

The prevention of hereditary breast cancer in Italy: towards the implementation of the national prevention plan in the Italian regions

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Breast cancer is the malignant cancer with highest incidence in females, representing 29% of all cancers, followed by colorectal cancer (13%), lung cancer (6%), thyroid cancer (5%), and uterine body cancer (5%). It has been estimated that in Italy almost 48,000 women were affected in 2015 [1]. The majority of breast cancers shows a multifactorial pathogenesis, however 5-7% shows a strong hereditary component, namely genetic factors that follow mendelian inheritance mechanisms. In fact, among affected woman, almost 2% of breast cancers is determined by genetic variants of *BRCA1* and *BRCA2* ("BRCA genes"), that show an high penetrance pattern of hereditary predisposition. Nevertheless, when considering only affected women younger than 40 years, the percentage of carriers of pathogenic variants *BRCA* genes rises up to 10%.

The prevalence of pathogenic variants of *BRCA* genes in the Caucasians is around 1/400 [2]. When applying this frequency to the whole Italian resident population in 2015, it can be estimated that in our country almost 152,000 people are carriers of these variants, and can therefore be at higher risk to develop breast cancer. In fact, the median estimate of cumulative risk of breast cancer in 70 years-old women is 57% for carriers of *BRCA1* variants and 49% for *BRCA2* [1]. Moreover, carriers of pathogenic variants show a tendency to develop breast cancer at earlier age, and are also at increased risk of ovarian cancer (lifetime risk is 40% and 18% for carriers of *BRCA1* and *BRCA2* variants, respectively [1]).

Considering the burden of disease due to breast cancer overall, national and international communities are strengthening the efforts in order to implement an adequate assistance for the affected women. In this framework, the Italian State-Regions Conference approved a Regulation on August, 5th, 2014 [3], that provides recommendations aimed at eliciting the set-up of integrated diagnostic-therapeutic pathways for affected women. These pathways, according to those from the European Union, are coordinated from the breast units, are supposed to offer high quality and appropriate assistance in the entire Italian landscape, taking care of patients in all the stages of their disease.

Concerning the efforts towards the prevention and the management of the highly penetrant hereditary forms of breast cancers, the National Prevention Plan 2014-2018 [4], approved by the Italian State-Regions Conference in November, 13th, 2014, called the Italian regions to implement by 2018 dedicated pathways for high risk woman well before the onset of the breast cancer. In fact, according to the most recent international guidelines [5,6] it is not indicated to perform a screening program for genetic testing of *BRCA* genes, neither in the general population nor in all women with breast cancer. There is a consensus, instead of, to perform the genetic testing only in the presence of specific anamnestic criteria that identify the high risk woman that might carry the *BRCA* mutations. How to identify, however, such high risk woman? None of the guidelines, unfortunately, suggests a gold standard pathway at population level in this sense. If we look at the economic evaluations, however, we find good evidences in support of the implementation of dedicated screening pathways to identify woman potentially carriers of the *BRCA* mutations. A recently published systematic review of the economical evaluations of *BRCA* screening strategies [7], reported that family history-based genetic testing is potentially very cost-effective. On the other hand, there was no evidence of cost-effectiveness for testing of newly diagnosed cases of cancers. Despite the presence of

a regulatory framework and of a potential cost-effectiveness, however, the practical implementation of integrated pathways for the identification of woman carriers of pathogenic variants is still at the beginning, either in Italy and abroad.

At international level, we are aware of only one dedicated screening pathway for high risk woman, namely one implemented in Georgia in 2012-2013 [8]. This pathway was realized in the context of primary care centers, where women were invited to complete a brief questionnaire; if an hereditary risk was suggested, the woman underwent a telephone interview and then, if appropriate, was referred to a genetic specialist. In Italy, we have the solitary example of the Emilia-Romagna Region, that since 2013 implemented a dedicated pathway to identify women at risk for hereditary breast cancer. Women who undergo traditional breast cancer screening with mammography are invited to complete a questionnaire to identify a potential risk based on anamnestic criteria. Those who have positive risk criteria are invited to undergo a genetic consultation and, when indicated, the genetic test. In principle, general practitioners can also refer women for screening of genetic predisposition. On the other hand, it is not clear who should be responsible for the screening of those women already diagnosed with breast cancer, who have not been included in the hereditary screening pathway. All the pathway is free of charge in Emilia-Romagna Region. Data on the efficacy of this program, however, are yet not available while very few critical issues, however, are already envisaged, and addressing such issues might potentially increase the effectiveness of such programs, that might work as an example also for other Countries. First of all, young women are not intercepted (the start age for mammographic screening program in Italy is 50 years old), and these are potentially those at higher risk of aggressive breast cancer if carrying *BRCA* mutations. In this sense, it might be envisaged to collect medical history (personal and familial) using dedicated questionnaire for hereditary breast cancer in the context of cervical cancer screening program. The second issue, as mentioned above, is about those women already diagnosed with breast cancer, as it should be clearly identified the most appropriate way of interaction between oncologists and geneticists in order to identify whom whom to test. Thirdly, it is essential to implement a strong educational program on hereditary breast cancer for all the health professionals that might be involved in the hereditary breast cancer pathway. Fourthly, it is essential that the laboratories performing *BRCA* genetic testing share the data with some central institution in order to know the epidemiology of *BRCA* mutations in Italy. Lastly, ongoing data collection and analysis of the performance indicators from the newly implemented hereditary breast cancer pathways is of paramount importance, as this allows to define benchmarks of efficacy, in order to provide the best possible prevention and care for high-risk women.

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