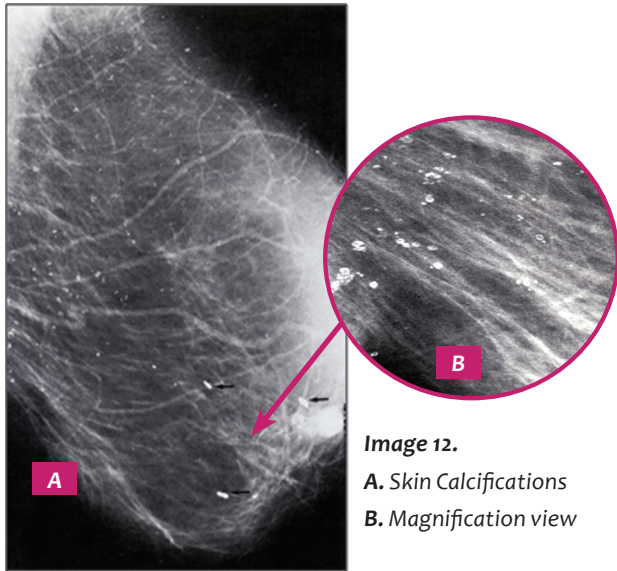


Image 12.

A. Skin Calcifications
B. Magnification view

the breast or multiple, similar, grouped calcifications covering the whole breast area.

- **Regional:** These are scattered calcifications in breast tissue more than 2cc in volume and do not have a ductal distribution.
- **Clustered:** These are at list five (5) calcifications that occupy a small volume of the tissue.
- **Linear:** They are distributed following a line towards a duct.
- **Segmental:** These represent calcium deposits in ducts and their branches that follow the distribution of a whole lobe or part of it (Image 9).

Scattered calcifications tend to be benign and those with close proximity tend to be malignant (Image 10).

Grouped calcifications could be both benign and malignant and are of intermediate concern. When clusters are scattered throughout the whole breast they tend to be benign whereas the existence of one cluster tend to be malignant. Linear distribution is indicative for DCIS.

Based on Density

By taking density under consideration, the comparison can be done both on each segments of a calcification individually and the density of all calcifications (Image 11). Heterogeneous density is more likely an indication of malignancy.

Based on Stability

In the past stability was an indicative argument for benignity. Nevertheless, nowadays stability is not a fact proving benignity. When calcifications share suspicious

morphological characteristics stability does not indicate benignity. It seems that the role of morphology of calcifications is far more important than stability. Stability could be indicative for benignity only when calcifications share non-malignant morphological characteristics. On the other hand, when calcifications decreases in number they must be considered as very suspicious because while DCIS changes to invasive cancer, there could be produced metalloproteinases (such as stromelysins), which has as result the dissolution of calcifications.

Management of Calcifications

Calcifications can be classified into the following types:

- A. Typically benign calcifications
- B. Suspicious calcifications
- C. Malignant calcifications

Typically benign calcifications

■ Skin Calcifications

They are developed in the sebaceous glands of the skin after a mild folliculitis, condensation and calcification of their context. They are rim like with a radiolucent centre and they can be easily identified, especially in tangential views, where they depicted on the skin (Image 12).

■ Vascular Calcifications

The deposit of calcium on the intima of the arteries of the breast can cause two linear, parallel, tram like calcifications. Usually these calcifications are reported on post-menopausal women suffering from atheromatosis or on pre-menopausal women suffering from diadetes (Image 13).

■ Dystrophic Calcifications

They are developed on the fibrous stroma, they vary in size and they are all different. They are coarse, dense, dig, with abnormal shape and they can exist in radiolucent sections. These calcifications are a result of benign situations like:

- oil necrosis from previous trauma
- radiation treatment
- treated abscess
- hematoma.

When they are scattered and bilateral, they can be a result of an inflammatory, degenerative or metabolic disease (renal failure, hyperparathyroidism) (Image 4). In this category we could also include calcifications that are

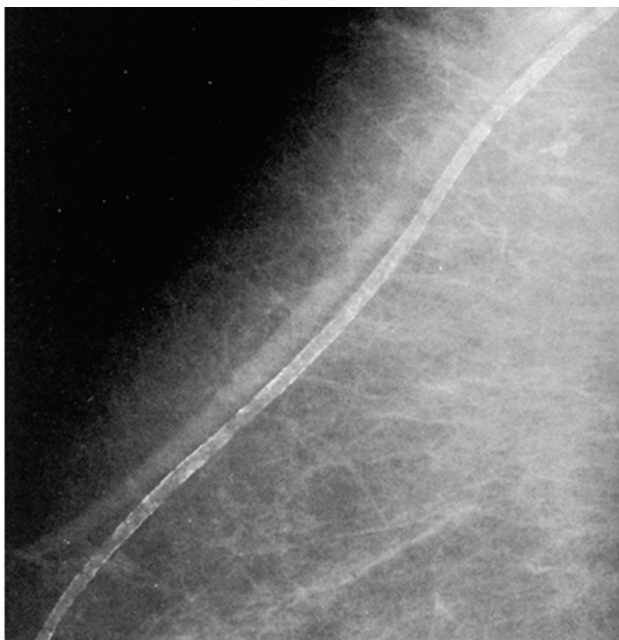


Image 13. Vascular Calcifications

formed on the hyalinised fibrous stroma of fibroadenomas, which are usually coarse with high and consistent density. They have three forms: pop corn like (**Image 15**), spot like (**Image 16**) and egg shell like (**Image 17**).

■ Ductal Calcifications

In some cases of mastitis, women may complain about a post nipple inflammation, usually bilateral, rarely unilateral or focal. The epithelial stroma of the ducts flattens and Calcium deposits on dead cells and on secretions, that coexists, and as a result highly radiopaque, rod like calcifications, with smooth outline are created. This way is formed plasmacell mastitis calcifications. They have a linear set-up with a direction towards the nipple (**Image 18**).

■ Lobular Calcifications

Lobules are groups of round glands that are constituted by Terminal Ductal Lobular Units (TDLUs). In these units, milk is produced during pregnancy and lactation. If these TDLUs do not undergo changes due to hyperplasia of the surrounding fibrous perilobular tissue, calcifications that develop in the acini are round, of high density, well defined and with smooth contour (adenosis). If the acini cavity is small due to pressure from the surrounding hyperplastic perilobular fibrous tissue, calcifications are spot like. These calcifications may have a clustered ar-

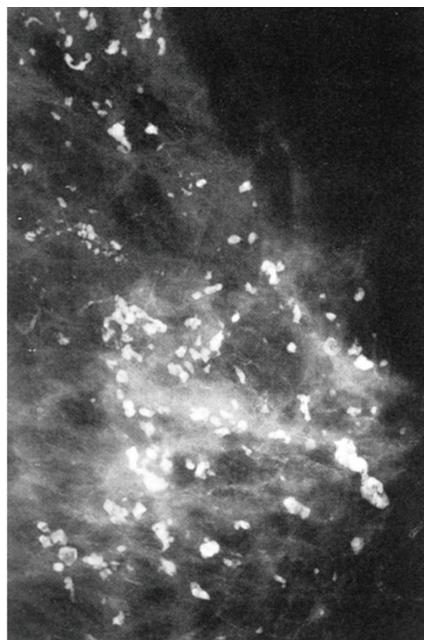


Image 14. Dystrophic Calcifications

angement, indicative for sclerosing adenosis. They also could be arranged bilaterally like thousands of small lights (**Image 19**).

■ Cysts Calcifications

When Calcium deposits on the walls of a cyst (simple or oil cyst), circular calcifications are formed with a radiolucent centre, with wall thickness less than 1mm and look like egg shells (**Image 20**). Some times for various reasons mainly cause of trauma or surgical procedures, solid fat liquefies and as a result oil cysts are developed (microcystic or macrocystic liponecrosis). Later on Calcium is deposited on the wall of the cysts (**Image 21**).

■ Milk of Calcium Calcifications

Sometimes small or big cysts contain calcium in solution. The depiction of Calcium is different in two mammographic views which have 90 angle difference. At the craniocaudal view the Milk of Calcium looks like a round, amorphous, undefined formation or like a cluster of round calcifications, because it precipitates at the lowest wall of the cyst. When the view is depicted in an angle of 90° (profile or lateral), Calcium precipitates at the lowest wall of the cyst and looks like a highly radiopaque semilunar calcification. The Milk of Calcium is rather often in women with dense breasts (**Image 22**).

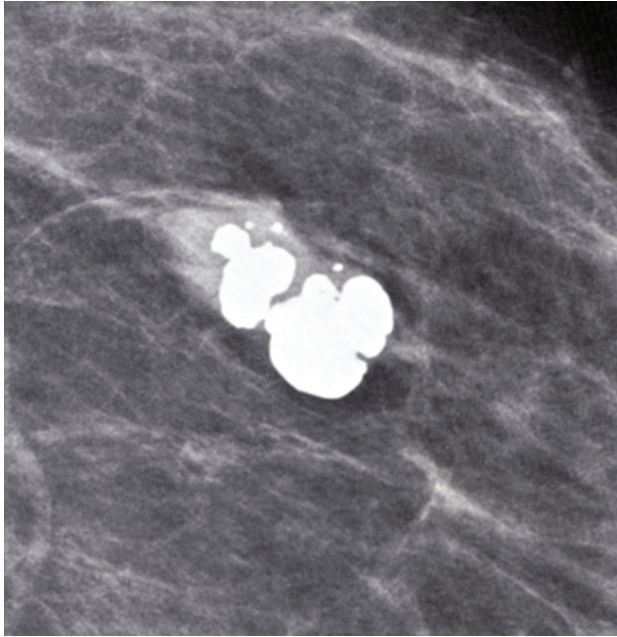


Image 15. Pop corn like Calcifications

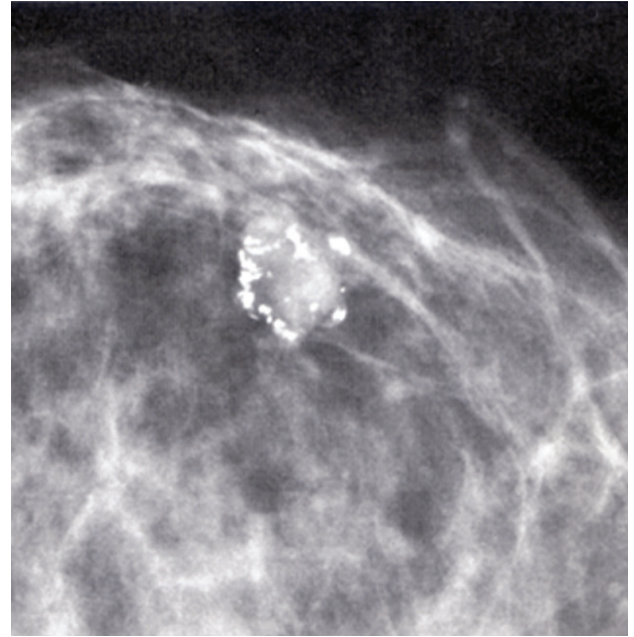


Image 16. Spot like Calcifications

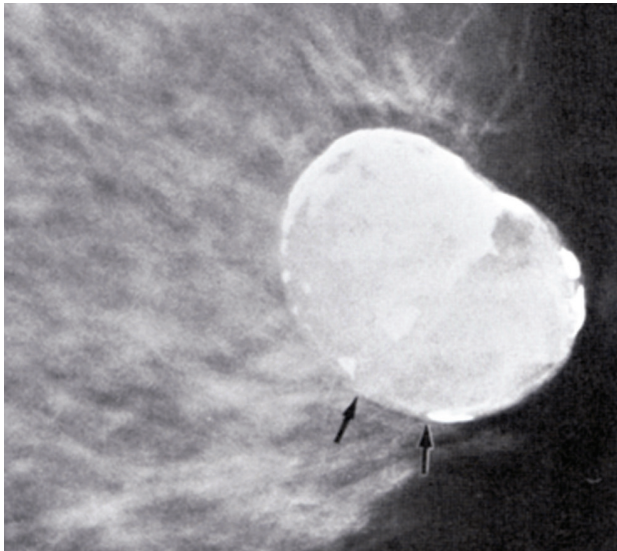


Image 17. Egg shell like calcifications

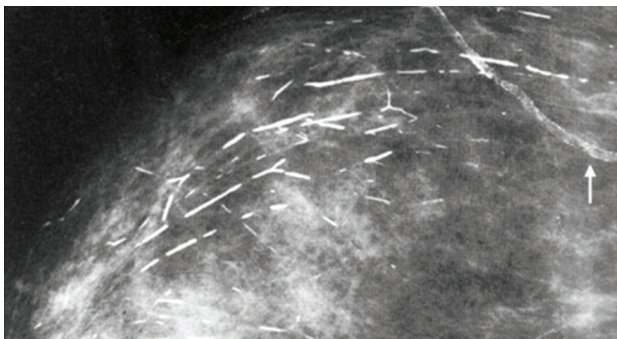


Image 18. Plasma cell Mastitis Calcifications

■ Sutures

Calcifications on suture from previous surgical procedures of the breast are rarely mentioned. They look like knots of equal distance and could be circular or more often linear with smooth contour, limited to the place of the previous surgical procedure. They are more often seen in segmentectomies and post radiotherapy. Radiation induces breast lesion, alters the mechanism of recovery, delays the adsorption of the catgut sutures and as a result there is enough material for Calcium deposits. These kind of calcifications are very rare in non radiated breasts (**Image 23**).

■ Parasites

In rare cases there could be calcifications caused by parasitosis. This includes Filariasis, Cysticercosis, Schistosomiasis etc. Dead parasites are calcified and lead to the development of linear, circular, spiral, spot like, bead like or serpent like calcifications (**Image 24**).

■ Artifacts

Artifacts could simulate calcifications, although they can be easily identified, and could sometimes cause diagnostic problems. Finger prints, scratches, dust on the enhancing plates, deodorants, Zinc oxale lotions, hair and tattoos are projected on the breast tissue and these are the most common artifacts that could simulate calcifications (**Image 25**).

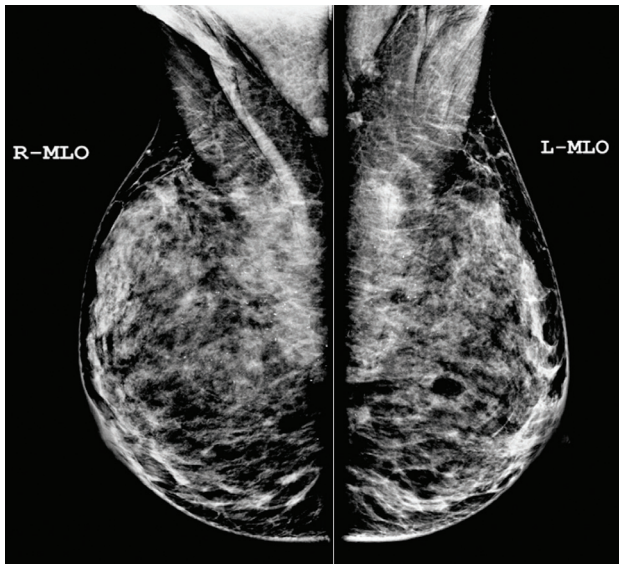


Image 19. Adenosis

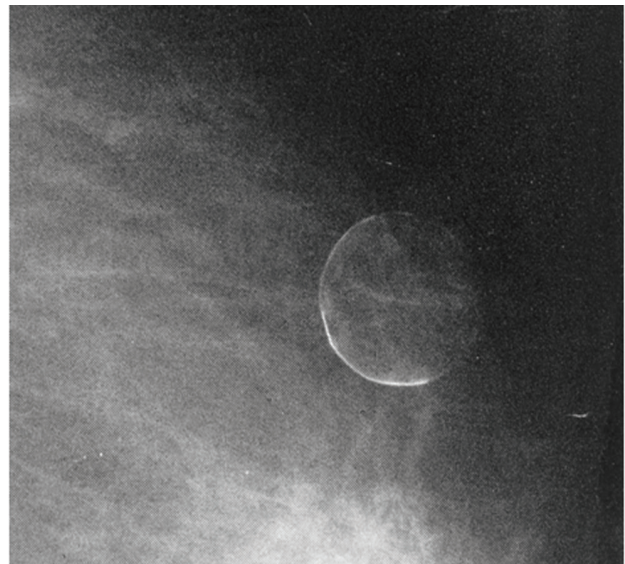


Image 20. Cyst: Egg shell Calcifications

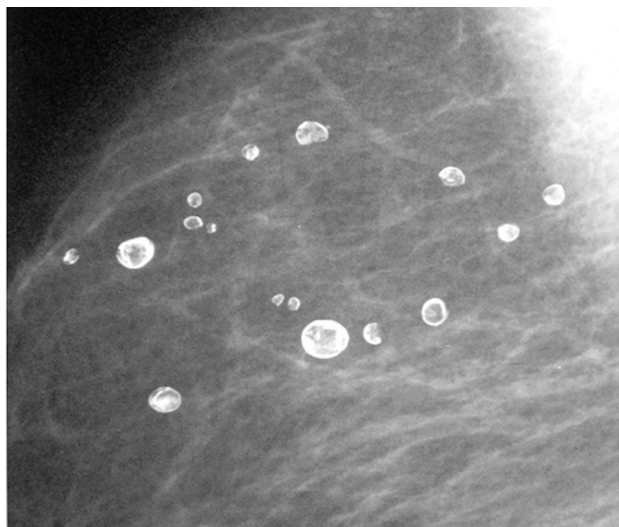


Image 21. Calcified Cysts from liponecrosis

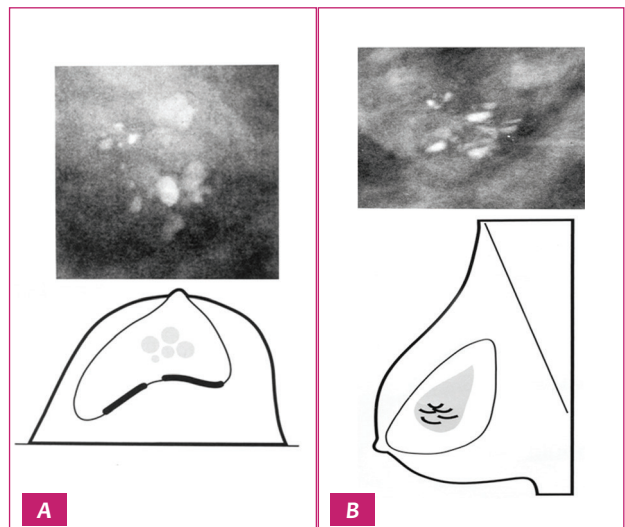


Image 22. Milk of Calcium. A. Craniocaudal view, B. Lateral view

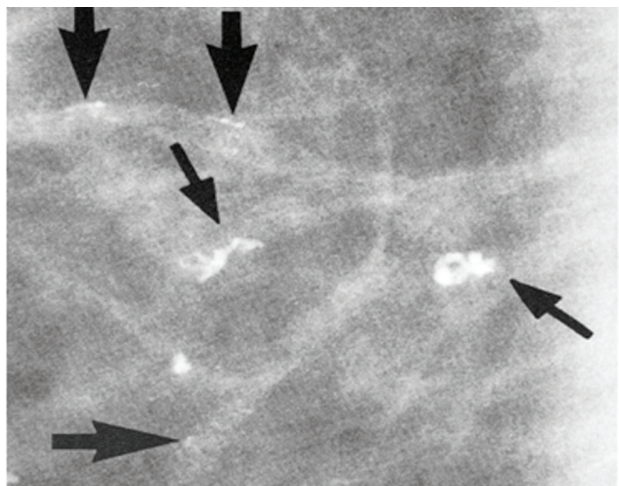


Image 23. Suture

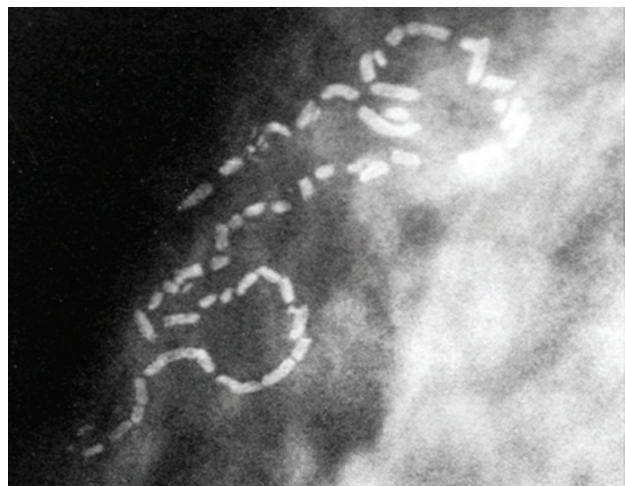


Image 24. Parasitosis

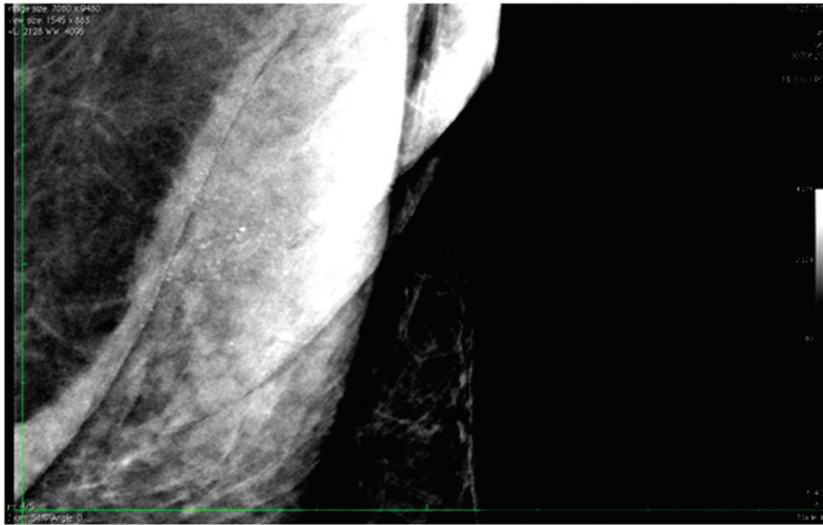


Image 25. Deodorant mimicking Calcifications

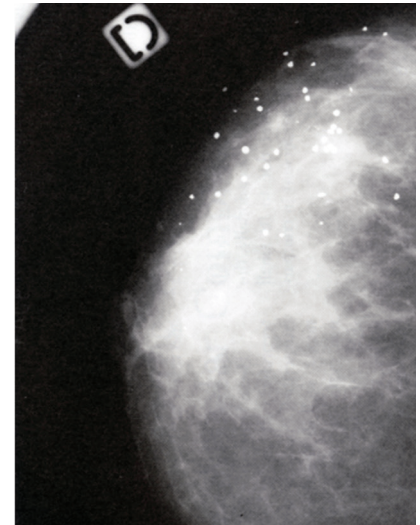


Image 26. Duckshots

■ Foreign Objects

The presence of foreign objects gives the impression of calcifications (**Image 26**).

Suspicious Calcifications & Malignant Calcifications

According to BIRADS Lexicon:

Punctate and spot like calcifications are classified as BIRADS 4a, crashed stone calcifications as BIRADS 4b and branch and pleomorphic calcifications as BIRADS 5.

Amorphous calcifications are classified as follows:

- BIRADS 2, when they are defused and bilateral
- BIRADS 3, when they are multiple, bilateral and clustered
- BIRADS 4, when they are unilateral, clustered or when they are newly developed and they appear during monitoring period or on a patient with an already diagnosed cancer in the other breast.

Typically, benign calcifications are classified as BIRADS 2 and are monitored every year.

Calcifications classified as BIRADS 3 are monitored with short intervals, while all the others need biopsy or surgical intervention. Biopsies must be done if we have suspicious calcifications and there is also coexisting one of the following: Positive familiar or personal history, findings in the clinical examination such as lump or tough in the side where calcifications are depicted on mammography, or a coexisting asymmetrical density on mammography or bloody nipple discharge.

Conflicts of interest

The authors declare that there are no conflict of interest regarding the publication of this paper. ■

REFERENCES

1. D'Orsi CJ, Sickles EA, Mendelson EB, Morris EA, et al. ACR BI-RADS® Atlas, Breast Imaging Reporting and Data System. Reston, VA, American College of Radiology; 2013
2. Tabar L, Dean PB, eds. Teaching atlas of mammography. Second revised edition. New York: George Thieme Verlag; 1985.
3. Tabar L, Tot T, Dean PB. Breast Cancer: Early Detection with Mammography Casting Type Calcifications: Sign of a Subtype with Deceptive Features. Stuttgart, Germany: Georg Thieme Verlag; 2007
4. Morrow M. Management of nonpalpable breast lesions. Principles and Practice of Oncology Updates. 1990;4: 1–11.
5. Harris JR, Lippman ME, Morrow M, Osborne CK, editors. Diseases of the Breast. 3rd ed. Philadelphia, PA: Lippincott Williams and Wilkins; 2004.
6. Breast radiological cases: Training with BIRADS classification. Balleyguier C, Vanel D, Athanasiou A, Mathieu MC, Sigal R. *Eur J Radiol* 2005 Apr;54(1):97-106.

Educational Case Presentation

A case from the Department of Mammography Screening, Paderborn, Germany

Regina Schwanitz-Gräwingholt, Axel Gräwingholt

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

ABSTRACT

In mammography screening women are not seen by a doctor at their first visit to the mammography unit. Therefore it is important that the technicians note all relevant information in order to avoid unnecessary recalls or pitfalls in the interpretation of the screening mammography. Furthermore it is important for the radiologists to always keep in mind that artifacts can be shown in a mammography imitating suspicious findings as in the demonstrated case

KEYWORDS: pitfalls; artifacts; unnecessary recall or recall; screening mammography

History

A 51 year old woman without clinical symptoms was invited for a first round screening appointment to our Center. There was no family history or known genetic predisposition for breast cancer (*Women in Germany are regularly invited to the organized breast cancer screening program of their region every two years with a fixed appointment*).

The performed two view bilateral what kind of mammography craniocaudal (CC) and mediolateral oblique (OBL) is performed by specially trained radiographers and the women return home after the imaging. The report is send to them after a maximum of one week.

Thereafter two radiologists independently read the mammograms. In case that one or both radiologists

find a suspicious radiological image the finding is presented and discussed in a Consensus Conference. With in the Conference the decision is made whether further assessment is necessary.

In the presented case, both radiologists noted a suspicious polymorphous calcification in the OBL view of the left breast in projection on the pectoral muscle. The CC view did not show any changes. The woman was recalled to assess the calcifications further in order to detect a DCIS.

The first step was a CC mammography in “Cleopatra” view hoping to see the calcification in the lateral part of the breast which might not have been seen in the “normal” CC view. The Cleopatra view did not show any calcification.

Corresponding author

Axel Gräwingholt

E - mail: axel.graewingholt@t-online.de

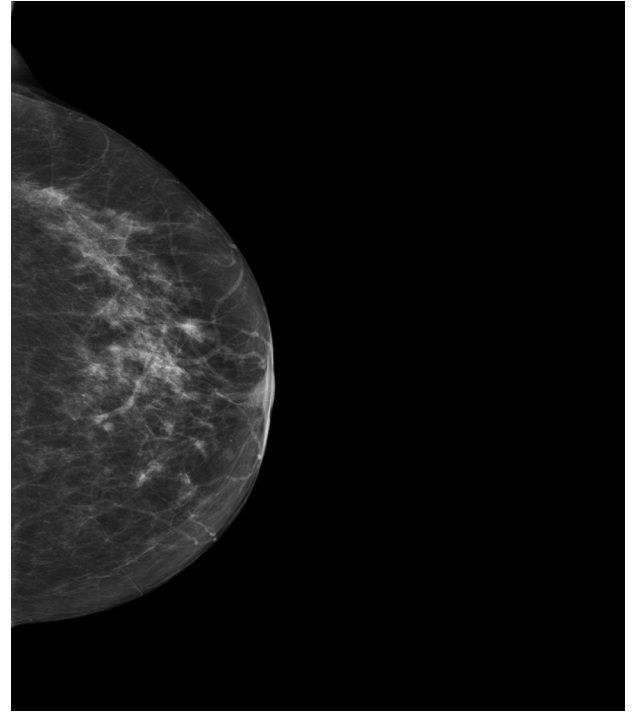
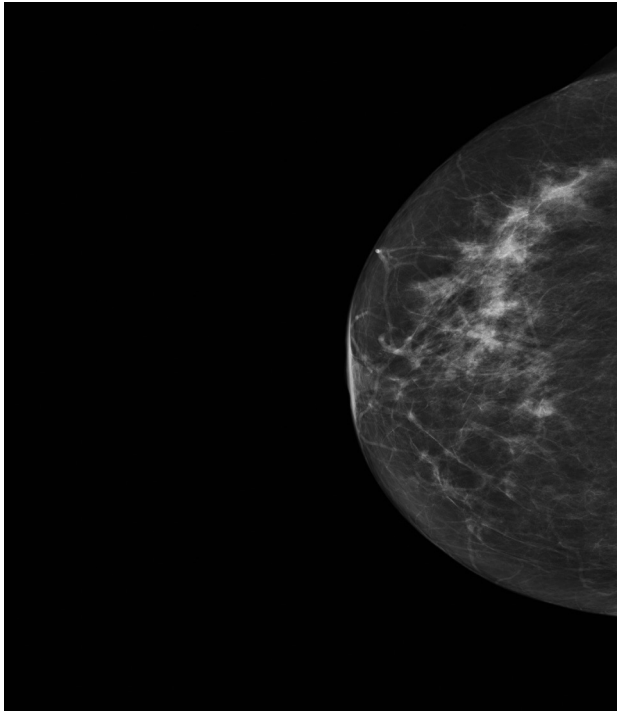


Image 1. CC view both sides

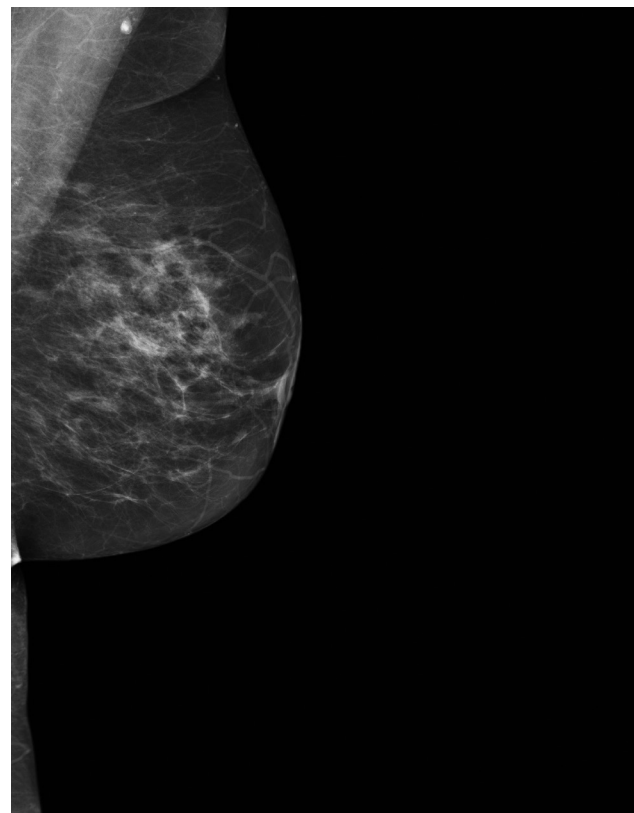
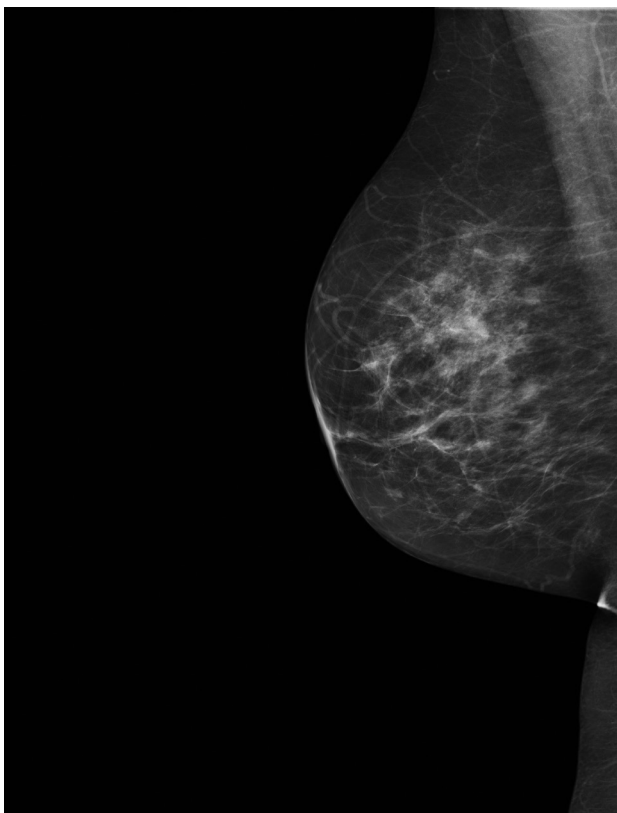


Image 2. OBL view both sides

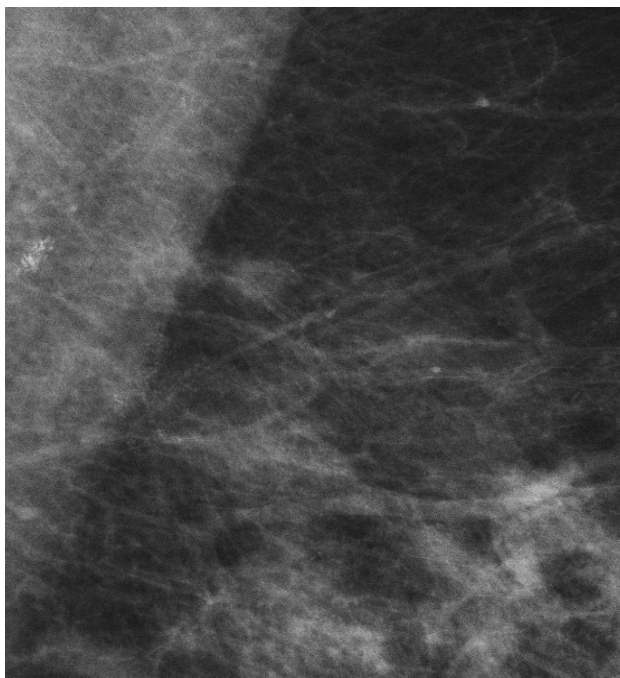


Image 3. “Enlargement” of the left oblique view showing the calcifications

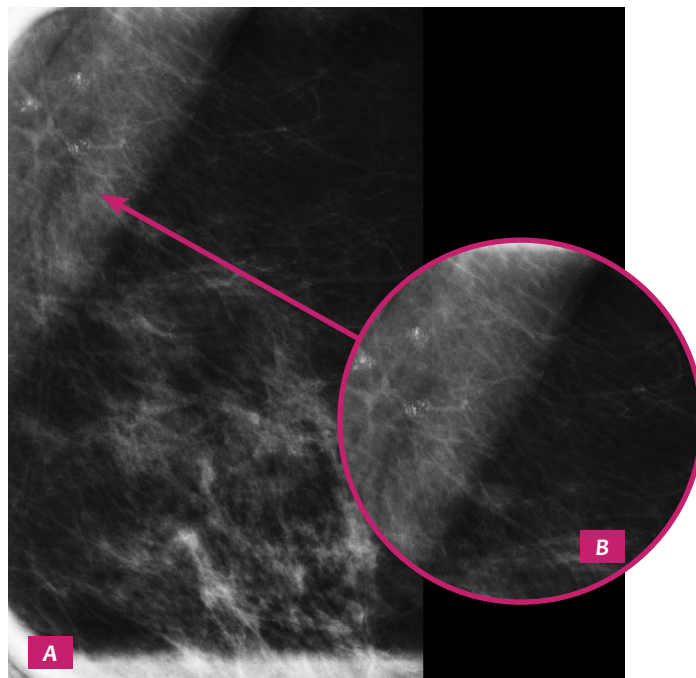


Image 4. A. Mammographic magnification Left oblique showing more calcifications. **B.** Enlarged. Also an ultrasound examination was normal

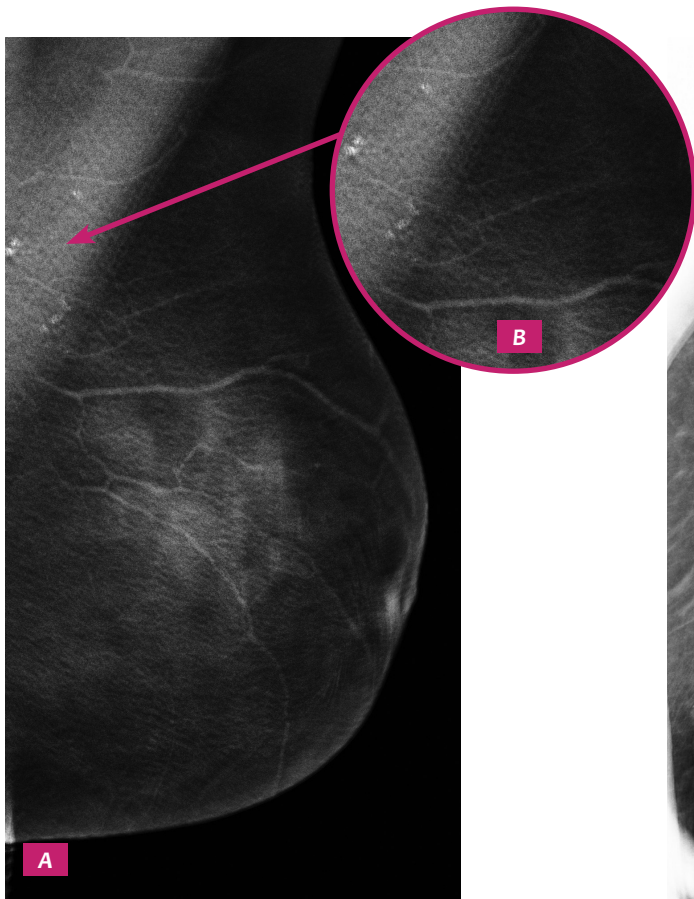


Image 5a. Tomosynthesis left side oblique most medial image. **b.** Enlargement of tomosynthesis image

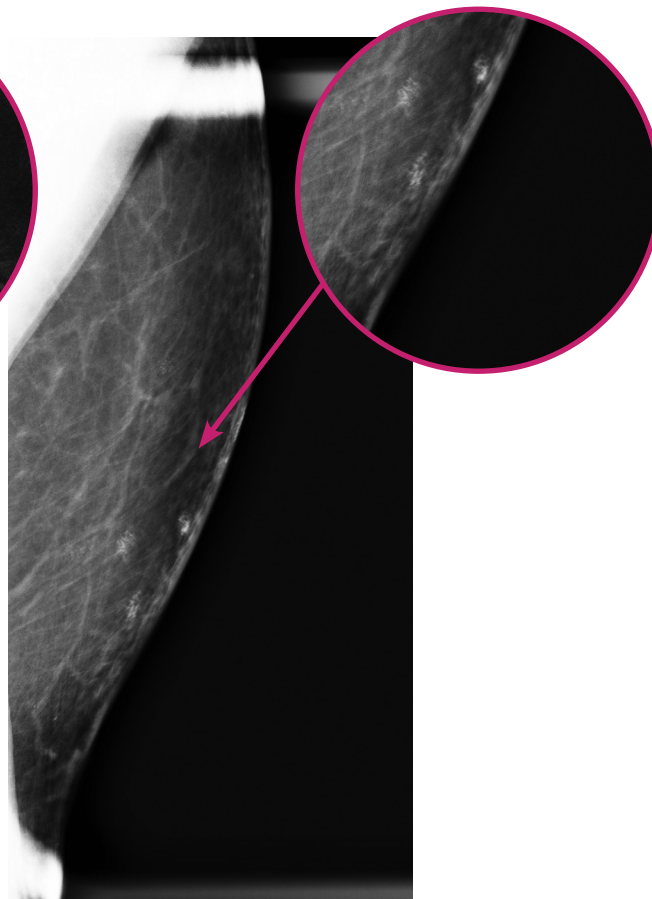


Image 6a. Magnification in tangential view left breast **b.** Enlargement of tangential view



Image 7. Example sketch of the tattoo that caused the calcification

Next step was a magnification view, to better evaluate the morphology of the calcification. This magnification, due to the sole visibility of the calcification in the oblique view was performed in the same OBL view as the original image. The magnification showed an even larger amount of polymorphous calcifications. Still there was the problem of localization of the calcification as it did not show in neither the original screening mammography nor in the “Cleopatra view”.

Therefore the assessing radiologist decided to perform a unilateral oblique view tomosynthesis to be able

to localize the lesion. The tomosynthesis showed that, in the most medial image of the series right underneath the skin, the calcification could be localized.

The clinical examination of the woman showed an old tattoo (app. 30 years) in the medial portion of the left breast. Finally it was decided to do a tangential magnification view of the tattoo to prove that the calcifications occurred due to a side effect of tattooing (*Image 7*).

Conclusion

Tattoos are very common now in the younger and middle-aged population. The body can react to tattooing in many ways, one of them is a subcutaneous calcification which was shown in this case as an artifact.

This case as a typical “pitfall” shows us that, even though many of the modern modalities for breast imaging were used, the clinical examination and clinical look together with a very simple tangential view gave us the final clue to the “diagnosis”. The woman was relieved being healthy after this assessment procedure.

Conflicts of interest

The authors declare that there are no conflict of interest regarding the publication of this paper. ■

Educational Case Presentation

Pitfalls in Mammography the role of Clinical examination

Lydia Ioannidou-Mouzaka MD, Ph.D

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

History

A 40-year-old man with a unilateral mastodynia and having the impression that he palpated a mass on the outer side of his right breast, before coming to my consultation, went to a G.P. who advised him to undergo a bilateral mammography. He had no hereditary or familial breast cancer history.

He underwent to a Radiological center where he was submitted to two view bilateral digital mammography, mediolateral oblique (OBL) and craniocaudal (CC) by a radiographer. The report received at the same day was BIRADS 4a.

Consequently, he wanted to be examined by a Senologist. He took an appointment and came to my consultation. He told me that he had a pain on the right breast for 15 days in addition to his impression that he had been palpating a mass on the outer side of his right breast. No any other problem.

I called my midwife to take him to the examination room and to prepare him for breast examination. As I entered the examination room, I saw on the overhead projector the two OBL incidences of him, with a severe asymmetric density and with an architectural distortion on the right breast. I examined very carefully the four incidences of the two breasts and I was almost sure that

the mammographic abnormality corresponded to a cancer. The man was already naked from the waist up and I returned towards him in order to perform the clinical examination, when I show the following image.

The right side of his thoracic area and the homolateral breast had a huge tattoo, reaching until the region of the nipple of the right breast. Immediately, I understood that the radiological abnormality, seen on mammography of the right breast, related to this tattoo.

Of course, the man was immediately reassured that he was healthy.

Conclusion

The above case is another typical proof that clinical examination is very important and despite new imaging modalities and the progress on these apparatus, clinical examination can solve many problems. In our days, tattoos are very common in the younger and middle-aged men, and this should be kept in mind especially when radiologist him/herself is not the person performing the mammography.

Conflicts of interest

The authors declare that there are no conflict of interest regarding the publication of this paper. ■

Corresponding author

Lydia Ioannidou-Mouzaka

Kifisias Avenue 18, P.C. 11526, Athens, Greece

E - mail: lydiamouzaka@yahoo.gr

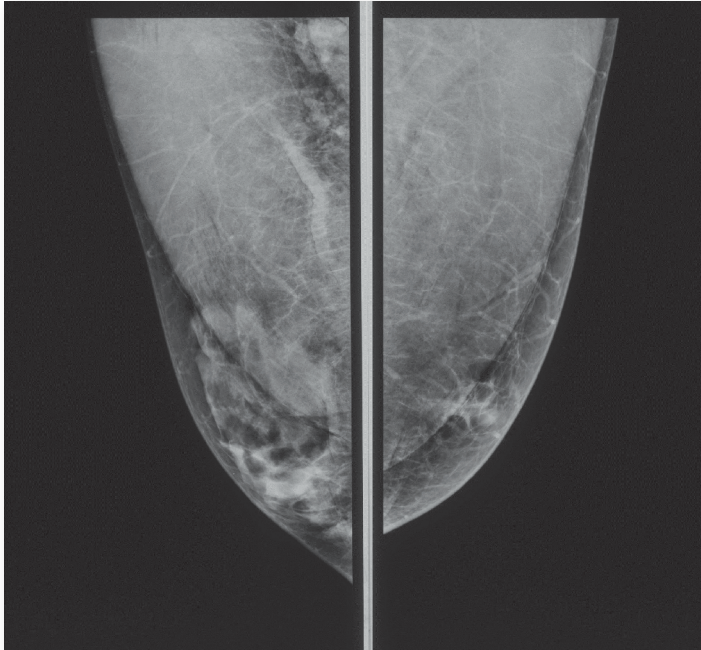


Image 1. The two OBL views of the breasts on the overhead projector. You can notice the asymmetric density and the architectural distortion on the right breast



Image 2. The right side of his thoracic area and the homolateral breast had a huge tattoo



Image 3. Magnification of the man's tattoo next to the nipple

To Umberto Veronesi

Lydia Ioannidou-Mouzaka MD, Ph.D

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

The International family of Senology since November 8th became poorer, as one of the most important colleagues who worked on the breast, abandoned the mundane and migrated to the Lord. The reason, for the very well known breast surgeon from Milan, Italy, Professor Umberto Veronesi.

Umberto Veronesi was born in Milan, Italy on 28 November 1925. He studied Medicine, he received his degree from the University of Milan in 1952 and devoted himself scientifically and professionally to the study and the treatment of cancer.

Veronesi was the founder of the conservative surgery in the treatment of breast cancer, inventing the technique of 'quadrantectomy' which challenged the prevailing until then, model and proved to the scientific field of Senology and his Colleagues, that breast cancer can be cured with a less aggressive surgery than mastectomy.

He supported and promoted the Scientific research aimed in, improving the conservative surgical techniques, including sentinel lymph node biopsy of the axilla instead of the axillary lymph nodes dissection, in cases of negative axilla.

He also contributed in breast cancer prevention by conducting studies with tamoxifen and retinoid, investigating their potential to prevent the creation of breast cancer.

He was an activist in anti-smoking campaigns. In 1994 he founded the European Institute of Oncology in Mi-



lan, which he directed until his death. In 2010 he was appointed Chairman of the Scientific Committee of the Italian-American Foundation. From April 2000 until June 11, 2001 he was the Minister of Health in Italy. In 2008 he was the main candidate for the Democratic Party (Veltro-ni) for the Italian Senate in Milan. Between 2010-2011 he was the President of Italy's Nuclear Safety Agency. He died on November 8, 2016 at the age of 91.

I had the honor and the privilege to work with him, both in Istituti di Tumori of Milan and in the frame of the Board of Directors of the EUSOMA, as elected Board Member (March 1996-March 2000). On behalf of the Board of Directors of the Hellenic Senologic Society and myself personally we are expressing our sincere condolences to his family and to the Italian people and may his memory be eternal. ■

Meetings, Conferences & Congresses

27-30 January 2017	ECCO2017 European Cancer Congress, Amsterdam, The Netherlands
17 - 19 February 2017	6th Asia - Pacific Breast Cancer Summit Hong Kong
9-12 March 2017	34th Annual Miami Breast Cancer Conference Fontainebleau Miami Beach
11-15 March 2017	27th Annual Interdisciplinary Breast Center Conference Paris Las Vegas
15 - 18 March 2017	15th St. Gallen International Breast Cancer Conference Primary Therapy of Early Breast Cancer Vienna, Austria
04 May - 06 May 2017	IMPAKT 2017 Breast Cancer Conference Brussels, Belgium
15-17 June 2017	5th World Congress on Breast Cancer, Theme: Pioneering Spirit of Enriching the Lives and Wellness of Women London, UK
16-18 October 2017	6th World Congress on Breast Cancer & Therapy (10Plenary Forums - 1Event). Theme: New Discoveries for Better Diagnosis and Treatments for Breast Cancer and to bring Awareness San Francisco, California, USA
26-28 October 2017	3rd World Congress on Controversies in Breast Cancer (CoBrCa) Tokyo, Japan
2-4 November 2017	4TH ESO-ESMO International Consensus Conference. Lisbon- Portugal
8 November 2017	Umberto Veronesi MBCC Breast Cancer Conference Milan
5-9 December 2017	San Antonio Breast Cancer Symposium Henry B. Gonzalez Convention Center San Antonio, Texas

Meetings, Conferences & Congresses

7- 8 Απριλίου 2018	Συνέδριο με θέμα: Καθ' οδόν προς τον βέλτιστο θεραπευτικό συντελεστή στην Ογκολογία, Αθήνα, Ξενοδοχείο Crowne Plaza
3- 5 Μαΐου 2018	4 ^ο Ελληνικό Συνέδριο Ογκολογίας, Θεσσαλονίκη, Ξενοδοχείο Makedonia Palace
10- 12 Μαΐου 2018	6 ^ο Επιστημονικό Forum «Τα Νέα Φάρμακα στην Ογκολογία: Από την έρευνα στην πράξη, Αθήνα, Ξενοδοχείο, Saint George Lycabettus
18- 19 Μαΐου 2018	5th Meeting: Debates On Cancer Treatments And Cost Effectiveness, Αθήνα, Ξενοδοχείο Royal Olympic
24-25 May 2018	22nd Global Annual Oncologists Meeting, Osaka, Japan
28-29 May 2018	World Haematology And Medical Oncology Conference-Osaka, Japan
16-18 Ιουνίου 2018	Σύγχρονοι Θεραπευτικοί Χειρισμοί για τον Ογκολογικό Ασθενή II. Από την έγκαιρη διάγνωση στην αποτελεσματική θεραπεία. Δράμα, Ξενοδοχείο Hydrama
01- 05 June, 2018	ASCO 2018, Chicago, USA
23-24 July 2018	Experts Meet On Cancer Therapy 2018, Melbourne, Australia
9-10 August 2018	8th World Conference On Women's Health And Breast Cancer Abu Dhabi, Uae
5-6 September 2018	15th Asia Pacific Oncologists Annual Meeting Tokyo, Japan
27-28 September 2018	3rd World Conference On Breast And Cervical Cancer Abu Dhabi, Uae
11-13 October 2018	36th World Cancer Conference Zurich, Switzerland
11-13 October 2018	Melbourne International Joint Breast Congress Melbourne, Australia

18-19 October 2018	Euro Breast Cancer Summit 2018 Amsterdam, Netherlands
22-24 October 2018	5th World Congress On Epigenetics And Chromosome Istanbul, Turkey
19-23 October 2018	Esmo 2018 Congress Munich, Germany
6-7 December 2018	20Th World Congress Of Senologic International Society Of Breast Healthcare Strasbourg, France
11-14 June 2020	21st International Congress on Senology-Breast Health Care of the SIS, Athens-Greece. Info: Hellenic Senologic Society, e-mail: reception2mastologia.gr Tel: +30 210 74 70 257 Fax: +30 210 77 16 834



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



“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 immedi-

ately 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. **It is the sole responsibility of authors to ensure that all images have the required resolution for production (300 dpi and better). The journal does not held any responsibility about the quality of the images.**

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».

Niki J Agnantis MD, PhD Pathologist, Emeritus Professor of Ioannina University, Medical School, Greece

Benjamin Anderson MD Professor of Surgery and Global Health Medicine, University of Washington (UW) in Seattle, Washington - USA

Dimitrios Bafaloukos MD Medical - Oncologist. Director of the Oncology Department at the Metropolitan Hospital Piraeus

Carol Ann Benn MD Breast Surgeon Johannesburg - South Africa

Mauricio Camus MD Breast Surgeon, Chief of the Department of Surgical Oncology at the Pontificia Universidad Católica de Chile, and President of the Chilean Society of Mastology (2014 - 2016)

Luigi Cattaliotti MD Emeritus Professor of General Surgery, past President EUSOMA

Eduardo Cazap MD, PhD Medical Oncologist, Founder of SLACOM, Latin American & Caribbean Society of Medical Oncology, Immediate Past President UICC, Buenos-Aires - Argentina

Evanthia Diamanti - Kandaraki MD, PhD Prof. of Endocrinology, University of Athens

Nikolaos Dimitropoulos MD Specialized Radiologist Director of Delta Imaging Center - Athens

Ivan Drinković MD, PhD Specialized Radiologist Zagreb University, Medical Faculty, President of the Croatian Senologic Society, Chairperson of the Standing Committee of the SIS

Enzo Durante MD Radiologist, Faculty Member of IBUS, Ferrara - Italy

Athanasios Exadactylos MD Plastic Surgeon, President of Medical Association of Thessaloniki, Vice president of the Hellenic Senologic Society

Stephen A. Feig MD, F.A.C.R., F.S.B.I Fong and Jean Tsai Endowed Professor of Breast Imaging. Uni of California, Irvine School of Medicine

Lina Florentin B.Sc, MD, PhD Molecular Biologist – Cytogeneticist, Director of Alfa Lab Molecular Biology and Cytogenetics Center, Hygeia Group Hospital - Athens

Andreas Foustanos MD, PhD, CCBC Plastic Surgeon, Iaso Hospital, Athens

Rufo de Freitas Junior MD President of the Brazil Society of Mastology, Coiania - Brazil

Hans Joachim Frischbier MD, PhD Emeritus Prof. of Gynecology-Radiology of the University Hospital in Eppendorf, Hamburg - Germany

Constatin Gennatas MD, PhD of Medical Oncology, Athens - Greece

Pierre Alain Goumot MD Specialized Radiologist, Paris - France

Axel Gräwingholt, MD Specialized Radiologist, Responsible physician of department of Mammography Screening Center, Radiologie am Theater, Paderborn, Germany, Visiting Professor Yerevan State Medical University, department of Diagnostic Radiology, Yerevan, Republic of Armenia, Consultant radiologist of Mammography screening centers in Fribourg, Thurgau and St. Gall, Switzerland, Member of Guidelines Development Group of ECIBC (European Commission Initiative on Breast Cancer)

Rahdi Hamza MD Service d'Imagerie Médical, EPS Charles Nicolle Tunis, Tunisie

Dimitrios Hapsas MD Plastic Surgeon, Artion Center of Plastic Surgery - Athens – Greece

Lydia Ioannidou - Mouzaka MD, PhD Gynecologist - Surgeon - Breast Specialist, National Representative of Greece for Breast Centers and Breast Cancer

in the European Union, Member of Guidelines Development Group of ECIBC (European Commission Initiative on Breast Cancer), Member of the UEMS Breast Cancer Surgery Training Group, Director of Studies of the Hellenic School of Senology

Dimitris Kelekis MD, PhD, EBIR Emeritus Professor of Radiology of University of Athens, Director of Radiology Dpt Evgenideion, Hospital - Athens

Antony Keramopoulos MD, PhD Ass. Prof. of Gynaecology - Breast Specialist, Iaso Hospital, Athens

Krystyna D Kiel MD Associate Professor Radiation Oncology Rush University Medical Center, Chicago ILL-USA

Michael Koutsilieris MD, PhD Prof. of Experimental Physiology, University of Athens - Greece

Pagona Lagiou MD, PhD Prof. of Hygiene and Epidemiology, University of Athens Medical School, Senior Fellow, Bureau of Epidemiologic Research, Academy of Athens

Nektaria Lambrinaki - Kalamata MD Plastic Surgeon, Artion Center of Plastic Surgery, Athens - Greece

Spyros Lazarou MD Specialist Radiologist

Helmut Madjar MD Gynecologist - Breast Ultrasound Specialist, Freiburg - Germany

Petros Malakasis MD Specialist Radiologist, Director of Mammography Department of Euroclinic - Athens

Robert Mansel MD, PhD Breast Surgeon, President of the EUSOMA

Shahla Masood MD Prof. and Chair Dpt of Pathology and Laboratory Medicine, University of Florida Jacksonville Medical Director, UF Health Breast Center Chief of Pathology and Laboratory Medicine Shands Jacksonville

Carole Mathelin MD Gynecologist Professeur des Uni-

versités – Praticien Hospitalier (PUPH), President of the French Senologic Society, Strasbourg - France

Leonardo McLean MD Breast Surgeon, Past President of the SIS, Buenos Aires - Argentina

Monica Morrow MD, FACS Chief Breast Service, Anne Burnett Windfohr Chair of Clinical Oncology, Professor of Surgery, Weill Cornell Medical College

Alexander Mundinger MD Professor of Radiology, Director of Radiologic Centre; Niels - Stensen - Clinics (NSC), Chief of Radiologic Department MHO and Breast Imaging Centre FHH (NSC), President of Senologic International Society (SIS)

Ezio Novais Diaz MD Breast Surgeon Bahia – Brazil

Ruben Orda Tel Aviv- Israel Chairman, SIS International School of Senology, Past President of the SIS

Valerijus Ostapenko MD Radiologist Chief of Breast, Gynecology, Photodynamic Therapy Dpt, Institute of Oncology, Vilnius University

Dimitrios Pektasidis MD, PhD Medical Oncologist Athens - Greece

Savvas Papadopoulos MD Pathologist Director of Pathology Department of Hygeia Hospital Athens - Greece

Tadeusz Pienkowski, MD PhD Clinical Director of Cancer Center, Warsaw, Poland

Edio Pusterla MD Director in Breast Unit Senologia Ticino Studio Medico Senologia / Ginecologia, Lugano, President of Istituto “Breast Unit. Senologia Ticino”

Emiel Rutgers MD, PhD, FRCS Surgeon, Clinical Director, The Netherlands Cancer Institute Antoni van Leeuwenhoek Hospital, Amsterdam

Arkadios Rousakis MD, PhD Radiologist, Director CT and MRI Department “Hygeia” and “Mitera” Hospitals - Athens

Ayşegül Şahin MD Vice President, Macroeconomic and Monetary Studies Function, Federal Reserve Bank of New York

Carlos Sánchez Basurto MD Vice-President of the Mexican Academy of Surgery, Mexico

Schlomo Schneebaum MD, PhD Head Breast Health Center, Head Radioguided Surgery Dept of Surgery, Tel - Aviv Sourasky Medical Center

Ashraf Selim MD Professor of Radiology Cairo - Egypt

Efthimios Sivridis MD Pathologist Alexandroupoli - Greece

Kalliopi P. Siziopikou MD, PhD Professor in Pathology, Director of Breast Pathology and Breast Pathology Fellowship Program, Northwestern University Feinberg School of Medicine, Robert H. Lurie Comprehensive Cancer Center, Chicago, ILL - USA

Antony Thomas Stavros MD, F.A.C.R. Experience in Ultrasound/Noninvasive Vascular Ultrasound. George Leopold Honorary Lecture - LARS Colorado, Denver - USA

Kyriakos Souliotis MD Assistant Professor of Health Policy at the Faculty of Social Sciences, University of Peloponnese, Athens - Greece

Laszlo Tabar MD Professor of Radiology at University of Uppsala School of Medicine, Sweden, Medical Director of the Department of Mammography, Falun Central Hospital, Sweden, and Consultant Radiologist for numerous Comprehensive Breast Centers in the United States

Tibor Tot MD Prof. of Pathology at the University of Uppsala School of Medicine, Sweden,

Serdal Türhal MD, PhD Medical Oncologist, Representative of Turkey to the UEMS for Medical Oncology, Istanbul - Turkey

Christina Tsionou MD Gynecologist - Breast Surgeon, Mitera Hospital, Athens - Greece

Carlos Vazquez Albaladejo MD Medical Oncologist, past president of the SIS, Valencia - Spain

Apostolos Zavos MD Surgeon Gynecologist. Sub-specialty Breast Diagnostic and Surgery. Board member of Hellenic Senologic Society. Member of the UEMS Breast Cancer Surgery Training Group, Larisa - Greece

Christopher Zielinski MD, PhD Medical Oncologist, Director of the Clinical Division of Oncology and Chairman of the Dpt of Medicine I at Medical University of Vienna. Coordinator of the Comprehensive Cancer Center at Medical University Vienna and the General Hospital in Vienna, President of the Central European Cooperative Oncology Group, Vienna, Austria

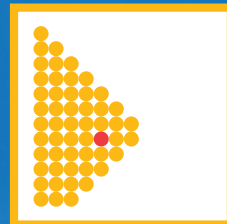
Georgios Zografos MD, PhD, F.A.C.S Professor and Chairman, 1st Department of Propaedeutic Surgery, University of Athens, Medical School, Hippocraton General Hospital of Athens, Vice Rector of the University of Athens - Greece

Gustavo Zucca - Mattes MD Plastic Surgeon with expertise in Oncology Cancer Hospital of Barretos, Associated Editors SIS Journal, Barretos - Brazil

Aggeliki D. Athanasiou.....	17
Axel Gräwingholt	36
Lydia Ioannidou-Mouzaka.....	9, 17, 40, 42
Georgios Kyropoulos.....	26
Regina Schwanitz-Gräwingholt	36
Kalliopi P. Siziopikou.....	10
Elisavvet Soilemezi.....	26
Apostolos Zavos	26

Abraxane[®]

nanoparticle albumin bound paclitaxel



ABX-KTX-BR-4/2015



Α. Κηφισίας 274, 15232 Χαλάνδρι, Αθήνα, Τηλ.: 210 8771500, Fax: 210 6891918
e-mail: info@genesishpharma.com, www.genesishpharma.com

Για περαιτέρω πληροφορίες απευθυνθείτε στη Γένεσις Φάρμα.

Είσαι γυναίκα. Είσαι δύναμη!

3 πόλεις
ΑΘΗΝΑ, ΘΕΣΣΑΛΟΝΙΚΗ, ΠΑΤΡΑ

26 εισηγητές

105 ώρες σεμιναρίων

3.307 θέσεις καλύφθηκαν

Συνεχίζουμε!

ΠΡΟΓΡΑΜΜΑ
ΕΝΗΜΕΡΩΣΗΣ
ΓΙΑ ΤΟΝ
ΚΑΡΚΙΝΟ
ΤΟΥ ΜΑΣΤΟΥ

Λίνα Καπετανέα, Performing Artist

ΥΠΟ ΤΗΝ ΑΙΓΙΔΑ ΤΗΣ

ΕΟΠΕ ΕΤΑΙΡΕΙΑ
ΟΓΚΟΛΟΓΩΝ
ΠΑΘΟΛΟΓΩΝ
ΕΛΛΑΔΑΣ

ΣΕ ΣΥΝΕΡΓΑΣΙΑ ΜΕ

Κ.Ε.Φ.Ι
Σύλλογος Καρκινοπαθών
Εθελοντών Φίλων Ιατρών

άλμα ζωής
ΠΑΝΕΛΛΗΝΙΟΣ ΣΥΛΛΟΓΟΣ
ΓΥΝΑΙΚΩΝ ΜΕ ΚΑΡΚΙΝΟ ΜΑΣΤΟΥ

άλμα ζωής
ΣΥΛΛΟΓΟΣ ΓΥΝΑΙΚΩΝ
ΜΕ ΚΑΡΚΙΝΟ ΜΑΣΤΟΥ
Ν. ΘΕΣΣΑΛΟΝΙΚΗΣ

Αγκαλιάζε
ΟΜΑΔΕΣ ΕΘΕΛΟΝΤΩΝ
ΚΑΤΑ ΤΟΝ ΚΑΡΚΙΝΟ

Αγκαλιάζε
ΟΜΑΔΕΣ ΕΘΕΛΟΝΤΩΝ
ΚΑΤΑ ΤΟΝ ΚΑΡΚΙΝΟ
ΝΟΜΟΥ ΑΧΑΪΑΣ

άλμα ζωής
ΣΥΛΛΟΓΟΣ ΓΥΝΑΙΚΩΝ
ΜΕ ΚΑΡΚΙΝΟ ΜΑΣΤΟΥ
ΝΟΜΟΥ ΑΧΑΪΑΣ

Όραμα και Ευθύνη για τον Ασθενή*

NOVARTIS