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A new approach to breast cancer terminology based on the anatomic site of tumour origin: The importance of radiologic imaging biomarkers

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ABSTRACT

Purpose: To use mammographic tumour features (imaging biomarkers) to classify breast cancer according to its apparent anatomic site of origin in the new era where tumours are found at their nonpalpable, earliest detectable phase.

Method: Large format, subgross, three-dimensional histopathologic images of breast cancer subtypes and their corresponding imaging biomarkers were correlated with large format thin section histopathology and long-term patient outcome.

Results: This systematic correlation indicates that breast cancers arise from three separate fibroglandular tissue components: the terminal ductal lobular units (TDLUs), the major lactiferous ducts, and in the stem cells of the mesenchyme. The resulting three cancer subgroups have distinctly different clinical, histopathological and mammographic presentations and different long-term outcomes. The relative frequency of these three breast cancer subgroups is approximately 75%, 20% and 5%, respectively. Classification of breast cancers according to their anatomic site of origin, as demonstrated with breast imaging and confirmed by subgross histopathology, correlates closely with the long-term patient outcome.

Conclusions: Classification of breast cancers according to their site of origin helps overcome the inconsistencies in the current histopathologic terminology with its ductal-lobular dichotomy. The ability of the imaging biomarkers to determine the site of tumour origin and serve as a prognostic indicator emphasizes the increasingly crucial role of breast imaging in the management of breast cancer. Basing breast cancer management upon anatomically relevant terminology challenges the conventional mindset. Our proposals are based on research results from an unprecedented number of prospectively collected nonpalpable breast cancers diagnosed at their earliest detectable phases and followed up for several decades. This article is a general introduction to a series of forthcoming articles describing in detail the breast malignancies originating from the three sites of origin.

1. Introduction

The breast, prostate and salivary glands are fluid-producing organs sharing many structural and functional similarities. The site of origin of cancers in the prostate and salivary glands is the basis for the terminology describing these malignancies, correlating closely with their long-term outcome. Despite the anatomic and functional similarities among these three malignancies, the terminology for breast cancer is not based on the anatomic site of origin because of the historical lack of access to tumours in the earliest phase of the disease. In the current era, tumours are frequently found at their nonpalpable, earliest detectable phase. We investigated whether breast cancer subtypes could be

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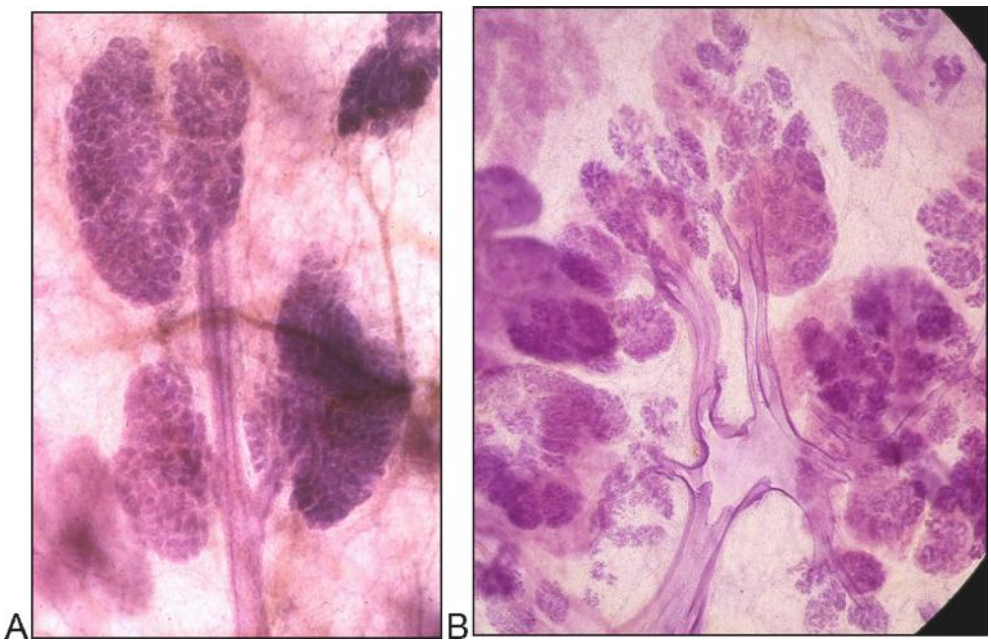


Fig. 1. Large format thick section histopathology images demonstrate the 3-dimensional structure of the terminal ducts and acini in non-lactating women's breasts.

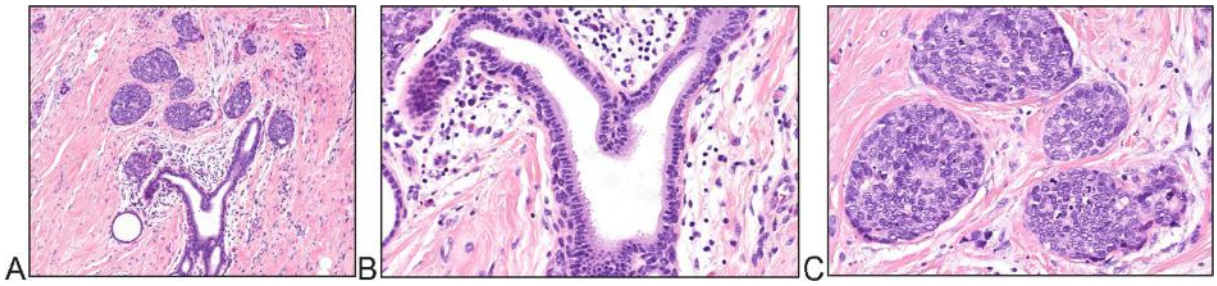


Fig. 2. Low power histopathology image of a TDLU (A). Higher power image of the normal terminal duct (B) and the cancer-filled acini (C).

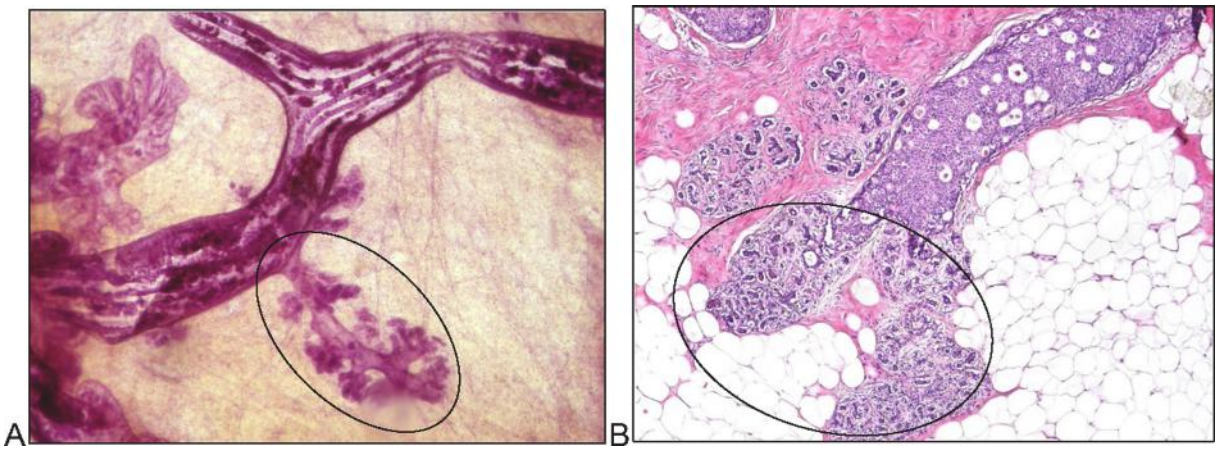


Fig. 3. Large format thick (A) and thin section (B) histopathology images showing two separate cases where the major lactiferous ducts are distended by cancer cells having micropapillary (A) and cribriform (B) tumour growth patterns while the associated TDLUs are free of cancer.

classified according to their apparent anatomic site of origin by using the mammographic tumour features correlated with large format thick and thin section histopathology, and long-term patient outcome. This approach represents a paradigm shift away from the current ductal-lobular dichotomy in breast cancer.

The growing trend of earlier diagnosis through greater awareness of symptoms and participation in mammography screening combined with improvements in breast cancer management have helped reduce mortality from breast cancer by 40–60% [1–5]. We have been particularly concerned that some of the women who have participated in mammography screening and received state of the art therapy have eventually died from breast cancer. This has driven our search for a

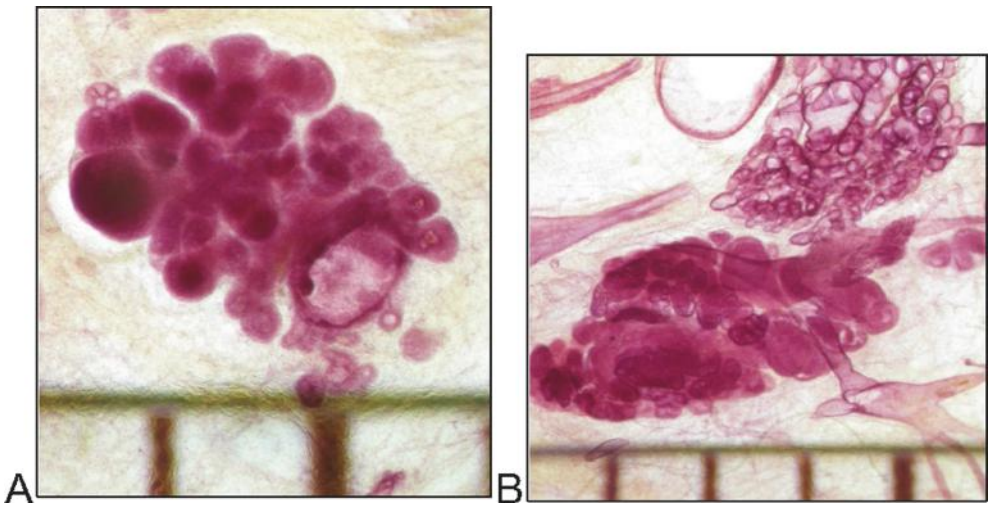


Fig. 4. Subgross, thick section histopathology images of the acini distended by the accumulating cancer cells in the TDLUs.

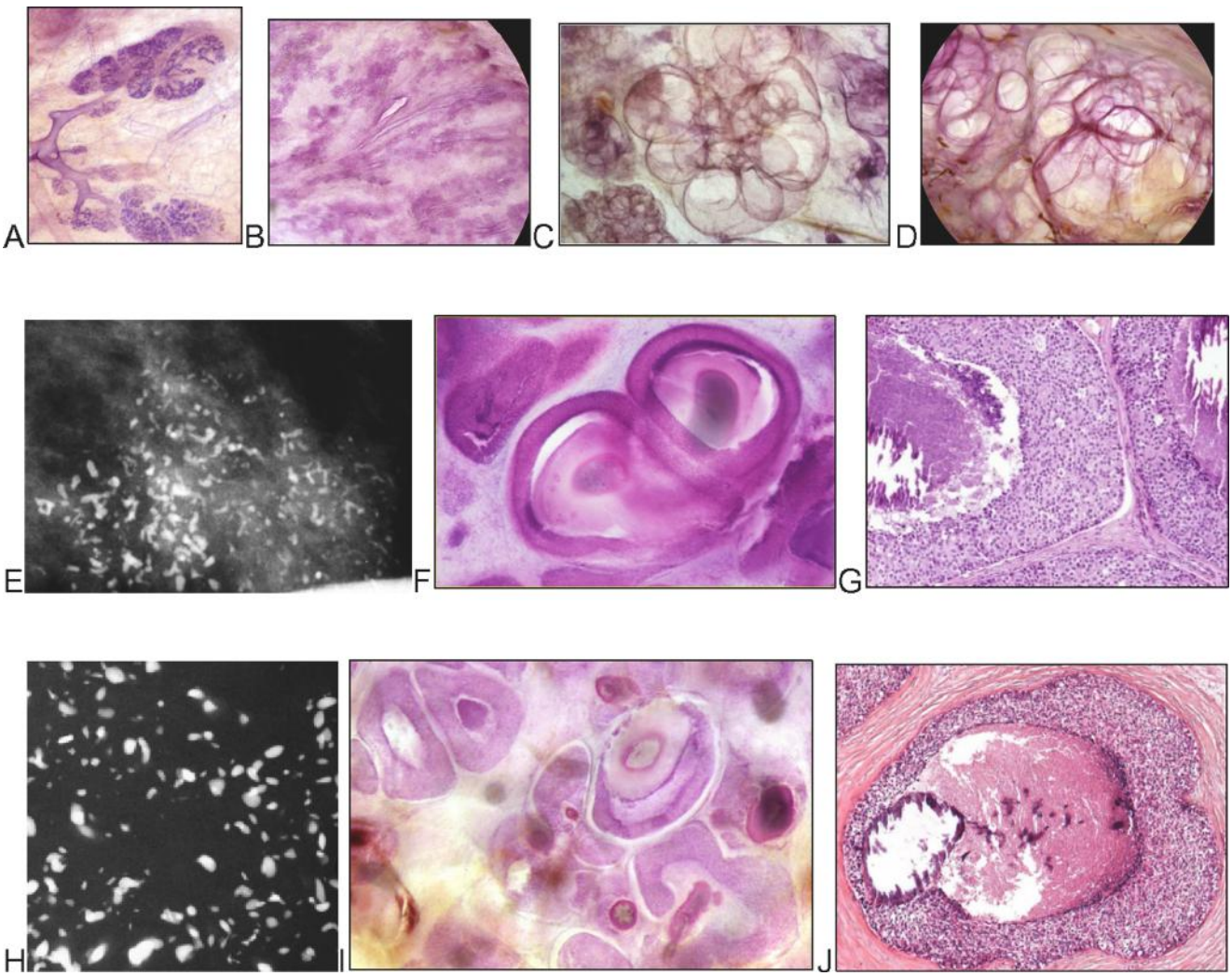


Fig. 5. Subgross histopathology images of the normal breast (A) and prostate (B); hyperplastic cystic changes in the breast (C) and prostate (D). Specimen radiography, subgross histopathology and thin section histopathology images of cancer of ductal origin in the breast (E-G) and in the prostate (H-J).

better understanding of these subtypes and innovative improvements in diagnosis and management that could facilitate better disease-specific outcomes.

In our efforts to explain why these fatalities occurred and how to help prevent them, we have used a comprehensive database prospectively collected since 1977, when the current population-based mammography

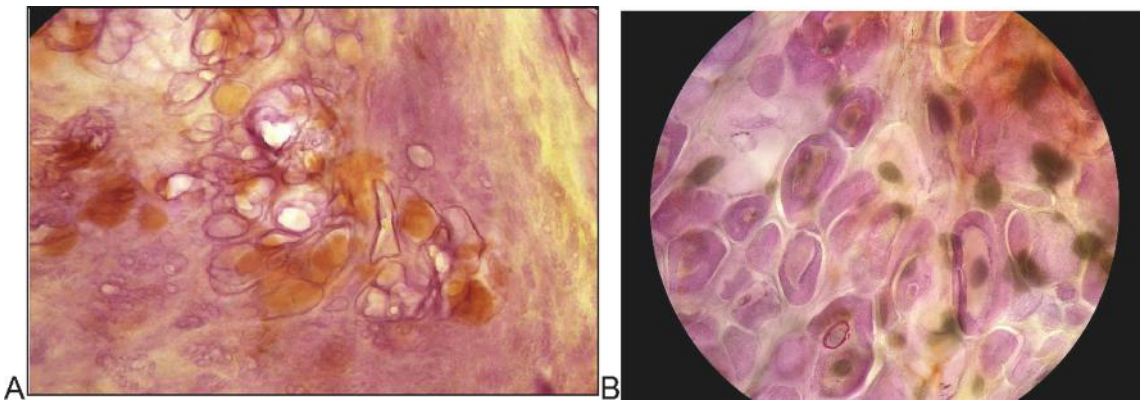


Fig. 6. Subgross histopathology image of prostate cancer of acinar origin (AAP) (A) and subgross histopathology image of prostate cancer of ductal origin (DAP) (B).

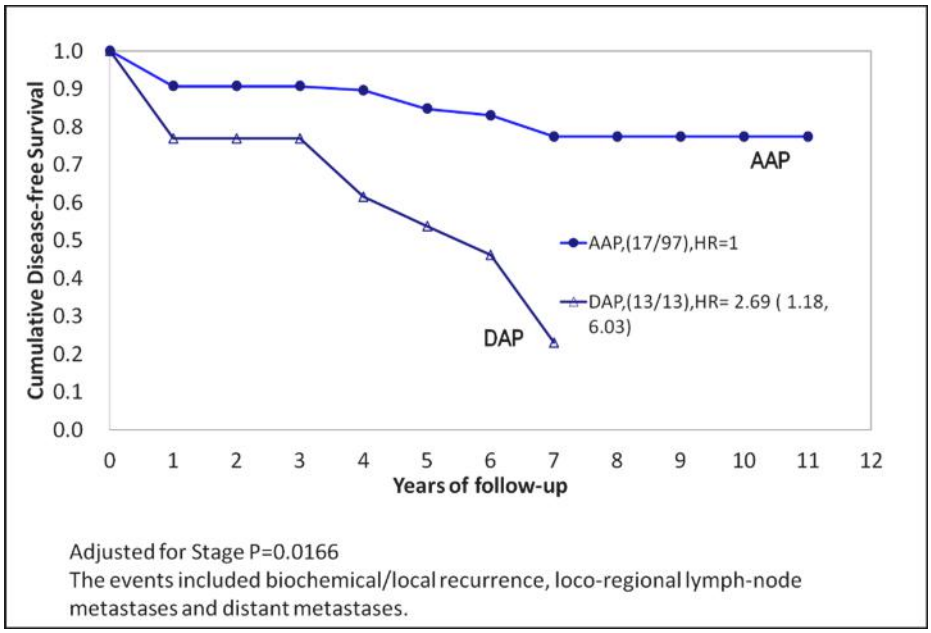


Fig. 7. Cumulative disease-free survival of acinar adenocarcinoma of the prostate (AAP) and ductal adenocarcinoma of the prostate (DAP) in our series of 110 total prostatectomy patients. Reprinted, with permission, from Tabár et al. A Proposal to Unify the Classification of Breast and Prostate Cancers Based on the Anatomic Site of Cancer Origin and on Long-term Patient Outcome. Breast Cancer: Basic and Clinical Research (SAGE) 2014:8, p.16. https://doi.org/10.4137/BCBCR.S13833.

screening began in Dalarna County, Sweden. These prospectively collected and carefully preserved records accumulating over four decades gave us the opportunity to observe that the mammographic tumour features (imaging biomarkers) reflect the underlying normal and abnormal subgross histologic structures, point to the site of tumour origin, and that the malignancies originating from each site are also closely correlated with the long-term patient outcome. As our cases of nonpalpable, primarily screen-detected breast cancers accumulated, it became apparent that the mammographic appearance provided a reliable differentiation between the subtypes arising from the TDLUs and from the major ducts. In contrast, the current histopathological terminology fails to reliably discriminate between the carcinomas originating from the terminal ductal lobular units (TDLUs) and those originating from the major lactiferous ducts. The same term, ductal carcinoma *in situ* (DCIS), is used to describe the accumulation of cancer cells within the TDLUs and within the major lactiferous ducts as if these profoundly different pathological processes were the same disease subtype. Similarly, the invasive carcinomas originating from the TDLUs are erroneously termed invasive ductal carcinoma. The correct description of the site of origin is important from a management and long-term outcome point of view.

We observed that the unifocal stellate and circular breast cancers smaller than 15 mm in diameter originating from the terminal ductal lobular units (TDLUs) were rarely fatal at long-term follow-up. Most of the women with 1–14 mm invasive stellate and circular tumours who died from breast cancer had an associated extensive high-grade carcinoma originating from the major ducts, conventionally termed "DCIS" at microscopic examination. These fatalities led to our recognition of the phenomenon of neoductgenesis, duct-forming invasive carcinoma, in which highly malignant cancer cells originate in the major lactiferous ducts (not in the TDLUs) and produce multiple, branching, cancer-filled duct-like structures, resulting in a massive tumour burden [6]. Neoductgenesis emphasizes the importance of the mammographic appearance of breast cancer as a defining feature of long-term prognosis. In contrast, the histopathologic diagnosis, DCIS, fails to recognize the potentially fatal nature of neoductgenesis by erroneously calling it "*in situ*".

Additionally, the "diffusely infiltrating lobular carcinoma" does not originate from the major lactiferous ducts because the cancer forms layers surrounding and compressing the duct containing entirely normal cells; it does not appear to originate from the TDLU either, since breast cancers originating from the TDLUs have an entirely different imaging

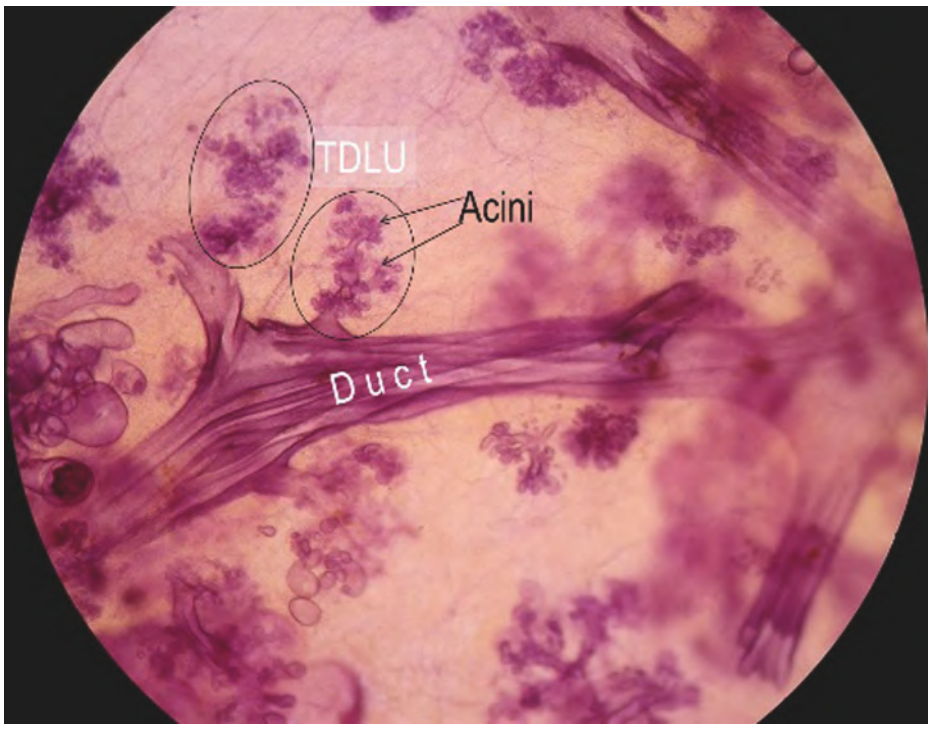


Fig. 8. Thick section histopathology image of normal breast ducts and TDLUs.

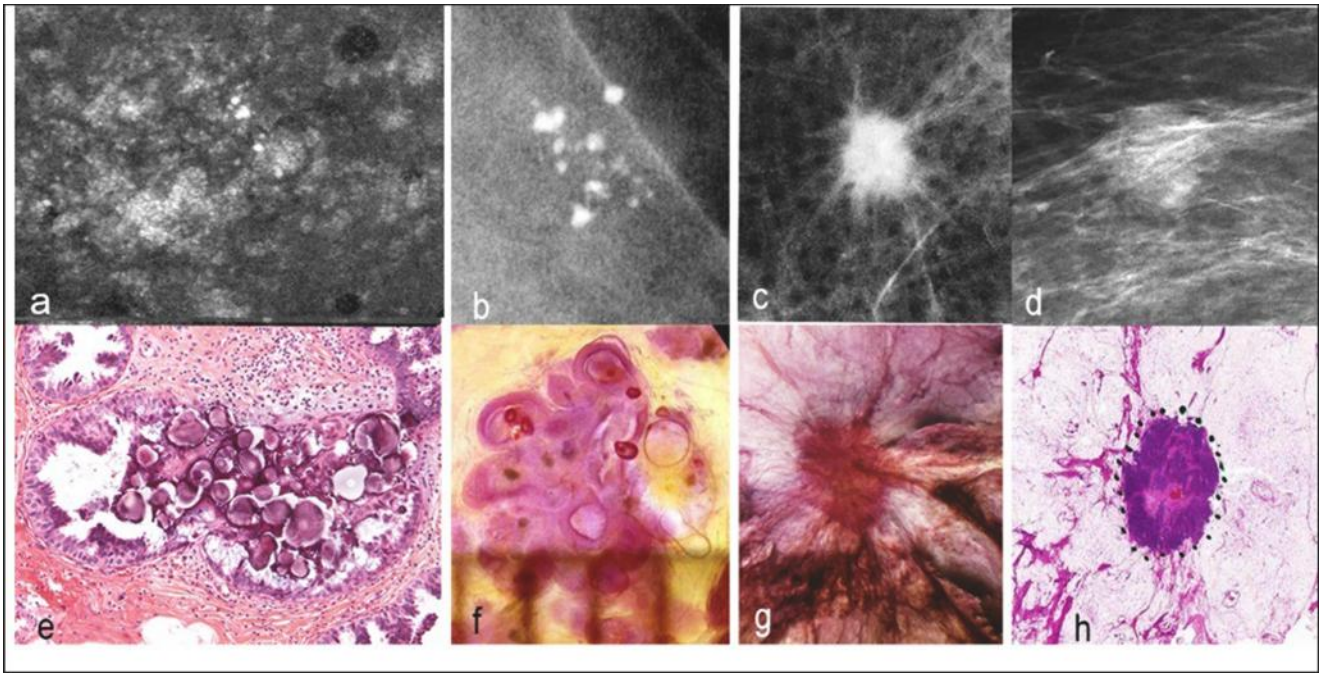


Fig. 9. Mammograms of powdery calcifications (A) and the corresponding histopathology images of psammoma body-like calcifications (E). Mammogram eith crushed stone-like calcifications (B) and the corresponding thick section histopathology image (F). Mammographic and subgross histopathologic appearances of invasive AABs: stellate/spiculated (C,G) and circular/oval-shaped (D,H).

and histopathologic presentation [7,8].

In order to understand why breast cancers have not been historically classified according to their site of origin, we reviewed the evolution of the current breast cancer terminology.

2. Historical review of the evolution of the histopathologic terminology for breast cancer

For most of the 19th century, breast cancers were classified primarily on gross features such as scirrhous, colloid, and medullary, and not on their biologic potential or site of origin. Pathologists often described breast masses simply as “carcinomatous” [9–11]. Warren lamented in

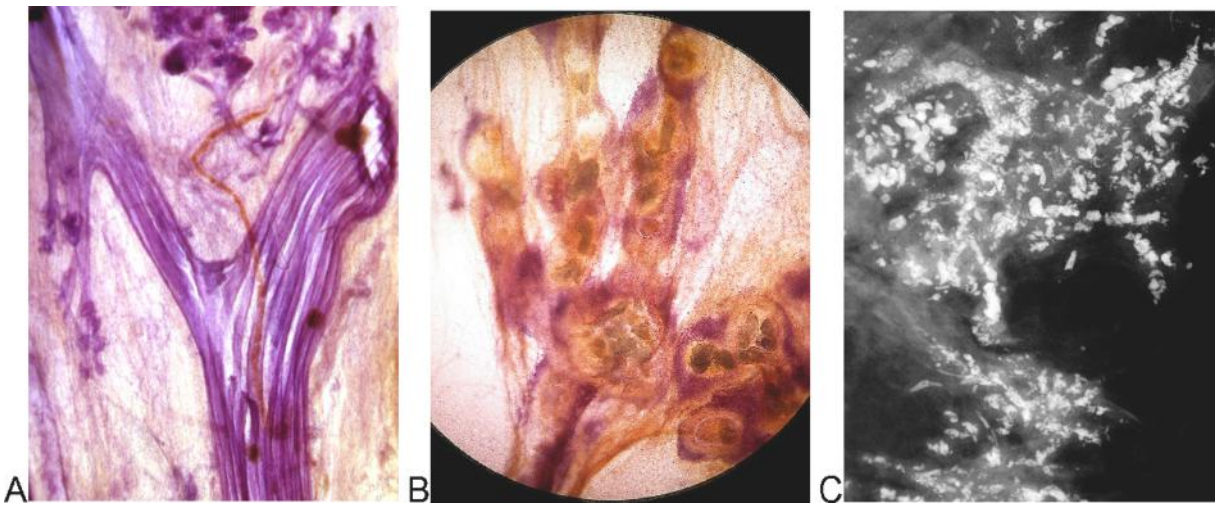


Fig. 10. Subgross, thick section histopathology image of a normal duct (A). Thick section histopathology image of neoducts containing microcalcifications. (B). Mammogram of numerous fragmented casting type calcifications (C).

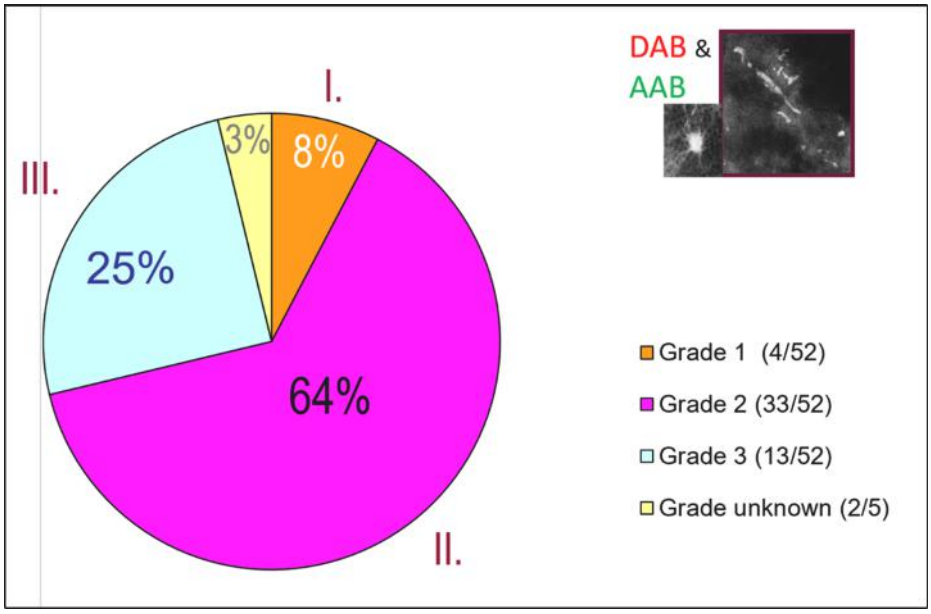


Fig. 11. Distribution of histological malignancy grade of 1–9 mm invasive AABs associated with casting type calcifications in DAB.

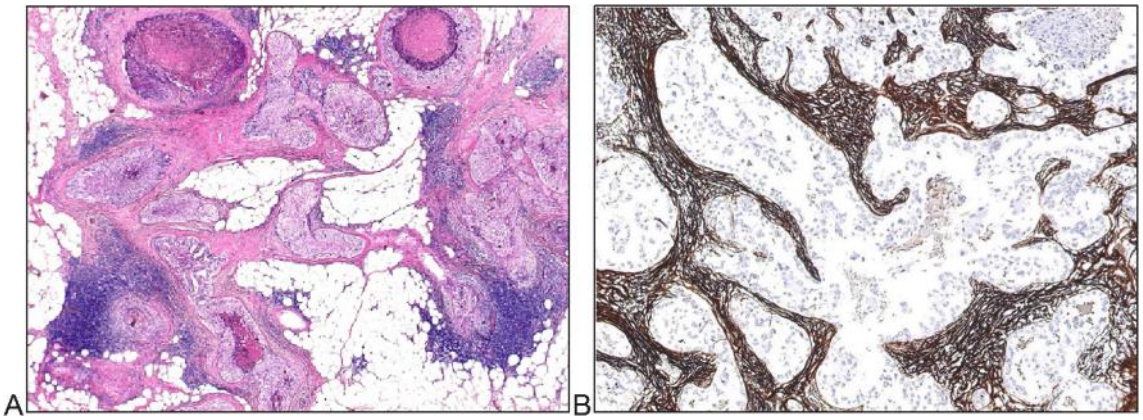


Fig. 12. Large format thin section histopathology image of neoductgenesis (A). Tenascin overexpression is a sign of invasion (B).

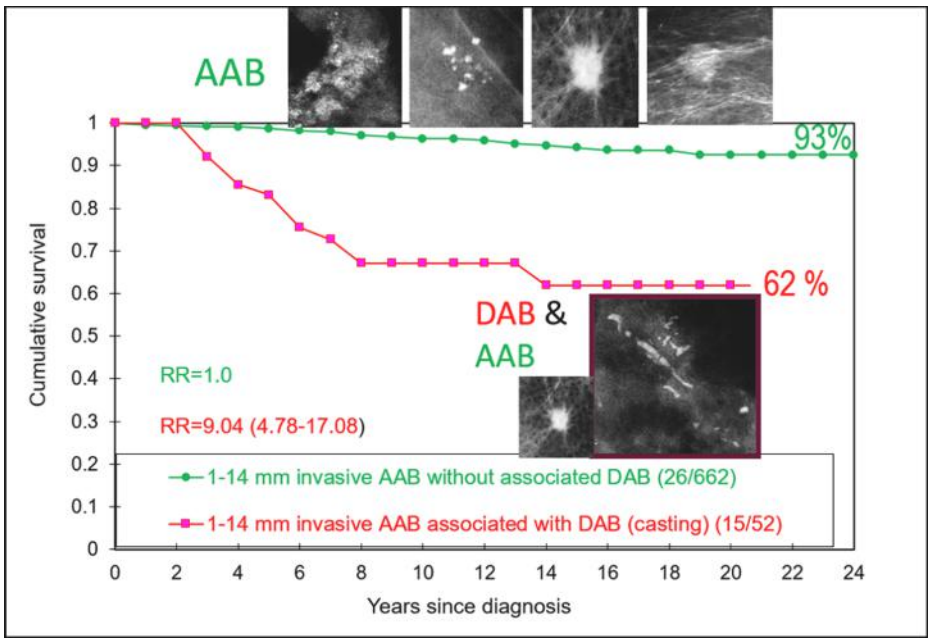


Fig. 13. 24-year cumulative survival of women aged 40–69 years having 1–14 mm invasive AAB but no associated DAB compared with women having 1–14 mm invasive AAB associated with DAB. Consecutive cases diagnosed in women aged 40–69 years in Dalarna County, Sweden.

1905 that [12]: "In no department of surgery has the classification of the diseases of an organ or the pathologic nomenclature been more confusing than in the case of the diseases of the mammary gland."

During the early 20th century there was a growing debate on the classification and origins of breast cancers. Paul, dissatisfied with the classification schemes prevailing in 1914, proposed another classification: "Notwithstanding an immense advance in the knowledge of the evolution and structure of these growths, there has been very little recent change in the nomenclature. If instead of basing the arrangement of breast tumours on their histological structure we named them in accordance with their mode of origin, the classification would be more simple." [13]. He made a clear distinction between acinous and ductal cancers, writing: "Carcinoma, apart from rare exceptions, originates, in my opinion, in the acini or ducts." [13].

Cheatle regarded breast cancers as primarily ductal, but also demonstrated some arising from the lobular acini [14,15]. Substantial confusion in the understanding of the anatomy and pathology of the TDLU was prevalent two decades later. Dawson summarized her view of the role of the TDLU in 1933: "A ductule is a tube-like outgrowth from a terminal duct, forming the "end-piece" of the glandular tissue in the quiescent (non-secreting) mamma. An acinus is the secreting element, lined by a single layer of epithelium, and normally present only during pregnancy and lactation. A lobule is a grouping of the terminal glandular structures of the breast and it may be quiescent or secreting. The quiescent form is composed of ductules, the secreting form of acini." [16].

The term "ductule" is rarely used today, having been replaced by the concept of the TDLU, which includes the terminal duct and lobular acini, whether or not they are actively secreting. Dawson's interpretation of the acini being anatomically and functionally separate from ductules is contrary to the evidence subsequently gained from large format thick section histopathology [17–20]. Thorough studies of the normal TDLUs [21,22] clearly show the presence of acini in non-lactating women (Fig. 1).

Dawson did not consider the acini to be an origin of breast cancer, neither in their secretory phase nor in their non-secretory "ductule" phase: "I have not yet been able to trace the origin of malignant growth in the breast tumours which I have examined to either of these forms of ductule or acinar activity. …The acceptance of these conclusions means the elimination of both acinar and ductule carcinoma from a scheme of classification based on histogenesis, for it designates all carcinoma of the mamma as primarily duct carcinoma. …my main conclusion in this discussion, [is] that all malignant tumours of the breast are, in their initial stages, duct carcinoma, and never either acinus or ductule carcinoma." [16].

Dawson's interpretation that most breast cancers originated in the terminal intralobular duct and should be termed "ductal" became widely accepted, although this blanket descriptor is also applied to cancers arising from anywhere within the duct system. Others, including Muir [23] and Azzopardi [21] continued to consider breast cancer as either intraductal or intra-acinar in origin.

Our own experience with the histologic examination of a large number of nonpalpable breast cancers, a case material that was never available to earlier investigators, has provided considerable evidence that most, approximately 75% of all breast cancers, originate within the acini and/or in the terminal duct of the TDLU. Our proposal is that these cancers be termed acinar adenocarcinoma of the breast (AAB), analogous to the term acinar adenocarcinoma of the prostate and parotid glands (AAP) [24,25]. Fig. 2 represents a typical *in situ* AAB where the cancer has originated in the acini. The current histopathologic term, ductal carcinoma *in situ* (DCIS), incorrectly implies that it originated from the ducts. As we see here, it has originated from the acini.

Foote and Stewart, in a report on lobular carcinoma *in situ* a few years later added to the confusion: "One is much less apt to think of carcinoma *in situ* as a disease of small lobular ducts and lobules. The latter process is relatively rare. … We have not as yet observed a mammary cancer which in our opinion might properly be considered acinar cancer. It is largely a question of terminology. We do not feel that we can draw sharp lines between terminal ducts and acini. We prefer to regard the acinus as a structure which develops during lactation and which thus constitutes a physiologic phase rather than an anatomic entity. It is to avoid confusion that we employ the term 'lobular carcinosis *in situ*.'" [26].

It is unfortunate for the succeeding generations of pathologists that Foote and Stuart contributed to the entrenchment of the current ductal-lobular dichotomy, not because of a clear and unambiguous understanding of the origins of breast cancer subtypes, but through misinterpretation of basic anatomic details and function of the TDLU.

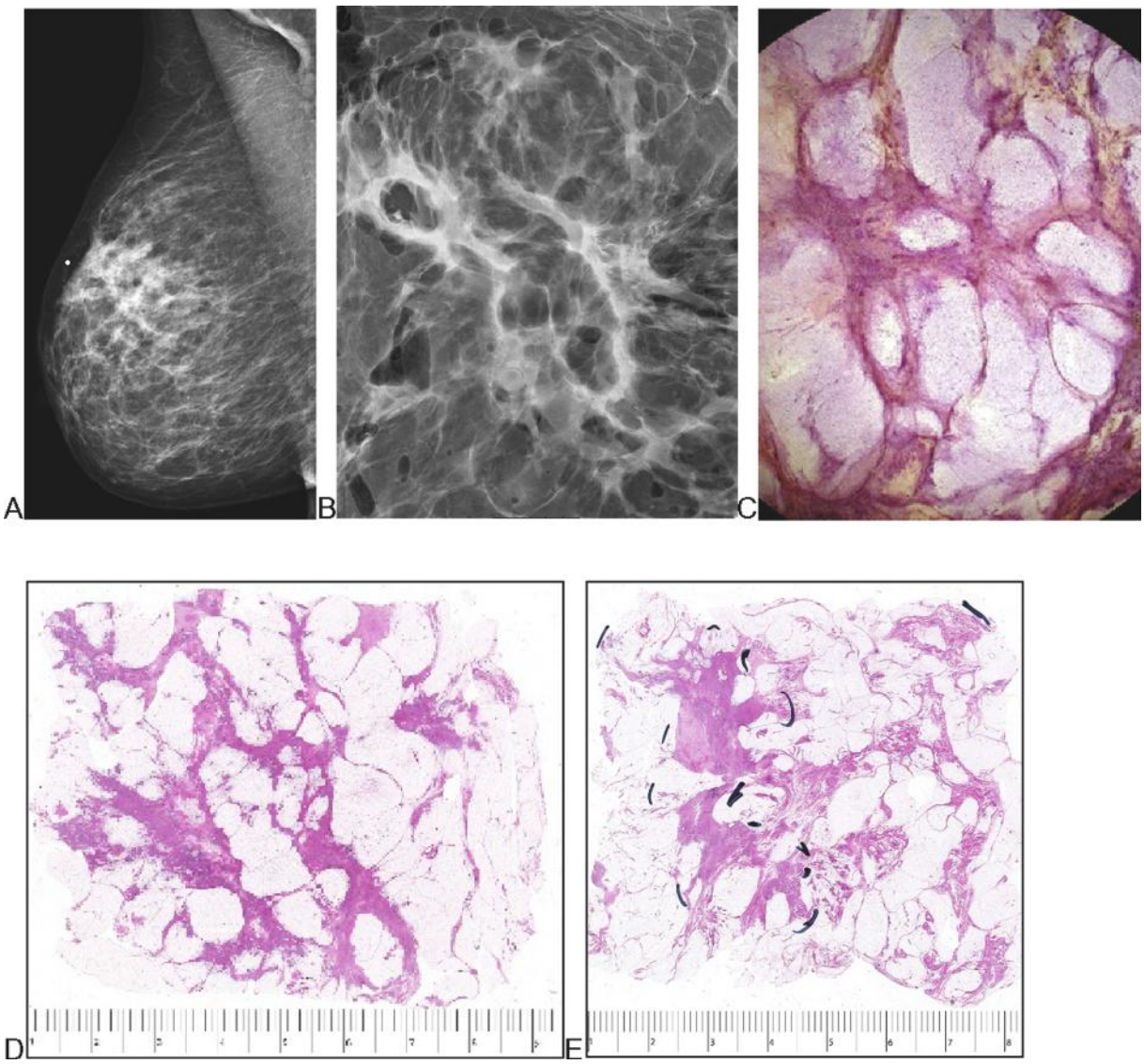


Fig. 14. Right breast, MLO projection (A). Microfocus magnification of one of the mastectomy specimen slices (B) and the corresponding subgross, thick section (C) and thin section (D, E) histopathology images of a diffusely infiltrating breast cancer of possible mesenchymal origin.

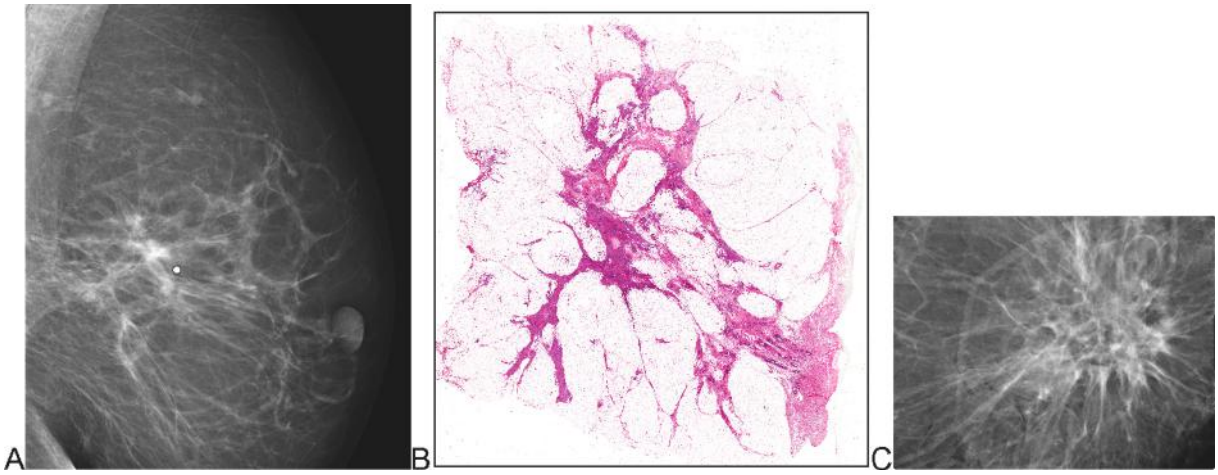


Fig. 15. Left breast, MLO projection (A) of a diffusely infiltrating breast cancer of possible mesenchymal origin, 8 cm in extent, with corresponding subgross, thin section histopathology image (B). Microfocus magnification of the surgical specimen slice (C).

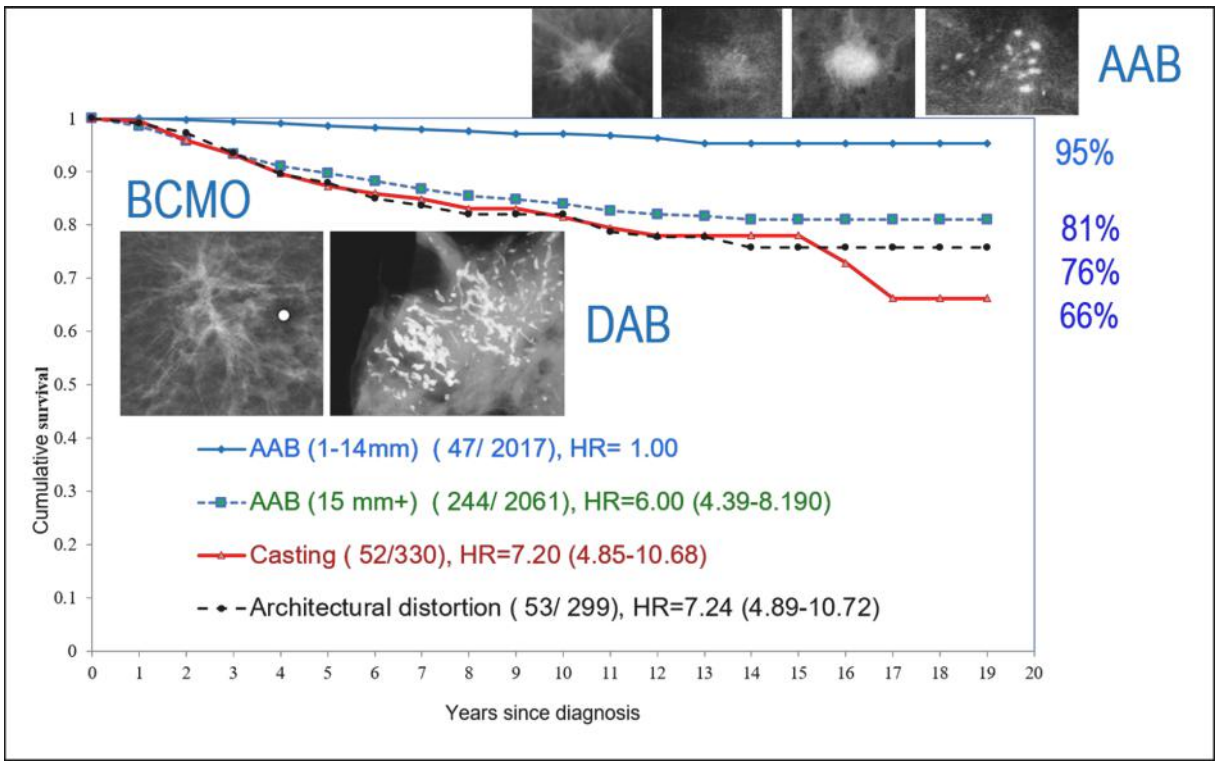


Fig. 16. Long-term cumulative survival of 4707 breast cancer cases classified according to the site of origin.

As Azzopardi stated: "…the notion of ductal carcinoma, with lobular participation excluded, became generally accepted. Once this erroneous belief was firmly entrenched in the literature and in the minds of pathologists it became so sanctified by tradition that it needed the elegant and exhaustive study of Wellings, Jensen and Marcum (1975) to demolish it convincingly." [21].

Wellings and Jensen published their subgross, thick section histopathology work on the origins of carcinoma *in situ* [27,28]. As Azzopardi emphasized, "The 'subgross pathology' method of Wellings, Jensen and Marcum is a simple and ingenious extension of the use of a very low magnification." [21]. Their work documents the origin of "ductal" carcinoma *in situ* in the terminal ductal lobular unit and shows how the acini, greatly distorted with carcinoma, can mislead the unwary pathologist into thinking they are viewing ducts in conventional 2-dimensional histologic sections. Jensen wrote: "Disease processes such as hyperplasias and neoplasia alter the terminal ductal-lobular units to such a degree that conventional light microscopic appearances make the structures appear as though they were ducts. However, the basic microarchitecture in three dimensions is preserved, proving the origin of cancer is the terminal ductal-lobular unit." [28].

These earlier efforts to classify breast cancer according to the site of origin were hampered by the lack of a sufficient number of cases in their early phases of development. As Dawson wrote, "…the majority of patients with breast lesions are first seen at a stage when malignant growth has extended considerably beyond the site of origin, and has, to a large extent, destroyed or obscured the normal mammary structure. …It seems also to lie behind the present unsatisfactory classification of breast tumours and the numerous terms in use in mammary pathology." [16].

Also the exhaustive studies of Wellings' group were seriously limited by their source material which included only 29 mastectomy specimens with breast cancer [17].

3. The concept of breast cancer originating from the major lactiferous ducts (comedocarcinoma) with no acinar involvement

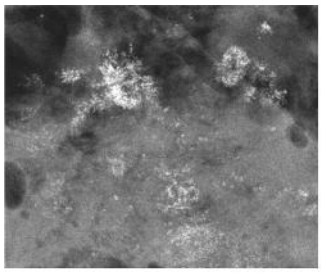
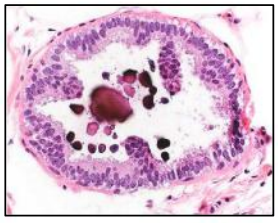
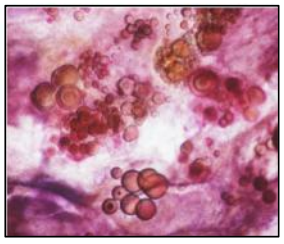
In 1908 Bloodgood used the term "duct cancer" and "comedo-adenocarcinoma" for tumours originating from the major lactiferous ducts and not having acinar involvement [29,30]. Others, including Muir [23] and Dawson [31], noted similar findings. Our large format thick and thin section histopathology images (Fig. 3) confirm Bloodgood's observations and show cancer-filled major ducts with accompanying normal TDLUs. This provides important evidence that there is a well-defined breast cancer subgroup, accounting for about 20% of all breast cancers, that originates from the major lactiferous ducts and not from the TDLUs. This subgroup, having the prominent feature of neoductgenesis, should be called ductal adenocarcinoma of the breast (DAB), analogous to ductal adenocarcinoma of the prostate and parotid glands (DAP).

4. Origins of the concept and terminology of invasive lobular carcinoma

Foote and Stewart also described a morphologically distinct form of invasive carcinoma which they believed to arise from the lobules (acini) but did not call it invasive lobular carcinoma. Instead, they wrote "Since distension of the lobule does not assume marked proportions prior to infiltration, some other factor must be invoked to explain the mass eruption of tumor cells. We suspect some lytic action of the tumor cells, naturally not to be detected by anatomic study. The question has arisen as to whether tumors of this type deserve the designation of "acinar" carcinoma. We have not as yet observed a mammary cancer which in our opinion might properly be considered acinar cancer." [26].

Despite the reluctance by Foote and Stewart to commit to the terminology of an invasive breast carcinoma of acinar origin, Ackerman and del Regato, in a standard textbook of surgical pathology and oncology, included in a classification of breast cancers an invasive form

Table 1a
Correlation of the apparent site of origin of breast cancer and the proposed new terminology with the dominant radiological appearance, the corresponding BI-RADS term, the currently used histopathologic terminology and disease distribution.

Apparent site of origin **Proposed terminology**	**Dominant radiological appearance** and the *corresponding BI-RADS term*	**Currently used histopathologic terminology**	**Unifocal, multifocal or diffuse**
Acinar / terminal duct. Grade 1 carcinoma *in situ* within the TDLU, **A**cinar **A**denocarcino-ma of the **B**reast (**AAB)**	**Powdery calcifications**  *Corresponding BI-RADS term: "Amorphous" calcifications".* NOTE: the term "amorphous" (Having no definite shape or form) is misleading because pathologists use it to describe calcifications arising within central necrosis (e.g., in Grade 2 or 3 "comedocarcinoma"). The powdery calcifications correspond to psammoma body-like crystals floating in the proteinaceous fluid the low-grade cancer cells have produced (see the accompanying thin and thick section histopathology images.	Grade 1 "**ductal"** carcinoma *in situ,* DCIS.  An acinus distended by the fluid produced by cancer cells with micropapillary tumour growth pattern.  3D histopathology images of the psammoma body-like crystals. Their summation is seen on the mammogram as powdery, cotton ball-like calcifications.	Multifocal

of lobular carcinoma arising from acinar epithelium and representing approximately 5% of all cancers [32]. Once established, invasive lobular carcinoma terminology was further cemented by the descriptions of Azzopardi, Newman, McDivitt, Stewart and Berg, and Fechner [21,33–35].

The large number of nonpalpable breast cancers detected at mammography screening has provided the quantity of early breast cancers needed for a search for the sites of breast cancer origin.

We have used the Dalarna County database as a rich source of prospectively collected cases necessary for correlating the breast imaging findings of thousands of early-stage breast cancers (*in situ* and 1–14 mm invasive acinar adenocarcinomas) and several hundred cases of diffusely invasive breast cancers with large format thin section histopathology. In 962 cases we also used the large format, subgross, thick section, 3-D histopathology technique, modified from Wellings [17,36]. In order to enable a direct comparison of the normal and abnormal breast tissue structure with the thick section histopathology images at a similar image resolution, microfocus magnification of the mammograms and specimen radiographs were used. Both methods demonstrate fine structural details as well as their alterations by benign and malignant breast diseases without showing cellular details [36,37].

Current breast cancer terminology, which is largely based on cellular features, does not correctly reflect the anatomic structures from which most breast cancers originate. Subgross, thick section histopathology images help bridge the gap between the appearance of breast cancer at preoperative imaging and its appearance on thin section histopathology and has provided crucial visual evidence for the apparent sites of origin of breast cancer subtypes.

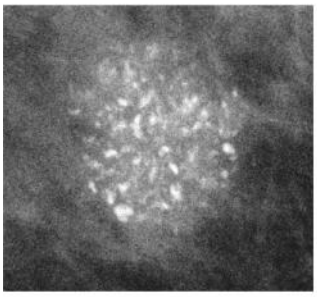
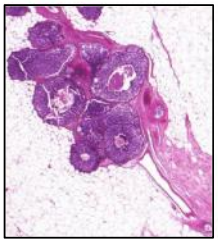
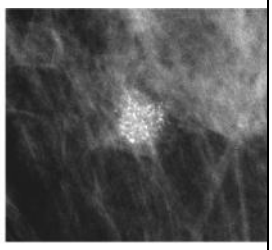
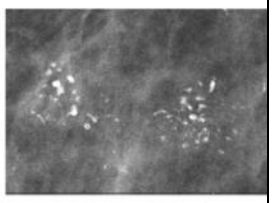
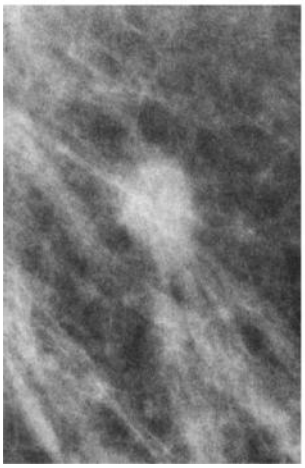
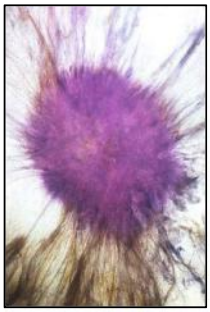
Using the large format, subgross, thick section histopathology technique, Jensen et al. concluded that "ductal carcinoma *in situ* of the human breast is of lobular origin. Progressive distension of ductules [acini] with dysplastic and anaplastic cellular elements leads to unfolding and coalescence of the ductules [acini] within the lobule to form larger ovoid structures. Such lesions falsely appear to be small ducts in conventional histology slides." [38].

Subgross, thick section histopathology images demonstrate the structure of *in situ* carcinoma developing within the TDLUs as described by Jensen et al. [38] (Fig. 4).

The failure to take heed of Jensen and Wellings' warning has resulted in breast cancers of both ductal and TDLU origin being termed "ductal", despite their vastly differing macroscopic structure and clinical outcome. This provides another example of the need for a new approach to breast cancer terminology based on the site of tumour origin.

Determination of the apparent site of tumour origin using imaging biomarkers is an innovative approach to understanding breast cancer biology.

Table 1b
Correlation of the apparent site of origin of breast cancer and the proposed new terminology with the dominant radiological appearance, the corresponding BI-RADS term, the currently used histopathologic terminology and disease distribution.

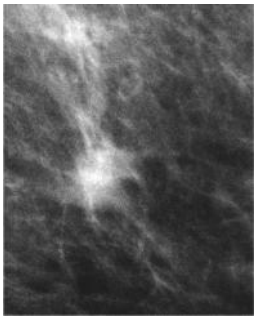
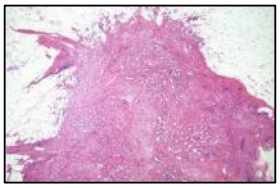
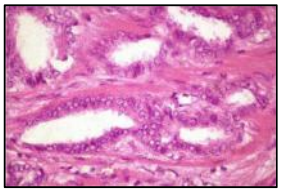
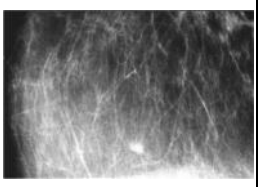
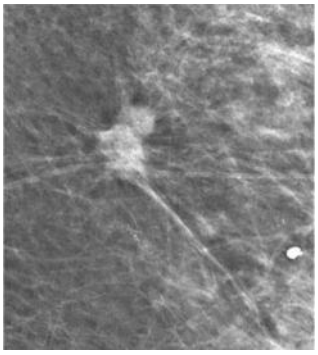
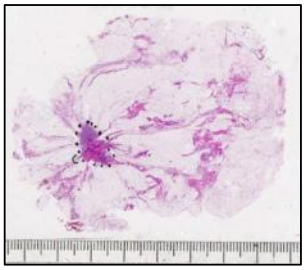
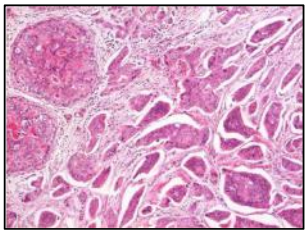
Apparent site of origin **Proposed terminology**	**Dominant radiological appearance** and the *corresponding BI-RADS term*	**Currently used histopathologic terminology**	**Unifocal, multifocal or diffuse**
Acinar / terminal duct. Grade 2 carcinoma cells within the TDLU, **AAB** Grade 2 CIS.	**Cluster(s) of crushed stone-like calcifications**  *Corresponding BI-RADS terms: Coarse heterogeneous, fine pleomorphic calcifications*	Grade 2 DCIS "**Ductal**" carcinoma *in situ*  The acini of a single terminal ductal lobular unit (TDLU) are distended by Grade 2 cancer cells.	Unifocal or multifocal  
Acinar / terminal duct. Well / moderately differentiated invasive **AAB,** NST (no special type)	**Stellate**  *Corresponding BI-RADS term: Spiculated.*	Well or moderately differentiated invasive "**ductal**" carcinoma, NST. 	Unifocal *or* Multifocal

During the continuous evaluation of the Dalarna County mammography screening program, we noted the strong prognostic value of the mammographic tumour features of breast cancer (imaging biomarkers) [39]. It also became apparent that certain histopathology terms and prognostic factors did not reliably predict the long-term outcome of women who, by the prevailing standards, would be characterized as having infiltrating "ductal" carcinomas smaller than 15 mm. Women with unifocal infiltrating "ductal" breast cancer smaller than 15 mm without an associated high grade "DCIS component" had an extremely good prognosis; on the other hand, women with smaller than 15 mm infiltrating "ductal" carcinomas, having similar tumour characteristics, who also had casting type calcifications caused by an associated high grade "DCIS component", had a high fatality rate. We concluded that the extensive and supposedly "*in situ*" component must be responsible for the high fatality rates [6,40]. The use of the large format thick section histopathology technique and Tenascin staining were key to elucidating this dilemma by revealing that the associated "DCIS" was in reality a duct forming invasive carcinoma (neoductgenesis) [6,41]. It is unfortunate that the prevailing histopathology criteria fail to identify the fatal component, calling it "DCIS" and thus not life-threatening, despite the fact that the disease is often extensive, high grade, and highly fatal.

The development of our new breast cancer classification based on the apparent site of tumour origin is supported by correlation with long-term patient outcome and was modelled after the terminology of prostate cancer

We arrived at our proposed new approach to breast cancer terminology during our comprehensive study of total prostatectomy specimens from 110 prostate cancer patients using large format thick and thin section histopathology [24,25]. Fig. 5 illustrates the obvious similarity in appearance of the prostate specimens to the normal anatomy and to

Table 1c
Correlation of the apparent site of origin of breast cancer and the proposed new terminology with the dominant radiological appearance, the corresponding BI-RADS term, the currently used histopathologic terminology and disease distribution.

Apparent Site of Origin **Proposed terminology**	**Dominant radiological appearance** and the *corresponding BI-RADS term*	**Currently used histopathologic terminology**	**Unifocal, multifocal or diffuse**
Acinar / terminal duct. Invasive **AAB**, tubular type	**Stellate/spiculated**  *Corresponding BI-RADS term: Spiculated*	Tubular  	Unifocal or Multifocal 
Acinar / terminal duct Invasive **AAB**, micropapillary type	**Stellate/spiculated**  *Corresponding BI-RADS term: Spiculated*	Invasive micropapillary carcinoma  	Unifocal or Multifocal

the hyperplastic and malignant lesions of the breast.

The terminology used to describe prostate cancer is logical in that it takes the anatomic site of origin into account, using the terms *acinar adenocarcinoma of the prostate* (AAP) to describe prostate cancers originating from the fluid producing acini. Cancer originating in the major ducts of the prostate is termed *ductal adenocarcinoma of the prostate* (DAP) or prostatic ductal adenocarcinoma [42] (Fig. 6). Occasionally DAP is called "intraductal carcinoma of the prostate", an error similar to calling DAB "DCIS".

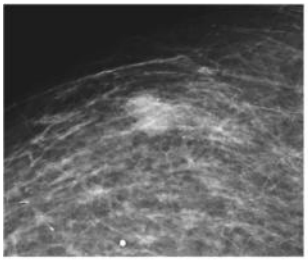
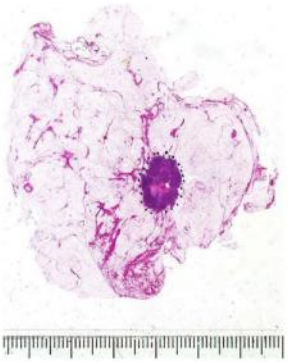
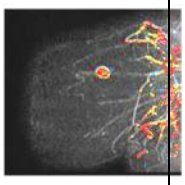
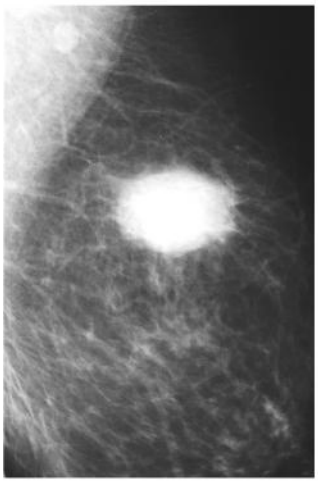
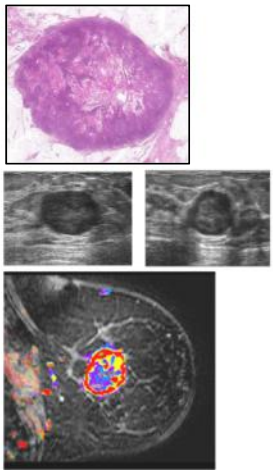
The clinical importance of using a terminology describing the site of origin of prostate and breast cancer also comes from the close correlation of this terminology with long-term patient outcomes. Patients with DAP have a significantly poorer prognosis than patients with AAP [43–45] (Fig. 7).

Similar nomenclature based on the site of cancer origin is used for describing cancers of the parotid gland, where the similarity of the aggressive form of parotid cancer to that of breast cancer of ductal origin has been noted [46]. Salivary duct carcinoma is one of the most aggressive of the salivary gland carcinomas, and phenotypically resembles high-grade ductal breast carcinoma, with comedo-type necrosis and calcification [47]. Despite the well-known similarity between the structure and function of the breast and prostate, there are fundamental differences in the terminology describing breast and prostate cancers. Using the large format, subgross, thick section histopathology technique, we developed a new approach to breast cancer terminology that is similar to the *logical* terminology used for describing prostate cancer.

Fig. 8 demonstrates the 3D images of a major lactiferous duct and associated TDLUs with supporting connective tissue.

Our correlative imaging-large format thick section histopathology studies provided new insights to the century-old debate on breast cancer

Table 1d
Correlation of the apparent site of origin of breast cancer and the proposed new terminology with the dominant radiological appearance, the corresponding BI-RADS term, the currently used histopathologic terminology and disease distribution.

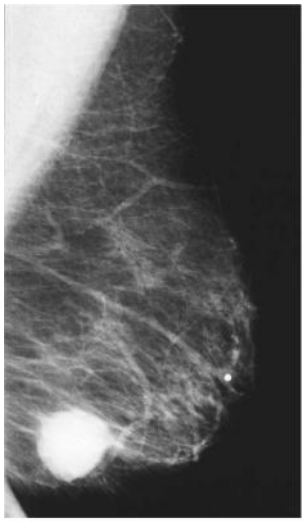
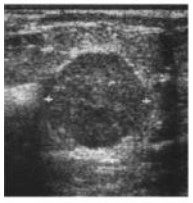
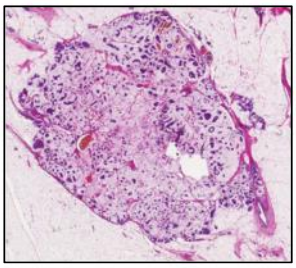
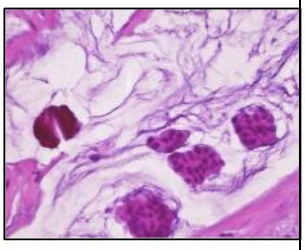
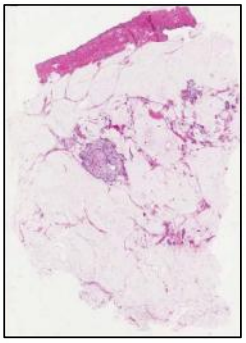
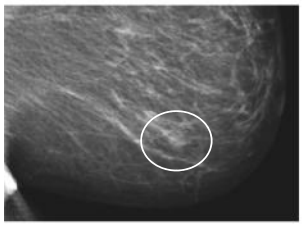
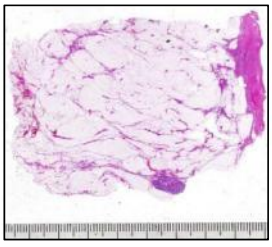
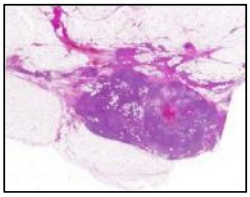
Apparent site of origin **Proposed terminology**	**Dominant radiological appearance** and the *corresponding BI-RADS term*	**Currently used histopathologic terminology**	**Unifocal, multifocal or diffuse**
Acinar / terminal duct Poorly differentiated invasive **AAB**, NST	**Circular or oval**  *Corresponding BI-RADS term: Includes Round, Oval, Circumscribed, Microlobulated*	Poorly differentiated invasive "**ductal**" carcinoma, NST 	Unifocal or Multifocal 
Acinar / terminal duct. Poorly differentiated, basal cell-type, triple negative invasive AAB	**Circular or oval**  *Corresponding BI-RADS term: Includes Round, Oval, Circumscribed, Microlobulated*	Invasive "**ductal"** carcinoma, triple negative / basal cell type  Multimodal demonstration	Unifocal or Multifocal

developmental anatomy, resulting in a new approach to morphological classification based on the following three apparent sites of origin of breast cancer subtypes.

This paradigm shift in breast cancer terminology is proposed as follows:

I. Breast cancers arising from the TDLU should be termed acinar adenocarcinoma of the breast, AAB. Fig. 9 shows mammographic and subgross, thick section histopathologic images of the four imaging presentations of *in situ* and invasive breast cancers developing in the TDLU (s). Grade 1 *in situ* AAB developing from the acini has the characteristic imaging biomarkers of multiple clusters of powdery calcifications on the mammogram, corresponding to the accumulation of psammoma body-like calcifications floating in the proteinaceous fluid produced by the Grade 1 cancer cells of the acini. Grade 2 *in situ* AAB developing from the acini has the characteristic imaging biomarkers of a single cluster or multiple clusters of crushed stone-like, pleomorphic calcifications on the mammogram. The Grade 2 *in situ* AAB cancer cells undergo necrosis, forming the amorphous microcalcifications in the central portion of the distended acini. Invasive AAB has two mammographic and subgross histopathologic appearances: stellate/spiculated and circular/oval-shaped, both of which also originate from the TDLU. These *in situ* and invasive cancers are currently termed "ductal" carcinoma *in situ* (DCIS)

Table 1e
Correlation of the apparent site of origin of breast cancer and the proposed new terminology with the dominant radiological appearance, the corresponding BI-RADS term, the currently used histopathologic terminology and disease distribution.

Apparent site of origin **Proposed terminology**	**Dominant radiological appearance** and the *corresponding BI-RADS term*	**Currently used histopathologic terminology**	**Unifocal, multifocal or diffuse**
Acinar / terminal duct. Invasive **AAB**, mucinous type	**Circular or Oval**   Ultrasound *Corresponding BI-RADS term: Includes Round, Oval Circumscribed, Microlobulated*	Mucinous carcinoma   Low and high power histopathology images of mucinous carcinoma of the breast.	Unifocal or multifocal  Multifocal mucinous carcinoma
Acinar / terminal duct. Invasive **AAB**, solid lobular type	**Circular or Oval**  *Corresponding BI-RADS term: Includes Round, Oval Circumscribed, Microlobulated*	Invasive lobular (solid type) 	Unifocal or multifocal 

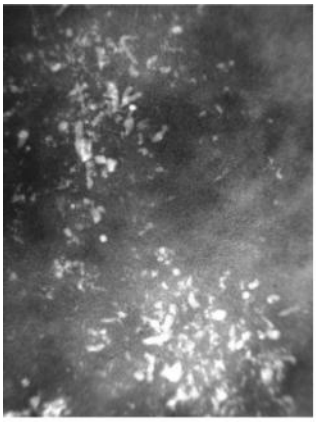
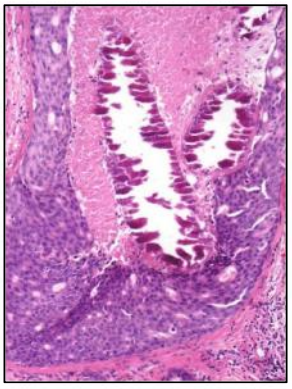
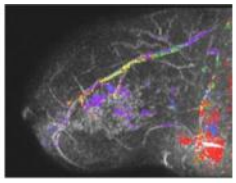
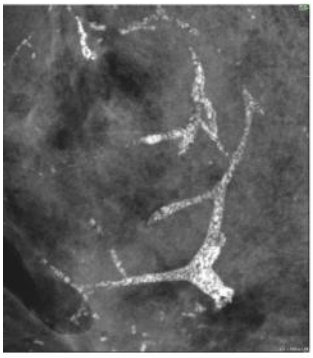
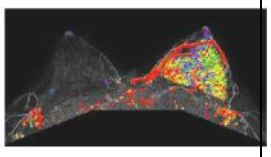
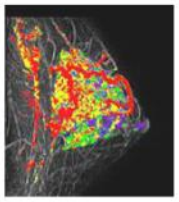
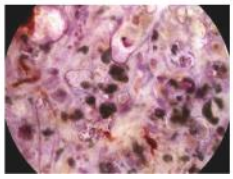
and invasive "ductal" carcinomas, terms which are misnomers, and are misleading and anatomically incorrect [48].

II. Breast cancers originating in the major lactiferous ducts should be termed ductal adenocarcinoma of the breast, DAB, reflecting the anatomic site of origin. Fig. 10 compares a normal duct and its associated TDLUs with cancer-filled, distended neoducts lacking associated TDLUs and having numerous fragmented casting type calcifications. These calcifications are one of the mammographic presentations of neoductgenesis.

The cancer cells originating from the lactiferous ducts distend and distort the normal ductal structure; in addition, the newly formed, tightly packed, cancer-filled duct-like structures have a massive tumour burden. This phenomenon of newly formed ducts has been termed neoductgenesis, [5 37] which acts as a duct-forming, poorly differentiated invasive carcinoma, accounting for the associated high fatality rate, especially when breast cancer of ductal origin (DAB) is combined with invasive breast cancer of acinar origin (AAB). Although the cancer cells within the neoducts are predominantly Grade 3, it is noteworthy that the majority (64%) of the associated invasive AABs are moderately differentiated (Fig. 11).

The newly formed duct-like structures are surrounded by

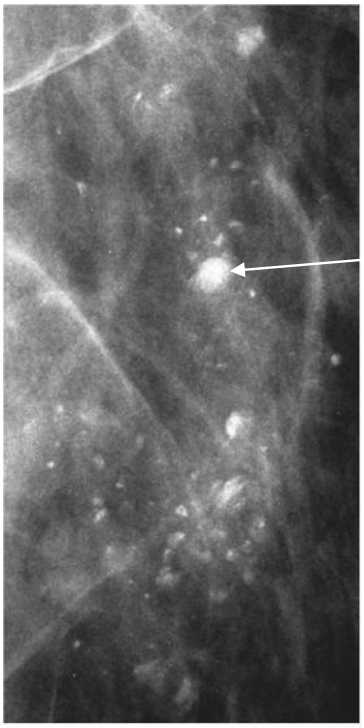
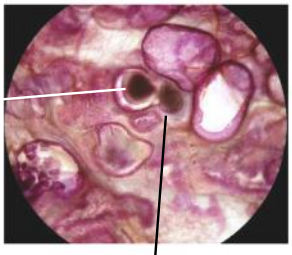
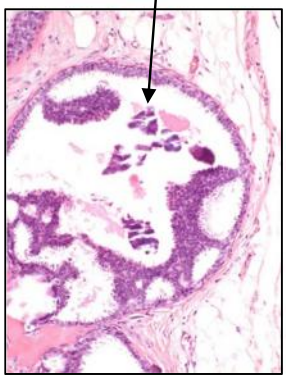
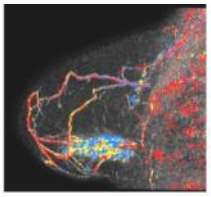
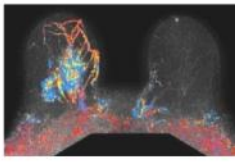
Table 1f
Correlation of the apparent site of origin of breast cancer and the proposed new terminology with the dominant radiological appearance, the corresponding BI-RADS term, the currently used histopathologic terminology and disease distribution.

Apparent site of origin. **Proposed terminology**	**Dominant radiological appearance** and the *corresponding BI-RADS term*	**Currently used histopathologic terminology**	**Unifocal, multifocal or diffuse**
Major lactiferous ducts. Ductal Adenocarcinoma of the Breast, **DAB with necrosis.** Neoductgenesis.	**Fragmented casting type calcifications**  *Corresponding BI-RADS term: Fine linear, fine linear branching calcifications*	**Ductal** carcinoma "*in situ*" (DCIS), Grade 3, with or without "microinvasion". Predominantly solid tumour growth pattern. 	Diffuse, lobar distribution  MRI showing the lobar distribution of DAB.  Low power histopathology image of DAB, neoductgenesis.
Major lactiferous ducts. **D**uctal **A**denocarcinoma of the **B**reast, **DAB** with necrosis. **Neoductgenesis**	Dotted casting type calcifications  *Corresponding BI-RADS term: No equivalent term*	Ductal carcinoma "*in situ*" (DCIS), Grade 3, with or without "microinvasion", predominantly micropapillary tumour growth pattern with necrosis. **NOTE:** The immunohistochemical biomarkers are not routinely determined from the cells within the ducts due to the erroneous assumption that this malignancy is an in situ process. However, when determined, the high-grade cells within the ducts are predominantly HER2 positive, and this result should be available to influence patient	Diffuse, lobar distribution   MRI 

lymphocytic infiltration and tenascin rich desmoplastic stroma containing cancer associated fibroblasts (CAF), which are considered to be the result of epithelial-mesenchymal transition (EMT). The tenascin overexpression is evidence for epithelial cell intrusion into the surrounding stroma [49–51], resulting in the formation of new, invasive, duct-like structures filled with carcinoma cells (Fig. 12).

Breast cancers originating from the major ducts (DAB) have considerable differences in their histopathologic structure and mammographic presentation compared with the breast cancers originating from the TDLUs (AAB), and also have a significantly different long-term outcome. As in prostate cancer, breast cancers of apparent TDLU origin have a better prognosis than those of apparent ductal origin [41,43,52–54]. Fig. 13 shows 24-year cumulative survival of women aged 40–69 years having 1–14 mm invasive AAB but no associated DAB compared with women having 1–14 mm invasive AAB associated with DAB. The poor long-term survival appears to be caused by the DAB

Table 1g
Correlation of the apparent site of origin of breast cancer and the proposed new terminology with the dominant radiological appearance, the corresponding BI-RADS term, the currently used histopathologic terminology and disease distribution.

Apparent site of origin. **Proposed terminology**	**Dominant radiological appearance** and the *corresponding BI-RADS term*	**Currently used histopathologic terminology**	**Unifocal, multifocal or diffuse**
Major lactiferous ducts Ductal Adenocarcinoma of the Breast, **fluid producing DAB,** with calcifications suspended in the viscous fluid. Neoductgenesis.	**Skipping stone-like calcifications.**  *Corresponding BI-RADS term: No equivalent term*	**Ductal** carcinoma *in situ* (DCIS), Grade 2-3, with or without "microinvasion", predominantly micropapillary tumour growth pattern **with fluid production.**   Micropapillary tumour growth patten with flat stone-like, skipping stone-like calcifications.	Diffuse, lobar distribution   Breast MRI images show the diffuse, lobar distribution of this fluid producing DAB.
NOTE: The immunohistochemical biomarkers are not routinely determined from the cells within the ducts due to the erroneous assumption that this malignancy is an *in situ* process. However, when determined, the high-grade cells within the ducts are predominantly HER2 positive, and this result should be available to influence patient management. Unfortunately, the biomarkers are routinely determined only from an associated invasive AAB, but not from the potentially fatal duct forming invasive carcinoma, the DAB component.			

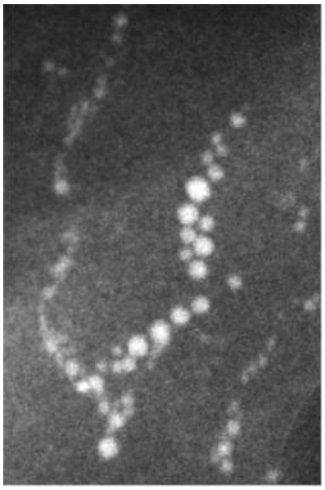
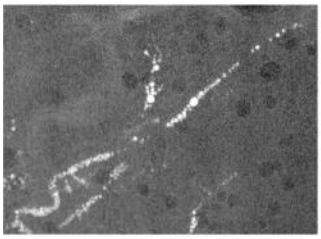
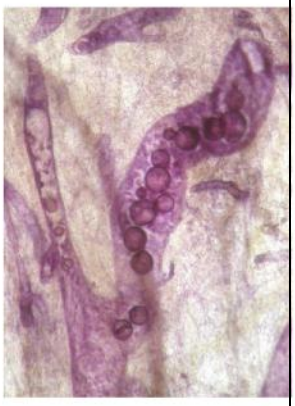
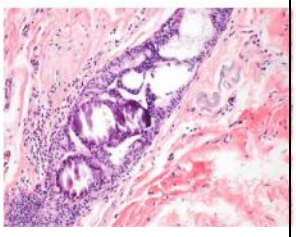
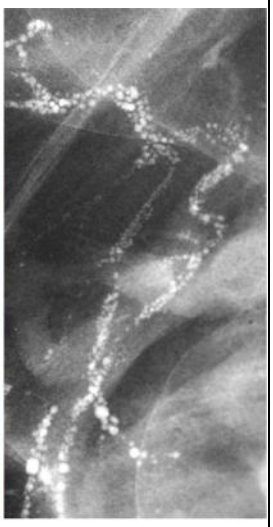
NOTE: The immunohistochemical biomarkers are not routinely determined from the cells within the ducts due to the erroneous assumption that this malignancy is an *in situ* process. However, when determined, the high-grade cells within the ducts are predominantly HER2 positive, and this result should be available to influence patient management. Unfortunately, the biomarkers are routinely determined only from an associated invasive AAB, but not from the potentially fatal duct forming invasive carcinoma, the DAB component.

component.

iii Breast cancer arising from the stem cells of the mesenchyme through mesenchymal-epithelial transition (MET) should be termed breast cancer of mesenchymal origin, BCMO.

This remaining 5–8% of all breast cancers, conventionally termed diffusely infiltrating lobular carcinoma, has features deviating considerably from the features of breast cancers originating from the TDLUs or the major lactiferous ducts. This malignancy usually presents with a palpable thickening in the breast, is extensive at the time of diagnosis, and is difficult to detect mammographically and remove surgically with clean margins. The fatality rate exceeds 30–40% [7,55]. This breast cancer subtype is characterized by an excess amount of fibrous connective tissue, which accounts for the clinical, mammographic and histopathologic findings. These features led us to propose that it may have a mesenchymal origin through the complex process of mesenchymal epithelial transition (MET) of the mesenchymal stem cells.

Table 1 h
Correlation of the apparent site of origin of breast cancer and the proposed new terminology with the dominant radiological appearance, the corresponding BI-RADS term, the currently used histopathologic terminology and disease distribution.

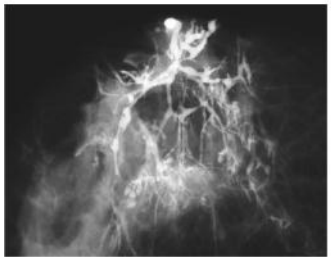
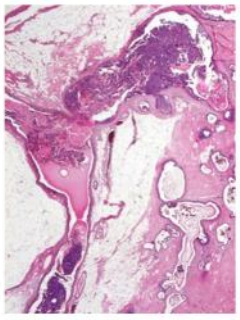
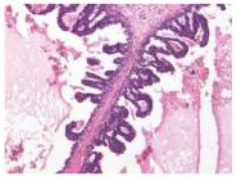
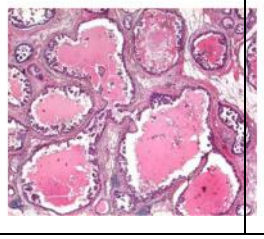
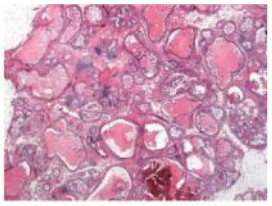
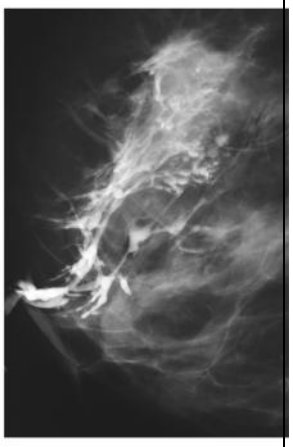
Apparent site of origin **Proposed terminology**	**Dominant radiological appearance** and the *corresponding BI-RADS term*	**Currently used histopathologic terminology**	**Unifocal, multifocal or diffuse**
Major lactiferous ducts. Ductal Adenocarcinoma of the Breast, **fluid producing DAB,** with calcifications suspended in the fluid. Neoductgenesis.	**String of pearl-like calcifications**   *Corresponding BI-RADS term: No equivalent term*	**Ductal** carcinoma "*in situ*" (DCIS), Grade 1-2, with or without "microinvasion", predominantly cribriform tumour growth pattern.   Low grade carcinoma cells associated with unusually large psammoma body-like calcifications within a major duct. These appear on the mammograms as a string of pearls.	Diffuse, lobar distribution 
NOTE: The immunohistochemical biomarkers are not routinely determined from the cells within the ducts due to the erroneous assumption that this malignancy is an in situ process. However, when determined, the high-grade cells within the ducts are predominantly HER2 positive, and this result should be available to influence patient management. Unfortunately, the biomarkers are routinely determined only from an associated invasive AAB, but not from the potentially fatal duct forming invasive carcinoma, the DAB component.			

NOTE: The immunohistochemical biomarkers are not routinely determined from the cells within the ducts due to the erroneous assumption that this malignancy is an *in situ* process. However, when determined, the high-grade cells within the ducts are predominantly HER2 positive, and this result should be available to influence patient management. Unfortunately, the biomarkers are routinely determined only from an associated invasive AAB, but not from the potentially fatal duct forming invasive carcinoma, the DAB component.

Figs. 14 and 15 show the mammographic-large format thin and thick section histopathologic correlation of the extensive architectural distortion.

There are considerable differences in our ability to influence the long-term outcome of the three breast cancer subtypes, AAB, DAB and BCMO. Fig. 16 shows the cumulative survival of 4707 women diagnosed with 1–14 mm and ≥15 mm invasive AAB as well as diffuse DAB and diffusely infiltrating breast cancer, possibly of mesenchymal origin. These cases were classified in Falun, Sweden, Roanoke, VA, USA and Turin, Italy. The 1–14 mm AAB cases have a 95% long-term survival,

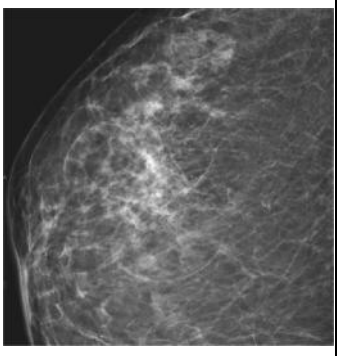
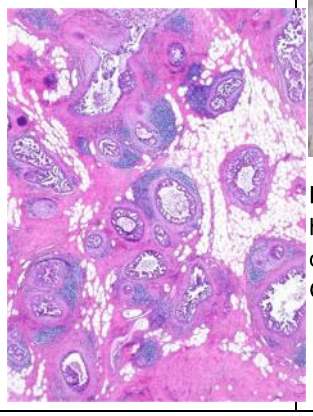
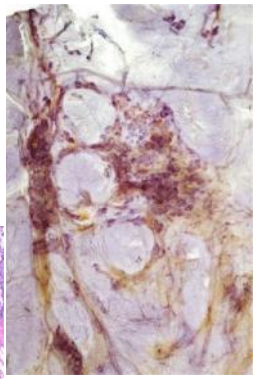
Table 1i
Correlation of the apparent site of origin of breast cancer and the proposed new terminology with the dominant radiological appearance, the corresponding BI-RADS term, the currently used histopathologic terminology and disease distribution.

Apparent site of origin **Proposed terminology**	**Dominant radiological appearance** and the *corresponding BI-RADS term*	**Currently used histopathologic terminology**	**Unifocal, multifocal or diffuse**
Major lactiferous ducts. **D**uctal **A**denocarcinoma of the **B**reast, ***fluid producing*** **DAB,** without mammographically detectable calcifications on the mammogram. **Neoductgenesis.**	**Occult on a mammogram, nipple discharge, detectable on a galactogram.**  *Corresponding BI-RADS term: No equivalent term*	**Ductal** carcinoma "*in situ* (DCIS), Grade 1-3, with or without "microinvasion", predominantly micropapillary tumour growth pattern.   	Diffuse, lobar distribution  Subgross, 3D histopathologylogy  Galactogram
NOTE: The immunohistochemical biomarkers are not routinely determined from the cells within the ducts due to the erroneous assumption that this malignancy is an in situ process. However, when determined, the high-grade cells within the ducts are predominantly HER2 positive, and this result should be available to influence patient management. Unfortunately, the biomarkers are routinely determined only from an associated invasive AAB, but not from the potentially fatal duct forming invasive carcinoma, the DAB component.			

NOTE: The immunohistochemical biomarkers are not routinely determined from the cells within the ducts due to the erroneous assumption that this malignancy is an *in situ* process. However, when determined, the high-grade cells within the ducts are predominantly HER2 positive, and this result should be available to influence patient management. Unfortunately, the biomarkers are routinely determined only from an associated invasive AAB, but not from the potentially fatal duct forming invasive carcinoma, the DAB component.

which decreases with increasing tumour size. Thus, early detection and treatment in early phase of AAB improves the long-term outcome of these cases. However, even in the era of mammography screening and the use of modern therapeutic regimens, the long-term outcome of the cancers originating in the major lactiferous ducts (DAB) and the malignancy currently termed diffusely infiltrating lobular carcinoma has not improved during recent decades. This evidence supports using the site of origin of breast cancer in interdisciplinary communication during the planning of breast cancer management. Due to the limited impact of the currently used therapeutic regimens on the long-term outcome of these two diffusely infiltrating breast cancers, we must improve the efficacy of earlier detection methodology. Ongoing efforts include the use of automated breast ultrasound and tomosynthesis to examine women with dense breasts and the regular use of artificial intelligence to cut

Table 1j
Correlation of the apparent site of origin of breast cancer and the proposed new terminology with the dominant radiological appearance, the corresponding BI-RADS term, the currently used histopathologic terminology and disease distribution.

Apparent site of origin **Proposed terminology**	**Dominant Radiological Appearance** and the *corresponding BI-RADS term*	**Currently used histopathologic terminology**	**Unifocal, multifocal or diffuse**
Major lactiferous ducts. Ductal Adenocarcinoma of the Breast, **DAB. Neoductgenesis**	**Architectural distortion, no associated calcifications**  *Corresponding BI-RADS term*: *Architectural distortion*	**Ductal** carcinoma "*in situ*" (DCIS), Grade 2-3, with or without "microinvasion", having any combination of the three tumour growth patterns. Both necrosis and fluid production may be present. 	Diffuse, lobar distribution  Large format 3D histopathology image of this extensive Grade 3 DAB.
NOTE: The immunohistochemical biomarkers are not routinely determined from the cells within the ducts due to the erroneous assumption that this malignancy is an in situ process. However, when determined, the high-grade cells within the ducts are predominantly HER2 positive, and this result should be available to influence patient management. Unfortunately, the biomarkers are routinely determined only from an associated invasive AAB, but not from the potentially fatal duct forming invasive carcinoma, the DAB component.			

NOTE: The immunohistochemical biomarkers are not routinely determined from the cells within the ducts due to the erroneous assumption that this malignancy is an *in situ* process. However, when determined, the high-grade cells within the ducts are predominantly HER2 positive, and this result should be available to influence patient management. Unfortunately, the biomarkers are routinely determined only from an associated invasive AAB, but not from the potentially fatal duct forming invasive carcinoma, the DAB component.

back on the number of cancers missed at screening.

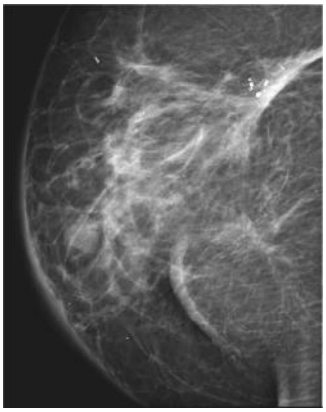
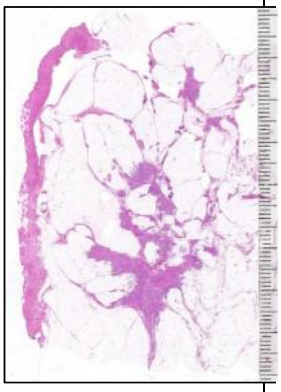
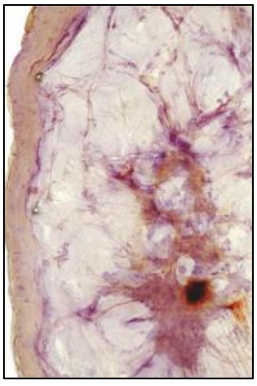
Tables 1a-1k shows how the proposed new terminology of breast cancer based on the apparent site of tumour origin correlates with the current breast cancer terminology.

5. Conclusion

The histopathologic terminology for breast cancer evolved in the absence of a sufficient number of cases detected early in their development. In the mammography screening era, where a large proportion of all breast cancers are detected when preclinical and nonpalpable, there is a need and an opportunity for revising the current histopathologic terminology. The large number of screen-detected cancers also exposes the diminishing impact of the immunohistochemical biomarkers with decreasing tumour size in AAB cases, and uncovers the fact that in DAB cases the immunohistochemical biomarkers are not routinely determined from the cells within the ducts due to the erroneous assumption that this malignancy is an *in situ* process, although it is a duct forming invasive carcinoma (neoductgenesis). However, when determined, the high-grade cells within the ducts are predominantly HER2 positive, and this result should be available to influence patient management. Unfortunately, the biomarkers are routinely determined only from an associated invasive AAB, but not from the potentially fatal duct forming invasive carcinoma, the DAB component. In the diffusely infiltrating breast cancers (BCMO) the immunohistochemical biomarkers are misleading since most of the cases are ER and PR positive, HER2 negative, and have a low (1–5%) proliferation index (Ki67). These values are at odds with the surprisingly poor long-term outcome (40% fatality rate) of BCMO cases.

From the viewpoint of the anatomic site of origin, the current histopathologic terminology is incorrect and adversely influences breast cancer management by failing to distinguish between subtypes with vastly different outcomes. Also, current practice assumes that the immunohistochemical biomarkers are as reliable in the earliest phases of breast cancer as in later phases. In combination, the result is overtreatment of many cancers of apparent acinar origin and undertreatment of cancers of apparent ductal and mesenchymal stem cell origin. These deficiencies could be alleviated by routine use of the imaging biomarkers since these not only provide a reliable indication of the apparent site of origin of the breast malignancy, but also serve as reliable

Table 1k
Correlation of the apparent site of origin of breast cancer and the proposed new terminology with the dominant radiological appearance, the corresponding BI-RADS term, the currently used histopathologic terminology and disease distribution.

Apparent site of origin **Proposed terminology**	**Dominant radiological appearance** and the *corresponding BI-RADS term*	**Currently used histopathologic terminology**	**Unifocal, multifocal or diffuse**
Mesenchyme through transformation of the mesenchymal stem cells to epithelial cells (mesenchymal-epithelial transformation, MET). **B**reast **C**ancer of apparent **M**esenchymal **O**rigin (**BCMO**).	**Architectural Distortion**  *Corresponding BI-RADS term: Architectural distortion*	Diffusely infiltrating *lobular* carcinoma 	Diffuse, crosses over lobar boundaries.  Large format subgross, thick section histopathology image
NOTE: The immunohistochemical biomarkers are misleading in this predominantly moderately differentiated breast cancer, since most of the cases are ER and PR positive, HER2 negative and have a low (1-5%) proliferation index (Ki67). These values are at odds with the surprisingly poor long-term outcome (40% fatality rate).			

NOTE: The immunohistochemical biomarkers are misleading in this predominantly moderately differentiated breast cancer, since most of the cases are ER and PR positive, HER2 negative and have a low (1–5%) proliferation index (Ki67). These values are at odds with the surprisingly poor long-term outcome (40% fatality rate).

predictors of long-term patient outcome. Since the mammographic tumour features (imaging biomarkers) are a reflection of the underlying subgross (3D) histopathologic image, they play a crucial role in breast cancer management, and help optimize interdisciplinary treatment decisions. The proposed terminology could lead to more specifically targeted therapy and better prediction of long-term outcome, facilitate individualized management planning and should also lead to a fundamental change in the current TNM/AJCC systems.

Accumulating evidence supports the need to carefully evaluate our management failures, rethink accepted beliefs with open minds, and work to improve breast cancer management accordingly. This introductory article, the first of a series, will be followed by detailed descriptions of each of the above-described breast cancer subgroups. This new paradigm challenges the conventional mindset concerning breast cancer diagnosis and treatment.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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