Chapter 6

Cancer Genetics: Risks and Mechanisms of Cancer in Women with Inherited Susceptibility to Epithelial Ovarian Cancer

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Introduction

In the foreword to the first book on oncofertility by Woodruff and Snyder, the authors stated that oncofertility bridges traditional areas of basic science and medical science to provide reproductive options to young people who survive life-preserving but fertility-threatening treatments for cancer. A part of this cohort of reproductive-aged women also includes those who are "previvors": specifically, women at increased risk for malignancies for who prevention may entail interventions that can adversely affect their ability to conceive and carry a pregnancy. However, women who are at increased risk for ovarian cancer based on family history or the presence of genetic mutations that predispose them to develop ovarian cancer at a higher frequency and younger age than is typically observed in the general population face not only a highly lethal malignancy but also interventions that temporarily or permanently prevent them from having children. So while preventive and therapeutic interventions for other malignancies can adversely affect the ability of affected women to reproduce, epithelial ovarian cancer (EOC) is unique in that for the highest risk women, preventive interventions should usually occur during the reproductive years, and that the most effective prevention involves ovarian extirpation, removing the capacity to produce biologic offspring. Nonetheless, advancements described throughout this book have given promise to these very women.

Epithelial ovarian cancer is associated with profound morbidity and high rates of mortality for which no effective screening protocol has yet been developed. It is important to recognize that most epithelial ovarian cancers occur in postmenopausal women with no noteworthy family history and no detectable deleterious gene mutations; indeed, genetic alterations are not even detected in the majority of women who develop *premenopausal* ovarian cancer. Nonetheless, the presence of mutations in specific genes, most commonly BRCA1 and BRCA2, will predispose women to develop ovarian cancer at a markedly higher frequency and younger age not commonly observed in the general population. While there is little doubt that perturbations of other genes are responsible for the development of ovarian cancers and other solid tumors, our current knowledge of the "oncogenome" relevant to EOC is somewhat limited to several genes that have been associated with the development of ovarian tumors and malignancies.

There are effective preventive approaches for reproductive-aged women at increased risk for developing epithelial ovarian cancer; however, these are invariably associated with either fertility delay (oral contraceptives) or permanent infertility (tubal ligation, bilateral salpingoophorectomy). As such, the identification of reproductive-aged women at the highest risk for developing ovarian cancer must entail a discussion of these preventive approaches and should include a frank discussion of family planning and fertility preservation for those women seeking to become pregnant.

Our knowledge of the oncogenome continues to expand and provide important information for delineating mechanisms of tumorigenesis that are of considerable value in the development of effective preventive, screening, diagnostic, and therapeutic protocols. In this way, oncofertility provides a bridge from basic science to clinical practice that can empower reproductive-aged women to conceive despite undergoing interventions chosen to prevent or treat malignancy. To familiarize readers with those genetic findings that increase a woman's likelihood of developing ovarian cancer, this chapter will provide a review of the disease and genomic epidemiology of EOC and genetic mechanisms associated with a predisposition to the development of epithelial ovarian cancer.

Epithelial Ovarian Cancer

Most ovarian malignancies are epithelial in nature and are characterized by differing histological subtypes including serous, mucinous, endometrioid, and clear-cell tumors. While cervical cancer remains the most common cause of gynecologic cancer death worldwide, EOC is the leading cause of death from gynecologic malignancy in the developed world. It is estimated that EOC is diagnosed in approximately 200,000 women worldwide and results in the deaths of 120,000–130,000 women each year [1]. In the United States, there are approximately 22,000 new cases of ovarian cancer diagnosed, with more than 15,000 deaths attributed to EOC annually [2]. One reason for this difference in causes of gynecologic cancer death in the industrialized and developing world is that EOC usually does not present with unique symptoms that would indicate the presence of an early malignancy, such as what occurs with bleeding per vagina and endometrial cancer. Additionally, there is as yet no effective screening algorithm to identify women with early ovarian cancer, as is available worldwide with the Papanicolau smear and cervical dysplasia and cancer. While early stage EOC is associated with generally good clinical outcomes, most ovarian cancers (approximately 70%) are unfortunately detected at a more advanced stage and are associated with generally poor survival rates despite continuing advancements in surgical techniques and chemotherapy regimens [3].

In addition to the lack of unique associated symptoms and an effective screening protocol, no specific patient characteristics (e.g., obesity and endometrial cancer) or lifestyle issues (multiple sexual partners and cervical cancer) are strongly associated with the development of EOC. Nonetheless, reproductive history does provide some information in assessing a woman's risk for developing EOC. Nulliparous women in the general population are at a higher risk for developing EOC than those women who have

been delivered of children. The birth of the first child reduces one's risk for developing EOC by 45%, with each additional pregnancy further reducing that risk by 15% for each pregnancy [4]. However, this reduction in risk for developing EOC in the general population is not observed among women with certain predisposing gene mutations (BRCA); indeed, the risk for EOC in BRCA mutation carriers paradoxically appears to increase with the number of children [5]. Risk reduction for EOC in the general population is also observed among women who breastfeed their infants [6].

Family history of EOC is the strongest risk factor associated with an increased likelihood for developing EOC (outside of the hereditary cancer syndromes). A woman with a first-degree relative (e.g., mother, sister, daughter) with EOC will have her risk increased two- to threefold (1.5–4%) while two affected relatives will increase a woman's risk fivefold to 7% [7, 8]. An additional factor in assessing risk in women with a family history of EOC is the age at diagnosis; Auranen and colleagues [9] showed that affected relatives with a diagnosis of EOC before the age of 55 conveyed a higher risk than those relatives with EOC diagnosed after the age of 55.

Despite there being no effective screening modality yet developed for EOC, risk reduction can be achieved by high- and low-risk women. Oral contraceptive (OC) use has been shown to reduce the risk of developing EOC in all women regardless of their underlying risk strata; the longer the use, the greater the preventive effect [5]. More recent studies not only confirm this beneficial effect of OCs, but show that more modern pills exert a similar risk reduction to that observed with older and higher dosed pill regimens [10]. In most studies, the use of OCs in BRCA mutation carriers does not appear to be associated with a consistently increased risk for developing breast cancer [11]. Other interventions that have been associated with risk reduction include breast feeding, tubal ligation, and bilateral salpingoophorectomy (BSO) [5]. All of these interventions, including OCs, are associated with an inability to conceive, with tubal ligation and BSO associated with permanent sterilization. For reproductive-aged women seeking future childbearing, consideration of the timing of future pregnancies is thus critical in the choice of a risk-reducing intervention. While the removal of the tubes and ovaries is associated with the most profound reduction in risk, BSO is the one approach that prevents any possible future childbearing (assisted reproductive technologies can be used by women who have undergone tubal ligation) and when done before the onset of menopause, it is associated with an increased risk for premature cardiovascular morbidity and all-cause mortality if postoperative estrogen therapy is not initiated [12, 12A].

Heritable Cancer Syndromes and EOC

The majority of EOC cases occur in women without a family history, indicating an increased risk. However, approximately 5–10% of EOC cases are associated with the inheritance of genes that predispose individuals to develop EOC. The delineated hereditary cancer syndromes involving EOC include breast/ovarian syndrome, site-specific ovarian cancer syndrome, and Lynch syndrome (previously referred to as hereditary nonpolyposis colorectal cancer, or HNPCC syndrome). These cancer predisposition syndromes are the result of the autosomal dominant transmission of highly

penetrant germline mutations in tumor-suppressing genes. The inheritance of a mutated copy of one of these genes not only conveys a markedly increased risk for developing EOC but also increases the likelihood of developing the malignancy at a far younger age than is usually observed in the general population. It is this characteristic of hereditary ovarian cancer that profoundly impacts the woman found to be a carrier of an inherited mutation in a tumor-suppressing gene and leads many to the consideration of risk reducing interventions that impact the ability to conceive and may preclude the possibility of any future pregnancies.

Genetic Mechanisms

The increased risk for developing cancer in women with mutations in cancer susceptibility genes invariably begins with the inheritance of a germline mutation from either parent. While EOC can only occur in females, genes that predispose to the development of EOC are autosomal in nature and thus can be inherited from either parent. This concept is critical with regard to family history information as both parents can transmit gene mutations; accordingly, obtaining careful family histories of an individual's maternal and paternal families is paramount to developing an accurate risk assessment.

By definition, this germline mutation is present at conception and thus every cell of the individual will have the gene mutation, a fact likely associated with the multiorgan effect of many cancer susceptibility genes. Nonetheless, the inheritance of a cancer susceptibility allele is only the *first* step in promoting the development of EOC. Its mere presence does not guarantee that an individual with an inherited susceptibility gene mutation will go on to develop EOC.

The development of EOC, as well as other heritable cancers, depends on the occurrence of a *second* step [13]. That an individual has inherited the first "step" serves to explain why such individuals have a higher risk for developing cancer than the general population and that the malignancy usually occurs at a younger age and why it is more likely to occur bilaterally than in the general population. Cancer is a disease of somatic cells; however, if two (or more) events are needed for the cells to become malignant, then inheriting the first step, as opposed to waiting for it to occur through environmental impact, will surely increase the likelihood of it occurring compared to those who do not inherit such mutations. The second (and any subsequent) step is invariably somatic in nature, also explaining why not everyone who inherits a susceptibility gene develops the malignancy. Molecular studies of cancers in individuals with malignancies arising from hereditary cancer syndromes frequently show a loss of heterozygosity at the genomic position of the tumor suppressor gene in tumor tissue. The loss in heterozygosity is the second step in the development of malignancies in individuals who have inherited mutated susceptibility genes.

There are numerous mechanisms that likely lead to this loss of heterozygosity and, thus, inactivation of the tumor suppressing gene. While such cellular and nuclear events are common and widespread mechanisms and are mostly random processes by which genes

and chromosomes are deleted, replaced, or rearranged, in the presence of an inherited gene mutation, such events can lead to the inactivation of tumor-suppressing gene function and predispose that organ to undergo malignant transformation. In such cases, this process is known as biallelic inactivation. Inherited biallelic mutations are exceedingly rare and present with a different clinical presentation than that described with monoallelic (dominant) inheritance.

It is interesting to note that while most hereditary cancer syndromes, including EOC, are mostly transmitted in and present as a classic autosomal dominant inherited condition, the requirement of a second step that inactivates both alleles (biallelic inactivation) makes the cellular mechanism necessary for the promotion of tumorigenesis to be recessive in nature.

Heritable Cancer Syndromes and EOC

Hereditary Breast and Ovarian Cancer (HBOC)

Hereditary breast and ovarian cancer syndrome (HBOC) is characterized by families with multiple members with breast cancer and EOC, with most such families having more cases of breast cancer than ovarian cancer. HBOC families, like other families with hereditary cancer predisposition syndromes, are characterized by a far earlier age of onset than is seen in the general population, as well as a higher likelihood of bilateral disease. In addition, HBOC families have a markedly higher frequency of family members with breast cancer and EOC occurring in the same individual and for some gene mutations, a strikingly higher risk for breast cancer in men.

The majority of families with HBOC have inherited mutations in two tumorsuppressing genes, BRCA1 and BRCA2. A recent study by Ramus and colleagues [14] showed that 81% of families with at least two cases of EOC and one case of breast cancer had a deleterious mutation in BRCA1 or BRCA2, thus confirming earlier studies and models demonstrating that the majority of cases of HBOC are associated with BRCA1/2 mutations [15].

BRCA1 is located on chromosome 17q21, contains 22 coding exons, and spans 80 kb DNA (Fig. 6.1), whereas BRCA2 is located on chromosome 13q12-13, contains 26 coding exons and spans 70 kb DNA (Fig. 6.2). Both genes are part of the DNA break repair pathway and appear to function as tumor-suppressor genes, with mutations resulting in highly penetrant susceptibility to EOC and breast cancer. Mutations of BRCA1 and BRCA2 associated with the development of EOC and breast cancer are found throughout the coding regions and at splice sites. Most of these mutations are small insertions or deletions that lead to frameshift mutations, nonsense mutations, or splice site alterations [16], all of which lead to premature protein termination and altered or absent proteins. In addition to these mutations BRCA1
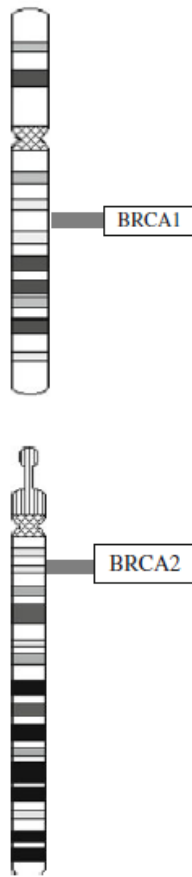
Fig. 6.1 BRCA1 locus on chromosome 17 BRCA2
Fig. 6.2 BRCA2 locus on chromosome 13

and some missense mutations, large deletions and rearrangements not detectable by standard PCR have been identified and are now part of the molecular testing provided to those undergoing BRCA analysis. Indeed, these large genomic alterations have been found to be relatively common in some populations from central Europe and the US [17]. As BRCA1 and BRCA2 are autosomal genes with high penetrance, transmission can occur either maternally or paternally; accordingly, equal attention must be paid to the paternal relatives of a woman being evaluated for a possible BRCA mutation. BRCA1 mutations do not frequently result in increased risk for cancer in men, whereas BRCA2 mutations increase the risk for male breast cancer; nonetheless, the relative dearth of paternally based malignancies must not deter one from considering a paternally transmitted BRCA mutation. Kessler and colleagues (Personal communication) found that among individuals at increased risk for heritable colon cancer, an equal distribution of paternal and maternal transmission of deleterious (and autosomal) genes was found. However, among individuals at increased risk for HBOC, an approximately 70/30 (maternal to paternal) distribution was delineated. This is despite the fact that genes

causing HBOC are autosomal and thus should be equally distributed between paternal and maternal lines of transmission. While those families with either few members or few females pose a challenge in counseling, as affected females provide the main evidence of the existence of a deleterious BRCA mutation, this perceived skewing of parental transmission shows that in many cases, affected females in the paternal lineage are either ignored or not considered on an equal status with affected members from the maternal lineage. This may occur because of a misperception that HBOC is a disease of women and that genetic events in paternal families do not play an important role.

The frequency of BRCA1 or BRCA2 mutations in the general population is estimated to be 1/300 to 1/800 [18]. BRCA mutations are found in approximately 6–8% of EOC cases, but in 80–90% of hereditary breast-ovarian cancer syndrome [2]. However, some populations and communities have a higher frequency of BRCA mutations than is found in the general population. In the United States, BRCA mutations are found in approximately 1 of every 40 individuals of Eastern European (Ashkenazi) Jewish ancestry, a frequency far higher than the general US population. What also distinguishes this community is that three mutations (185delAG and 5382insC in BRCA1 and 6174delT in BRCA2) account for approximately 98% of mutations detected. In Iceland, the 999del5 mutation in BRCA2 accounts for approximately 7% of all cases of EOC occurring in Icelanders. These mutations are known as "founder mutations," so named because in certain populations begun by a small ancestral group initially isolated by societal behavior or geography, certain genes in the original "founders" of a population can become far more common in succeeding generations than would occur in the general population.

The identification of founder mutations allows for more facile screening of individuals of those groups associated with founder mutations. As such, evaluating individuals of Eastern European Jewish ancestry for a BRCA1 or BRCA2 mutation is now accomplished by first determining the presence of one of these three mutations, unless previous analysis of an affected relative revealed a different (nonfounder) BRCA mutation associated with breast or ovarian cancer. However, even in some of these situations, a "single site" analysis would potentially be augmented with a founder mutation analysis if the family history indicates that another mutation may be present. If testing for a founder mutation is found to be negative, then gene sequencing and rearrangement analysis should be offered to provide a complete and thorough molecular evaluation.

BRCA1 mutations appear to confer a higher risk for developing EOC than BRCA2 mutations. Satagopan and colleagues [19] found that carriers of either of the two BRCA1 founder mutations in the Ashkenazi Jewish population (185delAG and 5382insC) were estimated to have a 37% risk for developing EOC by the age of 70, whereas those carrying the founder BRCA2 mutation (6174delT) were estimated to have a 21% risk. Mutations of either BRCA gene are associated mostly with the development of serous epithelial ovarian cancers, as opposed to mucinous or other histologic subtypes. Of interest is that the risk for developing breast cancer among carriers of all three founder mutations is similar and estimated to be approximately 85% by the age of 70.

Site-Specific Ovarian Cancer

Site-specific ovarian cancer syndrome is not associated with a single susceptibility gene; rather, it is a term used to describe families with several first- and seconddegree relatives with EOC. In actuality, it is used to describe families with several relatives with EOC, but with no relatives with breast cancer, endometrial cancer, colon cancer, or any of the other malignancies associated other hereditary cancer syndromes. While it is unlikely that site-specific ovarian cancer syndrome is caused by a gene or genes not yet identified, it may be a variant of a recognized heritable cancer syndrome, meaning that EOC either presents prior to the other associated malignancies or is representative of a genetic variant presenting with an overwhelming predominance of EOC over other malignancies.

In many of the families, site-specific ovarian cancer syndrome may appear to be transmitted in a dominant fashion. However, Stratton and colleagues [7] estimated the risk of EOC in such families to be 5%, considerably less than the 50% associated with a dominantly inherited condition. However, this same group [20] later estimated the risk to be higher, concluding that even when a BRCA mutation is not detected, that the prevailing risk model explains that most cases of familial EOC are associated with BRCA mutations, with the others attributed to sporadic clusters and issues of sensitivity of the mutational assays.

Regardless of whether the site-specific ovarian cancer syndrome is a variant of the HBOC or Lynch syndrome, or represents the phenotypic expression of susceptibility genes different from those that cause HBOC or Lynch syndrome, patients from such families carry increased risk for the development of EOC and should be offered ongoing evaluation and preventive interventions similar to that provided to women from families known to have a recognized cancer susceptibility genetic syndrome.

Lynch Syndrome

Colon cancer is the preeminent malignancy of this hereditary cancer syndrome, previously known as hereditary nonpolyposis colorectal cancer (HNPCC) syndrome. Indeed, Lynch syndrome (previously divided into Lynch I or Lynch II) is the most common cause of hereditary colorectal cancer. As with other cancer susceptibility syndromes, Lynch syndrome is associated with an increased risk for cancers in multiple organs including endometrial, urogenital, pancreatic, and biliary tract and EOC. Of note is that more recent study of Lynch families shows that female members of these families have a higher cumulative lifetime risk for developing endometrial cancer than for developing colorectal cancer [2].

Lynch syndrome is a result of gene mutations in the multistep mismatch repair system (MMR). MMR genes are located on five different chromosomes and encode for proteins that recognize and repair damage in the DNA that leads to DNA mismatches. One complex of proteins consisting of the protein MSH2 combined with MSH6 or MSH3 recognizes the DNA mismatch and binds to the site. An inactivating mutation of MSH2 blocks the ability to recognize a DNA mismatch negating the function of this complex.

Mutations of either MSH6 or MSH3, on the other hand, may not have a similar deleterious effect as these two proteins have overlapping functions and thus an inactivating or adverse mutation in one may not adversely affect the function of the overall MMR system. Once the mismatch is recognized, MLH1 (with PMS1 or PMS2) then provides the necessary steps to resynthesize the DNA strand in its original and correct sequence. A total of seven MMR enzymes have been delineated and mutations in each of the seven genes have been identified (Table 6.1) [21]. Mutations in the MLH1 and MSH2 genes are the most common and account for approximately 90% of observed mutations, followed in frequency by mutations in MSH6 and PMS2. Mutations in the remaining three genes are rarely observed in Lynch syndrome families.

Table 6.1 Genes associated with mismatch repair system

Gene name	Frequency in Lynch pts	Chromosome locus
MLH1	40–45%	3p21.3
MSH2	40–45%	2p22-p21
MSH6	7–10%	2p16
PMS1	unknown	2q31-q33
PMS2	<5%	7p22
MSH3	0	5q11-q12
MLH3	0	14q24.3

The type of MMR mutation provides important information as to the risk for developing a particular malignancy in women with Lynch syndrome mutations. Watson et al. [22] reported that the risk for EOCwas significantly higher in families with MSH2 mutations compared to families with MLH1 mutations. Analogously, Wijnen et al. [23] found that women carryingMSH6 mutations were twice as likely to develop endometrial cancer as women who carried MSH2 or MLH1 mutations.

It was surmised that the genetic mechanism for the increased risk for carcinogenesis in cases of MMR gene mutations was similar to that of BRCA mutations; namely, that dominant inheritance of a mutation provided for the germinal "firststep" and that a second somatic step led to the loss of the normal or "wild-type" co-allele and that this loss of heterozygosity eventually promoted the cellular aberration that resulted in malignant transformation of the cell and, eventually, organ. However, Aaltonen and colleagues [24] found no loss of heterozygosity at a locus coinciding with the MSH2 site on chromosome 2 linked to colorectal cancer in 14 cases from 3 families, suggesting a cellular mechanism different from the conventional mechanism attributed to biallelic inactivation and alteration of tumorsuppressing gene function in the development of tumors. Another explanation for the findings by Aaltonen and colleagues is that the MMR gene mutation, without the loss of heterozygosity, adversely affects the DNA mismatch repair mechanism, leading to a "domino-like" dysfunctional cascade on those cellular mechanisms responsible for proper growth and function. Perhaps the surprising findings of no loss of heterozygosity in Lynch colorectal cancer cases indicates that the genes being disrupted in the Lynch syndrome are those genes responsible for maintaining the proper DNA sequence and that adversely affecting their function, even with a only single allele and the maintenance of the wild-type allele, may be sufficient to initiate abnormal cellular and nuclear processes that lead to carcinogenesis.

These inactivating mutations not only prevent the repair of damaged DNA but also increase the rate of mutations at the DNA microsatellites of growth-regulating genes. Microsatellites are short (1–5 base pairs), polymorphic DNA sequences that are repeated 15–30 times at a given locus and distributed throughout the genome. Microsatellite instability (MSI) thus serves as a marker for MMR mutations; indeed, analysis for microsatellite instability or immunohistochemical (IHC) staining is the first diagnostic step in determining the presence of a DNA repair defect for many individuals at increased risk for MMR mutations. IHC can evaluate tumor tissue for the presence or absence of the proteins MLH1, MSH2, MSH6, and PMS2 but cannot assess the functionality of any of these proteins. As such, IHC cannot determine whether the protein present does not function properly because of a missense mutation and thus cannot definitively identify the gene with the mutation; accordingly, IHC should be combined with MSI to screen prospective tumors for MMR mutations. MSI is a common feature of Lynch-associated tumors; however, studies of MSI in ovarian tumor tissue from EOC have not provided consistent diagnostic correlation.

Although mutations of BRCA1/2 account for the majority of cases of hereditary EOC, Lynch syndrome mutations account for a small proportion of all cases of EOC [25]. Ovarian cancers associated with BRCA mutations are mostly serous in nature; conversely, MMR mutations are associated with a variety of ovarian cancer histologies including endometrioid and clear-cell cancers.

Assessing a family for Lynch syndrome is accomplished by determining whether the history meets Amsterdam II criteria (see Table 6.2). If a family history is suggestive of Lynch syndrome but the criteria cannot be met because of family size or other factors, consideration of risk can be accomplished using revised Bethesda criteria.

Table 6.2 Amsterdam II criteria for Lynch syndrome

At least 3 relatives with an HNPCC cancer:
Colorectal, endometrial, stomach, ovary, ureter/renal pelvis, brain, small intestine, hepatobiliary tract, or sebaceous tumor of skin
AND:
(1) One is a first-degree relative of the other 2
(2) At least 2 successive generations affected
(3) At least 1 of the HNPCC cancers was diagnosed at <50 years of age
(4) Familial adenomatous polyposis has been excluded

(Table 6.3). Women with Lynch mutations do not have an associated increased risk for developing breast cancer; as such, family histories with multiple family members with ovarian cancer and no cases of breast cancer, but having family members with Lynch-associated malignancies (e.g., colorectal cancer, endometrial cancer) should first be evaluated for MMR mutations rather than BRCA mutations [26].

Table 6.3 Bethesda guidelines to determine which colorectal tumors should undergo MSI testing

(1) Colorectal cancer diagnosed in a patient <50 years old
(2) Presence of synchronous or metachronous colorectal, or other HNPCC-associated tumor, regardless of age
(3) Colorectal cancer with the MSI-H histology diagnosed in patient <60 years old
(4) Colorectal cancer or HNPCC-tumor diagnosed <50 years old in at least one first-degree relative
(5) Colorectal cancer or HNPCC-associated tumor diagnosed at any age in 2 first-degree or second-degree relatives

Individuals who do meet Amsterdam II criteria are evaluated by obtaining peripheral blood for direct sequencing of the MLH1 and MSH2 genes. For those individuals whose families do not meet Amsterdam criteria but do meet Bethesda criteria, first evaluating tumor tissue for MSI and IHC (before mutation testing) is the preferred approach for screening at-risk individuals. This approach is associated with high (90–95%) sensitivity for detecting MMR gene mutation carriers, but as with IHC, provides no information as to which gene is mutated and thus which malignancy that individual may have the highest risk for developing.

The lifetime risk for developing EOC in women with a Lynch syndrome mutation is approximately 12%, a tenfold increase over the general population risk (1–1.5%) but less than the risk associated with BRCA1/2 mutations. Interestingly, while most cases of ovarian cancer in Lynch syndrome families are malignant epithelial tumors, most are well or moderately differentiated and are FIGO Stage I or II at the time of diagnosis. This is in sharp contradistinction to BRCA mutation-associated tumors, which tend to present in a more advanced stage and be more poorly differentiated. Most of the Lynch families with EOC who were studied were found to have germline mutations of the MLH1 or MSH2 genes [27]. However, Cederquist and colleagues [28] reported a high frequency of a variety of EOC in Swedish women withMSH6 mutations, with an estimated 33% lifetime risk of developing EOC in this Swedish cohort. As with other cancer susceptibility genes, certain mutations in particular populations may exert a different impact on cancer risk than that typically observed in the general population. However, similar to women with BRCA 1 or 2 mutations, women with Lynch mutations tend to develop EOC at a younger age (5th decade) than sporadic cases of EOC (7th decade).

Other Genetic Syndromes Associated with EOC

Ovarian cancer is found as an associated malignancy in other genetic syndromes (Table 6.4). Syndromes associated with EOC are rare and are usually associated with non-epithelial ovarian cancer, although some cases of serous and mucinous EOC have been reported. While ovarian cancers and tumors have been reported in women with these genetic conditions, the overall risk for developing ovarian cancer in women with these conditions appears to be similar to that of the general population. Notwithstanding, evaluation of the ovaries by ultrasound or laparoscopy in cases of adnexal masses of women affected by these uncommon Mendelian disorders is clearly warranted.

Table 6.4 Genetic syndromes associated with ovarian cancer

Syndrome	Inheritance	Gene (chromosome)	Clinical features	Ovarian cancer
Peutz-Jeghers	AD[a]	STK11 (19)	Melanocytic macules (mouth and lips); polyps in GI tract; increased risk of GI tract CA	Sex cord-stromal tumors (SCST); granulosa cell tumors
Ollier	Sporadic/AD?	PTHR1 (3)	Multiple enchondromas; Secondary chondrosarcomas; Orthopedic complications	Granulosa cell tumors
Gorlin	AD	PTCH (9)	Basal cell ca of the age 30; jaw cysts; vertebral abnormalities	Skin before fibrosarcoma; also benign fibromas
Cowden	AD	PTEN (10)	Hamartomatous lesions of skin and organs; macrocephaly; increased risk of breast, thyroid endometrial CA and endometrial cancers	Epithelial ovarian cancer

[a] autosomal dominant

Counseling of Women at Increased Risk for Developing EOC

While only a small percentage of ovarian cancers can be attributed to the inheritance of susceptibility genes, identifying those women at risk for inheriting a susceptibility gene is critical in order to provide optimal care and management. Hereditary EOC tends to occur at an earlier age than sporadic cases. Given the lack of an effective screening protocol for EOC, it is important to identify these high-risk women so that prevention and management options can be provided, which typically occurs during a woman's reproductive years. While effective breast screening protocols do exist for women at increased risk for breast cancer, and while some of the preventive interventions for breast cancer can reduce fertility (e.g., tamoxifen and raloxifene), *all* of the preventive measures available to reduce the risk of EOC in high-risk (and low-risk) women involve transitory or permanent inhibition of fertility. Tailoring these interventions that allow a clinician to provide optimal balance reducing the risk of EOC and allowing a woman to maintain her reproductive capacity for as long as she wishes to conceive is a key goal of cancer genetics programs. Conversely, testing the entire population for susceptibility genes is not currently feasible because of economic factors and the relative low frequency of these deleterious genes in the general population. Currently, the most effective tool for determining risk for hereditary EOC and for providing genetic testing is genetic counseling and cancer risk assessment.

The primary care clinician holds the key to effective identification of those individuals at increased risk for hereditable cancers, with a thorough assessment of the family history being the vital component. Individuals with a personal or family history suggestive of a hereditary or familial cancer should be referred for further counseling and cancer risk assessment. This can be performed at a genetics center, oncology center, or any facility that has trained personnel equipped to properly evaluate personal and family histories and

perform a cancer risk assessment. Such personnel are, but are not necessarily limited to, genetic counselors, geneticists, oncologists, gynecologists, internists, family medicine providers, nurse practitioners, or other professionals that provide care to those who are at risk for cancer and cancer syndromes and who have the expertise and interest to do so.

In no cases should patients be coerced into undergoing cancer risk assessment or genetic testing. The long-standing tenet of non-directive counseling must be followed when discussing cancer risk with patients and patient autonomy must always be respected. Indeed, counseling should serve to empower individuals to make informed decisions about their health management, not to dictate or mandate individuals to undergo (or forego) certain tests or management options based on the opinions of the counselor or provider. Women who are so identified as being at increased risk for hereditary EOC by their primary care provider may benefit from a thorough and detailed discussion with a specialist about their risk for developing cancer, the screening and testing that is available to refine their actual risk, and the preventive interventions that are available to them, even if they ultimately choose to forego any further evaluation or risk-reducing intervention. In addition to providing information that can reduce morbidity and mortality, such counseling can also address the anxiety and the numerous psychosocial issues that a personal or family history or cancer can induce.

The process and logistics used to identify and refer women who are at increased risk for hereditary cancer syndromes may be hampered by the considerable barriers to such endeavors. Taking a family history involves time, something in short supply for most primary care providers. Even if a complete family history is taken, medical records are needed to confirm the presence of a malignancy that may increase or decrease a woman's risk for developing cancer. "I was told that my grandmother died from stomach cancer" is a familiar statement in our practice. In many instances, medical records actually indicate that it was not "stomach" cancer. Whether it was actually metastatic ovarian cancer or ulcerative colitis would obviously and profoundly impact the cancer risk assessment of the woman. Unfortunately, many of these medical records are not obtainable. For those clinicians who are able to develop detailed family histories, existing written and electronic medical records systems frequently do not facilitate the updating of such family history information. Finally, even if all the proper components are in place, many primary care clinicians do not have the clinical experience to identify ancillary conditions that may herald a cancer predisposition syndrome. While breast and ovarian cancers in a family clearly place a woman at increased risk for those same malignancies, how does thyroid cancer affect that risk? What about colon polyps, or colon cancer? And if there are several cases of endometrial cancer in a family along with cases of breast and ovarian cancer, what would be the best test to offer a patient if the clinician is going to offer testing without referral for more detailed counseling? All of these issues serve to detract from our ability to accurately assess the risk of women with personal and family histories suggestive of an inherited predisposition to cancer development. However, new programs designed to facilitate data collection, such as HughesRiskApps [29], are now available that allow individuals to provide this type of family information outside of the actual face-toface visit time with their clinician (e.g., waiting room, mammography

center). Such systems should allow easily updated and evaluated histories to determine whether there is an increased risk that needs to be addressed with referral, counseling, or testing.

When a woman is referred for further counseling, a specific cancer risk assessment can be performed. While risk models are not available for all malignancies, risk models are available for HBOC and EOC. Risk models take into account a wide spectrum of family risk factors including age of onset, number and relation of affected members, and presence of associated cancers among other personal and disease characteristics. Two types of cancer risk assessment can be performed: a quantitative analysis determines the risk of an individual to be a carrier of a mutated susceptibility gene, and a qualitative analysis based on family history, medical records, and pathology reports, among other documents [30], which determine the risk of the individual to develop cancer. Both approaches to risk determination incorporate family history and medical information, but the endpoints are quite different, and it is incumbent on the provider to be sure the patient understands the difference. It is again important to emphasize that cancer susceptibility genes are autosomal and thus transmissible by either one's father or one's mother. Attention must be paid to both lineages, with the recognition that families with relatively few females may be difficult to identify as being a family with a cancer susceptibility gene for EOC because of the relatively few individuals with a potential for phenotypic expression (i.e., cancer) of the mutated susceptibility gene.

When genetic testing is decided upon, it is optimal to test the affected family member(s) as such individuals are most likely to possess deleterious mutations. Obviously, this is not always possible. In such cases, testing those family members who are most closely related to those affected members is appropriate. However, one should be aware that such testing is not always possible and testing individuals who are neither affected nor closely related to affected members may be appropriate. Indeed, in some cases family members who are either affected or are closely related to affected relatives may choose not to test or choose to not release test results, requiring less closely related family members to get testing to determine their mutation status.

Conclusions

Epithelial ovarian cancer remains a highly lethal malignancy, primarily as result of our inability to detect early, and more treatable, EOC lesions. While most cases of EOC are not associated with a family history and appear to be random event with some risk modification from one's reproductive history and exposure to sex steroids, a small percentage of cases are associated with a familial susceptibility to EOC. Such cases are likely to occur bilaterally and develop earlier in life than EOC in the general population, making the identification of such individuals an important priority given the lack of unique and novel symptoms of early stage (and more successfully treatable) EOC. However, until an effective screening algorithm is available, analysis of family history and cancer risk assessment will remain the main tools to assess one's risk for developing EOC.

Identifying those women who carry an increased risk for developing EOC allows them to initiate preventive measures to reduce their risk for developing EOC. Because these measures either temporarily or permanently reduce or eliminate the ability to conceive, appropriate counseling of such women regarding their plans and desires for reproduction is necessary. In this regard, the identification of high-risk women through family history and genetic testing also brings into the process the consideration of novel reproductive technologies that may allow women to reproduce or conceive even when electing to initiate preventive measures. Oncofertility counseling and interventions for reproductive-aged women at increased risk for EOC are thus important for providing effective overall care to these women and provide the potential for reproduction for women seeking EOC prevention with contraceptive measures.

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