Hereditary Risk of Breast Cancer: not only BRCA

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The BRCA1 and BRCA2 genes are involved in genetic susceptibility to breast cancer (BC). Nevertheless, in a relevant number of families displaying a disease pattern suggesting an inherited susceptibility to BC, mutational analysis fails to detect any defect in the BRCA genes. Therefore, women belonging to such families should be considered eligible for programs aimed at BC control in individuals at hereditary risk. A clinico-mammographic surveillance program for women at high genetic risk, as defined on the basis of pedigree, has been carried out at our centre for ten years, leading to the diagnosis of 19 new BC cases. Only in 13% of the families analysed, the underlying genetic defect was evidenced in BRCA1 or 2. Here we describe two BC prone families where, although no mutations were detected in BRCA genes, follow-up confirmed an increased BC incidence. In three women belonging to these families clinico-mammographic surveillance resulted to be successful in detecting early-stage BC, supporting the usefulness of screening women from high-risk families, irrespective of whether a mutation was found.

Key Words: Hereditary breast cancer, BRCA1, BRCA2, Clinico-mammographic surveillance

After the discovery of BRCA1 and BRCA2 genes in the mid-nineties, increasing attention has been focused on the proper management of BRCA mutation carriers, whose risk of breast cancer (BC) is reported to range from 36 to 85% (1,2). Nevertheless, no sufficient evidence has been found so far to definitely support specific recommendations for BC control in mutation carriers. For this reason, many studies are ongoing, aimed at evaluating the effectiveness of different strategies in the management of BC susceptible women, ranging from novel imaging techniques, to chemoprevention, to prophylactic surgery. Most of these studies exclusively enrol individuals with a deleterious mutation in BRCA genes identified by molecular analysis. However, BRCA mutations are detected only in a fraction of families displaying a disease pattern which strongly suggests an inherited susceptibility to BC. In the remaining kindreds, genes other than BRCA1 or BRCA2, or mutations of BRCA genes that fail to be detected by available diagnostic methods, are likely to be involved.

At the Centro per lo Studio dei Tumori Familiari della Mammella e dell'Ovaio, in Modena, research on Hereditary BC (HBC) started several years before BRCA genes were identified. Therefore, HBC used to be defined on the basis of epidemiological criteria applied to the pedigree, i.e.: number of BC cases, vertical transmission, degree of relationship between cases and occurrence of bilateral or early onset BC (3). Most of the so-identified families have been followed up during the last decade: an intensive surveillance program has been designed for asymptomatic women belonging to these families, and genetic testing has been offered since the mutational analysis of BRCA genes became available. To date, mutations in BRCA genes have been detected in 27 families out of 201 analysed (13%), with the highest rate of BRCA1 mutations predicted by early age at BC onset, aggressive breast tumour phenotype and association with ovarian cancer (4,5). When no mutations are identified, the family is managed according to our epidemiological classification: for families suggestive for hereditary BC (241 identified to date) surveillance consists of semiannual clinical breast examination and mammograms on a regular basis (every 2 years in the age-range 30-36, every year thereafter), with ultrasound added when appropriate. So far, the program has led to the detection of 19 BCs: among these, 11 were at a very early stage of devel-

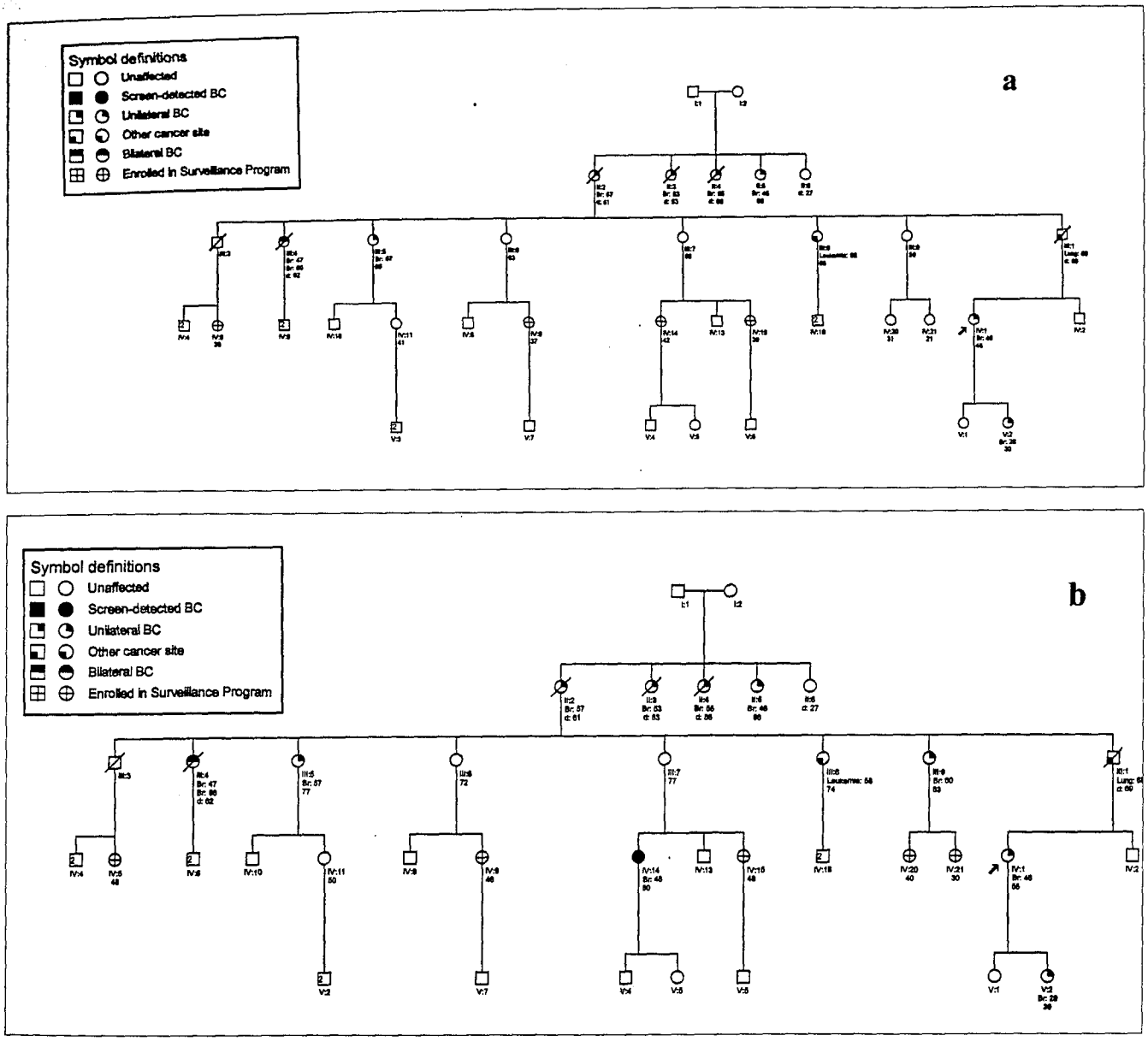

Fig. 1 - a) The pedigree of family 1 in 1992. b) The pedigree of the same family in 2001.
Under the symbol: type of cancer, if any, with age at diagnosis (Br = Breast Cancer); current age or age at death ("d").

opment (5 ductal carcinoma in situ and 6 infiltrating carcinomas smaller than 1 cm). Only one of these tumours was diagnosed in a woman who was subsequently found to carry a BRCA1 mutation.

We, therefore, propose that members of kindreds with clinico-epidemiological features suggestive of HBC should be included in prevention programs suitable for individuals at genetic risk, irrespective of whether a mutation has been found. Here we describe two families, among many in our experience, that support this recommendation.

Family 1

The history of this family was first collected in 1992. As shown in the pedigree (Fig. 1), in the second generation (the first for which information was available), 4 out of 5 sisters were reported to have developed BC. The fifth one died at a very young age. Nevertheless, no BC

were reported in the descendents of three of the affected relatives, including 4 women in peri- or post-menopausal age. By contrast, a significant number of BC occurred in descendents of individual II2. In this part of the family, 4 BC cases in three generations were reported, including a bilateral BC and a BC diagnosed at an extraordinarily early age (V2). According to Modena criteria, the family was considered as having hereditary BC, and asymptomatic women were considered eligible for intensive surveillance. At first, four women entered the screening program, all belonging to the part of the family with the highest BC incidence. In 1996, BRCA testing became available and individual IV1 gave her consent to be tested. No mutations were detected by automated sequencing of BRCA1 and BRCA2, which made it impossible to identify carriers and non-carriers of the genetic susceptibility.

In April 1997, the individual IV14, 46 years old, had a suspicious screening mammogram. The previous one (January 1996) had been negative, whereas now a nodule was evidenced. She was then diagnosed with grade I ductal carcinoma of the left breast: the tumour was 0.9 cm in its largest diameter and had not spread to axillary lymph nodes or distant sites (stage I). She underwent quadrantectomy and radiotherapy, and is currently disease-free.

In January 1998, the individual III9, aged 60, who had not entered the screening program, came to our Centre for having felt a lump in her left breast. Clinically, a 3 cm lump in the left breast and enlarged, firm lymph nodes in left axilla were detected. A biopsy led to the diagnosis of infiltrating ductal carcinoma. She underwent neo-adjuvant chemotherapy, then mastectomy and adjuvant chemotherapy. No relapse has been found to date. Following the diagnosis, both the daughters of this patient entered the surveillance program.

Family 2

This family came in 1995 for the first time. As the pedigree shows (Fig. 1a), the family history was significant for the occurrence of BC in three women in two generations, two of which were diagnosed at a young age (35 and 39). At that time, no affected individuals were available for genetic testing, as two patients were deceased and the third one, who lived in another town, was not interested in being tested. Regardless, three asymptomatic women were enrolled in the clinico-mammographic program and had annual mammograms at our Centre since 1996.

Individual III3 had microcalcifications, previously diagnosed as dystrophic, in her right breast. On the mammogram performed in February 2000, microcalcifications appeared to have increased, and a biopsy was performed, leading to the diagnosis of ductal carcinoma *in situ*. The patient, aged 42, underwent quadrantectomy and radiotherapy and is currently disease-free. In addition, she gave her consent to be tested for BRCA mutations. No mutations were identified in BRCA1, nor BRCA2.

In June 2001 a nodule was detected by mammogram in her sister (III4), aged 53. Exactly a year before she had had a negative mammogram. She was subsequently diagnosed with a 0.7 cm large infiltrating ductal carcinoma of the right breast. The tumour had histologic grade 3, negative hormone receptors and high proliferation rate (Ki67: 50%). Since no metastases were detected in axillary lymph nodes, it was classified as a first-stage BC. The patient underwent quadrantectomy and adjuvant chemotherapy and is currently under radiotherapy. The pedigree updated to 2001 is shown in Fig. 2b.

Discussion

Our group has identified at least 241 pedigrees with features suggestive of an inherited susceptibility to BC, but only in 27 out of 201 families analysed, the genetic defect has been detected in BRCA1 or BRCA2 gene. Since these defects follow an autosomal dominant mode of inheritance, the offspring of a mutation carrier has a 50% chance of inheriting the mutation. Therefore, the greatest value of finding a mutation in such kindreds is the capability of discriminating, within the family, between individuals who inherited the mutation, and who are really at increased risk, and relatives not carrying the mutation, who do not have a risk excess compared to the general population. The latter individuals can be reassured by a negative test result and can avoid unnecessary preventative measures. By contrast, if no mutations are found, every individual in the family is to be considered at high risk and should be offered the opportunity to enter specific prevention programs. At our Center in the last decade women belonging to BC-prone families have been offered an intensive clinical and mammographic surveillance program, which, to date, has led to the detection of 19 new BCs; among these, only one occurred in a BRCA1 mutation carrier. The effectiveness of such a screening for early BC detection is supported by the high rate of very early stage cancers detected (11 out of 19). Three of those "early cases" belong to the families here described. In these families no mutations have been identified in BRCA1 and 2 genes, despite the fact that pedigrees were suggestive of a genet-

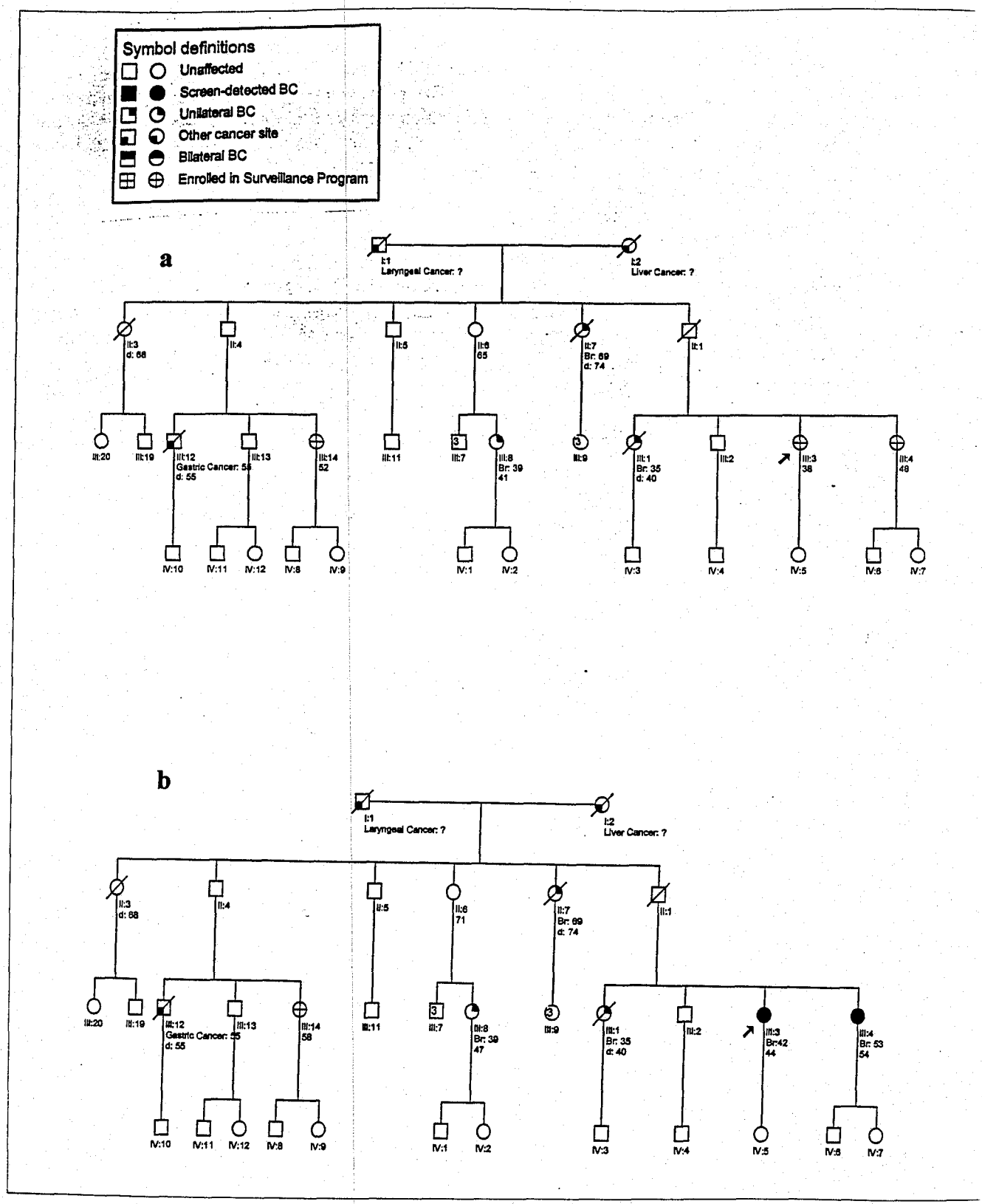

Fig. 2 - a) The pedigree of family 2 in 1995. b) The pedigree of the same family in 2001.
Under the symbol: type of cancer, if any, with age at diagnosis (Br = Breast Cancer); current age or age at death ("d").

ic risk. Actually, in family 2 some concerns about the adequacy of the index case can be raised, because the occurrence of ductal carcinoma in situ in carriers of BRCA1 mutations is controversial, and because this patient could be a phenocopy. In order to render the result more indicative, testing will be performed in the latter case as well. By contrast, in family 1 the index case is unlikely to be a phenocopy, as her daughter had developed BC at age 28, and therefore is considered representative.

Based on our experience, we strongly recommend not limiting attention to that minority of BC-susceptible families with a proven mutation in BRCA genes, as this could exclude women who are regardless at high genetic risk from proper management. In these women, screening measures suitable for the general population appear to be inadequate. In fact, in our area, mass mammographic screening recruits women aged 50-69 years, with mammogram performed every two years. Two out of three patients here described were younger than 50 at the time of diagnosis. The third one was 53, but she was diagnosed with a rapidly proliferating cancer, which, with a longer interval between mammograms, would have been diagnosed at a much more advanced stage. In addition, women from BC-prone families who do not undergo clinical and mammographic examinations on a regular basis are at high risk of being diagnosed with a late-stage cancer, as happened to the second case in family 1. Generally, compliance to BC screening programs is influenced by awareness in the general population. Moreover, since confidentiality issues do not allow the active recruitment of women from high risk pedigrees, adhesion in a family also depends on communication between members. Educational campaigns on BC risk factors should be launched in order to improve awareness, and subsequently compliance to screening, in women at both standard and increased risk.

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References

1. Easton D.F., Ford D., Bishop D.T. : Breast and ovarian cancer incidence in BRCA1-mutation carriers. Breast Cancer Linkage Consortium. Am. J. Hum. Genet. 56: 265-71, 1995.
2. Fodor F.H., Weston A., Bleiweiss I.J., et al.: Frequency and carrier risk associated with common BRCA1 and BRCA2 mutations in Ashkenazi Jewish breast cancer patients. Am. J. Hum. Genet. 63: 45-51, 1998.
3. Federico M., Maiorana A., Mangone L., et al.: Identification of families with Hereditary Breast Cancer for clinico-mammographic surveillance. The Modena Study Group Proposal. Breast Cancer Res.Treat. 55: 213-221, 1999.
4. Cortesi L., Turchetti D., Bertoni C., et a.l: The study of correlation between genotype and phenotype identifies an high risk population carrying BRCA1 mutations. Genes, Chrom. Cancer 27: 130-135, 2000.
5. Turchetti D., Cortesi L., Federico M., et al.: BRCA1 mutations and clinico-pathological features in a sample of Italian women with early-onset breast cancer. Eur. J. Cancer 36: 2083-2089, 2000.

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