Hereditary Factors in Gynecologic Cancer

HENRY T. LYNCH, a MURRAY JOSEPH CASEY, b TRUDY G. SHAW, a JANE F. LYNCH a

a Department of Preventive Medicine; b Department of Obstetrics and Gynecology, Creighton University School of Medicine, Omaha, Nebraska, USA

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Abstract
Cancer predisposition in some families is known to be the result of germ-line mutations. The most noteworthy hereditary gynecologic cancer syndromes include hereditary breast-ovarian cancer (HBOC) syndrome, wherein \( BRCA1 \) and \( BRCA2 \) germ-line mutations have been identified, and hereditary nonpolyposis colorectal cancer (HNPCC) of the Lynch syndrome II variant, wherein \( hMSH2, hMLH1, hPMS2, hMSH3, \) and \( hMSH6 \) germ-line mutations have been identified. DNA testing for specific cancer-associated germ-line mutations is now available for HBOC and HNPCC syndrome family members who are in the direct line of inheritance. Genetic counseling is mandatory prior to DNA testing and at the time of disclosure of findings. A patient found to be negative for the family’s particular cancer-associated germ-line mutation can revert to general population screening recommendations. When a deleterious mutation is identified, the physician is able to predict a patient’s lifetime susceptibility to breast and ovarian carcinomas in the HBOC syndrome or the cancers which characterize the Lynch syndrome II variant of HNPCC, particularly carcinomas of the colon, endometrium, and ovary. Management strategies can be offered which are designed to take advantage of the natural history of that distinct hereditary cancer syndrome.

We discuss the unfolding developments concerning familial and heritable susceptibilities, molecular genetics, and possible carcinogenic co-factors of the three most common gynecologic cancers: carcinomas of the uterine cervix, endometrium, and ovary. We offer rationales for management based on current epidemiologic and clinical data and emerging technologies. The Oncologist 1998;3:319-338

Identification of specific gene mutations associated with HBOC and HNPCC syndromes presents the opportunity for family members who are in the direct line of inheritance to have DNA testing. If found to carry a deleterious mutation, these patients may benefit from highly targeted surveillance and management strategies. If negative for the mutation, they can follow general population screening recommendations and may experience relief from the fear of cancer. It is crucial, however, that genetic counseling be performed prior to DNA testing and at the time results are disclosed. When patients learn about the possibility of anxiety, apprehension, intrafamily strife, and potential insurance or employment discrimination, they may reject being tested. On the other hand, most patients may view such testing in a positive manner. It may resolve questions concerning their cancer susceptibility, and this knowledge may enable them to participate in targeted screening and management programs.

This article will review the basics of inherited susceptibilities and possible environmental co-factors, discuss the...
current status of the underlying molecular genetics, and present the rationales for managing women who may be at increased hereditary risk for carcinomas of the uterine cervix, endometrium, and ovary, the three most common gynecologic cancers.

**Uterine Cervix Carcinoma**

One of the great successes of preventive medicine in the Western industrialized countries during the second half of our twentieth century has been the dramatic reduction in both the incidence of and mortality from cervical cancer, much of which is attributable to widespread Pap smear screening programs [17-20]. Cervical cancer remains the most common female genital malignancy in the developing countries of South America, Asia, and Africa, where early detection is limited and women present with advanced, often incurable stages of this disease [21].

During 1998 in the United States, 13,700 new cases and 4,900 deaths are projected for uterine cervix cancer [17]. Worldwide, the incidence and mortality from cervical carcinoma is second in women only to breast cancer [22].

The preponderance of epidemiologic studies implicates a sexually passed agent as the primary risk factor for intraepithelial and invasive neoplasms of the uterine cervix [23-27]. Presently, human papilloma virus (HPV) is the prime suspect, particularly the so-called oncogenic types, including types 16 and 18, and possibly types 31, 35, 45, and other higher types [28-37]. But other sexually transmissible infections [38-47] and environmental and hereditary factors, or lack thereof, may ultimately prove to be important for initiation and progression of these neoplasms [48-55]. While HPV type 16 DNA is recovered from the majority of high-grade squamous intraepithelial cervical neoplasms and cancers, this also is the most prevalent HPV type isolated from benign and neoplastic cervical lesions and one of the most common viruses recovered from the female genital tract [30, 36, 56-62].

In the Western countries, prevention of invasive squamous carcinomas through detection and elimination of the precursor lesions has coincided with an increase in the relative proportion of cervical adenocarcinomas and adenosquamous carcinomas [19, 20, 24, 63-65], particularly among young women in whom the absolute incidence of cervical granular neoplasms actually may be rising. However, these early observations led to an extensive international study of 60 population-based cancer registries which demonstrated an increasing cumulative incidence of cervical adenocarcinoma in young white and Hispanic populations from the United States but no change in incidence of this tumor in black Americans [66]. Although the cumulative incidence of cervical adenocarcinoma increased in the young women from most industrialized countries in Europe, Oceania, and Japan, the incidence decreased in Finland, France, and Italy, leading to speculation that increasing incidence of cervical adenocarcinoma, where it is seen, may be influenced by screening and detection practices or due to differences in the prevailing oncogenic HPV types [66]. Epidemiologic data from the United States and Europe indicate that the frequency of cervical adenocarcinomas rises, similar to cervical squamous neoplasms, with the number of sexual partners and with decreasing age at first intercourse [24, 28]. Several investigators have reported detecting HPV DNA, predominantly type 18 and, to a lesser extent, type 16, in cervical adenocarcinomas, adenosquamous carcinomas, and, possibly, precursor lesions, and cervical adenocarcinomas in situ (AIS) [28, 29, 67-78].

Taken together, the greatest risk for intraepithelial and invasive cervical neoplasms is associated with high oncogenic risk HPV types, and a molecular explanation for these observations is beginning to emerge. It is yet unsubstantiated whether or not tobacco and oral contraceptive use or relative deficiencies in dietary vitamins may act independently or as co-factors in the promotion of cervical neoplasia or whether these are merely surrogate markers of populations that are most susceptible to HPV infection because of their sexual practices.

**Molecular Genetics**

Cho [79] has extensively reviewed the molecular genetic basis of cervical carcinoma. So far, over 100 different HPV types have been identified based on differences in DNA sequences. However, only the E6 and E7 open reading frames of oncogenic HPV genomes appear to be necessary for immortalization of squamous cells [54, 80]. The transforming proteins of the oncogenic types of HPV interfere with the
function of the tumor suppressor proteins p53 and pRB protein-protein interactions, which disrupts cell cycle control and DNA repair mechanisms, thereby promoting genetic instability and the accumulation of mutations in HPV-infected cells [54, 80-85]. In contrast, in vitro studies show that low oncogenic HPV types 6 and 11 E6 and E7 proteins do not bind p53 and pRB proteins with high affinity, whereas somatic mutations of p53 and pRB genes were demonstrated in HPV-negative human cervical cell cancer lines [81, 82, 86]. Hendricks et al. [89] studied the fragile histidine triad (FHIT) gene which is located at chromosome 3p14.2. This has been shown to be altered in many epithelial cancers. Because previous investigations identified loss of heterozygosity (LOH) and cytogenetic abnormalities at the 3p region in carcinomas of the ovary, endometrium, and uterine cervix, these authors studied the status of the FHIT in 14 ovarian, eight uterine cervical, and four endometrial human cancer cell lines [89]. The results showed that aberrantly migrating FHIT transcripts were displayed in five of the eight cervical cancer cell lines when RNA isolated from the carcinomas was used in reverse transcription polymerase chain reaction (PCR) tests to amplify the FHIT gene; DNA from alterations were found by Southern blot analysis in four of the five cervical carcinoma lines tested, three of which exhibited no normally sized FHIT transcripts [89]. Only two of 14 ovarian carcinoma cell lines and none of the four endometrial cancer cell lines displayed abnormally migrating FHIT transcripts in RNA reverse transcription tests.

Greenspan and associates [90] using reverse transcription PCR found aberrant FHIT transcripts in six of seven cervical carcinoma cell lines and in 17 of 25 (67%) cervical carcinomas, while all normal tissues and cultured keratinocytes carried normal FHIT mRNA transcripts. Greenspan et al. [90] also found marked reduction or loss of FHIT protein expression in 25 of 33 (76%) cervical carcinomas, while FHIT protein was always markedly reduced or absent in the cervical carcinoma cell lines and tissues with absent or aberrant FHIT transcripts. These findings suggest that expression of the FHIT gene may be altered in cervical tumor tissue, potentially implicating this gene in cervical tumorigenesis; whereas the FHIT gene appeared to be less important in the development of ovarian cancer and endometrial cancer.

**Familial Associations**

Although cancer-provoking mutations may be either acquired or passed in the germ line, inherited factors appear to play a minor role in uterine cervix carcinogenesis. Kallander [91] identified several reports of familial clusterings of cervical carcinomas. Furgyik et al. [92] studied all patients who were hospitalized and treated for in situ and invasive carcinomas of the cervix at the Department of Gynecology in Malmö, Sweden, during 1982, and the first-degree relatives of these patients’ sexual consorts. They found that 14 of 177 known patients’ mothers (7.9%) and 14 of 188 sisters age 20 years or older (7.5%) had been diagnosed with cervical cancer, compared with only one of 103 consorts’ mothers (1.0%) and one of 93 consorts’ sisters age 20 years or older (1.1%). However, such observations are not unexpected given the high frequency of this disease and the manner in which it associates with environmental risk factors, some of which will be common lifestyle factors in these cervical-cancer-prone families. A four-generation study [93] involving 8,127 family members of 251 women with in situ or invasive cervical carcinomas in the San Francisco Bay area found no excess of multiple cancers or site-specific cervical cancers in relatives of the probands compared with 8,996 family members of case-matched control subjects; only an excess of skin cancers was found in family members of the cervical cancer and in situ cervical carcinoma patients. Furthermore, an analysis of 2,090 cancer patients identified among 4,635 lineages containing a total of 31,945 people in the Detroit area found no excess of cancers in families of cervical cancer patients [94].

“Uterine cervical cancer is particularly notable because it is one of the few cancers that is strongly associated with an infectious agent.”
A comprehensive review of histocompatibility and the many proposed etiologic factors and co-factors that may operate in the course of uterine cervix carcinogenesis is beyond the scope of this article. We have discussed these issues more thoroughly in another publication [85].

Prevention

Recognizing that HPV types 16 and 18 are associated with a large proportion of both squamous cell and granular cancers of the cervix and the high-grade intraepithelial precursor lesions, it would seem appealing to test and follow only those women whose cells and tissues yield DNA specific for the so-called high-risk types. However, the most recent studies of patients with squamous intraepithelial lesions and invasive cancers, using both commercially available HPV screening tests and very sensitive PCR techniques with type-specific primers, have detected high- and low-risk HPV types and double and multiple type HPV infections from normal women, low- and high-grade intraepithelial lesions and cancer [30, 57, 95-98].

Notwithstanding false negative Pap smear rates historically reported between 2% and 69% [99, 100], and estimated to be about 20% in centers of acknowledged excellence [101], among the highest risk factors for invasive cervical cancer are the failure of predisposed women to obtain Pap smears and lengthening intervals between screening [28, 102, 103], while reduction in the incidence of cervical cancer and its in situ precursor has been associated with the introduction of pelvic examination and Pap smear screening and follow-up programs [18, 104-107].

Given the success of Pap smears in detecting dysplastic cellular changes which lead to elimination of cervical neoplasms in their earliest forms, thereby resulting in the decline of invasive cervical cancer and deaths from this disease among populations in which screening programs have been implemented, the emphasis for cancer prevention should be on expanding availability and public awareness of screening and treatment programs.

ENDOMETRIAL CARCINOMA (EC)

As a result of the control of uterine cervix cancer, cancer of the uterine corpus has become the most common gynecologic malignancy in the United States. In 1998, uterine corpus cancer, predominantly arising in the endometrium, is expected to be responsible for 36,100 new cases and to result in 6,300 deaths [17]. The incidence of EC in the general population is age-dependent and is highest in persons between ages 55 and 75 [108]. An early suggestion of a putative host factor susceptibility to EC, in contrast to carcinoma of the uterine cervix, was its varying constitutional associations, namely diabetes mellitus, obesity, and hypertension [109]. Lynch et al. [110] studied these constitutional and pathologic factors, but also included genetic considerations in their evaluation of 154 consecutively ascertained patients with histologically confirmed ECs over a 20-year period [110]. They found obesity to be the most frequently occurring constitutional factor in this series, being present in 123 (80%) of the 154 EC patients. Obesity was extreme in many of these women: several weighed more than 300 pounds, and two weighed more than 400 pounds. Hypertension was present in 100 patients (65%) and diabetes mellitus was present in 66 patients (43%). Multiple primary malignant neoplasms were found in 17 patients (11%), five of whom had three primary malignancies. Twenty-six patients (16%) had first-degree relatives with ECs. In one family, three sisters had ECs, and two patients with EC had both a mother and daughter affected by this disease. Four of these kindreds in the 1960s were termed “cancer families,” some of which may have been what we now know as the HNPCC syndrome. The average age of onset of EC in the patients from these families was 50 years, which was in contrast to the average age of 65 years in sporadic cases. Multiple primary malignant neoplasms occurred frequently in each of the families, and when one of the malignancies was EC, colon cancer was the most frequently associated additional primary malignancy [110].

Cigarette smoking, notwithstanding its severe lifetime cancer and cardiac sequelae, has actually been shown to be protective against breast cancer in BRCA1 and BRCA2 mutation carriers [111]. Pertinent to gynecologic cancer, cigarette smoking has been shown to protect against EC [112]. Smoking is associated with reduced levels of circulating estrogens and with an earlier menopause [113].

EC and HNPCC Syndrome (Lynch Syndrome II)

An understanding of the clinical and genetic manifestations of the HNPCC syndrome began to emerge in the late 1960s when the association of ECs and colorectal cancers with excess occurrence in the proximal colon was found in the context of families with multiple primary cancers, many with early age of onset. In one family, Lynch et al. described multiple primary cancer clusters affecting various anatomic sites among eight direct-line relatives, three of whom had two or more primary malignancies. There were frequent tendencies to prolonged survival, a finding that is now well established in the HNPCC syndrome [114-116]. One such patient showed a remarkable tolerance to invasive cancer, having had four histologically verified malignant neoplastic lesions, involving the ovary, endometrium, colon, and myelogenous leukemia [114]. EC has now been identified as the most frequently occurring extracolonic malignancy affecting families with HNPCC syndrome [117].

As an autosomal dominant mode of transmission became established through extended pedigree analyses, it became...
clear that the majority of HNPCC syndrome families also had a statistically significant proclivity for carcinoma of the endometrium, ovary, stomach, small bowel, pancreas, ureter, and renal pelvis [10, 118]. Families that are affected with the HNPCC syndrome can now be distinguished by whether they are characterized by almost singular inheritance of colorectal cancer susceptibility, termed Lynch syndrome I, or whether tumor heterogeneity of colorectal cancer together with extracolonic malignancies are a prominent feature in the autosomal dominant inheritance of cancer susceptibility, termed Lynch syndrome II [10].

Watson et al. [117] analyzed combined data on EC from three large HNPCC registries in Finland, The Netherlands, and the United States. High-risk relatives were identified without regard to extracolonic cancer, and life table methods were used to estimate the risk of EC. There were 1,018 women from 86 families. The cumulative incidence for EC was 20% by age 70, compared with 3% in the general population. The average annual risk exceeded 1% during the highest-risk years (age 40-60 years) in this group. There was no significant difference among the registries, even though differing ascertainment practices regarding EC were used [117].

Menko et al. [119] described a family in which EC was diagnosed in four sisters; one of these patients and the father of the four sisters previously had manifested colorectal cancer. With this much information, we would consider this to be a putative HNPCC syndrome family of the Lynch syndrome II variant.

Fornasarig et al. [120] studied the family pedigrees and clinical risk factors which have been associated with endometrial carcinoma in 215 endometrial cancer patients in a northeastern Italian health care district from 1990 to 1995. The average age was 61 years (range 35-88 years), and risk factors included age at diagnosis, weight, diabetes, menstrual and reproductive pattern, and all synchronous and metachronous neoplasms. Although 120 (55.8%) of these patients had no cancer in their family histories, 29 patients (13.5%) had a family history of colorectal cancer. Eight (3.7%) endometrial cancer patients with colorectal cancer in first-degree relatives had pedigrees showing a dominantly inherited cancer pattern, two of which fully fit the criteria for HNPCC. All of the other 21 patients with colorectal cancer in first-degree relatives had at least one other relative with endometrial cancer. Nonspecific cancer aggregations were found in the families of 66 (30.7%) endometrial cancer patients, and no difference in risk factors was found in these women compared with patients who had family histories that were negative for cancer. However, the group of endometrial cancer patients with colorectal cancer in their pedigrees was significantly younger \( p < 0.001 \), more often premenopausal \( p < 0.001 \), and had lower body mass index \( p < 0.002 \). Multiple primary tumors were found in 9.3% of the endometrial cancer patients; however, a mild correlation with synchronous tumors was found only in the patients with colorectal cancer in their family histories, and there was no difference in the representation of metachronous tumors between patients with family cancer histories and those without.

Sumoi et al. [121] studied 326 patients with EC from Finland who were diagnosed at 60 years of age or younger. When one or both of the proband’s parents died of cancer, a thorough family history for cancer was undertaken, which yielded 291 patients with complete parental data. Nine families (3%) met a diagnosis of HNPCC syndrome, and nine other kindreds showed clustering of malignancies in two or more successive generations, suggesting familial cancer. Nonspecific cancer aggregations were identified in 112 probands’ families, while the family history was negative in 161 cases. None of the families showed gynecologic cancer as the only malignancies, but it is important to realize that in certain circumstances the diagnosis of HNPCC syndrome may be wholly dependent on gynecologic cancers (endometrial and ovarian), as evidenced in Figure 1. We have diagnosed many HNPCC families through ascertainment of gynecologic cancers [122].

**EC in the Absence of HNPCC Syndrome**

Epidemiologic studies have shown a significant cancer risk in the first-degree relatives of patients affected with EC. Analysis of the Cancer and Steroid Hormone Study indicated that mothers and sisters of EC patients had 2.7 times greater risk for EC than did matched controls [123].

Parazzini et al. [124] evaluated 726 patients with histologically confirmed EC (median age 61 years) in a case-control study with 2,123 control women (median age 59 years) in northern Italy between 1983 and 1993. Among the EC patients, 37 (5.1%) reported a history of EC in first-degree relatives, compared with ECs in 77 (3.6%) first-degree relatives of the control women. The odds ratio of EC in women with a history of EC in a first-degree relative was 1.5 when compared with women who lacked a family history of EC [124]. No relationship was identified between EC and a family history of breast or ovarian cancer. These authors concluded that a family history of EC increases the risk of contracting the same disease, although the proportion of cases attributable to this factor was small [124]; less than 1% of the ECs in this population were attributed to familial, and thereby potentially primary genetic, factors.

In certain EC-prone families, a classic hereditary syndrome diagnosis may not be present. For example, Lynch et al. [108] described a family whose EC was histologically verified in five women through three consecutive generations (Fig. 2). The triad of obesity, hypertension,
and diabetes mellitus was not observed. The combinations of carcinoma of the endometrium and ovary, and of ovary and lymphoma, were documented in two relatives in the direct genetic lineage of this pedigree. It was concluded that this aggregation of ECs, while lacking the diagnosis of any known hereditary cancer syndrome, nevertheless merited extensive surveillance and management strategies targeted to these high-risk family members. It is families such as these where molecular genetic studies may one day help in the elucidation of their etiology and classification.

Endometrial and Ovarian Carcinoma and Second Primary Cancers

Shiromizu et al. [125] evaluated 272 endometrial and 144 ovarian carcinoma patients treated from 1975 through 1990 and found that 28 (10.5%) of the women affected with EC and 13 (9.0%) of those with ovarian cancer developed a second primary malignancy. The risk of a second primary neoplasm was increased in EC-affected individuals whose parents or siblings and/or children also manifested cancers. Ovarian carcinoma patients who had first-degree relatives with malignant diseases tended to show an increased risk for a second primary cancer, but this risk did not reach statistical significance [125]. These authors also found no significant influence of tobacco smoking and/or alcohol consumption on the risk for second primary malignancies in endometrial and ovarian cancer patients. More than half of the second primary cancers involved the breast, colon, or stomach [125].

Molecular Genetics

In their review of previous reports, the findings of Ito et al. [126] suggest that K-ras proto-oncogene activation, which has been observed in 10%-30% of ECs, may play a role in the mechanism responsible for aggressive clinical behavior of EC, particularly among postmenopausal patients.

Risinger et al. [127] implicated chromosome 10 in the pathogenesis of EC, based on LOH, comparative genomic hybridization, cyogenetics, and a recently identified potential tumor suppressor gene in the chromosome 10q23-24 region, PTEN/MMAC1, which has homology to dual-specificity phosphatases as well as to the cytoskeletal proteins tensin and auxillin [128]. Tashiro et al. noted also that LOH on chromosome 10q has been reported in about 40% of ECs [129].

Liu et al. [130] investigated whether mutational alteration of the BRCA1 tumor suppressor gene occurred in sporadic forms of EC through the study of 33 consecutively collected EC tissues. Although polymorphisms were identified in three of these tumors through DNA sequencing analysis, the normal BRCA1 allele was retained in each case [130]. Therefore,
the heterozygous DNA alterations that were found should not be cancer predisposing according to the two-hit model of Knudson for inactivation of tumor suppressor genes, and defective BRCA1 was not likely involved in the development of these sporadic ECs. Since 1993, deleterious mutations in four genes, hMSH2 on chromosome 2p, hMLH1 on chromosome 3p, hPMS1 on chromosome 2q, and hPMS2 on chromosome 7p, have been linked to a predisposition to the characteristic cancers of HNPCC syndrome families [12-15]. Protein products of these genes are involved in the mechanism of recognizing and correcting errors which arise during DNA replication. It is hypothesized that mutational inactivation of both alleles of these mismatch repair genes leads to progressively accumulating secondary mutations which eventually result in the loss of cell growth regulation and thus malignant transformation [131, 132]. Together, hMSH2 and hMLH1 mutations account for approximately 50%-70% of HNPCC kindreds with about equal distribution of these two germ-line mutations, while hPMS1 and hPMS2 combined contribute to only about 5% of the germ-line mutations associated with HNPCC syndrome [133-140].

More recently, mutations of hMSH3 on chromosome 5 and hMSH6 on chromosome 2 have been identified in endometrial carcinoma and an endometrial carcinoma cell line, and in tumors from patients with HNPCC syndrome [141-144]. Examination of hMSH3 and hMSH6 function in human tumors and the yeast homologs of these genes indicates that they code proteins which interact with hMSH2 proteins forming complexes important for the recognition and repair of DNA replication errors [145-149]. Adverse hMSH2 germ-line mutations, such as those found in families with HNPCC syndrome, predispose to hMSH3 and hMSH6 mutations and the accumulation of other downstream gene mutations [142, 144]. Furthermore, reports from Japan have described at least two examples of hMSH6 germ-line mutations associated with colorectal, endometrial, and ovarian carcinomas in putative HNPCC syndrome patients lacking germ-line mutations of hMSH2 and hMLH1 [141, 150].

The demonstration of somatic mutations in the cell growth regulator gene TGFβRII and the proapoptotic gene BAX in tumors from HNPCC syndrome patients [141, 144] implicates progressive failure of the defective mismatch repair genes to correct DNA replication errors, leading to a cascade of genomic instability, loss of cellular growth regulation, and the escape of malignantly transformed cells from apoptosis.

Microsatellite instability, a characteristic of mutations in mismatch repair genes which results in strand-specific DNA replication errors (RER+), was first demonstrated by Risinger et al. [151] in six of 36 (16.6%) sporadic endometrial adenocarcinomas of all histologic grades, and in three of four ECs from patients of HNPCC syndrome families. Subsequently, Kowalski et al. [152] screened 125 endometrial adenocarcinomas with seven microsatellite markers and identified 25 (20%) with RER+; but using direct DNA sequencing, they found only one germ-line mutation in hMLH1 and a single somatic mutation in hMSH2. Likewise, Kobayashi et al. [153], who previously found RER+ in nearly one-quarter of sporadic ECs, screened 18 RER+ ECs for hMLH1 and
The projected incidence of ovarian cancer in the United States in 1998 is 25,400, and during this same year, 14,500 deaths are expected from this disease, ranking it fourth as a cause of cancer deaths in American women [17]. The lifetime risk for developing ovarian cancer is only about 1.5%; however, by the time of diagnosis, extension beyond the ovary will have occurred in three-quarters of affected women thereby seriously compromising their chances for survival [154]. Adjusted five-year survival rates of women affected with ovarian cancer decline rapidly from 93% when the tumor is confined to the ovary, to 55% with local spread, and to just 25% with distant metastasis [17]. So long as we remain constrained by currently available treatment modalities, prevention and early diagnosis will be paramount in the control of ovarian cancer.

Worldwide, ovarian cancer is the sixth most common malignancy in women. The highest incidence of this disease occurs in affluent nations of North America and Europe, particularly the Scandinavian countries [155]. The incidences of ovarian cancer in Israel, Australia, and New Zealand are comparable to those in Europe and North America, but the incidence of ovarian cancer in Japan is much lower and comparable with other Asian countries [156-159]. These observations have suggested that diet, endocrine, as well as reproductive and environmental factors may be important in the etiology of ovarian carcinoma. Based on a multitude of epidemiologic studies which demonstrate that multiparity and the use of ovulation suppressing oral contraceptive medications provide protective effects against ovarian carcinoma while early menarche and late menopause are associated with increased risk, it is hypothesized that a greater number of lifetime ovulations is a common underlying risk factor for ovarian carcinoma. But the strongest risk factor known to date is genetic susceptibility, which may account for as many as 10% of ovarian cancers.

**Ovarian Carcinoma**

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**Hereditary Breast-Ovarian Cancer Syndrome**

Genetic transmission of an autosomal dominant factor predisposing to both breast and ovarian cancer was recognized in the early 1970s to explain the familial association of ovarian and breast carcinomas in what is now known as the HBOC syndrome [2-4]. Landmark studies in molecular genetics during the 1990s demonstrated that a large majority (~76%-92%) of HBOC syndrome families are linked to a locus on chromosome 17q which recently had been shown to be linked with susceptibility for early-onset breast cancer [5, 6]. The responsible gene, mapped to chromosome 17q12-21, now known as BRCA1, was subsequently cloned [7]. The exact function which BRCA1 plays in ovarian and breast carcinogenesis in HBOC syndrome families is still unclear, but basic studies implicating BRCA1 as a tumor suppressor gene [130, 160]. Subsequently, a second breast cancer susceptibility gene on chromosome 13q, known as BRCA2, was identified by linkage analysis and then cloned [8, 9]. Studies indicate that BRCA2 also may be a tumor suppressor gene [160].

Approximately one-half of all hereditary breast-cancer-prone families, including those characterized as HBOC syndrome, are due to mutations of the BRCA1 gene; a slightly lower percentage of hereditary breast cancer is due to BRCA2 mutations. BRCA1 germ-line mutation carriers have a lifetime risk for breast cancer of about 85% and a risk for ovarian cancer which ranges between 40% and 66% [161, 162]. A similar 85% lifetime risk for breast cancer is associated with inheritance of BRCA2 mutations in hereditary breast cancer families, but their risk for ovarian cancer is only about 10%-20% [161, 162].

**Diet, endocrine, as well as reproductive and environmental factors may be important in the etiology of ovarian carcinoma.**
Historically, the high rates of 85% lifetime occurrence of breast cancer and 40%-66% of ovarian cancer were based upon large extended kindreds where cancers have been confirmed by pathology review. However, more recent investigations of BRCA1 and BRCA2 germ-line mutations among Ashkenazi Jews and other general breast cancer populations suggest that these penetrance estimates are perhaps too high [163-165].

Ashkenazi Founder Mutations

Struemeyer et al. [166] found BRCA1 or BRCA2 Ashkenazi founder mutations in 2% of 5,318 Jewish subjects in Washington, DC and estimated a 56% lifetime risk for breast cancer, a 16% lifetime risk for ovarian cancer, and a 16% lifetime risk for prostate cancer in mutation carriers by the age of 70 years [166]. They found no significant differences between BRCA1 and BRCA2 mutation carriers in their risk for breast cancer, and there was no increase of colon cancer in relatives of mutation carriers [166]. Couch et al. [163] examined 263 women with breast cancer and identified BRCA1 mutations in 16% of those who had a family history of breast cancer. The probability of detecting BRCA1 mutations was increased in younger women, in families with both breast and ovarian cancer, and in breast-ovarian cancer families with at least one member who had both breast and ovarian cancers. The probability of detecting BRCA1 mutations was highest in Ashkenazi Jewish breast-ovarian cancer families with a member who had both cancers [163].

In an effort to determine the role of germ-line BRCA mutations in Ashkenazi Jews with ovarian cancer, Beller et al. [167] investigated the three mutations associated with breast cancers in this ethnic group, 185delAG and 5382insC in BRCA1, and 6174delT in BRCA2, among 29 consecutive patients [167]. Six of these patients had both breast and ovarian cancers, and 23 manifested only ovarian cancer. In the group with breast and ovarian cancer, all patients carried BRCA1 or BRCA2 germ-line mutations. Of these six patients, two had 185delAG, two had 5382insC mutations of BRCA1, and two carried 6174delT mutations of BRCA2. Eleven (48%) of the 23 patients with only ovarian cancer were BRCA mutation carriers. Six of the 11 showed 185delAG, two showed 5382insC, and two showed 6174delT mutations. Of 13 women who lacked a family history for breast or ovarian cancer, three (23%) were BRCA mutation carriers, while 10 of the women with at least one first- or one second-degree relative with breast and/or ovarian cancer, including five with a family history suggestive of HBOC syndrome, eight (80%) were carriers of a BRCA mutation. In six patients with both breast and ovarian cancer, breast cancer always preceded the appearance of ovarian cancer, with a mean interval of 16 years (range 1-22 years). The mean age of ovarian cancer diagnosis in BRCA mutation carriers was 54.5 years (±14.7 years). These observations of very high rates of BRCA mutations among putative HBOC syndrome patients accrued from a Jewish population of ovarian cancer patients confirm the findings of extremely high probability of BRCA1 mutations in young Jewish breast cancer patients with strong family histories for both breast and ovarian cancer [167].

Abeliovich and colleagues [168] studied 199 Ashkenazi Jewish and 44 non-Ashkenazi Jewish women with breast and/or ovarian cancer for 185delAG, 188del11, and 5382insC mutations in the BRCA1 gene and 6174delT mutations in the BRCA2 gene. Mutations for one or another of these genes were found in 62% (13/21) of these Ashkenazi patients with ovarian cancer and in one of the five non-Ashkenazi Jewish women with ovarian cancer. Thirty-three percent of the ovarian cancer patients had BRCA1 185delAG mutations and 29% had BRCA2 6174delT mutations, but none of the ovarian cancer patients carried BRCA1 5382insC mutations. Mutations associated with breast cancers occurring before age 40 or breast cancer associated with ovarian cancer in the Ashkenazi women were 6.7% 185delAG, 2.2% 5382insC and 4.5% 6174delT [168]. Roa’s group screened 3,000 Ashkenazi Jewish women and found mutant gene frequencies of 1.09% for 185delAG, 0.13% for 5382insC, and 1.52% for 6174delT [169].

Ongoing molecular research may help define other specific intragenic mutations that are associated with increased or decreased predilection for ovarian cancer in members of hereditary cancer families who carry those mutations. For example, Gayther et al. identified “hot spot” mutations in the BRCA1 and in the BRCA2 genes which are carried by hereditary breast cancer families with the highest risk of ovarian cancers [170, 171].

Pathology and Survival of Hereditary Ovarian Cancer

Although most of the carcinomas associated with hereditary cancer syndromes are moderately to poorly differentiated, it is important to recognize that borderline and well-differentiated epithelial tumors confined to the ovary have been reported in these patients, raising the prospect that ovarian carcinogenesis in hereditary syndromes may follow a spectrum from early transformation and localized disease to dedifferentiation and metastases. Searching for premalignant changes, in an unblinded study, Salazar et al. [172] compared the histologic features of ovaries prophylactically removed from 20 women of HBOC syndrome families with those of a control group of women whose ovaries were removed for reasons other than hereditary cancer risk. Two unanticipated microscopic or near-microscopic malignant neoplasms and other benign and borderline tumors were discovered in the ovaries of the high-risk individuals. Moreover, among the high-risk women...
a statistically significant greater proportion of ovaries contained histologic features that the authors considered to represent premalignant characteristics, including epithelial pseudostratification and surface papillomatosis; deep cortical invaginations of the surface epithelium, frequently with multiple papillary projections into cystic spaces forming microscopic papillary cystadenomas; epithelial inclusion cysts, frequently with epithelial hyperplasia and papillary formations; cortical stromal hyperplasia and hyperthecosis; increased follicular activity; corpus luteum hyperplasia; or hilar hyperplasia. Two or more such changes were observed in 85% of ovaries from high-risk women compared with 30% of the control group \( (p = 0.001) \), and 75% of ovaries from high-risk women contained three or more of these changes compared with only 10% of the ovaries from the control group \( (p = 0.00007) \) [172]. These were highly significant differences, particularly considering the fact that detailed determinations of family histories of cancer in the control group were not possible. The authors concluded that ovaries removed prophylactically from these patients at hereditary risk for ovarian cancer showed preneoplastic histologic characteristics [172].

The ovarian cancers associated with HBOC syndrome are predominantly serous carcinomas, often showing papillary features [173-176]. Bewtra and her group [173] found that all of the 37 hereditary ovarian cancers examined from the Creighton Hereditary Cancer Institute were carcinomas, 89% were serous type, and 81% were moderate to poorly differentiated. In spite of this and other parameters which ordinarily would portend exceedingly poor prognosis for ovarian cancer patients from HBOC syndrome families, the converse is true; their survival was better than for women affected by sporadic ovarian cancers.

Rubin et al. [175] evaluated 53 ovarian cancer patients with \( \text{BRCA1} \) germ-line mutations. Forty-three (81%) of these ovarian tumors were serous carcinomas, and 81% were advanced, stages III and IV, when diagnosed. In four families in which 11 members developed ovarian carcinomas, nine tumors were papillary and seven were serous type, eight were poorly differentiated, and none was well differentiated. Rubin et al. found that the 43 patients with advanced ovarian carcinomas who carried \( \text{BRCA1} \) mutations had significantly \( (p < 0.001) \) better actuarial median survival of 77 months when matched for age, tumor stage, histologic type, and grade with ovarian cancer patients from the Society of Gynecologic Oncologists database, whose mean survival was only 29 months [175].

Buller et al. [176] reported significant differences in the Kaplan-Meier survival curves with 67% of the familial ovarian carcinoma patients living without evidence of cancer at 60 months compared with just 17% of 34agematched nonfamilial ovarian carcinoma patients. Ten of the 11 (91%) familial ovarian carcinoma cases were advanced stages, III and IV, compared with 32/34 (94%) stages III and IV carcinomas in the control group. One patient in each group had stage IIC ovarian carcinomas and died from their malignancies [176].

**Ovarian Carcinoma in HNPCC Syndrome (Lynch Syndrome II)**

Ovarian carcinoma occurs in about 5%-10% of HNPCC syndrome patients who manifest one of the deleterious HNPCC germ-line mutations. Aarnio found a 9% lifetime risk for ovarian cancer among members of HNPCC families who developed cancers [177]. Certain HNPCC syndrome families appear to have a marked excess of endometrial and ovarian carcinomas. Vasen et al. analyzed 34 HNPCC syndrome families and found 19 that were associated with either \( h\text{MLH1} \) or \( h\text{MSH2} \) mutations [136]. The lifetime risk for colorectal cancer was the same in families that carried \( h\text{MLH1} \) mutations (80%) as it was for families that carried \( h\text{MSH2} \) mutations. However, there was a trend, which did not reach statistical significance, toward higher frequency of ECs in \( h\text{MSH2} \) mutation carriers (61%), compared with \( h\text{MLH1} \) mutation carriers (42%). Only \( h\text{MSH2} \) mutation carriers had an increased relative risk for ovarian cancers based on age-specific rates of this disease in the Dutch National Registry [136]. On the other hand, Jäger et al. studied 21 HNPCC syndrome families for \( h\text{MLH1} \) and \( h\text{MSH2} \) mutations and discovered an \( h\text{MLH1} \) intron 14 mutation in five families who had significantly fewer extraluminal cancers than those who did not carry this mutation [178].

**Implications for Management**

Pursuant with their high risk for gynecologic cancers, women in the direct line of autosomal dominant transmission of the cancer susceptibility traits from HBOC and HNPCC...
syndrome kindreds are counseled regarding the availability of DNA testing and management strategies including surveillance, stressing its limitations, and the potential benefits of prophylactic surgery. Our most current data indicate a mean age for developing ovarian cancer of 51 years (SD = 10.7 years) in HBOC kindreds and 43 years (SD = 10.8 years) in families with HNPCC syndrome (Creighton Hereditary Cancer Registry). The youngest ages at which we have observed ovarian cancer was 26 years in the HBOC syndrome and 24 years in a patient with the HNPCC syndrome. The mean age at which EC was diagnosed in association with HNPCC syndrome was 48 years, and the youngest patient diagnosed with EC was 31 years of age (Creighton Hereditary Cancer Registry). Therefore, genetic counseling of these young women should begin in their late teens.

The discovery that ovarian cancer is highly associated with germ-line mutations in selected hereditary lineages, such as BRCA1 185delAG and BRCA2 6174delT mutations in Ashkenazi Jewish populations, helps to target genetic counseling and more finely focus DNA testing when acceptable to individual patients.

Presently available methodologies for ovarian cancer detection are insufficiently sensitive and too nonspecific to be recommended for general population screening [179]. However, from populations at such exceedingly high genetic risk for this disease as those discussed in this article, individuals may be selected by pedigree analysis, linkage studies, and DNA sequence testing for special attention. In such cases, screening and surveillance with baseline and interval multiple serum tumor marker titers and pelvic ultrasound screening are recommended. Serial determinations of multiple markers identified with ovarian carcinoma, together with transvaginal ultrasound scanning and intensive evaluation of any significant persisting rise in tumor marker titer or suspicious ultrasound change, is presently the most secure approach for following patients who are at increased genetic risk for ovarian cancer [180-193].

Encouraged by the strongly protective effect reported for oral contraceptive medications against endometrial and ovarian cancer and some indication that this may apply to women from families with ovarian cancer as well as the general population [194-198], we have previously recommended use of low-dose combined estrogen-progestin oral contraceptives to women from HBOC and HNPCC syndrome families before plans for conception and between pregnancies. However, though a large population-based study in Utah found increasing parity to be protective against ovarian cancer to an odds ratio of 0.29 for women with six or more children, increasing parity was not protective for women with strong family histories of ovarian cancer [199], and an analysis of 2,249 breast cancer cases from a cohort of 89,132 women ages 30-55 in the prospective Nurses Health Study [200] showed that the consistent risk for breast cancer in women whose mother or sister had this disease was increased approximately 50% by their first pregnancy. Parous women whose mother or sister had breast cancer were at higher risk for breast cancer than nulliparous women with a family history of breast cancer, in contrast to the protective effect pregnancy has for women without a family history [200]. Other recent studies indicate that oral contraceptive use has been associated with significantly increased risk for breast cancer among younger women and current or recent users [201-203].

It is quite possible that the increased scrutiny afforded young women on oral contraceptive medications may result in the detection of more and earlier breast cancers that could have gone unnoticed in other young women not using these drugs. Given the decreased efficacy of mammographic screening and physical examination for detecting small tumors in the dense breasts of young premenopausal women and the earlier ages at which breast cancers manifest in hereditary cancer families, until further data become available more clearly defining the relative risks for breast and ovarian carcinomas in BRCA1 and BRCA2 mutation carriers who use oral contraceptives, we are no longer able to recommend the drugs for cancer prophylaxis in women from HBOC syndrome families. On the other hand, there is substantial evidence that oral contraceptives are protective against EC as well as ovarian cancer [194-197, 199, 204, 205], and oral contraceptives are recommended for chemoprophylaxis in HNPCC syndrome patients who are not at such a significantly increased risk for breast cancer.

Management of women at genetic risk with HBOC syndrome includes semiannual physical breast and pelvic examinations and annual mammograms. They are also taught and encouraged to do monthly self breast examinations. We obtain baseline multiple tumor marker determinations, currently CA 125, CA 1S-3, CA 72-4, and NB/70-K, each of which is commercially available, and follow these at six-month intervals; ultrasound scans are followed at 6-12-month intervals, depending upon the ease of physical pelvic examination [180-193, 206-208]. Our follow-up strategies for women at genetic risk from HNPCC syndrome families also include a pelvic ultrasound scan, which allows evaluation of the ovaries and endometrium and quantitation of the endometrial stripe. These patients are advised to undergo endometrial screening for cytology and histology and annual colonoscopic examinations. All women in our clinics are advised to adhere to a balanced diet, restricting intake of fat and carbohydrates to maintain reasonable body weight for general good health, whether or not these measures provide any special protective value to women at genetic risk for gynecologic cancers.
To determine the probable efficacy of prophylactic mastectomy and oophorectomy for preventing breast and ovarian cancer, Schrag et al. [209] examined the effects of these procedures through a decision analysis comparing prophylactic mastectomy and oophorectomy with no prophylactic surgery among women who harbor mutations for BRCA1 and BRCA2. They concluded that 30-year-old women who carry BRCA1 or BRCA2 mutations gain from 2.9 to 5.3 years of life expectancy from prophylactic mastectomy and from 0.3 to 1.7 years of life expectancy from prophylactic oophorectomy.

Grann et al. [210] used a Markov model in order to determine the survival, quality of life, and cost-effectiveness of prophylactic mastectomy and prophylactic oophorectomy among women with BRCA1 or BRCA2 germ-line mutations. Their findings showed that prophylactic surgery at a young age substantially improved survival among women who tested positive for these mutations. However, unless the genetic risk for breast or ovarian cancer was high, it did not provide any benefit for quality of life. Prophylactic surgery was found to be cost-effective for years of life saved when compared with other medical interventions such as screening for ovarian cancer [210].

Prophylactic mastectomy may alter body image and decrease a woman’s sense of femininity, while oophorectomy will lead to premature menopause, increase the risk for osteoporosis and cardiovascular disease, and may require the burden of hormone replacement therapy. However, the study by Grann et al. did not take into account the reduction in anxiety that prophylactic surgery may provide to patients who are aware of a strong family history of breast and/or ovarian cancer. Certainly, some of these patients may be inordinately preoccupied with their life expectancy and the fear of dying of cancer, and therefore prophylactic surgery may be a prudent choice for such patients. On the other hand, prophylactic surgery may not be chosen by patients who have adjusted emotionally to their increased risk for cancer and believe that surveillance measures may successfully detect early, still-curable cancer. We have found in counseling women with BRCA1 and BRCA2 mutations, that most of those who consider the option of prophylactic oophorectomy or mastectomy state that they want to live to provide care for their young children.

Narod’s group [211] analyzed 333 BRCA1 mutation carriers and found ovarian cancer to be rare in women below age 40 years and a cumulative incidence of only 19.5% before age 50 years, while the cumulative incidence of breast cancer was 52.5% by age 50 years. In the model by Schrag et al. [209], gains of life expectancy declined with age at the time prophylactic surgery was done, but prophylactic oophorectomy in 30-year-old BRCA mutation carriers may be delayed for ten years with little loss of life expectancy [210]. Therefore, with thorough counseling and meticulous surveillance, mutation-positive women may elect to complete childbearing before proceeding with prophylactic oophorectomy.

In our experience [212-214], it has been the choice of most women confronted with this decision to delay prophylactic oophorectomy until the middle of their fourth decade of life or later after completing their planned childbearing.

When counseling regarding prophylactic oophorectomy, it is essential to consider the residual risk for primary peritoneal carcinomatosis, a disease which mimics ovarian serous carcinomas in both histology and morbidity. Whether or not women who carry genetic mutations predisposing to ovarian carcinomas also harbor an increased risk for primary peritoneal carcinoma is the subject of our ongoing investigations, but the best estimate from published cases and series is that this disease affects fewer than 5% of women who have undergone prophylactic oophorectomies because of ovarian cancers in first- and second-degree relatives [215-217].

These considerations, together with the patient’s personal perceptions and experience in dealing with cancer, often involving observations and care of afflicted family members, will influence her decisions regarding acceptance of proposed management strategies, including surveillance protocols and prophylactic surgery. Determination of a positive mutation carrier status through genetic linkage studies or DNA sequence testing makes the choice of prophylactic oophorectomy quite compelling.
When prophylactic surgery is undertaken for prevention of ovarian cancer, we prefer video laparoscopy, assisted bilateral salpingo-oophorectomies, and vaginal hysterectomy [218]. With little discomfort and low morbidity, this technique allows thorough inspection of the peritoneal and visceral surfaces, saline washings for peritoneal cytology, and biopsies of suspicious tissues, and it permits complete and wide extirpation of the adnexa, including fallopian tubes, ovaries, and surrounding ligaments with en bloc removal of the uterus per vaginam. Removal of the uterus and complete adnexa at the time of surgery simplifies and may improve the benefits and decrease the risks of hormone replacement therapy, removes the endometrium as a source of primary cancer in HNPCC syndrome, and removes the fallopian tubes, which may be at risk for primary cancer in patients with *BRCA1* mutations [219]. Improvements in postmenopausal cholesterol and high-density lipoproteins with estrogen replacement may be diminished by superimposing exogenous progestin, which must be given for endometrial protection if the uterus is left intact. Moreover, recent publications raise the possibility that progestin in addition to estrogen replacement may increase the risk for postmenopausal breast cancer still further [220, 221].

**CONCLUSION**

Significant progress has been made over the past 30 years in defining women who are at increased hereditary and environmental risk for gynecologic cancers and, in many cases, identifying the specific loci of responsible germ-line mutations through linkage analysis and/or DNA sequencing. However, negative tests pose no guarantee that a hereditary factor is not responsible. Much work needs to be done to elucidate possible recessive and low penetrant genes which increase cancer risk in conjunction with as-yet-undiscovered co-factors. Environmental and, perhaps, hereditary explanations are needed for so-called somatic mutations that seem to require “two hits” for loss of heterozygosity and initiation of carcinogenesis according to the Knudson hypothesis. Laboratory tests and linkage analysis will need to be expanded to encompass all the coding regions of all deleterious mutations. Techniques must be refined and results assured to avoid errors in collection, testing, and reporting. While genetic testing can be highly supportive to rational management decisions, responsible clinicians will expectantly counsel and wisely follow those patients whose extended pedigrees indicate passage of cancer susceptibility traits, even when genetic testing is negative, unavailable, or unacceptable. In addition, when pedigrees are more limited, the occurrence of multiple breast, ovarian, colorectal, and ECs in first- and/or second-degree relatives can provide the key to increased hereditary cancer risk, which the astute clinician will be wise to evaluate and follow [222-225].

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