

# Yale CANCER CENTER *answers*

WNPR Connecticut Public Radio



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## Future of Ovarian Cancer

### **Guest Expert:**

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## **Yale Cancer Center Answers**

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*Welcome to Yale Cancer Center Answers with doctors Francine Foss and Anees Chagpar. Dr. Foss is a Professor of Medical Oncology and Dermatology, specializing in the treatment of lymphomas. Dr. Chagpar is Associate Professor of Surgical Oncology and Director of the Breast Center at Smilow Cancer Hospital at Yale-New Haven. If you would like to join the conversation, you can contact the doctors directly. The address is [canceranswers@yale.edu](mailto:canceranswers@yale.edu) and the phone number is 1-888-234-4YCC. This week, Dr. Foss and Dr. Chagpar welcome Dr. Gil Mor. Dr. Mor is Professor of Obstetrics, Gynecology, and Reproductive Sciences at Yale School of Medicine, Division Director in Reproductive Sciences and Director of the Discovery to Cure Program. Here is Francine Foss.*

Foss            Gil, you have been at Yale for a number of years and have led a breakthrough program in terms of our understanding of ovarian cancer. Can you start off by telling us a little bit about ovarian cancer, and how frequent it is? Is it rising in incidence? How do we diagnose it?

Mor             Absolutely, as you pointed out, I have been here at Yale for almost 17 years and of those 17, I have dedicated much of my time to trying to understand ovarian cancer and why, because although ovarian cancer is a rare disease in terms of the incidence of the disease, it is one of the leading causes of mortality in gynecological cancers and we know that one in 72 women are at risk of developing ovarian cancer in their lives. The problem is that a high percentage, when the disease is diagnosed, will succumb to the disease and the question has always been, why have we not been able to cure the disease. At the same time, I can tell you that we have been successful in treating ovarian cancer. It may sound like I am contradicting myself, but if you look at the numbers, 80% of patients respond to the first line of chemotherapy, that is carboplatin and Taxol, 80% that is a significant number compared with many other cancers. So what is the problem? Almost 80% to 90% of those who responded will recur within five years and when the disease recurs we do not have anything that will be able to treat that patient.

Chagpar        I think the obvious follow-up then Gil is why do people recur?

Mor             That is correct. Why do people recur? But first I want to go to the recurrence, I would like to bring you a subject that I have been trying to understand, that is related to the recurrence. If we treat the tumor and the tumor disappears, where is it coming from. If the tumor follows what is written in the textbooks what we called the chronicity of the tumor where the mass of the tumor is just one mass, all of the cells that are inside of that mass are the same. If all of them are responding to the treatment it should disappear and as you correctly pointed out, why then would they recur. The first mistake is that the tumor is not homogenous, the tumor is just a small mass of similar cells growing without control. There is what we call heterogeneity in the tumor. There is a hierarchy in the tumor. There are some cells, which are the ones that we have been studying for many years, that do respond to the chemotherapy that we use. Those are the cells that disappear, that we successfully are able to kill when we give the treatment. There is another group of cells that do not

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respond to the treatment because they do not follow the same characteristics that we expect them to follow. They are left after the treatment. Those cells are the ones that recur.

Foss One might ask the question, can you detect those cells at the beginning? Do you know how many of those cells there are, and is there any way to detect them after you finish the treatment?

Mor Very good, that brings us to the other aspect, and that is early detection. We know that early detection of the disease is what brings success of the treatment. If we detect the disease in early stages that patient, as I like to say, will see her grandchildren graduate from college. However, in ovarian cancer the majority of patients are diagnosed with late stage disease, that is stage III, IV, when the treatment or with surgery it is difficult to remove everything that is there and we will talk a little later if there is an opportunity about the role of surgery on the success of therapy. We look at the literature and you will find that there are hundreds of groups trying to find markers for early detection, including ourselves. We developed a panel of markers for early detection for ovarian cancer and the problem has been that the expectation is to find one marker that will recognize all the ovarian cancers and guess what, in spite of thousands of publications, still we do not have an early detection test for ovarian cancer. The only marker is C-125, that is used today in the clinic together with ultrasounds, but neither C-125 nor ultrasound has the sensitivity or the capacity to recognize the disease at early stages and the question is why. I would like to bring to the discussion the question, if we are talking about atherogenicity of the tumor is ovarian cancer the same disease, are all the tumors that we find in ovarian cancer the same. Is ovarian cancer originated in the ovaries, and that is a very important question, why because understanding the origin, we will be able to understand the treatment, but important, the detection.

Foss One of the interesting things about ovarian cancer is that, as you alluded to, it does spread around to other areas within the abdomen and often times these patients undergo a very extensive surgical procedure because it is believed that if you can resect as much of that tumor as possible, patients will do better. Can you comment on that and with respect to your understanding of the biology, does that make sense?

Mor What we find is that when the disease spreads in the abdomen, and especially after chemotherapy, as I mentioned to you at the beginning, whatever cells are left there, if they are not properly removed, those cells will be in an environment that we call an environment of repair, and repair is based on the biological principle that when there is tissue damage they start fixing and fixing means growing more cells, the cells that remain in the abdomen after chemotherapy and left after surgery, they will recognize the damage and then is when they start growing and repairing. So if during the surgery everything is removed and nothing is left, the signals for repairing tissue for that abdomen will not exist, and then you will not have recurrence, that explains many of the patients who are alive today with ovarian cancer, a good surgery, a good removal, followed of course with chemotherapy or before chemotherapy, that is what allows survival, or explains survival of patients today.

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Chagpar I want to get back to this concept of heterogeneity and the fact that there may be some resistant cells. Is this the whole concept of a stem cell? And I want to get back to the issue that you raised, which was thought provoking, that with ovarian cancer it is important to understand the cell of origin, I am sure that many in the audience may be thinking, well if it is ovarian cancer, it must be from the ovary, talk a little bit about your paradigm shift in reference to that.

Mor We always thought that if you have a mass in the ovaries, it should be originated in the ovaries, but if you look at the different types of ovarian cancer, it is not just epithelial ovarian cancer or what is also called serous ovarian cancer, you have endometrioid ovarian cancer, you have the serous that I mentioned, you have clear cell carcinomas, you have mucin ovarian cancer and you have transitional, and when you look at the histology and look at the embryological origin, guess what, the majority of those tumors do not exist in the ovaries. A mucin type of cell, which is a glandular type, this may be in the colon, not in the ovaries, a clear cell carcinoma are a type of cell that does not exist in the ovaries. They exist in the vagina, and I could go on. Now if you'll allow me to do some epidemiology, which is very interesting, there are two major aspects in epidemiology that protects ovarian cancer. One is ovulation, if you block ovulation either by pregnancy or by taking the pill, you protect against ovarian cancer and the second is tubal ligation, if you ligate the fallopian tubes, you also prevent ovarian cancer. So the question here is, what is the connection? What does it mean that you close the tubes, and therefore are protecting against ovarian cancer? Or if you block ovulation, you protect against ovarian cancer. So, the answer that we are trying to provide today is twofold, one is that the tubes are like a highway with some malignant cells, as you mentioned potentially a cancer stem cell, traveling and ovulation is opening a door for malignant cells implanting in the ovaries. So, let me develop this idea a little more. Malignant cells can be originated from the vagina, let's say, or the endometrial and during the menstrual cycle of the woman those cells are released and they can travel through the uterus and through the fallopian tubes and then they can fall in the ovaries, or more important, it can also fall in the peritoneum. Now if you close the fallopian tube you close the highway, those cells cannot move and reach the peritoneum or the ovaries. So again, closing the highway, the ligation, indicating that the original cell is not originated in the ovary, at least for example with endometrioid ovarian cancer or the serous endometrial cancers or the clear cell carcinoma, they have been traveling.

Chagpar And with ovulation, presumably it prevents it from implanting in the ovary. We are going to take a short break now, but we are going to pick up that conversation right after we come back from this medical minute, so please stay tuned to learn more information about ovarian cancer with our guest Dr. Gil Mor.

*Medical*

*Minute* There are over 12 million cancer survivors in the US right now and the numbers keeps growing. Completing treatment for cancer is a very exciting milestone, but cancer and its treatment can be a life changing experience. The return to normal activities and relationships may be difficult and

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*cancer survivors may face other long term side effects of cancer including heart problems, osteoporosis, fertility issues, and an increased risk of second cancers. Resources for cancer survivors are available at federally designated comprehensive cancer centers like the one at Yale Cancer Center to keep cancer survivors well and focused on healthy living. This has been a medical minute brought you as a public service by Yale Cancer Center, more information is available at [yalecancercenter.org](http://yalecancercenter.org). You are listening to the WNPR Health Forum on the Connecticut Public Broadcasting Network.*

**Chagpar** Welcome back to Yale Cancer Center Answers. This is Dr. Anees Chagpar and I am joined today by my co-host Dr. Francine Foss. Today, our guest is Dr. Gil Mor and I want to pick back up on the conversation that we were having. You were talking about this whole concept of why it is that tubal ligation and ceasing ovulation can actually prevent ovarian cancer, and so the two questions that I have for you is first, if the idea is that the tube acts like a highway, why do these cells have a propensity to go on to cause ovarian cancer? And the second is, if tubal ligation cuts off that highway such that you now have a preventative effect for ovarian cancer, would that increase your risk of endometrial cancer or vaginal cancer?

**Mor** Those are excellent questions and this is what has been a challenge for us, and we have been breaking our heads to get an answer to that. I will try to summarize some of the information that we have. There is something that is called the epithelium. The epithelium is covering all these organs including the ovary and it functions like a beautiful barrier protecting the malignant cells as well as microorganisms, bacteria, viruses, but again malignant cells in our case could infiltrate inside of the tissue and formed the tumor. The epithelium is the barrier. Why the ovaries? The ovaries are a unique tissue because these are the only ones in the female reproductive tract that every menstrual cycle they will break the epithelium. Why do they break the epithelium? To release the egg, which will be travelling in the opposite way where the malignant cells are traveling, location and timing play a role here. If those malignant cells are traveling through the fallopian tube, the highway, and the door of the epithelium is broken because of ovulation, those malignant cells may take advantage of that open door and they fall in a nest in a beautiful environment that is called the corpus luteum, that is the place where the old site was before, after ovulation that is rich in hormones, that is rich in cytokines, growth factors and so on. They will sit there and the epithelium slowly will heal and the malignant cells will be left inside those ovaries. Now, why this is important in terms of our patients, we know that inhibiting ovulation is one of the best approaches in order to prevent ovarian cancer. So we know that early pregnancy prevents ovarian cancer. We know that the use of the contraceptive pill prevents ovarian cancer, why,

because two aspects are preventing the opening of the door, preventing the rupture of the epithelium and therefore allowing these malignant cells to come in. More important, the timing is

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critical here because if a woman has many years of opening and closing the door, ovulation and healing, the probabilities of those malignant cells falling or going inside the ovaries are much higher. That is an explanation of why pregnancies in later age, after 30, lose the protection for ovarian cancer. Closing the door in early ages, in a woman's 20s, or the pill, as I said preventing ovulation, will block or will prevent those malignant cells from going to the ovaries.

Foss In today's generation and women that are younger than me, a lot of women took the pill for a long time, should we then see downstream, a decrease in the incidence of ovarian cancer if your theory is correct?

Mor Yes, there is evidence proving exactly the point that the use of the pill, based on age, does have an effect on the prevention of ovarian cancer. Moreover, patients with genetic mutations such as BRCA1 or BRCA 2, one of the ways to help these patients to protect them is give them their contraceptive pills and prevent the ovulation.

Chagpar I want to get back to this whole concept of why we are failing in ovarian cancer, because that is something that I think all of our listeners are thinking about, why do woman, despite being adequately treated as you mentioned for ovarian cancer with novel treatments, recur? And subsequently succumb to their disease? This idea of cancer stem cells being incredibly difficult to detect and kill off, how are we doing in terms of that?

Mor If you look at the history of the treatments for ovarian cancer it is extremely interesting to see that around the 1970s when carboplatin was introduced, the only big modification since has been to add Taxol to the combination. These two treatments have indeed provided a better survival, five-year survival from 35% to 47%. So, we have done something in terms of survival but as far as cure, we have not been successful. What we found is that as you correctly pointed out, the stem cell, so the cancer stem cells, have unique characteristics in terms of their growth. The base of using carboplatin or Taxol or many of the other drugs is with the concept that the cancer cells are dividing very fast and when a cell divides very fast when you give cytotoxic drugs, will do damage that will induce cell death. These malignant cells, tumor initiating cells or cancer stem cells, they divide very slowly, so in the presence of the same compound of the same drug while the fast dividing cells start dying, those cells remain there and they survive because they are not dividing very fast. However, once the treatment has completed they see that somehow the tissue where they were has been damaged and then they will start the process of renovating of regrowing again.

Foss Why is it that women do not receive treatment after they get their carboplatin and Taxol? Is there a role for continuing maintenance therapy, why has that approach not worked?

Mor That is an outstanding question and that is our challenge because unfortunately we are just at the beginning of our understanding of identifying those cells. We are just at the beginning of recognizing what the characteristics of those cells are. Unfortunately, we do not have therapies in

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the clinic that could either prevent those cells from remaining, or that will kill those cells that are left, but what we know, going back to we talked about before, if you remove those cells with surgery then there is nothing to renew, so back to the approach that we have today, is to remove them by surgery. A targeted therapy or use of drugs is at the present time in development and we hope to see very soon drugs that target the cancer stem cells as either preventing the recurrence or targeting those cells when there is the recurrence.

Chagpar Along with those developments, as you try to find targeted therapies it would also be possible to find markers on those stem cells such that you could image them. So that when you did your surgery you would know whether you had left stem cells behind or whether those had in fact been completely removed. So what is the 5 year to 10 year horizon in terms of ovarian cancer research, where we are going to be?

Mor When going through your question, indeed one of the main aspects that we are trying to do is identify markers for those cells that were left and the more we analyze the different patients, it is surprising the variety, the high number of differences that we have seen in terms of markers for those ovarian cancer stem cells. So if you allow me now to put together some of the things we were talking about before, we say that many of these masses that we seen in the ovaries are coming from other parts of the reproductive organ. They may also come from the same peritoneum, organs in the peritoneum, the colon, the stomach, and so on and we always have been looking for the importance of markers that exist in the normal ovary and I can tell you, we cannot find that, so the question that I want to bring today is the question that we should all ask, does ovarian really exist in the way we have been finding so far?

Chagpar Can you elaborate on that?

Mor Absolutely, we always have discussed that the tumor, the malignant tumor, has to be originated from the organ where we give the diagnosis and therefore we give the treatment. So if we diagnose the patient with ovarian cancer we use the same markers and we use the same treatment. So if the patient with mucinous ovarian cancer comes today and in the afternoon comes the patient with serous ovarian cancer, histologically they are different, but because they were found in the ovaries the treatment is exactly the same, what I am telling you is maybe the two are not ovarian

cancers or moreover the two are completely different and therefore their markers and the treatments cannot be the same personalized medicine.

*Dr. Gil Mor is a Professor of Obstetrics, Gynecology, and Reproductive Sciences at Yale School of Medicine, Division Director in Reproductive Sciences and Director of the Discovery to Cure Program. If you have questions or would like to add your comments, visit [yalecancercenter.org](http://yalecancercenter.org) where you can also get the podcast and find written transcripts of past programs. You are listening to the WNPR Health Forum on the Connecticut Public Broadcasting Network.*