

Albanian Doctor's Extended Knowledge and Restricted Resources in Management of Breast Cancer's High Risk Women

Albana SHAHINI PhD, Erinda KOSTURI MD.

Abstract: ***Aim:** It has been widely acknowledged for decades the importance of family history of breast cancer in development of such condition in women. This factor has exponentially increased the need of further assessment in this high risk category, including the genetic screening. This article's objective is to present doctor's potential against restricted resources in the management of high risk women. **Material:** This is an informative article that underlines the lack of possibility of Albanian doctors to identify and categorize women, based on family history, into low, moderate and high risk, depending upon the assessed lifetime risk of breast cancer using the genetic screening. Instead, what we can do, are detailed anamnesis, excellent care and assumptions of low, moderate and high risk patients. We struggle, to identify high risk lesions and high risk women and afterwards create single follow-up protocols, with no precedents which makes it hard to sustain these women through the path of their potential condition. **Results:** Results of such approach, often fail us, not the patients, but us. Referring to and trying to adopt follow-up protocols, have a poor outcome, for reasons which will be explained further on, in this article. Even though we are highly aware of unproven long term results of approaches such as genetic screening chemoprevention and preventing surgery, we still believe that access to these alternatives can help identify and therefore prevent and treat at the best of our possibilities women for which the fate (genes and / or environment) decided to play an awful game. **Conclusions:** Predictive testing and radical approaches are a reality for a minority of families these days. Having access to such resources would open new perspectives to high risk women when it comes to breast disease. We are aware that these won't change radically the outcome, but might give a chance for better care, to patients.*

Keywords: genetic screening, brca1-2 carrier, genetic syndromes, risk assessment in breast cancer, preventive surgery, bilateral prophylactic mastectomy, prophylactic oophorectomy, chemotherapy, radiotherapy, HRT, OC

1. Introduction

Breast cancer is the most common cancer among women. Despite extended knowledge, improved medical care, higher awareness through women, still breast cancer is responsible for a high number of deaths. Numbers are climbing higher, even though much more is being done now days. Statistics are not very comforting: According to WHO and CDC, In the US alone, its estimated that about 1 in 8 women, will develop invasive breast cancer over the course of her lifetime. In 2013 about 232,340 new cases of breast cancer were expected to be diagnosed in US only, along with 64,640 non invasive breast cancer and about 39,620 of these women, were expected to die from such condition. The risk of encountering breast cancer doubles whenever a woman has a first degree relative diagnosed previously with this disease. About 5-10% of these cases can be linked to gene mutations inherited from one's parents. Women positive to a BRCA1 mutation have a 55-65% risk of developing cancer before they reach 70 years, and these women, unfortunately will be affected at a young age. Women positive to BRCA2 mutation have an increase of 45% risk for breast cancer. Both cases are also at increased risk for ovarian cancer.

On the other hand, let's remember that about 85% of breast cancer occur in women with no family history, and where the mutations happen as a result of aging process and environmental factors, rather than an inherited mutation. Depending on breast cancer risk, women may be classified into low, moderate (2-3 times the population risk) and high risk (greater than 3 times the population risk). What concerns the authors in this paper is exactly the last category. Based on evidence these women have a worse prognosis as well. Europe has provided regional genetics

centers that ensure appropriate support and treatment approaches.

2. Assessing the Risk

The most important epidemiological studies have underlined that approximately 80% of mutations carriers of genes such as BRCA1, BRCA2, will develop breast cancer in their lifetime. This is an important factor of high risk identification.

On this knowledge, unless there is family history, the risk counseled to unaffected women, is estimated to be 40-45%. Paternal side of the family affected by such disease will give an additional risk of 20% to the risk of breast cancer development through a lifetime. This inherited risk, requires also a genetic evaluation. The higher the number of family members affected, the higher the chance of breast cancer disease acquired through a lifetime. The earlier the onset of breast cancer in relatives of women, the higher is the risk for her to develop breast cancer on her own. A single relative affected by this malignancy will give to the women 1.5-3 fold increase in her risk to develop breast cancer. These categories are what we call high risk (theoretically, because no genetic assessment can be made in our country, for such).

On the other hand, there exist available programs such as Cyrillic, or large databases updated on regular intervals, extensive projects that collect data for decades, making it easy to estimate risk, forecast, establish prognosis, create protocols, and estimate the likelihood of BRCA1-2 mutation. Although we tend to rely on such technologies and massive projects to give ready-to-use data, a good family history collected would patients, would be all a genetic might need to calculate this risk. But what if the anamnesis

of a patient, can't be reliable? What if information is unreliable on? What if lack of education might put to risk the correct diagnosis and/or prognosis? What about this subgroup? What if genetists are unaware of specifics regarding gene mutations? Can we just go over such women?

Unlimited knowledge when it comes to the risk issue creates a lot of misunderstandings. To this point, we need to clear the concept of "lifetime risk" and "age specific risk". As we have limited resources on which to rely on, we can only assume what studies offer us from developed countries. So, if the incidence of a breast malignancy in a life time is 1 in 10 and we multiply it with personal risk that a woman might be affected by breast cancer if she has a mother with bilateral breast cancer their risk would tend to reach very high scores, which are wrong, which can't be communicated to patients, because will just raise the levels of stress, and provide no benefits.

At this point, the best way to assess risk would be getting back to the basis: family history and minor adjustments of other co-existing factors. (Simple right? What if the adjustments can't be made? What if there is no sufficient data's? What if there are no system of reference to help us guide a patient through her mysterious path of potential breast disease?)

3. Reproductive Risk

All possible is being done against breast cancer; awareness days, free consultations with radiologists and senologists, but still numbers are climbing high. Partially it looks that exposure to oestrogens might be the cause. Early menarche and late menopause prolong this exposure contributing to breast cancer. Life expectancy has improved and women want to preserve their sexual health, so more often than not, they opt for hormonal replacement therapy. Endogen oestrogens combined with OC or HRT, contribute to this risk increase by stimulating the breast cells. If used for more than a decade, HRT will increase the risk of encountering breast cancer. On our experience, we have only been able to follow this woman up to 6 years, but still have noticed major changes in breast tissue and ex novo lesions, as well as increase in diameters of pre-existing lesions.

Lifestyle changes have brought to our attention another phenomenon, as are the pregnancies at an older age. More and more women are conceiving after their 30s and are breastfeeding for smaller periods of time. On the other hand, we know that carriers of BRCA2 mutation, won't benefit from protection if they have a pregnancy before their 30s, getting back to the importance of genetic screening, in future follow-ups.

Is it enough though to be given a risk, depending on hormonal or reproductive history? To our point of view, the main indicative factor will remain the family history. But how exactly are we supposed to assess and communicate such risk based on anamnestic information? Everything will go back to assessing if there is a genetic mutation with a family history of breast cancer and the identification of a proliferative breast disease. Will this be enough? This is our

best shot theoretically. Practically the lack of genetic consultation and genetic screening, will not give us a sure answer for many other years.

How will we communicate the risk? Risk is a very abstract concept. Not all women might impart this concept. It will sound like a gamble more than a forecast. To this point, it might attract more attention the idea of fitting into a screening program more than risk figure itself. The lifetime risk and the remaining risk capture mostly the attention of women who are approaching their 50s. For instance, if a unaffected women, reports breast cancer with early onset in her family, this will give her a 40% risk to develop breast cancer, but what if she is 60 at this moment? We can conclude that if she would be a carrier of a gene mutation, she would have had breast cancer by now. So the risk will decrease at about 25% for her being a mutation carrier, and at 20% the risk of developing breast cancer. On the other hand, co-existence of other conditions that carry genetic mutations, should be known to the physicians and to some extend to the radiologists who may opt to propose mammography to this women, and therefore, exposing them to radiation(although small doses) which on the other hand can trigger deviation of cells normality. ATM is a condition related to 5-fold risk of developing breast cancer. Cowden syndrome (10q) account for high risk in families where such mutation has happened. BRCA1-2, account for over 80% of highly penetrant inherited breast cancer and a high risk of ovarian cancer, imposing special needs of follow ups as well as genetic and preventive counseling. Li-Fraumeni syndrome is related to early onset of breast cancer. In contrary to all above said, there is Turner syndrome, which is not known for breast cancer because of lack of oestrogen exposure, so different follow up would be needed compared to all above mentioned situations

4. Offering Predictive Genetic Testing

Simply unavailable in our country, offers the possibility to assess whether women might be at increased risk of developing breast cancer. Mostly health politics around the world tend to be cost-efficient. On this bases, rarely will a patient be advised to undergo such high-price analysis risking to come back with false-positive, and raising the question of including preventive surgery in different insurance politics.

But from a moral point of view, it's necessary to know what choices women will feel comfortable making. Under the sentence "no sufficient risk reduction to cease screening or preventative measures" it's no longer proposed to include these screening procedures into protocols.

5. Managing High Risk Women

We are encouraging women to practice BSE, suggesting that it is useful in early detection of every breast architectural changes, and most importantly early detection of breast changes. On the other hand, we have noticed that a certain level of anxiety has followed even some benign finding. On our concern benefits from this practice surpass the minimal anxiety this women face. BSE is a very good adjuvant to imaging diagnosis used in screening programs. We are

instructing every woman to self-exam her breast, and we are strongly pushing them to have lumps checked by ultrasound. In our country ultrasound is easily accessible, low-cost and a good way to familiarize women with breast check-up protocols.

Empirical data, recommend mammograms yearly for women under moderate risk starting from 35 years, which helps identify lumps but most importantly non-palpable masses. Imaging modalities for women under risk, include ultrasound, mammography and most importantly MRI, which provide accurate early stage detection of all breast masses and most importantly has no radiation. By high cost, makes MRI a luxurious modality, reserved to very high risk groups

6. Gynecological Check Ups

BRCA1-2 owes also a potential of ovarian malignancies. In women with family history of ovarian cancer, we tend to include to their protocols of follow ups the gynecological screening, for potential ovarian masses and simultaneous breast ultrasound follow-ups, no matter if we do not have data of BRCA1-2. In Britain, a trial for these women has included transvaginal ultrasound and Ca 125 estimation. In the authors opinion there is no point in using tumor markers such as CA 125 and CA 15-3 as slightly elevated results, and at times moderately high results create anxiety and excessive stress and give no specific information about underlying malignancies. Apart from cases in which US exam show evidence of any possible suspicious solid or liquid mass, we wouldn't use a tumor marker as a screening routine.

7. Available Prevention Strategies

What's accessible to us right now is very little. We can still rely only on our clinical data's, a good anamnesis, ultrasound and mammograms, a family plan, diet and exercise but nothing more. Being unable to stick to an extended follow-up and treatment plan, leaves us with very few options:

- We can advice to plan pregnancies at an early age, but yet this seems difficult for high educated women, who prefer to focus on their carriers first or to those who cannot afford raising a child at an early age.
- We can advice to stay away from hormonal therapies, yet having to face the controversies about this topic. It is believed the OC lower the risk of ovarian cancer, on the other hand they raise the risk of breast cancer. Women, who face menopause at a young age, want to preserve their sexual life, so we have to give them a chance by HRT. Lack of anamnesis collected by patients who are unaware of some family history may lead to the wrong treatment plan.
- Chemoprevention is only an extent of knowledge for us. Hormonal manipulation in order to lower the estrogen effects on breast tissue has been used for years abroad, but we haven't been able to implement such plan in Albania. On the other hand chemoprevention has the need of genetic testing before sticking to it, which is still very far from our everyday work.
- Preventive surgery both oophorectomy and mastectomy require first genetic screening for presence of BRCA1-2

and TP53. Even though there are doctors who do not appreciate these techniques there are substantial data's that show a decrease of 90% in the risk of developing a malignancy from the residual mammary tissue. This is a very radical approach which still requires evaluation of either physical or psychological sequelae. Nevertheless in terms of anxiety this is a technique that should be offered to women who test positive for gene mutations.

8. Conclusions

The last decade has been giving us enormous amount of knowledge; hence we know what should be done, and what we want to do. Nonetheless, the resources have not been very kind to us, and have let us down in the past, and are keeping doing so, as we write. While is now potentially possible, to offer treatment plans, curative plans if we want, we are stuck into collecting anamnesis, sometimes from women with low educational background, who will underestimate certain details, or who will fail to get examined on time, resulting in advance stages of the disease. What we hope to achieve in the years to come, is the possibility create protocols appropriate for high risk women. Special thoughts are reserved to extensive counseling, with specialist of different areas to provide preventive treatment in order to help patients make informed decisions. The unlimited knowledge has yet to surpass the difficulties of restricted resources, which for the moment seems to be an impossible task.

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Author Profile

ALBANA SHAHINI Ph.D

Born in Vlora, Albania on September 11th 1973

1998-1999 General physician

1999-2000 Medical specialist in Public Health Department in Dibra

2000-2004 Post graduate specialization in trades imaging in the Department of Radiology at University Hospital Center "Mother Teresa", Tirana, Albania

June 2003 – present Radiologist in many private practices and Hospitals in Tirana.

2009 – Present, active in breast diseases diagnosis, through different radiological modalities

Currently on doctorate process. Dissertation theme "Early diagnosis of breast disease"

ERINDA KOSTURI M.D.

Born in Tirana, Albania on June 24th 1985

Graduated from Medical Faculty in Tirana, Albania in July 2010.

Specialization on Family Medicine, graduated in April 2013

Certified Abdominal Ultrasonographer on June 2013

2011-present active on female health and screening procedures

Current position: Internal Medicine consultant at Ob-Gyn

Private Practice