

Genetics of Breast and Ovary Cancers Associated with Hereditary Cancers and their Clinical Management

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1. Abstract

1.1. Background: Carriers of the BRCA-1/2 mutation have increased and variable risks of Breast Cancer (BC) and ovarian cancer and vary or are modified by common genetic variants and their incidence genetic testing and risk-reducing surgery has increased, they should receive advice and evaluation by the physician with experience in genetics **1.2. Objective:** The genetics of BRCA-1/2 gene mutations and their impact on women have been reviewed.

1.3. Methods: We reviewed the publications in PubMed, Web of Science, Scopus, related to mutations of the BRCA-1/2 genes and hereditary cancers, to assess prevention, detection and management and how to improve quality of life **1.3. Results:** increased use was identified of tests, as well as risk-reducing surgery, the use of new screening strategies; Still, there is no effective detection protocol that has been shown to reduce mortality, only risk-reducing surgery, such as mastectomy and bilateral salpingo-oophorectomy; recommended after parity satisfied, has improved chemoprevention and reproductive capacity.

1.4. Conclusions: Identification of women who carry a pathogenic mutation in high-risk BRCA-1/2 genes; the clinical management, prevention and identification of related cancers improves the morbidity and mortality of these patients of their individual risk

2. Introduction

Mutations in the BRCA1 and BRCA2 genes were identified in

1994 and 1995 as a cause of hereditary breast and ovarian cancer [1, 2]. One in 400 women in the general population carries a germline BRCA-1 or BRCA-2 mutation; and they are at risk of developing Breast Cancer (BC) at 70 years between 45 and 88% [3]. The presence of these mutations increases the risk of developing some cancers other than BM, High-Grade Serous Ovarian Cancer (HGSC), uterine or fallopian tube and primary peritoneal cancer [3]. The specific patterns of BC and hereditary ovarian cancer are related to pathogenic variants in the BRCA-1/2 genes [4-5], Li-Fraumeni Syndrome (LFS), a rare hereditary syndrome, is related to pathogenic variants of the germ line of the TP53 gene. Genome-Wide Association Studies (GWAS) have identified 94 common Single Nucleotide Polymorphisms (SNPs) associated with BC risk and 18 associated with ovarian cancer risk; carrying a pathogenic mutation in the high-risk BRCA-1/2 genes [3,6].

Because women with BRCA1 and BRCA2 mutations are already at high risk of developing MC and ovarian cancers, the combined effects of the risk-modifying variants result in larger differences in the risk of developing them compared to the general population [7]. These inherited syndromes share several characteristics of the increased risk of BC; arise from pathogenic germline variants that are not found within sex-linked genes; are inherited from either parent; and they are associated with the onset of BM at an early age and the development of other types of cancer, with an autosomal dominant inheritance pattern. The offspring of an individual

with one of these hereditary syndromes has a 50% chance of inheriting the pathogenic variant. People with these syndromes share a higher risk of multiple early-onset and bilateral cancer cases; These pathogenic variants are highly pervasive, their manifestations (expression) are variable in individuals within a single family (age of onset, tumor site, number of primary tumors). The risk of developing cancer in people with one of these syndromes depends on variables; sex and age of the person, this article focuses on the risk of cancer, prevention and management of the risk of BC and / or ovarian cancer related to mutations in the BRCA genes and LFS; indications for BRCA-1/2 testing [8-12], Table 1.

3. BRCA-Related Breast and / or Ovarian Cancer Syndrome

BRCA-1 genes such as BRCA-2 encode proteins involved in tumor suppression [4,5]. At present, it is not clear if penetrance is related only to the specific or identified pathogenic variant in a family or if additional factors, genetic or environmental, affect the expression of the disease, it is generally accepted that BRCA-1 carriers / 2 pathogens have a higher risk of BC and / or ovarian cancer, which warrants more intensive preventive strategies and detection [13].

4. Risk of Breast Cancer (BC)

Penetrance estimates range from 41% to 90% lifetime risk of BC, with a higher risk of contralateral BC [14-26]. In unaffected BRCA-1/2 carriers it showed that the cumulative risk of MC at 80 years of age was 72% in carriers of a pathogenic BRCA-1 variant and 69% for BRCA-2 [4-16]. Estimates of the cumulative risk of contralateral BC 20 years after BC diagnosis are 40% for carriers of a pathogenic BRCA-1 variant and 26% for BRCA-2 [15-27].

The evidence that a pathogenic variant in BRCA-1/2 is associated with poor survival outcomes for MC has been inconsistent. A meta-analysis showed that carriers of a pathogenic BRCA-1 variant with MC had poorer Overall Survival (OS) compared to those without a BRCA mutation (hazard ratio [HR], 1.50; 95% CI, 1.11–2.04), having a BRCA-2 mutation was not associated with worse survival. A meta-analysis in patients with MC found that carriers of pathogenic BRCA-1 the variant had a worse OS compared to non-carriers (HR, 1.30; 95% CI, 1.11–1.52; P = 0.001) [28-30]. Carriers of a pathogenic BRCA-2 variant had poorer MC-specific survival compared to non-carriers (HR, 1.29; 95% CI, 1.03–1.62; P = 0.03), although OS was not significantly different. This meta-analysis also showed that, among patients with triple negative BC, BRCA-1/2 mutations are associated with better OS (HR, 0.49, 95% CI, 0.26 to 0.92, P = 0.03). Another meta-analysis showed that a BRCA-2 mutation was associated with worse BC-specific survival (HR, 1.57; 95% CI, 1.29–1.86). The sporadic versus hereditary BC study (POSH) in women with BC showed no significant differences in OS between carriers of a pathogenic BRCA-1/2 variant and non-carriers 2, 5, and 10 years after diagnosis [27-34].

In families that met the German Consortium for Hereditary Breast and Ovarian Cancer test criteria for BRCA-1/2 mutations, a mutation was detected in 13.7% of families with a single case of BC diagnosed before age 36 years; The analysis of patients diagnosed with BC before the age of 50 years showed that carriers of a pathogenic BRCA-1 variant had a worse OS compared to patients who did not carry a pathogenic BRCA-1/2 variant (HR, 1.28; 95% CI, 1.05-1.57; P = 0.01); not statistically significant due to the characteristics of the BC and its treatment (HR, 1.20; 95% CI, 0.97–1.47; p = 0.09); BRCA-2 mutations were not associated with decreased OS, except during the first 5 years of follow-up (HR, 1.56; 95% CI, 1.06–2.28; P = 0.02) [17–35].

There may be a genetic anticipation effect in carriers of the pathogenic BRCA-1/2 variant in that the age of disease onset may decrease with time as BRCA-1/2 mutation tests have been made. become common, increased knowledge about the best detection of BC in carriers of a pathogenic BRCA-1/2 variant, an analysis of families with a known BRCA-1/2 variant and more than 2 family members with BC, and / or ovarian cancer in consecutive generations showed that this decrease in the age of onset between generations is due to a cohort effect, specifically lifestyle or environment; factors such as increased use of oral contraceptives and increased rates of obesity. Some histopathological features occur more frequently in BC from individuals with a germline BRCA-1/2 pathogenic variant, and BRCA-1-related BC is more likely to be characterized as ER / PR-negative and HER2-negative (“triple negative”) [14-25]. BRCA-1 mutations are reported in 7-16% of triple-negative BM patients [18-49].

The incidence of BRCA-2 mutations ranges from 1% to 17% in triple negative BM not selected for age or family history [14-25,18-49]; Estrogen Hormone Receptor (ER) positive (ER +) and prototone positive (RP +) BC is associated with an absolute lifetime risk of 40% in carriers of the pathogenic BRCA-2 variant [14-25] and the rate of 20-year survival in carriers of a pathogenic BRCA-2 variant with ER + tumors was 62.2%, compared with 83.7% in those with ER-negative BM, although this difference was only statistically significant in those younger than 50 years (68.3% vs. 91.3 %, respectively; P = 0.03) [30,40-52].

A case-control study of carriers of the Icelandic founder BRCA2 variant 999del5 showed that ER-positive disease was associated with an increased risk of mortality, compared to those with ER-negative disease (HR, 1.94; 95% CI, 1.22-3.07; P = 0.005), the prevalence of negative ER disease was not significantly higher in carriers of a pathogenic BRCA-2 variant than in non-carriers (75.6 vs 70.2%, respectively; p = 0,7). In patients with triple negative BC, carriers of a pathogenic BRCA-1/2 variant were diagnosed at an earlier age compared with non-carriers. In patients with triple negative BC, the median age at diagnosis in carriers of the pathogenic BRCA-1 variant was 39 years. The patients were not

selected based on family history or age. In patients with early-onset triple-negative BC (age at diagnosis <40 years), the incidence of BRCA-1 mutations was 36%; the incidence was 27% in those diagnosed before 50 years of age. The result in POSH showed that in patients with triple negative BC, the OS at 2 years was higher in carriers of a pathogenic variant of BRCA-1/2 than in non-carriers (95% vs 91%, respectively; HR, 0.59; 95% CI %, 0.35-0.99; P = 0.047), but the OS at 5 and 10 years did not differ significantly in both groups [16-32].

Male carriers of a pathogenic BRCA-1/2 variant are at increased risk of susceptibility to BC. In men with BC not selected for family history, 4% and 14% tested positive for a BRCA-2 germline mutation. For men who are carriers of a pathogenic BRCA-2 variant, the cumulative lifetime risk of BC is estimated at 7-8%. The cumulative lifetime risk for men carrying a pathogenic BRCA-1 variant is 1.2%, for men not carrying the pathogenic BRCA-1/2 variant, the lifetime risk of BC is 0.1% (1 at 1,000).

5. Risk of Ovarian Cancer

Increased risks of ovarian, fallopian tube, and peritoneum cancers are seen in carriers of a pathogenic BRCA-1/2 variant. In the diagnosis of invasive ovarian cancer, a pathogenic BRCA-1 variant has been found in 3.8 to 14.5% of women and a pathogenic BRCA-2 variant in 4.2 to 5.7% of women carrying a pathogenic BRCA-1 variant have an estimated cumulative risk of 48.3% (95% CI, 38.8% -57.9%) of ovarian cancer at age 70, while the cumulative risk at age 70 is 20.0% (95% CI, 13.3% - 29.0%) for carriers of a pathogenic BRCA-2 variant [10].

Survival is more favorable in carriers of a pathogenic BRCA-1/2 variant in ovarian cancer patients compared to non-carriers. Survival results appear to be more favorable for carriers of a pathogenic BRCA variant, BRCA-2 mutations were associated with significantly higher response rates (compared to non-carriers or BRCA-1 mutation carriers) a In primary chemotherapy, BRCA-1 mutations were not associated with prognosis or better response to chemotherapy. The histology of ovarian cancers in carriers of a pathogenic BRCA-1/2 variant is more likely to be characterized as high-grade serous adenocarcinoma compared to ovarian cancers in carriers without a mutation, although cancers of clear cell ovary and endometrioid in the above population. The mutations are also associated with non-mucinous as opposed to mucinous ovarian carcinoma. Mucinous epithelial ovarian carcinomas are associated with other genetic mutations, such as TP53 mutations, that are involved in LFS. Non-epithelial ovarian carcinomas (sex cord stromal and germ cell tumors) are not significantly associated with BRCA-1/2 mutation. Low malignant potential ovarian tumors (borderline tumors) are also not associated with a BRCA-1/2 mutation.

In women with a BRCA-1/2 pathogenic variant who underwent risk-reducing bilateral salpingo-oophorectomy, occult gynecologi-

cal neoplasms, both invasive carcinoma and intraepithelial lesions, were identified in 4.5 to 9% of cases, according to rigorous pathologic examinations of the ovaries and fallopian tubes [21]. Tubal intraepithelial carcinoma (TIC) is believed to represent an early precursor lesion of serous ovarian cancers, and TIC (with or without other lesions) was detected in 5-8% of patients carrying the pathogenic variant of BRCA-1 / 2 that RRSO was performed. The fimbriae or distal tuba are the predominant site of origin for these early neoplasms found in carriers of the pathogenic BRCA-1/2 variant. Although TIC appeared to occur more frequently in carriers of the pathogenic BRCA-1/2 variant compared to non-carriers, SOBR was performed [53-56].

TIC occurs in patients with serous carcinomas not selected for family history or BRCA mutation status. Because TIC was identified in individuals who underwent RRSO (for carriers of a pathogenic BRCA-1/2 variant) or other gynecological indications, the incidence and significance of these early lesions within the general population is unclear [56,57].

6. Risk Management

Recommendations for the medical treatment of BRCA-related BM syndrome and / or ovarian cancer are based on the early onset of cancer, increased risk of ovarian cancer, and risk of BM in men who are carriers of the pathogenic BRCA-variant. 1/2. An individual from a family with a pathogenic BRCA-1/2 variant that tests negative for the familial variant, follow-up for it is in accordance with the recommendations for the general population [33,34].

Screening recommendations for initiating screening have changed from the early age of onset at which BC and / or hereditary ovarian cancer are diagnosed; in women with pathogenic BRCA-1/2, it is to raise awareness of regular monthly Breast Self-Examination (BSE) from 18 years of age, and BSE every 6-12 months, starting at 25 years of age. Between the ages of 25 and 29, Magnetic Resonance Imaging (MRI) of the breast with contrast (to be performed between 7 to 15 of the menstrual cycle in premenopausal women) is performed annually or mammograms annually; only if MRI is not available. The age to start screening is individualized if the family history includes a diagnosis of MC before the age of 30. Breast MRI screening is preferred to mammograms in the age group 25-29 years. Detection with high quality breast MRI, must have the ability to perform a biopsy under the guidance of MRI, experience and availability. Between the ages of 30 and 75, an annual mammograms and contrast-enhanced breast MRI are performed. After age 75, management becomes individualized; women treated for BC who have not undergone bilateral mastectomy, mammograms and breast MRI with contrast should continue according to the recommendations for their age [60]. mammograms have served as the standard screening modality for MC detection for the past decades; There are no data on mammograms that alone reduces mortality in women at genetically increased risk of BC,

false negative mammograms results are common and correlate with factors such as the presence of the BRCA-1/2 mutation and high density of breast tissue both of which occur more frequently in premenopausal women. Aggressive or fast-growing BC are more common in premenopausal women, and are associated with lower sensitivity of mammograms detection methods. Comparative surveillance modalities in women at high risk for familial BC (BRCA-1/2 confirmed pathogenic variant or presumed mutation based on family history) consistently report the highest sensitivity of MRI detection (77-94%) in compared to mammograms (33-59%) to detect BM. False positive rates were higher with MRI in some reports, resulting in slightly lower or similar specificity with MRI detection (81-98%) compared to mammograms (92-100%). The sensitivity with ultrasound screening (33-65%) is similar to mammograms in the high-risk population [mine]. The performance of annual MRI and mammograms in women (25 to 65 years) with confirmed pathogenic variant of BRCA-1/2, the sensitivity of MRI was higher compared to mammograms (86 vs 19%; $p < 0.0001$), factors such as age, type of mutation and tumor invasion did not influence the sensitivity of the 2 detection modalities; however, the majority (97%) of cancers detected by MRI screening were early stage tumors. The mean follow-up of 8 years from diagnosis, no surviving patients developed distant recurrence. In women with a family history of BC or who, with a genetic mutation associated with a higher risk of BC, the sensitivity of breast MRI screening is 79%, with a specificity of 86%.

In carriers of a pathogenic BRCA-1 variant and carriers of a pathogenic BRCA-2 variant, mammograms showed greater sensitivity on MRI and was higher in carriers of a pathogenic BRCA-2 variant (12.6%) than carriers of a variant. BRCA-1 pathogen (3.9%), a different screening interval was evaluated, using alternate mammograms and MRI every 6 months in women with confirmed pathogenic BRCA-1/2 variant, the sensitivity and specificity with MRI screening was 92 and 87 %, respectively.

The optimal surveillance approach in women at high risk for familial BC is uncertain, especially for women between 25 and 30 years of age; the association between exposure to radiation from mammograms is unlikely and the risk of BC is higher in carriers of the pathogenic BRCA-1/2 variant; suggested increased risk in women exposed to radiation at a young age exposure to diagnostic radiation (including mammograms) before age 30 was associated with increased risk of BC in women with confirmed pathogenic BRCA-1/2 variant (n=1993), one of the benefits of MRI in surveillance strategies includes minimizing the radiation risks associated with mammograms, the greater sensitivity of MRI screening in the detection of tumors; however, it is associated with higher false positive results and costs relative to mammograms. The combined use of two-dimensional (2D) digital mammograms together with digital breast tomosynthesis (DBT) appears to improve BC detec-

tion and reduce false positive rates. Tomosynthesis enables the acquisition of three-dimensional (3D) data using a moving X-ray and digital detector. This data is reconstructed using computer algorithms to generate thin sections of images. The combined use of 2D and digital breast tomosynthesis results in twice the radiation exposure compared to mammograms alone, this increase in radiation dose falls below the established radiation dose limits, for standard mammograms, the radiation dose is minimized by new tomosynthesis techniques that create a synthetic 2D image, the need for conventional digital imaging can obviate. When performing, mammograms tomosynthesis is recommended. In carriers of the pathogenic BRCA-1/2 variant younger than 30 years, MRI screening is preferred to mammograms because of the potential risk of radiation exposure and lower sensitivity for detecting BC associated with mammograms [60-62].

Women with a BRCA1 or BRCA2 gene mutation have up to an 80% lifetime risk of BC unless RRM is performed, many refuse or delay surgery and choose screening, hoping that if cancer occurs, is detected in a curable stage; MRI is currently a very reasonable option [63] for women carrying the BRCA mutation who wish to delay or avoid RRM.

Appropriate imaging and surveillance intervals are under investigation; a computer simulation model that evaluated different annual screening strategies in carriers of a pathogenic BRCA-1/2 variant, a screening approach that included annual MRI from 25 years of age combined with alternate digital mammograms / MRI from 30 years of age; Age was shown to be the most effective strategy when considering radiation risks, life expectancy, and false positive rates; in the future, different surveillance strategies will be evaluated in people at high risk of familial BC. Annual MRI as a complement to screening mammograms and BSE) in women aged 25 years or older with a genetic predisposition to BC.

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TABLE 1**INDICATIONS FOR BRCA-1/2 TESTS**

Person from a family with a known pathogenic or likely pathogenic variant of BRCA-1/2

Personal history of BM and > 1 of:

Diagnosed at age 45 or younger

Diagnosed between the ages of 46 and 50 with:

- 1 additional primary BM at any age

-> 1 close blood relatives with BC at any age

-> 1 close blood relatives with high-grade prostate cancer

- Unknown or limited hereditary-family history

Diagnosis at age 60 or younger with triple negative BM

Diagnosed at any age with:

-> 1 close blood relatives with any of the following:

BM diagnosed at age 50 or younger

Ovarian cancer

Male breast cancer

Metastatic prostate cancer

Pancreatic cancer

-> 2 additional diagnoses of MC at any age in patients or close blood relatives.

Ashkenazi Jewish ancestry

Personal history of ovarian cancer

Personal history of pancreatic cancer

Personal history of male BM

Personal history of metastatic prostate cancer

Personal history of high-grade prostate cancer at any age with any of:

> 1 close blood relatives with ovarian cancer, pancreatic cancer, or metastatic prostate cancer at any age, or BC at age 50 or younger

> 2 close blood relatives with BC or prostate at any age

Ashkenazi Jewish ancestry

BRCA1 / 2 pathogenic variant detected by tumor profile

An individual who does not meet the criteria but has 1 or more 1st blood relatives. And 2nd., Grade that meet the criteria *

* There are limitations to testing an unaffected person.

Post-test counseling in women with a confirmed BRCA-1/2 variant (or suspected of having it in the family) includes discussion of risk-reducing mastectomy and / or RRM; on the scope in reducing / protecting the risk of cancer, the risks associated with surgeries, options for breast reconstruction, management of menopausal symptoms and reproductive desires; in addition to the psychosocial aspects and quality of life on surgical procedures to reduce risk.

Women with a BRCA1 or BRCA2 gene mutation have up to an 80% lifetime risk of BC unless RRM is performed, many refuse or delay surgery and choose screening, hoping that if cancer occurs, is detected in a curable stage; MRI is currently a very reasonable option [63] for women carrying the BRCA mutation who wish to delay or avoid RRM.

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Ovarian cancer screening procedures that are sensitive or specific enough have yielded mixed results. Multimodal screening with transvaginal ultrasound (TVUS) and CA-125 versus TVUS alone or without screening, showed that multimodal screening is effective in detecting early-stage cancer; after a median of 11 years of follow-up, with no reduction in mortality; screening for familial ovarian cancer; women with an estimated lifetime risk of ovarian cancer not less than 10% were screened for ovarian cancer by CA-125 testing every 4 months; the Ovarian Cancer Risk Algorithm (ROCA) used to interpret the results and TVUS (annually or within 2 months if the ROCA score is abnormal) [25]; the sensitivity, Positive Predictive Value (PPV), and negative predictive value (NPV) for screening for ovarian cancer at 1 year were 94.7, 10.8, and 100%, respectively. For women screened at risk of familial / genetic ovarian cancer, ROCA every 3 months had better early stage sensitivity with high specificity and a low but possibly

acceptable PPV compared to CA125 > 35 U / ml every 6 / every 12 months, warranting a larger cohort assessment [64].

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In women with increased familial / genetic risk of ovarian cancer (with the known pathogenic variant BRCA-1/2) in the family and / or family history of multiple MCs and / or ovarian cancer) ROCA-based screening Serum CA-125 every 3 months with annual TVUS annually or earlier depending on CA-125 test results) incidental ovarian cancers were identified, 50% early stage [26]; however, it is unknown whether detection affects survival. The SOBR is the current standard of care for the management of the risk of ovarian cancer in carriers of the pathogenic variant BRCA-1/2 For women who have not chosen bilateral RRSO, TVUS and serum CA-125 is considered from the 30 to 35 years of age at the discretion of the doctor.

7. Risk Reduction Surgery

To control this risk, women may opt for risk reduction surgery to remove breast tissue, ovaries, and fallopian tubes. Surgery should increase survival, but it can negatively affect the quality of life of women on a psychological and psychosexual level. Interventions are needed to facilitate psychological adjustment and improve quality of life after surgery to reduce risk; it is still controversial, particularly in this new era. genomics, where testing may become more common and many more women are identified as gene carriers [65]. Prophylactic bilateral mastectomy reduces risk of BC and mortality [65,66] Risk Reducing Mastectomy (RRM) provides a high degree of protection against BC in women carriers of a pathogenic BRCA-1/2 variant, discussion of the option of RRM for women on an individual basis, providing advice on the degree of protection offered by such surgery and degree of cancer risk [66-68].

Because the risk of BC continues to increase with age in carriers

of a pathogenic BRCA-1/2 variant, this counseling considers age and life expectancy, and family history; it is important to address the possible psychosocial effects of RRM; Although patients are generally satisfied with their decision, negative impacts on body image and sexuality have also been reported, and the psychosocial impact of RRM needs to be evaluated [29]. RRM is also associated with long-term physical symptoms, such as decreased sensitivity to touch, pain, tingling, infection, and edema [28]. A multidisciplinary management is recommended before surgery and include discussions on risks and benefits of surgery and options for surgical breast reconstruction and immediate is an option, and is recommended for those considering immediate or delayed reconstruction; nipple-sparing mastectomy is a safe and effective risk reduction strategy for patients with a pathogenic BRCA-1/2 variant [30], although more data and long-term follow-up are needed [69]. Risk-reducing bilateral salpingo-oophorectomy; women with a confirmed BRCA-1/2 pathogenic variant are at increased risk for BC and / or ovarian cancer (including fallopian tube cancer and primary peritoneal cancer). Although the risk of ovarian cancer is generally considered to be lower than the risk of MC in carriers of a pathogenic BRCA-1/2 variant. the absence of reliable methods of early detection and the poor prognosis associated with advanced ovarian cancer, it is decided to perform bilateral RRSO in women with satisfied parity.

Women carrying a pathogenic BRCA-1/2 variant showed that ovarian cancer is more prevalent in people carrying a pathogenic BRCA-1 variant (4.2%) than in BRCA-2 (0.6%). In carriers of a pathogenic BRCA-1 variant, the prevalence of ovarian, fallopian tube, and peritoneal cancers found during surgery reduced the risk by 1.5% in those under 40 years of age and 3.8% between 40 and 49 years of age. The highest incidence rate for carriers of a pathogenic BRCA-1 variant was between the ages of 50 and 59 years (annual risk, 1.7%); for carriers of the pathogenic BRCA-2 variant, the highest incidence rate was observed between the ages of 60 and 69 years (annual risk, 0.6%), the recommended age for SOBRR should be lower for women who were carriers of a pathogenic variant BRCA-1 than for the BRCA-2 variant. The efficacy of bilateral RRSO to reduce the risk of ovarian cancer in carriers of a pathogenic BRCA-1/2 variant has been demonstrated in a meta-analysis, a reduction in 80% of the risk of ovarian or fallopian tube cancer after bilateral RRSO [70]; Also, I decreased the risk of BRCA-1-associated gynecologic tumors (including ovarian, fallopian tube, or primary peritoneal cancers) by 85% compared to observation over a 3-year follow-up period (HR, 0.15; 95%, 0.04-0.56; P = 0.005); women carrying the pathogenic BRCA-1/2 variant showed that SOB reduces the risk reduces the risk of ovarian, fallopian tube or peritoneal cancer by 80% (HR, 0.20; 95% CI, 0.13-0.30) and all causes mortality in 77% (HR, 0.23; 95% CI, 0.13-0.39). bilateral RRSO reduces mortality at all ages in carriers of a pathogenic BRCA-1 variant; in BRCA-2, bilateral RRSO is

only associated with reduced mortality between the ages of 41 and 60 years [70].

A residual risk of 1 to 4.3% is reported for primary peritoneal carcinoma; in carriers of a pathogenic BRCA-1/2 variant who developed peritoneal carcinomatosis after bilateral RRSO, 86% were carriers of the pathogenic BRCA-1 variant specifically [31]; comparing carriers of a pathogenic BRCA-1/2 variant who did not develop peritoneal carcinomatosis after bilateral RRSO, the women who eventually developed peritoneal carcinomatosis were older at the time of bilateral RRSO ($p = 0.025$) with a higher percentage of serous tubal intraepithelial carcinoma in bilateral RRSO ($P < 0.001$), supporting the removal of the fallopian tubes as part of the risk reduction procedure ($n = 1,083$) showed an increased risk of serous and / or serous-like endometrial cancer in women carrying the pathogenic variant of BRCA-1 that bilateral RRSO was performed without hysterectomy. Bilateral RRSO provides an opportunity for gynecologic cancer screening in high-risk women; bilateral RRSO showed that invasive or intraepithelial ovarian, tubal, or peritoneal neoplasms were detected in 4.6% of carriers of a pathogenic BRCA-1 variant and 3.5% of carriers of the pathogenic BRCA-2 variant. The pathogenic variant of BRCA-1/2 was associated with the detection of clinically occult neoplasms during bilateral RRSO ($p = 0.006$).

Bilateral SOBRR reduces the risk of bC in carriers of a pathogenic BRCA-1/2 variant [165,176,179,180,183-186]; 56% (OR, 0.44; 95% CI, 0.29-0.66; $P < 0.001$) and 43% (OR, 0.57; 95% CI, 0.28-1.15; $P = 0.11$) the risk reduction of BC (adjusted for the use of oral contraceptives and parity) after bilateral RRSO in carriers of a pathogenic BRCA-1 and BRCA-2 variant, respectively; Comparing the risk of BC in women carriers of a pathogenic BRCA-1/2 variant who underwent bilateral RRSO in carriers of these mutations who opted for surveillance also showed a reduced risk of MC in women who underwent bilateral RRSO (HR, 0.47; 95% CI, 0.29-0.77), a meta-analysis reported similar reductions in the risk of MC 50% for carriers of a pathogenic BRCA-1/2 variant after SOBRR. SOBRR is associated with a greater reduction in the risk of BC for carriers of a pathogenic variant of BRCA-2 compared to BRCA-1; In another report of women with stage I or II MC and a pathogenic variant of BRCA-1/2, it showed that bilateral RRSO was associated with a decreased risk of BC mortality in BRCA-1 carriers (HR, 0.38; 95% CI %, 0.19-0.77, $p = 0.007$), but not in BRCA-2 ($p = 0.23$).

The reduction in the risk of BC after bilateral RRSO one study found no difference in the incidence of BC between BRCA-1/2 carriers who opted for bilateral RRSO and women who did not, regardless of whether the mutation was for BRCA-1 or BRCA-2. The 50% decrease in the risk of BC may have been influenced by biases; although, an analysis found a protective effect of bilateral RRSO on the incidence of MC in BRCA-1/2 carriers (HR, 0.59;

95% CI, 0.42 to 0.82, $P < 0.001$); in another analysis of BRCA-1/2 carriers unaffected by BC (who were eventually diagnosed) showed that when bilateral RRSO was treated as a time-dependent variable, it was no longer associated with BC risk [33]. A meta-analysis of the association between bilateral RRSO, risk and mortality from BC showed a protective effect ($n = 3$) [32]; Furthermore, greater reductions in the risk of BC were observed with BRCA-1 who had an bilateral RRSO at 40 years of age or younger (OR, 0.36; 95% CI, 0.20-0.64), relative to BRCA-1 carriers of 41 to 50 years of age who underwent this procedure (OR, 0.50; 95% CI, 0.27 to 0.92), a non-significant reduction in the risk of BC was found for women 51 years of age or older; they also suggested that bilateral RRSO after 50 years of age is not associated with a decreased risk of BC; bilateral salpingo-oophorectomy was not associated with a decrease in the risk of BC in BRCA-1/2 carriers ($n = 3,722$), stratified analyzes in BRCA-2 carriers diagnosed with BC before 50 years of age showed that bilateral salpingo-oophorectomy was associated with a reduction 82% in BC (HR, 0.18; 95% CI, 0.05-0.63; $P = .007$). The risk reduction in BRCA-1 carriers was not significant ($p = 0.51$). A study of premenopausal BRCA-1/2 carriers; premenopausal bilateral RRSO decreased the risk of BC in BRCA-1 (HR, 0.45; 95% CI, 0.22-0.92) but not in BRCA-2 (HR, 0.77; 95% CI, 0.35-1.67) [34]. Studies suggest a benefit of bilateral RRSO on the risk of BC, but the magnitude of the effect is not well understood and the evidence is mixed regarding the age at which bilateral RRSO should be performed and the specific mutation (BRCA-1 vs. BRCA-2).

Hormone replacement therapy (HRT) reviews do not nullify the risk reduction for MC associated with surgery [35,36]; showed that the risk of MC tended to be lower in women with estrogen-only HRT, compared with estrogen plus progesterone (OR, 0.62; 95% CI, 0.29–1.31) [35]. Discussion of the risks and benefits of HRT in carriers of mutations after bilateral salpingo-oophorectomy is important [45,71-73]. Rates of salpingectomy (surgical removal of the fallopian tube with retention of the ovaries) are increasing, especially in women under 50 years of age [note mine], some evidence on the safety and feasibility of this procedure requires data on its efficacy to reduce ovarian cancer risk, BRCA-1/2 carriers who undergo salpingectomy without oophorectomy may not get BC risk reduction suggest they are BRCA-1/2 carriers, may receive; salpingectomy is not recommended for reduce risk alone as the standard of care in BRCA-1/2 carriers; or interval salpingectomy with delayed oophorectomy. Some studies suggest a link between BRCA-1/2 and the development of serous uterine cancer (mainly with BRCA-1), although the overall risk of uterine cancer was not increased by tamoxifen use [21]; whether women who undergo hysterectomy at the time of bilateral salpingo-oophorectomy are candidates for estrogen-only HRT, which is associated with a lower risk of BC, compared to the combination of estrogen and progesterone, which is required when the uterus is left in situ;

whether patients choose to undergo bilateral RRSO; and the risks and benefits of concurrent hysterectomy are analyzed; Still, data are needed to determine the association between BRCA-1/2 variants and the development of serous uterine cancer.

Bilateral salpingo-oophorectomy is recommended for women with known BRCA-1/2, generally between 35 and 40 years of age for BRCA-1; Ovarian cancer onset tends to be later in BRCA-2 positive women, it is reasonable to delay bilateral salpingo-oophorectomy for ovarian cancer risk management until 40 to 45 years of age, unless age at diagnosis in the family justify an earlier age to consider prophylactic surgery, peritoneal washes are performed during surgery and pathological evaluation should include thin cuts of the ovaries and fallopian tubes.

The decision to perform an bilateral salpingo-oophorectomy is complex and ideally, it should be discussed between the physician and the patient if the latter wishes for an bilateral salpingo-oophorectomy before the age at which it is normally recommended (i.e., 35 years) and the impact on reproduction, risk of BC and ovary, the risks associated with premature menopause (osteoporosis, cardiovascular disease, cognitive changes, vasomotor symptoms, sexual dysfunctions) and other medical problems to understand how it affects quality of life [74].

8. Chemoprevention

The use of Selective Estrogen Receptor Modulators (SERMs), that is, tamoxifen or raloxifene, reduces the risk of BC in postmenopausal women considered at high risk for its development, especially ER positive, only limited data are available on the use Specific to these agents in patients with BRCA-1/2, who are diagnosed with BC have a high risk of developing contralateral BC. In evaluated BRCA-1/2 carriers, the mean cumulative lifetime risk of contralateral MC was estimated to be 83% for carriers of a pathogenic BRCA-1 variant and 62% for BRCA-2 carriers; BRCA-1/2 carrier patients with intact contralateral breast tissue (not undergoing bilateral RRSO or receiving chemoprevention) have an estimated 40% risk of contralateral BC at 10 years. In hereditary BC, the use of tamoxifen protected against contralateral BC with a risk ratio (OR) of 0.38 (95% CI, 0.19-0.74) to 0.50 (95% CI, 0.30 –0.85) in BRCA-1 and 0.42 (95% CI, 0.17–1.02) to 0.63 (95% CI, 0.20–1.50) in BRCA-2 carriers. This translates into a 45-60% reduction in the risk of contralateral BC in BRCA-1/2 carriers with MC; Another report revealed that the risk of BC was reduced 62% in BRCA-2 who received tamoxifen (risk ratio, 0.38; 95% CI, 0.06-1.56), an analysis of women who developed BC showed that the use of tamoxifen was not associated with a reduction in MC risk in BRCA-1 carriers. These findings are related to a greater likelihood of developing estrogen receptor-negative MC in BRCA-1 carriers compared to BRCA-2, this BRCA-1/2 analysis ($n = 19$; 7% of participants diagnosed with BC). Common single nucleotide polymorphisms in genes (ZNF423) that participate in estrogen-depen-

dent regulation of BRCA-1 expression have been identified and associated with a decreased risk of BC during SERM's therapy [75]. These genetic variants were associated with alterations in the risk of BC during treatment with SERMs and, eventually, predict the probability of benefit with chemoprevention in individual patients. The Aromatase Inhibitors (AI) exemestane and anastrozole are effective in preventing BC in postmenopausal women considered at high risk of developing it; there is little evidence to support the use of AI as an effective chemopreventive method for individuals with BRCA-1/2. A study on AI reported a reduction in the risk of contralateral MC in BRCA-1/2 and ER-positive BC women taking adjuvant chemotherapy.

Evidence on the effect of oral contraceptives on the risks of ovarian cancer in women with known BRCA-1/2, reduces the risk of ovarian cancer by 45-50% in BRCA-1 and 60% in BRCA-2, the risks decrease with longer duration of oral contraceptives use; In a meta-analysis of BRCA-1/2 carriers with and without ovarian cancer, oral contraceptives use reduced the risk of ovarian cancer by 50% for both BRCA-1 carriers (relative risk [RR], 0.51; 95% CI, 0.40–0.65) and BRCA-2 (RR, 0.52; 95% CI, 0.31–0.87); another meta-analysis; also showed an inverse association between ovarian cancer and having ever used oral contraceptives (OR, 0.58; 95% CI, 0.46-0.73) Studies on oral contraceptives on the risk of BC in BRCA-1 carriers / 2 are contradictory, oral contraceptives use was associated with increased risk of BC in BRCA-1 (OR, 1.20; 95% CI, 1.02-1.40), with risk of BC in carriers, is associated with ≥ 5 years of oral contraceptives use (OR, 1.33; 95% CI, 1.11-1.60), BM diagnosed before age 40 (OR, 1.38; 95% CI, 1.11-1.72) and oral contraceptives use before 1975 (OR, 1.42; 95% CI, 1.17–1.75). The use of oral contraceptives was not associated with BC in BRCA-2 carriers; in another study, oral contraceptives use for at least 5 years was associated with an increased risk of MC in BRCA-2 carriers (OR, 2.06; 95% CI, 1.08–3.94); when only cases with OC use from 1975 onwards were considered. oral contraceptives use for at least 1 year was not associated with the risk of BC in BRCA-1 or 2 carriers, oral contraceptives use at low doses for at least 1 year less than 1 year was associated with decreased BC risks in BRCA-1 carriers (OR, 0.22, 95% CI, 0.10 to 0.49, $P < 0.001$), although not for BRCA carriers -two. In studies, the use of oral contraceptives is not associated with the risk of BC in BRCA-1/2 carriers; there are differences in the studies on the impact of oral contraceptives on the risk of BC in BRCA-1/2 carriers [76].

9. Reproductive Management Options

Genetic test results impact the reproductive future of people of reproductive age who are carriers of BRCA-1/2. There is evidence that BRCA-2 variants are associated with the rare autosomal recessive condition of Fanconi anemia, they have also identified bi-allelic BRCA-1 mutations that cause a disorder similar to Fanconi anemia [37], information to the person studied on the possible risk

of hereditary cancer for relatives and options for risk assessment and management, advice on reproductive options such as prenatal diagnosis and assisted reproduction through Preimplantation Genetic Testing (PGT) is justified in couples concerned about the carrier status of their future offspring of a BRCA-1/2 variant, it should include a thorough discussion of the potential risks, benefits, and limitations of reproductive options, including cost.

Prenatal diagnosis involves postimplantation genetic analysis of an early embryo, using chorionic villi or amniotic fluid cell samples; genetic testing is performed between the 12th and 16th week of gestation, and the test results potentially lead to the couple's decision to terminate the pregnancy. PGT has emerged as an alternative method of genetic testing of early embryos. PGT involves testing 1 or 2 cells from embryos in very early stages of development (6 to 8 cells) after in vitro Fertilization (FIV); it allows the selection of unaffected embryos for transfer to the uterus and offers the advantage of avoiding possible interruption of pregnancy. The PGT process requires the use of FIV regardless of the fertility status of the couple (applies to couples without infertility problems), and FIV cannot always lead to a successful pregnancy, technology or expertise may not be available in the geographic location of a couple [77].

Several factors, both medical and personal, must be weighed in the decision to use prenatal diagnosis or PGT. Medical considerations include factors such as age of onset of hereditary cancer, penetrance, severity or morbidity and mortality associated with cancer, and availability of effective cancer risk reduction methods or effective treatments; the use of prenatal diagnosis or PGT is established for serious hereditary disorders with high penetrance and / or early onset, its use in conditions associated with low penetrance and / or late onset (BC syndrome and / or hereditary ovarian cancer) is controversial ethics and normatively. Personal considerations for the decision to use prenatal diagnosis or PGT include individual ethical beliefs, value systems, cultural beliefs, religious, social and economic factors. Successful deliveries with PGT and FIV have been reported in carriers of a BRCA-1/2 variant; but, still very limited, there are no data regarding long-term safety or outcomes of PGT and assisted reproduction in BRCA-1/2 carriers.

10. Li-Fraumeni Syndrome (LFS)

LFS is a rare hereditary cancer syndrome associated with pathogenic variants of the TP53 germline, it is involved in 1% of cases of hereditary BC Other studies suggest that mutations of the germline TP53 gene are common, with estimates of 1 in 5,000 to 1 in 20,000; there are some 300 informed families registered. The tumor suppressor gene, TP53, is found on chromosomes 17 and the protein product of the TP53 gene (p53) is found in the cell nucleus and binds directly to DNA, called the "guardian of the genome" with an important role in controlling the cell cycle and apoptosis and germline mutations in the TP53 gene are observed

in 50 to 70% of families that meet the classic definition of LFS to investigate the possibility that other genetic mutations in families that meet these criteria do not carry germline TP53 mutations. LFS is a highly pervasive cancer syndrome associated with a high lifetime cancer risk; one analysis showed a cumulative lifetime cancer incidence of nearly 100%. LFS is characterized by a wide spectrum of neoplasms that occur at an early age; it is associated with soft tissue sarcomas, osteosarcomas (although Ewing's sarcoma is less likely to be associated with LFS), premenopausal BC, colon cancer, gastric cancer, adrenocortical carcinoma, and brain tumors. Sarcoma, BM, tumors of the adrenal cortex, and certain brain tumors have been termed LFS "core" cancers, represent the majority of cancers seen in people with TP53 germline variants, and in one study, at least one of these. Cancers were found in one or more members of all families with a germline mutation of the TP53 gene. Hypodiploid acute lymphoblastic leukemia is also associated with LFS, and case reports have suggested an association between melanoma and LFS [38]; Cumulative incidence rates at age 70 in women are 54, 15, 6, and 5% for BM, soft tissue sarcoma, brain cancer, and osteosarcoma, respectively, in BM showed that TP53 mutations were significantly associated with BM HER2 positive, regardless of whether the disease was ER positive (OR, 11.95, 95% CI, 5.84-23.0) or negative (OR, 22.71, 95% CI, 10.45-45.49) [3] reported a high frequency of HER2-positive BC (67-83%) in patients with germline TP53 mutations, HER2 amplification arises in conjunction with germline TP53 mutations. This association justifies the benefit of chemoprevention therapies that incorporate HER2-targeting agents.

Individuals with LFS often develop certain cancers (soft tissue sarcomas, brain tumors, adrenocortical carcinomas) in early childhood and are at increased risk of developing multiple primary cancers during their lifetime; Family history of patients with childhood soft tissue sarcoma showed that carriers of germline TP53 mutations had estimated cancer risks of 60 and 95% at 45 and 70 years, respectively, similar cancer risks are seen in men and women with LFS when gender-specific cancers are not considered, BC in the female is associated with the syndrome, estimates of cancer risks associated with LFS are limited at least to some degree by selection, and it is likely that identify affected families. Several different sets of criteria have been used to identify people with LFS, 2 sets of these criteria are used to facilitate the identification of people who are candidates for testing for pathogenic TP53 or probable pathogenic variants.

The classic LFS criteria [41]: a member of a family with a known TP53 variant; the combination of an individual diagnosed <45 years with a sarcoma and a first-degree relative diagnosed with cancer <45 years; and an additional first or second degree relative in the same lineage with cancer diagnosed before age 45 or sarcoma diagnosed at any age. The classic LFS criteria have been estimated to have a high Positive Predictive Value (PPV) (estimat-

ed at 56%) as well as high specificity, although the sensitivity is relatively low (estimated at 40%), it is not uncommon for individuals with Cancer patterns outside of these criteria are carriers of germline TP53 mutations.

Other groups have expanded the classic LFS criteria to facilitate the identification of individuals with LFS, the criteria for TP53 testing recommend testing patients with multiple primary tumors for at least 2 types of "central" tumors (sarcoma, BM, carcinoma adrenocortical, brain tumors) diagnosed in <3 6 years of age or patients with adrenocortical carcinoma diagnosed at any age, regardless of family history; they have an estimated PPV of 20–35% and, when incorporated as part of the TP53 test criteria along with the classic LFS criteria, improve the sensitivity of 95% of patients with TP53 mutations; It is recommended to evaluate people with choroid plexus carcinoma or embryonal anaplastic subtype rhabdomyosarcoma diagnosed at any age and regardless of family history, based on the significant incidence of TP53 mutations found in patients with these rare forms of cancer. Wider age limits were supported, which detected germline TP53 mutations in affected individuals with late-onset tumor.

Women with early-onset BC (diagnosis ≤ 30 years), with or without a family history of central tumor types, are another group to consider for the TP53 gene mutation test. In women <30 years with BC and no family history, the incidence of TP53 mutations is 3–8%; other studies have found a lower incidence of germline TP53 gene mutations, 0.7% of unselected 33-year-old women were reported to be carriers of a germline TP53 mutation; another report found no germline TP53 mutation in unselected women with early-onset BC who previously tested negative for BRCA-1/2 mutations; If the family history of tumors associated with LFS is taken into account, the prevalence of the germline TP53 mutation increases; In a study of patients with early-onset BC with a negative BRCA-1/2 mutation (age at diagnosis ≤ 35 years), deleterious mutations in TP53 were identified in (75%) with a family history of at least 2 LFS-associated tumors (BC, bone or soft tissue sarcoma, brain tumors or adrenocortical carcinoma) and in (6%) with a family history of BC only, all women younger than 30 years with BC who had a first or second degree relative with at least one of the major cancers had germline TP53 mutations.

A member of a family with a known pathogenic variant of TP53 is considered to be at sufficient risk to warrant testing for the variant, even in the absence of other risk factors. Individuals who do not meet the testing criteria should be followed according to recommendations tailored to their personal cancer history and family history, and testing for other inherited syndromes may be considered. If a TP53 mutation is detected through the tumor profile, and there are clinical implications if a germline TP53 mutation is identified, then germline testing for a TP53 variant may be considered, depending on careful examination of the personal and family history of the individual. Pathogenic / probably pathogenic variants

of TP53 are common in tumors, if a somatic mutation of TP53 is found in the absence of a paired germline analysis, then germline testing is not warranted unless there is clinical suspicion of a variant germ line pathogen.

11. Advice, Evaluation and Risk Management

In the approach of families with other inherited MC syndromes, such as LFS, BM reflex, and / or hereditary ovarian cancer in many ways, there are some syndrome-specific differences with regard to evaluation and treatment. In LFS, there are multiple associated cancers, pediatric and adult, that must be reflected in the extended lineage. Cancers associated with LFS include, but are not limited to, premenopausal BC, bone and soft tissue sarcomas, Central Nervous System (CNS) tumor, adrenocortical carcinoma, hypodiploid acute lymphoblastic leukemia, unusually early onset of other adenocarcinomas, or other childhood cancers. your sometimes very rare check of a cancer is particularly important.

The use of a screening protocol that includes MRI improves the early detection of cancer in people with LFS [39]; expert recommendations were made [40]; for the management of LFS apply specifically to adults with LFS, and should address the limitations of detection of many cancers associated with this syndrome. Pediatricians should be aware of the risk of childhood cancers in affected families and review with these families the screening recommendations for children with LFS [40] and it is important to address psychosocial aspects and quality of life of this syndrome; with follow-up in specialized centers with experience in this syndrome [78,79].

For those at risk of BC, training and education in BSE should begin at 18 years of age, and conducted regularly each month; For members of families with LFS, BC surveillance by BSE every 6 to 12 months is recommended, starting at age 20 (or at the age of the earliest known BC in the family, if it is under 20 years) due to the very early age of appearance of BC that is observed in these families. Recommendations for BM screening in LFS are similar to those for treatment of BRCA-related BM syndrome and / or ovarian cancer, although screening is initiated at an earlier age; including annual screening for MRI of the breast with contrast (preferred) or Mastography oral contraceptives if MRI is not available for women ages 20-29; Annual mastography and Breast MRI Detection with Contrast in Women 30 to 75 Years Old; and individualized management for women over 75 years of age. For women with a family history of BC diagnosed before age 20, MRI of the breast with contrast can begin at the earliest age at diagnosis. In women treated for BC who have not undergone bilateral mastectomy, mastography and MRI of the breast with contrast should continue according to the recommendations for age. When an mastography is performed, it is recommended to consider tomosynthesis, as in BRCA-1/2 carriers, breast MRI is preferred in women under 30 years of age to mastography due to the potential risk

of radiation exposure and lower sensitivity for the BM detection. There are no data on risk reduction surgery in women with LFS, the options for risk reducing mastectomy are individual; include discussion of cancer risk reduction / protection, risks associated with surgery, age-specific degree of cancer risk, reconstructive options, and competing risks of other cancers; family history and life expectancy should be considered during this counseling [80].

Many of the other cancers associated with germline TP53. Pathogenic variants do not lend themselves to early detection, and general recommendations include complete physical examinations (including neurologic) every 6 to 12 months, especially when there is a high index of suspicion for second malignancies in cancer survivors and rare cancers. Clinicians must address the limitations of screening for other cancers associated with LFS. Colonoscopy and upper gastrointestinal endoscopy are performed every 2 to 5 years, starting at age 25 or 5 years before the earliest known colon cancer diagnosis in the family history (whichever occurs first). Education about signs and symptoms of cancer is important; inform patients about the risk for relatives, and genetic counseling for relatives is recommended. The annual dermatological examination is performed from 18 years of age.

Whole-body MRI for the detection of cancers associated with LFS is being evaluated, it is attractive due to its wide anatomical coverage and the potential to reduce the number of imaging studies that are subjected to. A meta-analysis of TP53 mutations showed that baseline whole-body MRI identified cancer in 7%, with 83% of cancers localized and capable of being treated with curative intent; incorporate clinical surveillance for carriers of the TP53 mutation from families affected by LFS; surveillance included biochemical methods (i.e., blood tests to evaluate 17-OH-progesterone, total testosterone, dehydroepiandrosterone sulfate, androstenedione, complete blood count, erythrocyte sedimentation rate and lactic dehydrogenase, and 24-hour urine cortisol) and imaging, such as brain MRI, annual rapid whole-body MRI, ultrasound of the abdomen, pelvis, and colonoscopy, BC surveillance, is similar to environmental protection management; surveillance is beneficial, 84% of patients who were diagnosed with cancer who opted for surveillance were alive at the end of follow-up, compared with 49% of patients who were diagnosed with cancer who had not opted for non-surveillance (p = 0.012). The 5-year OS was higher with surveillance (88.8%) compared with patients without surveillance (59.6%), p = 0.013; clinical surveillance warrants further evaluation; Annual whole-body MRI is recommended as a category 2B recommendation [40]. Patients who do not have access to full-body MRI should be encouraged to use alternative full-length imaging methods; whole-body MRI of all people with LFS gives false-positive results and overdiagnosis [42], the usefulness of whole-body MRI has not been evaluated in people with a pathogenic TP53 variant that does not have a classic family history of LFS, group

that is most identified through multigene tests. The brain can be examined as part of a whole-body MRI or as a separate exam.

Limited data on the use of prenatal genetic / diagnostic tests for TP53 mutations in families with LFS. Counseling on reproductive options such as prenatal diagnosis, PGT, and assisted reproduction is warranted for couples who express concern about the carrier status of future offspring of a pathogenic or likely pathogenic variant; Counseling includes a thorough discussion of potential risks, benefits, and limitations of reproductive options.

12. Discussion

Genetic testing for BRCA1 and BRCA2 began in 1995 and has expanded this century; by the greater number of laboratories, cost reduction, and evidence of its clinical benefit. Women diagnosed with a BRCA-1/2 mutation have some options to reduce their risk of cancer and cancer-related death. One option is to opt for screening with the main objective of identifying early-stage cancers to improve prognosis and reduce morbidity and mortality. Ovarian cancer screening tests include annual bimanual pelvic exam, TVSU, and serum CA 125 measurements [68]. There is currently no evidence of a reduction in mortality, the most effective option for BRCA-1/2 mutation carriers at this time it is chemoprevention or risk-reducing surgery; preventive mastectomy and bilateral RRSO in women with BRCA mutations and should be discussed individually [68] where it is reported little increase in the performance of bilateral RRSO; but, it is higher for preventive bilateral mastectomy; the growing evidence that this surgery is oncologically safe: there are still differences in the acceptance of cancer risk reduction options by country. In general, many women with a BRCA mutation are opting for cancer surveillance or prevention, women who underwent genetic testing more recently, bilateral prophylactic mastectomy as use of MRI is greater than those who received genetic testing more than 10 years [20].

Genetic testing for cancer susceptibility is an established part of medical practice. Until recently, the tests were performed primarily in patients with a strong family history of cancer and involved a limited number of genes known to be associated with a high risk of cancer or with specific cancer syndromes. With the advent of affordable sequencing, testing with larger gene panels has become possible [80-82]. The risk ratios for BC associated with variants in BRCA-1/2 are quite different (10.6 and 5.9, respectively) and correspond to lifetime risks of 55 and 45%, the cumulative risk of MC at 80 years of age it was 72% (95% Confidence Interval [CI], 65 to 79) for BRCA-1 carriers [81]. Population estimates of breast cancer risk associated with germline pathogenic variants in cancer predisposition genes are critically needed for risk assessment and treatment in women with inherited pathogenic variants. These estimates may inform cancer screening and testing and improve clinical management strategies for women in the general population with inherited pathogenic variants in these genes [20,80-82].

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