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Short Communication

Familial Breast and Ovarian Cancer: Genetic Counseling and Clinical Management in Italy

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In Italy, where the health system is mainly public (although the number of private clinics is increasing), genetic counseling on inherited predisposition to cancer and related genetic tests are generally offered on the basis of research projects, lacking specific national guide lines. Genetic counseling services on familial breast and ovarian cancer have been established in Milan, Modena, Naples, Varese and Genoa, while their organization is in progress in Aviano, Chieti, Florence, Padova, Pisa, Rome and Turin. Counseling is usually offered as an outpatient service in the context of medical genetics services departments of oncology, university and/or local programs of mammography screening with direct access for the general population. Due to the different locations and purposes of these services, it is difficult to assess how many Italian women have been evaluated during the last three years. Roughly, we can estimate that approximately 1500 women have been consulted because of a relevant family history of breast/ovarian cancer and/or early onset of the same tumors. Most of the counseling services already established involve multiple health care professionals. Usually, oncologists, medical geneticists, surgeons, gynecologists, psychologists and radiologists collaborate to offer an evaluation of the cancer family history, an estimation of the prior probability of carrying a major genetic defect, breast cancer risk assessment for relatives, psycho-social support and an appropriate follow-up program. Laboratories that already perform molecular screening for germline BRCA1 and BRCA2 are located in Milan, Pisa, Aviano, Modena, Padova, Rome and Turin. Although there are no unified eligibility criteria for BRCA1 and BRCA2 testing, most laboratories and referral counseling services offer a genetic test in the presence of a 10% cut-off prior probability in favor of a genetic defect, with few differences among centers (see Table 1). Approximately 730 eligible families have been selected to date, with a free decision in favor of genetic testing ranging from 66% to 86%, depending on personal and familial disease history. For example, refusal of testing was higher among women with early onset ovarian or breast cancer and negative family history (50% and 23%, respectively) than in cases of familial breast cancer (10% refusal). The lowest rate of refusal was observed when the index case had developed multiple tumors (bilateral breast cancer cases: 7%, breast + ovarian cancer cases: 4.5%, all with positive family history). In general, Italian women tend to agree with genetic testing, mainly because they want “to do” something for their family. They believe in the utility of early diagnosis and want to know more about their disease. Many women have experienced in their own case, or in family members, that early diagnosis correlates with a better prognosis and this increases their confidence in the utility of clinical surveillance programs. Among women refusing a genetic test there is a strong worry about the possibility of developing further malignancies (a second breast cancer or an ovarian cancer) and of transmitting the putative genetic defect. As expected, the feeling of danger for daughters is the main reason

Table 1
Eligibility criteria for BRCA1 and BRCA2 testing in Italy

Referral center	Age at breast cancer (BC)	Age at ovarian cancer (OC)	Family history (FH)
All centers	< 35–36 yrs.		independently of FH
Most centers (Milan)	Bilateral BC any age (or< 43)		independently of FH
All centers	Male BC any age		independently of FH
Rome, Naples		< 40 yrs.	independently of FH
Milan		< 47 yrs.	
Most centers	BC	+ OC any age	independently of FH
Milan	BC	+ OC < 52 yrs.	
Milan	Bilateral BC	+ OC < 56 yrs.	
Most centers		OC any age	Another OC any age
Milan	BC < 50		Another BC < 50 or bilateral BC any age or OC any age
Rome, Naples	BC < 40		Another BC any age
Most centers	BC any age		2 relatives (1 first degree) BC any age
Modena	BC < 40		2 relatives (1 first degree) BC any age (Amsterdam criteria “like”)
Most centers	BC any age		3 or more relatives BC or OC any age

for accepting or refusing a genetic test among Italian women. In Italy, molecular analysis of BRCA genes is performed mainly by PTT (protein truncation test) on BRCA1 exon 11 and BRCA2 exons 10-11 and SSCP (single strand confor-mational polymorphism) on the remaining exons (Aviano, Milan, Padova, Pisa, Rome), direct sequencing (Modena) and Southern blot analysis (Padova, Aviano). To date, among the laboratories contributing data, 166 Italian families carrying deleterious BRCA germline mutations have been identified, 118 in BRCA1 and 48 in BRCA2 genes. In different laboratories, 4–27% of the identified mutations recurred among apparently unrelated families, with slight differences depending on geographic region. In the experience of the National Cancer Institute in Milan, which collected families from all over Italy, just 11.7% of the identified mutations were recurrent in 2 to 13 families. With the exception of BRCA1 5382insC and 1499insA identified in 13 and 4 different families, respectively, the other “recurrent” mutations were usually present in 2 or 3 apparently unrelated families. Therefore, complete screening of both BRCA1 and BRCA2 genes is the testing procedure of choice in Italy. Approximately 280 carriers (211 affected and 69 healthy) have already been identified while 132 at risk family members were non-carriers of specific genetic defects. Although the option of prophylactic breast surgery is generally accepted among the Italian medical community, as far as we know, no Italian woman followed by the referral centers underwent this treatment. Breast prophylactic surgery appears to most Italian women a kind of “over treatment”, in relation to the breast cancer risk and from personal family experience. Even on diagnosis of a second breast cancer, the most frequent choice is conservative surgery, although an aesthetic reconstruction is always offered. The general surveillance protocol is based on breast clinical examination every 6 months and annual breast imaging (usually mammography in oblique projection under 35 years of age, and in three projections

after 35 years). One Center suggests breast ultrasound every 6 months while at the National Cancer Institute in Milan young women carriers of BRCA mutations will be followed by mammography alternating with MRI 12 months apart. For those women who experienced in their family ovarian cancers, prophylactic oophorectomy seems a reasonable choice. Although Italian women have the general feeling that mothers or sisters died from ovarian cancer because diagnosis was made too late, the pain caused by an ovarian cancer treatment (surgery, chemotherapy, second-look and so on) seems to justify prophylactic surgery. Usually this decision is undertaken after 45 years of age and the surgery of choice is laparoscopic bilateral oophorectomy together with a transvaginal hysterectomy. In the experience of the National Cancer Institute of Milan, approximately 50% of carriers of deleterious germline mutations decided in favor of prophylactic oophorectomy, even when informed about the risk of an ovarian cancer outside the ovaries. Pre-menopausal women usually decide to postpone prophylactic surgery by a few years, undertaking a surveillance program. There is a general agreement in suggesting gynecological examination, transvaginal ultrasound and CA125 every 6 to 12 months, depending on family history or type of germline mutation. In conclusion, all over Italy, a number of referral centers have been established, or their organization is in progress. They are now involved in research projects to evaluate the clinical relevance of genetic counseling, molecular testing and follow-up programs in familial breast and ovarian cancer. Research projects also include testing of chemoprevention and/or dietary intervention, aimed at a modulation of genetic risk.

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