



Gynecologic Oncology: Part II

Hosted by: Anees Chagpar, MD

Guest: Gloria Huang, MD, FACOG,
Associate Professor of Obstetrics, Gynecology &
Reproductive Sciences, Yale School of Medicine

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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 it is a conversation about gynecologic oncology with Dr. Gloria Huang. Dr. Huang is an Associate Professor of Obstetrics-Gynecology and Reproductive Sciences at Yale School of Medicine and Dr. Chagpar is an Associate Professor of Surgery at Yale and the Assistant Director for Global Oncology at Yale Comprehensive Cancer Center.

Chagpar Gloria, let's talk about GYN cancers. What incorporates that spectrum of GYN cancers? When we talk about gynecologic malignancies, it is really more than just one organ right?

Huang Absolutely. GYN cancers are cancers that arise from the female reproductive tract. The three most common are ovarian cancer, uterine cancer – of which the most common is endometrial cancer, and cervical cancer. I did pull a few statistics related to these cancers and their incidence in Connecticut since we are in the state of Connecticut. There are about 270 new cases per year of ovarian cancer in Connecticut and about 160 deaths per year. This is a slightly higher incidence in Connecticut compared to nationally, but a lower death rate. Endometrial cancer is the most common GYN cancer, 890 cases per year in Connecticut and 120 deaths per year. Again, this is a bit higher than the incidence nationally; however, again a lower death rate compared to the rest of the United States. And cervical cancer is less common due to the availability of effective screening, about 120 new cases per year in Connecticut.

Chagpar One of the things I think that is important to point out to our audience members is that people often get very perturbed when they hear about higher incidence numbers, but to your point having a higher incidence and a lower mortality is often a hallmark of good screening. When you have good screening, you find more cancers, but you tend to find them at an earlier stage so that mortality is lower. Tell us a little bit about the screening for various gynecologic malignancies. Do we have good screening?

Huang That is a great question. First of all, to touch on your point, yes, I think in Connecticut, we are doing very well in general with cancer screening. I also reviewed that, and I saw that we are among the top, doing the best among all states in the US with regard to breast cancer screening and colon cancer screening. About 80% and 75% of Connecticut citizens are getting the appropriate screening, which is much better than almost any other state in the United States. In terms of cervical cancer, one of the most effective ways of preventing cervical cancer and cervical pre-cancers is

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vaccination against the human papilloma virus. For HPV vaccination, we are also doing pretty well in Connecticut compared to the rest of the US. Of course, still not as good as some other western countries in general, but in Connecticut, currently more than half of girls are being vaccinated and almost half of boys, so that is in the top quartile among the United States and in the upper half for boys. So, that is pretty good and hopefully it will continue in that direction.

Chagpar Let's pause there for a minute and talk about prevention. When we talk about screening, I think it is important for our audience to remember that screening is not prevention, at least not primary prevention. I often will have people come to me and say, I have been getting a mammogram every year and now you found breast cancer, but that is the point of screening. Screening helps us to find more cancers. But the nice thing about the HPV vaccine is that it really is primary prevention. It prevents people from getting cancer to begin with. But one of the things that you mentioned, and I think it is really important to highlight, is that the HPV vaccine is both for girls and for boys, although it is often thought of as prevention for cervical cancer and of course that does not really apply to boys. Can you go over for us what are the guidelines for vaccination for HPV in this country, who should be vaccinated, at what age, how many doses and why is it that it is important that boys also get vaccinated?

Huang First of all, in terms of cancer prevention, there is protection against HPV-associated precancers and other HPV-associated cancers besides cervical cancer. Other cancers of the genital tract and of the anal area as well as head and neck cancer and oropharyngeal cancers, many of which can be HPV associated. In terms of why it is so important for both boys and girls to be vaccinated not only for their own personal protection as we talked about but also for the concept of herd immunity. So, what we find in other countries, once they reach a certain threshold of the population being vaccinated, there is a much less transmission and transmission rates. So even people who cannot be vaccinated or do not get vaccinated are protected. In terms of when vaccination is effective, so this is a preventive vaccine, there is currently no FDA approved therapeutic vaccine for HPV, and so really it is effective when it is given prior to any exposure to HPV, that is why it is recommended to be given as part of routine childhood vaccines in the pediatrician's office, usually between ages 9 and 11. I believe it is currently typically covered by insurance between at least age 9 to 26, but I think the optimal age range is towards the younger part of that age range.

Chagpar For our audience members, remember that young girls and young boys before they have ever gotten exposed to HPV should really get vaccinated because this is not just for cervical cancer, it is for anal cancers, it is for head and neck cancers, it prevents even precancerous conditions, genital warts and so on, really important to get vaccinated. And while herd immunity is a good concept, if all of us thought, well

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everybody else will get vaccinated and we will benefit from her immunity, that concept does not work. So, do yourselves and your children and the world a favor and get vaccinated, my short plug for the hour. But let us talk a little bit now about secondary prevention or what many of us call screening – early detection. When we think about cervical cancer, endometrial cancer, ovarian cancer, do we have good screening techniques, good ways of picking up these cancers early before they can present at a late stage. So, really preventing death from these cancers by picking them up early.

Huang Yeah, that is a great question. Let me start with ovarian cancer because that is the leading cause of GYN cancer death. It is the fifth most common cause of cancer death in women and unfortunately a lot of that is because most patients present at the time of diagnosis already with advanced metastatic disease. So, patients who have had known people who have died of ovarian cancer or are aware of the lethality of ovarian cancer often ask me, why doesn't everyone just get an ultrasound or CA-125 blood test, wouldn't that be helpful? Unfortunately that is not the answer either because there have been very large randomized controlled trials which is the gold standard of clinical trials looking at what kind of population-based screening can be used for average patients, not particularly those at high risk but those at average risk. And enrolling hundreds of thousands of women, the largest trials were done in the United States and in the UK and basically the bottom-line is there was no reduction in ovarian cancer mortality in the screened groups compared to the control groups using different modalities of screening, whether it is a blood test such as CA-125 together with an ultrasound, ultrasound alone or even what looked the most promising, which is the rate of change of the CA-125 blood tests. There was some suggestion in the UK trial that perhaps a slight stage shift to earlier stage of diagnosis seen in the CA-125 rate of change algorithm testing but still demonstrating no survival benefit overall, no decrease in ovarian cancer mortality using this population-based screening. So, what we can focus on are things that can be done to decrease the risk of developing ovarian cancer. And so then, as I said, we need to hopefully do research and determine new and better ways to do ovarian cancer screening effectively, but in the meantime, I do want to share a few factors which we know are protective and can lead to a reduced risk of developing ovarian cancer. So, some of these are things that we very commonly do in our everyday life. One would be taking oral contraceptive pills, birth control pills. Taking birth control pills during reproductive years for at least a year actually is associated with 50% decreased risk approximately of developing ovarian cancer or endometrial cancer in later life. Both ovarian and endometrial cancer are more common in the postmenopausal older age group. So, that is one thing and another thing is tubal ligation or hysterectomy, both of those are associated with a decreased risk as well as IUD use. Now, one thing I also wanted to talk about which seems to be even more effective than tubal ligation is removal of the fallopian tubes. Previously,

there was a suggestion, why not remove the ovaries prophylactically for patients who are undergoing hysterectomy for a benign condition like fibroids. Unfortunately, a large study, one of which was published a couple of years ago in the *Nurses' Health Study Group* showed that removing the ovaries before menopause for preventive reasons actually had significant downsides. That could be associated with increased risk of heart disease, coronary artery disease or even stroke at a later age. So, there are significant downsides to removing the ovaries; however, what is very interesting is large registry-based trials have shown that the patients who have had their fallopian tubes removed, which does not affect the hormones, actually could have 25 to even 65% reduced risk of ovarian cancer and this goes along with what we know about ovarian cancer that most of the high-grade aggressive types actually arise from the tips of the fallopian tubes, the fimbriae, rather than the ovaries. So, potentially you can have the protection against ovarian cancer without the downsides of the changes in the hormones and the early menopause. So, that is something that I think is being widely used. It is something that I have always done for patients undergoing benign hysterectomy, typically remove the fallopian tubes because it really adds minimal operative time or risk while having the benefit not only of decreasing ovarian cancer but also reducing risks of cysts and other problems. So, that is something I would highly encourage patients to discuss with their GYN.

Chagpar Certainly an option for people undergoing surgery. We are going to have to take a short break for a medical minute. When we come back after the break, we will talk more about how you can reduce your risk and potentially novel treatments for gynecologic cancers with my guest, Dr. Gloria Huang.

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This is a medical minute about pancreatic cancer, which represents about 3% of all cancers in the US and about 7% of cancer deaths. Clinical trials are currently being offered at federally designated comprehensive cancer centers for the treatment of advanced stage and metastatic pancreatic cancer using chemotherapy and other novel therapies. FOLFIRINOX, a combination of 5 different chemotherapies is the latest advance in the treatment of metastatic pancreatic cancer and research continues at centers around the world looking into targeted therapies and a recently discovered marker HENT-1. This has been a medical minute brought to you as a public service by Yale Cancer Center. More information is available at YaleCancerCenter.org. You are listening to Connecticut Public Radio.

Chagpar This is Dr. Anees Chagpar, and I am joined tonight by my guest, Dr. Gloria Huang. We are here talking about gynecologic cancers. Right before the break, Gloria, you were

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telling us that sadly, although ovarian cancer is the leading gynecologic malignancy causing death in this country, there really is not good screening. In other words, there is no blood test, there is no ultrasound that is going to find ovarian cancer early. There are things, however, that can reduce your risk – taking oral contraceptive pills for example may reduce your risk of developing cancer of the ovaries in later years and one of the things that you mentioned right before the break which is seemingly highly effective is salpingo-oophorectomy, prophylactically removing the ovarian tubes to reduce cancer because many ovarian cancers actually do not arise from the ovary themselves but actually from the fimbria, the little finger-like projections that come off of the fallopian tubes. Now, clearly, Gloria, you would not recommend that for somebody at average risk who is not undergoing surgery, would you or is this something that everyone should get simply to reduce their ovarian cancer risk down the line after they are finished having children and they no longer need that part of their tubes?

Huang What I was referring to is sometimes called opportunistic salpingectomy. Basically, removing the tubes at a convenient time if the patient is undergoing pelvic surgery anyways such as a laparoscopic hysterectomy for another reason or if they are having an elective tubal ligation because they have completed childbearing instead of having a tubal ligation to transect the tube, which in itself does confer some protection, people hypothesize because it is blocking factors or cells from coming from the uterus, but actually removing the fallopian tube which really only adds a few minutes and does not really add to the complexity of the surgery much. So, that would be an option is the opportunistic salpingectomy in average-risk women who are undergoing surgery for other reasons. Now, in terms of who should be having surgery specifically for risk reduction, that would be patients who are at increased risk for ovarian cancer. So, that would include patients who for example have a hereditary inherited change in the BRCA-1 or BRCA-2 mutation or there are some other hereditary syndromes that also increase the risk of ovarian cancer that are a bit less commonly associated but those would include Lynch syndrome and then some less common ones such as Cowden syndrome. But at any rate, patients who have a family history – first of all, if you have a family history of ovarian cancer, all patients who have been diagnosed with ovarian cancer should see a genetic counselor and consider undergoing genetic testing because up to 1 in 5 women with ovarian cancer do have a change in most commonly the BRCA-1 or 2 gene that they have inherited from their mother or father and they may not even be aware of that because there may not be any known family history. So all patients with newly diagnosed ovarian cancer should see a genetic counselor and consider

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having genetic testing. For patients who have a first-degree relative with ovarian cancer, again I would suggest seeing a genetic counselor or if they have a personal history of breast cancer at a younger age or multiple family members with breast cancer or a secondary first- or second-degree relatives with ovarian cancer, all of those would prompt consideration of genetic testing. The patients who are known to be at elevated risk of ovarian cancer, currently the standard of care would be to remove the tubes and the ovaries, which is called risk-reducing salpingo-oophorectomy but there are clinical trials going on now to see if the patients may have another option which would be a salpingectomy alone with a delayed oophorectomy at an age closer to natural menopause. Again, that would not be considered standard of care at this time, but it is something that is being evaluated as a potential alternative to try to avoid some of the harms of early menopause.

Chagpar So there seems to be some good both surgical and potentially medical ways to reduce your risk of ovarian cancer. What about other cancers?

Huang Endometrial cancer as I said is actually the most commonly diagnosed GYN cancer and one of the major risk factors for endometrial cancer is being overweight or obese. In Connecticut, actually we have a slightly lower rate of overweight or obesity compared to the rest of the United States; so about a quarter of women in Connecticut are in the obese range, but more than half, well over half, 62%, are overweight or obese, although that is lower than the general United States population. We do know that trying to maintain an ideal body weight, physical activity and plenty of vegetables can be helpful for protecting against endometrial cancer. One of the major risk factors for developing endometrial cancer is having had a history of endometrial hyperplasia. So, when your uterine lining shows signs of abnormal growth or proliferation and atypia and that is often driven by factors that are related to obesity, such as too high estrogen levels or unopposed estrogen.

Chagpar Let us say you are overweight, many of us are overweight and you have endometrial proliferation or whatever you have as a result of being overweight, you hear this show on Yale Cancer Answers and you decide, I am going to try to lose weight because that will reduce my risk not only of endometrial cancers but a whole variety of other cancers, not to mention heart disease and many other things that take people prematurely. If you lose weight afterwards, do you in fact lower your risk or is it that if you were overweight during your reproductive years, your fate is kind of sealed?

Huang There definitely can be immediate benefits to weight loss. For example, in patients who have undergone – well this would be a more abrupt example, but patients who have undergone bariatric surgery and have had their endometrium looked at, some of those changes can actually reverse quite rapidly with weight loss. You are right that

there are some factors related to lifetime exposures, so for example, cancer risk can even be influenced by childhood or adolescent age obesity, but there are still clear benefits to weight loss even in the short term. Regarding how to manage hyperplasia—that is the abnormal growth of the endometrium. If there is atypia in the cells, that is really considered on the continuum of a true endometrial cancer and often there can be concurrent cancer cells mixed in with that. And so, really the standard care is hysterectomy for patients who have hyperplasia with atypia. It can be individualized for patients who are younger and want to retain their uterus because of childbearing purposes or other reasons, then there can be medical management using progesterone agents to try to counteract the changes induced by the excess estrogen. However, many times the problem can persist or return and so the more definitive management is hysterectomy.

Chagpar As we talked about in the first example of ovarian cancer, if you are at average risk for ovarian cancer but you have endometrial hyperplasia and you are going to undergo a hysterectomy as a result, should you have your tubes taken at the same time?

Huang Yes, you should definitely have your tubes taken at the same time because there is basically no downside to it and it is protective against ovarian cancer.

Chagpar Okay, there you go. That leads us to cervical cancer right?

Huang Cervical cancer is quite different from ovarian and endometrial cancer because there are very effective proven screening methods that are very effective at detecting precancers, cervical precancer – another word for that is cervical dysplasia or the technical term is cervical intraepithelial neoplasia. That is when cells have shown changes resulting from persistent HPV infection and the changes have not led to any invasive cancer yet, but are at a state where they can still be very easily treated and therefore prevent cervical cancer.

Chagpar And so, basically when we are talking about cervical cancer screening, we are talking about Pap smears right? There are some of us who were born in an era prior to when HPV vaccine was implemented, so did not get vaccinated and so therefore undergo cervical cancer screening. The people who are now coming through the pipe are children who are vaccinated, do they still need cervical cancer screening with Pap smears?

Huang Yes, absolutely. At this time, cervical cancer screening is the same for women who were previously vaccinated or not previously vaccinated, although for all groups the frequency of screening has been greatly reduced because of the improvements in screening. So, in the first days of Pap smears, it was literally a smear of cells on a slide

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that we stained and looked at under a microscope. Now the standard is a liquid cytology, so that means cells are put into a liquid fixative and basically instead of getting clumps of cells, you have nice single cells and usually most labs have a combination of automated screening as well as review by an expert. And then, on top of that, it is very common these days to have co-testing, so detection of high-risk HPV types which is done from the very same container, actually from the very same container that you have the cytology that is looking at the cells, you can also test for high-risk HPV types, you can even test for the exact strain of high-risk HPV which is very commonly done since high-risk types 16 and 18 are associated with more persistence, higher risk of persistence, and even screening for cervical infections such as Chlamydia or gonorrhea can all be done from the same vial of fluid.

Chagpar One of the questions that I think our audience members may be asking themselves is, many of the vaccines that are available for HPV now really are very protective against those high-risk strains. So, HPV-16, 18, so why is it that people still need to get Pap smears if they have already been vaccinated?

Huang That is a good question, but I would have to say that because we are so recently into the era of HPV vaccination, we do know that they are highly, highly protected against the types contained in the vaccine which as long as there has not been a prior exposure, I think right now first of all the uptake of vaccination and the age groups being vaccinated is highly variable and even some patients may recall being vaccinated but only went for one shot and not the two or three shots, so there is a lot of variability and so how this will in the future impact screening remains to be determined. Of course, many of the patients also are much younger than the peak incidence of these changes. For cervical cancer, the peak incidence is later in life in the 40s, so there are a lot of unknowns still in terms of how we might be able to modify cervical cancer screening in the future.

Dr. Gloria Huang is an Associate Professor of Obstetrics-Gynecology and Reproductive Sciences 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.