Universitat de Girona
Facultat de Medicina

PROPHYLACTIC EXTERNAL RADIOTHERAPY VERSUS SCREENING STRATEGY IN WOMEN WITH BRCA 1/2 MUTATION

A multicenter, randomized, open-labelled clinical trial

Final Degree Project

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ABSTRACT

BRACKGROUND

Breast cancer is the most prevalent cancer worldwide. It is the cancer that causes the most disability-adjusted life year globally, and the leading cause of death from cancer in women. Of all breast cancers, 5-10% correspond to hereditary cancer, in which BRCA is the main mutation with a 70% lifetime risk of developing breast cancer.

In patients with BRCA 1/2 mutation, prophylactic mastectomy may be offered to reduce the risk of breast cancer. However, only 35.7% of women accept this measure, and it is an irreversible surgery with numerous complications and disadvantages.

In order to offer new prophylactic options to these women, the use of contralateral prophylactic external radiation therapy has been studied in women with early breast cancer. This treatment demonstrated an 80% reduction of contralateral breast cancer and a delay in its onset.

OBJECTIVE

The aim of this study is to prove that prophylactic external radiotherapy of the breast can reduce the risk of subsequent breast cancers, compared to screening strategy.

DESIGN AND SETTING

The study will be based on a **randomised, parallel-group, multicentre, and open-labelled clinical trial**. It will be designed as a comparison between prophylactic external radiotherapy plus screening strategy vs. only screening strategy. It will be carried out in 3 hospitals of Institut Català d'Oncologia (ICO), with the ICO Girona being the coordinator center.

PARTICIPANTS

Women diagnosed with a deleterious mutation in BRCA 1/2 gene, without the presence of breast cancer, who declined undergoing bilateral prophylactic mastectomy.

METHODS

216 patients will be enrolled with a **consecutive non-probabilistic sampling**. Recruitment will last 2 years and 6 months. Patients will be randomized in two groups: **Group 1**: Prophylactic external radiotherapy plus screening strategy (n= 108). **Group 2:** Only screening strategy (n=108). After the intervention there will be a subsequent follow-up of 5 years.

KEYWORDS

BRCA, breast cancer, external radiotherapy, screening strategy, prophylactic, mastectomy

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1. ABREVIATIONS

DALY - Disability-adjusted life year

DCIS - Ductal carcinoma in situ

OS - Overall survival rate

PFSR - Lower short-term progression-free survival rate

HBOC - Hereditary breast and ovarian cancer

CBC - Contralateral breast cancer

PBM – Prophylactic bilateral mastectomy

SSM - Skin-sparing mastectomy

SLNB - Sentinel lymph node biopsy

BIRADS - Breast Imaging, Reporting & Data System

MRI - Magnetic resonance imaging

CNB – Core needle biopsy

FNAB - Fine needle aspiration biopsy

ER - Estrogen receptor

PgR - Progesterone receptor

HER2 - Human epidermal growth factor receptor 2

WHO - World Health Organization

TNM - Staging method tumor, nodule, metastasis

CT - Computerized tomography

NST - No special type

TNBC - Triple-negative breast cancer

AJCC - American Joint Committee on Cancer

PARP - Adenosine diphosphate-ribose polymerase

RIS - Radioinduced sarcoma

RP – Radiation pneumonitis

CAD – Coronary artery disease

SPSS - IBM Statistical Package for Social Science

UARC – Unitat alt risc oncològic

CTCAE - Common Terminology Criteria Adverse Events

ADL - Activities of daily living

SRF - Spontaneous rib fracture SRF

ECG - Electrocardiogram

BSA - Body surface area

BSO - Bilateral salpingo-oophorectomy

HRT - Hormone replacement treatment

CPP – Primary care center

2. INTRODUCTION

Breast cancer is defined as a condition in which abnormal cells are found in the breast tissues. It is produced by an anomalous and uncontrolled growth of breast cells as a result of a genetic abnormality. It is a complex disease whose most notable characteristic is the instability of the genome, which allows the accumulation of other genetic defects, increasing the susceptibility to develop cancer (1,2).

Breast cancer is considered a **multifactorial entity**, where heredity, environment, and life habits interact.

About 70% of breast cancers are considered **sporadic** and associated with somatic mutations in breast cells that are acquired during a person's life. In this case, the mutations are not inherited and neither aggregated in families.

On the other hand, 15-20% of breast cancer cases correspond to cases of **family aggregation,** which implies the presence of several members affected with multiple neoplasms in a family and different generations. Family aggregation is not always associated with the presence of a risk mutation, and it could also be due to **environmental factors,** such as exposure to carcinogens shared by family members or similar lifestyles that increase risk.

The remaining 5-10% correspond to **hereditary breast cancers** caused by mutations in the germline that are transmitted from generation to generation through an autosomal dominant inheritance pattern. Many mutations confer risk of breast cancer (ATM, CDH1, CHEK2, PALB2, PTEN ....), but the most frequently diagnosed are **the BRCA1/2 gene** (3,4).

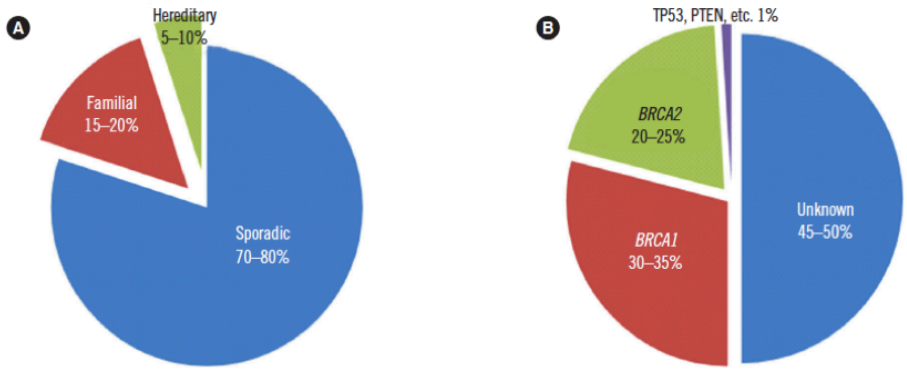


Figure 1. Incidence of breast cancer (5)
A: Prevalence of hereditary breast cancer, B: BRCA1/BRCA2 pathogenic variant prevalence in hereditary breast cancer

2.1. EPIDEMIOLOGY

In 2020, the most frequently diagnosed tumor worldwide was breast cancer, with 2,261,419 new cases and 68,000 deaths. It is considered the leading cause of death from cancer in women. At the end of 2020, there were a total of 7.8 million women alive who were diagnosed with breast cancer in the last 5 years, making it the most prevalent cancer in the world. In addition, it is the type of cancer that causes the most loss of disability-adjusted life year (DALYs) globally (6).

In Spain, during 2020, 32.953 women were diagnosed with breast cancer, with 6,606 cases of death. Moreover, it is estimated that by the end of 2021, 33,375 new cases of breast cancer will be diagnosed in Spain. However, this result may vary since it has not been possible to consider the effect of COVID-19 in the screening programs carried out this year, which may cause a decrease in the number of diagnoses (7).

In Catalonia, each year, 16,000 cases of cancer are diagnosed, of which about 5,000 correspond to breast cancer (8). The prevalence of breast cancer in Catalonia during 5 years is 21,421 cases, with 542 cases per 100,000 inhabitants.

Finally, in Girona, the prevalence of breast cancer is 2,060 cases during 5 years, with 527 cases per 100,000 women (9). Regarding mortality, 124 women died of breast cancer in Girona in 2020.

2.2. BRCA 1/2 MUTATION

This section focuses on women with a BRCA gene mutation who have not yet developed any breast cancer. In these cases, a genetic study must be carried out to diagnose the mutation, and subsequently, apply the necessary measures to reduce the risk of developing a breast tumor.

The BRCA1 gene is located on the long arm of chromosome 17 (17q21) and the BRCA2 gene on chromosome 13 (13q12). They are tumor suppressor genes involved in DNA repair of other genes that induce human cancers, and they are essential for activating DNA repair in response to cellular stress. In addition, they also contribute to chromatin remodeling, transcription control, cell cycle regulation, and DNA repair processes.

Therefore, when they present a mutation, the person has a greater risk of developing **hereditary breast and ovarian cancer (HBOC)** (10).

As already mentioned, 5-10% of diagnosed breast cancers are due to **hereditary cancers.** It may seem a smaller percentage, but it is important to highlight that for women born with a BRCA1/2 germline mutation, the lifetime risk of developing breast cancer at the age of 70 years old is approximately **70%** for BRCA1 mutation, and **45-69%** for BRCA2 mutation, compared to **9%** in sporadic cases (11). Furthermore, breast tumors of BRCA mutation carriers tend to develop at a **younger age**, and **bilateral disease** is more common than in sporadic cases (12).

Figure 2. Comparative graphic of the lifetime risk of developing breast cancer

2.2.1. Risk factors

Several risk factors influence the likelihood that a woman with BRCA mutation will develop breast cancer. The most important are **the genetic predisposition, personal and family history**, and the **patient's age.**

The risk increases progressively as more affected first-degree relatives the person has. It is important to know that there is significant interindividual variability due to the variability in phenotypic expression and penetrance, which determines that there may be differences in the same family carrying the BRCA1/2 mutation (10).

As in sporadic breast cancer, we can find **modifiable risk factors** and **non-modifiable risk factors.** They can be seen summarized in the table 1 (13–18):

Table 1. Risk factors of BRCA1/2-positive breast cancer

NON-MODIFIABLE FACTORS	MODIFIABLE FACTORS
Age: More risk from 35 years	Hormone replacement treatment
Genetic predisposition: - Mutation in BRCA1 and BRCA2 - Li-Fraumeni syndrome (p53) - Cowden syndrome (PTEN) - Ataxia-telangectasia syndrome (TMJ) - Peutz-Jeugher syndrome (STK11)	Reproductive factors: - Nulliparity - Older age at first pregnancy
	Body fat ratio
Hormonal status: - Early menarche (before 12 years) - Early thelarche (before 10 years) - Older age onset of menopause	Oral contraceptives
	Alcohol consumption
Family or personal background: - First or second-degree relatives with breast cancer - Previous cancer (More risk of CBC)	Tobacco
	Overweight after menopause
Breast tissue density	Ionizing radiation exposure due to diagnostic or therapeutic processes

CBC: Contralateral breast cancer

2.2.2. Genetic study

BRCA1 and BRCA2 are the most important known genes for breast cancer susceptibility in **high-risk women** (19).

To assess the risk, the following data must be taken into account (20):

- **Complete family history:** Information from at least three generations of the family indicating all cancer cases.
- **Documentation that allows the confirmation of the diagnoses of any neoplasia and associated diseases** (if possible, the pathological reports).
- **Bilateral or multifocal involvement.**
- **Periodic updating of genealogical trees.**

Based on this information, three levels of risk have been established:

Table 2. Risk categories of developing a breast cancer. Adapted from (21)

Low risk	- No first-or second-degree relatives with breast or ovarian cancer. - One second-degree female relative with breast cancer (in one breast only) diagnosed after age 50.
Moderate risk	- One or two first-degree or two second-degree female relatives with breast cancer (in one breast only), with both relatives diagnosed after age 50 - One or two first or second-degree relatives with high grade prostate cancer
High risk	Families with a single case of breast cancer - Breast cancer diagnosed before the age of 40 - Bilateral primary breast cancer before age 40 (at least one of the tumors) - A breast cancer and an ovarian cancer in the same patient - Male breast cancer - Triple negative breast cancer
	Families with two cases in first degree relatives - Two cases of breast cancer or bilateral breast cancer, at least one diagnosed before the age of 50 - Two or more cases of ovarian cancer (regardless of age) - One breast cancer and one ovarian cancer in two relatives (regardless of age) - One cases of male breast cancer and one female breast/ovarian cancer (regardless of age)
	Families with three or more cases affected by breast cancer, at least two in first-degree relatives

A genetic study is recommended for all women at high risk.

There are many different mutations in the BRCA1 and BRCA2 genes that can be detected during mutation testing. The technique used to detect these mutations depends on the characteristics of the patient (22):

- Most patients undergo the multigene panel test as they can detect a wide range of BRCA1 and BRCA2 mutations and pathologic mutations in other genes that can increase cancer risk.
- If a particular mutation has been found in a family member, specific tests can be performed to detect that mutation.

Once the test is done, the following results can be obtained (23):

- Positive for the mutation tested.
- Negative for the mutation tested.
- Positive for a variant of unknown significance: A genetic variant has been found, but it is not clear if it affects the risk of developing cancer.

The genetic diagnosis of HBOC is summarized in ANNEX 1.

2.2.3. Risk reduction techniques

Risk reduction measures can be taken once the BRCA 1/2 mutation has been detected in a patient who **does not have any tumor yet** to reduce the risk of developing a breast tumor in the future (or to reduce the risk of contralateral breast cancer [CBC]). The algorithm of risk reduction measures can be found in **ANNEX 2**.

Diet and lifestyle

Currently, there is insufficient evidence to confirm that diet or lifestyle can impact cancer risk. Even so, extrapolating from general population data of women at increased risk of breast cancer, it is recommended to reduce dietary fat and alcohol consumption, avoid obesity, and engage in regular physical activity (19).

Screening strategy

A screening in patients with genetic mutations is carried out to promote the **early detection** of neoplasms.

The screening must include (20):

- **Monthly breast self-examination from 18-20 years.**
- **Clinical breast examination by an expert doctor from the age of 25-30, every 3-4 months.**
- **Annual mammography and echography from 25-30 years.** Even so, it should be taken into account that mammograms are not very sensitive (30-40%) in this group of patients because they are younger, they have a higher breast density, and the tumor growth rate is faster.
- **Annual magnetic resonance from the age of 30.**

Chemoprevention

Tamoxifen taken for 5 years by women at high risk of breast cancer reduces this risk by 50%. Some research suggests that tamoxifen may help to reduce the risk of breast cancer in women with BRCA1 and BRCA2 mutations. However, as women with BRCA1 mutations are more likely to develop hormone receptor-negative cancers, it may not be as effective in their case (24).

Nevertheless, there is still not enough scientific evidence to administer chemoprevention in clinical practice. In the meantime, patients with the BRCA1/2 mutation should be offered the possibility of participating in chemoprevention clinical trials (20).

Surgery

Surgery with preventive intention is the most effective strategy today. When contemplating prophylactic bilateral mastectomy (PBM), several factors should be considered (25):

- Absolute risk of CBC: The younger the age at first breast cancer diagnosis, the greater the absolute risk of subsequent CBC. For example, the absolute risk of CBC for BRCA2 carriers diagnosed before age 40 is 68% versus 20% if diagnosed at age 50.
- The prognosis of current breast cancer or other cancers (eg. ovary).
- Ability and willingness of the patient to undergo surgery.
- Ability of the patient to tolerate treatment for subsequent breast cancer.
- Comorbidities.
- Life expectancy.

The decision of whether and when to perform a risk-reducing bilateral mastectomy is very complex. If a woman opts for prophylactic mastectomy, it is essential to offer the most effective technique possible. There are different types of surgery (26):

- Modified radical mastectomy: It includes complete removal of the breast with preservation of the pectoralis major and minor muscles and dissection of level I and II axillary lymph nodes.
- Simple mastectomy: With complete excision of the breast without excision of lymph nodes.
- Skin-sparing mastectomy (SSM): All breast tissue is removed, along with the areola-nipple complex, while preserving as much viable skin as possible to optimize the cosmetic result.
- Total skin-sparing mastectomy: It consists in trying to preserve the entire complex (mastectomy with preservation of the nipple and areola), or only the

areola with the extraction of the nipple (mastectomy with preservation of the areola). These procedures are also performed with SSM.

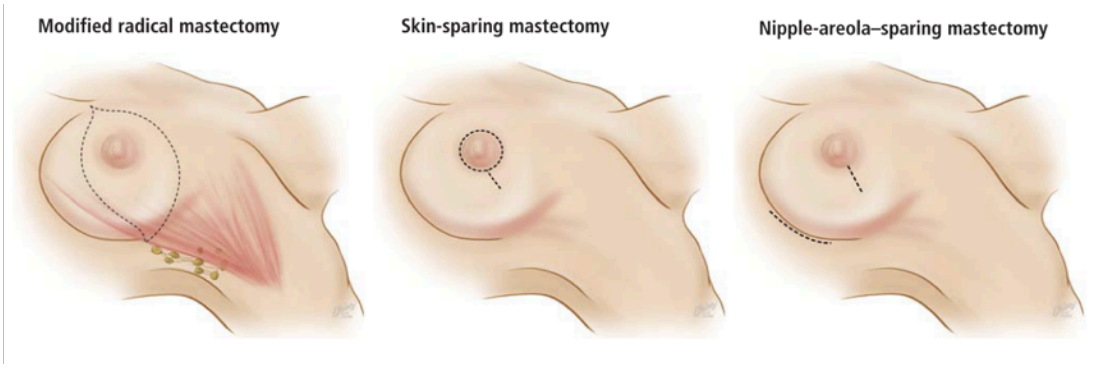


Figure 3. Common types of mastectomy and their incision line (26)

Most experts recommend **total skin-sparing mastectomy** (19). Also, after performing a PBM, **breast reconstruction** is performed in the same surgical intervention (immediate reconstruction) since it allows the same incision of the skin-sparing mastectomy to be used. In addition, it preserves the skin envelope of the breast, minimizes scars on the breast, and improves its contour and symmetry. Implants (prostheses) or own tissues (grafts such as transverse abdominal plasty) can be used (20).

Sentinel lymph node biopsy (SLNB) is not recommended routinely in patients undergoing prophylactic mastectomy since it is not a completely benign procedure and the risk of finding occult cancer is low: 3.2% for DCIS and around 1.8% for invasive cancer (27).

PMB has been shown **to decrease the risk of breast cancer by 90%,** according to the results of a prospective study carried out at the University of Rotterdam in a Family Cancer Program (28).

Therefore, although this technique can significantly reduce the risk of breast cancer**, it does not completely eliminate it**, and for this reason, a long-term clinical follow-up of these patients is necessary (19).

The rate of prophylactic mastectomy in women at high risk of breast cancer has increased during the years 2004-2008, reaching 35.7% for bilateral mastectomy and 22.9% for contralateral mastectomy (29). However, there are a large number of patients who do not accept this surgery due to the **disadvantages and complications** that it entails. The study carried out by M.Barton et.al. has seen that two-thirds of women who

undergo a PBM experience at least one complication after surgery (30). Some of the main **disadvantages** of PBM are (31–34):

- It is an **irreversible and disfiguring surgical procedure** that can significantly affect the quality of life. One study reported that only 55-60% of women who had previously undergone a mastectomy would opt for the same procedure again, as they are aware of the psychological effects of such breast alteration.
- PBM has a **negative impact on sexuality and body image**. This is caused by a reduction of self-confidence, loss of erogenous zones, and the presence of pain and discomfort in the breasts. It has been reported that one year after PBM, more than 50% of women feel less physically attractive and dissatisfied with their physical appearance.
- After this operation, the nipple may not have a good blood supply, which can **atrophy or deform the tissue.**
- The nipple is often **numb or insensitive** because the sensory nerves in the breast can also be affected. In addition, a prevalence of **breast pain** after mastectomy of 69% has been reported.
- Women who have a PBM will not have the ability to **breastfeed** when pregnant.
- Some women experience **anxiety or depression** about the change in her body image. Some patients feel that a mastectomy is like an organ amputation. Therefore, this causes them a high level of stress, and makes them prone to mood disorders.

2.3. HEREDITARY BREAST CANCER

This section focuses on women with a BRCA gene mutation who have already developed breast cancer. In these cases, risk reduction measures are no longer applied. Instead, the diagnostic process must be initiated in order to apply the appropriate treatment.

2.3.1. Clinical implications

BRCA1/2-positive patients with breast cancers have different clinical, molecular, morphological, and immunohistochemical characteristics than sporadic and familial breast cancers.

At a clinical level, it has been found that these patients are usually diagnosed at a younger age and have a higher risk of developing a second contralateral tumor after the diagnosis of previous cancer (with a risk of 5% per year) (10).

BRCA1 mutation breast tumors have the following characteristics (5,24):

- They tend to present at 40 years old.
- They are frequently bilateral (40%).
- They usually progress directly to invasive disease without a precancerous ductal carcinoma in situ (DCIS) component.
- 60%-80% of breast cancers in women with a BRCA1 mutation are triple-negative.
- Approximately 75% of BRCA1 breast cancers are invasive ductal carcinoma, and 10% are atypical medullary cancer.
- A higher frequency of mutations in TP53 and p53 expression is observed at the molecular level.

In the case of breast tumors with a BRCA2 mutation, it has been found that (5,24):

- They tend to present in patients younger than the general population but older than BRCA1.
- 70%-80% of breast cancers in women with a BRCA2 mutation are estrogen receptor-positive, progesterone receptor-positive, and HER2 negative.
- In BRCA2 breast cancers, the most frequent are the lobular or ductal with lobular types (up to 10% of cases).

2.3.2. Prognosis

Many studies agree that BRCA1-positive breast tumors have a worse prognosis than sporadic tumors, although contradictory results have been found in the literature.

Despite this, it has been seen that tumors linked to BRCA1 present a more aggressive phenotype (triple-negative), and those associated with BRCA2 do not show substantial differences compared to sporadic breast cancer.

In addition, Lee et. al. showed that BRCA1-positive women have a lower short-term and long-term overall survival (OS) rate and a lower short-term progression-free survival rate (PFSR) (22).

2.3.3. Diagnosis

Breast cancer diagnosis, both sporadic and hereditary, is achieved by clinical examination, complementary tests, and histological confirmation.

Clinical examination

It should include a complete anamnesis with personal and family medical history (history of breast/ovarian cancer), bimanual palpation of the breasts and regional lymph nodes, and the search for distant metastases by examination of the liver, lungs and bones, and neurological examination (if symptoms are present).

Supplementary tests

There are a wide variety of imaging tests that can be used in the diagnosis of breast cancer. According to the "SEOM clinical guidelines" a bilateral mammogram and an ultrasound of the breast and regional lymph nodes should be performed in patients with suspected breast cancer (35,36).

Diagnosis should be based on the Breast Imaging, Reporting & Data System (BIRADS), which is a system for standardizing the results of mammograms, ultrasound scans, and magnetic resonance image (MRI) of the breast depending on the degree of malignancy (37). The BIRADS can be found in ANNEX 3.

Laboratory tests are also routinely performed. However, these tests have not been shown to improve the detection of hidden metastases.

Once the diagnosis is made, MRI can be used for staging. It is the most sensitive imaging test for breast cancer staging, but it must still be confirmed by histology due to

the presence of false positives. For this reason, the use of MRI is not mandatory, but it can be considered in the case of breast cancer with a BRCA mutation (35,36).

Histological confirmation

The pathological diagnosis is made by core needle biopsy (CNB), guided by "stereotactic guidance" or by ultrasound. It is recommended to obtain a minimum of 2-3 biopsies. Ultrasound-guided fine needle aspiration biopsy (FNAB) or CNB of suspicious lymph nodes should also be performed.

The pathological diagnosis should include the study of estrogen receptor (ER), progesterone receptor (PgR), human epidermal growth factor receptor 2 (HER2), and gene expression.

Moreover, the pathological diagnosis should be based on the World Health Organization (WHO) classification and the staging method tumor, nodule, metastasis (TNM).

Extension study

The early-breast cancer staging is based on the study of locoregional disease, since asymptomatic metastases are rare. That is why most patients do not benefit from full laboratory tests (tumor markers, radiological stratification).

In the case of advanced breast cancer, it will be necessary to carry out an extension study to determine the presence of metastases (38):

- Blood analysis: It allows us to suspect the presence of medullary metastasis (if there is pancytopenia), liver metastasis (impaired liver function) and bone metastasis (elevated alkaline phosphatase).
- Bone gammagraphy: It allows the study of the bones' metastasis.
- Thoracic-abdominal CT.
- PET: In case of high suspicion of metastasis and it has not been diagnosed by the previous tests.

2.3.4. Classification and staging

Once the diagnosis is made, the tumor must be classified using the following methods.

Histological classification

The histological classification is based on the WHO classification (ANNEX 4). Within this classification, it can be sub-classified into:

- Preinvasive: The most frequent is "no special type" (NST) in situ, and lobular carcinoma in situ.
- Invasive: The most frequent are NST (anterior ductal carcinoma) (70-75%) and lobular carcinoma (12-15%). The other 18 subtypes exhibit specific morphological features and are rare (0.5-5%) (35).

Immunohistochemical classification

Currently, immunohistochemical classification is used, which is a more precise classification with greater correlation with the disease's diagnosis, treatment, and relapse, based on histology and molecular biology.

It uses the proliferation marker Ki67 (for which an optimal cut-off point has not been established, but a value of 20% is accepted), the HER2 amplification or overexpression, and the hormonal receptors state (- / +) (39).

Using all these data, breast tumors can be classified into four subtypes: luminal A, luminal B, HER2 positive, and triple-negative (TNBC).

This classification is summarized in table 3:

Table 3. Breast cancer subtypes based on biomolecular markers and Ki67.
Adapted from (40)

Tumor subtype	Luminal A-like	Luminal B-like		Triple negative	HER-2 enriched
		HER2 negative	HER 2 positive		
Molecular Biology	ER positive	ER positive	ER positive	ER negative	ER negative
	PgR positive	PgR positive	PgR positive	PgR negative	PgR negative

	HER 2 negative	HER 2 negative	HER 2 positive	HER 2 negative	HER 2 positive
	Ki67<20%	Ki67>20%	Ki67>20%		
Characteristic data	Best prognostic	Worse prognostic than luminal A-like subtype		Survival from relapse is lower	Most frequent subtype of CNS relapse
Treatment options	Hormonotherapy	Chemotherapy, hormonotherapy and anti-HER2		Only chemotherapy	HER-2 target treatment and chemotherapy

ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PgR, progesterone receptor; CNS, central nervous system

TNM stage

The TNM system of the American Joint Committee on Cancer (AJCC) is the most widely used staging system for breast cancer. It has both clinical and pathological staging systems for breast cancer (ANNEX 5).

Clinical staging is used to help plan treatment. However, there are times when cancer has spread beyond what the clinical stage estimates and may not predict the patient's prognosis as accurately as a pathological stage.

Pathologic staging is determined by examining tissue removed during an operation (41).

TNM is based on three factors, tumor size (T), lymph node involvement (N), and the presence of distant metastases (M) (26).

Prognostic stage

The AJCC committee created the prognostic staging protocol, which integrates biomarkers into the TNM staging system. Biomarkers indicate tumor grade, hormone receptor status, and HER2.

There are two prognostic stages: the Clinical Prognostic Stage, which is assigned to all patients regardless of the type of treatment performed, and the Pathologic Prognostic Stage, which is assigned to those patients who have received surgical treatment (ANNEX 6) (42).

In these prognosis, stage 0 implies carcinoma in situ, while stages I-IV indicate the presence of invasive cancer. Stage IV already implies the presence of distant metastases (26).

2.3.5. Treatment

Once breast cancer has been diagnosed, risk reduction measures are no longer carried out, but a treatment directed against the tumor is performed. Treatment will vary depending on whether it is an early breast cancer or advanced breast cancer.

Early breast cancer

Treatments for BRCA1 / BRCA2 positive breast cancer are similar to those for BRCA negative breast cancer and are based on **locoregional treatment** (surgical treatment and radiotherapy), and **systemic therapy** (chemotherapy and hormonal therapy).

Surgical treatment

- **Surgical management of the primary tumor:** It may be the first step in early-breast cancer treatment, or it may be preceded by systemic therapy, depending on tumor size, tumor biology, and comorbidities.

  In the case of hereditary breast cancer, women who prefer breast preservation, **conservative surgery + RT should be offered** whenever clinically appropriate.

  The most critical factor in conservative surgery is the **tumor margin** since a positive tumor margin (cancer cells that extend beyond the border) implies a significant impact on local recurrence after conservative surgery. That is why when performing this surgery, the report must specify the state of the margins. In case of obtaining **positive margins**, additional surgery will be required (26).

  Although conservative surgery is a valid option, many BRCA1/2 carriers with breast cancer choose **unilateral or bilateral mastectomy** (with both therapeutical and prophylactic intention) because of an increased risk of second primary tumors and CBC (12,25).

  A **nipple-sparing mastectomy** with immediate or delayed breast reconstruction for women with BRCA1/2 positive breast cancer is the most appropriate option (25).

- **Surgical management of the armpit:** Management of the armpit is necessary for all patients with invasive breast cancer since the status of the axillary lymph nodes is **the most important prognostic factor** in early breast cancer.

  Currently, if the preoperative axillary ultrasound and FNAB are negative, the initial treatment of choice is **SLNB,** which consists of locating in the operating room by isotopic activity the lymph nodes that may be affected and analyzing them by biopsy (43).

  The SLNB allows **lymph node staging**, and based on this, the treatment to be followed is decided (table 4):

Lymph node stage		Recommendation	Level of evidence
pN0		Observation, follow-up, without radiotherapy or axillary lymphadenectomy	IA
pN1	pN1mic	Observation, monitoring	IA
	pN1	Observation, monitoring, axillary lymphadenectomy or axillary radiotherapy	IB
pN2-N3		Axillary lymphadenectomy + axillary radiotherapy	IA

Table 4. Axillary treatment recommendations according to lymph node involvement. Adapted from (44)

If **previous neoadjuvant treatment** has been carried out, the following is performed: selective adenectomy of the node previously marked with a scout probe + biopsy of the sentinel node + intraoperative biopsy of all the extracted nodes.

Radiotherapy

Radiation therapy is used as adjunctive treatment in all women treated **with conservative surgery** and in women at **high risk of recurrence** if treated with mastectomy. Patients with 4 or more positive nodes, large primary tumors (T3-T4) and positive resection margins are considered at high risk of recurrence (45).

External radiation therapy is applied in case of conservative surgery. It is based on administering fractions of 1.8-2Gy/day, five times a week, for 4-5 weeks until reaching a total dose of 45-50 Gy.

An additional 2 weeks can also be added if an extra dose is administered into the tumor bed to prevent tumor recurrence (46). The boost indication will be considered in patients with risk factors for local recurrence (47).

Hypofractionated radiotherapy can be performed in order to shorten the treatment time. It consists of administering the same treatment volume but with a higher dose per fraction (> 2Gy / day) (48).

Systemic treatment

In patients with early-stage BRCA1/2-positive breast cancer, both neoadjuvant and adjuvant treatment can be offered as they produce similar results (49). The goal is to prevent recurrences and treat micro-metastatic disease.

Different types of systemic treatment (chemotherapy and hormonal treatment) may be offered depending on the type of tumor.

- Triple-negative tumor: They are not candidates for hormonal treatment, but can be treated with chemotherapy (50,51). Most patients with a high-risk triple-negative tumor are treated with neoadjuvant chemotherapy. The addition of poly adenosine diphosphate-ribose polymerase (PARP) may be considered in patients with deleterious BRCA1/2 mutations.
- Hormone receptor positive tumor: Both chemotherapy and adjuvant hormone therapy can be administered in tumors with a positive hormone receptor (ER+ or PR+). Hormonal treatment varies depending on the woman's menstrual status. In premenopausal women, tamoxifen is used +/- ovarian suppressive medication; while in postmenopausal women, tamoxifen and aromatase inhibitors can be used alone or in sequence (51).

Advanced breast cancer

Advanced breast cancer comprises inoperable locally advanced breast cancer (which has not spread to distant organs), and metastatic breast cancer (stage IV). Common localities of spread are bone, the lungs and the liver.

It is treatable but an incurable disease, and the metastases are the principle cause of death in almost all patients, with a median overall survival of 2–3 years.

Treatments for metastatic breast cancer aim to relieve their symptoms and to prolong quality-adjusted life expectancy.

Surgical treatment

In patients with metastatic breast cancer, surgical treatment can be considered for two purposes (26):

- **Resection of metastases**: It remains controversial, but may be an option for selected patients based on the pattern and chronicity of the disease.
- **Palliative surgery:** It can be an option in individual situations to achieve adequate locoregional control.

Radiation therapy

It is used to relieve the symptoms of bone, brain and soft tissue metastases. It should be prescribed individually according to the severity of the injuries and the life expectancy of the patient (26).

Systemic treatment

It is the basis of treatment in metastatic tumors. Systemic therapy is guided by the type of tumor (26):

- **Luminal type:** Several lines of endocrine therapy should be used until endocrine resistance appears, except in cases of rapid progression or a visceral crisis (severe organ dysfunction).
    - In premenopausal patients, ovarian suppression or ablation is performed combined with another endocrine therapy agent (tamoxifen, an aromatase inhibitor, or fulvestrant).
    - In postmenopausal patients, first-line endocrine therapy may be an aromatase inhibitor, fulvestrant, or tamoxifen.

  When chemotherapy is needed (for example, once endocrine therapy options have been exhausted or no response is obtained with them), **PARP** inhibitors are administered in patients with a BRCA gene mutation.
- **Triple-negative:** PARP inhibitors are administered as the first line of treatment.

- HER2+: Chemotherapy treatment is combined with immunotherapy (dual HER2-blockade with trastuzumab and pertuzumab).

The systemic treatment in advanced breast tumors is summarized in **ANNEX 7**.

2.4. EXTERNAL RADIOTHERAPY

External radiation therapy is commonly used as a therapeutic option for women who already have breast cancer. Nevertheless, its prophylactic use in women with a BRCA 1/2 gene mutation who have not yet developed a breast tumor is unknown. This section focuses on the operation of external radiation therapy and its biological effects to understand its application as a preventive method.

2.4.1. Definition

Radiation therapy is the use of high-powered X-rays or other particles to eliminate cancer cells. External radiation therapy is characterized by giving radiation from a machine that is located outside the body. The linear accelerator creates the radiation beam, and a computer program adjusts the size and shape of the beam to direct it toward the tumor.

The radiation dose is measured in Gy and corresponds to the amount of energy absorbed by the tissue (Jules/Kg).

The total dose of a treatment is divided into several small fractions delivered daily over weeks until the total dose is reached. It is done this way because the dose/fraction size response is different for rapidly dividing tumor tissue than slowly dividing healthy tissue. The small dose/fraction protects healthy tissue more than tumor tissue, increasing the therapeutic window, causing more significant tumor cell death and greater protection of healthy tissue (52).

2.4.2. Biological effects of radiation to cancer cells

The biological effects of radiotherapy derive from the damage that radiation produces to the cells' DNA. Radiation can affect DNA in two different ways (53):

- Direct effect: The DNA chain is broken by the action of the photon.

- Indirect effect: They can ionize other molecules in the cell, especially water molecules, to form free radicals that damage DNA. The ionization or substitution of one of the DNA bases occurs by interaction with free radicals.

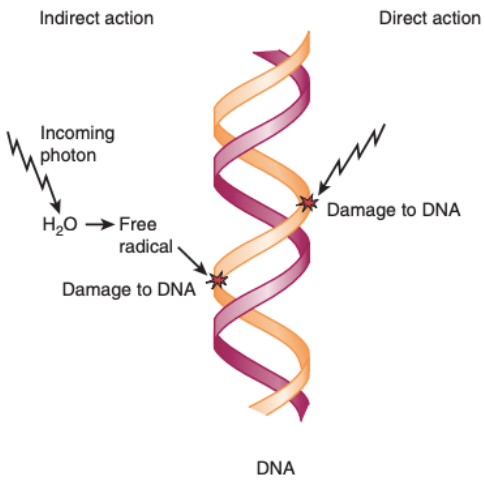


Figure 4. Direct and indirect actions of radiation (53)

The goal of radiation is to induce cell death in tumor cells and induce as minor damage as possible in healthy cells capable of repair. However, if healthy cells are damaged and not repaired correctly, it can lead to two effects (53):

- Stochastic effects: The mutation caused by ionizing radiation produces a transformation of the cell. It can lead to the development of radioinduced tumors.
- Deterministic effects: They occur due to the death of a large number of cells in a tissue or organ. There is visible damage that reflects a loss of tissue function.

These two effects will lead to the development of side effects.

Radiosensitivity

Radiosensitivity is the susceptibility of cells to the harmful effect of ionizing radiation. Cells have different degrees of radiosensitivity depending on several factors: reproduction's degree, availability of oxygen, total radiation dose, cell type, radiation type, stage of cell division, part of the body exposed, general state of health, the volume of the tumor, and time interval during which the dose is received.

Actively reproducing cells are more sensitive because dividing cells need cellular DNA to be in good condition for descendant cells to survive. Direct interaction on an active cell can induce its death, while direct interaction with an inactive cell will have a lesser effect.

Malignant cells are an example of a very sensitive cellular system. The outer layer of cells reproduces rapidly and has a good supply of blood and oxygen. In contrast, **anoxic cells** (cells with insufficient oxygen) tend to be inactive, like cells inside tumors. To destroy a tumor, the patient is exposed to **small daily radiation fractions** that allow the outer layer of dividing cells to be killed. This gives healthy tissue a chance to recover from any damage while gradually shrinking the highly sensitive tumor (53).

In the case of **prophylactic external radiotherapy**, the objective is to eliminate tumor cells that have not been diagnosed yet due to the lack of more sensitive diagnostic systems. In this way, we eliminate the tumor in such early stages that it cannot even be detected.

2.4.3. Radiation process

Radiation therapy consists of different stages (52):

1. **Simulation:** First, the patient is immobilized in a position that allows to reproduce the same position throughout the entire treatment.

   Standard or customized fasteners are used for positioning and immobilization. For example, in the case of breasts radiation, the patient must be in a supine position with the arms raised above the head. A breast bracket and one or two pole positions can be used to immobilize the arms (54).

   Once the patient is positioned, a CT scan is performed to obtain images that define the irradiation area. Then, the patient is marked with a small tattoo on the skin to be aligned to the treatment machine.

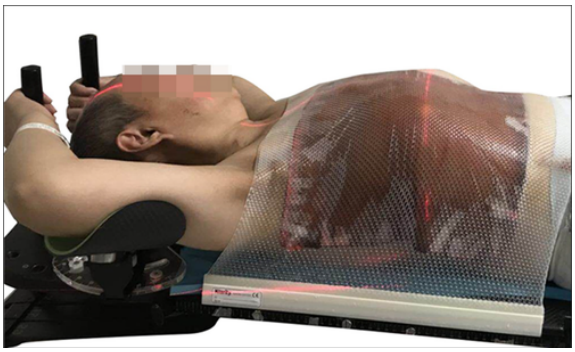


Figure 5. Breast bracket and double-pole position(54)

2. **Definition of treatment volumes**: The different images are merged into the CT-simulator image to allow optimal spatial correlation.

The radiation oncologist must define the area to be irradiated and the healthy organs close to the tumor.

The images of the CT-simulator without contrast are used to calculate the dose distribution since they generate an electronic density map that allows quantifying the radiation absorption for each tissue.

3. **Design and calculation of the treatment:** A computerized planning system is used to design the radiation therapy plan. Initially, the radiation oncologist defines the volume of treatment and the organs at risk to be protected, the total dose, the fractionation, and the dose limits for the organs at risk.

   This information is given to the physics and dosimetry team to develop the plan. The plan's position, number, direction, shape, energy, and dose ratio for the radiation beams or fields are optimized.

   Finally, the planner calculates the dose distribution and presents the result graphically on the volumes drawn or mathematically using a dose-volume histogram.

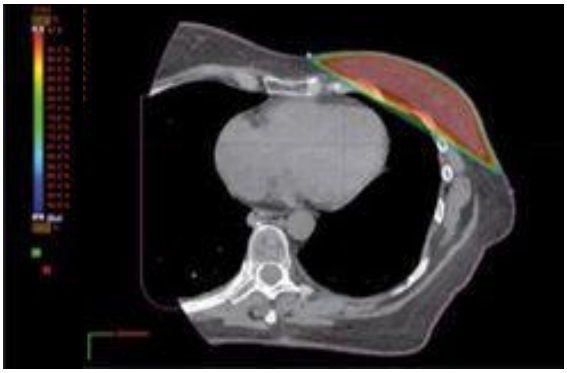


Figure 6. Dose distribution in the breast (52)
The area colored in red corresponds to the distribution of the radiation dose.

4. **Registration and verification systems:** As radiotherapy treatments are very complex, computerized systems are used to record the information generated in the planner, take it to the treatment machine and verify that each of the planned parameters is reproduced.

5. **Treatment:** The patient is positioned on the treatment table in the same position of the simulation. Verification radiographs are taken with the linear accelerator, and the position is corrected if necessary. Then the corresponding radiotherapy fraction is applied.

   The application of radiation is reproduced daily throughout the treatment.

Before using radiotherapy machines, these must be calibrated according to the previously established conditions.

2.4.4. Side-effects of breast external radiotherapy

The development of side-effects on healthy organs depend on the organ, the amount of volume irradiated, the total dose, the daily dose or fraction, and the time between fractions. The adverse effects of radiation therapy occur only in the area of the body that has been irradiated. They can be divided into (55–57):

Common side effects

- Acute side effects: It occur up to 6 months after finishing treatment.
    - Erythema: It appears in the first 24 hours and reaches a maximum after 20-40 Gy.
    - Pruritus: It appears due to obliteration of the sebaceous glands and dry desquamation.
    - Mild-moderate fatigue: It is one of the most common side-effects.
    - Hyperpigmentation: It is possible that radiation activates the melanocytes, promoting the formation of melanin and hyperpigmentation.
    - Armpit discomfort/pain.
    - Loss of hair in the armpit: The hair might fall out in the area under the arm (armpit) on the treated side.
    - Edema: Radiotherapy can cause damage to the lymphatic system and reactions to surrounding tissues, which can lead to breast edema.
    - Dryness of the skin.
- Long-term side effects: It occur months or even years after treatment ends.
    - Radiation dermatitis: It appears after 2-10 years of treatment. It manifests with hyperpigmentation, erythema, dry desquamation, or moist desquamation.
    - Arm swelling (lymphedema): Lymphedema is characterized by an abnormal swelling that can develop in the arm, hand, breast, or torso. It can appear during the months or even years after treatment ends, particularly in cases where lymph nodes are treated.

Less common side effects

- Short-term side effects:
  - Acute pericarditis and myocarditis: Pericarditis and myocarditis are rare complications (<1%). They usually manifest with chest pain with pleuritic features or dyspnea.
  - Radiation pneumonitis (RP): It can manifest within weeks or months after radiotherapy. It appears in approximately 3% of patients.
  - Brachial plexopathy: It can occur in breast cancer patients who receive radiation therapy to the supraclavicular and axillary lymph node regions.
  - Erythema multiforme and Stevens Johnson syndrome: It is a very rare side-effect (<1%). Normally it appears when radiotherapy is combined with certain drugs (antiepileptic, antineoplastic, methotrexate, antituberculostatic).
- Long-term side effects:
  - Clavicle fractures: The bones are weakened by radiation therapy. It is detected in approximately 2% of patients.
  - Pulmonary fibrosis: It appears in 1% of patients between 6-12 months following completion of radiotherapy, and can continue to progress for 2 years.
  - Heart problems: Long-term side effects may appear years after radiation therapy (some of them >20 years post-treatment). It includes coronary artery disease, constrictive pericarditis, valvular heart disease, arrythmias, and heart failure.
  - Radioinduced sarcoma (RIS): It can originate in either the irradiated bone or soft tissues after a period of latency. The risk of RIS is approximately 1 in 1000 patients per decade of follow-up.

3. JUSTIFICATION

Breast cancer is the **most prevalent** cancer in the world. Also, it is the cancer that causes the most **DALYs** globally and the **leading cause of death** from cancer in women (6).

For women born with a germline BRCA1/2 mutation, the lifetime risk of developing breast cancer is approximately **70%.** Furthermore, breast tumors of BRCA mutation carriers appear in **younger women** and are **more aggressive tumors**. Besides, the risk of contralateral breast cancer is 25-30% for 10 years, compared to 3% in non-BRCA mutation carriers (5,58). This is why risk reduction measures are applied.

Currently, the most accepted risk reduction measure is **prophylactic bilateral mastectomy** since it reduces the risk of breast cancer by **90%.** In general, a total skin-sparing mastectomy is recommended (28).

However, 64.3% of patients do not agree to undergo this surgery due to the disadvantages and complications that it entails: it is an irreversible and disfiguring surgical procedure that can leave the nipple insensitive and the breasts sore, it has a negative impact on sexuality and body image, it can generate depression or anxiety due to body image change, and women who undergo a PBM will not have the ability to breastfeed if pregnant (40–43).

To seek alternatives to PBM, this study aims to evaluate the use of prophylactic external radiation therapy in women with BRCA gene mutation. External radiation therapy is currently used as a treatment for breast cancer, but **it is not established as a prophylactic treatment,** and **no study has tested it**. Therefore, our clinical trial would be **the first one worldwide** to assess the efficacy of prophylactic external radiation therapy and raise the possibility of offering new prevention techniques to these patients.

We consider it a feasible alternative because a single phase-II trial has been conducted to evaluate the use of prophylactic radiotherapy in the contralateral breast for BRCA mutation carriers with early-stage breast cancer. In this study, prophylactic external radiation therapy of the contralateral intact breast in addition to standard locoregional treatment of the affected side achieved an 80% reduction of breast cancer and delayed its onset (32 versus 92 months) (12).

In conclusion, external radiation therapy seems to be a valid prophylactic option, but studies still lack in order to consider its use in clinical practice.

4. HYPOTHESIS

The primary hypothesis of this study consists of:

- In women over 40 years old with BRCA 1/2 mutation, the use of prophylactic external radiation of the breasts can reduce the risk of subsequent breast cancers, compared to screening strategy.

The secondary hypothesis of this study is:

- In women over 40 years old with BRCA 1/2 mutation, the increase in adverse effects caused by prophylactic external radiation therapy will not be clinically relevant.

5. OBJECTIVES

The primary objective of this study consists of:

- To assess the number of patients who develop breast cancer after using prophylactic external radiotherapy compared to screening strategy, in women over 40 years old with BRCA 1/2 mutation.

The secondary objective of this study is:

- To study the incidence of side effects of prophylactic external radiation therapy compared to screening strategy, in women over 40 years old with BRCA 1/2 mutation.

6. METHODOLOGY

6.1. STUDY DESIGN

The study will be a **randomised, parallel-group, multicentre, and open-labelled clinical trial.** It will be designed as a comparison between prophylactic external radiotherapy plus screening strategy vs. only screening strategy.

The study will be carried out in 3 hospitals of the Institut Català d'Oncologia (ICO) of the community: ICO Girona (which works together with the Dr. Josep Trueta University Hospital), ICO of l'Hospitalet de Llobregat and ICO Badalona. The ICO Girona will be the reference center.

In each of the centers we will assign a **principal researcher** (a gynecologist) who will propose to the patients to enter into the study and do the corresponding follow-up; a **radiologist** for the external radiation therapy and the breast-image evaluation, and an **oncologist**, in case patients develop breast cancer.

6.2. STUDY POPULATION

The population of this study will be women more than 40 years old diagnosed with a BRCA1/2 germline mutation without any breast cancer, who do not want to undergo prophylactic bilateral mastectomy, and who attend to "Unitat d'alt risc oncologic" (UARC) of the ICO hospitals (ICO Girona, ICO Badalona and ICO Hospitalet de Llobregat).

All patients must meet the following inclusion and exclusion criteria.

6.2.1. Inclusion criteria

- **Women.**
- **Carriers of a deleterious mutation in BRCA1/2.**
- **Over 40 years old**: 40 years old is chosen as the cut-off point because it is the average age of onset of breast cancer in patients with a BRCA gene mutation (59).
- **Absence of breast cancer.**

6.2.2. Exclusion criteria

- Patients with BRCA 1/2 mutation who accept prophylactic bilateral mastectomy.
- Presence of breast cancer.
- Patients with other primary tumors diagnosed before the study.
- Patients with other deleterious mutations that increase the risk of breast cancer.
- Pregnant women.
- Previous irradiation of the breast.
- Women with scleroderma and systemic lupus erythematosus.
- Woman with breast prosthesis.

6.2.3. Withdrawal and replacement of patients

Whenever possible, an attempt should be made to have patients complete the study. Patients starting the study should continue the follow-up according to the protocol unless there is a justified reason:

- Patient lost to follow-up: When the investigator tries to contact the patient to assess her health status, and the patient does not attend scheduled visits. If, after two documented calls, the investigator is unable to communicate with the patient, she will be considered lost to follow up.
- Request from the patient or legal representative: Consent is withdrawn for the study.
- Death.

A record of the loss of the patient should be kept during follow-up with her documents along with the reason.

6.2.4. End of the study

All patients will be followed until breast cancer development, completion of study or death.

Initially, a recruitment time of 2 years and 6 months has been estimated with a 5-year follow-up. Even so, every year statistical analyzes will be carried out. It will allow to monitor both the efficacy and side effects of prophylactic external radiation therapy. In case of demonstrating a great efficacy of external radiotherapy or in case of observing

serious side effects in a period less than 5 years, the study will be concluded and the results will be published.

6.3. SAMPLING

6.3.1. Sample size

We estimated the sample size using the **GRANMO software**, and the setting for two independent proportions.

The 5-year cumulative risk of developing breast cancer in women who carry the BRCA 1/2 mutation is **11%** (60). Based on Evron. et.al, we expect to see an **80% risk reduction of breast cancer** with prophylactic external radiotherapy. Considering that, we will see a cumulative risk of **2% over 5 years** in women who accept irradiation.

We assumed a risk alpha of 0,05 and a risk beta of 0,2 in a two-sided test. The estimated loss at follow-up is 5%.

Using these variables, GRANMO calculated 108 subjects in each group to ensure a significant difference. Therefore, a total of 216 patients will be needed.

6.3.2. Estimated time of recruitment

In 2020, **183 new cases** of women with a BRCA gene mutation were diagnosed.

64.3% of women with a BRCA gene mutation do not agree to undergo a PBM and prefered the screening strategy. We estimate that 80% of these patients will accept to enter the study. Therefore, 94 patients will be recruited each year. Thus, it will take **2 years and 6 months** to recruit **216 patients** (108 patients to each group).

6.3.3. Sample selection

Our sample will be obtained through a **consecutive non-probabilistic sampling**. The choice to enter the study will be offered only to BRCA 1/2 carrier patients **who decline PBM.**

All patients with BRCA mutation who attend to the ICO hospitals plus meet the inclusion criteria will be asked to participate and will be given the information document and the informed consent. Physicians will highlight the confidentiality and voluntary aspects of patients' participation.

The sample recruitment will take place in the UARC of the ICO Girona, ICO Badalona and ICO Hospitalet de Llobregat.

6.4. RANDOMIZATION AND MASKING

Every woman who enters the study diagnosed with BRCA1/2 mutation who decline BPM and meet the inclusion criteria will be randomized into one of the two groups:

- Group 1 (study group): Patients who will receive prophylactic external radiation plus screening strategy.
- Group 2 (control group): Patients who will only undergo the screening strategy.

Because one group will receive an intervention and the other will not, a triple-blind study is not possible. Both the patient and the researcher will be aware of the assigned group. Therefore, the only possibility to reduce the risk of bias is that the statistician will be blinded.

6.5. VARIABLES

6.5.1. Independent variable

Risk reduction option

It will be a dichotomic qualitative variable: prophylactic external radiotherapy plus screening strategy or only screening strategy.
It will be expressed by a percentage of patients who undergo prophylactic external radiotherapy plus screening strategy, and patients who undergo only screening strategy.

6.5.2. Dependent variables

Development of breast cancer

The development of breast cancer will be the main variable of the study and will be evaluated by clinical controls every 3-4 months and bi-annual imaging test (alternating ultrasound and mammography with MRI). If a suspicion of a breast tumor appears in any of the controls, a CNB will be performed, and the woman will be considered to have a breast tumor if she obtains a positive malignant histology.
It will be a dichotomic qualitative variable:

- Presence of breast tumor.
- Absence of breast tumor.

Side effects

- Radiation dermatitis

  It is defined as "a finding of cutaneous inflammatory reaction occurring as a result of exposure to biologically effective levels of ionizing radiation"(61).

  It will be diagnosed by **physical examination** when the investigator detects the presence of hyperpigmentation, erythema, dry desquamation, or moist desquamation.

  Then it will be classified according to the **Common Terminology Criteria Adverse Events (CTCAE)** (61):

  - Grade 1: Faint, erythema or desquamation.
  - Grade 2: Moderate to brisk erythema or patchy, moist desquamation confined to skin folds and creases. Moderate swelling.
  - Grade 3: Confluent, moist desquamation greater than 1.5 cm diameter, which is not confined to the skin folds. Pitting oedema (severe swelling).
  - Grade 4: Skin necrosis or ulceration of full-thickness dermis (middle layer of skin).

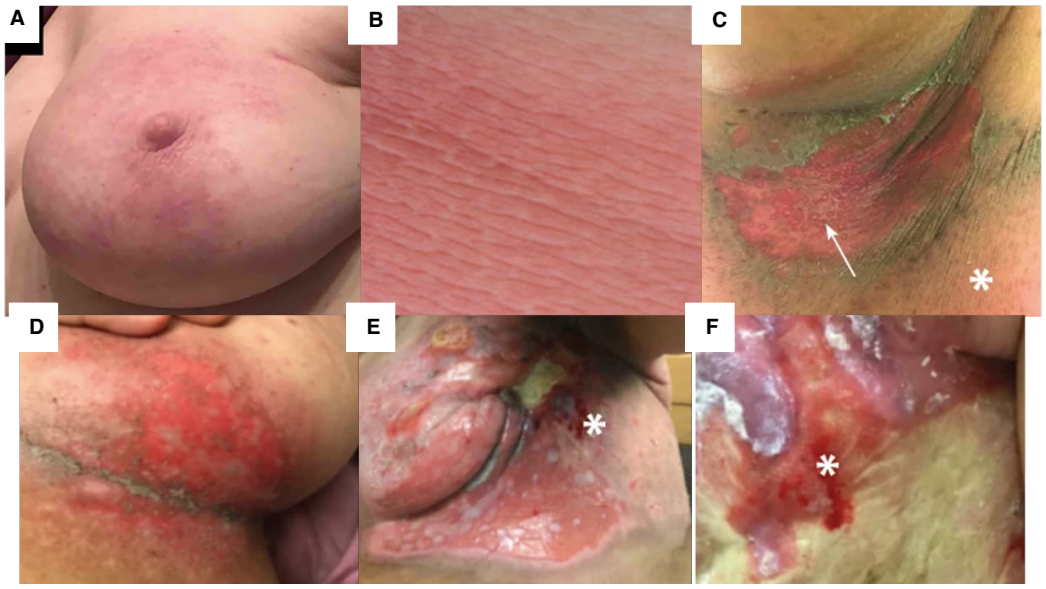


Figure 7. Grades of radiation dermatitis. Adapted from (62)

A-B: Represent grade 1 dermatitis with hyperpigmentation and erythema of the breast. C-D: Represent grade 2-3 dermatitis with desquamation. E-F: Represent grade 4 dermatitis with ulceration

It will be **dichotomized** into two options:

- **Presence of radiation dermatitis:** If the patient presents a CTCAE score of 1 or higher.
- **Absence of radiation dermatitis:** If the patient does not present the side effect.

- Lymphedema

It is defined as "a disorder characterized by excessive fluid collection in tissues that causes swelling" (61). It can appear on the arms and also the breasts.

It will be diagnosed by **physical examination.** Then it will be classified according to the **CTCAE** (61):

- Grade 1: Trace thickening or faint discoloration.
- Grade 2: Marked discoloration; leathery skin texture; papillary formation; limiting instrumental activities of daily living (ADL)*.
- Grade 3: Severe symptoms; limiting self-care ADL**.

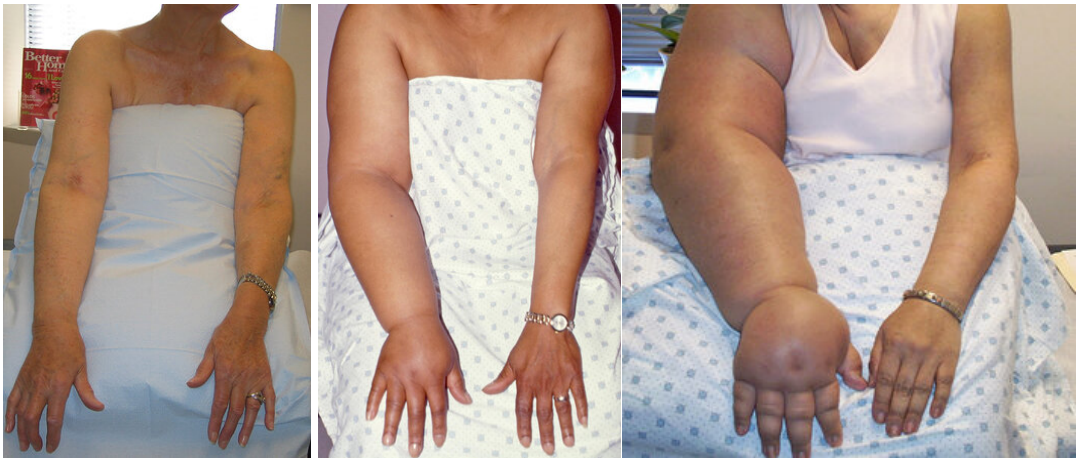


Figure 8. Examples of arm lymphedema (63)

It will be **dichotomized** into two options:

- Presence of lymphedema: If the patient presents a CTCAE score of 1 or higher.
- Absence of lymphedema: If the patient does not present the side effect.

- Spontaneous rib fracture (SRF)

SRF is defined as fractures without apparent blunt-force trauma.

*Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
**Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

A **chest X-ray** will be performed when the patient presents symptoms compatible with a rib fracture (pain in the chest wall that gets worse when breathing, moving, or coughing; shortness of breath; difficulty taking a deep breath). If chest X-ray is negative, a **computed tomography (CT) scan** will be performed.

SRF will be diagnosed when a rib fracture is seen on X-ray or CT scans following external radiation to the thorax in the absence of surgery, trauma, tumor or metastases.

It is a **qualitative dichotomic variable**:

- Presence of SRF.
- Absence of SRF.

- **Radiation pneumonitis (RP):** It is defined as "the development of pneumonitis that lasts from 4 to 12 weeks after radiation" (61). Diagnosis is made by exclusion using clinical assessment and radiological findings.

  A **chest X-ray** and a **pulmonary function test** will be done when symptoms appear (fever, cough, chest congestion, dyspnea, chest pain). Then, it will be classified based on **CTCAE system:**

  - Grade 1: Asymptomatic; clinical or diagnostic observations only; intervention not indicated.
  - Grade 2: Symptomatic; medical intervention indicated; limiting instrumental ADL.
  - Grade 3: Severe symptoms; limiting self-care ADL; oxygen indicated.
  - Grade 4: Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation).
  - Grade 5: Death.

  It will be **dichotomized** into two options:

  - Presence of RP: If the patient presents a CTCAE score of 1 or higher.
  - Absence of RP: If the patient does not present the side effect.

- Other minor acute side-effects

  Other minor side-effects that self-limit after a few days will also be discussed. They have been grouped into the same variable due to their lesser clinical relevance. It will include (61):

- Pruritus: It is defined as “a disorder characterized by an intense itching sensation”.
- Breast pain: It is defined as “a sensation of marked discomfort in the breast region”.
- Hyperpigmentation: It is defined as “a disorder characterized by darkening of the skin due to excessive melanin deposition”.
- Fatigue: It is defined as “a state of generalized weakness with a pronounced inability to summon sufficient energy to accomplish daily activities”.
- Loss of hair in the armpit: It is the loss of body hair in the area exposed to radiation therapy.
- Dryness of the skin: It is defined as “a disorder characterized by flaky and dull skin; the pores are generally fine; the texture is a papery thin texture”.
- Edema: It can be manifested with an increased breast volume, peau d’orange, heaviness of the breast, redness of the skin, breast pain, skin thickening, hyperpigmented skin pores, and a positive pitting sign.

All of them will be diagnosed by physical examination and anamnesis, and will be classified following the CTCAE system (61).

Each of them will be classified in:

- Presence of side-effect: If the patient presents a CTCAE score of 1 or higher.
- Absence of side-effect: If the patient does not present the side effect.

Then, we will analyze it as a discrete quantitative variable (number of minor side-effects).

- Other major side effects

Some serious but very rare (<1%) side effects have been grouped within the same variable. Considering that the group of patients receiving external radiation therapy is 114 patients, we hope to find any or only one patient with each of the following side effects.

- Radioinduced sarcoma (RIS)

  Sarcomas are rare malignant tumors that arise from mesenchymal tissues at any location. To be classified as RIS, sarcoma must meet the following (64):

  - The malignant neoplasm must histopathologically be a sarcoma.
  - The development of sarcoma must occur in an irradiated field.
  - There must be a long latency period (typically 4 years).

  RIS will be diagnosed by histological confirmation. Upon suspicion of RIS, a FNAB will be executed. If the result is negative, but there is high clinical suspicion, a CNB will be performed.

  It is a qualitative dichotomic variable:

  - Presence of RIS.
  - Absence of RIS.

- Lung fibrosis: It is defined as "a disorder characterized by the replacement of the lung tissue by connective tissue, leading to progressive dyspnea, respiratory failure or right heart failure" (61).

  A chest X-ray and a pulmonary function test will be done when symptoms appear (dyspnea, respiratory failure, hemoptysis, airway obstruction, bronchitis). Then, it will be classified based on CTCAE system:

  - Grade 1: Radiologic pulmonary fibrosis <25% of lung volume associated with hypoxia.
  - Grade 2: Evidence of pulmonary hypertension; radiographic pulmonary fibrosis of 25 - 50% associated with hypoxia.
  - Grade 3: Severe hypoxia; evidence of right-sided heart failure; radiographic pulmonary fibrosis >50-75%.
  - Grade 4: Life-threatening consequences (e.g,hemodynamic/pulmonary complications); intubation with ventilatory support indicated; radiographic pulmonary fibrosis >75% with severe honeycombing.
  - Grade 5: Death.

- Radiation pericarditis: It is defined as "a disorder characterized by irritation to the layers of the pericardium" (61).

It will be diagnosed with clinical examination and an electrocardiogram (ECG). Then, it will be classified using the CTCAE system:

- Grade 1: Asymptomatic, ECG or physical findings (e.g., rub) consistent with pericarditis.
- Grade 2: Symptomatic pericarditis (e.g., chest pain).
- Grade 3: Pericarditis with physiologic consequences (e.g., pericardial constriction).
- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death.

- Radiation myocarditis: It is defined as "a disorder characterized by inflammation of the muscle tissue of the heart" (61).

  It will be diagnosed by clinical examination and cardiac MRI. Then, it will be classified using the CTCAE system:

  - Grade 2: Symptoms with moderate activity or exertion.
  - Grade 3: Severe with symptoms at rest or with minimal activity or exertion; intervention indicated; new onset of symptoms.
  - Grade 4: Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support).
  - Grade 5: Death.

- Stevens Johnson syndrome: It is defined as "a disorder characterized by less than 10% total body skin area separation of dermis" (61).

  It will be diagnosed by clinical examination, and it will be classified using the CTCAE system:

  - Grade 3: Skin sloughing covering <10% of body surface area (BSA) with associated signs (e.g., erythema, purpura, epidermal detachment, and mucous membrane detachment)
  - Grade 4: Skin sloughing covering 10-30% BSA with associated signs (e.g., erythema, purpura, epidermal detachment and mucous membrane detachment)
  - Grade 5: Death.

Then, the variable will be **categorized** into:

- Presence of major side-effects: If the patient presents one or more of the major side-effects with a CTCAE score of 1 or higher.
- Absence of major side-effects: If the patient does not present any of the major side-effects.

Table 5 shows a summary of the study variables:

Table 5. Dependent variables

DEPENDENT VARIABLE	DESCRIPTION	MEASUREMENT	CATEGORIES
Development of breast cancer	Qualitative nominal dichotomous	Histological confirmation by CNB	- Presence of breast cancer - Absence of breast cancer
Radiation dermatitis	Qualitative nominal dichotomous	Physical examination, using the CTCAE system	- Presence of radiation dermatitis (CTCAE score of 1 or higher). - Absence of radiation dermatitis
Lymphedema	Qualitative nominal dichomotous	Physical examination	- Presence of lymphedema (CTCAE score of 1 or higher) - Absence lymphedema.
Spontaneous rib fracture	Qualitative nominal dichotomous	Chest X-ray or CT scan	- Presence of SRF - Absence of SRF
Radiation pneumonitis	Qualitative nominal dichomotous	Chest X-ray and a pulmonary function test, using the CTCAE system	- Presence of RP (CTCAE score of 1 or higher). - Absence of RP
Other minor acute side effects *(pruritus, breast pain, hyperpigmentation, fatigue, loss of hair in the armpit, dryness of the skin, edema)*	Quantitative variable	Physical examination, using the CTCAE system	
Other major side effects *(RIS, lung fibrosis, radiation pericarditis, radiation myocarditis, Stevens-Johnson syndrome)*	Qualitative nominal dichotomous	Physical examination and specific complementary tests for each side effect. Use of CTCAE system	- Presence of major side-effects - Absence of major side-effects

RIS: Radio-induced sarcoma; SRF: Spontaneous rib fracture; RP: Radiation pneumonitis; CTCAE: Common Terminology Criteria Adverse Events, CT: computed tomography scan, CNB: Core needle biopsy

6.5.3. Covariables

All possible covariates have been defined to describe the characteristics of the patients and identify possible risk factors associated with unfavorable outcomes in external radiation therapy.

- Age: It will be a quantitative continuous variable, expressed in years.
- Type of mutation: The information will be obtained through the clinical history (the patient will have undergone a genetic study). It will be a qualitative dichotomic variable:
  - BRCA1 mutation.
  - BRCA2 mutation.
- Number of first or second-degree relatives with breast cancer: It will be a quantitative discrete variable. The information will be obtained through the anamnesis.
- Bilateral salpingo-oophorectomy (BSO): BSO is another risk reduction measure used in women with a BRCA gene mutation, and it reduces the risk of ovarian cancer. It has been documented that BSO reduces both ipsilateral and contralateral breast cancer in carrier patients of BRCA1/2 mutation. The information will be obtained from the clinical history. It will be a qualitative dichotomic variable:
  - Yes: The patient has undergone BSO.
  - No: The patient has not undergone BSO.
- Combined hormone replacement treatment (HRT): It is a hormone replacement treatment in which estrogen and progesterone are administered. Breast cancer risk increases the most during the first 3 years of taking combination HRT, but goes back to average about 2 years after the patient stops taking combined HRT (13).

  The information will be obtained from the anamnesis (self-referred). It will be a qualitative dichotomic variable:
  - Yes: When the patient is currently taking combined HRT for less than 3 years, or if she is no longer on treatment but has taken it for less than 3 years in the previous 2 years.
  - No: When the patient is currently taking combined HRT for more than 3 years or if she is no longer on treatment for more that 2 years.
- Estrogen-only HRT: It increases the risk of breast cancer, but only when used for more than 10 years (13).

The information will be obtained from the anamnesis (self-referred). It will be a qualitative dichotomic variable:

- Yes: When the patient has received estrogen-only HRT for more than 10 years.
- No: When the patient has not taken estrogen-only HRT or has taken it for less than 10 years.

- Oral contraceptives: It has been shown that women who take oral contraceptives for more than five years may be at higher risk for breast cancer. This risk goes back to average about 10 years after the patient stops taking it (14).

  The information will be obtained from the anamnesis (self-referred). It will be a qualitative dichotomic variable:

  - Yes: If the patient has been taking oral contraceptives for more than 5 years, or has taken them for more than 5 years and left them less than 10 years ago.
  - No: If she has not taken oral contraceptives, has been taking them for less than 5 years, or has left them more than 10 years ago.

- Tobacco consumption: The WHO definition of "daily smoker" is "a person who has smoked at least one cigarette a day, during the last 6 months" (65).

  Women who have been smoking for more than 10 years appear to have a higher risk of breast cancer than women who have never smoked (66).

  The information will be obtained from the anamnesis (self-referred). We will classify patients into:

  - Daily smoker: A person who has smoked at least one cigarette a day during the last 6 months.
  - Non-daily smoker: A person who has smoked less than 1 cigarette a day during the last 6 months, or a person who has smoked at least 1 cigarette a day for less than 6 months.

  Then, we will create a dichotomous qualitative variable based on the years the patient has been smoking:

  - Risk tobacco consumption: Any daily smoker who has smoked for more than 10 years.

- Non-risk tobacco consumption: Any daily smoker who has smoked for less than 10 years, or any non-daily smoker woman.

- **Alcohol consumption:** Women who have three alcoholic drinks* per week regularly have a higher risk of breast cancer (16).

  The information will be obtained from the anamnesis (self-referred). It will be a **qualitative dichotomic variable:**

  - Risk alcohol consumption: Any woman who has three alcoholic drinks per week regularly.
  - Non-risk alcohol consumption: Any woman who has less than three alcoholic drinks per week.

- **Menarche**: Is the occurrence of a first menstrual period in a female adolescent. Early menarche (<13 years old) is associated with an increased risk of breast cancer (18).

  The information will be obtained from the anamnesis (self-referred). It will be a **qualitative dichotomic variable:**

  - Menarche development <13 years old.
  - Menarche development >13years old.

- **Thelarche**: Is the beginning of breast development at the onset of puberty. Early thelarche (<10 years old) is associated with a 20–30% increased risk of breast cancer (18).

  The information will be obtained from the anamnesis (self-referred). It will be a **qualitative dichotomic variable:**

  - Thelarche development <10 years old.
  - Thelarche development >10 years old.

- **Breast tissue density:** Women with dense breasts have a higher risk of developing breast cancer compared to women who don't have dense breasts (67). The greater the amount of dense tissue, the higher the risk.

  The information will be obtained by mammography. It will be a **qualitative non-dichotomous variable**, classified according to BI-RADS:

* One alcohol drink equals to 200ml of beer, 100ml of wine, 25mL of distilled beverage.

a. Mostly fatty: The breasts are made up of mostly fatty tissue and contain very little fibrous and glandular tissue.
b. Scattered fibroglandular densities: The breasts are mostly fatty tissue, but there are a few areas of fibrous and glandular tissue visible on the mammogram.
c. Heterogeneously dense: A mammogram shows many areas of fibrous and glandular tissue.
d. Extremely dense: The breasts have large amounts of fibrous and glandular tissue.

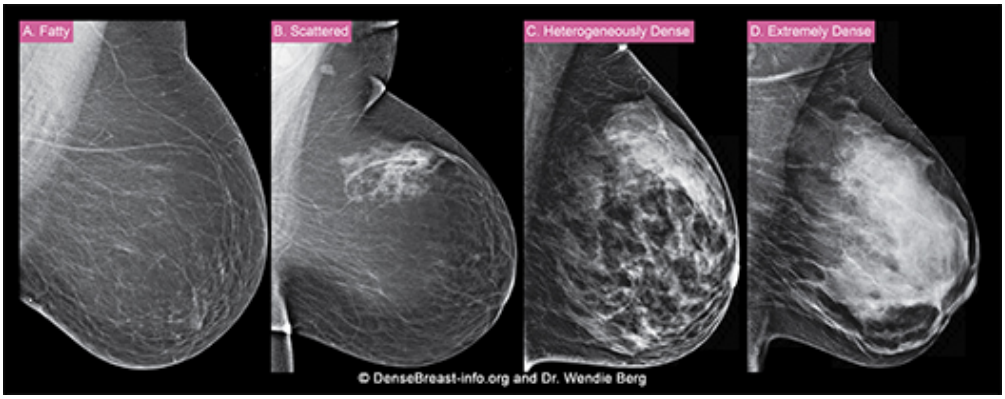


Figure 9. Mammogram of breasts with different levels of density (67)
A: Fatty, B: Scattered, C: Heterogeneously dense, D: Extremely dense.

- **Menopause:** Menopause is the time that marks the end of a woman's menstrual cycles. It is diagnosed after 12 months without a menstrual period. Having late menopause (after 55 years old) is associated with an increased risk of breast cancer (68).

  The information will be obtained from the anamnesis (self-referred). It will be a **qualitative non-dichotomic variable**:

  - Pre-menopause: Patient with less that 12 months without a menstrual period.
  - Younger age onset of menopause: Patient with more than 12 months without a menstrual period, diagnosed before 55 years old.
  - Older age onset of menopause: Patient with more than 12 months without a menstrual period, diagnosed after 55 years old.

- **Breastfeed:** It is the action of feeding the baby with the mother's breast milk. Breastfeeding can lower breast cancer risk, especially if a woman breastfeeds

for longer than 1 year (69). The variable will be measured through the clinical history. It will be a dichotomous qualitative variable:

- Yes: When the patient has breastfed for more than 1 year in at least 1 pregnancy.
- No: When the patient has not breastfed at any pregnancy or has breastfed for less than 1 year.

- **Reproductive factors:** It has been seen that nulliparous women have a higher risk of breast cancer (70).

  The information will be obtained from the anamnesis (self-referred). It will be a qualitative dichotomic variable:

  - Nulliparity: The woman has never given birth to a child, or has never carried a pregnancy.
  - Multiparity: The woman has given birth to a child or has carried a pregnancy.

Table 5 shows a summary of the study covariables:

Table 6. Covariables

CO-VARIABLE	DESCRIPTION	MEASUREMENT	CATEGORIES
Age	Quantitative continuous	Self-referred	
Type of mutation	Qualitative nominal dichotomous	Genetic test	BRCA 1 / BRCA2
BSO	Qualitative nominal dichotomous	Clinical history	Yes / No
Number of relative with breast cancer	Quantitative discrete	Self-referred	
Combined HRT	Qualitative nominal dichotomous	Clinical history	Yes / No
Estrogen-only HRT	Qualitative nominal dichotomous	Clinical history	Yes / No
Oral contraceptives	Qualitative nominal dichotomous	Clinical history	Yes / no
Tobacco consumption	Qualitative nominal dichotomous	Self-referred	Risk tobacco consumption / Non-risk tobacco consumption

Alcohol consumption	Qualitative nominal dichotomous	Self-referred	Risk alcohol consumption / no risk alcohol consumption
Menarche	Qualitative nominal dichotomous	Self-referred	- Early menarche (<12 years old) - Menarche >12 years old
Thelarche	Qualitative nominal dichotomous	Self-referred	- Early thelarche (<10 years old) - Thelarche >10 years old
Breast tissue density	Qualitative nominal non-dichotomous	Mammography	- A: Almost fatty tissue - B: Scattered areas of fibroglandular density - C: Heterogeneously dense - D: Extremely dense
Menopause	Qualitative nominal non-dichotomous	Self-referred	- Pre-menopause - Younger age onset of menopause - Older age onset of menopause
Breastfeed	Qualitative nominal dichotomous	Self-referred	Yes / no
Reproductive factors	Qualitative nominal dichotomous	Clinical history	Nuliparity / multiparity

BSO: Bilateral salpingo-oophorectomy, HRT: Hormone replacement treatment

6.6. INTERVENTION

6.6.1. External radiotherapy

Women who are randomized to the prophylactic external radiation therapy group will need to follow several steps:

1. **Simulation CT:** A CT scan will be performed. It is used to mark the exact point where radiation therapy should be applied using immobilizers. In the CT images the tumor and neighboring critical organs are delimited. Also, a 3D planning of radiotherapy is made.
2. **First visit with nursing:** In this visit, the patient is explained how her day to day will be during radiotherapy, skin cures, dietary recommendations if necessary, and possible side-effects.
3. **Calculation of the dose and performance of dosimetry:** In this case, 40Gy will be applied in hypofractionated therapy, with 15 sessions of 2.66Gy / session.

When planning breast irradiation, tolerance of critical organs should be considered:

1. Lung: The V20 value is used, which refers to the percentage of lung irradiated with 20Gy or more. This value must be less than 15%.
2. Heart: The average dose is used, and it should be less than 2 Gy.

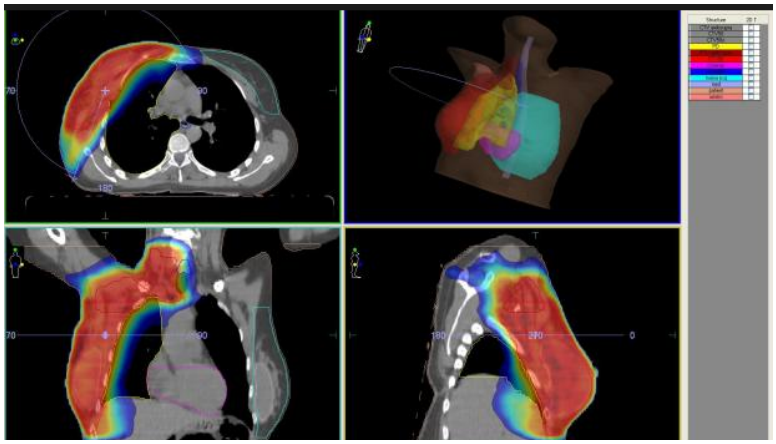


Figure 10. Example of CT with dosimetry

4. Radiotherapy committee: Each case is taken to the radiotherapy committee to verify that the calculations have been performed correctly.
5. First day of radiotherapy: In this visit the entire procedure is verified again to ensure everything is correct, especially the patient's placement according to the established measures.
6. Daily radiotherapy visits: During the 15 days of radiotherapy, periodic medical and nursing controls will be carried out (one control per week will be carried out).

6.6.2. Screening strategy

The two groups will follow a screening strategy, the currently accepted measure for women who do not want to undergo PBM.

The screening will consist of:

- Clinical controls every 3-4 months: In each clinical control, a breast palpation will be performed, and the presence of side effects and the general condition of the patient will be asked.
- Biannual breast image: Alternating MRI with mammography and echography. Diagnosis will be based on the BIRADS.

6.7. METHODS OF DATA COLLECTION

For data collection, we will create a computer-based database using Microsoft Excel. The information will be collected from the electronic medical records of the SAP System. Also, the patients' identity will be codified in order to purse a **pseudonymization procedure.** The following information will be used for the study:

- **Electronic clinical history:** It will provide information on the patient characteristics.
- **Radiology report:** MRI or mammography and echography reports will be used biannually to follow up the patients.
- **Pathology report**: If any suspicious nodule is detected, a CNB must be done in order to confirm the malignant tumor development.
- **Other tests**: In case of presenting secondary effects to radiotherapy, the necessary tests will be carried out to diagnose them.

All patients who meet all the inclusion and none of the exclusion criteria will be asked to participate to the study. The patient must accept and give written consent after reading the information sheet.

First visit

We will consider the first visit when a patient comes to our consultation in the **UARC**.

Patients can enter the study when they are diagnosed with a BRCA1/2 gene mutation based on family history and refuse to undergo PBM.

The following tasks will be carried out on the first visit:

1. The **procedure and details of the study** will be explained: the risk reduction measures available, the possible unwanted effects of external radiotherapy, and all the details related to the study (duration of each phase, follow-up, confidentiality, etc.)

   In case of agreeing to enter in our study, the patient will be given the **Protocol information sheet** (**ANNEX 8**) and **the informed consent document** (**ANNEX 9**).
2. Analyze the entire **medical history** and ask for personal history (concomitant diseases, previous cancers, previous surgeries) and family history of breast cancer. Also, a breast palpation will be performed by the doctor.

3. Collect all the covariates. Most of them can be obtained from the clinical history and from the anamnesis. A mammogram will be performed if the women has not had previous mammograms and/or the breast density cannot be obtained from the medical history.

MRI control

An MRI will be performed prior to the intervention in both groups of patients.

Randomization

Once the study is explained, the patients will be randomized into two groups:

- Group 1 (study group): Patients receiving external radiation therapy plus screening strategy.
- Group 2 (control group): Patients doing screening strategy.

Intervention

- Group 1 (control group): Hypofractionated therapy of 40Gy will be used in 15 sessions of 2.66Gy / session. It will be applied following the steps previously explained in section 6.6.1.
- Group 2 (control group): The patient will not receive any intervention.

Screening strategy

Subsequently, both groups will carry out controls through the breast pathology unit, as explained in section 6.6.2. If a suspicious nodule is detected during successive visits, CNB should be performed to confirm malignancy.

In addition, in the clinical controls, special attention will be paid to the appearance of side-effects. In case of presenting signs or symptoms compatible with any adverse effect that requires complementary examinations, the necessary tests described in section 6.5 will be carried out to correctly diagnose each adverse effect.

Then, any adverse effect that the patient develops will be collected, along with the moment in which it appeared.

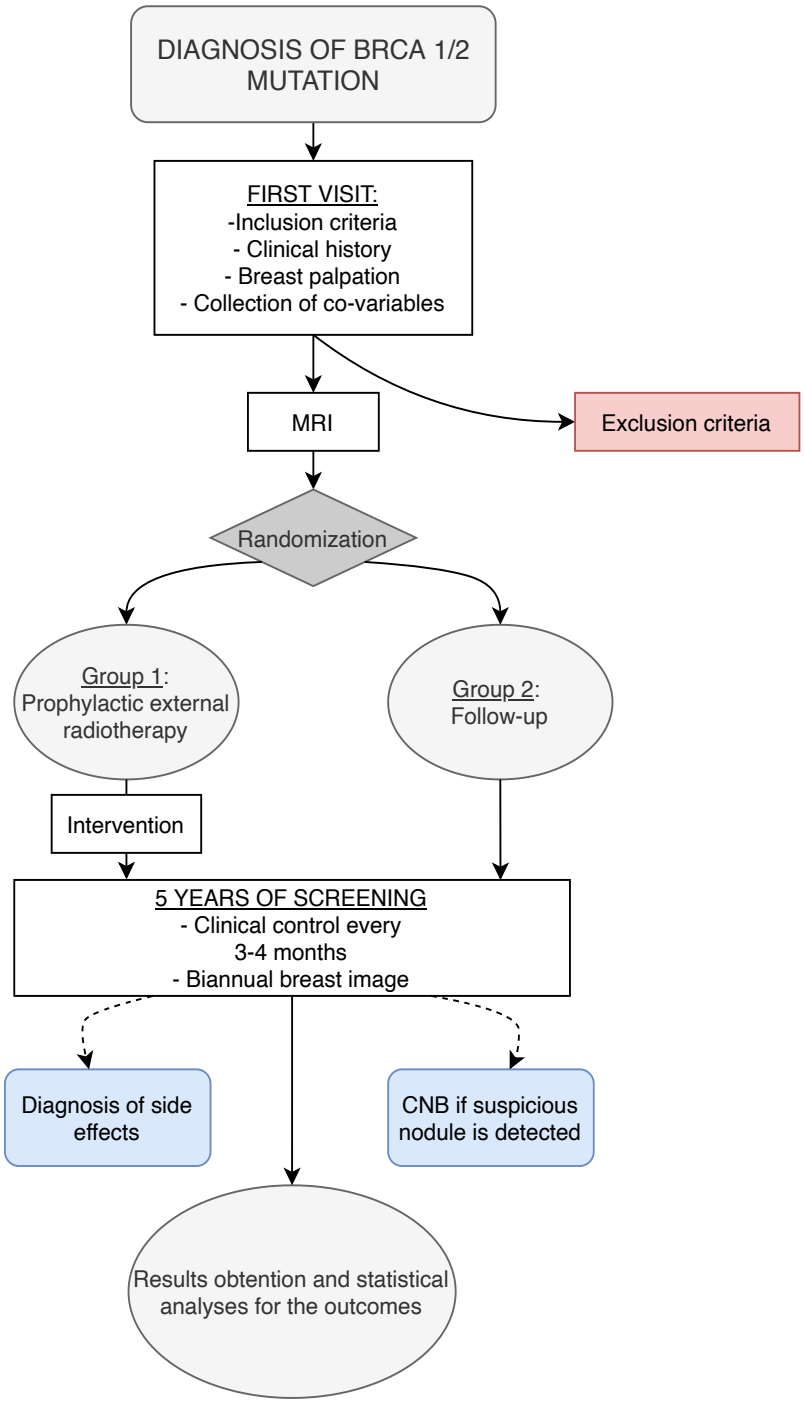


Figure 11. Methods of data collection's diagram

7. STATISTICAL ANALYSIS

The IBM Statistical Package for Social Science (SPSS) will be used to perform the statistical calculations.

7.1. DESCRIPTIVE ANALYSIS

First of all, we will summarize all dependent, independent, and covariables:

- Qualitative variables: Will be summarized by mean proportions, with a confidence interval of 95%.
- Quantitative variables: Will be summarized through means, standard deviations, medians, and interquartile ranges.

7.2. BIVARIATE INFERENCE

Different tests will be used depending on the co-variables compared:

- When comparing the independent variable with qualitative co-variables the Chi square test will be used, as we are comparing two qualitative variables.
- When comparing the independent variable with quantitative co-variables the T-Student test will be used ((if the co-variable is distributed as a normal), or U de Mann-Whitney (if the co-variable is not normally distributed).

The co-variables that obtain significantly different results in the two groups of interventions will be candidates for confounding variables.

7.3. MULTIVARIATE ANALYSIS

The association between the variable “breast cancer development” and the intervention will be assessed by a Cox regression model, controlled by the confounding candidate covariates.

The association between the qualitative variables “radiation dermatitis”, “lymphedema”, “spontaneous rib fracture”, “radiation pneumonitis”, and the intervention will be also adjusted in a Cox regression model, controlled by confounding candidate covariates.

The association between the quantitative variable “other minor acute side effects”, and the intervention will be assessed by a lineal regression model, controlled by the confounding candidate covariables.

The association between the qualitative variable “other major side effects” and the intervention will be assessed by a **logistic regression model**, controlled by the confounding candidate covariables.

8. ETHICAL AND LEGAL CONSIDERATIONS

This study will be conducted under the ethical principles and guidelines established by **The World Medical Association in the Declaration of Helsinki** (last revised in October 2013), and the principles of **The Principles of Biomedical Ethics by Beauchamp and Childress** of 1979:

- **Benefit:** It is the moral obligation to act for the benefit of others. All actions must be carried out thinking about what is best for the patient. In our study we comply with this principle because we are applying a preventive treatment that we hope will reduce the risk of breast cancer by 80%.
- **Autonomy**: It is the obligation to respect the values and personal options of each individual in the basic decisions that affect them. All patients participating in the study will be informed by gynecologist physicians and will receive the **protocol information sheet (ANNEX 8).** If they understand and sign voluntarily the **informed consent document (ANNEX 9),** they will be included in the study. Before signing the informed consent, physicians will emphasize to every individual that they can accept or decline to participate in the study without modifying the quality of its medical care.
- **Justice:** It consists of the equitable distribution of the benefits of vital well-being, avoiding any discrimination in access to health resources. In this study, no participant is discriminated against because of their ethnicity, socioeconomic status, or other reasons that may imply discrimination against a group of people.
- **Non-maleficiency**: No malicious intent is being done to the patients participating in the study. Patients who could be affected by the use of external radiation therapy have been excluded.

The protocol will be presented to the **CEIC** of HUJT for its evaluation and approval before starting the project. The committee will ensure that the protocol fits the ethical requirements and any modifications proposed will be considered and introduced.

Additionally, considering the "***Reglament (UE) 2016/679 del Parlament i del Consell Europeu , de 27 d'abril de 2016****, relatiu a la protecció de les persones físiques en quant al tractament de dades personals i a la lliure circulació d'aquestes dades*", and the "***Llei***

Orgànica 3/2018, de 5 de desembre*, de Protecció de Dades Personals i Garantia dels Drets Digitals (LOPD- GDD)*", the study will provide anonymity to patients by identifying them with numbers in the database, and will respect and protect personal data cession, data processing and confidentiality. All data collected will only be used for the intended purpose of this study.

All the investigators will have to declare no conflict of interest, and they will also have to agree to publish all data and results with total transparency, including unfavorable data or events.

9. WORKING PLAN

The research team will be multidisciplinary, formed by:

- Research manager: He/she will be in charge of ensuring the correct coordination of the three hospitals, that the protocol is correctly applied and the information is correctly stored.
- Study coordinator: She will be responsible for the supervision of the project and coordination of the research team.
- Main investigator: She will be responsible for the elaboration of the protocol, and writing of the conclusions and results publication.
- Co-investigators: In each hospital one of the co-investigators will be the co-coordinator from each team. Co-coordinators will meet once every 6 months with the research manager and the study coordinator.
- Statistic specialist: He/she will perform the statistical analysis.

9.1. STUDY STAGES

Stage 0. Study design (September 2021 – November 2021)

1. First meeting (September 2021):

   The development of this project was accorded by Dr. Ester Vila (study coordinator) and Jana Baltà (main investigator).

2. Protocol elaboration (September 2021-November 2021):

   The protocol has been developed during September-November 2021. A bibliographic research has been carried out, and the objectives, hypotheses and methodology have been established.

Study coordinator and main investigator will be the main responsibles.

Stage 1. Ethical evaluation of the protocol (November 2021)

1. Presentation and approval by the Ethics Committee (November 2020).

   The protocol will be presented to the research ethics committee (CEIC) at Hospital Josep Trueta. Any necessary modification of the protocol will be done to achieve CEIC's conditions.

2. Contracting an insurance (November 2020).

Study coordinator and main investigator will be the main responsibles.

Stage 2. Coordination (December 2021)

1. First meeting of research team (December 2021):

   First meeting will be done in order to meet the principal investigators of each hospital center included in the study. This meeting will also be used to distribute and organize tasks.

2. Training (December 2021):

   The coinvestigators will receive information about the study protocol. They will be taught to collect and register data and give information to the patient. This will help to avoid differences when diagnosing and treating, and it will ensure the homogeneity required to obtain representative conclusions.

All team will be responsible.

Stage 3. Sample collection and follow up visits (January 2022 – June 2029)

1. Patient recruitment (January 2022 – June 2024)

   A sequential non-probabilistic sampling will be used. Patients will be enrolled in our study if they accomplish the inclusion and exclusion criteria and if they accept the informed consent. Subsequently, the patients will be randomized into the two groups.

2. Intervention and follow-up visits (January 2022 – June 2029)

   Prophylactic external radiation therapy will be applied to the study group. Afterwards, the two groups will perform a screening with clinical controls every 3-4 months and biannual check through imaging test (MRI alternated with mammography and echography).

3. Record of data (January 2022 – June 2029)

   The specialists will record all the data collected from the different variables in the database.

Investigators and co-investigators will be the main responsibles.

During this stage, co-coordinators of each hospital will meet with the study coordinator and research manager once every 6 months to evaluate if the protocol is being well fulfilled. If something does not work, they will take the necessary decisions to fix it.

Stage 4. Data analysis and interpretation (January 2024 – December 2029)

4. Annual statistical analysis (January 2024, 2025, 2026, 2027, 2028): It will allow to monitor both the efficacy and side effects of prophylactic external radiation

therapy. In case of demonstrating a great efficacy of external radiotherapy or in case of observing serious side effects in a period less than 5 years, the study will be concluded and the results will be published.

The statistical analysis will be performed by a subcontracted statistician who will be blinded for the intervention groups.

1. Final statistical analysis (July 2029 – September 2029)

   If conclusive results have not been obtained in the previous analyzes, the final statistical analysis of the study will be carried out with all the information collected.

2. Data interpretation (November 2029 – December 2029)

   The data will be interpretated by the main investigator and the study coordinator. Then, the discussion and conclusion will be elaborated.

The statistic and the main investigator will be the main responsibles.

Stage 5. Results publication (January 2030 – February 2030)

5. Publication and dissemination of the results (January 2030 - February 2030)

   The main investigator and the study coordinator will write two journal articles and present the findings to a national congress and an international congress.

The main investigator and the study coordinator will be the main responsibles.

STAGE	TASK	PERSONNEL	PERIOD																					
			2021			2022	2023	2024				2025		2026		2027		2028		2029				2030
			Sep	Nov	Dec	Jan-Dec	Jan-Dec	Jan	Febr-May	June	Aug-Dec	Jan	Feb-Dec	Jan	Feb-Dec	Jan	Feb-Dec	Jan	Feb-Dec	Jan-May	June	July-Sept	Nov-Dec	Jan-Feb
Stage 0 Study design	First meeting	Main investigator and study coordinator																						
	Protocol elaboration	Main investigator																						
Stage 1 Ethical evaluation	Presentation to Ethics Committee	Main investigator, study coordinator and CEIC																						
Stage 2 Coordination	First meeting of research team	All team																						
	Training	All team																						
Stage 3 Sample collection and follow up visits	Patient recruitment	Investigators and co-investigators																						
	Follow-up visits	Investigators and co-investigators																						
	Record of data	Investigators and co-investigators																						
Stage 4 Data analysis and interpretation	Annual statistical analysis	Statistic																						
	Final statistical analysis	Statistic																						
	Data interpretation	Main investigator and study coordinator																						
Stage 5 Results publication	Publication and dissemination of the results	Main investigator and study coordinator																						

10.BUDGET

This project will compare the use of external radiotherapy plus screening strategy vs. only screening strategy. External radiation therapy is used daily in the hospitals involved in this study, but it is not used as a prophylactic measure in women with a BRCA gene mutation. That is why the cost of radiotherapy has been included in the budget.

On the other hand, the screening of patients with a BRCA gene mutation is carried out routinely, and the techniques used for screening (mammography, echography, MRI, and CNB if needed) are implemented in the hospital's clinical practice. Therefore, no additional material or goods will be required.

The investigators will perform patient recruitment, data collection, and interpretation of results as part of their work activity.

ITEM	QUANTITY	COST PER UNIT	SUBTOTAL
Personnel costs			
Investigators	0	0€	0€
Qualified statistic	1 (30h/year)	30€/hour	5.400€
Research manager	1 (4h, 2 day/month) during 8 years	30€/hour	23.040€
Insurance policy			
Trial policy	1	25.000€/trial	25.000€
Materials			
External radiotherapy (radiation, simulation, CT, volume delineation, dosimetry)	114 (1 per patient)	2.500€	285.000€
Dissemination and publication			
Inscription to national congress + costs of the trip (flights, accomodation)	2	900€	1800€
Inscription to international congress + costs of the trip (flights, accomodation)	2	2175€	4350€
Publication	2	2.000€	4.000€
TOTAL			**348.590€**

11.LIMITATIONS OF THE STUDY

The limitations of the study can be summarized as follows:

Sample collection

The sampling method will be consecutive non-probabilistic, which implies the risk of selecting a non-representative sample. The consecutive method has been chosen because it is one of the non-probabilistic methods that induce less bias. The advantages are that this type of sampling is useful for rare pathologies such as BRCA mutation.

To minimize the selection bias, the inclusion and exclusion criteria have been meticulously chosen. Thus, although the population studied will not be the same as the general population, we believe it will be very similar to the one that can benefit from the outcomes.

Blinding

Given that a preventive measure is applied in only one group of patients and the other does not, the patient and investigator cannot be masked. However, to try to reduce the risk of bias, the statistician will be blinded to the participants' intervention.

Collaborating hospitals

It is a multicenter study. Information collection bias may occur since it is difficult to standardize a protocol for all 3 hospitals and to control it is well executed. To prevent it, meetings every 6 months will be held to ensure the study's correct development. These meetings must be attended by the co-coordinators, the main study coordinator and the research manager.

Duration

A 5-year follow-up period has been established to ensure conclusive results. This is because the appearance of subsequent tumors (both primary breast tumor and RIS) can take several years.

However, we are aware that it is a long time, and we consider the possibility of obtaining the results in a shorter time. For this reason, statistical analyzes will be carried out every year, and when conclusive results are obtained, the study will be considered completed and the results will be published.

Budget

The clinical trial will cost a total of 348,590€. We are aware that it is a high cost, but we consider that this study's impact on the public health system can be so significant that the cost is fully justified.

Side-effects

In this study we wanted to give great importance to the possible side effects of external radiotherapy to make a correct balance between the benefits of the treatment and the secondary risks.

However, not all adverse effects can be evaluated, since some of them do not appear until 10 or 20 years after exposure to radiotherapy (especially cardiac adverse effects). Therefore, to evaluate them, further studies must be carried out in the future.

On the other hand, the most frequent adverse effects are included in our study, and therefore, although we cannot assure that we will analyze all the side effects produced by radiotherapy, we will study the most representative ones.

12.IMPACT

Breast cancer is the most prevalent cancer worldwide in women and a significant cause of death. Also, although the treatment for sporadic breast cancer is well established, there is a lack of risk reduction techniques for women with BRCA1/2 mutation. Only a major surgery with many risks and complications is available nowadays.

It is important to remember that only 35.7% of women with a BRCA1/2 gene mutation agree to undergo a prophylactic bilateral mastectomy. This leaves 64.3% of women without the ability to reduce their likelihood of cancer and with the only option to do a screening strategy to see if they develop, or not, breast cancer. Moreover, these women are subjected to high levels of anxiety and worry throughout their lives.

Based on our hypothesis, prophylactic external radiation therapy could be an alternative for all those women who do not wish to undergo an irreversible operation, reducing the risk of breast cancer.

Furthermore, external radiation therapy would avoid the mutilating aesthetic defects of mastectomy, helping to reduce mood disorders.

At the present protocol, there has not been published any clinical trial that analyzes the effectiveness of external radiation therapy in women with BRCA1/2 mutation. Therefore, it would be the first study testing it and a step forward in preventing this cancer.

This is a multicenter study performed with the ICO, which has experience conducting many clinical trials. Consequently, if the results are promising, they could be used for future studies and establishing prophylactic external radiotherapy in clinical practice.

Another factor to consider is that the implementation of prophylactic external radiation therapy would reduce the cost to the public health, as far fewer women would be diagnosed with breast cancer and would not have to undergo further treatments.

13.FEASABILITY

This project will be carried out in **3 third-level hospitals** of the Institut Català d'Oncologia, with the Josep Trueta University Hospital as the reference center.

The project will be conducted in the **breast pathology unit**, a multidisciplinary team made up by gynecologists, general surgeons, oncologists, radiotherapists, nursing staff, plastic surgeons, radiologists, and pathologists. All the professionals have sufficient experience to attend to the needs of the patients and carry out the study procedures.

It will only be necessary to hire a **research manager** to ensure good coordination between hospitals, and a **statistician** to perform the statistical analysis.

The number of patients needed to perform this study is 216, which will be collected in 2 years and 6 months. This is a reasonable time, from a logistical point of view.

The price of the study is high, but we have no doubt that we will obtain the necessary financing to carry it out.

Regarding patient screening, all the techniques used are also routine in hospitals, so that all phases of the study will be carried out in the same hospital.

14. BIBLIOGRAPHY

1. National Cancer Institute Dictionary [Internet]. Breast Cancer; 2017. Bethesda: NIH; 2021 [cited 2021 Sep 19]. Available from: https://www.cancer.gov/publications/dictionaries/cancer-terms/def/breast-cancer
2. Robles L, Balmaña J, Barrel I, Grandes S, Graña B, Guillén C, et al. Consenso en cáncer hereditario entre la Sociedad Española de Oncología Médica y las sociedades de atención primaria. Semergen. 2013;39(5):259–66.
3. Paluch-Shimon S, Cardoso F, Sessa C, Balmana J, Cardoso MJ, Gilbert F, et al. Prevention and screening in BRCA mutation carriers and other breast/ovarian hereditary cancer syndromes: ESMO clinical practice guidelines for cancer prevention and screening. Ann Oncol [Internet]. 2016;27(Supplement 5):v103–10. Available from: http://dx.doi.org/10.1093/annonc/mdw327
4. Godet I, M. Gilkes D. BRCA1 and BRCA2 mutations and treatment strategies for breast cancer. Integr Cancer Sci Ther. 2017;4(1).
5. Lee A, Moon BI, Kim TH. BRCA1/BRCA2 pathogenic variant breast cancer: Treatment and prevention strategies. Ann Lab Med. 2020;40(2):114–21.
6. Liu J, Wang J. Disability-Adjusted Life-Years (DALYs) for Breast Cancer and Risk [Internet]. Suzhou; 2017 [cited 2021 Nov 4]. Available from: https://www.medrxiv.org/content/10.1101/2020.04.02.20050534v1.full.pdf
7. Sociedad española de oncologia médica [Internet]. Cifras del cancer en españa. Madrid: SEOM; 2021. Available from: www.seom.org
8. Junts contra el càncer [Internet]. Estadístiques de càncer; 2020. Barcelona: FECEC; 2021 [cited 2021 Jul 13]. Available from: http://www.juntscontraelcancer.cat/cancer/el-cancer/estadistiques-de-cancer/
9. Asociación Española Contra el Cáncer. Impacto del cáncer en Cataluña; 2020. Madrid: AECC; 2021.
10. Cantero Muñoz P, Pego Triñanes Y. Mastectomía reductora de riesgo de cáncer de mama en mujeres portadoras de mutación en BRCA1/BRCA2 frente a otras opciones preventivas [Internet]. Madrid: Ministerio de Sanidad, Servicios Sociales e Igualdad; 2017. Available from: https://www.aetsa.org/download/publicaciones/avalia-t201605MastectomiaProfilactica.pdf
11. Pollán M, García-mendizabal MJ, Pérez-gómez B, Aragonés N, Pastor R, Ramis R, et al. Situación epidemiológica del cáncer de mama en españa. 2007;4:231–48.
12. Evron E, Ben-David AM, Goldberg H, Fried G, Kaufman B, Catane R, et al.

Prophylactic irradiation to the contralateral breast for BRCA mutation carriers with early-stage breast cancer. Ann Oncol [Internet]. 2019;30(3):412–7. Available from: https://doi.org/10.1093/annonc/mdy515

13. Breastcancer [Internet]. Using HRT (Hormone Replacement Therapy). Ardmore: Breastcancer.org; 2021 [cited 2021 Nov 4]. Available from: http://www.breastcancer.org/risk/factors/hrt

14. National Cancer Institute [Internet]. Oral Contraceptives (Birth Control Pills) and Cancer Risk; 2018. Bethesda: NIH; 2021 [cited 2021 Nov 4]. Available from: https://www.cancer.gov/about-cancer/causes-prevention/risk/hormones/oral-contraceptives-fact-sheet

15. Breastcancer.org [Internet]. Smoking and breast cancer. Ardmore: Breastcancer.org; 2021 [cited 2021 Nov 4]. Available from: https://www.breastcancer.org/risk/factors/smoking

16. Breastcancer.org [Internet]. Drinking Alcohol and Breast Cancer. Ardmore: Breastcancer.org; [cited 2021 Nov 2]. Available from: https://www.breastcancer.org/risk/factors/alcohol%0Ahttp://www.breastcancer.org/risk/factors/alcohol

17. Breastcancer.org [Internet]. Berg W, Harvey J, Jochelson M; Dense Breast Tissue and Breast Cancer Risk. Ardmore: Breastcancer.org; 2021 [cited 2021 Nov 4]. Available from: https://www.breastcancer.org/risk/factors/dense_breasts

18. Goldberg M, D'Aloisio AA, O'Brien KM, Zhao S, Sandler DP. Pubertal timing and breast cancer risk in the Sister Study cohort. Breast Cancer Res. 2020 Dec 1;22(1).

19. OncoGuía del consejo y asesoramiento genéticos en el cáncer hereditario. Versión breve para la aplicación de la práctica clínica. Barcelona: Agència d'Avaluació de Tecnologia i Recerca Mèdiques. CatSalut. Departament de Salut. Generalitat de Catalunya.; 2006.

20. Guía de práctica clínica en cáncer hereditario. València: Generalitat Valenciana. Conselleria de Sanitat; 2009.

21. Centers for Disease Control and Prevention [Internet]. Breast and Ovarian Cancer and Family Health History; 2020. Atlanta: CDC; 2021 [cited 2021 Sep 16]. Available from: https://www.cdc.gov/genomics/disease/breast_ovarian_cancer/risk_categories.htm

22. Petrucelli N, Daly MB, Pal T. BRCA1- and BRCA2-Associated Hereditary Breast and Ovarian Cancer. GeneReviews® [Internet]. 1993 Dec 15 [cited 2021 Sep 19]; Available from: http://www.ncbi.nlm.nih.gov/pubmed/20301425

23. American Cancer Society [Internet]. Asesoramiento y pruebas genéticas para

el riesgo de cáncer de seno; 2019. Atlanta: American Cancer Society; 2021. Available from: https://www.cancer.org/es/cancer/cancer-de-seno/riesgos-y-prevencion/pruebas-geneticas.html

24. Cancer.net [Internet]. Hereditary Breast and Ovarian Cancer; 2020. Alexandria: American Society of Clinical Oncology (ASCO); 2021 [cited 2021 Sep 16]. Available from: https://www.cancer.net/cancer-types/hereditary-breast-and-ovarian-cancer

25. Tung NM, Boughey JC, Pierce LJ, Robson ME, Bedrosian I, Dietz JR, et al. Management of hereditary breast cancer: American society of clinical oncology, American society for radiation oncology, and society of surgical oncology guideline. J Clin Oncol. 2020;38(18):2080–106.

26. Hammer C, Fanning A, Crowe J. Overview of breast cancer staging and surgical treatment options. Cleve Clin J Med. 2008;75(SUPPL.1):10–6.

27. Valero MG, Golshan M. Management of the axilla in early breast cancer. Cancer Treat Res [Internet]. 2018 [cited 2021 Sep 18];173:39–52. Available from: https://doi.org/10.1007/978-3-319-70197-4_4

28. Rebbeck TR, Friebel T, Lynch HT, Neuhausen SL, Van't Veer L, Garber JE, et al. Bilateral prophylactic mastectomy reduces breast cancer risk in BRCA1 and BRCA2 mutation carriers: The PROSE study group. J Clin Oncol. 2004;22(6):1055–62.

29. Alaofi RK, Nassif MO, Al-Hajeili MR. Prophylactic mastectomy for the prevention of breast cancer: Review of the literature. Avicenna J Med. 2018;8(03):67–77.

30. Barton MB, West CN, Liu ILA, Harris EL, Rolnick SJ, Elmore JG, et al. Complications following bilateral prophylactic mastectomy. Journal of the National Cancer Institute. Monographs. 2005. p. 61–6.

31. Gahm J, Wickman M, Brandberg Y. Bilateral prophylactic mastectomy in women with inherited risk of breast cancer - Prevalence of pain and discomfort, impact on sexuality, quality of life and feelings of regret two years after surgery. Breast [Internet]. 2010 [cited 2021 Oct 27];19(6):462–9. Available from: https://www.sciencedirect.com/science/article/pii/S0960977610001335

32. Breastcancer.org [Internet]. Prophylactic Mastectomy Risks; 2017. Ardmore: Breastcancer.org; 2021 [cited 2021 Sep 21]. Available from: https://www.breastcancer.org/treatment/surgery/prophylactic_mast/risks

33. Margolis GJ, Goodman RL, Rubin A, Pajac TF. Psychological Factors in the Choice of Treatment for Breast Cancer. Psychosomatics [Internet]. 1989 [cited 2021 Oct 26];30(2):192–7. Available from: https://pubmed.ncbi.nlm.nih.gov/2710917/

34. Lewis-Smith H. Physical and psychological scars: the impact of breast cancer

on women's body image. J Aesthetic Nurs. 2015 Mar 2;4(2):80–3.

35. Cardoso F, Kyriakides S, Ohno S, Penault-Llorca F, Poortmans P, Rubio IT, et al. Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol [Internet]. 2019;30(8):1194–220. Available from: https://doi.org/10.1093/annonc/mdz173

36. Ayala de la Peña F, Andrés R, Garcia-Sáenz JA, Manso L, Margelí M, Dalmau E, et al. SEOM clinical guidelines in early stage breast cancer (2018). Clin Transl Oncol [Internet]. 2019;21(1):18–30. Available from: https://doi.org/10.1007/s12094-018-1973-6

37. Liberman L, Menell JH. Breast imaging reporting and data system (BI-RADS). Radiol Clin North Am. 2002;40(3):409–30.

38. Palacio RD, Negret PJ, Velásquez-Tibatá J, Jacobson AP. Fundamentos de Ginecología. Angewandte Chemie International Edition, 6(11), 951–952. Madrid: Sociedad Española de Ginecología y Obstetrícia (SEGO); 1967.

39. Bhushan A, Gonsalves A, Menon JU. Current state of breast cancer diagnosis, treatment, and theranostics. Pharmaceutics. 2021;13(5):723.

40. Alcaide Lucena M, Rodríguez González C, de Reyes Lartategui S, Gallart Aragón R, Sánchez Barrón M, García Rubio J, et al. Molecular classification of breast cancer. Treatment and prognosis implications. Cirugía Andaluza. 2021;32(2):155–9.

41. American Cancer Society [Internet]. Understanding a Breast Cancer Diagnosis; 2020. Atlanta: American Cancer Society; 2021. Available from: www.cancer.org/treatment/understanding-your-diagnosis/tests/understanding-

42. Koh J, Kim MJ. Introduction of a new staging system of breast cancer for radiologists: An emphasis on the prognostic stage. Korean J Radiol. 2019;20(1):69–82.

43. Clinical Guidelines for the Management of for Breast Cancer [Internet]. West Midlands Expert Advisory Group Breast Cancer; 2016 [cited 2021 Sep 18]. 12 p. Available from: https://www.england.nhs.uk/mids-east/wp-content/uploads/sites/7/2018/02/guidelines-for-the-management-of-breast-cancer-v1.pdf

44. García Novoa A, Acea Nebril B. Estado actual del tratamiento de la axila en la cirugía primaria del cáncer de mama: Revisión sistemática de su impacto en la supervivencia. Cir Esp. 2017;95(9):503–12.

45. Vaquero JMS. Radioterapia intraoperatoria en cáncer de mama. Actual (Cir Andal [Internet]. 2012;23:48–51. Available from: https://www.asacirujanos.com/admin/upfiles/revista/2012/2012-vol23-n1-2-act11.pdf

46. Algara López M. The different types of radiation therapy: external, brachytherapy and intraope-rative. Indications. Med Segur Trab. 2016;107–12.

47. Jalali R, Singh S, Budrukkar A. Techniques of tumour bed boost irradiation in breast conserving therapy: Current evidence and suggested guidelines. Acta Oncol (Madr) [Internet]. 2007 [cited 2021 Aug 24];46(7):879–92. Available from: https://www.tandfonline.com/doi/abs/10.1080/02841860701441798

48. De Las Peñas Cabrera MD, García JM, Luis ÁM, Arenas i Prats M, López MA. Recommended technology and techniques in external radiation of breast cancer. Rev Senol y Patol Mamar [Internet]. 2013 Oct 1 [cited 2021 Aug 24];26(4):138–45. Available from: https://www.elsevier.es/es-revista-revista-senologia-patologia-mamaria--131-articulo-tecnologia-tecnicas-recomendadas-irradiacion-externa-S0214158213000340

49. Clifton K, Gutierrez-Barrera A, Ma J, Bassett R, Litton J, Kuerer H, et al. Adjuvant versus neoadjuvant chemotherapy in triple-negative breast cancer patients with BRCA mutations. Breast Cancer Res Treat. 2018;170(1):101–9.

50. Tutt ANJ, Garber JE, Kaufman B, Viale G, Fumagalli D, Rastogi P, et al. Adjuvant Olaparib for Patients with BRCA1 - or BRCA2 -Mutated Breast Cancer . N Engl J Med. 2021 Jun 24;384(25):2394–405.

51. UpToDate [Internet]. Burstein, Harold J; Selection and administration of adjuvant chemotherapy for HER2-negative breast cancer. Waltham: Wolters Kluwer; 2021 [cited 2021 Sep 17]. Available from: https://www.uptodate.com/contents/selection-and-administration-of-adjuvant-chemotherapy-for-her2-negative-breast-cancer

52. Pelayo BDC. Radioterapia externa: lo que el médico general debe saber. Rev Médica Clínica Las Condes [Internet]. 2013 Jul 1 [cited 2021 Nov 5];24(4):705–15. Available from: https://www.elsevier.es/es-revista-revista-medica-clinica-las-condes-202-articulo-radioterapia-externa-lo-que-el-S0716864013702104

53. Yashar CM. Basic principles in gynecologic radiotherapy [Internet]. Ninth Edit. Clinical Gynecologic Oncology. Elsevier Inc.; 2018. 586-605.e3 p. Available from: http://dx.doi.org/10.1016/B978-0-323-40067-1.00023-1

54. Xiang Q, Jie W, Zhu K, Wang Q, Cheng J. Which technique of positioning and immobilization is better for breast cancer patients in postmastectomy IMRT, single-pole or double-pole immobilization? J Appl Clin Med Phys [Internet]. 2019 Jan 1 [cited 2021 Nov 5];20(1):168–74. Available from: https://onlinelibrary.wiley.com/doi/full/10.1002/acm2.12506

55. Verdú Rotellar JM, Algara López M, Foro Arnalot P, Domínguez Tarragona M, Blanch Mon A. Atención a los efectos secundarios de la radioterapia. MEDIFAM - Rev Med Fam y Comunitaria. 2002;12(7):426–35.

56. Brunt AM, Haviland JS, Sydenham M, Agrawal RK, Algurafi H, Alhasso A, et al.

Ten-year results of fast: A randomized controlled trial of 5-fraction whole-breast radiotherapy for early breast cancer. J Clin Oncol. 2020;38(28):3261–72.

57. Chowdhury AS, Tamanna S. Radiation-induced side effects in breast cancer patients and factors affecting them. Asian J Med Biol Res. 2020 Jul 7;6(2):138–48.

58. Menes TS, Terry MB, Goldgar D, Andrulis IL, Knight JA, John EM, et al. Second primary breast cancer in BRCA1 and BRCA2 mutation carriers: 10-year cumulative incidence in the Breast Cancer Family Registry. Breast Cancer Res Treat. 2015;151(3):653–60.

59. Okano M, Nomizu T, Tachibana K, Nagatsuka M, Matsuzaki M, Katagata N, et al. The relationship between BRCA-associated breast cancer and age factors: an analysis of the Japanese HBOC consortium database. J Hum Genet. 2021;66(3):307–14.

60. ASK2ME: All Syndromes Known to Man Evaluator [Internet]. Massachusetts: Ask2me; 2017 [cited 2021 Oct 29]. Available from: http://ask2me.org/index.php

61. Common Terminology Criteria for Adverse Events [Internet]. Bethesda: NIH; 2020 [cited 2021 Oct 30]. Available from: https://www.meddra.org/

62. Cancernetwork.com [Internet]. Leventhal J, Young M; Radiation Dermatitis: Recognition, Prevention, and Management; 2017. Pennsilvania: Cancernetwork.com; 2021 [cited 2021 Oct 30]. Available from: https://www.cancernetwork.com/view/radiation-dermatitis-recognition-prevention-and-management

63. Lipedema.com [Internet]. Photos of Lymphedema and Lipedema. Lipedema.com; 2021 [cited 2021 Nov 3]. Available from: https://www.lipedema.com/basics-photos-of-lymphedema-and-lipedema

64. Sheth GR, Cranmer LD, Smith BD, Grasso-LeBeau L, Lang JE. Radiation-Induced Sarcoma of the Breast: A Systematic Review. Oncologist [Internet]. 2012 Mar [cited 2021 Oct 30];17(3):405–18. Available from: /pmc/articles/PMC3316927/

65. Ascanio S, Barrenechea C, De León M, García T, Gómez E, González G, et al. Manual Nacional de Abordaje del Tabaquismo. Montevideo: Ministerio de Sanidad Pública de la República de Uruguay; 2009.

66. Ewertz M. Breastcancer.org [Internet]. Smoking and breast cancer. Ardmore: Breastcancer.org; 2021 [cited 2021 Nov 2]. Available from: https://www.komen.org/breast-cancer/facts-statistics/research-studies/topics/smoking-and-breast-cancer-risk/

67. Breastcancer.org [Internet]. Berg W, Harvey J, Jochelson M; Dense breast tissue, mammograms and breast cancer risk. Ardmore: Breastcancer.org; 2021

[cited 2021 Nov 3]. Available from: https://www.breastcancer.org/risk/factors/dense_breasts

68. MD Anderson Cancer Center [Internet]. How does menopause affect cancer risk? Texas: MD Anderson Cancer Center; 2015 [cited 2021 Nov 4]. Available from: https://www.mdanderson.org/publications/focused-on-health/FOH-menopause-cancer.h20-1589835.html

69. Breastcancer.org [Internet]. Breastfeeding history and Breast Cancer. Ardmore: Breastcancer.org; 2021 [cited 2021 Nov 4]. Available from: http://www.breastcancer.org/risk/factors/breastfeed_hist

70. Gleicher N. Why are reproductive cancers more common in nulliparous women? Reprod Biomed Online [Internet]. 2013 [cited 2021 Nov 4];26(5):416–9. Available from: https://pubmed.ncbi.nlm.nih.gov/23518034/

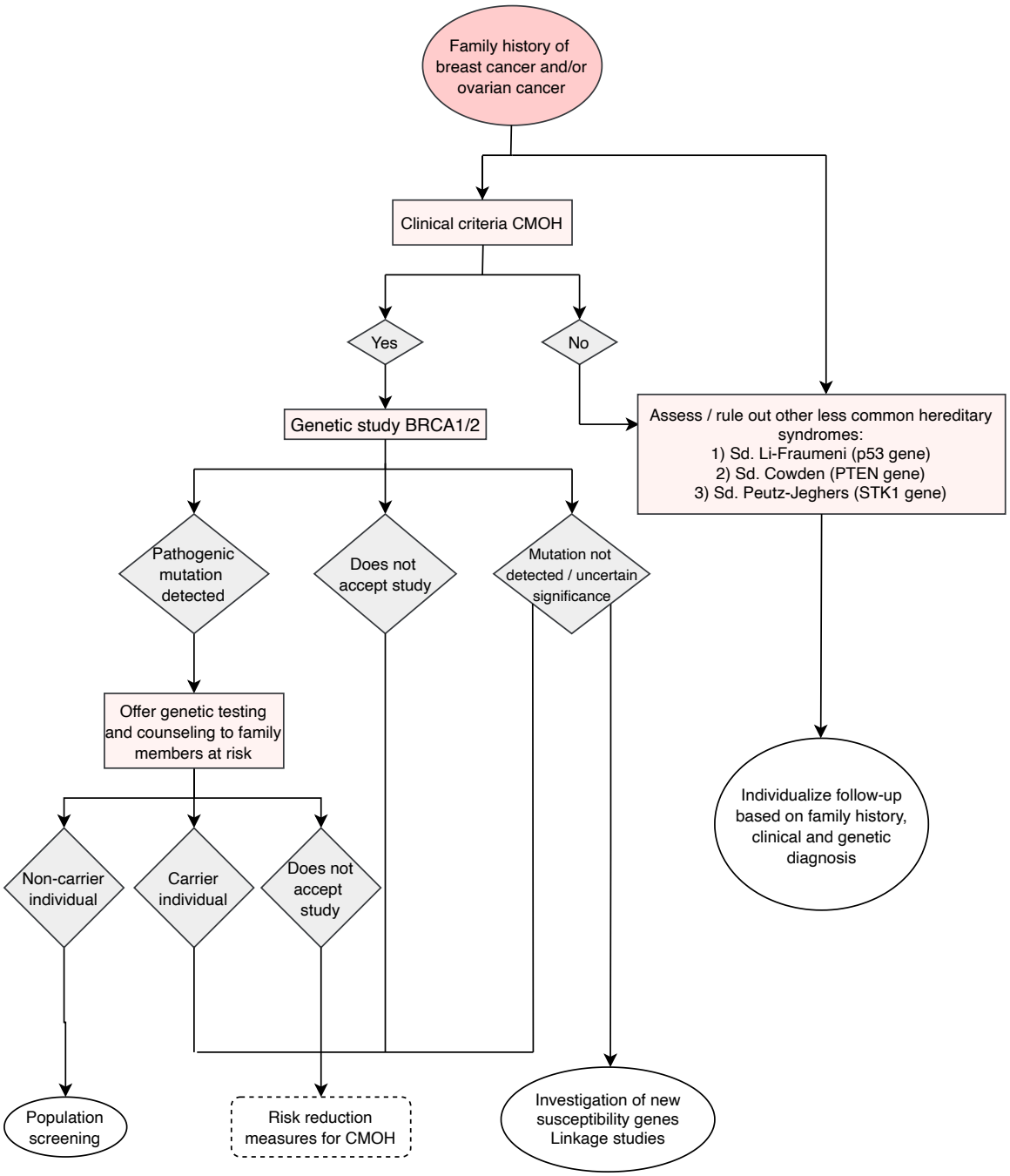
71. Pathology Outlines [Internet]. Adhikari L, Lewis A; WHO classification. Bingham Farms: Pathology Outlines; 2021 [cited 2021 Jun 28]. Available from: https://www.pathologyoutlines.com/topic/ovarytumorwhoclassif.html

72. Harbeck N, Penault-Llorca F, Cortes J, Gnant M, Houssami N, Poortmans P, et al. Breast cancer. Vol. 5, Nature Reviews Disease Primers. 2019.

15. ANNEXES

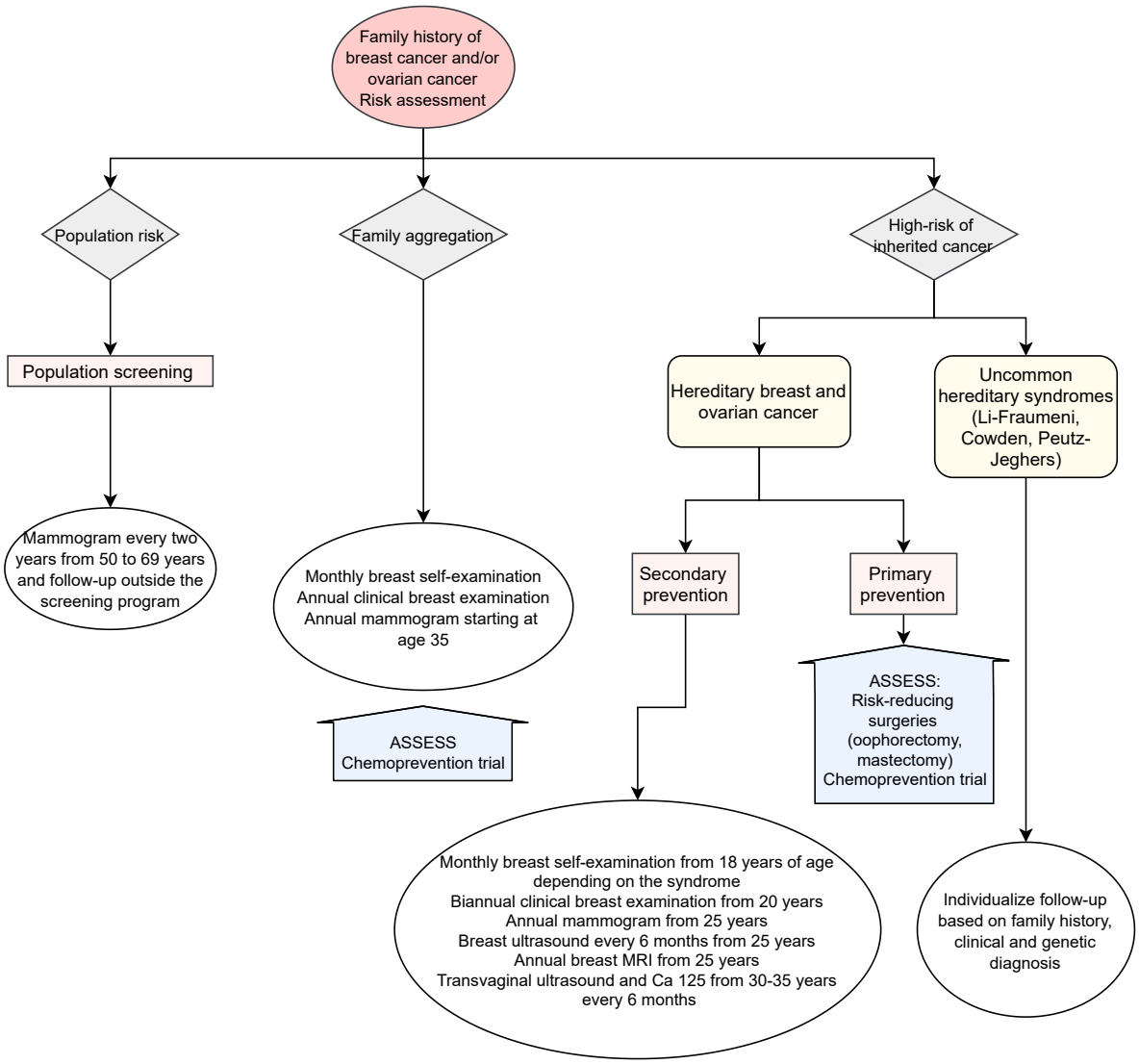
ANNEX 1. Genetic diagnosis of hereditary breast and ovarian cancer

Adapted from (19)



ANNEX 2. Algorithm of risk reduction measures

Adapted from (51)



ANNEX 3. BI-RADS (37)

MAMMOGRAPHY

Breast composition	a. The breasts are almost entirely fatty b. There are scattered areas of fibroglandular density c. The breasts are heterogeneously dense, which may obscure small masses d. The breasts are extremely dense, which lowers the sensitivity of mammography	
Masses	Shape	Oval
		Round
		Irregular
	Margin	Circumscribed
		Obscured
		Microlobulated
		Indistinct
		Spiculated
	Density	High density
		Equal density
		Low density
		Fat-containing
Calcifications	Typically benign	Skin
		Vascular
		Coarse or "popcorn-like"
		Large rod-like
		Round
		Rim
		Dystrophic
		Milk of calcium
		Suture
	Suspicious morphology	Amorphous
		Coarse heterogeneous
		Fine pleomorphic
		Fine linear or fine-linear branching
	Distribution	Diffuse
		Regional
		Grouped
		Linear
		Segmental
Architectural distortion		
Asymmetries	Asymmetry	
	Global asymmetry	
	Focal asymmetry	
	Developing asymmetry	
Intramammary lymph node		
Skin lesion		
Solitary dilated duct		
Associated features	Skin retraction	
	Nipple retraction	
	Skin thickening	
	Trabecular thickening	
	Axillary adenopathy	
	Architectural distortion	
	Calcifications	
Location of lesion	Laterality	
	Quadrant and clock face	
	Depth	
	Distance from the nipple	

ULTRASOUND

Tissue composition *(screening only)*	a. Homogeneous background echotexture – fat b. Homogeneous background echotexture – fibroglandular c. Heterogeneous background echotexture	
Masses	Shape	Oval
		Round
		Irregular
	Orientation	Parallel
		Not parallel
	Margin	Circumscribed
		Not circumscribed - Indistinct - Angular - Microlobulated - Spiculated
	Echo pattern	Anechoic
		Hyperechoic
		Complex cystic and solid
		Hypoechoic
		Isoechoic
		Heterogeneous
	Posterior features	No posterior features
		Enhancement
		Shadowing
		Combined pattern
Calcifications	Calcifications in a mass	
	Calcifications outside of a mass	
	Intraductal calcifications	
Associated features	Architectural distortion	
	Duct changes	
	Skin changes	Skin thickening
		Skin retraction
	Edema	
	Vascularity	Absent
		Internal vascularity
		Vessels in rim
	Elasticity assessment	Soft
		Intermediate
		Hard
Special cases	Simple cyst	
	Clustered microcysts	
	Complicated cyst	
	Mass in or on skin	
	Foreign body including implants	
	Lymph nodes – intramammary	
	Lymph nodes – axillary	
	Vascular abnormalities	AVMs (arteriovenous malformations/ pseudoaneurysms)
		Mondor disease
	Postsurgical fluid collection	
	Fat necrosis	

MAGNETIC RESONANCE IMAGING

Amount of fibroglandular tissue (FGT)	a. Almost entirely fat b. Scattered fibroglandular tissue c. Heterogeneous fibroglandular tissue d. Extreme fibroglandular tissue	
Background parenchymal enhancement (BPE)	Level	Minimal Mild Moderate Marked
	Symmetric or asymmetric	Symmetric Asymmetric
Focus		
Masses	Shape	Oval Round Irregular
	Margin	Circumscribed Not circumscribed - Irregular - Spiculated
	Internal enhancement characteristics	Homogeneous Heterogeneous Rim enhancement Dark internal septations
Non-mass enhancement (NME)	Distribution	Focal Linear Segmental Regional Multiple regions Diffuse
	Internal enhancement patterns	Homogeneous Heterogeneous Clumped Clustered ring
Intramammary lymph node		
Skin lesion		
Non-enhancing findings	Ductal precontrast high signal on T1W	
	Cyst	
	Postoperative collections (hematoma/seroma)	
	Post-therapy skin thickening and trabecular thickening	
	Non-enhancing mass	
	Architectural distortion	
	Signal void from foreign bodies, clips, etc.	

Associated features	Nipple retraction	
	Nipple invasion	
	Skin retraction	
	Skin thickening	
	Skin invasion	Direct invasion Inflammatory cancer
	Axillary adenopathy	
	Pectoralis muscle invasion	
	Chest wall invasion	
	Architectural distortion	
Fat containing lesions	Lymph nodes	Normal Abnormal
	Fat necrosis	
	Hamartoma	
	Postoperative seroma/hematoma with fat	
Location of lesion	Location	
	Depth	
Kinetic curve assessment Signal intensity (SI)/ time curve description	Initial phase	Slow Medium Fast
	Delayed phase	Persistent Plateau Washout
Implants	Implant material and lumen type	Saline Silicone - Intact - Ruptured Other implant material Lumen type - Single - Double - Other
	Implant location	Retroglandular Retropectoral
	Abnormal implant contour	Focal bulge
	Intracapsular silicone findings	Radial folds Subcapsular line Keyhole sign (teardrop, noose) Linguine sign
	Extracapsular silicone	Breast Lymph nodes
	Water droplets	
	Peri-implant fluid	

BI-RADS® ASSESSMENT CATEGORIES

Category 0:	**Mammography:** Incomplete – Need Additional Imaging Evaluation and/or Prior Mammograms for Comparison **Ultrasound & MRI:** Incomplete – Need Additional Imaging Evaluation	
Category 1:	Negative	
Category 2:	Benign	
Category 3:	Probably Benign	
Category 4:	Suspicious	Mammography & Ultrasound: Category 4A: Low suspicion for malignancy Category 4B: Moderate suspicion for malignancy Category 4C: High suspicion for malignancy
Category 5:	Highly Suggestive of Malignancy	
Category 6:	Known Biopsy-Proven Malignancy	

ANNEX 4. Histological classification

Adapted from (71)

Epithelial tumors
Invasive breast carcinoma - Infiltrating duct carcinoma (NOS) - Oncocytic carcinoma - Lipid rich carcinoma - Glycogen rich carcinoma - Sebaceous carcinoma - Lobular carcinoma NOS - Tubular carcinoma - Cribriform carcinoma NOS - Mucinous adenocarcinoma - Mucinous cystadenocarcinoma NOS - Invasive micropapillary carcinoma of breast - Metaplastic carcinoma NOS
Rare and salivary gland type tumors - Secretory carcinoma - Acinar cell carcinoma - Mucoepidermoid carcinoma - Polymorphous adenocarcinoma - Adenoid cystic carcinoma - Classic adenoid cystic carcinoma - Solid basaloid adenoid cystic carcinoma - Adenoid cystic carcinoma with high grade transformation - Tall cell carcinoma with reversed polarity
Neuroendocrine neoplasms - Neuroendocrine tumor, NOS - Neuroendocrine tumor, grade 1 - Neuroendocrine tumor, grade 2 - Neuroendocrine carcinoma NOS - Neuroendocrine carcinoma, small cell - Neuroendocrine carcinoma, large cell
Epithelial - myoepithelial tumors - Pleomorphic adenoma - Adenomyoepithelioma NOS - Adenomyoepithelioma with carcinoma - Epithelial-myoepithelial carcinoma
Non invasive lobular neoplasia - Atypical lobular hyperplasia - Lobular carcinoma in situ NOS - Classic lobular carcinoma in situ - Florid lobular carcinoma in situ - Lobular carcinoma in situ, pleomorphic
Ductal carcinoma in situ (DCIS) - Ductal carcinoma, non infiltrating, NOS - DCIS of low nuclear grade - DCIS of intermediate nuclear grade - DCIS of high nuclear grade
Benign epithelial proliferations and precursors - Usual ductal hyperplasia - Columnar cell lesions including flat epithelial atypia - Atypical ductal hyperplasia
Adenosis and benign sclerosing lesions - Sclerosing adenosis - Apocrine adenoma - Microglandular adenosis

- Radial scar / complex sclerosing lesion

Papillary neoplasms
- Intraductal papilloma
- Ductal carcinoma in situ, papillary
- Encapsulated papillary carcinoma
- Encapsulated papillary carcinoma with invasion
- Solid papillary carcinoma in situ
- Solid papillary carcinoma with invasion
- Intraductal papillary adenocarcinoma with invasion

Adenomas
- Tubular adenoma NOS
- Lactating adenoma
- Duct adenoma NOS

Mesenchymal tumors

Vascular tumors
- Hemangioma NOS
- Perilobular hemangioma
- Venous hemangioma
- Cavernous hemangioma
- Capillary hemangioma
- Angiomatosis
- Atypical vascular lesion
- Lymphatic atypical vascular lesion resembling lymphangioma
- Vascular atypical vascular lesion resembling hemangioma
- Postradiation angiosarcoma
- Epithelioid angiosarcoma
- Angiosarcoma
- Epithelioid angiosarcoma

Fibroblastic and myofibroblastic tumors
- Nodular fasciitis
- Myofibroblastoma
- Desmoid type fibromatosis
- Inflammatory myofibroblastic tumor

Peripheral nerve sheath tumors
- Schwannoma NOS
- Neurofibroma NOS
- Granular cell tumor NOS
- Granular cell tumor, malignant

Smooth muscle tumors
- Leiomyoma NOS
- Cutaneous leiomyoma
- Leiomyoma of the nipple and areola
- Leiomyosarcoma NOS

Adipocytic tumors
- Lipoma NOS
- Angiolipoma NOS
- Liposarcoma NOS

Other mesenchymal tumors and tumor-like conditions
- Pseudoangiomatous stromal hyperplasia

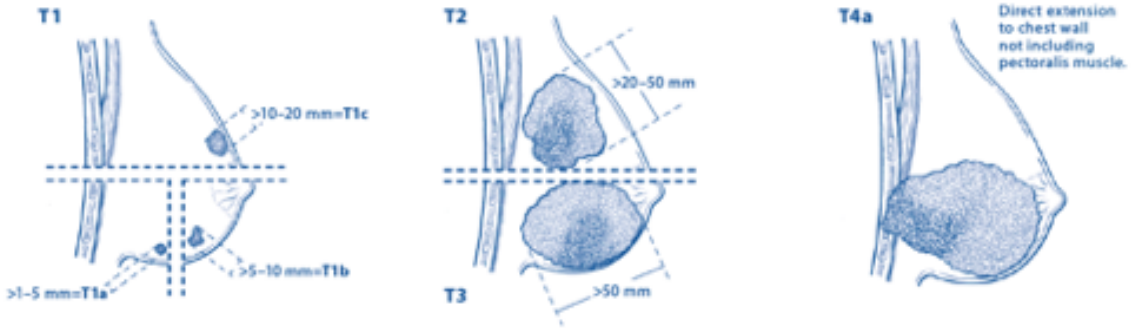
Fibroepithelial tumors
- Fibroadenoma NOS
- Phyllodes tumor NOS
- Periductal stromal tumor
- Phyllodes tumor, benign
- Phyllodes tumor, borderline
- Phyllodes tumor, malignant
- Hamartoma

Tumors of the nipple - Nipple adenoma - Syringoma NOS - Paget disease of the nipple
Malignant lymphoma - Diffuse large B cell lymphoma NOS - Burkitt lymphoma NOS/Acute leukemia, Burkitt type - Endemic Burkitt lymphoma - Sporadic Burkitt lymphoma - Immunodeficiency associated Burkitt lymphoma - Breast implant associated anaplastic large cell lymphoma - Mucosa associated lymphoid tissue lymphoma - Follicular lymphoma NOS
Metastatic tumors - Tumors of the male breast - Gynecomastia - Carcinoma - Invasive carcinoma - In situ carcinoma

ANNEX 5. TNM stadification

Adapted from (26)

PRIMARY TUMOR		
TX	Primary tumor cannot be assessed	
T0	No evidence of primary tumor	
Tis	Carcinoma in situ	
	Tis (DCIS)	Ductal carcinoma in situ
	Tis (LCIS)	Lobular carcinoma in situ
	Tis (Paget's)	Paget's disease of the nipple NOT associated with invasive carcinoma and/or carcinoma in situ (DCIS and/or LCIS) in the underlying breast parenchyma. Carcinomas in the breast parenchyma associated with Paget's disease are categorized based on the size and characteristics of the parenchymal disease, although the presence of Paget's disease should still be noted
T1	Tumor ≤ 20 mm in greatest dimension	
	T1mi	Tumor ≤ 1 mm in greatest dimension
	T1a	Tumor > 1 mm but ≤ 5 mm in greatest dimension
	T1b	Tumor > 5 mm but ≤ 10 mm in greatest dimension
	T1c	Tumor > 10 mm but ≤ 20 mm in greatest dimension
T2	Tumor > 20 mm but ≤ 50 mm in greatest dimension	
T3	Tumor > 50 mm in greatest dimension	
T4	Tumor of any size with direct extension to the chest wall and/or to the skin (ulceration or skin nodules) Note: Invasion of the dermis alone does not qualify as T4	
	T4a	Extension to the chest wall, not including only pectoralis muscle adherence/invasion
	T4b	Ulceration and/or ipsilateral satellite nodules and/or edema (including peau d'orange) of the skin, which do not meet the criteria for inflammatory carcinoma
	T4c	Both T4a and T4b
	T4d	Inflammatory carcinoma

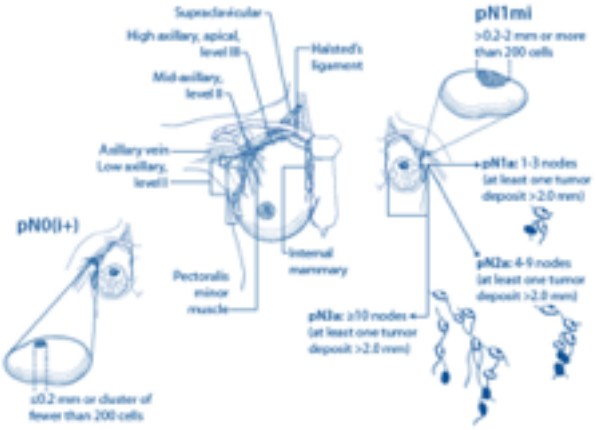


REGIONAL LYMPH NODES (N) - CLINICAL		
NX	Regional lymph nodes cannot be assessed	
N0	No regional lymph node metastases	
N1	Metastases to movable ipsilateral level I, II axillary lymph node(s)	
N2	Metastases in ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted; or in clinically detected* ipsilateral internal mammary nodes in the absence of clinically evident axillary lymph node metastases	
	N2a	Metastases in ipsilateral level I, II axillary lymph nodes fixed to one another (matted) or to other structures

	N2b	Metastases only in clinically detected* ipsilateral internal mammary nodes and in the absence of clinically evident level I, II axillary lymph node metastases
N3	Metastases in ipsilateral infraclavicular (level III axillary) lymph node(s) with or without level I, II axillary lymph node involvement; or in clinically detected* ipsilateral internal mammary lymph node(s) with clinically evident level I, II axillary lymph node metastases; or metastases in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement	
	N3a	Metastases in ipsilateral infraclavicular lymph node(s)
	N3b	Metastases in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
	N3c	Metastases in ipsilateral supraclavicular lymph node(s)
REGIONAL LYMPH NODES (N) - PATHOLOGIC		
pNX	Regional lymph nodes cannot be assessed (for example, previously removed, or not removed for pathologic study)	
pN0	No regional lymph node metastases identified histologically	
	pN0 (i-)	No regional lymph node metastases histologically, negative IHC
	pN0 (i+)	Malignant cells in regional lymph node(s) no greater than 0.2 mm (detected by H&E or IHC including ITC)
	pN0 (mol-)	No regional lymph node metastases histologically, negative molecular findings (RT-PCR)
	pN0 (mol+)	Positive molecular findings (RT-PCR)**, but no regional lymph node metastases detected by histology or IHC
pN1	Micrometastases; or metastases in 1–3 axillary lymph nodes; and/or in internal mammary nodes with metastases detected by sentinel lymph node biopsy but not clinically detected***	
	pN1mi	Micrometastases (greater than 0.2 mm and/or more than 200 cells, but none greater than 2.0 mm)
	pN1a	Metastases in 1–3 axillary lymph nodes, at least one metastasis greater than 2.0 mm
	pN1b	Metastases in internal mammary nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected***
	pN1c	Metastases in 1–3 axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected
pN2	Metastases in 4–9 axillary lymph nodes; or in clinically detected**** internal mammary lymph nodes in the absence of axillary lymph node metastases	
	pN2a	Metastases in 4–9 axillary lymph nodes (at least one tumor deposit greater than 2.0 mm)
	pN2b	Metastases in clinically detected**** internal mammary lymph nodes in the absence of axillary lymph node metastases
N3	Metastases in 10 or more axillary lymph nodes; or in infraclavicular (level III axillary) lymph nodes; or in clinically detected**** ipsilateral internal mammary lymph nodes in the presence of one or more positive level I, II axillary lymph nodes; or in more than three axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected***; or in ipsilateral supraclavicular lymph nodes	
	pN3a	Metastases in 10 or more axillary lymph nodes (at least one tumor deposit greater than 2.0 mm); or metastases to the infraclavicular (level III axillary lymph) nodes

	pN3b	Metastases in clinically detected**** ipsilateral internal mammary lymph nodes in the presence of one or more positive axillary lymph nodes; or in more than three axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected***
	pN3c	Metastases in ipsilateral supraclavicular lymph nodes

*Classification is based on axillary lymph node dissection with or without sentinel lymph node biopsy. Classification based solely on sentinel lymph node biopsy without subsequent axillary lymph node dissection is designated (sn) for "sentinel node," for example, pN0(sn).
** RT-PCR: reverse transcriptase/polymerase chain reaction.
*** "Not clinically detected" is defined as not detected by imaging studies (excluding lymphoscintigraphy) or not detected by clinical examination.
**** "Clinically detected" is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination and having characteristics highly suspicious for malignancy or a presumed pathologic macrometastasis based on fine needle aspiration biopsy with cytologic examination.



DISTANT METASTASES (M)		
M0	No clinical or radiographic evidence of distant metastases	
	CM0(I+)	No clinical or radiographic evidence of distant metastases, but deposits of molecularly or microscopically detected tumor cells in circulating blood, bone marrow, or other nonregional nodal tissue that are no larger than 0.2 mm in a patient without symptoms or signs of metastases
M1	Distant detectable metastases as determined by classic clinical and radiographic means and/or histologically proven larger than 0.2 mm	

ANNEX 6. Prognostic stage (42)

Clinical Prognostic Stage

			ER+, PR+, HER2+	ER+, PR+, HER2-	ER+/PR-, HER2+	ER-/PR+, HER2+	ER-, PR-, HER2+	ER+, PR-, HER2-	ER-, PR+, HER2-	ER-, PR-, HER2-	Anatomic stage
TisN0	M0	G1-3	0	0	0	0	0	0	0	0	0
T1N0 T0N1mi T1N1mi		G1	IA	IA	IA	IA	IA	IA	IA	IB	IA
		G2	IA	IA	IA	IA	IA	IA	IA	IB	IA
		G3	IA	IA	IA	IA	IA	IA	IB	IB	IA
T0N1 T1N1 T2N0		G1	IB	IB	IIA	IIA	IIA	IIA	IIA	IIA	IIA
		G2	IB	IB	IIA	IIA	IIA	IIA	IIA	IIB	IIA
		G3	IB	IIA	IIA	IIA	IIA	IIB	IIB	IIB	IIA
T2N1 T3N0		G1	IB	IIA	IIA	IIA	IIB	IIB	IIB	IIB	IIB
		G2	IB	IIA	IIA	IIA	IIB	IIB	IIB	IIIB	IIB
		G3	IB	IIB	IIB	IIB	IIB	IIIA	IIIA	IIIB	IIB
T0N2 T1N2 T2N2 T3N1		G1	IIA	IIA	IIIA	IIIA	IIIA	IIIA	IIIA	IIIB	IIIA
		G2	IIA	IIA	IIIA	IIIA	IIIA	IIIA	IIIA	IIIB	IIIA
		G3									

ER- = estrogen receptor-negative, ER+ = ER-positive, G = grade, HER2- = HER2 negative, HER2+ = HER2-positive, mi = micrometastasis, PR- = progesterone receptor-negative, PR+ = PR-positive, Tis = in situ

Pathologic Prognostic Stage

			ER+, PR+, HER2+	ER+, PR+, HER2-	ER+/PR-, HER2+	ER-/PR+, HER2+	ER-, PR-, HER2+	ER+, PR-, HER2-	ER-, PR+, HER2-	ER-, PR-, HER2-	Anatomic stage
TisN0	M0	G1-3	0	0	0	0	0	0	0	0	0
T1N0 T0N1mi T1N1mi		G1	IA	IA	IA	IA	IA	IA	IA	IA	IA
		G2	IA	IA	IA	IA	IA	IA	IA	IB	IA
		G3	IA	IA	IA	IA	IA	IA	IA	IB	IA
T0N1 T1N1 T2N0		G1	IA	IA	IB	IB	IIA	IB	IB	IIA	IIA
		G2	IA	IA	IB	IB	IIA	IIA	IIA	IIA	IIA
		G3	IA	IB	IIA	IIA	IIA	IIA	IIA	IIA	IIA
T2N1 T3N0		G1	IA	IA	IIB	IIB	IIB	IIB	IIB	IIB	IIB
		G2	IB	IB	IIB	IIB	IIB	IIB	IIB	IIB	IIB
		G3	IB	IIA	IIB	IIB	IIB	IIB	IIB	IIIA	IIB
T0N2 T1N2 T2N2 T3N1 T3N2		G1	IB	IB	IIIA	IIIA	IIIA	IIIA	IIIA	IIIA	IIIA
		G2	IB	IB	IIIA	IIIA	IIIA	IIIA	IIIA	IIIB	IIIA
		G3	IIA	IIB	IIIA	IIIA	IIIA	IIIA	IIIA	IIIC	IIIA
T4N0 T4N1 T4N2 AnyN3		G1	IIIA	IIIA	IIIB	IIIB	IIIB	IIIB	IIIB	IIIB	IIIB
		G2	IIIA	IIIA	IIIB	IIIB	IIIB	IIIB	IIIB	IIIC	IIIB
		G3	IIIB	IIIB	IIIB	IIIB	IIIB	IIIC	IIIC	IIIC	IIIB
Any	M1	Any	IV	IV	IV	IV	IV	IV	IV	IV	IV

Additionally, pT1, pT2, pN0, M0, ER+, and HER2- cancers are assigned as Pathologic Prognostic Stage group IA when Oncotype DX recurrence score is less than 11.

ANNEX 7. Systemic treatment in advanced breast cancer (72)

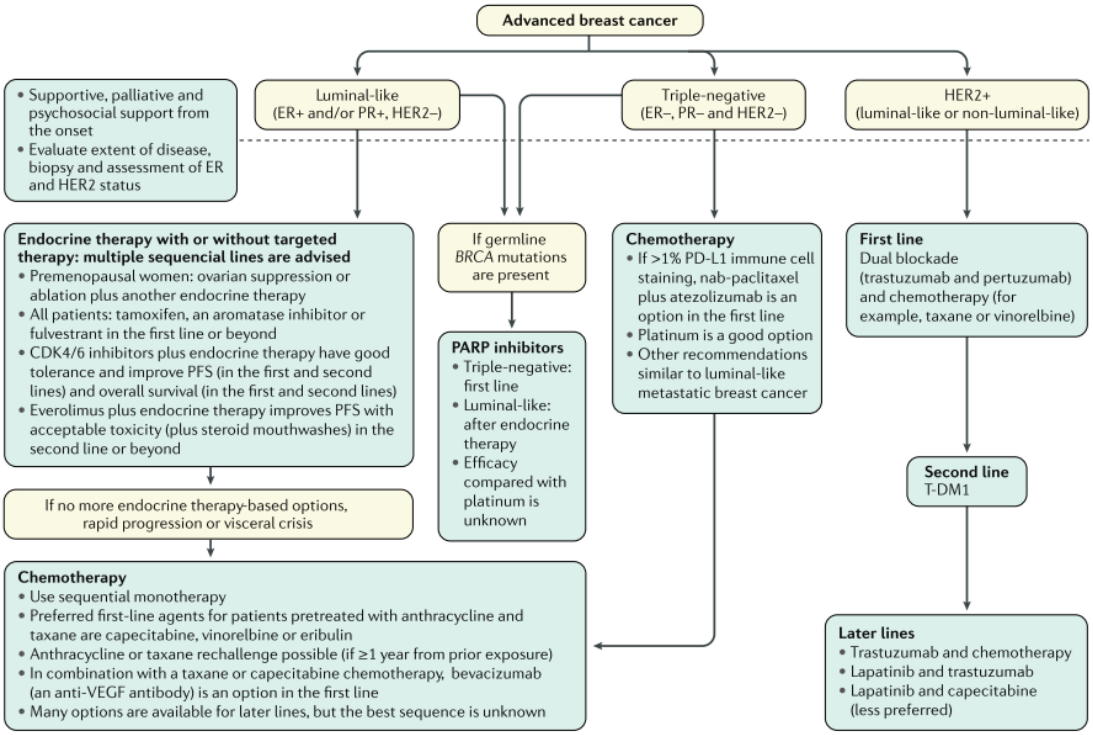


Fig. 10 | **Algorithm for advanced breast cancer.** Management of advanced breast cancer with distant metastases should be according to subtype as well as disease characteristics and patient preferences. Supportive, palliative and psychosocial support are crucial from the time of diagnosis. Biopsy of a metastatic site and assessment of oestrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) status, at least once in the metastatic setting, are also necessary. Endocrine therapy, with or without targeted therapy, is the mainstay for luminal-like disease, and — unless life-threatening — several lines are to be used before commencing chemotherapy. When chemotherapy is used, sequential monotherapy is advised. For triple-negative disease, chemotherapy is the main treatment, with no specific recommendations except that platinum is one of the preferred options. Triple-negative tumours with immune cells expressing programmed death-ligand 1 (PD-L1) may be candidates for first-line immunotherapy. For HER2-positive disease, it is crucial to continue blocking the HER2 pathway, with a sequence of anti-HER2 agents and chemotherapy; combinations of endocrine therapy with anti-HER2 therapy can also be used in ER-positive, HER2-positive disease, preferentially as maintenance therapy. For women harbouring germline *BRCA* mutations, poly(ADP-ribose) polymerase (PARP) inhibitors are an additional therapy option. The management algorithm takes evidence-based registered therapy options into account. Availability and reimbursement of individual diagnostic or therapeutic options may differ regionally and require adjustments of the treatment concepts outlined here. –, negative; +, positive; PFS, progression-free survival; T-DM1, ado-trastuzumab emtansine; VEGF, vascular endothelial growth factor.

ANNEX 8. Protocol information sheet

FULL INFORMATIU

NOM DE L'ESTUDI: ESTUDI COMPARATIU DE L'ÚS DE RADIOTERÀPIA EXTENRA PROFILÀCTICA O CRIBRATGE EN DONES AMB MUTACIÓ DEL GEN BRCA1/2

INVESTIGADORA PRINCIAL: Jana Baltà Salvador

CENTRE: Servei de Ginecologia, Hospital Universitari dr. Josep Trueta, Girona.

Ens dirigim a vostè per informar-la de que ha estat convidada a participar en un estudi d'investigació.

Abans que vostè decideixi participar en l'estudi llegeixi amb atenció aquest formulari i faci totes les preguntes que tingui, per assegurar que entén els procediments de l'estudi, riscos i beneficis; de tal manera que vostè pugui decidir voluntàriament si desitja participar o no.

Si després de llegir aquest document té algun dubte, demani a l'investigador responsable o personal de l'estudi que li expliqui. Té absoluta llibertat per preguntar sobre qualsevol aspecte que l'ajudi a aclarir els seus dubtes.

Aquest estudi es realitza als tres centres d'ICO (ICO de Girona, ICO de Badalona i ICO de l'Hospitalet). El present estudi ha estat aprovat pel Comitè d'Ètica i Investigació Clínica (CEIC) de l'Hospital Univesitari Josep Trueta.

Per què es realitza aquest estudi i quin és el seu objectiu?

Aquest estudi té com a principal objectiu avaluar l'ús de la radioteràpia externa profilàctica en dones amb mutació en el gen BRCA 1/2. Actualment la mesura de reducció del risc més àmpliament acceptada és la mastectomia profilàctica bilateral, que aconsegueix una reducció del risc d'aparició d'una neoplàsia de mama del 90%. No obstant això moltes dones no accepten aquesta tècnica perquè és molt invasiva i consta de nombrosos riscs i complicacions.

Amb l'avaluació que es durà a terme, es pretén identificar una nova tècnica de reducció de risc que permeti oferir noves alternatives a totes les dones amb mutació del gen BRCA1/2.

Què implicarà la meva participació?

L'estudi s'oferirà a aquelles pacients amb mutació del gen BRCA ½ que no acceptin sotmetre's a la mastectomia bilateral profilàctica. Un cop la pacient accepti participar en l'estudi, serà aleatoritzada en un dels dos grups d'estudi (grup amb radioteràpia externa profilàctica i cribratge o grup amb només cribratge).

A totes les pacients se'ls realitzarà un seguiment clínic cada 3-4 mesos i una prova d'imatge cada 6 mesos (RMN alternat amb mamografia i ecografia). El seguiment es realitzarà durant un total de 5 anys.

Quins són els riscos?

Els efectes secundaris de la radioteràpia externa es divideixen en:

EFECTES SECUNDARIS COMUNS:

- Efectes secundaris a curt termini:
    - Dermatitis aguda.
    - Fatiga lleu-moderada.
    - Canvis en la sensació de la pell.
    - Malestar a l'aixella.
    - Pèrdua de pèl a l'aixella.
- Efectes secundaris a llarg termini:
    - Dermatitis crònica.
    - Nàusees.

EFECTES SECUNDARIS MENYS COMUNS:

- Efectes secundaris a curt termini:
    - Eritema multiforme i síndrome de Stevens Johnson.
    - Limfedema.
- Efectes secundaris a llarg termini:
    - Fractures de clavícula.
    - Problemes cardíacs i pulmonars.
    - Sarcoma radioinduït.
    - Dany als nervis.

És obligatòria la participació?

La participació a l'estudi és totalment voluntària, per la qual cosa si decideix no participar-hi no afectarà ni modificarà el pla assistencial que ha de rebre ni la relació amb l'investigador.

A més a més, en cas d'acceptar la participació, vostè té el dret de revocar el consentiment en qualsevol moment, sense cap mena de perjudici en el seu tractament mèdic.

Com es protegirà la meva confidencialitat?

La informació recollida en aquest estudi serà tractada segons la Llei Orgànica de Protecció de Dades de Caràcter Personal i Garantia dels Drets Digitals (3/2018) i el Reglament 2016/679 del Parlament i del Consell Europeu.

Les dades es tractaran de forma confidencial, sense accés per part de tercers, i només seran utilitzades amb finalitat d'investigació.

Què se'n farà de la informació obtinguda de l'estudi?

En cas de publicar els resultats a través de publicacions i/o congressos per tal que altres centres i pacients puguin aprofitar les troballes del nostre estudi, les dades de caràcter personal es tractaran de forma anònima de forma que en cap moment sigui possible la identificació dels participants.

Quina és la compensació econòmica?

La participació a l'estudi no suposa cap cost per la pacient, i tampoc rebrà cap compensació econòmica.

Si està d'acord en participar en aquest estudi, se li entregarà una còpia d'aquest document i el formulari de Consentiment Informat, que haurà de signar d'acord amb les normatives legals vigents.

ANNEX 9. Informed consent document

CONSENTIMENT INFORMAT

Declaració de la pacient:

Jo, _____,

amb DNI _____, de nacionalitat_____, major d'edat o autoritzat pel meu representat legal, amb domicili _____

declaro que he llegit el document informatiu sobre l'estudi que se m'ha entregat i he estat correctament informada pel membre responsable de l'equip investigador a sota esmentat. Entenc que la participació en l'estudi és totalment voluntària, i que puc sol·licitar la retirada i eliminació de les meves dades personals en qualsevol moment de l'estudi sense haver d'afectar a la meva assistència sanitària.

Dono el meu permís perquè les dades de la meva història clínica siguin utilitzades per l'equip investigador per fins relacionats amb aquest estudi. He estat informada sobre l'ús de caire científic que es farà de les meves dades personals.

Entenc que es respectarà la confidencialitat de les meves dades. He pogut formular les preguntes que he considerat oportunes, i si durant el transcurs de la investigació, sorgeix informació rellevant per continuar participant en l'estudi, l'investigador m'entregarà aquesta informació.

Declaro que se m'ha entregat una còpia del Full d'Informació pel Pacient i una còpia d'aquest Consentiment Informat.

SIGNATURA DE L'INVESTIGADOR/A: DATA:

_____ _____

SIGNATURA DEL PACIENT: DATA:

_____ _____

REVOCACIÓ DEL CONSENTIMENT

Jo, _____,

amb DNI _____, revoco el consentiment de participar en l'estudi anteriorment esmentat.

SIGNATURA: DATA:

_____ _____

Si el pacient així ho desitja, podrà sol·licitar que li sigui lliurada tota la informació que s'hagi recaptat sobre ella, amb motiu de la seva participació en el present estudi.