Hereditary cancer syndromes

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Summary

The identification of susceptibility genes for specific types of cancer provided the necessary information for the complete characterization of inherited cancer syndromes. The close observation of carrier families has significantly enriched our knowledge on distinct phenotypical features, age of onset and survival rates for each syndrome and gave the opportunity to further understand the molecular basis of hereditary cancer. Recent advances in cancer genetics involve the identification of novel genes with moderate risk to cause cancer, after synergism with particular environmental factors, and therefore reinforcing the genetic component in relation to cancer predisposition. The available genetic tests can constitute an essential step of primary health care, as they can dramatically affect the quality of a cancer patient’s life and they can also offer prompt diagnosis for the patient’s close relatives. This review reports the most characteristic hereditary cancer syndromes along with their phenotypical and genetic variables that have been described, but it mainly focuses on Hereditary Non-Polyposis Colorectal Cancer (HNPCC), which is linked to pathogenic mutations in one of the mismatch repair (MMR) genes MLH1, MSH2, MSH6, Familial Adenomatous Polyposis (FAP) caused by high-penetrant mutations within the APC gene and Hereditary Breast/Ovarian Cancer (HBOC) linked to mutations within BRCA1 and BRCA2 genes.

Key words: BRCA, FAP, hereditary cancer syndromes, HNPCC

Introduction

The establishment of sensitive genetic tests over the last years has assisted the identification of genes conferring susceptibility to tumorigenesis. Cancer inheritance was successfully spotted in families where specific types of cancer were clustered amongst family members. The most common types of hereditary cancers involve breast and ovarian cancer, primarily caused by mutations in BRCA1 and BRCA2 genes; colorectal cancer (CRC), caused by mutation in one of the DNA MMR genes; and mutations within the APC gene are linked to colorectal adenomatous polypsis. Germline pathogenic mutations of these genes are inherited as autosomal dominant traits and are characterized by their high penetrance. Recent studies focus their interest on mutations with unknown pathogenicity, which seem to collaborate with environmental and/or additional genetic factors for the onset and progression of cancer. The most crucial event in achieving successful prediction of a hereditary cancer syndrome is a well-documented family history, where all healthy and affected family members, all types of cancers, characteristic phenotypic features and age of onset for each inflicted person should be recorded [1]. The appropriate genetic test for the corresponding gene will then identify the causative mutation maximizing the patient’s preventative potential.

The cancer syndromes already known along with their phenotypic features and susceptibility genes are summarized on Table 1. Recently identified genes conferring moderate risk of breast or ovarian cancer are included in the Table although they do not yet constitute defined cancer syndromes. CRC accounts for 12% of all cancer cases in the Western World. Up to 15% of all CRC cases are attributed to familial predisposition, while 3-5% and 0.5-1% are confirmed to carry a pathogenic mutation in one of the DNA MMR genes and
Table 1. Most common cancer syndromes described along with their susceptible genes and their phenotypical features. The most predominant phenotypical feature for each cancer syndrome is highlighted in bold.

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene</th>
<th>Phenotypic features</th>
<th>Mode of inheritance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hereditary Breast/Ovarian Cancer (HBOC) 1</td>
<td>BRCA1</td>
<td>Female breast, ovarian and colorectal cancer</td>
<td>Dominant</td>
</tr>
<tr>
<td>Hereditary Breast/Ovarian Cancer (HBOC) 2</td>
<td>BRCA2</td>
<td>Male and female breast, ovarian, prostate and pancreatic cancer</td>
<td>Dominant</td>
</tr>
<tr>
<td>Moderate Risk Breast/Ovarian Cancer</td>
<td>CHEK2, ATM, NBS1, RAD50, BRIP1, PALB2, FGFR2, TNRC9, MAP3K1, LSP1, CASP8</td>
<td>Breast and ovarian cancer</td>
<td></td>
</tr>
<tr>
<td>Familial Adenomatous Polyposis (FAP)</td>
<td>APC</td>
<td>Multiple colorectal and upper GI adenomatous polyps, desmoid tumors, epidermoid cysts and CHRPE</td>
<td>Dominant</td>
</tr>
<tr>
<td>Hereditary Non-Polyposis Colorectal Cancer (HNPPC)</td>
<td>MLH1, MSH2, MSH6, PM52, PMS1</td>
<td>Colorectal, endometrial, ovarian, gastric, urinary tract and brain cancer</td>
<td>Dominant</td>
</tr>
<tr>
<td>MUTYH Associated Polyposis</td>
<td>MYH</td>
<td>Colorectal polyps and colorectal cancer</td>
<td>Recessive</td>
</tr>
<tr>
<td>Multiple Endocrine Neoplasia (MEN) 1</td>
<td>MEN1</td>
<td>Parathyroid adenomas, lipomas, entero-pancreatic tumors, facial angiofibromas, gastrinomas, collagenomas, insulinomas, anterior pituitary tumors</td>
<td>Dominant</td>
</tr>
<tr>
<td>Multiple Endocrine Neoplasia (MEN) 2</td>
<td>RET</td>
<td>Medullary thyroid carcinomas, parathyroid carcinomas, pheochromocytomas</td>
<td>Dominant</td>
</tr>
<tr>
<td>Li-Fraumeni</td>
<td>TP53</td>
<td>Breast cancer, sarcomas, leukemia and brain tumors</td>
<td>Dominant</td>
</tr>
<tr>
<td>Tuercot</td>
<td>APC, MLH1, MSH2</td>
<td>Colorectal polyps, medulloblastomas, glioblastomas and astrocytomas</td>
<td>Dominant</td>
</tr>
<tr>
<td>Juvenile polyposis</td>
<td>SMAD4, BMP1A</td>
<td>Hamartomatous intestinal polyps and stomach polyps (rare)</td>
<td>Dominant</td>
</tr>
<tr>
<td>Muir-Torre</td>
<td>MLH1, MSH2</td>
<td>Adenomatous colorectal polyps and endometrial cancer</td>
<td>Dominant</td>
</tr>
<tr>
<td>Von-Hippel-Lindau</td>
<td>VHL</td>
<td>Renal cell carcinoma, retinal angiomas, cerebellar and spinal glioblastomas</td>
<td>Dominant</td>
</tr>
<tr>
<td>Peutz-Jeghers</td>
<td>STK11</td>
<td>Hamartomatous intestinal polyps, lung, breast, and urinary tract cancer, hyperpigmented perioral and buccal mucosa</td>
<td>Dominant</td>
</tr>
<tr>
<td>Hereditary Diffuse Gastric Cancer (HDGC)</td>
<td>CDH1</td>
<td>Diffuse gastric cancer, lobular breast cancer</td>
<td>Dominant</td>
</tr>
<tr>
<td>Cowden</td>
<td>PTEN</td>
<td>Breast, gastrointestinal, thyroid, brain, and skin hamartomas developing in cancer</td>
<td>Dominant</td>
</tr>
<tr>
<td>Bannayan-Ruvalcaba-Riley</td>
<td>PTEN</td>
<td>Hamartomatous intestinal polyps, microcephaly, lipomatosis, hemangiomas</td>
<td>Dominant</td>
</tr>
<tr>
<td>Familial Retinoblastoma</td>
<td>RB1</td>
<td>Primary eye cancer</td>
<td>Recessive</td>
</tr>
<tr>
<td>Wilm’s tumor</td>
<td>WT1</td>
<td>Kidney cancer</td>
<td>Recessive</td>
</tr>
<tr>
<td>Familial Melanoma</td>
<td>CDKN2A(p16)</td>
<td>Melanoma</td>
<td>Dominant</td>
</tr>
<tr>
<td>Ataxia Telangiectasia</td>
<td>ATM</td>
<td>Lymphoma, breast cancer</td>
<td>Recessive</td>
</tr>
<tr>
<td>Bloom Syndrome</td>
<td>BLM</td>
<td>Solid tumors</td>
<td>Recessive</td>
</tr>
<tr>
<td>Xeroderma Pigmentosum</td>
<td>XPA</td>
<td>Skin cancer</td>
<td>Recessive</td>
</tr>
<tr>
<td>Fanconi’s Anemia</td>
<td>FANCA (A,B,C,D1,D2,E,F,G,L,L,M,N)</td>
<td>Acute myeloid leukaemia</td>
<td>Recessive</td>
</tr>
<tr>
<td></td>
<td>FANCD1/BRCA2, FANCI/BACH1/BRIP1, FANCN/PALB2</td>
<td></td>
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</tr>
</tbody>
</table>
APC gene, respectively [2]. On the other hand, breast cancer is the most common type of cancer affecting 1 in 10 women, while 20-30% of these cases underlie genetic predisposition, 30% of which are caused by mutations in BRCA1 & BRCA2 genes [3]. This review will mainly focus in colorectal and breast/ovarian cancer syndromes.

**Lynch syndrome (HNPCC)**

CRC is amongst the most common cancers (2nd to 4th) in industrialized countries [4]. HNPCC or Lynch syndrome, named after the oncologist who pioneered the study of this disease, accounts for 3-5% of all CRC cases. It is inherited in an autosomal dominant manner and characterized by 80% and 60% penetrance for colorectal and endometrial cancer, respectively. Extracolonic cancers are also observed in ovaries, stomach, brain, small bowel, pancreas, hepatobiliary and urinary tract, which are estimated to have lifetime risks from 2% to 13%. In addition, there is an excess of synchronous (multiple CRCs within 6 months of surgical intervention) or metachronous CRCs (CRC occurring later than 6 months or more after surgery) [1, 5].

Mutations in the DNA MMR genes (MLH1, MSH2, MSH6 and PMS2) predispose to Lynch syndrome. The main function of MMR genes involves DNA repair during replication. Most pathogenic mutations have been identified in the MSH2 and MLH1 genes. MSH2 mutations account for about 39% of HNPCC cases, whereas MLH1 mutations account for about 50% of the cases. Mutations are scattered throughout the coding regions of the MLH1 and MSH2 genes without obvious hotspots and therefore mutation screening strategies must cover the entirety of these genes [6]. MSH6 mutations account for 10-15% of all HNPCC germline mutations. A characteristic feature of families with MSH6 mutations is the older age at onset as compared to families carrying MLH1 and/or MSH2 mutations. This may be due to the fact that the mismatch repair capacity is partially retained in MSH6 mutated cells. Nevertheless, approximately in half of the MSH6 families studied, at least one member developed CRC or endometrial cancer by her/his fourth decade of life. This indicates a significant variability of penetrance as a function of age, probably reflecting the influence of additional genetic and/or environmental factors. Furthermore, the frequency of CRC is lower in MSH6 families, whereas the frequency of extracolonic tumors, especially of endometrial cancer, seems to be higher compared to the MSH2 families [7].

Pinto and coworkers conducted a research to identify the presence of germline MSH6 mutations in patients diagnosed with CRC before the age of 45 with no HNPCC family history. It was evident that MSH6 mutations contributed to a subset of early-onset CRC, whereas MLH1 and MSH2 mutations were scarce in this group of “high-risk” patients. Further studies should be conducted to identify the genetic and environmental factors which modify the risk conferred by mutations in the MSH6 gene [8].

The clinical diagnosis of Lynch syndrome was mainly based on the Amsterdam I criteria, which were proposed by the International Collaborative group of HNPCC. A characteristic pedigree of Lynch syndrome is depicted in Figure 1. Because these clinical criteria proved too strict, they were modified in order to become more applicable (Amsterdam criteria II, Box 1). Although the Amsterdam II criteria are characterized by 98% specificity, they are still not sensitive enough [1, 9]. Therefore, the revised Bethesda guidelines (Box 2) were introduced for the selection of tumor specimens which should be subjected to microsatellite instability (MSI) analysis. The National Cancer Institute has proposed a panel of 5 markers for the assessment of the MSI levels. Nearly all HNPCC-related colorectal tumors exhibit high levels of MSI (MSI-H) as a consequence of the MMR deficiency. However, 15% of sporadic CRC cases may also be characterized as MSI-

**Figure 1.** Pedigree indicative of Lynch syndrome. Arrow indicates the proband.
H, due to acquired changes in the MLH1 gene. For that reason, MSI-H samples should be further screened for the presence of BRAF V600E, a mutation strongly associated with sporadic CRC [10]. BRAF mutations are rare or absent in Lynch syndrome tumor samples [11]. Although the revised Bethesda guidelines may show up to 95% sensitivity, they are characterized by 38% specificity only [9].

As the identification of mutation carriers is really important for their further clinical management, various algorithms combining family history data with molecular tumor characteristics have been developed to facilitate the diagnosis of Lynch syndrome. Recently, 3 new algorithms were presented for the evaluation of the likelihood of carrying a germline mutation in a MMR gene [12].

- Balmana et al. have developed the PREMM1,2 model, which is available at http://www.dfci.org/premm. This model incorporates personal and family history (first-, second-degree relatives) of cancer and adenomas and can help the clinician to determine the most appropriate family member for genetic testing [13].
- Barnetson et al. have developed another model, which is available at www.1.hgu.mrc.ac.uk/Softdata/MMRpredict.php for the identification of mutation carriers in MMR genes among patients with CRC. The carrier probability is estimated using the following clinical features: age at diagnosis, tumor location (proximal or distal), presence of synchronous or metachronous tumor, age of youngest relative with CRC, and presence of endometrial cancer within the family [9].
- Chen et al. have created the MMRpro software, which is available at http://astor.som.jhmi.edu/BayesMendel/. This model evaluates the risk of genetic susceptibility to Lynch syndrome based on estimates of mutation prevalence and penetrance of the MMR genes in a population [14]. Mutation carriers, as well as their relatives or individuals with high clinical suspicion of Lynch syndrome should be subjected to a particular surveillance programme. The International Collaborative group on HNPCC recommends colonoscopy every 1 to 2 years, starting around the age of 20 or 10 years earlier than the age (at the time of diagnosis) of the youngest patient in the immediate family diagnosed with CRC. Endometrial screening is also recommended, which includes transvaginal ultrasonography and measurement of CA-125 every 1 to 2 years, beginning around the age of 30. There are no standard screening recommendations for the other extracolonic tumors. If the clinician observes a particular tumor spectrum in a family, screening for the specific tumors may be offered [7].

**Familial adenomatous polyposis (FAP)**

FAP is one of the most well described forms of hereditary CRC accounting for 1% of all CRC cases. Germline mutations in the tumor-suppressor APC gene, which is located at locus 5q21 encoding a 2843 amino acid protein and composed by 15 exons, are the genetic cause of FAP syndrome. These FAP-causing mutations result in truncated and, therefore, non-functional APC protein [15]. APC mutations are inherited in an autosomal dominant manner and achieve almost 100% penetrance. Through binding of APC protein to β-catenin, the cellular levels of β-catenin are regulated. Inactivation of APC protein results in the accumulation of β-catenin in the cytoplasm and nucleus. β-catenin is implicated in the upregulation of the Wnt-pathway, affecting the expression of numerous oncogenes [16].

The phenotypic hallmark of FAP is the development of hundreds to thousands adenomatous polyps in the colon and rectum of the affected individuals diagnosed before the third decade of life. Malignant transformation takes place by the fourth to fifth decade of life, if these polyps are not surgically removed [17]. Figure 2 represents schematically the transition of normal epithelium to adenoma and carcinoma. One

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**Box 1: Modified Amsterdam Criteria**

- ≥ 3 relatives with HNPCC-related cancer (colorectal, endometrial, stomach, ovarian, brain, small bowel, hepatobiliary & urothelial tract) (≥ 1 must be first-degree relative of the other 2)
- ≥ 2 successive generations affected
- ≥ 1 individual diagnosed with cancer at an age < 50 years
- Familial adenomatous polyposis should have been excluded

**Box 2: Revised Bethesda Guidelines**

<table>
<thead>
<tr>
<th>Tumors should be tested for MSI when one or more of the following exists:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• CRC in a patient younger than 50 years</td>
</tr>
<tr>
<td>• Synchronous or metachronous CRC or other HNPCC-associated tumors regardless of age</td>
</tr>
<tr>
<td>• MSI-H colon tumor or with particular histology* in a patient &lt; 60 years</td>
</tr>
<tr>
<td>• CRC or tumor associated with HNPCC &lt;50 years in at least one first-degree relative</td>
</tr>
<tr>
<td>• CRC or tumor associated with HNPCC at any age in 2 first- or second-degree relatives</td>
</tr>
</tbody>
</table>

*Presence of tumor infiltrating lymphocytes, Crohn disease-like lymphocytic reaction, mucinous or signet-ring differentiation, or medullary growth pattern. For abbreviations see text.
quite common clinical manifestation observed in FAP patients is the appearance of numerous fundic gland polyps (FGPs) in the stomach, which occurs at a young age. These polyps are small sessile growths characterized by hyperplasia of fundic glands [18]. Figure 3 represents a typical family carrying an APC mutation.

The majority of FAP patients develop extracolonic manifestations. Most of them do not affect the clinical condition of the patient, but on the other hand, some of them can be lethal [19]. Thyroid cancer is a type of malignancy that is usually diagnosed around the age of 30 in APC-mutation carriers. These tumors tend to be non-aggressive and have a low metastatic potential, while they seem to have a strong preference to females with a fascinating ratio female: male of 17:1 [20]. Additionally, rapidly progressive hepatoblastomas, which are in most cases lethal, are often seen in families with FAP syndrome, affecting children around the age of 2 [21]. Although desmoid tumors are quite rare, they comprise one of the leading causes of death of FAP patients [22]. The median age at diagnosis is 32 years and they manifest in the abdomen, and specifically in the small bowel mesentery or the abdominal wall. A very interesting observation is that occurrence of sebaceous cysts and osteomas in FAP patients predispose to desmoid tumor development, which can be helpful for an early diagnosis [23]. Brain tumors, and predominantly astrocytomas and medulloblastomas in patients that have not completed their first decade of life have also been reported in few APC-mutation carriers [24].

A great proportion of FAP patients (almost 90%) develop characteristic ophthalmic flat pigmented lesions, bilateral in most cases, at the level of the retinal pigment epithelium, generally referred to as congenital hypertrophy of the retinal pigment epithelium (CHRPE) [25]. Although this characteristic phenotypic feature does not affect the patient’s clinical status, it is considered as a great disease marker and diagnostic tool, as it specifically affects FAP patients.

A FAP variant, called attenuated FAP (AFAP) is basically characterized by a milder progression of the phenotypic features accompanying the syndrome. Specifically, 10-100 adenomatous flat polyps manifest at AFAP patient’s proximal colon with a delayed onset compared to the classic FAP, whilst CRC arises later, around the age of 55. Generally, these individuals lack extracolonic features, with the exception of the presence of few gastric polyps [26].

Quite recently, an autosomal recessive type of
polyposis with a mild phenotype has been characterized, called the MUTYH-associated polyposis (MAP). MUTYH mutations are susceptible for the specific phenotype, where individuals show few adenomatous polyps (5-50) around the age of 50 and a delayed onset of CRC. MUTYH gene is a base excision repair gene and its inactivation causes accumulation of mutations within the APC gene [27]. The phenotypical and molecular differences between the 3 FAP variants are summarized in Table 2.

The severity of FAP, age of onset and detailed pathological findings that may (or may not) be associated to cancerous lesions can dramatically help in the identification of the specific coding region within the APC gene that is pathogenically mutated. A characteristic example is the occurrence of CHRPE, which is associated with mutations between codons 311 to 1444 [28]. This phenotype to genotype correlation is quite persistent even between different populations and can help reduce the cost of genetic tests. Apart from the classic surgical procedure of proctocolectomy, the pharmaceutical therapy that seems to have a beneficial effect towards colorectal polyp formation in APC mutation carriers is the administration of cyclooxygenase-2 inhibitors, such as celecoxib [29].

**Hereditary breast and ovarian cancer syndrome (HBOC)**

Breast cancer is the second leading cause of cancer-related deaths while ovarian cancer is the sixth most common cancer amongst women [30]. In the past decade, 2 major familial breast and ovarian cancer susceptibility conferring genes were discovered through genetic linkage studies [31]. Mutations in BRCA1 and BRCA2 tumor suppressor genes are identified in approximately 30% of families with severe history burden of these cancers [32]. BRCA1 and BRCA2 genes contribute to genome integrity (DNA repair, cell-cycle-checkpoint control, protein ubiquitillation, chromatin remodelling) [33]. According to a recent meta-analysis the mean cumulative risks for mutation carriers at the age of 70 are the following:

- ovarian cancer risk of 40% for BRCA1 and 18% for BRCA2 mutation carriers
- breast cancer risk of 57% for BRCA1 and 49% for BRCA2 mutation carriers [34].

Mutations in the aforementioned genes account for only 2-3% of all breast cancer cases [33]. Several other “breast cancer” genes have been identified, such as CHEK2, ATM, NBS1, RAD50, BRI1, and PALB2. Mutations in the so-called moderate or low penetrance alleles may double the risk for breast cancer development [35]. Additionally, new susceptibility loci conferring for breast and ovarian cancer moderate risk have been identified, containing the following plausible causative genes: FGFR2, TNRC9, MAP3K1, LSP1, CASP8 [36,37]. It has been assumed that a third high-penetrant gene exists, named BRCA3, as a substantial proportion of typical breast cancer families have no genetic explanation. Up to date, the search for the BRCA3 locus has not yielded any conclusive result [33], and therefore the polygenic model seems to explain a part of these cases [36,37].

Up to now, hundreds of distinct mutations, polymorphisms and unclassified variants have been recorded in the Breast Cancer Information Core Database (BIC), which are characterized by variable penetrance and prevalence in different populations. For instance, ac-

<table>
<thead>
<tr>
<th>Features</th>
<th>FAP</th>
<th>FAP variants</th>
<th>MAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gene/location</td>
<td>APC (MCR exon 15)</td>
<td>APC (5’-end)</td>
<td>MUTYH</td>
</tr>
<tr>
<td>Mode of inheritance</td>
<td>Autosomal dominant</td>
<td>Autosomal dominant</td>
<td>Autosomal recessive</td>
</tr>
<tr>
<td>Polyps’ morphology</td>
<td>3-D structure and pedunculated</td>
<td>flat</td>
<td>flat</td>
</tr>
<tr>
<td>No. of polyps</td>
<td>100-5000</td>
<td>10-100</td>
<td>5-50</td>
</tr>
<tr>
<td>CRC diagnosis</td>
<td>30-40 yrs</td>
<td>40-50 yrs</td>
<td>50-70 yrs</td>
</tr>
<tr>
<td>Desmoid tumors</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Fundic gland polyps in stomach</td>
<td>Yes</td>
<td>Rare</td>
<td>No</td>
</tr>
<tr>
<td>CHRPE</td>
<td>Yes</td>
<td>No</td>
<td>Rare</td>
</tr>
<tr>
<td>Thyroid cancer</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Hepatoblastomas</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Brain cancer</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

For abbreviations see text
According to surveys conducted in the Greek population, despite its genetic heterogeneity, there is a mutation cluster region which is located within exon 20 of the \textit{BRCA1} gene. Figure 4 illustrates a graphic representation of the mutational spectrum in Greek population. Two mutations were identified as the most frequently encountered in the Greek population: 5382insC and the missense G1738R. The latter one seems to be a Greek founder mutation according to the results of haplotype analysis. Hence, sequencing of exon 20 of \textit{BRCA1} gene is proposed as the first step in a mutation screening protocol adjusted to the distinct mutation spectrum of the Greek population [38]. In addition, genomic rearrangements have been shown to account for approximately 10% of the \textit{BRCA1} mutations in Greek patients with breast and ovarian cancer family history and therefore, screening for genomic rearrangements in the \textit{BRCA1} gene seems to be worthwhile in the Greek population [39]. Other populations are also characterized by the presence of particular pathogenic germline mutations in \textit{BRCA1} and \textit{BRCA2} genes, such as Ashkenazi Jews, Icelanders and Norwegians. Screening for the particular alterations has been incorporated in the routine clinical practice as far as high-risk patients are concerned [38].

Certain clinical criteria have been developed for the selection of the appropriate candidates for genetic testing for \textit{BRCA1} or \textit{BRCA2} mutations (Box 3) [32]. Figure 5 depicts an indicative of HBOC syndrome pedigree. The following mathematical models were also developed to predict carrier likelihood and cancer risks:

- The BRCAPRO model calculates the probability of each family member to carry a germline mutation in \textit{BRCA1} and \textit{BRCA2} genes. It is based on data regarding mutation prevalence and disease penetrance proposed either from Claus et al. [40,41] or from Ford et al. [42].
- The MENDEL algorithm estimates cancer risk based on locus and pedigree information, which is

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure4.png}
\caption{Mutational spectrum of \textit{BRCA1} and \textit{BRCA2} genes found in Greek families with history of breast and/or ovarian cancer. Red bars show mutation positions along the \textit{BRCA1} gene, with height relative to times found.}
\end{figure}
Box 3: Criteria for BRCA gene mutation analysis

- Multiple cases of breast cancer (particularly where diagnosis occurred <50 years) and/or ovarian cancer (any age) in the family in more than one generation
- One woman with breast cancer <40 years
- A family member with both breast and ovarian cancer
- Breast and/or ovarian cancer in Ashkenazi Jewish families
- Family member(s) with primary cancer in bilateral breast cancer (one or both <50 years)
- A family member with invasive serous ovarian cancer at any age
- One person with breast or ovarian cancer <50 years and a second BRCA-related cancer at any age (breast, ovarian, endometrial, bowel, gastric, biliary, pancreatic, prostate, melanoma, sarcoma)
- One first-degree male relative with breast cancer at any age

It is noteworthy that women with BRCA1 mutations, and especially those with node-negative disease, seem to have worse survival than BRCA2 mutation carriers or mutation-negative patients. Indeed, there is only a weak relation between the size of the primary cancer and the number of infiltrated axillary lymph nodes. This provides an explanation to the fact that the pathological stage at diagnosis in BRCA1 cases shows weak or no association with survival. Hence, the timely identification of the mutational status of a woman who belongs to the high-risk group, when it comes to developing breast or ovarian cancer, is essential for her further clinical management [31,44].

Salpingo-oophorectomy is well established as an efficient prophylactic procedure in both BRCA1 and BRCA2 mutation carriers. Moreover, this procedure has been proven to have a protective effect with regard to breast cancer development, by reducing the risk as much as 60% for the particular type of cancer and it is strongly advised to female carriers after completing childbearing. As far as the use of tamoxifen in BRCA1 and BRCA2 mutation carriers is concerned, its protective effect is still under debate [45].

Conclusion

The collaboration between clinicians and geneticists could lead to a significant reduction of morbidity and mortality from hereditary forms of cancer. If a clinician accomplishes to classify an individual in a “high-risk” group based on her/his family history, genetic counseling should be offered to her/him. Then, if the individual is willing to undertake the appropriate genetic tests, the initial clinical risk classification may be verified or not. Once a pathogenic germline mutation is identified, the opportunity to choose between an intense surveillance program and a prophylactic treatment (surgical mostly) will be offered to the carrier. The offered options should be based on detailed clinical data about the benefits and the drawbacks of the required procedures. The family relatives can be screened for the particular mutation or may receive an assessment of their risk to develop a specific type of cancer. This aims to support the right decision-making on whether to follow a tailored program for cancer prevention or not.

Although the hereditary forms of cancer correspond to a relatively small percentage of cancer incidents when compared to the total number of cancer cases, there are still many aspects of the genetic basis of cancer to be explored. The so-called unclassified variants as well as common polymorphisms which confer variable risks for the development of a specific cancer

Figure 5. A typical pedigree of hereditary breast/ovarian cancer. The arrow indicates the proband.

available at http://www.genetics.ucla.edu/software/mendel.html [43].

BRCA1-related cancers seem to possess some distinct pathological features, whereas BRCA2-related cancers have the tendency to resemble sporadic cancers. BRCA1-related breast cancers are commonly high grade infiltrating ductal carcinomas and are characterized as estrogen receptor, progesterone receptor and HER2 or p27<sup>kip1</sup> negative. In addition, they usually express high levels of p53, cytokeratin and cyclin E, while on the other hand, BRCA2-related cancers over-express cyclin D1, more commonly found in sporadic tumor specimens.

It is noteworthy that women with BRCA1 mutations, and especially those with node-negative disease, seem to have worse survival than BRCA2 mutation carriers or mutation-negative patients. Indeed, there is only a weak relation between the size of the primary cancer and the number of infiltrated axillary lymph nodes. This provides an explanation to the fact that the pathological stage at diagnosis in BRCA1 cases shows weak or no association with survival. Hence, the timely identification of the mutational status of a woman who belongs to the high-risk group, when it comes to developing breast or ovarian cancer, is essential for her further clinical management [31,44].

Salpingo-oophorectomy is well established as an efficient prophylactic procedure in both BRCA1 and BRCA2 mutation carriers. Moreover, this procedure has been proven to have a protective effect with regard to breast cancer development, by reducing the risk as much as 60% for the particular type of cancer and it is strongly advised to female carriers after completing childbearing. As far as the use of tamoxifen in BRCA1 and BRCA2 mutation carriers is concerned, its protective effect is still under debate [45].

Conclusion

The collaboration between clinicians and geneticists could lead to a significant reduction of morbidity and mortality from hereditary forms of cancer. If a clinician accomplishes to classify an individual in a “high-risk” group based on her/his family history, genetic counseling should be offered to her/him. Then, if the individual is willing to undertake the appropriate genetic tests, the initial clinical risk classification may be verified or not. Once a pathogenic germline mutation is identified, the opportunity to choose between an intense surveillance program and a prophylactic treatment (surgical mostly) will be offered to the carrier. The offered options should be based on detailed clinical data about the benefits and the drawbacks of the required procedures. The family relatives can be screened for the particular mutation or may receive an assessment of their risk to develop a specific type of cancer. This aims to support the right decision-making on whether to follow a tailored program for cancer prevention or not.

Although the hereditary forms of cancer correspond to a relatively small percentage of cancer incidents when compared to the total number of cancer cases, there are still many aspects of the genetic basis of cancer to be explored. The so-called unclassified variants as well as common polymorphisms which confer variable risks for the development of a specific cancer
type, and the interplay amongst genes or between a gene and environmental factors that may function as modifiers of the penetrance of specific genetic alterations still remain to be elucidated.

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