

Yale CANCER CENTER *answers*

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The Origin of Ovarian Cancer

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Welcome to Yale Cancer Center Answers with your hosts doctors Anees Chagpar, Susan Higgins and Steven Gore. Dr. Chagpar is Associate Professor of Surgical Oncology and Director of the Breast Center at Smilow Cancer Hospital, Dr. Higgins is Professor of Therapeutic Radiology and of Obstetrics/Gynecology and Reproductive Sciences, and Dr. Gore is Director of Hematological Malignancies at Smilow and an expert on myelodysplastic syndromes. Yale Cancer Center Answers features weekly conversations about the research, diagnosis and treatment of cancer and if you would like to join the conversation, you can e-mail your questions and comments to canceranswers@yale.edu or you can leave a voicemail message at 888-234-4YCC. This week, it is a conversation about ovarian cancer with Dr. Gil Mor. Dr. Mor is Professor of Obstetrics/Gynecology and Reproductive Sciences at the Yale School of Medicine. Here is Dr. Anees Chagpar.

Chagpar Right before the show started, I was talking to Dr. Mor, and Dr. Mor started with this very intriguing question, he said, do you think ovarian cancer actually exists? And I thought, my goodness, I think it exists, we talk about it existing, many patients feel that they have had ovarian cancer. What exactly did you mean by that Dr. Mor?

Mor I have not been drinking, so when I told you that, I really mean it, and I know you have many people involving cancer coming here and discussing it and I am sure you have been impressed as I am by the improvement in cancer treatment, cancer detection in the majority of the cancers, including breast cancer, which is your area. However, when we look at ovarian cancer, which is one of the most lethal forms of gynecological cancers, 16,000 women dying per year of this disease, nothing has improved in the treatment since 1977. And we are in 2016. The survival has not been improved. There is improvement in terms of the surgery, but the majority of the patients continue to die of the disease because the disease appears in late stages. And when we talk about the detection, there was just a big study from England that came out last week, trying to see whether early detection would improve survival. That also failed. It caused conflict. We know if we detect the disease in early stage, that patient, as I like to say, will see her grandchildren graduate from college, we know that. We know that when detected in later stages, the patient will die within 2-5 years. So why can't we detect the disease early. And why have we not improved the treatments. That is what brought me to the question, are we really aware of the disease that we are treating. Do we really have a disease that is called ovarian cancer? And why I am saying this is because we call ovarian cancer the tumors that we find in the ovaries. But let me tell you this, when we look at the different types of ovarian cancers -- you have patients with endometrial ovarian cancer, clear cell ovarian cancer, mucinous ovarian cancer, classical high-grade serous ovarian cancer. Now, if we look at all these types of tumors, do you know what they have in common, nothing. The only thing that they have in common is that they localized in the ovaries - first thing, and second thing is that if we compare those tumors with other tumors from outside of the ovaries, let us take endometrial ovarian cancer; if we are going to compare with endometrial cancer, they are 95% equal. If you compare the clear cell carcinoma as I mentioned to you, nothing in common with the other ones, but we compare with endometriosis or with renal cancer,

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between 90-98% similarity; with endometriosis, for example, clear carcinoma. And mucin with colon cancer. So, hold it. We see that we have multiple types of tumors in the same organ and moreover no one of these tumors have anything in common with cells, normal cells that exist within the ovaries that will be defined as the tumor-initiating cells, the precursors of the cells. So, that is why I brought you that question. We really are talking about ovarian cancer as when you find a disease, when we talk about breast cancer, we say the malignant cell was originated in the breast. You find the cell with a mutation within the breast, and you look for the precursor for the early detection within the breast. I am questioning, are we looking at the right place. Are we looking for markers that really do not exist? Because the origin of disease is not within the ovaries.

Chagpar I think what you are getting at, Gil, which is a very intriguing point, is that maybe many cancers are really not so much defined by their organ of origin as they are the genetic mutations that cause them.

Mor Absolutely. And that is one of the changes that we need to start thinking. And when we mention this, maybe what we are dealing with, in terms of what we call ovarian cancer, is a peritoneal disease, which has multiple sites of origin. But then comes the question, why the ovaries? Because we know all those patients, they come with masses in the ovaries. And when we send it to the pathologist and when the pathologist looks at the tumor and does sections, there are malignant cells within the stroma of the ovaries. And that is the reason, it is evidence, not the stroma, within the tissue. It means the malignant cells, if they are within the tissue, the dogma says, it must come from within the tissue. So, what we asked several years ago is, if they are not originated within the tissue, how they are reaching and where are they coming from? And I bring you two interesting things that are epidemiological studies. Two major things protect against ovarian cancer. One is ligation of the fallopian tubes. And the second is inhibition of ovulation. Let me put it in other words, continuous ovulation is a risk for ovarian cancer and tubal ligation is prevention for ovarian cancer. What do they have in common, these two things? One is physiologically a biological process where you have the release of the oocyte and the other one is just closing of the fallopian tube, which is the communication between the uterus and the ovaries. And those two things are intriguing to me. What is their relationship? And the conversation that we can develop is exactly in that aspect. What is the role of ovulation and what is the role of the fallopian tubes in terms of understanding the origin of ovarian cancer. And I do not know where you would like to start.

Chagpar Start with either one.

Mor Let me give you one more epidemiological study that is very interesting. And you will see now as we discuss how important this is for the prevention of ovarian cancer and the oophorectomies that people do. When we talk about tubal ligation as a protection of ovarian cancer it is incorrect as well as correct. What do I mean? I am not trying to contradict myself. The protection is mainly for endometrial ovarian

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cancer, potentially cervical ovarian cancer or clear cell carcinoma, ovarian cancer. So, tubal ligation is protecting against those types of ovarian cancer, but it does not protect against peritoneal ovarian cancer or mucinous ovarian cancer. So the protection is also very specific. Now, what is tubal ligation? Basically, you are closing a highway and that highway is the fallopian tube, I mentioned to you that it is communicating the endometrium and the ovaries. So, when you close that, malignant cells that maybe originated in the uterus are not able to travel and reach the ovaries.

Chagpar Let me ask you something about that Gil. I understand that concept, but then it would make sense that if all endometrial ovarian cancers originated as endometrial cancers, that all endometrial ovarian cancers would be concomitant with an endometrial cancer. Is that always the case?

Mor It is not always the case. And this is a very good point. And that brings us to the second aspect. Why the ovaries. Let me go through some basic concepts to also help your listeners. Every cycle in a woman, there is this important event for reproduction that is called ovulation. Ovulation is the process where you have this mature oocyte that needs to be released from the ovary. Now, the ovary is a beautiful encapsulated organ. It is protected and things will not go inside. It is only during the process of ovulation that nature uses a knife and it cuts the surface epithelium of the ovary, opens the door of the ovary and releases the oocyte outside towards the fallopian tube. At the same time, that it is releasing the oocyte, the cells that have been keeping the oocyte secrete a lot of factors that we call chemokines. They are messengers that are released by the ovary to code the other component of reproduction, the sperm, and telling the sperm where to come and meet the oocyte. And those factors we call an inflammatory process that is necessary for fertilization for the meeting of the oocyte with the sperm. This is the dramatic finding that we have, this factor, this inflammatory process that has a good role may also be attracting malignant cells. Because as you may recall, the movement of cell from endometrium is not only down, in menstruation for example through the vagina, they can also go retrograde, up. And the cells which have this capacity to migrate in the opposite direction are mainly what we call stem-like cells. Those are cells that have the capacity to survive during the process of migration where there is no oxygen, there is no blood, they are just floating. And the response, like the sperm, the response to inflammatory signals to these chemokines, they tell them where to go. They travel from the uterus, through the fallopian tube by these signals. And now, in the majority of the cases, they would just fall down and disappear. And I will tell you more in a minute because this is one of the exciting points what is ovulation doing to the cells.

Chagpar We are going to learn about what happens during ovulation to these cells with chemokines and how this all plays into ovarian cancer after a short break for a medical minute. Please stay tuned to learn more information about ovarian cancer with my guest, Dr. Gil Mor.

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Medical

Minute *There are over 13 million cancer survivors in the United States and over 100,000 here in Connecticut. Completing treatment is an exciting milestone, but cancer and its treatment can be a life-changing experience. Following treatment, cancer survivors can face several 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 to help keep cancer survivors focused on healthy living. The survivorship clinic at Yale Cancer Center focuses on providing guidance and direction to empower survivors to maximize their health, quality of life and longevity. This has been a medical minute brought to you as a public service by Yale Cancer Center and Smilow Cancer Hospital at Yale-New Haven. More information is available at yalecancercenter.org. You are listening to WNPR, Connecticut's public media source for news and ideas.*

Chagpar Welcome back to Yale Cancer Center Answers. This is Dr. Anees Chagpar, and I am joined tonight by my guest, Dr. Gil Mor. We are talking about ovarian cancer. And at the top of the show, Gil was saying, is there any such thing as ovarian cancer? The idea being that there are many different kinds of ovarian cancers, none of which really are related to each other but may relate to other cells. For example, in the endometrium, in the colon, in the peritoneum. And then the question is, how did they get to the ovary? Right before the break, just to recap, we were talking about inflammation and these chemokines that are excreted by the ovary during ovulation that send signals to tell cells where to go. Gil, pick up the story from there and tell us a little bit more about how this all relates to ovarian cancer.

Mor Thank you for summarizing this perfectly. Something that I forgot to tell you before the break is that the signals are not only going to the fallopian tube, they are also secreted towards the peritoneum, that cavity where the ovaries are located and where you have also all the other organs that we mentioned before. Now, I mentioned to you that the critical aspect of the whole story that is what we found is the rupture of the epithelium at the time of ovulation. Because that is the opening of the door to a tissue that is the inside of the ovaries that is extremely rich in hormones and growth factors and especially in molecules that regulates growth. So, when a malignant cell by luck finds that open door, responds to the attraction, they go through the rupture of the epithelium and they meet a group of cells that are called the corpus luteum. The corpus luteum is another extremely important reproductive organ. Because if there the sperm and the oocyte, the corpus luteum goes on to produce progesterone and hormones that will keep the uterus alive for the implantation. And guess what, that is the place where these malignant cells will stick, will attach and they will be fed by these cells. And as the ovulation ends, there is what we call the normal process of repair. The epithelium has to be healed. The door has

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to be closed. The wound needs to be repaired. And the interesting thing is that the epithelium of the ovaries starts repairing the ovaries and will engulf, will keep inside the malignant cells that invade or took advantage of the open door, and when it heals, it appears that nothing happened.

Chagpar I have two questions here Gil. One is, if the theory is that by ovulation and this open door and these signals and these factors that malignant cells are attracted, that by definition means that there are malignant cells somewhere else.

Mor Exactly.

Chagpar But, do you always find malignant cells outside of the ovary, because if it were the case that these malignant cells always came to the ovary which then sealed over and then you think of it as an ovarian cancer, you would always find a concomitant cancer elsewhere. Is that always the case?

Mor Unfortunately, that is the case my dear. And it is an excellent question. Because we mention that the majority of the ovarian cancer patients are diagnosed stage III or stage IV. That means there is a mass within the ovaries and there are multiple tumors in the peritoneal cavity. And we always thought that that original mass is shedding cells to the peritoneum.

Chagpar And you think it is the opposite.

Mor And here is what we are going to discuss, I hope we have time, about prevention and so on. The seeding is happening to all of those at the same time. And that is at the time when the woman is ovulating. So, the seeding and the primary tumor within the ovaries happen when there is the opening, but the seeding also is happening in multiple places in the peritoneum. And that has been always my question even in my old years when I was seeing patients, was will I see somebody that comes in January, we do ultrasound, CT scan and maybe you have those patients and you do not find anything and 6 months later or 7 months later, she comes again and she has a stage III ovarian cancer. I could not explain how that happens. First of all, you have in 6 months the growth of primary disease and you are sharing these malignant cells and they start growing everywhere. So, what I am bringing you is two questions. One is, seeding is happening during the reproductive age. And there is a synchronization of the burst of all these tumors that is happening almost at the same time. But they happen always in late age in the majority of the cases. Because as you may recall, the majority of the patients develop or present with ovarian cancer after 50 or 60 years old.

Chagpar That was going to be my second question, if all of this is related to ovulation, would you not have expected that these cancers would have then presented in much younger women.

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Mor Exactly. And the only patients with ovarian cancer in early age is BRCA-1 patients. BRCA-2 patients is late stage. Now, BRCA-1 patients, their ovaries become nonfunctional at an early age, which is becoming atrophic. As you know, BRCA-1 patients have problems with fertility. They will respond poorly to hormonal stimulation for example for in vitro fertilization and so on. The ovaries become atrophic in early age in BRCA-1 patients and they develop tumors in early stage. Now I brought you to the second aspect. If the seeding is happening during the period of ovulation, what is triggering this burst of the tumors? And the answer is, the atrophy of the ovaries. The ovaries, as I mentioned to you are unique organs, and please do not forget to ask me about whether it is good or not to remove the ovaries if I forget to tell you. The ovaries are incredible organs and they produce factors that are controlling, for example, the growth of the granular cells. They maintain those cells not growing. So, every month there is a different follicle that grows. When the malignant cells are seeded within the ovaries, they also affect those factors. They maintain a stage that we call latency, sleeping. They are the sleeping cells. And the same happens in the peritoneum, especially in the fat which is the place where you find the big tumors. As the ovaries become atrophic, there is again a dramatic change in the body of the woman especially related to hormones. And there are two aspects. One is inflammation and the second one is an increase in some of the hormones that usually were maintaining the normal status of the ovary. So, the ovary dies, loses the capacity to control or maintain the cells, the follicles die, and the factors that were controlling those cells, maintaining in the latent stage, the sleeping stage, are gone. And I mentioned to you that the malignant cells that were seeding are very much like stem cells. They are stimulated when they need to repair. And the environment of the ovary is dying, that is when they become stimulated and they start growing. Now, the inflammation that I mentioned to you is not just local, unfortunately it is systemic. And the burst of these hormones that characterize menopause and the burst of these inflammatory cytokines that characterize menopause, we think and that is work in progress, are the factors that are triggering that burst. And what I tell you is because look at the markers that we have been using for early detection and we cannot detect early. CA-125 is a great marker for ovarian cancer, but it is always stage III or IV because we are not looking at the right biological phenomenon. Because maybe the markers associated with the burst of the tumor with the development of the disease as we will diagnose when the patient comes at the age of 60 or later is associated with the hormonal changes and the inflammatory process due to the end of the normal function of the ovaries.

Chagpar Gil, let me you ask you this then, if the whole idea is you go through these ovulatory cycles, the door is opened, malignant cells come in, the epithelium is sealed over, the cells stay in a latent state until there is atrophy of the ovaries at menopause and then because of this atrophy and because of the inflammation, there is a burst and peritoneal seeding, would not everybody get ovarian cancer, or cancer of the ovary, we can debate about the terminology, after menopause, but not everybody gets ovarian cancer.

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Mor Very good. Let me bring you some statistics. We know that the best prevention for ovarian cancer is early pregnancy, for example. And what is early pregnancy doing, decreasing the number of ovulations. How do you protect patients with BRCA-1 mutation that they would not develop ovarian cancer, give them the pill. What is the pill doing, is preventing ovulation. Any woman where the prevention of continuous ovulation has taken place, her risk for developing ovarian cancer decreases significantly. Today girls are getting pregnant much later and when you had an early onset of ovulation and until the age of 34 you are ovulating every single month, that lady is at high risk of developing ovarian cancer because what you are doing is you are opening that door all the time reproducing malignancy and I agree with you, and not all of the women develop ovarian cancer. And again, early pregnancy or if we took the pill preventing ovulation and so on, it will decrease the risk of ovarian cancer.

Chagpar You asked me to remind you, and I think now is a good time to do this, what about prophylactic oophorectomy? A lot of women who are at high risk will consider this option. In our last 30 seconds or so, tell us what you think about prophylactic oophorectomy.

Mor That is a challenge and my answer is absolutely not. Because it is a misconception, the ovaries are not just a gland that is producing estrogen in all sites. They produce so many hormones, cytokines, growth factors that are acting systemically. And what I mean is, the brain, the bones, the sexual life and so on. At the age of 35 remove the tubes and prevent ovulation, that is it. Let me just finish, we are running out of time. When the woman is reaching menopause, then remove the ovaries.

Dr. Gil Mor is Professor of Obstetrics/Gynecology and Reproductive Sciences at Yale School of Medicine. We invite you to share your questions and comments, you can send them to canceranswers@yale.edu or you can leave a voicemail message at 888-234-4YCC, and as an additional resource archived programs are available in both audio and written form at yalecancercenter.org. We would like to thank the Yale Cancer Center for providing production support for this program. I am Bruce Barber hoping you will join us again next Sunday evening at 6:00 for another edition of Yale Cancer Center Answers here on WNPR, Connecticut's Public Media Source for news and ideas.