Every year, approximately 22,000 women are diagnosed with ovarian cancer. In the United States, the disease is the fifth leading cause of cancer-related deaths among women and is the deadliest of gynecologic cancers. The American Cancer Society estimated that 14,240 women would die of ovarian cancer in 2016.

One major challenge in treating ovarian cancer is that there is no reliable screening test for early detection. In addition, the disease’s initial symptoms tend to be vague or nonspecific, further compounding the difficulty in detection. However, even in later stages, a diagnosis of ovarian cancer is not necessarily a death sentence. For many patients, advances in chemotherapy, surgery, and other treatment resources offer hope for long-term survival or even a cure. Indeed, researchers are cautiously optimistic that advances in understanding the etiology of ovarian cancer will eventually lead to an early detection breakthrough and significant improvement in the long-term outlook for many patients.

**Types and stages**

What do we know about ovarian cancer? Surprisingly, it is not just one disease. In fact, there are more than 30 different types of ovarian cancer, as defined by the cell type responsible for the disease’s origin. How the cancer behaves can vary considerably depending on the cell type where the cancer began.

“When we talk about ovarian cancer, in general, we’re talking about some common specific types,” says Gary Leiserowitz, MD, MS, chair of...
Risks and research

“Ovarian cancer doesn’t seem to have a prolonged precancerous stage, or even a prolonged Stage I when it’s confined to the ovaries, that is easy to detect. Unlike some other cancers, such as cervical or colon cancer, we don’t always have the opportunity to catch it early while it’s still much more treatable and curable. Many women can go very quickly from being asymptomatic or disease-free to having advanced cancer when it spreads beyond the ovaries, to Stage III, the most common stage when we find the disease.

“Early screening and prevention is also complicated by the fact that there are many different types of cancer of the ovaries, including low-grade serous, high-grade serous, clear cell, endometrioid, and mucinous cancer, each with distinct etiologies. The processes these types go through in becoming cancerous is probably very different. This has made it much more complicated to get at specific prevention strategies and novel early screening detection techniques for these smaller subsets of ovarian cancer. It also makes research more difficult, as far as getting enough patients among these five different subsets together.”

—Kristin Zorn, MD

Significantly, when ovarian cancer is confined to the ovary, the five-year survival rate is more than 90 percent.1 However, Dr. Leiserowitz notes that most cases are diagnosed at the more advanced stage III (or stage IV), for which the five-year survival rate is less than 40 percent. Overall, most ovarian cancers fall into the category of “high-fatality cancers,” alongside lung and pancreatic cancer, for example.

What types of ovarian cancer are diagnosed most frequently? “There are three major types of ovarian cancer, the most common of which is epithelial cancer,” says Dr. Leiserowitz, who is also the chief of gynecologic oncology at the UC Davis Comprehensive Cancer Center. “The most common among the epithelial cancers is called serous cancer. [Approximately] 75 to 80 percent of the cancers of the ovary are epithelial, of which most turn out to be what are called high-grade serous cancers. Another type of ovarian cancer is germ cell cancer. This is more commonly seen in young patients in their teens and 20s, and represents about 10 percent of ovarian cancers. Then there is a third group, called sex cord–stromal tumors. These are uncommon and represent about 5 to 10 percent of ovarian cancer cases.”

Notably, the prognosis and treatment for ovarian cancer will depend on not only the cancer type but also the stage at the time of diagnosis. Dr. Leiserowitz summarizes the stages as follows:

- **Stage I.** The cancer is confined to the ovary.
- **Stage II.** The cancer has spread to the pelvic organs.
- **Stage III.** One or both of the following are present:
  - The cancer has spread to the organs within the abdominal cavity outside of the pelvis.
  - The cancer involves the lymph nodes around the pelvic and aortic regions.
- **Stage IV.** The cancer has either spread into the fluid in the chest or into a solid organ like the liver.

There are also substages within these four stages, reflecting more specific disease location. The current staging definitions are based on guidelines adopted in 2012 by the International Federation of Gynecology and Obstetrics (FIGO), which are updated from the 1988 guidelines.4

Diagnostic challenges

As noted, a timely diagnosis of ovarian cancer can be difficult because early symptoms of the disease tend to be vague, involving such common ailments as abdominal discomfort, fatigue, or other nonspecific issues. A challenge for primary care physicians is that when a woman presents with nonspecific symptoms, the physician has to think of the whole range of diseases that could possibly be the root cause, according to Dr. Leiserowitz. “As a physician, you typically consider the most common conditions first before you move to the less common diseases. Ovarian cancer is an uncommon disease that mimics many more conditions. Because of this, consideration of other conditions by the patient and her physician may lead to a delay in diagnosis that ranges from weeks to months.”

To illustrate these diagnostic challenges, Dr. Leiserowitz asks us to consider two scenarios from recently diagnosed cases. The first involves a woman in her early 80s who presented with progressive abdominal swelling, tightness, bloating, and decreasing appetite. These symptoms progressed over several months. Seen by several physicians, the initial clinical impression was that she might have either gastroesophageal reflux disease (GERD) or other stomach problems. Further evaluation involved looking for possible gallbladder problems or perhaps irritable bowel syndrome (IBS).

“In this case, the physician investigates if the patient has reflux disease or irritable bowel syndrome, or perhaps gastroenteritis or something of that nature,” remarks Dr. Leiserowitz. “But eventually the patient does not respond to the normal treatments and ends up getting an imaging test, such as an ultrasound or CT scan.
Then, lo and behold, the person is found to have a pelvic mass, intra-abdominal metastases, and ascites [i.e., abnormal accumulation of fluid in the abdominal cavity]. At this point, with the results of an imaging test at hand, it’s not hard to figure out that ovarian cancer might be the explanation. Unfortunately, this is a scenario in which the diagnosis has been delayed.

The second patient scenario involves a woman who presents with a hard pelvic mass. “In this case, the patient is examined and the mass is felt in the abdomen,” says Dr. Leiserowitz. “The patient then has an imaging test, a CT scan, or an ultrasound that finds a pelvic mass. She may not have ascites or another disease, but it’s pretty obvious she needs an operation. So we proceed to surgery and remove the mass, which may turn out to be a less aggressive cancer that may have grown slowly over a longer period of time but hasn’t spread.”

As these two scenarios illustrate, the presentation of ovarian cancer and its prognosis may vary considerably from patient to patient. “The second patient has a good prognosis, but the first patient’s prognosis is not as good,” notes Dr. Leiserowitz. “And yet they both have an ovarian cancer. In the second case, what we see is that … it’s the behavior of the cancer that gives us time to figure out the problem. But in the first scenario, the vague, nonspecific symptoms allow the cancer to delay detection by flying under the radar. This makes the diagnosis very difficult to figure out, until finally somebody gets an imaging test to determine what is going on.”

At present, two tests are used as diagnostic tools for ovarian cancer: transvaginal ultrasound (TVUS) and the CA 125 blood test. While patients identified as high-risk often undergo these tests, neither one is recommended for routine screenings for ovarian cancer.

At UC Davis Comprehensive Cancer Center, Dr. Leiserowitz and his colleagues have been involved in research designed to identify potential early biomarkers for ovarian cancer. One area of investigation for the UC Davis team focuses on the role of glycans, which are sugars connected to proteins that change in the presence of ovarian cancer. The hope is to eventually develop a blood test that would provide a reliable diagnostic measure of these changes in the body.

“In our case, we looked at sugar molecules that are attached to the proteins that are altered as a consequence of the cancer process itself,” explains Dr. Leiserowitz. “There are also other types

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of compounds that are by-products of metabolic processes that happen in the ovaries that may be an indication of ovarian cancer.”

Overall, this area of research involves what is called “-omics,” notes Dr. Leiserowitz, examples of which include proteomics (the study of protein compounds), glycomics (the study of the sugar molecules), and metabolomics (the study of the by-products of metabolic events from the ovary itself). Much of this complex and challenging research into identifying reliable biomarkers for ovarian cancer remains under active investigation.

**The promise of genetics**

Another promising area of research involves the genetics of ovarian cancer. Notably, about 20 to 25 percent of ovarian patients have a hereditary link to the disease. Hereditary breast and ovarian cancer (HBOC) syndrome, as the name suggests, includes women who have an increased risk for breast, ovarian, and other cancers. About 15 percent of women with ovarian cancer have a mutation in *BRCA1* or *BRCA2*, the two most common genes in HBOC. However, research is now suggesting that other genes that work in the same cellular pathways as *BRCA1* and *BRCA2* also can be involved in HBOC.7

“We now have increased understanding of the ways genetics impact ovarian cancer,” says Kristin Zorn, MD, director of the Division of Gynecologic Oncology at the University of Arkansas for Medical Sciences in Little Rock.

“One way is through inherited mutations that are being passed through the family in what we call *germline mutations*. This means that a parent of either sex can pass on the mutation to a child of either sex because it is an autosomal dominant inheritance pattern. As well, we’re also understanding that many times the tumor itself has mutations called *somatic mutations* that are extremely important in ovarian cancer.”

Women with germine mutations in *BRCA1* or

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**Favorable factors**

Factors that may *decrease* the risk of ovarian cancer include the following:

- Oral contraceptive use (birth control pills)
- Pregnancy
- Breastfeeding
- Hysterectomy or tubal ligation

**Concerning characteristics**

Factors that may *increase* the risk of ovarian cancer include the following:

- Older than 55
- No pregnancies
- Menopausal hormone replacement therapy
- Endometriosis

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BRCA2 have up to an 85 percent lifetime risk of breast cancer and up to a 46 percent lifetime risk of ovarian, tubal, and peritoneal cancers, according to the Society of Gynecologic Oncology (SGO). Notably, the SGO recommends that all women diagnosed with epithelial ovarian, tubal, and peritoneal cancers should be offered genetic testing and counseling, even without a family history of cancer.8

For Dr. Zorn and other researchers, new insights into understanding the genetics of ovarian cancer are extremely significant. “We actually have therapy now that is impacted by our knowledge of genetic mutations,” says Dr. Zorn. “We know that women who have germline or somatic mutations in BRCA1, BRCA2, or related genes are more likely to respond to chemotherapy. They’re also more likely to respond to a new class of medications called PARP [poly (ADP-ribose) polymerase] inhibitors. This knowledge has really revolutionized our field and changed the standard of care. Now, when a woman is diagnosed with ovarian cancer, or one of the related cancers, [for example,] fallopian tube or peritoneal cancer, we need to think about the genetic question and have that be part of our basic treatment plan for her.”

From understanding the link with BRCA1 and BRCA2, there are now at least 11 genes proven to be associated with increased risk of ovarian cancer, says Dr. Zorn. “This knowledge has expanded our ability to identify families that have one of these mutations. Perhaps the biggest way we’re impacting ovarian cancer prevention right now is by identifying people who carry these mutations and therefore can undergo prevention strategies to manage that risk. Rather than waiting for them to get ovarian cancer, we’re now trying to prevent the cancer before it ever starts.”

In many ways, the popular impression of ovarian cancer as essentially a death sentence is indeed a misunderstanding. “A lot of the negative news about ovarian cancer is based on the fact that we do have a relatively low cure rate, only about 20 to 30 percent,” acknowledges Dr. Zorn. “But what is sometimes missed is that we also have very effective treatment strategies that, for some women, do end in a cure. Other women, even if they have a recurrence, can significantly prolong their lives and still have a very reasonable quality of life. We have many women with ovarian cancer who are now living five years, seven years, and even longer past their diagnosis. It’s not necessarily time off from chemotherapy, but it’s still valuable time when most of them are able to enjoy many aspects of their lives.”

Concurrently, ovarian cancer is often quite responsive to treatment. “Ovarian cancer is actually one of the cancers that is most sensitive to chemotherapy,” says Dr. Zorn. “When a woman is first starting her treatment for ovarian cancer, she has about a 75 percent chance that her cancer is going to respond to the chemotherapy and go into remission. It’s usually the combination of surgery and chemotherapy that accomplishes this. However, about 75 percent of the time it’s going to come back despite treatment. So while we can’t cure as many women as we would like with chemotherapy, for many women we are able to control the disease for long periods of time.”

**Diagnosis not a prognosis**

A recent UC Davis study of 11,541 individuals with epithelial ovarian cancer found that nearly one-third survived at least 10 years after diagnosis.9 What is especially significant about these findings is that among 3,582 long-term survivors, 954 were classified as high-risk for recurrence due to either the advanced stage or high grade of their tumor, or their age at the time.
of diagnosis. Generally, long-term survival is associated with younger patients with early-stage cancer and lower-grade tumors. "The first important message from this study is that a diagnosis of ovarian cancer does not by itself tell a patient about her prognosis," says Dr. Leiserowitz, who with lead author and UC Davis epidemiologist Rosemary Cress, MPH, PhD, contributed to a 2015 paper on the study for Obstetrics and Gynecology.10 “You need a lot more information about the cancer because there are very different kinds of biological aggressiveness. The second message is that there is a significant segment of people who have high-risk, advanced-stage disease who have an amazing response to their treatments and are long-term survivors.”

There are likely multifactorial causes for why some patients with similar ovarian cancer profiles survive much longer than others, says Dr. Leiserowitz. “For people who have advanced-stage disease, we know that aggressive surgery with the goal of removing all of the visible disease is key. Use of chemotherapy is critical. And, when appropriate, use of intraperitoneal chemotherapy [i.e., inserting anticancer drugs directly into the abdominal cavity] turns out to be very effective. It’s also important to figure out whether somebody has the [hereditary] breast-ovarian cancer syndrome. It turns out that if they do, we know those people survive for longer periods of time, and there are specific, newer medications that these cancers respond to. This is an emerging area of new therapeutic options. But there will be new factors that impact treatment and prognosis that we haven’t yet figured out. There may be genetic differences contained within the cancers themselves that determine behavior that is different from the appearance of the cell type under the microscope.”

Supportive care

Naturally, a serious illness like ovarian cancer can be both a physical and emotional challenge for patients. As patients undergo treatment, they need not only appropriate clinical care but also social and psychological support.

“A diagnosis of cancer can feel like the bottom has dropped out of your world,” says Elizabeth Isham Cory, an ovarian cancer survivor from Huntley, Illinois, and national vice chair on the board of directors of the National Ovarian Cancer Coalition (NOCC). Cory is a more-than-11-year survivor of ovarian cancer, diagnosed at the age of 46 in May 2005. “Certainly there’s no denying that feeling and the reality of such a diagnosis. But it doesn’t have to be devastating. In fact, there is a lot of hope for patients.”

Cory was diagnosed with what was considered a mildly aggressive form of Stage IB cancer. “In my case, it hadn’t spread beyond the one ovary, but the form of the cancer was a little more aggressive than usual,” she says. “I underwent surgery and then had six rounds of chemotherapy. Fortunately, I’ve been cancer-free since.”

Like many patients, Cory says her initial symptoms did not suggest cancer. As she recalls, “I was experiencing leg pain and thought I might have pulled a muscle shoveling snow. But the leg pain persisted and woke me up at night, so I went to my family practice physician, who sent me to physical therapy. But as I went through physical therapy and the core strengthening exercises, the pain only increased. I knew then it was time for me to visit the gynecologist. I actually suggested that I needed an imaging test. That’s when they did the ultrasound and saw the tumor.”

As a patient advocate, Cory strongly recommends that every ovarian cancer patient be under the care of a gynecologic oncologist. “Gynecologic oncologists are incredibly knowledgeable about this disease,” she says. “They know the kind of treatment that you need and how to tailor it to minimize the side effects. Today, compared with when I was diagnosed, they also know so much more about the types and subtypes of cancer and tailoring that treatment to the particulars of your tumor and genetic specificities in the patient.”

Regarding long-term follow-up care, Cory has since graduated to an annual physical exam. “As a cancer survivor, there is always the question of the long-term effects of chemotherapy,” she explains. “So I have regular screenings for my lungs, heart, osteoporosis, and other tests. Those visits also involve a blood test, the CA 125 for ovarian cancer. Not everybody is sensitive to this test, but I am and if I had another tumor growing it would probably show up on that test. Thankfully, ever since diagnosis and surgery my CA 125 [levels] have been consistently very low.”

As a patient advocate, Cory recognizes how valuable it is not only to work with a gynecologic oncologist but also for patients to develop a strong network of supportive family and friends. This support network may include other ovarian cancer patients and the entire health care team.

“I want to emphasize how important all the health care support staff and caregivers are to patients who come to them in
a very vulnerable state,” says Cory. “I still remember the random acts of kindness shown to me by clinic staff during my journey. The staff should understand that their knowledge and caregiving can make such a difference.”

That is an observation that rings true for Karen Harvey, CMA (AAMA), a clinical quality assurance auditor for Eastern Maine Healthcare Systems (EMHS) in Brewer, Maine. Harvey is a former staff member at EMHS’s Cancer Care of Maine clinic in Brewer. She is also the granddaughter of an ovarian cancer patient.

“As support staff, I believe it’s very important for us to be cognizant of what patients are going through,” she says. “Often, these patients have a lot of anxiety coming in for chemotherapy, radiation treatment, and transfusions, especially during their first treatments. There’s a lot of anxiety and fear of the unknown. Is it going to be a good day or a bad day?

“Of course, medical assistants are often very rushed, but my experience with cancer patients generally is that you just have to slow down a little. You have to take the time to say, ‘How are you feeling today?’ and try to provide that personal touch. It can help to take away the fear.”

Harvey notes that the tenor and tone of staff interactions with cancer patients can go a long way toward influencing how patients feel not only about their health care appointments but also themselves. “I’ve seen patients who, in a sense, start to feel ‘they are cancer,’ instead of the person they’re used to being,” she observes. “I think it’s really important that we always remember we’re treating the person, not just the cancer.”

Harvey has also observed that cancer patients may at times be inclined to share more informally with support staff some personal fears or concerns that they hesitate to raise with their physicians. “I might be doing blood work or some other task and a patient would start telling me they’ve been feeling a certain way lately and didn’t know what to do about it. Maybe they’re having a disagreement with a family member about their treatment, or there’s some other issue. I would listen and perhaps encourage them to bring the issue up with their doctor. As medical assistants, we’re very much a sounding board for some patients.”

New hope

While ovarian cancer remains a serious and challenging disease, modern medicine has much to offer today’s patients. Advances in minimally invasive surgery have led to shorter recovery times and improved outcomes. Newer medications and treatment strategies have made chemotherapy both more refined and effective.

“When I started in this field we thought of ovarian cancer as sort of one lump-sum entity, and we had one treatment plan for it,” concludes Dr. Zorn. “Although we haven’t had that breakthrough in terms of early detection that some other cancers have seen, we have continued to make incremental progress. There’s been tremendous research, and we’ve gained many insights into ovarian cancer and our understanding of the different subtypes. Ultimately, this research is going to lead us to the understanding of the biology of cancer and treatment to prevent ovarian cancer altogether, or allow us [to achieve] early detection and an improved cure rate.”

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References


