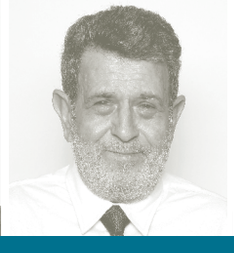
JUNE 2016 SCOR inFORM

BREAST CANCER IN WOMEN

DELPHINE LABOJKA
Method & Process Manager

Dr PATRICK MALAMUD
Oncologist, Medical Officer

Dr XUÂN-VIÊT PHAM
Rheumatologist, Medical Officer



SCOR Global Life

Reminders and up-to-date data
03

Anatomy, histology and physiology of the breast
04

Breast cancers anatomopathology and classification
05

Immunohistochemistry and gene expression profiling
08

Prognostic factors and treatments
09

Conclusion
10

Breast cancer in women – Reminders and up-to-date data

Breast cancer in women is a real public health issue. All doctors, whatever their specialty, are confronted to some extent with patients with this type of tumour. It is the second most common type of cancer in the world. Breast cancer is responsible for more than 520,000 deaths[1] each year, and is the fifth most frequent cause of death in the world. Breast cancer represents 25% of cancers diagnosed worldwide and 31.5% of all malignant tumours identified in France. The figures sometimes translate an extremely heterogeneous reality of tumour pathology, in particular wide geographical and ethnic disparities. Recent epidemiological data in oncology concerning this organ, as well as new diagnostic and therapeutic techniques, have led to the risk connected with cancer in general and breast cancer in particular being re-evaluated.

1
WOMAN IN
8
RISKS DEVELOPING BREAST CANCER IN HER LIFETIME

12 000
DEATHS A YEAR IN FRANCE

BREAST CANCER STATISTICS

In order to put the extent of breast cancer into perspective, it is important to recall some figures: One woman in eight risks developing breast cancer in her lifetime; one woman in 28 risks dying from breast cancer. According to epidemiological data from 2012, 6.3 million women[1] have been diagnosed with breast cancer in the world in the last five years. Breast cancer is the most common cancer in women and is responsible for a death rate of 15% or 12.9 per 100,000 in an age-standardised mortality rate. In France, that represents 12,000 deaths a year (mortality[2]), and almost 50,000 new cases diagnosed per year (incidence[3]). Worldwide, 1.7 million new cases are diagnosed every year, or an age-standardised incidence rate of 43.1 for 100,000.

However, a reduction in mortality from breast cancer is being observed in countries with a high standard of living (down 22.2% in 12 years), which can be attributed to the progress made in several areas, in particular systematic screening and improvements in therapies. The drop in the incidence observed since 2005 is more difficult to explain. According to the INVS (French national institute for public health surveillance), it is thought to be due to reduced prescribing of menopause treatments in France.

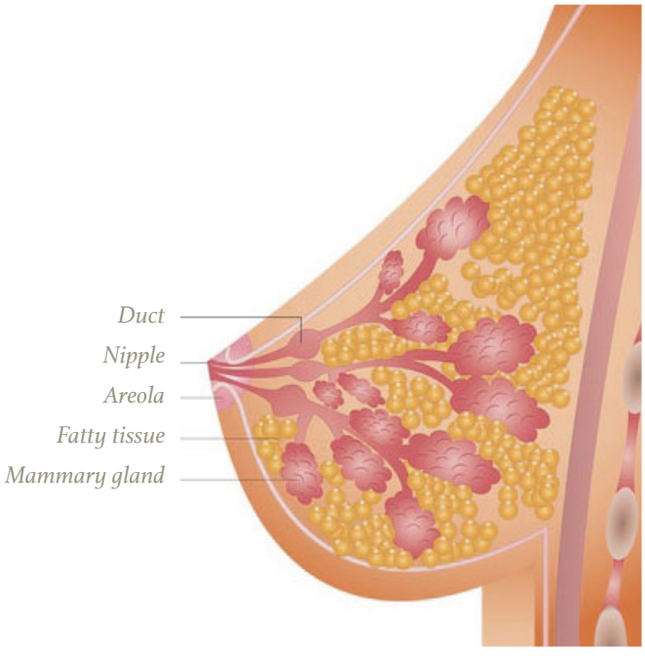
1 GLOBOCAN 2012 (IARC) Section of Cancer Surveillance: http://globocan.iarc.fr
2 Mortality: Number of people who die from a given disease, in a particular territory over a defined time interval. In this case, it refers to the number of women who died of breast cancer in France during the year 2012..
3 Incidence: Number of new cases of a given disease, in a particular territory, over a defined time interval. In this case, it refers to the number of new cases of breast cancer recorded in France during the year 2012.

Anatomy, histology and physiology of the breast

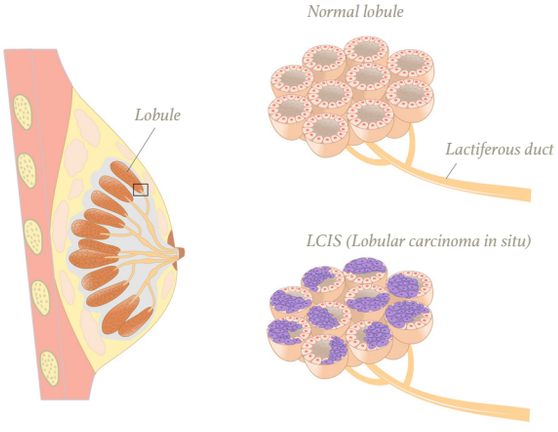
The function (physiology) of a breast is lactation. The breast is subject to cyclical hormonal stimulation, in particular by oestrogens (until menopause), which constitute one of the main factors contributing to the emergence of breast cancer.

The breast consists of two essential anatomical structures: the lobules (or mammary glands) and the lactiferous ducts. These two structures can both be affected by a tumour and should be distinguished when breast cancer is discovered. It will be said to be «lobular» when it affects the lobules or «ductal» when it affects the lactiferous ducts.

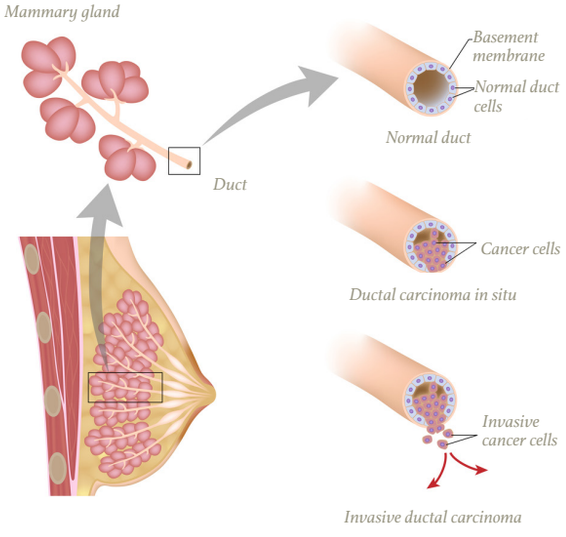
Each lactiferous duct is lined by a mono-layered epithelium which rests on a basement membrane. 80% of breast cancers originate in this epithelium. The remaining 20% originate in the milk-secreting lobules.



SIMPLE BREAST ANATOMY



LOBULAR CARCINOMA IN SITU



EVOLUTION OF DUCTAL BREAST CANCER

Breast cancers anatomopathology and classification

MAIN CLASSIFICATION

The classification used is the pTNM staging system (p = pathologic examination). This is recommended in order to be able to analyse any excess risk that the applicant for insurance may pose. This stage is the result of a pathologic examination, in other words a macroscopic, microscopic and histological examination, unlike the cTNM staging system which is based on clinical examination and/or imaging. In the absence of neoadjuvant therapy, the clinical does not give the most reliable information on the severity of a tumour for rating purposes. For the past 25 years, the pathologic examination has been completed by an immunohistochemical analysis.

The pTNM staging system is based on the analysis of three distinct zones:

- **pT**: The *primary tumour* and its immediate environment,
- **pN**: The *regional lymph nodes*, the chains of lymph nodes that drain the organ affected by the cancer and the neighbouring anatomical structures,
- **pM**: Distant metastasis (existence or otherwise of metastases).

It is necessary to be aware of misused terms: it is common to hear talk of «metastatic nodes», when in fact it is the «regional lymph nodes» that are affected and not metastases, which by definition must be situated in an organ independent from the original site.

The pT classification refers to the size of the infiltrating tumour in its largest dimension, by measuring the resection specimen. It is known to a tenth of a millimeter, and the tumour borders are defined precisely.

The pN classification refers to the involvement of the regional lymph nodes after histological examination. The involvement of the regional lymph nodes can be established to within a few dozen cells. In practice, only the axillary lymph nodes are explored, unless there is a clinical suspicion of the involvement of the other two chains of lymph nodes that drain the breast: the internal mammary lymph node (sometimes known as «external thoracic») or the subclavicular lymph nodes.

The pM classification refers to the existence of otherwise of distant metastases with histological evidence.

FURTHER CLASSIFICATIONS

Two other classifications complete the pTNM staging system:

PEV or « Poussée Evolutive » (inflammatory breast cancer)

- **PEV I**: Marked increase in size (less than 6 months);
- **PEV II**: Clinical signs of inflammation of the tumour or around the tumour;
- **PEV III**: Mastitis carcinosa, general inflammation of the breast.

The SBR (Scarff, Bloom and Richardson) grading system was the first histological prognostic grading system consisting of several items.

Item measured	SCORE		
	1	2	3
Tubular differentiation	> 75%	10 to 75%	< 10%
Nuclear pleomorphism (nucleus anomalies)	Low	Moderate	Intense everywhere
Mitotic index	1 mitosis for 10 fields	1 to 5 mitoses for 10 fields	Over 5 mitoses for 10 fields

➜ The total score varies from 3 to 9		
Total from 3 to 5	=	Score SBR I
Total from 6 to 7	=	Score SBR II
Total from 8 to 9	=	Score SBR III

The first item indicates the capacity of the tumour cells to differentiate into tubules, that is to say the configuration of non-malignant cells.

The second item looks at nucleus anomalies. They vary in number and nucleolus form, morphology of the nucleus, colouring anomalies, etc.

The third item concentrates on the number of mitoses seen in a certain number of clearly defined fields. It provides information on the capacity for growth and aggressiveness of the tumour examined.

Depending on the total scores obtained for the three, the SBR system gives one of three grades: I, II or III. At the present time, **SBR I** breast cancers differ from those graded **SBR II or III**.

CLASSIFICATION OF CANCER IN SITU

So-called **in situ** cancers (pTis) are tumours that **do not go beyond the basement membrane** and have a limited extension into the spaces between the ducts and lobules. However, these tumours can be very large in size, up to several centimeters. In situ cancers are **classified separately using the Van Nuys system**, which has a prognostic index and classification in groups.

PARAMETER	1 point	2 points	3 points
Size	⩽ 15 mm	16 - 40 mm	> 40 mm
Grade	I - II	Grade I - II + Necrosis	Grade III
Margins	⩾ 10 mm	Between 1 and 9 mm	< 1 mm
Ages	> 60	40 - 60	< 40

Van Nuys Prognostic Index: scoring system

		Most common treatment regimen
4 - 6 points	Group I	Excision without radiotherapy
7 - 9 points	Group II	Excision + radiotherapy
10 - 12 points	Group III	Excision + sentinel lymph node + mastectomy?

Van Nuys groups according to score

Tumours classed in **groups I and II** are considered completely **cured** after the treatment. On the other hand, tumours classed in **group III** may be aggressive with the possibility of micro-invasions and migration via the lymph vessels. This is why a procedure known as t**he sentinel lymph node procedure** is often performed and a radical operation such as a mastectomy is considered.

Immunohistochemistry and gene expression profiling

NB : This section deals only with «tumour genes» that are not hereditary. These are acquired anomalies.

Immunohistochemical analysis and genetic profiling of the tumour are complementary to the previous classification systems (pTNM, PEV and SBR).

Immunohistochemistry allows us to look for antigen receptors that are situated either in the cell nucleus or in the cytoplasm or in the cell membrane. For breast cancers, the search is done in the nucleus and the cell membrane:

• In the nucleus: we search for oestrogen receptors (OR or ER), progesterone receptors (PR) and the expression of the nuclear marker Ki67;

• In the cell membrane: the presence and abundance of the Her-2 or c-erbB2 receptors are examined.

Searching for receptors is fundamental as it allows treatments to be adapted to the type of cancer, and when tests are positive it is possible to discuss the introduction of hormone treatment (such as Tamoxifen for ER+ or oestrogen receptor positive for example), which considerably improves the prognosis for breast cancer. The Her-2 membrane receptor is also an important one to know, for when it is over-expressed, a specific treatment, Herceptin™, is indicated.

Genetic profiling does not concern the individual's genome. It is not a question of analysing a person's genes, but rather those of the tumour. There are several genetic profiling techniques that enable more than a million genes to be analysed in a tumour to find the over-expressions.

These techniques have led to the identification of a certain number of profiles, including four main phenotypes:

• **ER+ breast cancers** account for 80% of breast cancers:

- Luminal A (60% of cases),

- Luminal B (20% of cases),

• **ER- breast cancers** account for 20% of breast cancers:

- Basal cell or «triple negative» (10% of cases),

- Her2 (10% of cases).

These tumour profiles are important as they are an essential factor in the prognosis for breast tumours. Other new profiles have been discovered in the RE- group, for example: *Claudin low, Interferon rich, Mol apocrine Her2+ / Her2-*. These molecular classifications will be used more systematically in years to come.

Prognostic factors and treatments

The classic factors involved in the prognosis of breast cancer are those that have already been mentioned, namely, the size of the tumour (representing the number of malignant cells), lymph node involvement, SBR grade and immunohistochemistry with the search for hormonal receptors, the Her2 receptor and the expression of the nuclear marker Ki67.

In the short or medium term, tumour profiles will be added to this list of prognostic factors.

The latter will orient the choice of treatment strategy, which is done systematically in France at a multi-disciplinary consultation meeting (RCP), which was rendered mandatory by the National Health Authority (HAS), and which is attended by all the doctors and surgeons concerned. This RCP gives rise to a report, which is an essential document when studying an insurance application.

In the treatment strategy, the sentinel node procedure is important. This procedure is only performed for infiltrating tumours with a diameter of 2 cm maximum and in high grade in situ tumours. It is not done for prognostic purposes, but it can help to reduce complications linked to lymph node clearance, a source of serious sequelae in this type of cancer (lymphedoema). Lymph node dissection will not be performed if the sentinel node is not involved and the tumour will then be classified pN0(sn) (sn = sentinel node). On the other hand, if the histological analysis reveals involvement, axillary dissection will be performed. If no involvement is found in the dissection, the tumour will still be classified pN1 as the sentinel node was involved.

PRICING

Patient survival varies according to the different prognostic factors for breast cancer and in particular the hormone receptors. ER+ tumours, for example, have a better prognosis than ER- tumours in the first five years after discovering the cancer. Nevertheless, the curves are reversed after five years, and it is then that breast cancers expressing oestrogen receptors (ER+) have the highest level of recurrence.

Concerning pricing, the «specific» mortality of breast cancers diminishes over time. The pricing must therefore not be carried out based on excess mortality, but on «extra-mortality» (per thousand, ‰).

CONCLUSION

The classifications, specific markers, different diagnostic elements, treatments prescribed, and their chronology are what enable the risk from breast cancer to be better understood.

SCOR Global Life's R&D team works on specific areas in risk assessment and claims management. Thanks to the body of experience we have built, our teams are able to work closely with our partners to help them develop specific underwriting strategies.

Do not hesitate to contact the local teams and to consult our different medical publications at www.scor.com.

Publisher
Paolo De Martin

life@scor.com

© June 2016 - ISSN: 2417-517X
All rights reserved. No part of this publication may be reproduced in any form without the prior permission of the publisher. SCOR has made all reasonable efforts to ensure that information provided through its publications is accurate at the time of inclusion and accepts no liability for inaccuracies or omissions.
Photo Credit © Nathalie Oundjian © Shutterstock

SCOR Global Life

SCOR Global Life
5, avenue Kléber - 75795 Paris Cedex 16
France

www.scor.com