Review

Hereditary ovarian carcinoma: Heterogeneity, molecular genetics, pathology, and management

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ABSTRACT

Hereditary ovarian cancer accounts for at least 5% of the estimated 22,000 new cases of this disease during 2009. During this same time, over 15,000 will die from malignancy ascribed to ovarian origin. The bulk of these hereditary cases fits the hereditary breast-ovarian cancer syndrome, while virtually all of the remainder will be consonant with the Lynch syndrome, disorders which are autosomal dominantly inherited. Advances in molecular genetics have led to the identification of BRCA1 and BRCA2 gene mutations which predispose to the hereditary breast-ovarian cancer syndrome, and mutations in mismatch repair genes, the most common of which are MSH2 and MLH1, which predispose to Lynch syndrome. These discoveries enable relatively certain diagnosis, limited only by their variable penetrance, so that identification of mutation carriers through a comprehensive cancer family history might be possible. This paper reviews the subject of hereditary ovarian cancer, with particular attention to its molecular genetic basis, its pathology, and its phenotypic/genotypic heterogeneity.

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1. Introduction

During this year, approximately 22,000 new cases of ovarian cancer will be diagnosed in the United States and more than 15,000 women may die from malignancies ascribed to ovarian origin (Jemal et al., 2008). About 90% of cancers believed to arise in the ovaries are carcinomas, with the remaining primary ovarian malignancies being closely split between stromal and germ cell origin (Auersperg et al., 2001; Ozols et al., 2005). Familial ovarian cancer confers a 4.6 relative risk (RR) (95% confidence interval [CI] = 2.1–8.7) of this disease in the proband’s mother and a 1.6 RR (95% CI = 0.2–5.9) in the proband’s sister (Ziogas et al., 2000). This translates to a lifetime risk estimate of about 2.5% for the sister of an ovarian cancer patient and a 7.0% risk for the patient’s mother.

The present communication will focus on ovarian carcinoma arising in women with inherited susceptibilities, which are estimated to account for some 5–15% of ovarian cancer...
and thus as many as some 3300 new cases of the cancer in the United States within the next year. Many such cancers may be preventable (Boyd, 1998; Claus et al., 1996; Pal et al., 2005; Rubin et al., 1998).

With emerging evidence, so-called “ovarian” carcinomas are now believed to predominantly arise de novo by malignant transformation of the ovarian surface epithelium, and/or the serous epithelium of the fallopian tube, especially the distal portion (Auersperg et al., 2001; Bassis, 1960; Casey and Bewtra, 2004; Gray and Barnes, 1962; Lauchlan, 1972; Lynch et al., 1986; Parmley and Woodruff, 1974; Piek et al., 2004; Woodruff, 1979). The biological mechanism for this transformation remains elusive, although mounting evidence indicates that it likely involves a multi-step process with the accumulation of genetic lesions in at least three classes of genes, namely proto-oncogenes, tumor suppressor genes, and mutator genes.

Epithelial ovarian cancer, along with related Mullerian duct adenocarcinomas of the peritoneum and fallopian tube, carries the highest fatality to case ratio for all gynecologic malignancies diagnosed in the U.S.A. and is the fifth leading cause of cancer death in women. Because the majority of patients with epithelial ovarian cancer are diagnosed at an advanced stage and because the efficacy of standard therapy is limited in such advanced cases, primary and secondary prevention strategies are critical to reduction of both cancer incidence and mortality. The development of effective prevention methods depends on the identification of the anatomic origins of disease as well as specific carcinogenic mechanisms.

At least two defined inheritable genetic aberrations are known to predispose to ovarian cancer. Mutations in the breast cancer-associated genes BRCA1 and BRCA2 account for approximately 90% of the ovarian cancers in the hereditary breast–ovarian cancer (HBOC) syndrome (Easton et al., 1995, 1997; Ford et al., 1994; Narod et al., 1995a,b; Schubert et al., 1997), and some 65–85% of all hereditary ovarian cancers (Bewtra et al., 1992; Malander et al., 2006; Rubin et al., 1998); mutations in at least four mismatch repair (MMR) genes (MLH1, MSH2, MSH6 and PMS2) (National Center for Biotechnology Information [NCBI], 2008) in the Lynch syndrome account for another 10–15% of hereditary ovarian carcinomas (Bewtra et al., 1992; Lynch et al., 1998; Malander et al., 2006).

Hereditary ovarian cancer syndromes appear to be genotypically and phenotypically heterogeneous diseases, characterized by variable clinical courses. Prevention of hereditary ovarian carcinoma depends on knowledgeable physicians understanding the natural history of these hereditary syndromes in which ovarian cancer is an integral lesion. Comprehensive family histories are currently fundamental for the diagnosis of hereditary cancer syndromes, thereby enabling clinical management, research and, ultimately, the prevention of ovarian-like carcinomas in genetically susceptible individuals. Today’s epidemiological, clinical, and pathological investigations and the current search for molecular pathways in sporadic and hereditary ovarian carcinogenesis are basic for the prophylaxis, early detection, treatment, and final elimination of these cancers in the future.

2. Historical breakthroughs in hereditary ovarian cancer

2.1. Hereditary Breast–Ovarian Cancer (HBOC) syndrome

Hereditary transmission of an autosomal dominant trait predisposing women to both breast and ovarian cancers was first published in the early 1970s by Lynch’s group at Creighton University (Lynch et al., 1972, 1974; Lynch and Krush, 1971). In 1990, Hall et al. (1990) reported linkage between a site in chromosome 17q and site-specific breast cancer arising in disproportionately larger than expected numbers of young women in some cancer prone families. Less than a year later, Narod et al. (1991) demonstrated that this same genetic locus was linked to cancers in the HBOC syndrome described twenty years earlier by Lynch et al. (Lynch et al., 1972, 1974; Lynch and Krush, 1971; Narod et al., 1991) (Figure 1). This gene, located at chromosome 17q21 (National Center for Biotechnology Information, 2008) was termed BRCA1 and subsequently cloned by Miki et al. (1994). A second gene locus at chromosome 13q12.3 (National Center for Biotechnology Information, 2008) was linked to breast cancers in several other families, designated as BRCA2, and cloned by Wooster et al. (1994, 1995). Data from the Breast Cancer Linkage Consortium (Ford et al., 1998) showed that 90% of families afflicted with four or more breast cancers and even one ovarian cancer in the linear pedigree were linked to either BRCA1 (Figure 2) or BRCA2 (Figure 3).

2.2. The Lynch syndrome

More than 40 years ago, Lynch and co-workers (Lynch et al., 1966; Lynch and Krush, 1967) were responsible for defining and bringing to attention a familial syndrome characterized by autosomal dominant transmission of susceptibility to colorectal cancer (CRC) with predilection to the right of the splenic flexure in younger than expected adult patients (mean ~45 years of age) but with no excess of adenomatous colon polyps. As experience continued to accumulate regarding families with predilections to hereditary nonpolyposis colorectal cancer (HNPCC) it became evident that members of these kindreds were prone to an excess of primary synchronous and metachronous CRCs and to primary tumors of other organs as well, including especially carcinomas of the endometrium and ovary, stomach, small bowel, hepatobiliary tract, pancreas, renal pelvis, ureter and brain tumors, particularly glioblastomas (Aarnio et al., 1999; Lynch et al., 2006a, 2008; Lynch and de la Chapelle, 1999; Lynch and Lynch, 1979; Myrhol et al., 1997).

Emerging data from several centers have now demonstrated that among female members of Lynch syndrome families, the cumulative lifetime risk (to age 70 years) for primary endometrial cancer is greater than their risk for CRC (Dunlop et al., 1997; Quehenberger et al., 2005; Vasen et al., 2001). In several of these studies the lifetime risk and standardized incidence ratios (SIRs) for primary ovarian cancer, compared to population risk, exceed that of all other primary extracolonic malignancies besides endometrial cancer in the women
Figure 1 – The pedigree of one of the families involved in the linkage studies that demonstrated that the 17q12–q23 locus for early-onset breast cancer was also associated with hereditary ovarian cancer (Narod et al., 1991).
Figure 2 – Pedigree of an HBOC family with multiple occurrences of ovarian cancer in concert with carcinoma of the breast wherein a BRCA1 mutation was found. Note also the strikingly early onset of ovarian cancer shown in III-2 with onset at age 33, along with early onset in additional individuals shown in the pedigree.
of Lynch syndrome kindreds (Aarnio et al., 1999; Vasen et al., 1999; Watson and Lynch, 2001). Aarnio et al. (1999) calculated an SIR of 13 (95% CI = 5.3–25) compared with their population-based data and a 12% cumulative lifetime risk for ovarian cancer in Finnish women from Lynch syndrome families who were carriers of MLH1 or MSH2 mutations. In their recent study of pooled data from four large hereditary cancer registries in Europe and the United States, Watson et al. (2008) determined a 6.7% lifetime risk for ovarian cancer in proven or probable MSH2 and MLH1 mutation carriers from Lynch syndrome families. Data from The Netherlands Hereditary Nonpolyposis Colorectal Cancer Registry and the Clinical Genetics Centre of the Radiumhospital in Oslo were analyzed by Vasen et al. (2001), who reported a cumulative lifetime risk (to age 70 years) of 10.4% for ovarian cancer in MSH2 mutation carriers, which would exceed a 3.4% lifetime risk for ovarian cancer in the carriers of MLH1 mutations in women from Lynch syndrome families. In the families associated with MLH1 mutations the mean age at which ovarian cancer was diagnosed in carriers was 51 years (range, 35–75 years), and in families associated with MSH2 mutations the mean age of ovarian cancer diagnosis was 45 years (range, 37–58 years) (Vasen et al., 2001) (see Figures 4 and 5).

3. Genetics of hereditary ovarian cancer

3.1. Hereditary ovarian cancer linked to mutations in BRCA1 and BRCA2

The estimated risk for developing ovarian cancer during the lifetime of women selected from HBOC syndrome families who inherit cancer-associated mutations in BRCA1 has been estimated to be as low as 11% to as high as 66% (Brose et al., 2002; Easton et al., 1993, 1995; Ford et al., 1994, 1998; King et al., 2003; Milne et al., 2008; Satagopan et al., 2002; Struwing et al., 1997). The lifetime risk for ovarian cancer in BRCA2 mutation carriers from HBOC syndrome families has been estimated between 10% and 20% (King et al., 2003; Satagopan et al., 2002; Struwing et al., 1997). Antoniou et al. (2003) estimated average cumulative lifetime risks for ovarian cancer in BRCA1 carriers to be 39% and 11% in BRCA2 carriers, unselected for family histories using pooled data from 22 published studies.

3.1.1. Specific BRCA1 and BRCA2 mutations carried in closed populations

Certain relatively closed and geographically confined populations carry well-defined mutations (founder mutations). Some populations are known to be particularly susceptible to ovarian cancer because of founder mutations in BRCA1 and/or BRCA2. The most studied of these populations are Ashkenazi Jews (Jewish families who trace their ancestries to Eastern Europe) in North America and Israel, with specific founder mutations 185delAG and 5382insC in the BRCA1 gene and 6174delT in the BRCA2 gene. The lifetime ovarian cancer risk associated with carriers of one or another of these Ashkenazi mutations was 23% in a study by the New York Breast Cancer Study Group (King et al., 2003). Of 92 consecutive Ashkenazi women diagnosed with ovarian cancer in the New York area, Tobias’s group found that 14 carried the 185delAG mutation and 2 carried the 5382insC mutation in BRCA1, while 7 carried a 6174delT mutation in BRCA2, for a 25% (23/92) incidence of these known cancer-associated mutations (Tobias et al., 2000). A New England study of 32 Jewish women with

Figure 3 – Pedigree depicting an HBOC family with a known BRCA2 mutation. Notable are the two individuals with ovarian and breast cancer (II-2, II-3).
Figure 4 – Pedigree of a family showing the Lynch syndrome as evidenced by early-onset colorectal cancer as shown in individual III-3, in whom the disease was diagnosed at 32 years of age with death at the same age. Note also occurrences of carcinoma of the ovary and endometrium in individuals IV-9, IV-15, and IV-16. Individual III-7 was diagnosed with ovarian cancer; her mother (II-4) had “uterine cancer,” but we do not have the pathology so we cannot exclude endometrial cancer.
Figure 5 – Pedigree of another example of a Lynch syndrome family with multiple occurrences of early-onset ovarian cancer. Note individual II-6 with carcinoma of the ovary and endometrium at age 46 years, carcinoma of the cecum at age 47 years, and of the sigmoid colon at age 56 years. That individual has a daughter with early-onset ovarian cancer (III-13) and another daughter (III-16) with carcinoma of the ovary, endometrium, and colon.
ovarian cancer found that 8 carried a 185delAG mutation in BRCA1 and 6 carried a 6174delT mutation in BRCA2, an incidence of 44% (14/32) for one or another of the known ovarian-associated genetic mutations carried in Ashkenazi populations (Lu et al., 1999). Forty-eight per cent of 71 Jewish ovarian carcinoma patients tested in Los Angeles carried one of the three known Ashkenazi founder mutations; 31% (22/71) of these patients carried a mutation in BRCA1 and 17% (12/71) carried a mutation in BRCA2 (Cass et al., 2003).

A specific 999del5 mutation in BRCA2 accounts for 8.5% of the breast cancer and 6.0–7.9% of the ovarian cancer in Iceland (Johannesdottir et al., 1996; Rafnar et al., 2004). Rafnar et al. (2004) of the Icelandic Genomics Corporation and colleagues at the University of Iceland and Landspitali University Hospital in Reykjavik, estimated that inheritance of the 999del5 founder mutation conveys a highly significant 20.65 odds ratio (OR) (95% CI 7.75–57.02) risk of developing ovarian cancer. From the Icelandic Cancer Registry data, Tulinius et al. (2002) calculated a significantly increased ovarian cancer risk of OR = 1.48 (95% CI = 1.08–1.96) for first-degree relatives and an increased ovarian cancer risk of OR = 1.32 (95% CI = 1.00 1.63) for second-degree relatives of affected probands carrying this mutation.

Soegaard et al. (2008) examined BRCA1 and BRCA2 genes for coding sequence mutations and large genomic rearrangements in 445 confirmed cases of ovarian cancer from Denmark. They focused upon associations between their clinical characteristics in concert with their mutation status; they then extended this to cancer risk for first-degree relatives as well as clinicopathologic features of the tumors. Findings showed pathogenic BRCA1 or BRCA2 mutations in 26 cases (5.8%) of ovarian cancer patients, in which 5 differing mutations were identified in more than one individual, a finding consonant with the possibility of ovarian cancer founder mutations in Denmark. Mutation carriers were diagnosed at a significantly earlier age than noncarriers (median, 49 and 61 years, respectively; \( p = 0.0001 \)). BRCA1 mutations were carried by 23% of women diagnosed before the age of 40 years, 15% of those diagnosed at 40–49 years, 4% of those diagnosed at 50–59 years, and 2% for women diagnosed when 60 years of age or older (\( p = 0.00002 \)). First-degree relatives of mutation carriers had greater relative risks of both ovarian cancer (RR = 10.6, 95% CI = 4.2 26.6; \( p < 0.0001 \)) and breast cancer at less than 60 years (RR = 8.7, 95% CI = 3.0–25.0; \( p < 0.0001 \)).

3.2. Ovarian cancer cluster region (OCCR) and BRCA2 mutation

The OCCR of the BRCA2 gene appears to predispose to an excess of ovarian cancer. Gayther et al. (1995, 1997) identified truncating mutations clustered in a BRCA2 region of approximately 3.3 kb in exon 11 in families with the highest risk of ovarian cancer in relation to breast cancer (\( p = 0.0004 \)). Based on a subsequent study by Lubinski et al. (2004), this was found to be attributable to both the relatively high risk of ovarian cancer and the relatively low risk of breast cancer. Lubinski et al. (2004) studied 440 families with 140 distinct BRCA2 mutations, which supported the assignment of the OCCR to the region spanned by nucleotides 3035 and 6629. Families with mutations located within this region were approximately twice as likely to contain women affected with ovarian cancer as families with other mutations (OR = 2.21; \( p = 0.0002 \)). Thompson et al. (2001, 2002a) reported higher ratios of ovarian to breast cancer in the central regions of BRCA1 and BRCA2 and confirmed reduced risk for ovarian cancer with 3′ mutations in BRCA1.

Both the position of the mutation and the ethnic background of the family appear to contribute to the phenotypic variation observed in families with BRCA2 mutations, and therein Lubinski et al. (2004) concluded that their study provided “…compelling evidence that the risk of ovarian cancer in all BRCA2 families is not uniform.” This lack of uniformity of risk due to the OCCR may therefore be modified by ethnicity, yet-to-be-identified modifier genes, and/or environmental exposures.

If further investigations such as these ultimately define that specific mutations in BRCA1 and/or BRCA2 are associated with significantly increased or decreased risks for ovarian carcinoma, the implications for genetic counseling and clinical management are obvious.

3.3. Hereditary ovarian cancers linked to mismatch repair (MMR) genes

Replication errors in somatic DNA without chromosomal allelic loss of heterozygosity (LOH), demonstrated by PCR-based amplification and electrophoretic mobility testing, were found to manifest phenotypically as sequentially repeated banding patterns (Ionov et al., 1993), now termed “microsatellite instability” (MSI). Such patterns are known to represent the possibility of significant nucleotide deletions and other nucleotide rearrangements (van der Klift et al., 2005), and have been demonstrated by investigators at the Mayo Clinic Foundation and the University of Helsinki in colon cancers from the majority of Lynch syndrome patients (Aaltonen et al., 1993; Thibodeau et al., 1993). Simultaneously, a collaborative international group under the leadership of Peltonäki in Helsinki reported linkage of HNPPC to a microsatellite marker (D2S123), that previously was mapped in the region of chromosome 2p16–15, in two large families subsequently determined to have Lynch syndrome (Peltonäki et al., 1993). This genetic locus ultimately was mapped to chromosome 2p22–21 (NCBI, 2008), cloned and recognized to be the human homologue, designated MSH2, of a bacterial MMR gene (MutS) (Fishel et al., 1993; Green et al., 1994; Leach et al., 1993; Schmutter et al., 1998). Rapidly thereafter, other MMR homologues were analyzed, and the next most frequent human MMR gene linked to HNPPC was found in chromosome 3p11 (NCBI, 2008) and designated MLH1 (Bronner et al., 1994; Lindblom et al., 1993; Papadopoulos et al., 1994; Tannergård et al., 1994). Subsequently, mutations in these genes (MSH2 and MLH1), as well as two other human mismatch repair genes, MSH6 in chromosome 2p21–16 and PMS2 in chromosome 7p22 (NCBI, 2008), were linked to other cancers that have been found to be integral to Lynch syndrome (Akiyama et al., 1997; Miyaki et al., 1997; Nakagawa et al., 2004; NCBI, 2008; Nicolaides et al., 1994; Schmutter et al., 1998). Further research to characterize the locations of MSH2 and MSH6 on chromosome 2p discovered that they map to a region within just 1 MB from one another (Schmutter et al., 1998).
The genetic closeness in chromosome 2p of the MSH2 and MSH6 loci implied that there may be a functional relationship in somatic mismatch repair, which in vitro molecular chemistry research with HeLa cells has shown to involve a complex of MSH2 and MSH6 proteins, termed hMutSα, that is necessary for mismatch binding and repair (Drummond et al., 1995; Iaccarino et al., 1998; Palombo et al., 1995). Although the hMutSα protein complex was necessary for repair of small base-base and nucleotide loop repairs, in vitro experiments indicated that it may not be needed or involved in the correction of larger DNA defects that are manifested in colorectal cancers by high microsatellite instability (MSI-H) but may be necessary for mismatch repair in MSI-low tumors, such as those associated with hereditary mutations in MSH6 (Drummond et al., 1995; Genschel et al., 1998; Wu et al., 1999). For mismatch recognition, the MSH2 protein thus binds with the MSH6 protein to form the hMutSα complex for the correction of single base mispairs (Acharya et al., 1996; Peltonäkki, 2003). Another mismatch repair complex, MutSβ, first identified in the yeast Saccharomyces cerevisiae, involves proteins coded by MSH2 and MSH3 (Acharya et al., 1996; Marsischky et al., 1996; Das Gupta and Kolodner, 2000), and an hMutSβ protein complex has been demonstrated in several human cell lines, where it also supports the repair of single nucleotide mispair and 2–8 nucleotide insertion/deletion, but was not active in mismatch repair of larger defects (Genschel et al., 1998). Either the hMutSβ protein complex of MSH2 and MLH3 or the hMutSα heterodimer of MSH2 protein with MSH6 protein is necessary for recognition and repair of insertion–deletion errors (Acharya et al., 1996; Peltonäkki, 2003). MSH2 protein is integral for mismatch recognition in both of these MMR complexes; however, the molecular deficiencies associated with inheritance of cancer-associated mutations in MLH1 so far are less well explored.

Several in vitro experiments have addressed problems of defining the mechanism of defective MMR that accompanies inheritance of mutated MLH1 in Lynch syndrome. One of these investigations that bears mentioning was by Koi et al. (1994), a group from the University of Michigan and the Institute of Environmental Health Sciences, Research Triangle, North Carolina, who restored microsatellite stability by introducing Environmental Health Sciences, Research Triangle, North Carolina, who restored microsatellite stability by introducing environmental tolerance to which is accompanied by loss of MMR (Koi et al., 1994). The work was followed by further experiments in which Carethers et al. (1996) showed that transfer of chromosome 3 into the MMR defective HCT116 cell line with homologous MLH1 mutations corrected its failure to arrest cell growth in the G2 phase, a “checkpoint” at which DNA damage may be repaired or replication of mutated DNA prevented. Boland et al. (2008) recently offered evidence that a complex of MLH1 and PMS2 proteins may be required for MMR activity. This group found that transfer of chromosome 3 into HCT116 cells, previously deficient of both MLH1 and PMS2 proteins in spite of already “robust presence” of PMS2 mRNA, led not only to increased MLH1 activity but also the expression of both MLH1 and PMS2 proteins. Although, germline mutations in MSH3 have not been associated with CRC in the classical Lynch syndrome (Huang et al., 2001); somatic mutations in MSH3, due to the loss of its MSH3 protein products, may be instrumental in potentiating further deleterious mutations in other DNA repair genes. Thus, failure of the MMR system in families with Lynch syndrome through inheritance of a deleterious MSH2, MLH1, or MSH6 mutation with LOH or mutation of the normal allele results in unchecked hypermutability with the accumulation of repeated nucleotide sequences phenotypically expressed as MSI, beginning a cascade to ultimate tumorigenesis (Eshleman et al., 1995;Ionov et al., 1993; Malkhosyan et al., 1996; Peltonäkki, 2003).

European and multi-institutional studies have shown that some 90% of American and European Lynch syndrome families tested with DNA- or RNA-based techniques carried mutations in MSH2 or MLH1 (Peltonäkki et al., 1997; Peltonäkki and Vasen, 2004; van der Klift et al., 2005; Wagner et al., 2003; Wijnen et al., 1998), and absence of MSH2 and MLH1 functional expression appears to be the fundamental defect in the majority of typical Lynch syndrome families, such as those families that feature both CRC and endometrial carcinomas and meet the Amsterdam criteria (Peltonäkki and Vasen, 2004; Vasen et al., 1999). Interestingly, in one of these studies, four of 48 nucleotide rearrangements found in Lynch syndrome families were not actually within the genetic coding regions, but three families carried nucleotide deletions immediately upstream of MSH2, and one family carried a deletion upstream of MSH6 in chromosome 2p, presumably, thereby affecting MMR gene expression (van der Klift et al., 2005). At least 175 germline MSH2 and 225 MLH1 mutations associated with Lynch syndrome had been registered in the International Society of Gastrointestinal Hereditary Tumors database by 2003, accounting, respectively, for 39% and 50% of the MMR germline mutations in 748 Lynch syndrome families, worldwide (Peltonäkki and Vasen, 2004).

Hereditary transmission of MSH6 mutations is less common in Lynch syndrome families, accounting for only 7% in the International Society of Gastrointestinal Hereditary Tumors database (Peltonäkki and Vasen, 2004), and although germline mutations in MSH6 have been associated with an attenuated form of Lynch syndrome with later onset of tumors, the 71% cumulative lifetime risk for endometrial carcinomas seems to be greater in these kindreds than in those which are associated with germline mutations in MLH1 and MSH2 (Hendriks et al., 2004; Peltonäkki and Vasen, 2004; Wijnen et al., 1999). Only 4% of the germline MMR gene mutations recorded in the International Society of Gastrointestinal Hereditary Tumors databases were in PMS2 and MLH3, and these were reported only in atypical variants of the Lynch syndrome (Peltonäkki and Vasen, 2004), such as Turcot syndrome, characterized by brain tumors, usually glioblastomas, colonic polyps and café au lait spots, lipomas and multiple basal cell carcinomas of the scalp.

Although a few cases of homozygous inheritance of defective MSH2 and MLH1 have been reported in profoundly affected children with neurofibromas, lymphomas, leukemia, café au lait spots, and brain tumors (Ricciardone et al., 1999; Vilkkilä et al., 2001; Wang et al., 1999; Whiteside et al., 2002), in the classical Lynch syndrome, a defective MSH2 or MLH1 and more rarely a defective MSH6 is inherited and paired with its normal “wild-type” allele from the non-affected parent to be somatically replicated together until chance or an exogenous
mutagen results in mutation or somatic loss of the wild-type allele (LOH), initiating oncogenic transformation (Liu et al., 1996; Nyström-Lahti et al., 1996; Wijnen et al., 1999). However, contrary to their expectation, a collaborative group headed by Aaltonen (Aaltonen et al., 1993) found no LOH at the D2S123 locus coinciding with the MSH2 site in chromosome 2p linked to CRC in 14 tested tumors from three Lynch syndrome families, leading them to speculate that for those who inherit a defective gene at this locus, LOH may not be necessary for initiation of carcinogenesis. Notwithstanding, MMR gene mutation or allelic LOH in turn adversely affect the interaction of these genes and their proteins with MSH6, MSH3, and PMS2 protein products in mismatch repair (Aaltonen et al., 1993; Chang et al., 2000; Plassche et al., 2004; Schweizer et al., 2001). Thereafter, the impaired MMR mechanism fails to correct DNA replication errors induced by exogenous mutagens or occurring by chance during mitosis and cell division (Ionov et al., 1993; Thibodeau et al., 1993), resulting in hypermutability, an oncogenic cascade, and the accumulation of nucleotide sequences, more or less phenotypically expressed as the nucleotide bands (Eshleman et al., 1995).

Early studies with various markers reported microsatellite instability (MSI) in 8–17% of sporadic ovarian carcinomas (Fujita et al., 1995; Han et al., 1993; Osborne and Leech, 1994). In 1998 the U.S.A. National Cancer Institute (NCI) Workshop on Microsatellite Instability proposed specific markers (BAT25 and BAT26 for two mononucleotide repeats, and DSS346, D2S123 and D17S250 for three dinucleotide repeats) to be used in the recognition of tumors with defective MMR (Boland et al., 1998). Sood et al. (2001) of the University of Iowa studied 109 unselected ovarian cancers and reported that only 28% of the non-serous tumors were microsatellite stable (MSS), that is, showing normal nucleotide length at all marker loci in the NCI panel, compared with 42% of the serous carcinomas being stable at all marker loci. Using the NCI five marker panel, Gras et al. (2001) at the Autonomous University of Barcelona studied 52 sporadic ovarian tumors (35 malignant, 7 borderline, and 10 benign); they identified MSI in only two of the 52 tumors (4%), one an endometrioid carcinoma and the other a clear cell carcinoma. This led Gras et al. (2001) to expand their investigation to a total of 56 ovarian endometrioid and clear cell carcinomas in which 7 (12.5%) were found to have MSI. A subsequent study by the Barcelona group using the NCI panel found MSI in 3/17 (18%) of the endometrioid ovarian carcinomas and 1/16 (6%) of the clear cell ovarian carcinomas that they studied (Catásius et al., 2004). Testing in turn a series of 74 sporadic endometrioid ovarian carcinomas for MSI with a four marker panel consisting of BAT25, BAT26, DSS346, and D17S250, Liu et al. (2004) found high level MSI (MSI-H) in 20% of the tumors of which 9/15 (60%) were demonstrated to have lost MLH1 and/or MSH2 protein with immunohistochemical staining. Nine (12%) of the endometrioid ovarian carcinomas studied by Liu et al. (2004) showed low level MSI (MSI-L), and the remaining 50 tumors (68%) were MSS. Though not reaching statistical significance, the endometrioid ovarian carcinomas that showed MSI-H in this series tended to be low grade tumors (p = 0.053).

Cai et al. (2004) used the NCI battery of markers to study 42 ovarian clear cell carcinomas from Yale University and the University of Texas M.D. Anderson Cancer Center and found that 6 tumors (14%) were MSI-H, 3 tumors (7%) were MSI-L and the remaining 33 tumors (79%) were MSS. This group found that 4/6 ovarian clear cell carcinomas with MSI-H demonstrated loss of MLH1 or MSH2 protein expression with immunohistochemical staining; whereas, none of the 3 clear cell carcinomas with MSI-L and only 2/33 of the MSS clear cell carcinomas demonstrated loss of MLH1 or MSH2 protein expression (Cai et al., 2004). On the other hand, loss of MLH1 and MSH2 protein expression is highly predictive of MSI-H in unselected sporadic ovarian carcinoma (Rosen et al., 2006). Malander et al. (2006) tested 128 ovarian carcinomas from patients at the Lund University Hospital for MSI using the mononucleotide markers BAT25, BAT26, BAT40, BAT34C4 and the dinucleotide markers D2S123 and DSS346 in immunohistochemical testing for expression of MSH2, MLH1, MSH6 and PMS2 proteins. This Swedish group found that 3 of the 128 ovarian carcinomas (2.3%) lost MMR protein expression, and each of these was MSI positive. Two of these ovarian tumors, which showed loss of both MLH1 and PMS2 proteins, were mucinous carcinomas, one of which was mixed with endometrioid elements; and one ovarian tumor, which showed loss of MSH6 protein, was a clear cell carcinoma. Family histories consistent with Lynch syndrome were obtained from the patient with clear cell carcinoma and the patient with mixed mucinous-endometrioid carcinoma (Malander et al., 2006), the latter fulfilling the revised Amsterdam criteria for HNPCC (Vasen et al., 1999). Rubin et al. (1998) examined 116 consecutively unselected ovarian cancer patients treated at the University of Pennsylvania for mutations in MSH2, MLH1, BRCA1 and BRCA2. Among these ovarian cancer patients, 10 were found to carry germline mutations in BRCA1, one patient carried a germline mutation in BRCA2 and two patients carried MMR gene mutations. One of these was an MSH2 mutation in a 46-year-old woman who had survived colon cancer at age 29 years, and the other was a 64-year-old woman who carried an MLH1 mutation and was diagnosed with synchronous ovarian and endometrial carcinomas; however, neither of these women's families fulfilled the Amsterdam criteria for HNPCC (Rubin et al., 1998; Vasen et al., 1999).

In 72 proven or probable mutation carriers, who were diagnosed with ovarian cancer from an international study of 261 Lynch syndrome families, reported by Watson et al. (2008), the risk for this disease was significantly higher in families that carried defective MSH2 compared with familial MLH1 mutations (p < 0.006). A collaborating group from the Netherlands and Norway, led by Wijnen et al. (1999), found that women who carried MSH6 mutations were more than twice as likely to have endometrial carcinomas and atypical endometrial hyperplasia (73%) than women who inherited defective MSH2 (29%) or MLH1 (31%); and, based on their finding of instability of the mononucleotide TGFβR2(A)10 in colorectal and urothelial tumors, but not in endometrial or ovarian tumors, Wijnen et al. hypothesized that there are different tumorigenic pathways toward endometrial and ovarian cancers in those who inherit cancer-associated MSH6 mutations. Although this group made no distinction between the various histological types of ovarian cancer in their report, a study by Zhai et al. (2008) recently reported that MSH6 protein expression is found in significantly higher proportions of non-serous ovarian carcinomas (23.2%) than in ovarian serous carcinomas (8.7%).
Thus, it appears that studies to date indicate that MSI-H and associated loss of MMR gene expression are found more frequently in ovarian carcinomas of non-serous ovarian histologies, particularly endometrioid and related clear cell types, than in serous carcinomas, which are more common in general populations. An international collaborative group headed by Kuusmanen et al. (2002) of the University of Helsinki studied 44 colorectal cancers and 57 endometrial cancers from well characterized Lynch syndrome families that carried either MSH2 or MLH1 mutations. Their investigations showed that CRCs displayed more consistent patterns of oncogene instability, particularly TGFβR2 (Transforming Growth Factor Beta Receptor II in chromosome 3p22) in 73% of the CRCs compared with 18% of the endometrial cancers; while endometrial cancers with the loss of PTEN (Phosphatase and Tensin homologue, also known as MMAC1), a tumor suppressor gene at chromosome 10q23.3 (NCBI, 2008), was found in 20% of endometrial cancers but only 5% of CRCs (Kuusmanen et al., 2002). PTEN protein acts as a phosphatase to dephosphorylate phosphatidylinositol (3,4,5)-trisphosphate (PtdIns (3,4,5)P3 or PIP3). PTEN specifically catalyses the dephosphorylation of the 3′ phosphate of the inositol ring in PIP3, resulting in the biphosphate product PIP2 (PtdIns(4,5)P2). This dephosphorylation is important because it results in inhibition of the AKT signaling pathway; so with loss or dysfunction of this gene and encoded protein, proliferation of transformed cells continues unabated (Sakurada et al., 1999). More than ten years ago, Peiffer et al. (1995) from the University of Washington studied endometrial cancers using 39 microsatellite markers representing all human chromosomal arms except X and found that the most frequent LOH was on chromosome 10q at the D10S610 marker site in the 10q23–26 region, which was found in 8/20 (40%) of the informative cases. Since then, several groups have reported PTEN mutations and LOH at the PTEN locus in chromosome 10q of endometrioid tissues.

Risinger et al. (1997) found PTEN mutations in 34% (24/70) of the endometrial cancers they studied. While Tashiro et al. (1997) found PTEN mutations in 62% (16/26) of endometrioid endometrial cancers, when they stratified for microsatellite stability, PTEN mutations were found in 86% (12/14) of the MSI+ endometrioid endometrial carcinomas but in just 33% (4/12) of the MSS endometrioid endometrial carcinomas. LOH of microsatellite markers surrounding the PTEN locus in chromosome 10q was found in 48% (11/23) of the endometrial cancers but only in 17% (6/35) of the CRCs tested by Kong et al. (1997). Mutter et al. (2000) found PTEN mutations in 83% (25/30) of the endometrioid endometrial carcinomas but in none of the 10 normal endometria that they studied; and although most of the endometrial carcinomas (23/30) showed mutations in only one PTEN allele, all seven of the 30 carcinomas with LOH of markers within or flanking PTEN had mutations in the remaining allele. Moreover, in this investigation by Mutter et al., there was complete loss of PTEN protein expression in 61% (20/33) and moderate to mild diminutions of PTEN expression in 97% (32/33) of the endometrioid endometrial carcinomas; but only 2 of the 8 (25%) non-endometrioid carcinomas tested by Mutter et al. completely lost PTEN expression. According to their reported data there was moderate to mild loss of PTEN expression in another 50% of the non-endometrioid carcinomas; although there was no significant difference between absent PTEN expression in endometrioid compared with any expression in non-endometrioid endometrial carcinomas (p = 0.115) (Mutter et al., 2000). Taken all together, the studies by Mutter et al. (2000) showing high PTEN mutation rates, PTEN LOH, and absent or diminished PTEN expression indicate probable biallelic inactivation of PTEN in most of the endometrioid endometrial carcinomas.

LOH of PTEN has been reported by Obata et al. (1998) at the University of Southampton in 43% of sporadic endometrioid ovarian carcinomas (13/30), and 21% of the endometrioid ovarian carcinomas (7/34) had somatic mutations in PTEN. PTEN mutations were accompanied with allelic LOH in 6 of these 7 endometrioid ovarian carcinomas, and two somatic mutations were demonstrated and expected to be on separate alleles in the remaining endometrioid carcinoma (Obata et al., 1998). One predominately mucinous ovarian carcinoma with foci of endometrioid differentiation showed LOH in chromosome 10q and a PTEN mutation (Obata et al., 1998). Though less frequently, LOH in chromosome 10q has been reported in ovarian clear cell carcinomas (8–14%) (Catasúes et al., 2004; Obata et al., 1998) than in ovarian serous carcinomas (28%) (Obata et al., 1998). Obata et al. (1998) found no PTEN mutations in 8 clear cell and 25 serous ovarian carcinomas. Tashiro et al. (1997) of Johns Hopkins University found no PTEN mutations in 12 serous carcinomas of the ovary. In sporadic endometrioid ovarian carcinomas studied at the Autonomous University of Barcelona, Catasúes et al. (2004) demonstrated MSI in 3/17 (17.5%) and PTEN mutations in 3/21 (14%) of the tumors. This group found MSI in 1/16 (6%) ovarian clear cell carcinomas and in 1/10 (10%) mixed endometrioid–clear cell carcinomas; and PTEN mutations were found in 1/18 (5.5%) clear cell carcinomas and 1/15 (6.5%) of the mixed endometrioid–clear cell carcinomas. What is most interesting, however, is that in the tested tumors 3/5 (60%) of the endometrioid ovarian carcinomas that carried PTEN mutations showed MSI (Catasúes et al., 2004). PTEN mutations have been reported in other human malignancies (Li et al., 1997). Of most importance to our current discussion, PTEN mutations are frequently found in endometrioid endometrial carcinomas (Kong et al., 1997; Risinger et al., 1997; Tashiro et al., 1997), including some 34–55% of all sporadic tumors (Kong et al., 1997; Risinger et al., 1997; Tashiro et al., 1997) and 78–86% (12/14) of those that were selected for MSI (Kong et al., 1997; Tashiro et al., 1997). Whereas, none of the 6 serous endometrioid carcinomas tested by Tashiro et al. (1997) showed MSI or had PTEN mutations.

Reduced PTEN protein expression has been reported in both endometrial hyperplasias and advanced endometriosis (Ali-Fehmi et al., 2006; Levine et al., 1998; Martini et al., 2002; Maxwell et al., 1998; Mutter et al., 2000; Sato et al., 2000). During their studies of PTEN mutations in endometrioid endometrial carcinomas, Mutter et al. (2000) also tested several “endometrial intraepithelial neoplasias” (EIN) or “precancers,” which others often describe as endometrial hyperplasia and found that 55% (16/29) of these lesions had PTEN mutations. Although PTEN mutations have been reported in 20–24% of endometrial hyperplasias, most were somatic mutations (Levine et al., 1998; Maxwell et al., 1998); however, Levine et al. (1998) of Johns Hopkins University found a germline PTEN mutation
in one of 11 complex atypical endometrial hyperplasias associated with endometrioid endometrial carcinoma.

Reduced PTEN expression was found by Martini et al. (2002) of the Catholic University–Rome in 15% (7/46) cases of stage IV endometriosis, and two of the cases which coexisted with endometrioid cancer had hypermethylated MLH1, while a collaborative group headed by Ali-Fehmi (Ali-Fehmi et al., 2006) of Wayne State University – Harper Hospital, Detroit found LOH of chromosome 10q23.3 loci, corresponding to PTEN, in 7/23 (30%) of their cases of endometriosis, 3/12 (25%) of atypical endometriosis, 3/6 (50%) ovarian endometrioid carcinomas and 3/5 (60%) ovarian clear cell carcinomas. Sato et al. (2000) at the University of Tsukuba, Japan demonstrated LOH at the chromosome 10q23.3 locus in 8/19 (42%) informative cases of endometrioid ovarian carcinoma, 13/23 (57%) solitary benign endometrial ovarian cysts and 6/22 (27%) of ovarian clear cell carcinomas. Somatic PTEN mutations were identified in 4/20 (20%) endometrioid ovarian carcinomas and in 7/34 (21%) benign endometrial ovarian cysts but in just 2/24 (8%) of the ovarian clear cell carcinomas studied by Sato et al. Common PTEN LOH in both carcinoma and endometriosis was found by Sato et al. in 3/5 (60%) of the endometrioid ovarian carcinomas with synchronous endometriosis and 7/12 (50%) of the ovarian clear cell carcinomas with synchronous endometriosis. Although PTEN LOH was not found in any of 12 specimens of benign ectopic endometrium studied by Sato et al., one of the endometrioid carcinomas and 3 of the clear cell carcinomas associated with endometriosis had PTEN LOH only in the ovarian cancer and not in the endometriosis, and the other endometrioid and clear cell ovarian carcinomas did not show PTEN LOH in either cancer or endometriosis. From these findings, Sato et al. (2000) inferred that PTEN mutations or inactivation and allelic loss of heterozygosity are early events that lead to the genesis of endometrioid and clear cell carcinomas. Ali-Fehmi et al. (2006) found MSI in 19/23 (83%) of their cases of endometriosis, 9/12 (75%) cases of atypical endometriosis and 4/6 (67%) cases of atypical endometriosis adjacent to ovarian carcinomas (2 endometrioid carcinoma, 2 clear cell carcinoma and 1 serous carcinoma).

The foregoing observations and data suggest that endometrioid carcinoma may arise from malignant transformation through the loss of MMR in benign or estrogen stimulated endometrium, endometrial hyperplasia or even endometriosis. Thus, unfolding molecular science investigations are beginning to shed light on the genesis of endometrioid and perhaps mixed and clear cell ovarian carcinomas, which may apply to patients who inherit cancer-associated mutations in MMR genes. It is, therefore, interesting to speculate that inheritance of defective mutations in one or more of the major MMR genes implicated in Lynch syndrome may be paired with a wild-type allele which becomes destabilized or lost, or which mutates; thereby down-the-line adverse somatic mutations are not rectified and continue to accumulate in other MMR genes so that their protein products fail to bind and/or correct subsequent somatic mutations until finally irreparable biallelic mutations occur or there are deleterious allelic mutations along with LOH in key tumor suppressor genes such as, possibly, PTEN, causing loss of their protective functions.

Somatic mutations in CTNNB1 located in chromosome 3p21 which codes for β-catenin also have been implicated in the genesis of ovarian endometrioid and clear cell carcinomas (Catásus et al., 2004; Gamallo et al., 1999). Gamallo et al. (1999) of the Hospital La Paz in Madrid demonstrated nuclear β-catenin expression in 9/13 (70%) of the endometrioid ovarian carcinomas and 2/16 (13%) serous ovarian carcinomas but in none of the 18 clear cell, 13 mucinous or 9 mixed ovarian carcinomas that they studied. Gamallo et al. (1999) tested 25 ovarian carcinomas of various histologies by DNA sequencing and found oncogenic CTNNB1 mutations in only 7/13 (54%) of their endometrioid carcinomas. However, they noted limitations in their analysis and also commented that genetic alterations other than mutation might explain this discrepancy. In a DNA analysis by Wright et al. (1999) at Queensland University and the Queensland Institute of Medical Research, CTNNB1 mutations were found in only 10/63 (16%) endometrioid ovarian cancers. Catásus et al. (2004) at the Autonomous University of Barcelona reported nuclear staining of β-catenin with immunohistochemistry in 8/21 (38%) and accompanying CTNNB1 mutations in 5/21 (24%) of the endometrioid ovarian carcinomas and 1/8 (13%) of the mixed endometrioid–clear cell ovarian carcinomas that they studied; while PTEN mutations were found in 3/21 (14%) of the endometrioid ovarian carcinomas and in 3/18 (16%) of mixed endometrioid–clear cell ovarian carcinomas. Nuclear β-catenin expression was found in only 1/18 (6%) of the ovarian clear cell carcinomas, none of which showed a CTNNB1 mutation, and a PTEN mutation was found in only 1/18 (6%) of ovarian clear cell carcinomas tested in this study (Catásus et al., 2004). Eighteen percent (3/17) of the endometrioid ovarian carcinomas and 6% (1/16) of the clear cell ovarian carcinomas showed MSI. All of the 26 endometrioid and endometrioid–clear cell carcinomas in this series still were confined to the ovary when they were removed, and Catásus et al. noted that 24/54 (46%) of the total ovarian cancer cases, including 9/18 (50%) of the endometrioid carcinomas, 4/8 (50%) of the mixed endometrioid–clear cell carcinomas, and 10/18 (56%) of the pure clear cell carcinomas, were associated with endometriosis. In a follow-up investigation, the Hospital La Paz group in Madrid studied differential expression of β-catenin and found nuclear staining in 9/13 (70%) of the endometrioid ovarian carcinomas and in 2/16 (13%) serous ovarian carcinomas, but in none of 18 clear cell, 13 mucinous, or 9 mixed ovarian carcinomas (Sarrió et al., 2006). Nuclear expression of β-catenin was demonstrated by Sarrió et al. (2006) in all of the seven endometrioid ovarian carcinomas in which CTNNB1 mutations were found. Herein, another avenue of investigation has been opened to pursue to the end of ovarian carcinogenesis in tumors that most resemble those found in the Lynch syndrome. Whether immediately fruitful or not, it is always basic science that lays the foundations for preventive and clinical applications that will finally relieve the suffering and increase the longevity of those who inherit genetic predispositions to cancer and other diseases.

3.4. Specific MMR gene mutations carried in closed populations

Like the findings in HBOC syndrome kindreds that carry common BRCA1 and BRCA2 mutations in relatively close-knit, closed populations, a common specific MSH2 founder
mutation has been described in Ashkenazi Jews with Lynch syndrome (Foulkes et al., 2002; Yuan et al., 1999). This mutation is a nucleotide substitution, MSH2*190G → C, which results in a substitution of proline for alanine in the MSH2 protein. It is believed to have arisen in northeastern Europe during the seventeenth century and now is found in Ashkenazi Jews of at least five countries, though it was not identified in individuals of non-Jewish descent (Foulkes et al., 2002; Sun et al., 2005). Although the pedigree of an Ashkenazi Jewish New York family did not fulfill the Amsterdam criteria for the HNPPC syndrome, a tested proband, studied by Foulkes et al. (2002), was a 41-year-old patient with an MSI-H ovarian cancer carrier who carried a germline MSH2*1906G → C mutation, and she descended directly from a maternal grandmother who was diagnosed with ovarian cancer and died in her fifth decade.

During the early studies that led to the association of Lynch syndrome with MLH1 mutations, a genealogical investigation by Nyström-Lahti et al. (1994) linked at least eight Finnish HNPPC families to a region in chromosome 3p, and traced their common ancestry to a progenitor who lived in an isolated rural area of south-central Finland early in the sixteenth century. Only after mass migration to Helsinki during and following World War II did it appear that this trait became more disseminated in the population (Nyström-Lahti et al., 1994). Further studies demonstrated that an identical heterozygous germline deletion of 165 base pairs in codon 16 of MLH1 was responsible for the CRC susceptibility trait in fourteen Finnish families, and this was termed “mutation 1” by Nyström-Lahti et al. (1995). A separate MLH1 mutation carried by another 5 Finnish HNPPC kindreds that originated in or was introduced into southern Finland during the early eighteenth century is a 92 base pair splice site deletion in codon 6, designated as “mutation 2” (Nyström-Lahti et al., 1995). Together these two germline mutations account for some 60% or more of CRC associated with Lynch syndrome in Finland (Moisio et al., 1996; Nyström-Lahti et al., 1995), and therefore may be used for primary screening of these families (Aalto nen et al., 1998, Salovaara et al., 2000).

Though seemingly less geographically or culturally constrained, a genomic deletion of exon 1–6 in MSH2 (Wagner et al., 2002) has been identified in several Midwestern American families and initially traced to an alleged common ancestor of German stock, who was born in Alabama around 1814 (Wagner et al., 2003), although no European investigations had yet detected this mutation (Lynch et al., 2004; Wijnen et al., 1998). With the accumulation of further families and pedigrees, it became recognized that this mutation was far more widely dispersed than at first recognized, and it was postulated that it may have arisen in eastern Pennsylvania during the early eighteenth century and then followed westward migration to California and the Southwestern United States and also into the Southeastern States and Florida (Lynch et al., 2004). Based on this history, it was estimated that there were some 19,000 (estimated from a female founder) to over 34,000 (estimated from a male founder) carriers of this American Founder Mutation (AFM) in MSH2 scattered among unknown related families throughout the United States (Lynch et al., 2004, 2006b). Clendenning et al. (2008) further investigated the genomic sequence flanking the deletion and identified a common disease haplotype in all probands, which provided evidence for a common ancestor between these extended families. However, their work has estimated the mutation’s age at approximately 500 years (95% CI, 425–625). Collectively, their results would place the founding event at a much earlier time than first thought, likely occurring in a European or Native American population. The consequence of this finding would be to increase the estimated number of AFM carriers in the United States significantly over those previously predicted (Clendenning et al., 2008).

Up to 20% of all deleterious mutations within this MMR gene, including the AFM, are large germline deletions which would not have been detectable prior to the methodology developed by Wagner et al. (2002) and used to identify the AFM. Now, because of the prevalence of this mutation, a specific assay can be utilized in routine DNA analysis to screen American Lynch syndrome families without already determined cancer-associated mutations (Clendenning et al., 2008; Lynch et al., 2004, 2006b; Wagner et al., 2003).

A fascinating discovery made in Canada was that a specific A → T at nt942 + 3 mutation in MSH2, though previously demonstrated worldwide, is found in 27% of Lynch syndrome families of the relatively isolated Province of Newfoundland. Although specific, this mutation was not traceable by haplotype analysis to Lynch syndrome families from England, Italy, Hong Kong, and Japan who carry it, leading Desai et al. (2000) to conclude that spontaneous A → T change at 942 + 3 may be a relatively common de novo mutational event.

4. Survival of ovarian cancer in HBOC and Lynch syndrome

For several years improved prognosis and response to standard antineoplastic chemotherapy of epithelial ovarian cancers diagnosed in carriers of BRCA1 and BRCA2 mutations from HBOC syndrome families has been noted by the majority of investigators (Aida et al., 1998; Ben David et al., 2002; Boyd et al., 2000; Cass et al., 2003; Chetrit et al., 2008; Pal et al., 2007; Rubin et al., 1996; Tan et al., 2008). However, the earliest report from the University of Pennsylvania by Rubin et al. (1996) claiming a survival advantage for patients with ovarian cancer associated with BRCA1 and BRCA2 mutations was severely challenged by other authors citing the Pennsylvania group’s failure to secure detailed information concerning surgical resection and residual disease, to histologically review and classify a majority of the cases, to meticulously ascertain survival status, to confirm chemotherapy drugs and regimens and to consider lead-time bias, etc. (Canistra, 1997; Whitmore, 1997). Then studies soon followed by Jøhannsson et al. (1998) from the University Hospital, Lund, and by Pharoah et al. (1999) at the University of Cambridge which failed to confirm improved survival of ovarian cancer patients from HBOC syndrome families associated with BRCA1 or BRCA1 and BRCA2 mutations. All the same, it bears noting that a subsequent study by the Cambridge group, which selected carriers confined to the Ashkenazi Jewish mutations 185delAG and 5382insC in BRCA1 and 6174delT in BRCA2, found that ovarian cancer patients who carried one or another of these mutations had a survival advantage over noncarriers, though the difference did not reach significance (Ramus et al., 2001). On the
other hand, 3 relatively small studies of ovarian cancer patients, selected because their families had strong family histories for breast and/or ovarian cancer or they were presumed carriers of either germline or sporadic BRCA1 mutations or they were carriers of 1675delA or 1135insA founder mutations in BRCA1 without regard to ethnicity, found no significant differences in the survival of these patients compared with ovarian cancer patients who were not considered to bear increased hereditary risk (Buller et al., 2002; Kringen et al., 2005; Zweemer et al., 2001). Pursuant to those observations, 4 further studies in which ovarian cancer patients were selected because they carried an Ashkenazi mutation found significant survival advantages among carriers compared with ovarian cancer patients who were not mutation carriers. These larger series, which included 88 mutation carriers reported by Boyd et al. (2000), 229 carriers reported by Ben David et al. (2002), 34 carriers reported by Cass et al. (2003), and 213 carriers reported by Chetrit et al. (2008), found significantly improved 3–5-year survival rates in mutation carriers compared with noncarriers. Studies reported from Tel Aviv University by Ben David et al. (2002) and later by Chetrit et al. (2008), demonstrated significantly higher survival rates at 3 years of 65.8% and at 5 years of 38.1% in carriers of Ashkenazi mutations compared with 51.9% at 3 years and 24.5% at 5 years in noncarriers (p < 0.001). In an extended follow-up of this series, the median survival of 53.7 months in mutation carriers, compared with a median survival of just 37.9 months in noncarriers, also was significantly longer in mutation carriers (p = 0.002) (Chetrit et al., 2008). The greatest differences found in 5-year survival rates by the Tel Aviv investigators were in carriers compared with noncarriers who had advanced stages and poor grade ovarian cancers (p < 0.001) (Chetrit et al., 2008). Boyd et al. (2000) at the Memorial Sloan-Kettering Cancer Center (MSKCC) in New York found not only improved survival after the diagnosis of ovarian cancer in their group of BRCA1 and BRCA2 Ashkenazi mutation carriers compared to noncarriers (p = 0.004), but mutation carriers in their series also demonstrated a significantly longer median time to recurrence (p < 0.001) with positive mutation carrier status being an independent predictor of survival even in cases having advanced cancers (p = 0.03). Histology, cancer grade and stage and the results of cytoreductive surgery were similar between the hereditary and sporadic cases in the MSKCC series, leading these authors to speculate that the observed improved median survival and longer recurrence-free intervals after treatment of BRCA-mutation associated ovarian cancers may be due to a slower rate of cell division with more indolent behavior and/or more susceptibility to primary antineoplastic chemotherapy. Boyd’s group did, however, note that the observed improvement in survival was greater among BRCA1 mutation carriers (p = 0.008) than it was for BRCA2 mutation carriers (p = 0.08), though their numbers of BRCA2 mutation carriers were smaller, compared with noncarriers (Boyd et al., 2000).

Using the Kaplan–Meier method, Pal et al. (2007) from the H. Lee Moffitt Cancer Center of the University of South Florida actually estimated a higher expected 4-year survival of 83% among their 12 BRCA2 mutation carriers with ovarian cancer than the expected survival of 37% among their 20 BRCA1 mutation carriers with ovarian cancer. This survival rate in BRCA2 mutation carriers was significantly higher than the expected 4-year survival rate of 12% in 200 sporadic ovarian cancer control cases (p = 0.013), but the difference between expected 4-year survival rates between BRCA2 and BRCA1 carriers was not significant. Byrd et al. (2008) in a collaborative British study looked at the contribution of BRCA2 carrier status compared with BRCA1 carrier status to life expectancy. They found a significantly increased death rate in BRCA1 mutation carriers compared with BRCA2 mutation carriers (p = 0.04), and this was attributable to increased deaths from ovarian cancer in BRCA1 carriers rather than breast cancer death rates, which were slightly higher in BRCA2 carriers. Kaplan–Meier analysis by Byrd et al. showed that the improvement in survival at 5 years, 10 years and 20 years in BRCA2 mutation carriers was due largely to improved prognosis for early stage disease; because both BRCA1 and BRCA2 mutation carriers with ovarian cancers were diagnosed with similar proportions of advanced disease and the difference in survival with advanced ovarian cancers was not significant.

Cass et al. (2003) at Cedars-Sinai Medical Center and the University of California – Los Angeles found not only an improved median survival of 91 months among a combined group of carriers of Ashkenazi mutations in BRCA1 (n = 22) and BRCA2 (n = 12) with advanced ovarian carcinoma compared with 54 months median survival among patients who had advanced sporadic ovarian carcinoma (p = 0.046); but also the group with BRCA1 and BRCA2 mutations had a significantly higher 72% (21/29) response rate to primary antineoplastic chemotherapy than the 36% (9/25) response rate in patients with sporadic disease (p = 0.01). Ninety-one per cent (31/34) of the ovarian carcinomas in BRCA-mutation carriers and 78% (29/37) in noncarriers were serous type. In spite of similar 83% (15/18) optimal results from cytoreductive surgery in mutation carriers and 100% (11/11) optimal cytoreduction in noncarriers, 62% (18/29) of mutation carriers had negative second look operations compared with 28% (7/25) negative second look operations in noncarriers (p = 0.01). Cass et al. discovered that in vitro chemoresistance tests to platinum chemotherapy were highly predictive of BRCA-mutation carrier status. Following this lead, Tan et al. (2008) in the United Kingdom matched 22 patients with ovarian carcinoma who carried germline mutations in BRCA1 or BRAC2 with 44 nonhereditary ovarian carcinoma patients. Ninety-six per cent of the patients in both groups had serous or unspecified adenocarcinomas. Patients were matched for age, year of diagnosis, stage and histopathology, and the authors found significantly increased response rates in the mutation carriers to first, second and even third line platinum based chemotherapy in the BRCA-mutation carrier group compared with the sporadic ovarian cancer control group. Tan et al. reported response rates of 95.5% (21/22) to first line treatment, 91.7% (11/12) to second line treatment and an amazing 100% (7/7) to third line treatment, compared with 59.1%, 40.9% and 14.3%, respectively, in the control group. The complete response rate to first line platinum based chemotherapy was 81.8% in the BRCA-mutation carriers but just 43.2% in the control patients (p = 0.004), and the time to relapse following first line chemotherapy was 5 years in mutation carriers compared with 1.6 years to relapse in noncarriers (p < 0.001). In contrast with the series
reported by Cass et al. (2003) in which all test subjects carried Ashkenazi mutations in BRCA1 or BRCA2, only 6/22 (27%) of the test subjects in the case-control study reported of Tan et al. (2008) carried Ashkenazi mutations.

Cass et al. (2005) also examined the outcomes of 12 women with primary fallopian tube carcinomas who carried mutations in BRCA1 (n = 11) or BRCA2 (n = 1) and compared these with 16 cases of sporadic fallopian tube carcinoma. Eighty-three per cent (10/12) of BRCA-mutation associated fallopian tube carcinomas and 94% (15/16) of the sporadic fallopian tube carcinomas were serous, and all others were endometrioid. When the site of primary cancer could be determined, 9/12 (81%) of those in BRCA1 and BRCA2 mutation carriers and 6/16 (67%) of those in noncarriers arose in the distal or middle fallopian tubes, and overexpression of p53 was demonstrated in 71% (5/7) of the BRCA-mutation associated cases and 72% (8/11) of the sporadic cases that were tested. There were no significant differences in the proportions of associated dysplastic epithelium, bilateral carcinomas, immunohistochemical staining for Ki67, ER or PR in benign, dysplastic and cancerous epithelium in the fallopian tubes of mutation carriers and noncarriers. However, the median 2-year survival rate of 100% and 4-year survival rate of 75% in carriers exceeded the median 2-year survival rate of 74% and 4-year

Figure 6 – Schematic representation of a dualistic model depicting the development of ovarian cancer. Low-grade carcinomas are thought to develop in a stepwise manner from an atypical proliferative tumor through a noninvasive stage (LMP) before becoming invasive. These tumors are frequently associated with K-RAS or BRAF mutations and loss of PTEN. Somatic high-grade carcinomas (most commonly serous) develop from the ovarian surface epithelium and/or inclusion cysts without morphologically recognizable intermediate stages. K-RAS and BRAF mutations are less common in these tumors, whereas TP53 is frequently mutated as well as members of the PI3K/AKT pathway. In hereditary forms of this disease (far left), the initial step in BRCA1 or BRCA2 mutation carriers is thought to consist of a TP53 mutation followed by genotoxic injury (p53 signature). In the fimbria, a tubal intraepithelial carcinoma (TIC) develops in some instances and may invade locally or spread to other peritoneal surfaces, such as the ovary and pelvis. Depending on the location and rate of tumor growth, the tumor might be diagnosed as a primary tubal, ovarian, or peritoneal carcinoma. Whether somatic ovarian cancers arise via the fimbria route remains to be demonstrated.
survival rate of 50% in noncarriers; although these differences did not reach significance in such a small series. While the median survival of 68 months in mutation carriers with fallopian tube cancers exceeded the 37 months median survival in noncarriers ($p = 0.14$).

Finally, the groups of Boyd et al. (2000), Cass et al. (2005), and Pharoah et al. (1999) each found that the mean or median ages of ovarian carcinoma diagnosis among BRCA1 mutation carriers were significantly younger than the ages at which ovarian carcinomas were diagnosed in those who carried BRCA2 mutations.

These observations and data raise the hope of proving more favorable prognosis and higher expectations from platinum based chemotherapy for ovarian carcinoma arising in BRCA1 and BRCA2 mutation carriers. But much meticulous work remains to be done. Determining whether median age of onset, survival rates and disease-free interval results may be skewed by inclusion of certain mutations, such as those found in Ashkenazi Jewish populations, will require further and larger investigations stratified as to specific BRCA1 and BRCA2 mutations.

5. Pathology of hereditary ovarian carcinomas

Ovarian tumors can be classified according to their cells of origin into three main categories: surface epithelial tumors, germ cell tumors, and sex cord-stromal tumors. Ovarian surface epithelial (OSE) cancers are the most common type of malignant ovarian tumor and the predominant type in the context of hereditary ovarian cancer (Bewtra et al., 1992; Seidman et al., 2002). Traditionally, the OSE tumors have been histologically classified according to their cellular appearances into (i) serous (ciliated columnar cells of tubal type), (ii) mucinous (goblet, mucinous cells), (iii) endometrioid (pseudostratified columnar, endometrial type), (iv) clear cell (vacuolated cytoplasm), and (v) Brenner type (grooved nuclei) (Seidman et al., 2002). Out of these, the first four types are most pertinent in the context of hereditary ovarian cancers.

5.1. Histology of ovarian carcinomas associated with BRCA1 and BRCA2 mutations

The predominant cell type of ovarian cancers associated with the HBOC syndrome and BRCA1 and BRCA2 mutations is serous carcinoma (Bewtra et al., 1992; Lakhani et al., 2004; Mæhle et al., 2008; Pal et al., 2005; Piver et al., 1996; Rubin et al., 1996), which also is the histology of most primary fallopian tube and peritoneal carcinomas as well as intra-abdominal carcinomatosis.
diagnosed in patients who have had previous salpingo-oophorectomies (Casey et al., 2005; Casey and Bewtra, 2004; Piek et al., 2003a). Review of our own Creighton University Hereditary Cancer Center database showed that 84% (37/44) of the “ovarian” cancers in BRCA1 and BRCA2 mutation carriers were serous carcinomas (MJC, unpublished data). Actually, 24% (9/37) of the serous carcinomas in BRCA1 and BRCA2 mutation carriers registered as ovarian carcinomas, appear possibly to have arisen from the fallopian tube (MJC, unpublished data). This proportion of serous carcinomas is consistent with the collaborative study reported by Rubin et al. (1996) to which we contributed, that found 81% (43/53) of ovarian cancers in BRCA1 mutation carriers were serous carcinomas, compared with 29% serous ovarian carcinomas in noncarriers. Only 14% (5/35) of the primary ovarian cancers in our BRCA1 and BRCA2 mutation carriers were endometrioid carcinomas, and evidently none of these arose from areas of endometriosis (MJC, unpublished data).

5.2. **Histology of ovarian carcinomas associated with the Lynch syndrome**

A Finnish study of malignancies in 50 Lynch syndrome families that carried cancer-associated MSH2 or MLH1 mutations recovered 13 cases of ovarian cancer. Eight of these ovarian cancers were in women who were proven (n = 6) or obligate (n = 2) MLH1 mutation carriers. No ovarian cancers were registered in the 3 families that carried MSH2 mutations. Serous carcinomas made up just half (4/8) of the ovarian malignancies in these MLH1 mutation carriers; whereas, two of the ovarian tumors were clear cell carcinomas and two ovarian tumors were mucinous carcinomas (Aarnio et al., 1999). These findings are comparable to the histological characteristics of ovarian cancers associated with the Lynch syndrome in the Creighton registry (MJC, unpublished data), and a marked deviation from the accumulated literature on the histological diagnoses of ovarian cancers occurring sporadically in the general population (Ozols et al., 2005), as well as from the ovarian malignancies reported in HBOC syndrome families and the ovarian cancers that we have found in BRCA1 and BRCA2 mutation carriers (MJC, unpublished data; Piek et al., 2003a; Rubin et al., 1996).

Of 57 cases registered as ovarian carcinomas from mutation carriers of BRCA1, BRCA2, MLH1 or MSH2 in our Creighton registry, we found only 25% serous carcinomas in those who carried MMR gene mutations compared with serous carcinomas in 84% of women who carried BRCA1 and BRCA2 mutations (MJC, unpublished data). The remaining 75% of ovarian carcinomas from MLH1 and MSH2 mutation carriers were endometrioid, mixed endometrioid–clear cell–serous, or mixed mucinous–serous (MJC, unpublished data). And 3/8 of these cancers were associated with adjacent endometriosis (MJC, unpublished data). Whereas, excluding possible primary fallopian tube carcinomas, 8 of 9 of which were papillary serous, just 20% of primary “ovarian” cancers in the Creighton registry’s BRCA1 and BRCA2 mutation carriers were endometrioid, clear cell, or mixed endometrioid–clear cell carcinomas (MJC, unpublished data). Currently we are definitively re-evaluating all gynecological pathological specimens, blinded as to genetic mutation status.

6. **Pathogenesis of ovarian cancer**

Based on extensive clinical–pathologic and molecular genetic studies, a dualistic model of ovarian tumorigenesis has been proposed in which ovarian cancers can be divided into 2 sub-groups: Type I (also referred to as the low-grade pathway) and Type II (high-grade pathway; see Figure 6) (Kurman and Shih, 2008; Shih and Kurman, 2004). Type I tumors include low-grade micropapillary serous carcinoma,
mucinous, endometrioid, and clear cell carcinomas, and malignant Brenner tumors. This pathway typically involves a multi-step process, such that these tumors may exhibit a spectrum from benign to malignant. Examples include endometriosis and endometrioid carcinoma, or a combination of benign, borderline, and malignant serous or mucinous ovarian tumors (Singer et al., 2005). Type II tumors are rapidly growing and highly aggressive neoplasms. They include high-grade serous carcinomas, malignant mixed mesodermal tumors (carcinosarcomas), and undifferentiated carcinomas; epidemiologically, Type II disease represents most of the current public health burden for epithelial ovarian cancer, and a putative precursor lesion for this type of cancer remains unidentified.

Benign serous cysts, cystadenomas, and serous carcinomas (Figure 7), are the most common types of ovarian tumors. Serous ovarian cysts and low-malignant potential borderline tumors occur in younger women (Seidman et al., 2002), are often bilateral and multifocal, and are typically less responsive to chemotherapy. Pathological studies of ovarian tumors have found that approximately 60% of low-grade serous carcinomas contain areas of serous borderline tumors (Malpica et al., 2004), supporting the idea that low-grade serous carcinomas may arise from the micropapillary type borderline lesions through the adenoma–carcinoma Type 1 (Bell, 2005). In contrast, the common high-grade serous carcinomas, which comprise approximately 60–80% of all ovarian cancers, as well as those most ovarian carcinomas in the HBOC syndrome, are considered to arise de novo, from the OSE and/or the lining cells of the tubal fimbria (Powell, 2006). These malignancies are rapidly growing, relatively chemosensitive, and seem to occur without a definitive histological precursor lesion. Several hypotheses concerning the pathological processes that may increase the risk of malignant transformation of the ovarian epithelium have been proposed (Fathalla, 1971) and reviewed (Landen et al., 2008).

Molecular analyses of these different ovarian epithelial tumor subtypes are beginning to shed light on their genetic pathogenesis. Mutations in the K-RAS and BRAF genes, rarely detected in high-grade invasive carcinomas, are present in 30–50% of borderline ovarian tumors, low-grade adenocarcinomas, and often in adjacent benign epithelium (Mok et al., 1993; Shih le and Kurman, 2004; Singer et al., 2003a,b; Teneriello et al., 1993). In contrast, the TP53 gene is mutated in 50–80% of

Figure 11 – Immunohistochemical analysis of a tubal intraepithelial carcinoma (TIC) and a concurrent ovarian serous carcinoma diagnosed in a 59 year old. The tumor and TIC both stained strongly for p53 and MIB1 (the proliferative marker Ki-67). Images were taken under 40× and 400× magnification, respectively (Q. Cai and Godwin, unpublished data).
high-grade invasive ovarian carcinomas, but rarely in other ovarian cancer subtypes or borderline serous tumors (Kohler et al., 1993; Kupryjanczyk et al., 1993; Skilling et al., 1996). Epidermal growth factor receptor (EGFR) (also referred to as ERBB1/HER1) is overexpressed in 30–70% of high-grade serous ovarian carcinomas, with the varying frequency estimation reflecting the assessment technique used, e.g., immunohistochemistry, Northern blot, or radioreceptor assay. The relationship between the assessment technique used, e.g., immunohistochemistry, carcinomas, with the varying frequency estimation reflecting HER1) is overexpressed in 30–70% of high-grade serous ovarian mal growth factor receptor (EGFR) (also referred to as ERBB1/et al., 1993; Kupryjanczyk et al., 1993; Skilling et al., 1996). Epider-

ovarian cancer subtypes or borderline serous tumors (Kohler high-grade invasive ovarian carcinomas, but rarely in other
diagnosis is not clear, with some reports suggesting a clear prognostic importance (Maihle et al., 2002), and others refuting that association (Elie et al., 2004). Increased EGFR signaling is detected more often in metastases than in primary epithelial ovarian cancer tumor samples (Scambia et al., 1992). EGFR homodimerizes or heterodimerizes with other members of the ERBB family upon ligand binding; this is potentially significant, given that ERBB2 (also known as HER2/neu) is overexpressed in 20–30% of serous ovarian high-grade carcinomas, but rarely in low-grade and borderline tumors (LaFay et al., 2008). The significance of the PI3K/AKT (including PIK3CA, PIK3CB, PIK3R1, AKT1 and AKT2) pathway in ovarian cancer is clear (Vivanco and Sawyers, 2002); evidence of deregulation of the PI3K/AKT signaling pathway in ovarian cancer includes gain-of-function mutations and amplifications of PI3-kinase genes; amplification of AKT2; and allelic imbalance and mutations of PTEN (Nakayama et al., 2006). Previous studies have reported that patients with alterations of AKT2 have a poor prognosis, with amplification of AKT2 being especially frequent in undifferentiated tumors, suggesting that AKT2 alterations may be associated with tumor aggressiveness (Bellacosa et al., 1995). The finding of copy number gains of AKT2 (Cheng et al., 1992), but not the related genes AKT1 or AKT3, suggests a particular significance of AKT2 overexpression in serous ovarian tumorigenesis. Germane to this, overexpression of AKT2, but not other AKT family members, has been shown to lead to up-regulation of β1 integrins, increased invasion, and metastasis of ovarian cancer cells (Arboleda et al., 2003).

Although BRCA1 and BRCA2 genes are rarely mutated in sporadic ovarian cancer (Merajver et al., 1995), epigenetic changes, alternative splicing, and other genetic factors may influence BRCA function in a significant fraction of sporadic occurrences, and molecular pathology studies, such as these, may be the linchpin between heritable ovarian cancers and those which occur in the general population (Baldwin et al., 2000; Chen et al., 2006, 2008; Esteller et al., 2000; Hilton et al., 2002). Clinically, patients with BRCA1 or BRCA2 mutations tend to develop Type II epithelial ovarian cancer, though these patients may have independently more favorable outcomes than those with sporadic disease (Cass et al., 2003). Recently, Levanon et al. (2008) have proposed that serous columnar glandular epithelial cells of the fallopian tube fimbrial mucosa may be the putative precursor cells for these tumors in BRCA1 and BRCA2 germline mutation carriers (see below). Borderline tumors have much less frequent incidence of BRCA mutations which also suggests a different molecular origin (Gotlieb et al., 2005).

Mucinous tumors (Figure 8) are the next most common type of sporadic ovarian carcinoma, are less common than serous and endometrioid carcinomas in HBOC syndrome, and mucinous carcinomas are the least common histologic type we found in ovarian carcinoma in MMR gene mutation carriers (MJC, unpublished data). These are often slow-growing carcinomas which may be associated with the benign and borderline foci, suggesting an adenoma–carcinoma Type 1 sequence, perhaps involving K-RAS and BRAF mutation pathways, among others (Bell, 2005). Non-genetic exogenous risk factors, such as cigarette smoking and excess alcohol consumption, may also be involved (Pal et al., 2008b). These tumors as well as low-grade and borderline serous tumors may arise in the cortical inclusion cysts which often undergo Müllerian metaplasia into tubal or endocervical type epithelia (Levanon et al., 2008).

The next most common epithelial cancer overall is the endometrioid type (Figure 9). Endometrioid and clear cell carcinomas (Figure 10) are sometimes seen associated with endometriotic foci with atypical hyperplasia, similar to that seen in the endometrium. Synchronous endometrioid carcinomas are also described and perhaps involve similar molecular pathways with PTEN and β-catenin mutations (Bell, 2005; Obata et al., 1998; Wu et al., 2001). High-grade tumors, however, may involve the p53 pathway similar to their serous counterparts. Endometrioid carcinomas, frequently mixed with clear cell, serous, and mucinous elements, predominate among the Lynch syndrome-related ovarian cancers (MJC unpublished data; Pal et al., 2008b).
7. Carcinoma precursor lesions

Numerous studies have compared the macroscopically normal ovaries and fallopian tubes from women with elevated genetic risk who have undergone prophylactic salpingo-oophorectomy with general population controls in terms of atypical ovaries and fallopian tubes from women with elevated ovarian cancer risk. Studies have shown increased atypical cells, micropapillae, etc., and others have not (Casey et al., 2000).

7.1. Fallopian tube lesions

Recent pathological and molecular studies (Levanon et al., 2008; Medeiros et al., 2006) suggest that the secretory epithelium of the fallopian tube may be the site of origin for the high-grade serous ovarian tumors in the hereditary ovarian cancer setting. Some of these studies have shown increased atypical cells, micropapillae, etc., and others have not (Casey et al., 2000).

7.2. Peritoneal carcinoma

The extra-ovarian peritoneal serous carcinomas identified in families with BRCA1 and BRCA2 mutations appear morphologically similar to the high-grade ovarian serous cancers but often show no significant lesions in the ovaries. In times past, the fallopian tubes in many such cases were examined minimally, with one routine section from the middle portion of the tube that showed no obvious pathology. However, thorough sectioning of the fallopian tube, particularly the fimbria, with immunostaining for p53 and cell proliferation marker Ki-67, shows positive stains and preneoplastic features in the mucosal cells when compared with normal fimbria. Approximately 50% of peritoneal serous carcinomas cases with unknown BRCA mutation status showed these microscopic changes (Crum et al., 2007a,b).

As discussed above, Piek et al. (2003b) have shown tubal dysplasia and increased cell proliferation in the tubes removed prophylactically in HBOC patients with high risk of ovarian cancer. Crum et al. (2007b) have serially sectioned the tubes from prophylactic salpingo-oophorectomy cases and by increased (>75%) positive immunostaining of Ki-67 and p53, have shown occult micro carcinomas (TICs), most commonly in the tubal fimbria (Medeiros et al., 2006; Powell, 2006). Levanon et al. (2008) have postulated that fimbrial mucosal dysplasias may be the precursor lesions of the high-grade serous ovarian cancers, BRCA1 and BRCA2 related ovarian cancers, and potentially all extra-ovarian serous peritoneal cancers; however, this claim is far from proven. These lesions may often go undiagnosed in the routine examination of the tube and their identification may require thorough examination of the fimbria with p53 and Ki-67 immunostains (Figure 11). Powell (2006) has shown 4.4% of adenexa from prophylactic salpingo-oophorectomies to harbor occult carcinomas. Eighty per cent of these extra-ovarian tumors appear to be of tubal origin and relatively few are from ovarian or peritoneal surface. In addition, Powell found increased incidence of these lesions with the BRCA1 gene and increased age, with very few lesions identified before age 40. This may be a factor in the prophylactic surgical management of these cases. Nevertheless, an important question remains regarding the association of premalignant lesions in the fallopian tubes and the subsequent risk of developing ovarian cancer. Studies at Fox Chase Cancer Center in Philadelphia, Pennsylvania, using overtly normal ovarian and fallopian tube specimens from women undergoing total abdominal hysterectomy and bilateral salpingo-oophorectomy examined p53 expression. Fallopian tubes were analyzed using a procedure for sectioning and extensively examining the fimbriated end (SEE-FIM) protocol (Medeiros et al., 2006). All ovaries and fimbriated tubes were sectioned and stained with H&E, subjected to immunohistochemical staining for p53 and MIB1 and evaluated by conventional microscopy. The prevalence of the p53 signature, defined as 12 or more consecutive p53 positive cell nuclei (for example, Figure 12), in fallopian tubes (mostly within the fimbriated end) was approximately 32% (13/41) (AKG, unpublished data). The number of cortical inclusion cysts (CICs) in the ovaries was also recorded. As recently reported by Folkins et al. (2008), there was no correlation between the presence of
a p53 signature and the number of CICs in ovaries. Importantly, the occurrence of TP53 mutated cells in the fimbria of these women was much more frequent than the average risk predicted for sporadic ovarian cancer in unselected populations (approximately 1% by age 70 years), and this suggests that either there is a long latency period for preneoplastic cells in the tubes before they acquire additional mutations that lead to rapid tumor development, or these lesions regress over time and are not the precursor of epithelial ovarian tumors. Similarly, Folkins et al. (2008) have reported that the prevalence of p53 tubal signatures in BRCA-mutation carriers is similar to women with unknown BRCA status (38 versus 33%). However, as the 11–66% lifetime risk of developing ovarian cancer in BRCA1-mutation carriers and 10–20% lifetime risk for ovarian cancer in BRCA2 mutation carriers are sufficiently higher, these results suggest that a p53 mutation in the background of a BRCA mutation may be an important early event in the pathogenesis of hereditary forms of the disease (Figure 6).

7.3. Endometriosis

Endometriosis is a common disorder, occurring in some 7–20% of women of reproductive age. In the general population, endometriotic foci are seen in association with up to 21% of endometrioid and clear cell ovarian cancers and the preneoplastic atypical hyperplasia–carcinoma has been described in the ectopic endometrium, similar to that seen in the uterus (Bell, 2005; Seidman et al., 2002). In the Creighton registry, we found that 3/8 endometrioid and mixed endometrioid carcinomas in Lynch syndrome MMR gene mutation carriers were associated with endometriosis (MJ C, unpublished data).

8. Genes commonly associated with hereditary ovarian cancer

8.1. Proto-oncogenes (Bell, 2005; Seidman et al., 2002)

c-ERBB-1 (EGFR) is a member of the type I tyrosine kinase receptor family HER (i.e., ERBB) that is expressed in normal ovarian surface epithelium and overexpressed in 35–70% of ovarian cancers. However, the gene is rarely amplified or mutated in ovarian cancer.

c-ERBB2 (HER2-neu) is a member of the type I tyrosine kinase receptor family HER (i.e., ERBB). HER2 expression in ovarian cancer varies widely; overexpression is found in 20–30% of cases. It has been reported that approximately 40% of HBOC cases overexpress HER2 (Seidman et al., 2002).

c-Myc is a transcription factor that regulates expression of many genes. The c-Myc gene is amplified in both hematopoietic and solid neoplasms, including more than 30% and 40% of endometrioid and clear cell carcinomas, respectively. Overexpression of c-Myc has been reported in 30% of all ovarian tumors, but most frequently in serous adenocarcinomas.

K-RAS is a G-protein that promotes growth through MAP kinase pathway. Mutations in the K-RAS gene have been reported in approximately 60% of borderline tumors, in nearly 70% of low-grade tumors, and in 50% of mucinous adenocarcinomas.

β-Catenin (CTNNB1) is a regulator of the Wnt signaling pathway and is often mutated and deregulated in human malignancies. β-Catenin is a subunit of the cadherin protein complex, and in the absence of Wnt signal it becomes phosphorylated by GSK-3 and targeted for degradation by the ubiquitin–proteasome system. It is positively expressed in up to 16% of endometrioid carcinomas of the ovary, and nuclear β-catenin expression is strongly associated with endometrioid histological subtype. Similar positivity has also been noted in endometrial carcinomas.

8.2. Tumor suppressor genes (Bell, 2005; Piek et al., 2004)

TP53 is an example of a prototype tumor suppressor gene that promotes cell cycle arrest/apoptosis in cells with DNA damage. Mutation of this gene is seen in many human malignancies including 50–60% of ovarian serous carcinomas. TP53 mutations have also been detected in ovarian inclusion cysts adjacent to cystadenocarcinomas, in microscopic ovarian cancer, and in tubular intraepithelial carcinomas removed prophylactically from patients with BRCA1 mutations, suggesting that the p53 inactivation may be a relatively early event in ovarian cancer pathogenesis. Serous endometrial carcinomas are also p53 mutation positive as are the “dysplastic” ovarian surface cells from prophylactic salpingo-oophorectomies.

PTEN is one of the most frequently mutated genes in human cancer and acts as a tumor suppressor by dephosphorylating the plasma membrane lipid second messenger phosphoinositide-3,4,5-trisphosphate (PIP3) generated by the action of P13Kinases back into PIP2. Mutations are seen in the endometrioid type of ovarian and uterine carcinomas.

BRCA1 (breast cancer susceptibility gene 1) is one of the most intensively studied susceptibility genes and has a profound role in breast and ovarian cancer etiology owing to its involvement in several important cellular processes. Deleterious mutations in BRCA1 are found in 5–6% of ovarian cancers, but up to 80–90% in HBOC cancer cases. Among its many biological functions, the BRCA1 protein is involved in DNA repair.

BRCA2 (breast cancer susceptibility gene 2) is a tumor suppressor that shows similar but less common associations with HBOC as compared with BRCA1. Extensive genetic and biochemical characterization has shown that BRCA2 is involved in the maintenance of chromosomal stability and that it has an important role in recombination-mediated double-strand DNA break repair.

8.3. Epigenetic changes (hypermethylations)

Up to seven mismatch repair (MMR) gene mutations and epigenetic hypermethylations are seen in ovarian cancers associated with the Lynch syndrome, most of which are non-serous epithelial carcinomas (Pal et al., 2008a). MSI is detected in 50% of low-grade endometrioid tumors.
9. Diagnosis and management

9.1. Ovarian cancer associated with the HBOC syndrome

The foundation for detection and diagnosis of the HBOC syndrome and Lynch syndrome is the extended family history with all possible pathology verification. Since kindreds often are small, if possible at least three extended generations should be included to correctly diagnose hereditary cancer syndromes (Lynch et al., 1992). In the case of HBOC, even a single first-degree relative and two or more second-degree relatives with ovarian cancer and/or breast cancer will indicate an increased long-term ovarian cancer risk. These women and those from populations known to bear a high prevalence of cancer-associated BRCA1 and BRCA2 mutations should be offered cancer genetics counseling and considered for DNA testing. In the case of the Lynch syndrome, similar strategies should be employed, given knowledge of its genotypic (MMR mutations) and phenotypic features.

Women determined by pedigree to be obligate carriers of an HBOC susceptibility trait and those found to harbor germline cancer-associated BRCA1 or BRCA2 mutations are known to bear 10–66% cumulative lifetime risk for ovarian carcinoma, which might be more precisely defined in some families by specific gene and location determination of the aberrant mutation through DNA testing (Brose et al., 2002; Easton et al., 1993, 1995; Ford et al., 1994, 1998; King et al., 2003; Satagopan et al., 2002; Struwing et al., 1997; The Anglian Breast Cancer Study Group, 2000). From accumulating data in the literature, it appears that the penetrance of adverse BRCA1 mutations in predisposing to ovarian carcinoma slightly exceeds that of BRCA2 mutations (Antoniou et al., 2000; Brose et al., 2002; Easton et al., 1997; Ford et al., 1995, 1998; King et al., 2003; Satagopan et al., 2002). Using pooled data, Antoniou et al. (2003) estimated from 22 studies an average of 39% cumulative lifetime risk for ovarian cancer in carriers of BRCA1 mutations and an average of 11% cumulative lifetime risk for ovarian cancer in carriers of BRCA2 mutations. Struwing et al. (1997) studied carriers of three Ashkenazi mutations, namely 185delAG and 5382insC in BRCA1 and 6174delT in BRCA2, and estimated accumulated risks for ovarian cancer by age 70 years of 22% in carriers of the 5382insC mutation, 12% in carriers of the 185delAG mutation, and 18% for carriers of the 6174delT mutation. In another study of ovarian cancer penetrance in carriers of the Ashkenazi mutations, Satagopan et al. (2002) showed greater risks for ovarian cancer in carriers of mutations in BRCA1 than in carriers of BRCA2 mutations. In their penetrance studies of these same three Ashkenazi mutations, Satagopan et al. (2002) estimated a 37% risk for ovarian cancer by 70 years age for carriers of the 185delAG and 5382insC mutations in BRCA1 and a 21% risk for ovarian cancer by 70 years age for carriers of the 6174delT mutation in BRCA2.

9.2. Prophylactic bilateral salpingo-oophorectomy

Prophylactic oophorectomy with and without salpingectomy and hysterectomy has removed previously undiagnosed occult ovarian carcinomas and lowers the risk of subsequent ovarian cancer and disseminated intra-abdominal carcinomatosis in women who are likely or proven carriers of cancer-associated BRCA1 or BRCA2 mutations (Casey et al., 2005; Kauff et al., 2002; Rebbeck et al., 2002; Rutter et al., 2003). The groups of Rebbeck et al. (2002) and of Kauff et al. (2002) reported historical series of women deemed to be at increased risk for ovarian cancer because of their family histories (Rebbeck et al., 2002) or because they carried BRCA1 or BRCA2 mutation (Kauff et al., 2002), showing decreased risk for this disease in family members who had undergone oophorectomy. In our own material, only 5 cases of intra-abdominal carcinomatosis were diagnosed among 238 carriers of cancer-associated BRCA1 and BRCA2 mutations from which a 3.5% cumulative risk was calculated through 20 years of follow-up after prophylactic oophorectomy (Casey et al., 2005). Four of these 5 patients also had hysterectomy, and retrospective review of the surgical specimens showed a borderline serous papillary tumor on an ovary in 2 patients, one with possible early stromal invasion (Casey et al., 2005).

The results of a large collaborative study, involving 11 separate institutions, of 498 BRCA1 mutation carriers recently reported by Kauff et al. (2008) showed an 85% reduction in gynecological cancers among subjects who elected prophylactic salpingo-oophorectomy compared with subjects who chose surveillance. Fewer than 1% of the BRCA1 mutation carriers who underwent prophylactic surgery were diagnosed with intra-abdominal carcinoma during a mean follow-up of 41 months in this study; whereas gynecologic cancers, including invasive carcinomas of the ovary, fallopian tube, or peritoneum, were diagnosed in 6% of the BRCA1 mutation carriers who chose surveillance (p = 0.001). Likewise, there was an observed reduction in risk for gynecologic cancers in BRCA2 mutation carriers who elected prophylactic salpingo-oophorectomy compared with those BRCA2 mutation carriers who chose surveillance during 39 months’ mean follow-up, although the difference did not reach significance. This study also indicated a 72% reduction in breast cancers among BRCA2 mutation carriers and suggested a reduction in breast cancers among BRCA1 mutation carriers who underwent prophylactic salpingo-oophorectomy (Kauff et al., 2008).

Since the report of fallopian tube carcinoma in the 48-year-old proband of one of the first two families in which pedigree analysis was used by Lynch et al. (1974) to establish the familial association of breast and ovarian cancers, as well as the confirming report of fallopian tube cancer by history in a 42-year-old member of a breast-ovarian cancer family by Fraumeni et al. (1975) just one year later, it has become increasingly evident that primary fallopian tube carcinoma is an integral cancer in the HBOC syndrome and these cancers are associated with germline mutations in BRCA1 and BRCA2 (Agoff et al., 2002; Aziz et al., 2001; Casarsa et al., 2004; Cass et al., 2005; Colgan et al., 2001; Friedman et al., 1995; Hartley et al., 2000; Hébert-Blouin et al., 2002; Jongasma et al., 2002; Lamb et al., 2006; Leeper et al., 2002; Levine et al., 2003; Mæhle et al., 2008; Medeiros et al., 2006; Meeuwissen et al., 2005; Olivier et al., 2004; Paley et al., 2001; Peyton-Jones et al., 2002; Piek et al., 2003a; Powell et al., 2005; Rose et al., 2000; Scheuer et al., 2002; Schubert et al., 1997; Simard et al., 1994; The Breast Cancer Linkage Consortium, 1999; Tong et al., 1999; Tonin et al., 1995; Zweemer et al., 2000). Brose et al. (2002) estimated that
there is a 120-fold increased lifetime risk for fallopian tube cancer in BRCA1 mutation carriers.

Although Brose et al. noted no increased risk for uterine cancer in their study of 483 BRCA1 mutation carriers, the Breast Cancer Linkage Consortium (Thompson et al., 2002b) reported significantly increased relative risks of 2.65 (95% CI 1.26–4.06, p = 0.004) for uterine corpus cancer and 3.72 (95% CI 2.26–6.10, p ≤ 0.001) for cancer of the uterine cervix among 11,847 individuals from cancer families associated with BRCA1 mutations. Finding germline Ashkenazi BRCA1 and BRCA2 mutations in only three of 199 consecutive Jewish endometrial carcinoma patients, a frequency of 1.5 compared with the expected frequency of 2.0 in the general population, Levine et al. (2001) concluded that the lifetime risk for endometrial carcinoma is not increased in BRCA1 and BRCA2 mutation carriers.

On the other hand, Beiner et al. (2007) reported the diagnosis of 6 endometrial cancers in a collaborative study of 857 BRCA1 and BRCA2 mutation carriers during an average follow-up time of 3.3 years compared with just 1.13 endometrial cancers expected in the general population. This is a significantly increased standardized incidence ratio (SIR = 5.3, p = 0.001) for endometrial cancer in the mutation carriers reported by Beiner et al. However, in this study, 4 of the 6 mutation carriers diagnosed with endometrial carcinoma had been treated with tamoxifen. Excluding these 4 cases, Beiner et al. calculated a 2.7 SIR for endometrial cancer among mutation carriers never exposed to tamoxifen, a difference from the general population which did not reach significance (p = 0.17); however, the 11.6 relative risk for endometrial cancer among 226 participants who used tamoxifen was highly significant (p = 0.0004), leading these authors to conclude that tamoxifen treatment was the main contributor to the increased diagnosis of endometrial cancer among BRCA1 and BRCA2 mutation carriers in their study (Beiner et al., 2007).

All of the 5 BRCA1 and 4 BRCA2 mutation carriers who were diagnosed with endometrial cancers in the series reported by Levine et al. (2001) and by Beiner et al. (2007) were endometrioid type. Our preliminary review of gynecological cancers in BRCA1 and BRCA2 mutation carriers from the Creighton registry, found that 2/6 (33.3%) of the primary endometrial carcinomas, 8/9 (89%) of the fallopian tube cancers, and all 5 of the peritoneal carcinomas were serous type, an extraordinary proportion of serous endometrial carcinomas compared with 30/35 (86%) endometrioid endometrial carcinomas with only 3/35 (14%) showing clear cell or papillary forms but not serous elements in hMLH1 and hMSH2 mutation carriers (MJC, unpublished data). So not only does the finding of asymptomatic occult endometrioid endometrial carcinomas, particularly in patients who have received tamoxifen, have implications in managing women at hereditary risk for HBOC, but even more significant may be the possibility that endometrium, as well as ovarian fallopian tube epithelium, might be a site of primary transformation to serous carcinoma in carriers of cancer-associated BRCA1 and BRCA2 mutations (Casey and Bewtra, 2004).

Apropos our observations, Hornreich et al. (1999) reported a case of uterine serous papillary carcinoma in an Israeli woman who carried the same Ashkenazi germline BRCA1 mutation as her sister who also was diagnosed with ovarian papillary serous carcinoma, and subsequently this group found that BRCA1 mutations were carried by 4 of their 20 patients (20%) with papillary serous uterine carcinoma (Lavie et al., 2004). Ashkenazi BRCA1 or BRCA2 founder mutations were found in 7/22 (32%) consecutive cases of papillary serous uterine carcinoma in Jewish women studied by Biron-Shental et al. (2006). Three of the BRCA1 and BRCA2 mutation carriers with uterine serous carcinoma in the series of Biron-Shental et al. had past histories of breast cancer and 4 of these patients had first-degree relatives with breast or ovarian cancers. For the purpose of retrospectively assessing the effectiveness of antineoplastic chemotherapy, particularly platinum compounds for treating endometrial cancer in BRCA1 and BRCA2 mutation carriers, Kwon et al. (2008a) recently searched the London Health Sciences Centre database in Ontario. They identified only 8 patients with a diagnosis of endometrial cancer among 587 mutation carriers. Four of these women had endometrioid carcinomas and their tumors were confined to the corpus, one endometrial cancer patient had a mixed endometrioid–clear cell carcinoma with extension to the uterine cervix and 3 of the 8 women (38%) had cancer beyond the pelvis. Two of the advanced endometrial cancers were papillary serous type and one was a sarcomatoid carcinoma. The discovery by Kwon et al. (2008a) that 2/8 (25%) endometrial cancers were papillary serous type in this database of BRCA1 and BRCA2 mutation carriers is most curious, especially since these women were relatively young for this histological type at 59 years and 64 years, respectively. In comparison, only 3.9% of 7496 uterine corpus cancer patients reported in the International Federation of Gynecology and Obstetrics 25th Annual Report on the Results of Treatment of Gynecological Cancer were papillary serous carcinomas (Creasman et al., 2003).

Finally, it should be kept in mind that though rare, families and individuals may harbor more than a single dangerously mutated gene. This is of special risk in culturally and geographically restricted populations. For instance, germline mutations in the genes associated with both HBOC syndrome and the Lynch syndrome have been reported in a single kindred (Borg et al., 2000). Therefore, whenever suspicion arises from family history, an extended pedigree over at least three generations should be developed, and when cancer patterns are not confined to those that characterize the two major hereditary syndromes associated with increased susceptibility to ovarian cancer, the most diligent accumulation of records, pathology review and DNA testing may be needed to sort out and isolate the culprit gene(s) and mutation(s).

With these considerations, we believe it is prudent to advise proven female carriers of cancer-associated BRCA1 or BRCA2 mutations and other women at highest risk for HBOC syndrome, who have chosen prophylactic surgery, that bilateral salpingo-oophorectomy and complete hysterectomy are the surest means to reduce the risk of genetically determined cancers and disseminated intra-abdominal carcinomatosis that may arise from the ovary, fallopian tube, and perhaps from endometrial epithelium.

Although the risk for ovarian cancer in BRCA1 and BRCA2 mutation carriers exceeds population risk for this disease even at ages of 39 years and younger, data from the literature indicates that the cumulative incidence for ovarian cancer in
BRCA1 and BRCA2 mutation carriers is quite low before the age of 40 years (King et al., 2003; Milne et al., 2008; Satagopan et al., 2002). Satagopan et al. (2002) calculated ovarian cancer penetrance of only 3% (95% CI = 1–7%) before age 40 years in BRCA1 mutation carriers and just 0.7% (95% CI = 0–1%) before age 40 years in BRCA2 mutation carriers. In the Creighton database, 51 years was the median age at which ovarian cancer was diagnosed in both BRCA1 (age range, 33–73 years) and BRCA2 (age range, 30–73 years) mutation carriers. Eight percent of the ovarian cancers in BRCA1 and BRCA2 mutation carriers in our registry were diagnosed before age 40 years, but only 18% were diagnosed before their 45th birthday (CLS, unpublished data). So, although the risk for ovarian carcinoma in carriers of cancer-associated mutations in BRCA1 and BRCA2 before age 40 years may be relatively small, this risk is not insignificant, and patients should be counseled accordingly. If women, well informed of their genetic risk for ovarian cancer, are willing to accept these risks to complete their plans for childbearing, they should be offered the best available surveillance until they may elect to proceed with prophylactic surgery, preferably, if they choose, before age 40 years.

The Prevention and Observation of Surgical Endpoints ("PROSE") Study group found that the observed favorable reduction of breast cancer risk by some 56% in BRCA1 mutation carriers and 46% in BRCA2 mutation carriers who have undergone oophorectomy was not obviated at least by the short-term use up to 3.6 years of estrogen replacement therapy (Eisen et al., 2005; Rebbeck et al., 2005). Because the fourth and fifth decades of life are still relatively early for women to lose the favorable effects of endogenous estrogen, well earlier than the expected age of natural menopause, many who elect prophyllactic salpingo-oophorectomy will choose transplant estrogen hormone replacement therapy for relief of postmenopausal symptoms and protection against premature osteoporosis. However, unopposed exogenous estrogen replacement therapy is by now an established risk factor for endometrial carcinoma (Casey, 1977; Feeley and Wells, 2001; Gambrell, 1977; Gambrell et al., 1983; Jick et al., 1993). Although it has been expected that sufficiently protracted treatment with progestins along with continuous estrogen replacement may be protective against endometrial hyperplasia and thence carcinoma (Feeley and Wells, 2001; Gambrell et al., 1983; Jick et al., 1993; Newcomb and Trinh-Dietz, 2003), a recent analysis of data from the National Cancer Institute’s Breast Cancer Detection Project calls into question the protective effect of progestins against endometrial cancer in women receiving estrogen replacement, and protracted use may increase the risk for breast cancer (Lacey et al., 2005). Lacey et al. (2005) of the National Cancer Institute Division of Epidemiology analyzed the records of 541 endometrial carcinoma patients enrolled in the study and determined an increased relative risk (RR) for this disease of 3.0 (95% CI = 2.0–4.6) in women receiving estrogen replacement with <15 days/month of sequential progestin and an RR of 2.3 (95% CI = 1.3–4.0) in women on continuous >15 days/month regimens compared with those who received no hormone therapy at all (Lacey et al., 2005). Other women at increased hereditary risk for both breast and ovarian cancers will be prescribed selective estrogen receptor modulators (SERMs) for chemoprophylaxis or treatment of breast cancer (Cuzick et al., 2003; Fisher et al., 1998; King et al., 2001; Narod et al., 2000; Vogel et al., 2006) and skeletal support (Chang et al., 1996) after surgical removal of their ovaries. While tamoxifen may decrease the risk of breast cancer in both BRCA1 (Narod et al., 2000) and BRCA2 (King et al., 2001) mutation carriers, use of this SERM has been associated with increased risk for endometrial carcinoma (Bergman et al., 2000; Bernstein et al., 1999; Fisher et al., 1998; Matsuyama et al., 2000; Mignotte et al., 1998; Peters-Engl et al., 1999; Pukkala et al., 2002; Ursic-Vrscak et al., 2001). Although later generation SERMs, such as raloxifene, as yet have not been associated with the significantly increased risks for endometrial cancer that were found in patients treated with tamoxifen (Cauley et al., 2001; Martino et al., 2004; Vogel et al., 2006), the effectiveness of later SERMs for protecting against breast cancer in genetically susceptible women has not been established (Shelly et al., 2008). With these considerations, we believe that hysterectomy at the time of salpingo-oophorectomy in members of HBOC syndrome families further simplifies decisions regarding hormone replacement, chemoprophylaxis and treatment in women so highly at risk for breast, ovarian, fallopian tube and, perhaps, endometrial carcinomas with poor prognosis.

Currently available techniques for ovarian cancer screening are far from satisfactory. Nonetheless, for BRCA1 and BRCA2 mutation carriers and others at high risk for ovarian carcinomas who delay prophylactic or indicated salpingo-oophorectomy and hysterectomy, we offer surveillance using currently available screening methods. Albeit, the potential for early detection of invasive ovarian carcinomas in high-risk patients through transvaginal ultrasound screening is problematic. van Nagell et al. (2000) published the 12-year results from their University of Kentucky annual screening program that involved transvaginal ultrasound scans on 14,469 women over age 50 years or over age 25 years with at least one first- or second-degree relative who had ovarian cancer. They reported that all 11 patients whose ovarian tumors were detected while confined to the ovary and 3 patients with ovarian tumors detected while limited to the pelvis were alive without evidence of ovarian cancer 1.8–9.8 years (median, 4.5 years) after their diagnoses. However, inspection of this series reveals that 2 of the 11 tumors detected while still confined to the ovary were borderline (18%) and 2 of the other early ovarian tumors were granulosa cell tumors (18%); on the other hand, 3 of the ovarian carcinomas that were detected by screening, 4 interval ovarian carcinomas that were diagnosed <12 months after falsely negative transvaginal ultrasound scans and multiple screenings and 4 symptomatic ovarian carcinomas, diagnosed at 14, 15, 20 and 62 months respectively following their last screening tests, already were disseminated to the upper abdomen. Only one invasive ovarian carcinoma was diagnosed in a women younger than 40 years in van Nagell’s series. Even in the screening of postmenopausal women, Kobayashi et al. (2008) found no significant difference in the overall detection and proportion of primary carcinomas diagnosed by histological types and/or while still confined to the ovary between subjects prospectively randomized to a program of physical examination, ultrasound scanning and serum CA-125 determinations and control subjects randomized to routine follow-up over 3–14 years (mean, 5.4 years). Kobayashi et al. reported that 63% of
of ovarian cancer during 16 months mean follow-up. The first and second screenings of the remaining women detected just one primary carcinoma still confined to the ovary and one borderline ovarian tumor, but 2 disseminated intra-abdominal carcinomas were detected during the first screening and 4 more patients were diagnosed with disseminated carcinomas during the next 12 months (Gaarenstroom et al., 2006). In another Dutch study, Oei et al. (2006) similarly offered DNA mutation analysis followed by either prophylactic salpingo-oophorectomy or annual surveillance with physical examinations, transvaginal ultrasound scanning, and serum CA-125 testing to 512 women at high risk for ovarian cancer by family histories. Of those who had DNA testing, 265 were found to be actual carriers of BRCA1 and/or BRCA2 mutations. Surveillance was chosen by 343 of all subjects in this study with their screening beginning between ages 20 and 75 years (median 42 years). Seventy-three per cent of those choosing surveillance were premenopausal. A third of the subjects (169/512 = 33%) elected prophylactic salpingo-oophorectomy, and their median age was 45 years (range, 29–70 years). One ovarian cancer was found among those electing surgery, and this was in a 60-year-old BRCA2 mutation carrier with prior breast cancer who had a primary carcinoma extended beyond the ovary but still limited to the pelvis. During the median follow-up time of 2.07 years (range, 0–9.4 years), Oei et al. found persisting abnormalities on screening tests which led to 24 diagnostic operations with the discovery of one disseminated ovarian carcinoma in a 52-year-old BRCA1 mutation carrier with history of a previous breast cancer (Oei et al., 2006).

Both van Nagell et al. (2000) at the University of Kentucky and Bosse et al. (2006) at the University of Cologne commented on the low positive predictive values (PPV) of 9.4% and 10% from their respective screening studies. Olivier et al. (2006), whose cases were composed of 49% known BRCA1 and BRCA2 mutation carriers, determined that the PPV from their combined screening methods, using physical examination, transvaginal ultrasound scanning, and serum CA-125 determinations, was only 40%. While PPV and specificity are important when considering all screening modalities, even the demonstration of nonfunctional ovarian cysts and tumors that have led to reported low PPV and low specificity values with transvaginal ultrasound scanning and tumor marker determinations that would not be efficacious in populations with relatively low prevalence of ovarian cancer, the use of these methods is not precluded for surveillance of premenopausal women at high genetic risk for gynecological tumors. We believe that the reported low yields of early ovarian carcinoma from surgical exploration prompted by the results of transvaginal ultrasound scans and tumor marker determinations ought not preclude offering these methods in the periodic surveillance of women at risk for carcinomas of the HBOC syndrome proven through extended pedigree analysis and/or by DNA testing for cancer-associated BRCA1 or BRCA2 germline mutations.

A further problem arises in the care of women whose personal and/or family histories suggest that they may be at risk for gynecologic cancers, but who decline mutation tests or whose results have not demonstrated deleterious mutations in BRCA1 or BRCA2 (see Figure 13). For, as noted (vide supra), data from the Breast Cancer Linkage Consortium (Ford et al.,
Figure 13 - This remarkable family contains an excess of ovarian carcinoma in association with carcinoma of the breast. It appears from the clinical standpoint to be a classical HBOC kindred. However, BRCA1, BRCA2, p53, and PTEN have all been evaluated only to find a complete absence of any cancer-causing mutations. This pedigree clearly shows the diagnostic dilemma that may take place in assessing pedigrees with the advantage of a molecular genetic search for cancer-causing germline mutations while turning up an absence of any diagnostic certainty.
indicate that families afflicted with four or more breast cancers and even one ovarian cancer in their lineage are likely linked to either BRCA1 or BRCA2 mutations. Kauff et al. (2005) at the Memorial Sloan-Kettering Cancer Center in New York City addressed this matter by enrolling 184 such women, whom they considered to be at “intermediate risk” for ovarian cancer, into a screening program of semi-annual physical examinations, transvaginal ultrasound scans, and serum CA-125 determinations. All subjects were age 30 years or older, and the mean age was 50 years; 50% were post-menopause, 61% had a personal history of previous breast cancer, and 50% were of Ashkenazi Jewish descent. As may be expected, no gynecological cancers were detected in this small group of intermediate risk women, all followed fewer than 4 years (mean follow-up, 19.9 months; range, 4.4–41.7 months), but abnormal ultrasound findings led to endometrial sampling in 13 asymptomatic women of unreported age and menopausal status. Short-term follow-up was necessary because of findings in 19.4% of ultrasound scans, and 4.7% of serum CA-125 results were abnormal in premenopausal patients; while during the study there was a mean progressive decline in self-assessed Quality of Life among those who participated (Kauff et al., 2005). These issues therefore must be completely reviewed and discussed with women of both high and intermediate genetic risks for gynecologic cancers, when they are considering their options and timing for surveillance and surgical prophylaxis.

A comprehensive approach based on these principles, such as that detailed in a report by the Clinical Genetics Group at Memorial Sloan-Kettering Cancer Center, seems at present to be promising (Scheuer et al., 2002). Scheuer et al. (2002) counseled and offered DNA testing for cancer-associated mutations in BRCA1 and BRCA2 to 1865 women from whom 267 subjects were found to be mutation carriers. Two hundred and thirty-three female mutation carriers, two-thirds in BRCA1 and one-third in BRCA2, were involved in protocols which offered prophylactic risk-reducing surgery or surveillance for breast and ovarian cancers. Twenty-one of these women had a personal history of ovarian cancer, and 29 women already had undergone bilateral oophorectomy. Of the remaining 179 women, 90 (50%) chose to have prophylactic bilateral salpingo-oophorectomy, and 20% of these were done with concomitant hysterectomy (Scheuer et al., 2002). At the time of this surgery, one 51-year-old woman was found to have a primary cancer confined to her ovary and another woman, age 46 years, had an in situ carcinoma in her fallopian tube. Both of these unsuspected gynecological cancers were in subjects with normal transvaginal ultrasound scans less than a month before surgery, and the latter patient had a normal serum CA-125 titer shortly before surgery. Overall, 78% of mutation carriers younger than 40 years opted for surveillance with physical examinations, transvaginal ultrasound scanning, and serum CA-125 determinations, whereas only 36% of the mutation carriers aged 40 years and older chose surveillance. In 84 of these patients for whom ovarian screening data were available, abnormal transvaginal ultrasound scans or elevated serum CA-125 titers were found in 22 subjects (36%) of whom 10 were subjected to surgical intervention with the detection of 4 ovarian and one peritoneal carcinoma involving the ovary. Three of the 4 ovarian cancer patients and the patient with peritoneal carcinoma had elevated serum CA-125 titers. All 4 ovarian cancer patients had persistent complex pelvic masses, and 3 of the 4 (75%) had cancers still confined to the ovary. Six of the 7 gynecological cancers in this series were in BRCA1 mutation carriers, and only one was in a BRCA2 mutation carrier. No interval gynecological or peritoneal cancers were diagnosed during intervals between semi-annual screening (Scheuer et al., 2002). This raises the serious question, when caring for female members of HBOC syndrome families, of who should be offered the option of prophylactic surgery? Mæhle et al. (2008) in Norway identified 1582 women deemed to be at very high risk for ovarian cancer because of their family histories, including known carriers of cancer-associated BRCA1 and BRCA2 mutations. These women were offered prophylactic salpingo-oophorectomy or screening with annual transvaginal ultrasound screening and serum CA-125 determinations. Eleven gynecologic tumors were diagnosed during the initial screening, and 7 further gynecologic tumors were found during follow-up. A total of 781 subjects chose prophylactic surgery either initially or during follow-up, and 27 cancers were found or later reported in this group. What is most remarkable in this series of Mæhle et al. is that all but one of 47 invasive carcinomas of the ovary (40), fallopian tube (1), and peritoneum (6) were in BRCA1 (45/47 = 96%) or BRCA2 (1.47 = 2%) mutation carriers (Mæhle et al., 2008).

In the case of known and likely mutation carriers from HBOC syndrome kindreds, we consider surveillance programs employing thorough history and physical examinations, ultrasound scans and serum tumor marker determination at best to be temporizing until better methods become available for the detection of early ovarian carcinoma or until such high-risk patients ultimately undergo prophylactic surgery. When persisting abnormalities suspicious for nonfunctional ovarian tumors are found on ultrasound scans and/or suspicious serum tumor marker elevations are determined, whether predicting benign or malignant lesions, we advocate counseling not only for invasive operative procedures but also for possible prophylactic surgery, whatever may be the intraoperative findings, as well as explanation of the procedures, their purpose and possible untoward effects, along with consent and preparation for major cancer debulking procedures. Our first step in the operating protocol, unless technically contraindicated, is thorough exploratory laparoscopy, collection of cytological and histological specimens for diagnosis, then either termination or, depending on our patient’s desire for further childbearing and her age, proceeding with prophylactic adnexectomy and hysterectomy. Although others subsequently have reported successful use of laparoscopy for prophylactic removal of the ovaries in women at hereditary risk for ovarian cancer (Eltabbakh et al., 1999; Morice et al., 1999), long before this we advocated laparoscopic examination and assisted transvaginal bilateral salpingo-oophorectomy with hysterectomy in women at genetic risk for gynecologic cancers (Casey et al., 1995). Unless technically contraindicated, we believe that videolaparoscopy provides excellent exploration, retrieval of peritoneal fluid and washings for cytology and biopsies as may be indicated, to be safely followed by assisted wide adnexectomy incorporating the entire fallopian tubes and ovaries removed en bloc with vaginal
hysterectomy (Casey et al., 1994, 1995). If gross cancer is discovered at laparoscopy the patient will have been counseled, consented, and prepared for appropriate tumor extirpation.

9.3. Follow-up after Prophylactic Salpingo-oophorectomy

Although prophylactic salpingo-oophorectomy reduces the likelihood of disseminated gynecological and peritoneal cancers in women from HBOC syndrome families, these women remain at lifetime risk for intra-abdominal carcinomatosis (Casey et al., 2005; Casey and Bewtra, 2004; Kauff et al., 2008; Rebbeck et al., 2002; Struwing et al., 1995). From among 1291 women who were screened and followed at the Gilda Radner Ovarian Cancer Detection Program in Los Angeles, Liede et al. (2002) selected a series of 290 Ashkenazi Jewish women with family histories of ovarian cancer at any age or breast cancer younger than 50 years in a first- or second-degree relative. Subjects were counseled, offered testing for the BRCA1 185delAG and 5382insC mutations and the BRCA2 6174delT mutation often found in this population, and they were screened and followed with transvaginal ultrasound scans and serum CA-125 determinations. The mean age at which these subjects entered their program was 44.8 years, and 15% ultimately elected prophylactic salpingo-oophorectomy between 1 year and 9 years after they entered. During a mean follow-up time of 5.3 ± 2.2 years in all participants and 7.2 ± 1.7 years in 33 participants who tested positive for the Ashkenazi BRCA1 or BRCA2 mutations, 9 women were diagnosed with pelvic-abdominal malignancies, including one patient with uterine cervix cancer, 2 ovarian carcinomas, 5 peritoneal carcinomas, and one fallopian tube carcinoma. All of the ovarian, peritoneal and fallopian tube cancers were papillary serous carcinomas and 7 of these 8 cancers were in carriers of the BRCA1 185delAG mutation. One of the ovarian cancer patients and the patient who was diagnosed with cervical cancer were not mutation carriers. Only one of the 8 ovarian, peritoneal, and fallopian tube cancers was detected by transvaginal ultrasound scan while still confined. Serum CA-125 titers were elevated in 3 of these cancer patients, and each had disseminated intra-abdominal carcinoma when diagnosed. All 5 of the peritoneal carcinoma patients had normal ovaries on ultrasound scans in the authors’ program or an affiliate 1–17 months (mean, 8 months) prior to the diagnosis (Liede et al., 2002). These results hold disappointing implications not only for the early diagnosis of gynecological cancers in women from HBOC syndrome families but also for the ability to offer early diagnosis of intra-abdominal carcinomatosis in women remaining at risk for peritoneal carcinoma following prophylactic surgery (Casey et al., 2005; Casey and Bewtra, 2004; Liede et al., 2002).

Currently, after prophylactic salpingo-oophorectomy with or without hysterectomy, we offer to follow patients because of their small but continued genetic risk for peritoneal carcinomatosis with at least yearly or at more frequent semi-annual intervals when proven and likely carriers of cancer-associated mutations so choose. Members of HBOC syndrome families are, of course, at high risk for breast cancer, which already may have been treated or for which they may remain at risk, and so they are counseled regarding prophylactic chemotherapy, mastectomy, and breast cancer screening. Patients whom we continue to follow are counseled to be alert to symptoms and signs that may be related to abdominal-pelvic cancer, while making every effort to allay anxiety and alarm. During visits, the physician examiner carefully dissects all of the patient’s complaints and performs a complete review of systems and physical examination, addressing the patient’s concerns and obtaining appropriate consultation, laboratory, and scanning studies as may be indicated. Although we cannot express confidence that improved outcomes will be achieved through pre-symptomatic detection of peritoneal carcinoma by abdominal–pelvic ultrasound scans and/or tumor marker tests, specifically serum CA-125 titer determinations for which we evaluate any persisting upward deviation, these screening methods usually are chosen by objectively-informed individuals, who are relieved by negative periodic examinations, that, confessedly, also are somewhat reassuring to us.

Clearly, much work needs to be done to expand and improve surveillance protocols for the early detection of ovarian, fallopian tube, and peritoneal carcinoma through the development of additional techniques and refinement in the use of those which are available, with critical analysis of the results of management if cancers are diagnosed.

9.4. Ovarian cancer associated with the Lynch syndrome

When analysis of family pedigrees implicates an individual to be at ≥50% risk of inheriting the autosomal dominant cancer-susceptibility traits of Lynch syndrome, and in those individuals in whom the personal and family risk assessment determines a high likelihood of inheriting predispositions to Lynch syndrome-related cancers, genetic counseling should be offered. In circumstances of known cancer-associated MMR gene mutations being carried within families and when specific MMR gene mutations are prevalent within determined populations, these individuals can be effectively tested; mutation carriers are then counseled and offered cancer-targeted management programs (Lu, 2008; Lynch and Casey, 2007; Lynch and de la Chapelle, 1999). See Table 1 for cardinal features of the Lynch syndrome.

Although combined estrogen–progestin oral contraceptives effectively reduce general population risks for both endometrial and ovarian cancers; and endometrial cytological and histological samplings can detect the presence of otherwise occult intrauterine cancer and transvaginal ultrasound scans are capable of demonstrating endometrial and ovarian abnormalities that portend endometrial and ovarian neoplasms and carcinomas, even in early stages (Bell et al., 1998; Bourne et al., 1993; Casey and Madden, 1976; Patai et al., 2002; Rijcken et al., 2003); as yet there are no available clinical studies to confirm the efficacy of these prophylactic and screening measures for preventing morbidity and mortality in Lynch syndrome families (Lu, 2008). On the other hand, Schmeler et al. (2006) retrospectively matched 61 cancer-associated MMR gene mutation carriers who had undergone hysterectomy with or without bilateral salpingo-oophorectomy with 210 MMR gene mutation carriers who had not undergone hysterectomy, and noted that occult endometrial cancer was found in 3 of the extirpated uteri. None of the 61 MMR gene
Mutation carriers who underwent hysterectomy developed either endometrial or ovarian cancer during an average of 13.3 years (range, 0.5–38 years) post-surgery follow-up; whereas, 32.7% (69/210) of the MMR gene mutation carriers who did not have surgery were diagnosed with endometrial cancer during average follow-up of only 7.4 years (range, 0.1–35 years). Schmeler et al. also matched 46 MMR gene mutation carriers who had undergone hysterectomy and bilateral salpingo-oophorectomy with 223 MMR gene mutation carriers who had not undergone hysterectomy, and they found that no ovarian or peritoneal cancers were diagnosed in the group which had had surgery compared with the diagnosis of ovarian cancer in 5.4% (12/223) of the group that did not have surgery during 20 years of follow-up. In this study, the median age at which ovarian cancer was diagnosed in the control group of MMR gene mutation carriers who did not have hysterectomy, and they found that no ovarian or peritoneal cancers were diagnosed in the group which had had surgery compared with the diagnosis of ovarian cancer in 5.4% (12/223) of the group that did not have surgery during 20 years of follow-up. In this study, the median age at which ovarian cancer was diagnosed in the control group of MMR gene mutation carriers who did not have hysterectomy was 46 years (range, 31–48 years), and the median age at which endometrial cancer was diagnosed in the control group who did not have hysterectomy was 46 years (range, 30–69 years) (Schmeler et al., 2006). So the problem is to develop management strategies that might be offered to protect carriers of mutated MMR genes and others at high risk for ovarian and endometrial cancers in Lynch syndrome families.

At the University Hospital Groningen in The Netherlands, Rijcken et al. (2003) enrolled 41 women into their screening program for members of Lynch syndrome families. Thirty-four of these subjects fulfilled the Amsterdam criteria for HNPCC families, but in retrospect 7 subjects were considered to have <25% risk of being an MMR gene mutation carrier. Eight of the women were proven to carry MLH1 mutations, 2 women carried mutations in MSH2, and one women carried a MSH6 mutation. Using annual physical examinations, transvaginal ultrasound scans, and serum CA-125 determinations, this group was screened for both endometrial and ovarian lesions. Abnormally thickened or irregular endometrium on ultrasound scans led to the diagnosis of atypical complex hyperplasia of the endometrium in 2 premenopausal and one postmenopausal enrollees. During the median follow-up of 5 years (range, 5 months to 11 years), one subject presented with postmenopausal bleeding just 5 months after a normal transvaginal sonogram demonstrated the endometrial thickness to be <5 mm, and endometrioid carcinoma with myometrial invasion though still confined to the uterine corpus was diagnosed. Eighteen other endometrial sampling procedures were done without recovery of pathological endometrium, 16 on premenopausal subjects and 2 on postmenopausal subjects, as a result of ultrasound abnormalities. All serum CA-125 titers were within normal range, and no ovarian abnormalities were demonstrated during this screening program of Lynch syndrome subjects. However, Rijcken et al. presented 24 cases of primary gynecologic cancers from Lynch syndrome patients in their database. These included 18 patients with endometrioid uterine carcinomas, 3 of which showed clear carcinoma components, and 3 of the endometrial cancers were accompanied with simultaneous primary ovarian carcinomas. Five primary ovarian carcinomas without co-existing uterine cancers were diagnosed; 3 of these were serous

### Table 1 – Cardinal features of Lynch syndrome.

- Autosomal dominant inheritance pattern seen for syndrome cancers in the family pedigree.
- Earlier average age of CRC onset than in the general population:
  - average age of 45 years in Lynch syndrome versus 63 years in the general population
- Proximal (right-sided) colonic cancer predilection:
  - 70–85% of Lynch syndrome CRCs are proximal to the splenic flexure.
- Accelerated carcinogenesis (tiny adenomas can develop into carcinomas more quickly):
  - within 2–3 years in Lynch syndrome versus 8–10 years in the general population
- High risk of additional CRCs:
  - 25–30% of patients having surgery for a Lynch syndrome-associated CRC will have a second primary CRC within 10 years of surgical resection if the surgery was less than a subtotal colectomy
- Increased risk for malignancy at certain extracolonic sites:
  - endometrium (40–60% lifetime risk for female mutation carriers)
  - ovary (12–15% lifetime risk for female mutation carriers)
  - stomach (higher risk in families indigenous to the Orient, reason unknown at this time)
  - small bowel
  - hepatobiliary tract
  - pancreas
  - upper uro-epithelial tract (transitional cell carcinoma of the ureter and renal pelvis)
  - brain (in the Turcot’s syndrome variant of the Lynch syndrome)
- Sebaceous adenomas, sebaceous carcinomas, and multiple keratoacanthomas in the Muir–Torre syndrome variant of Lynch syndrome
- Pathology of CRCs is more often poorly differentiated, with an excess of mucoid and signet-cell features, a Crohn’s-like reaction, and a significant excess of infiltrating lymphocytes within the tumor.
- Increased survival from CRC.
- The sine qua non for diagnosis is the identification of a germline mutation in a mismatch repair gene (most commonly MLH1, MSH2, or MSH6) that segregates in the family; i.e., members who carry the mutation show a much higher rate of syndrome-related cancers than those who do not carry the mutation.
ovarian carcinomas and 2 were endometrioid ovarian carcinomas. Thirteen of the 18 endometrial cancers in these women were still confined to the uterine corpus; none of the 13 endometrial cancers were deeply invasive and 8 of the 13 were well differentiated. Interestingly, in the Groningen database, 6 of the 7 (86%) ovarian cancers for which staging was noted were still confined to the ovary, and the other ovarian cancer was still within the pelvis when diagnosed, though 4 of these carcinomas were associated with malignant peritoneal cytology. Thus, in this series of gynecological cancers diagnosed in Lynch syndrome patients, 33% (8/24) of the cancers were either primary ovarian carcinomas or synchronous primary ovarian carcinomas co-existing with endometrial carcinomas. The mean age at which ovarian cancers were diagnosed in the Groningen series was 50 years (range, 40–61 years), but 4/8 (50%) of the ovarian cancers were diagnosed while patients still were in their fifth decades of life. The mean age of 45 years (range, 28–53 years) at which endometrial cancers were diagnosed was even younger. Forty-four per cent (8/18) of the endometrial cancers in this Lynch syndrome series were diagnosed during the fifth decade, and 3 were diagnosed in women younger than 40 years (Rijcken et al., 2003). In our own series, although the median age at which ovarian cancer was diagnosed in MMR gene mutation carriers was 46 years (range, 30–69 years), 18% of the ovarian cancers in mutation carriers were diagnosed before age 40 years, and 39% were before their 50th birthday (CLS, unpublished data).

One retrospective study of 269 women from English and Dutch registries whose pedigrees suggested them to be at 50% risk or more of carrying a dominantly inherited predisposition of Lynch syndrome, disclosed that no asymptomatic patient was detected by ultrasound scans with either endometrial or ovarian cancers during periods up to 13 years, and the only two patients who were found in this review to have been diagnosed with endometrial cancer both presented with symptomatic bleeding (Dove-Edwin et al., 2002). However, it should be noted that the older of these patients, a postmenopausal woman of 51 years followed seven years post-operatively for synchronous Duke’s A and B colorectal carcinomas, had only one negative trans-abdominal scan and was diagnosed with endometrial carcinoma confined to the uterine corpus, some 27 months thereafter (Dove-Edwin et al., 2002). We would ordinarily strongly recommend hysterectomy with bilateral adnexectomy at the time of colectomy in women of this age who are found to have two synchronous colorectal carcinomas and deemed to be a 50% or greater risk for Lynch syndrome. Moreover, while transvaginal ultrasound scanning is capable of detecting early ovarian cancer and, if negative, lessening the current risk for the presence of post-menopausal asymptomatic endometrial carcinomas, there is no evidence that trans-abdominal ultrasound scanning holds this same promise.

Renkonen-Sinisalo et al. (2006) provided surveillance for 175 asymptomatic Finnish women who were proven carriers of MMR gene mutations from 103 Lynch syndrome families employing not only transvaginal ultrasound scans and serum CA-125 determinations but also intrauterine endometrial sampling. They compared the results of this program with the diagnoses and outcomes of 83 endometrial cancer patients from the same families who presented with symptoms prior to and during their study. In this study, transvaginal ultrasound scans showed endometrial abnormalities in 4 patients with endometrioid carcinomas, 2 with associated clear cell carcinoma components, but ultrasound scans missed 6 additional cases of endometrial carcinoma that were detected with endometrial sampling. All except one of the endometrial cancers detected by screening were still confined to the uterine corpus. An additional 14 cases of complex endometrial hyperplasia, 4 with atypia, were picked up with endometrial sampling, but only 6 of these demonstrated endometrial abnormalities on ultrasound scans. During the median 3.7 years of follow-up, none of the women whose endometrial cancers were detected by screening died with this disease; whereas 6/83 (7%) of the symptomatic women died from their endometrial cancers. Four women enrolled in the Finnish gynecological surveillance program for MMR gene mutation carriers were diagnosed with endometrioid ovarian cancers, but none of these were detected by screening. Two of the ovarian cancers, one confined to the ovary and the other with intra-abdominal dissemination, were diagnosed in asymptomatic women, ages 45 years and 41 years, only 2 months and 5 months, respectively, after normal screening. Two of the ovarian carcinomas were diagnosed incidentally in women aged 42 years and 50 years, while still confined to the ovaries, during surgery for endometrial hyperplasia and carcinoma. Only 6 patients reported by Renkonen-Sinisalo et al. had serum CA-125 elevations, and half of these were transient. None of the ovarian cancer patients showed serum CA-125 elevations, and only one titer of 179 units/ml was associated with an endometrial carcinoma, which was found to have extended into the cervix when this was evaluated. In this series, the mean age of patients whose endometrial cancers were detected by screening was 51 years, which was comparable with the 50 year mean age of endometrial cancer diagnosis in the group’s symptomatic patients. The mean age of ovarian cancer diagnosis in this Finnish series of MMR gene mutation carriers was 44.5 years (range, 41–50 years), and 3 of the 4 women diagnosed with ovarian cancers because of symptoms or incidentally at surgery for endometrial neoplasms were still in their fifth decade, but none was younger than 40 years (Renkonen-Sinisalo et al., 2006).

Kwon et al. (2008b) at the University of Texas M.D. Anderson Cancer Center employed Markov decision models to analyze the cost-effectiveness and net benefit in quality-adjusted life years to test several management strategies for a hypothetical cohort of Lynch syndrome patients, and they concluded that annual surveillance with endometrial sampling, transvaginal ultrasound scans, and CA-125 determinations from age 30 years until prophylactic hysterectomy–salpingo-oophorectomy at age 40 years is the most effective cancer prevention strategy measured in quality-adjusted life years. Given the efficacy of endometrial cancer screening and later ages of ovarian cancer diagnosis in this series, with alertness to symptoms and signs and rapid diagnostic intervention if they occur, it is reasonable to support female carriers of MMR gene mutations, who choose to do so, by surveillance during the childbearing years of their third and fourth decades and until they may elect bilateral salpingo-oophorectomy–hysterectomy for surgical prophylaxis (Lynch and Casey, 2007).
Notwithstanding the disappointing results of the National Institutes of Health National Ovarian Cancer Early Detection Program, as noted in our discussion on management and screening of women at risk for HBOC, the selection criteria for that study favored subjects more likely to acquire perhaps more aggressive fast growing serous carcinomas rather than non-serous ovarian malignancies, such as may be more common in women from Lynch syndrome families (MJC, unpublished data; Fishman et al., 2005; Rijcken et al., 2003). Given that ovarian and endometrial carcinomas in MMR gene mutation carriers have been diagnosed as young as their 31st year in our Lynch syndrome cohort (CLS, unpublished data), and given lifetime risks of 6–12% for ovarian cancer and 30–60% for endometrial cancer in these subjects (Aarnio et al., 1999; Quehenberger et al., 2005; Vasen et al., 1996, 2001; Watson et al., 2008), and the fact that 5–10% of ovarian cancers in Lynch syndrome families were diagnosed before their 35th birthday (Brown et al., 2001; Watson et al., 2008), we recommend that young women from Lynch syndrome kindreds should receive professional cancer genetics counseling soon following their 21st birthday. Those who are found to carry cancer-associated MMR gene mutations, and obligate carriers, are advised to be engaged in programs of periodic transvaginal pelvis ultrasound scans and endometrial screening beginning in their 26th year until they elect prophylactic surgery, which may cautiously be delayed until they have completed child-bearing and before their fifth decade of life, when the risks for ovarian and endometrial cancers begin to substantially accumulate (CLS, unpublished data; Brown et al., 2001; Watson et al., 2008). With advances in surgical techniques, these procedures may be safely accomplished with laparoscopic assistance, delivering the uterus and adnexa en bloc through the vagina, while also permitting extensive direct video-visualization of the peritoneal cavity and affording the opportunity to collect samples for cytological and histological studies (Casey et al., 1994, 1995).

9.5. Future prospects: DNA variants modify HBOC and LS cancer risk

What does the future hold with respect to molecular genetics and cancer control in hereditary cancer, inclusive of HBOC and Lynch syndrome? This projection relates to the truism that cancer-causing mutations do not act in a vacuum, since they are likely to be impacted by additional low-penetrant modifier genes in concert with myriad environmental events. For example, in the HBOC syndrome, the work of Smith et al. (2007) estimated that in high-risk families the breast cancer risk might be caused not only by the BRCA2 mutation, but also may be increased by modifier genes. This is important, since in genetic counseling we have ensured mutation-negative family members from BRCA kindreds that they are at general population risk rather than at extremely high cancer risk. The implication is that they do not require intensive screening recommendation. However, if these findings are confirmed, then patients testing negative for a BRCA mutation in the setting of HBOC families with BRCA relatives, should be considered for continued surveillance, perhaps less than we would recommend they be positive for the BRCA mutation but, nevertheless, more than we would recommend for those individuals who are judged to be more truly sporadic and thereby at general population risk. However, these findings merit confirmation in a well-designed prospective study (Gronwald et al., 2007).

In the case of Lynch syndrome, Wijnen et al. (2009) have shown that genome-wide association studies have identified common low-risk variants impacting CRC. These investigators genotyped these variants in 675 individuals from the Dutch Lynch Syndrome Registry who were known carriers of Lynch syndrome-associated mutations. They genotyped 8q24.21, 8q23.3, 10p14, 11q23.1, 15q13.3, and 18q21.1. Results disclosed a significant association between CRC risk in these Lynch syndrome mutation carriers and the single nucleotide polymorphisms (SNPs) rs16892766 on chromosome 8q23.3 and rs3802842 on chromosome 11q23.1. They concluded that the two loci which they identified may be helpful in identifying Lynch syndrome family members who require more intensive surveillance specifically for CRC. The possibility exists that the presence of one of these identified low-risk variants may slightly increase risk of CRC for members of Lynch syndrome families who are negative for an MMR mutation.

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