Hereditary Cancer Syndromes and Risk Assessment

**ABSTRACT:** A hereditary cancer syndrome is a genetic predisposition to certain types of cancer, often with onset at an early age, caused by inherited mutations in one or more genes. Cases of cancer commonly encountered by obstetrician–gynecologists or other obstetric–gynecologic providers—such as breast cancer, ovarian cancer, and endometrial cancer—are features of specific hereditary cancer syndromes. The most common hereditary cancer syndromes related to gynecologic cancer include hereditary breast and ovarian cancer syndrome, Lynch syndrome, Li–Fraumeni syndrome, Cowden syndrome, and Peutz–Jeghers syndrome. A hereditary cancer risk assessment is the key to identifying patients and families who may be at increased risk of developing certain types of cancer. Screening should include, at minimum, a personal cancer history and a first- and second-degree relative cancer history that includes a description of the type of primary cancer, the age of onset, and the lineage (paternal versus maternal) of the family member. In addition, a patient’s ethnic background can influence her genetic risk. If a hereditary cancer risk assessment suggests an increased risk of a hereditary cancer syndrome, referral to a specialist in cancer genetics or a health care provider with expertise in genetics is recommended for expanded gathering of family history information, risk assessment, education, and counseling, which may lead to genetic testing.

**Recommendations**

- A hereditary cancer risk assessment is the key to identifying patients and families who may be at increased risk of developing certain types of cancer. This assessment should be performed by obstetrician–gynecologists or other obstetric–gynecologic providers and should be updated regularly.

- If a hereditary cancer risk assessment suggests an increased risk of a hereditary cancer syndrome, referral to a specialist in cancer genetics or a health care provider with expertise in genetics is recommended for expanded gathering of family history information, risk assessment, education, and counseling, which may lead to genetic testing.

**Introduction**

A hereditary cancer syndrome is a genetic predisposition to certain types of cancer, often with onset at an early age, caused by inherited mutations in one or more genes. Frequently, these genetic mutations also result in cancer that affects multiple organs. Most hereditary cancer syndromes exhibit autosomal dominant inheritance. Cases of cancer commonly encountered by obstetrician–gynecologists or other obstetric–gynecologic providers—such as breast cancer, ovarian cancer, and endometrial cancer—are features of specific hereditary cancer syndromes. The most common hereditary cancer syndromes related to gynecologic cancer include hereditary breast and ovarian cancer syndrome, Lynch syndrome, Li–Fraumeni syndrome, Cowden syndrome, and Peutz–Jeghers syndrome (Table 1). Obstetrician–gynecologists or other obstetric–gynecologic providers play an important role in the identification and referral of women at risk of these conditions. The focus of this Committee Opinion is hereditary cancer syndromes that include risks of breast cancer, ovarian cancer, and endometrial cancer.

**Family and Medical History Screening**

A hereditary cancer risk assessment is the key to identifying patients and families who may be at increased risk of developing certain types of cancer. This assessment...
should be performed by obstetrician–gynecologists or other obstetric–gynecologic providers and should be updated regularly.

A patient intake form, which includes a review of systems and conditions that may exist in the patient or her family, is used in many office settings to gather information quickly. The American College of Obstetricians and Gynecologists’ Committee Opinion 478, Family History as a Risk Assessment Tool, establishes the general concept of collecting a family history and designing a pedigree (1). However, specific information must be considered when assessing the risks related to hereditary cancer syndromes. Online versions of an intake form, similar to the Surgeon General’s “My Family Health Portrait,” exist to facilitate the documentation of a comprehensive family history (2). In addition, the American Society of Clinical Oncology Cancer Genetics Subcommittee convened a consensus conference in February 2012, leading to the “American Society of Clinical Oncology Expert Statement: Collection and Use of a Cancer Family History for Oncology Providers” (3). The hereditary cancer risk assessment should be updated regularly to reflect changes in the patient’s medical and family history and to gather information regarding diseases that may be associated with familial cancer syndromes. Screening should include, at minimum, a personal cancer history and a first- and second-degree relative cancer history that includes a description of the type of primary cancer, the age of onset, and the lineage (paternal versus maternal) of the family member (Box 1). In addition, a patient’s ethnic background can influence her genetic risk; thus, understanding this background is relevant in assessing a patient’s predisposition to a hereditary cancer syndrome (eg, BRCA mutations and Ashkenazi Jewish descent). Individuals typically are considered to be of Ashkenazi Jewish descent if their Jewish relatives originate from Eastern or Central Europe. Certain features of a person’s personal or family medical history suggest a possible hereditary cancer syndrome. Clues that a hereditary cancer syndrome may be present include the following (3):

- Cancer diagnosed at an unusually young age
- Several different types of cancer in the same person

### Table 1. Summary of Syndromes With Malignant Manifestations Associated With Breast Cancer and Ovarian Cancer

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Breast</th>
<th>Ovarian</th>
<th>Endometrial</th>
<th>Colon</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hereditary breast and ovarian cancer</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>Gastric, ureteral, biliary, pancreatic, glioblastoma</td>
</tr>
<tr>
<td>Lynch</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>Sarcomas, bone, brain, adrenocortical</td>
</tr>
<tr>
<td>Li–Fraumeni</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>Thyroid, benign hamartomas</td>
</tr>
<tr>
<td>Cowden</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td>Cervical, pancreatic, gastric (Hamartomas)</td>
</tr>
<tr>
<td>Peutz–Jeghers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Committee Opinion No. 634

If a hereditary cancer risk assessment suggests an inherited cancer or hereditary cancer syndrome, referral to a Genetics Specialist may be recommended as a means of identifying patients at risk of a hereditary cancer syndrome. There are numerous resources that address genetic counseling as a means of determining which patients have a genetic basis for a cancer diagnosis. The document “A Practice Guideline From the American College of Medical Genetics and Genomics and the National Society of Genetic Counselors: Referral Indications for Cancer Predisposition Assessment” can help identify patients who would benefit from genetic counseling.

Referral to a Genetics Specialist

There are numerous resources that address genetic counseling as a means of identifying patients at risk of a specific inherited cancer or hereditary cancer syndrome. If a hereditary cancer risk assessment suggests an increased risk of a hereditary cancer syndrome, referral to a specialist in cancer genetics or a health care provider with expertise in genetics is recommended for expanded gathering of family history information, risk assessment, education, and counseling, which may lead to genetic testing. Although such condition-specific documents are valuable, complex algorithms and narrow focus limit their usefulness in a clinical setting. The 2015 practice guideline published by the American College of Medical Genetics and Genomics and the National Society of Genetic Counselors circumvents these barriers by allowing a personal or family history of nearly any cancer to be cross-referenced to cancer-specific medical and family history, so the appropriateness of cancer genetic counseling can be determined. Personal and family histories are key elements in determining the appropriateness of genetic counseling for cancer. Appropriateness of genetic counseling is distinct from who is an appropriate candidate for genetic testing. Genetic testing is discussed in the genetic counseling visit. Genetic testing is guided by family history, pedigree analysis and, in some cases, risk models that include such things as pathology reports and confirmation of cancer diagnoses with medical records, death certificates, or both. Genetic testing requires specific patient education and informed consent. Referral for genetic evaluation and genetic testing of affected family members may be recommended to help determine if there is a genetic basis for a cancer diagnosis. The document “A Practice Guideline From the American College of Medical Genetics and Genomics and the National Society of Genetic Counselors: Referral Indications for Cancer Predisposition Assessment” can help identify patients who would benefit from genetic counseling.

Most Common Hereditary Cancer Syndromes Related to Gynecologic Cancer

Hereditary Breast and Ovarian Cancer Syndrome

Hereditary breast and ovarian cancer syndrome is caused by germline mutations in one or both of the autosomal dominant DNA repair genes BRCA1 and BRCA2. Although most cases of breast cancer and ovarian cancer in the United States occur sporadically, BRCA1 and BRCA2 mutations are present in 5–15% of cases of these types of cancer. The carrier frequency of hereditary breast and ovarian cancer syndrome is approximately 1 in 500 individuals in the general population, but it has a prevalence of 1 in 40 individuals in the Ashkenazi Jewish population. In men, BRCA mutations are associated with breast cancer, prostate cancer, and pancreatic cancer. Therefore, it is important to inquire about maternal and paternal ancestry in male and female relatives. Hereditary breast and ovarian cancer syndrome, as well as many of the other hereditary cancer syndromes, displays incomplete penetrance (meaning that not everyone with a gene mutation will develop cancer). Women with hereditary breast and ovarian cancer syndrome have a 65–74% lifetime risk of breast cancer and a 39–46% (BRCA1) or a 12–20% (BRCA2) risk of ovarian cancer.

Lynch Syndrome

Lynch syndrome, also known as hereditary nonpolyposis colorectal cancer, is a highly penetrant autosomal dominant hereditary cancer syndrome caused by defects in the DNA mismatch repair system. It has a population prevalence of approximately 1 in 600 to 1 in 3,000 individuals. The presence of Lynch syndrome increases the lifetime risk of colon cancer (52–82%), endometrial cancer (25–60%), and ovarian cancer (4–24%). Lynch syndrome accounts for most cases of hereditary uterine cancer and colorectal cancer and is the second most common cause of inherited ovarian cancer (after hereditary breast and ovarian cancer syndrome). Approximately 3–5% of cases of uterine cancer are attributable to a
hereditary cause, whereas 8–24% of cases of ovarian cancer are likely inherited (13).

Other neoplasms associated with Lynch syndrome include gastric cancer, small-bowel cancer, hepatobiliary cancer, and renal pelvis and ureteral cancer, as well as some types of breast cancer, certain brain tumors, and sebaceous skin tumors (13). By identifying individuals at risk of Lynch syndrome, physicians are able to offer screening and prevention strategies to reduce morbidity and mortality due to this syndrome. For more information on identifying individuals at risk of Lynch syndrome, please see Practice Bulletin 147, *Lynch Syndrome*, as well as the 2015 practice guideline published by the American College of Medical Genetics and Genomics and the National Society of Genetic Counselors (7, 13).

**Li–Fraumeni Syndrome**

Li–Fraumeni syndrome is a rare autosomal dominant condition with increased risk of multiple tumors, including osteosarcoma, breast cancer, colon cancer, adrenal cortical carcinoma, leukemia and lymphoma, and brain cancer. The exact prevalence of Li–Fraumeni syndrome is unknown. One U.S. registry of patients with Li–Fraumeni syndrome suggests that approximately 400 people from 64 families have this condition (15). Li–Fraumeni syndrome is caused by germline mutations in the tumor suppressor gene, *TP53*; more than 70% of individuals with a clinical diagnosis of Li–Fraumeni syndrome have a detectable mutation in the *TP53* gene (16). Li–Fraumeni syndrome is highly penetrant, with a 90% risk of cancer by age 60 years (17). Patients with a personal diagnosis of Li–Fraumeni syndrome-associated malignancies (eg, soft tissue sarcomas, osteosarcomas, premenopausal breast cancer, brain tumors, and adrenocortical carcinomas), especially with multiple family members with these types of cancer (due to the high penetrance of the disease), should be referred to a specialist in cancer genetics for further evaluation for Li–Fraumeni syndrome.

**Cowden Syndrome**

Cowden syndrome is an autosomal dominant condition caused by mutations in the phosphatase and tensin (*PTEN*) gene, which is involved in cell cycle control (18). It is relatively rare, with a population prevalence of 1 in 200,000 (19). Cowden syndrome is one of the hamartomatous syndromes and is characterized by benign and malignant neoplasms of the thyroid, breast, and endometrium. Affected individuals usually have macrocephaly (20). Pathognomonic skin lesions, including papillomatous papules on the face and mucous membranes (Fig. 1), are nearly always present by age 30 years. Cowden syndrome carries a high lifetime risk of

---

breast cancer (25–50%) and endometrial cancer (5–10%) and should be suspected in any family with Cowden syndrome-associated neoplasms and conditions, which are classified as pathognomonic, major and minor criteria (7). Given the complexity of determining which patients and families should be referred for genetic counseling for further evaluation of Cowden syndrome, clinicians should consult frequently updated guidelines such as GeneReviews® to determine which patients are appropriate for further genetic evaluation (20).

Peutz–Jeghers Syndrome

Peutz–Jeghers syndrome is an autosomal dominant condition caused by mutations in the serine/threonine kinase 11 (STK11) gene. It is characterized by the presence of two of the following three criteria: 1) two or more hamartomatous polyps throughout the gastrointestinal tract; 2) mucocutaneous hyperpigmentation of the mouth, lips, nose, eyes, genitalia, or fingers (Fig. 2); and 3) a family history of Peutz–Jeghers syndrome (7). Peutz–Jeghers syndrome also is associated with an increased risk of breast cancer, ovarian cancer, cervical cancer (especially the histologic diagnosis of adenoma malignum), uterine cancer, pancreatic cancer, lung cancer, stomach cancer, gastric cancer, and colon cancer, as well as ovarian sex cord tumors. Women with Peutz–Jeghers syndrome have a 50% lifetime risk of developing breast cancer as well as an increased risk of ovarian cancer, uterine cancer, and cervical cancer. Given the complexity of determining which patients and families should be referred for genetic counseling for further evaluation of Peutz–Jeghers syndrome, clinicians should consult frequently updated guidelines such as GeneReviews® to determine which patients are appropriate for further genetic evaluation (21).


Resources

The following resource is for information purposes only. Refer to this source does not imply the endorsement of the American College of Obstetricians and Gynecologists. This resource is not meant to be comprehensive. The exclusion of a source or web site does not reflect the quality of that source or web site. Please note that web sites are subject to change without notice.


References


