

Support for Yale Cancer Answers comes from AstraZeneca, providing important treatment options for women living with advanced ovarian cancer. Learn more at astrazeneca-us.com. Welcome to Yale Cancer Answers with doctors Anees Chagpar and Steven Gore. I am Bruce Barber. Yale Cancer Answers features the latest information on cancer care by welcoming oncologists and specialists who are on the forefront of the battle to fight cancer. This week in observance of ovarian cancer awareness month, it is a conversation about gynecologic oncology with Dr. Gloria Huang. Dr. Huang is an Associate Professor of Gynecologic Oncology at Yale School of Medicine and Dr. Chagpar is an Assistant Professor of Surgery and the Assistant Director for Global Oncology at Yale Comprehensive Cancer Center.

Chagpar Gloria, let us start by talking about ovarian cancer. I think that a lot of people know a little bit about it, but not a lot. Let's start by laying the ground work. What exactly is ovarian cancer, how common is it and what should people know?

Huang Ovarian cancer is one of the cancers that we treat as GYN oncologists. So, cancers that arise from the female reproductive tract. What is interesting is that ovarian cancer actually encompasses a number of different diseases. It is a very heterogenous group of diseases that fall under the umbrella of ovarian cancer. We treat the cancers according to the type of disease it is. Ovarian cancer refers to tumors and cancers that arise from the ovary, generally speaking. It is one of the less common GYN cancers, and in general, women in the United States have about 1 to 1.5% risk of developing ovarian cancer in their lifetime. However, ovarian cancer is one of the more difficult to treat cancers if detected at a later stage. Something interesting about ovarian cancer, as I said it is actually an umbrella term that encompasses many different diseases, is that some ovarian cancers, actually one of the common types, arises from the fallopian tubes but it tends to seed onto the ovary and grow into a mass on the ovary, which is why it is recognized as an ovarian cancer. Other ovarian cancers interestingly actually may arise from endometriosis implants on the ovary. So, these are tissues that originate most likely from the endometrium, that is the uterine cavity, implant on the ovary or peritoneal pelvic surfaces and can grow into a malignancy. So, those are some of the etiologies of some of the ovarian cancers that we encounter.

Chagpar One of the things that you mentioned was that, ovarian cancer is really difficult to treat if picked up late. But before we even get to that, let us talk about whether there is anything that people can do to prevent themselves from getting ovarian cancer. Is there any primary prevention, anything that people can do to reduce their risk, maybe eating or not eating particular foods, smoking, drinking, environmental risk factors, what are the risks and the risk factors for developing ovarian cancer and is there anything that people can do to reduce their risk, short of just hoping and praying that you do not get ovarian cancer?

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Huang That is a great question. First of all, one of the factors that can greatly increase a woman's chance of developing ovarian cancer is actually if she was born with a genetic change that increases her risk of ovarian cancer. You may have heard of BRCA-1 or BRCA-2 mutations, so these are risks that can be passed down from the mother to the baby or from the father to the baby, and you could be born with an increased risk of developing ovarian cancer in your lifetime. Now, the good thing is that there are very accurate tests to determine if your DNA has a change in the BRCA-1 or 2 or some related genes that have a similar risk. So, it is very important that if there is a family member who has had ovarian cancer or breast cancer, those are things to be aware of and to figure out your family history if there is a sign of perhaps a hereditary risk. If that is the case, the affected patient, if your mother had ovarian cancer, your mother should be tested for a genetic predisposition. This is something that is a very important message for any patient who is newly diagnosed with ovarian cancer, we strongly encourage the patients to have genetic testing and that is because patients with ovarian cancer, even without any family history of cancer, could have up to 20% risk of carrying a genetic risk. And this is very important for themselves to know for prevention of other cancers as well as for their family members to know what they may be needing to be tested for. So, any patient who has a new diagnosis of ovarian cancer should ideally see a genetic counselor and have testing for a genetic risk factor. Women who have family members with a cancer history should also see a genetic counselor for genetic testing. We have very effective ways of decreasing risk of ovarian cancer for patients at increased risk.

Chagpar And if you are, let us suppose that a BRCA mutation runs in your family, you were tested, you have not developed ovarian cancer yet, for some patients they may feel like that may just be a ticking time bomb that tells them that they are at increased risk. What can they do to prevent ovarian cancer in that situation and when should they be doing that?

Huang These are great questions too. In general, things that lower cancer risk that everyone should do, including those at increased risk, are physical activity, exercise, trying to maintain a healthy body weight, having excess body weight can lead to imbalance of hormones, higher estrogen levels, higher insulin levels and can actually increase the risk of many cancers, not just gynecological cancers. I also encourage patients to eat plenty of vegetables and fruits. Now, in terms of specifically patients who are at high risk of developing ovarian cancer, we do offer monitoring, but fortunately the risk of developing ovarian cancer, even for those at high risk, typically does not develop until later in the reproductive years, so patients can be assured that they have time to complete their families if they desire children and we can work closely with reproductive specialists as well to ensure that they are able to successfully create their families and also to offer counseling regarding your families as well.

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Chagpar Let's unpack that a little bit. What does the screening involve for these patients who are at high risk?

Huang In terms of ovarian cancer screening, we do not have a perfect test for screening yet. Some things that patients may hear about are transvaginal ultrasound, which is basically very low risk – there is no radiation involved and an ultrasound probe is placed in the vagina, and you can usually get a very good view of the ovaries and during reproductive ages, it normal to have small simple fluid-filled cysts that come and go; however, if cysts are getting larger or have solid components, they may be more worrisome. The other test that people talk about which is again on its own not a very accurate test, is a CA-125 blood test and that is something that is useful for monitoring the patients who have a diagnosis of ovarian cancer, but is not a very effective screening test on its own. There are a number of prospective studies and what we have learned from these studies looking at the change in CA-125 over time is more accurate than a single snapshot of the blood test.

Chagpar So, if you have somebody who is let us say a BRCA mutation carrier and who wants to complete her family, and you want to screen her because she is clearly at increased risk of developing ovarian cancer, how often would you do a transvaginal ultrasound and a CA-125?

Huang Me personally, I like to see the patients twice a year for assessment of any change in symptoms, examination and then on an individualized basis blood test and/or ultrasound, but this is something that we are actually actively investigating what might be more effective ways for screening or early detection because as we talked about, we do not have a perfect test right now.

Chagpar Yes, so clearly there is a need to develop that and I know that especially with cancers where it is really hard to treat at a late stage, we really want to focus on trying to find those cancers early. Now, let us suppose you have a patient who is a BRCA mutation carrier but has completed her family, is removing her ovaries an option that she should consider to reduce her risk, and if so, what about the other cancer types that fall under the umbrella of ovarian cancer -- you talked about cancers that arise from the fallopian tubes, should those be removed; what about endometriosis and endometrial deposits, peritoneal surfaces – how does all of that work?

Huang For patients having preventative surgery, prophylactic surgery, it is essential that not just the ovaries but the fallopian tubes are removed, and that removal of the tubes and ovaries will greatly reduce the risk of developing ovarian cancer. Often we do offer patients a preventative hysterectomy as well because endometrial cancer in the

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general population is a relatively more common cancer. About 1 in 35 US women will develop endometrial cancer in their lifetime, and that is just in terms of the

general population. Again, some things that can reduce endometrial risk are maintaining a healthy weight and physical activity. Removing the uterus also can simplify the regimen if the patient requires hormone replacement.

Chagpar For patients who are premenopausal, who are undergoing a prophylactic oophorectomy or removing their ovaries and their fallopian tubes to prevent ovarian cancer, that then puts them into menopause right? And you would prescribe hormone replacement therapy, is that right?

Huang Yes. Removing the ovaries in a premenopausal woman would lead to a decrease in the estrogen produce. Now, even after natural menopause or surgical menopause, the amount of female hormone in the body is not zero because actually estrogen is produced in the fat cells of the body by conversion of adrenal hormones. So, it is not as though there is complete absence of estrogen.

Chagpar So, hormone replacement therapy, is that something that women should take after prophylactic oophorectomy or is it something that they should avoid? Because a lot of women may have questions about hormone replacement therapy especially as they hear things like the fact that it increases breast cancer risk?

Huang Right. It is very important to have a coordinated and whole person approach to hormone replacement therapy. So, the patients who are known to carry a BRCA-1 or 2 mutations are typically managed together with a breast specialist. And whether or not the patient is on hormone replacement and what regimen will depend on many factors such as whether they had prophylactic mastectomy to prevent breast cancer and also the regimen will depend on whether or not they have retained their uterus or not. So, it is definitely individualized.

Chagpar Perfect. We are going to take a short break for a medical minute and then learn a whole bunch more about gynecologic cancers, especially ovarian cancers.

Medical Minute Support of Yale Cancer Answers comes from AstraZeneca, dedicated to advancing options and providing hope for people living with cancer. More information at astrazeneca-us.com. This is a medical minute about smoking cessation. There are many obstacles to face when quitting smoking as smoking involves the potent drug nicotine, but it is a very important lifestyle change,

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especially for patients undergoing cancer treatment. Quitting smoking has been shown to positively impact response to treatments, decrease the likelihood that the patients will develop second malignancies and increase rates of survival. Tobacco treatment programs are currently being offered at federally designated comprehensive cancer centers and operate on the principles of the US Public Health Service Clinical Practice Guidelines. All treatment components are evidence based and therefore all patients are treated with FDA approved first-line medications for smoking cessation as well as smoking cessation counseling that

stresses appropriate coping skills. More information is available at YaleCancer-Center.org. You are listening to Connecticut Public Radio.

Chagpar We are talking about gynecologic cancers and specifically ovarian cancers along with options for women. Now, before the break, we spent a lot of time talking about ovarian cancer and touched a little bit on prevention. Obviously, the good things to do are the good things to do always – maintain a healthy body weight, exercise, eat right, and we talked a little bit about genetics and some of the prophylactic surgeries that people can have to reduce their ovarian cancer risk if they are at genetically high risk. But Gloria, some people are going to be diagnosed with ovarian cancer who may not have a genetic predisposition, who may just present with ovarian cancer. So, let us start there. You said that ovarian cancers are really difficult to treat when diagnosed at a late stage. What are the symptoms that women should be paying attention to that may prompt them to seek help? Because certainly not all women are going to have screening on a regular basis for ovarian cancer.

Huang Ovarian cancer can present with symptoms that are somewhat vague in nature, but what is important is that symptoms that are persistent and severe are things that should prompt a doctor's visit or to the gynecologist. For example, abdominal bloating, we all feel bloated from time to time and if you feel bloated one day and you feel fine the next, it is not as concerning as if you have persistent abdominal bloating and increase in your waist size, which progressively worsens over time. I always tell patients if they have persistent symptoms every day for about 2 weeks of the month or more, that should prompt a doctor's visit.

Chagpar Given the fact that unlike for example breast cancer or colon cancer where there is a screening test, are most ovarian cancers caught late?

Huang Run of the mill types of ovarian cancer, the most common types -- epithelial ovarian cancers, are often detected at a stage III or IV where there has been some spread of cancerous cells to other parts of the pelvis or abdomen. So, one of the ways that patients sometimes present is having a distended abdomen because fluid can collect in the abdomen, which we call ascites.

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Chagpar That is unfortunate. And until we come up with better screening tests that are able to detect cancers early and are part of routine health maintenance, I suppose that this is always going to be the case. Is that right?

Huang Well, at this time, yes, but on the other hand, I think we are also at the same time developing more effective treatments for ovarian cancers and advanced ovarian cancer, and also making those treatments, including surgery, less toxic.

Chagpar Let's talk about that. Let us suppose somebody did have abdominal bloating and they go to see their family physician or their gynecologist, how is a

diagnosis of ovarian cancer made because you can imagine that having abdominal bloating could be due to many, many different things – from gastrointestinal problems to all kinds of issues, how do you actually make the diagnosis of ovarian cancer?

Huang Besides the history of symptoms, the examination is an important part. As I said, often a patient might have abdominal distention -- a pelvic exam might reveal enlarged ovaries, masses on the ovaries. Another type of exam that we often do in the GYN office is a rectovaginal exam to feel the surfaces behind the uterus which could reveal nodularity in that area called the cul-de-sac. And so, those are things that would prompt further evaluation should they be detected on exam. Some ways that adnexal or ovarian mass would be further studied is to do as I mentioned a transvaginal ultrasound to determine if it is a simple cyst or a solid mass, and then if we are suspecting a possible ovarian cancer, I would typically order a CT scan, a CAT scan, and that would allow me to evaluate the upper abdomen and other surfaces and lymph nodes and help with the planning for the optimal treatment.

Chagpar And if you find something, a solid mass on an ovary on transvaginal ultrasound or CT, does that automatically cinch the diagnosis of ovarian cancer or do you still need a biopsy and how does that happen?

Huang Yes. That is a great question. Even in women at higher risk, which are postmenopausal older women, even a concerning-looking mass on transvaginal ultrasound has a 90% chance of being benign, but often the best way to determine that is by removing the ovary surgically. We do not like to do a biopsy because that could theoretically release malignant cells into the surrounding pelvis or abdomen. So, the best way to determine the nature of a suspicious or concerning mass usually is through a minimally invasive surgical approach, laparoscopy and removal of the ovary and attached tube. Typically, the pathologist can actually take a look during the surgery and get an immediate impression which is called a frozen section and that will give us a good idea if the mass is benign or malignant.

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Chagpar And if on frozen section this turns out to be malignant, what happens then?

Huang It is very important -- the surgical management of ovarian cancer is a critical factor in optimizing the best possible outcome for the patient and their cancer. So, it is really important for patients to have their surgery done by a specialist in GYN cancer and ovarian cancer and that would be a gynecologic oncologist, and the reason is that first of all, it is critical to know the extent of spread of the cancer, called staging, and that is assessed surgically, and also it is very important to reduce the tumor, remove and resect visible tumor and that is called tumor debulking or cytoreduction. And we know that this can really

impact how well a patient does, and so, it is so critical for patients to be under the care of a gynecological oncologist for their surgery for ovarian cancer.

Chagpar And if they are under the care of a qualified gynecologic oncologist, the surgeon removes the ovary, sends it to the pathologist, the pathologist does one of these quick frozen sections and typically will call the surgeon right in the operating room and say, I think this is malignant, would the surgeon then go ahead and do this debulking and the staging all at the same time and what does that involve exactly?

Huang Again, it is individualized to the patient. If I were highly suspecting a possible malignancy before surgery, I would have counseled the patient about in the event that cancer is found, how should we proceed and also if it is a younger patient – what their fertility desires are. The good news is for younger patients who desires to maintain their fertility, for certain types of ovarian cancers, we can maintain their fertility by maintaining a normal ovary and uterus without affecting their future fertility. Again, that is individualized but that is something that we frequently do. For older patients, typically the surgery for ovarian cancer does remove both tubes and ovaries, the uterus as well as removing this fatty tissue called the omentum where sometimes the cancerous cells tend to hone into and implant and then checking the lymph nodes as well for spread, which sometimes is difficult to detect on CT scan.

Chagpar And so, the surgery sounds like it could be quite extensive. And you mentioned that most ovarian cancers are diagnosed as stage III or stage IV, in many other cancers, there is this multidisciplinary approach, especially with stage IV cancers, which have typically spread outside of the origin of the cancer itself because it requires more systemic therapy. So, some sort of medicine, chemotherapy, endocrine therapy, immunotherapy, all kinds of therapy that the people can put into the blood stream to fight cancer wherever it is. Is the same thing true in ovarian cancer and how is that multidisciplinary approach managed?

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Huang Absolutely. For advanced ovarian cancer, chemotherapy is an important part of the treatment and as you said, by giving drugs systemically that can eliminate microscopic disease that could be in the abdomen or other areas. What is interesting is that, ovarian cancer tends to be quite sensitive to chemotherapy. So, between surgery and first-line chemotherapy, we are actually very successful at achieving a clinical remission, a complete response to therapy in the majority of patients even with stage III and IV disease. However, these patients are very high risk for recurrence. Meaning that there are undetectable cells that can recur and develop into recurrent cancers. So, actually there is a lot of investigation and we are doing clinical trials that we are enrolling patients into, which would offer patients besides standard surgery and chemotherapy, the addition of a targeted therapy or immunotherapy to decrease the risk of having a recurrence.

Chagpar And, the one mode of therapy that we have not really mentioned is radiation. Does radiation play a role in ovarian cancer?

Huang For run of the mill, ovarian cancer, it is not as commonly used. There are some select instances where it can be useful, but not so commonly used for run of the mill types of ovarian cancer.

Chagpar And one can imagine why that would be the case because within the abdomen there are lots of other things there that you would not want to damage with radiation. And it sounds like at least the initial outcomes with chemotherapy and surgery are quite good, but this idea of relapse is something that I think a lot of patients may be concerned about. So, tell me more about the prognosis of ovarian cancer. If you are diagnosed with ovarian cancer, stage III or IV, which is the majority of cases that you see that is treated with surgery and chemotherapy, how often do those patients recur and what is their survival rate like?

Huang Again, I can say a chance of recurrence, but it is very individualized. Of course, we all have patients who do not recur at all, and so, giving a number like a 5-year percent of patients may or may not recur may not be so meaningful for the individual patient.

Chagpar Granted.

Huang Some patients may never recur, some patients after many years and some patients who are not as responsive to chemotherapy, they may recur earlier. So, there is a huge range of possible outcomes and as I said, every patient and their cancer is different. What was your question again?

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Chagpar Having said that, however, an individual patient is looking at their life and wondering well what is the average? I mean, what is the average prognosis? Should this be something that I should really be starting to put my house in order and write a will and make sure that my kids are taken care of or is this something that I have on average a prolonged life expectancy such that when you talk about fertility that I can plan a family that I can live for a number of years with my ovarian cancer, albeit relapsing perhaps intermittently. What do you tell patients when they ask you about average prognosis, understanding your caveat which is well taken which is that it is an individual disease for any given patient?

Huang I hate to make generalizations because there are so many different types of ovarian cancers and so many different factors. But yes, patients who have advanced ovarian cancer are at high risk, I would say more than half will recur at some point. The length of time of the disease-free interval that they are doing great without signs of cancer is a factor that we look at, and because a shorter time until recurrence may indicate that the tumor cells are not as sensitive

to chemotherapy. So, that is something that we consider as we optimize and develop the strategy for treating the recurrence.

Dr. Gloria Huang is an Associate Professor of Gynecologic Oncology at Yale School of Medicine. If you have questions, the address is canceranswers@yale.edu and past editions of the program are available in audio and written form at YaleCancerCenter.org. I am Bruce Barber, reminding you to tune in each week to learn more about the fight against cancer here on Connecticut Public Radio.