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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Reducing the Rise of Uterine Cancer in the United States

Dr. Turck:
Uterine cancer is the most common type of gynecologic malignancy in the United States, and disease mortality is on the rise, but with no standard screening strategies in place, how can we diagnose our patients earlier?

Welcome to *Project Oncology* on ReachMD. I'm Dr. Charles Turck. And joining me to help answer that question is Dr. Richard Penson, who is a medical oncologist working in gynecologic oncology at Mass General Hospital in Boston.

Dr. Penson, thanks for joining me today.

Dr. Penson:
Thank you.

Dr. Turck:
Now to get us started, Dr. Penson, would you tell us about the trends we're currently seeing in regard to uterine cancer diagnoses and deaths?

Dr. Penson:
So uterine cancer is getting all too common. It's the commonest gynecologic cancer, and it's always been considered a bit of a Cinderella to other cancers like breast cancer. For example, hormonal therapy, which really should work, we've never really done the definitive studies, and the old therapies with an excess cardiovascular risk with thrombosis and thromboembolic disease with progestins has really clouded progress. And we've entered a new era where the new approaches to therapy, the better diagnosis and better understanding the basic biology of endometrial cancer has really blown this area open, and so we're very excited about the changes that have happened.

Dr. Turck:
And from your vantage point, what's contributing to the relatively recent rise in uterine cancer cases?

Dr. Penson:
Yeah. So cancer is all too common, so one in two men, one in three women. Endometrial cancer is really at the front of that epidemic with an aging and increasingly heavier population. So about 1 in 1,000 women in the U.S. in their 60s will get endometrial cancer this year, and we think a large part of that is driven by the obesity epidemic. So being obese is a body mass index more than 30 kilograms per square meter, so for a five foot, nine inch woman, that's 203 pounds or more. And 40 percent of our population in the U.S. is obese with 10 percent seriously obese, and it truly is a catastrophic problem in terms of common serious and horribly costly in terms of individuals and our country's health. In the COVID-19 pandemic, the average weight gain has been estimated at 29 pounds.

And so we now know for endometrial tumors, which make up the biggest proportion of endometrial cancer, there is this very clear

progression from the normal glandular structure to a simple atypical hyperplasia in which less than 10 percent are going to become cancer to complex atypical hyperplasia in which a third are going to turn into cancer. And so for average cancers, a body mass index related to relative risk is very little different, breast cancer a little higher than one, lung cancer a little lower than one, but endometrial cancer there's a three-fold greater risk as your BMI increases, and we think that it's obesity driving carcinogenesis through estrogen metabolized from adipose tissue in the body.

Dr. Turck:
For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Richard Penson about the rising rates of uterine cancer in the United States.

So continuing along in our discussion, Dr. Penson, what are the risk factors for uterine cancer? You've mentioned obesity. Are there any others?

Dr. Penson:
Yeah. So the peak age is early 60s, 63, so like all cancers in complex mammalian biology, aging plays a big part in the development of cancer. With respect to estrogen, we know that a large drive is from obesity. Diabetes, type 2 diabetes is a cause, but it's really hard to disentangle whether that's just through obesity. But excess estrogens, for example, tamoxifen as a breast cancer adjuvant therapy in the past or granular cell tumors are associated with endometrial cancer, and there is a risk from polycystic ovarian syndrome where estrogen is higher.

For example, in the Women's Health Initiative, which is a huge study that completely changed how we think about hormonal replacement therapy in 100,000 women, there were eight new breast cancers a year, but there was no excess risk of endometrial cancer because when you give estrogen and progesterone, that really does protect the endometrium, so it's really just excess estrogen that's the risk.

So aging and obesity, excess estrogen, and then the other group is the family history. So Lynch syndrome, which is when a family inherits a predisposition mutation in the mismatch repair genes that predisposes to endometrial cancer and colorectal cancer, that's the other big group, and that's the group where this topic for today, screening is really important. If you have what we call an index case, a matriarch and a family pedigree where colorectal cancer or endometrial cancer has been diagnosed, that's the opportunity where we can prevent future cancers in that family.

Dr. Turck:
And how should we diagnose patients when there are no widely adopted screening strategies?

Dr. Penson:
So there's two stories in this that tell completely different parts of a really interesting biology. So the first is the tamoxifen in the P-1 study that looked at prevention of breast cancer with tamoxifen. There was a bit of a crisis because endometrial cancer happened as a consequence, and especially, some of the poor prognosis histologys, carcinosarcomas so in black women, that was a big healthcare scare. It was this intervention that has an unintended consequence with the development of high-risk endometrial cancer. It turned out, actually, that a screening strategy with ultrasounds wasn't necessary because for the vast majority of patients they present with postmenopausal bleeding, and then the diagnosis is made, and for 85 percent of patients with endometrial cancer, surgery is the cure.

And then we touched on it just now. Lynch syndrome is this completely different story. And now we have this great strategy with pathology departments staining both colorectal cancers and endometrial cancers in many institutions routinely, prospectively for predictors of this hereditary nonpolyposis colon cancer syndrome or Lynch syndrome named after Henry Lynch from Utah. And so the two most common genes and the LH1 and MSH2, but there's now seven genes that are associated with it, and they limit the ability to repair DNA and increase the risk of colorectal and endometrial cancer.

So in women with this syndrome, you have a 70 percent risk of developing endometrial cancer, and so if you can identify these families from simple staining in the pathology where this cancer is a very high risk, you can then go and track down other members of the family, and prophylactic surgery or screening with colonoscopy are really effective in terms of prevention of cancer.

Dr. Turck:
Now if we bring it back to treatment for just a moment, you mentioned surgery. What other options do we have particularly in those patients who are ineligible for surgery?

Dr. Penson:
Right. So as we said, 85 percent are cured by surgery, but their adjuvant therapies have been transformed. So we are waiting for the results of the RAINBOW study, which is a big international collaboration, but since the Cancer Genome Atlas has identified different subsets of cancer, we're now taking completely a different approach, and we really are looking to rewrite the history books of the adjuvant therapy, surgery, and what do you do next. So for the high-risk patients who have a p53 mutation, we are looking at chemotherapy or chemoradiation therapy with a PARP inhibitor in trials. For the mismatch repair-deficient patients where immunotherapy completely changes the outcome for patients, immunotherapy, and actually, the RAINBOW trial uses durvalumab.

And that group is a little different from the patients who have a POLE ε mutation. About five percent of endometrial cancer will have a POLE ε mutation, and that increases even more the chance that you'll get a fabulous response to immunotherapy. And so that does not have an intervention. It's just your own immune system against the cancer, and so we are looking to deescalate therapy.

And as I said about hormonal therapy, the fourth group, the no specific mutation profile, we are actually going back to look at just two years of hormonal therapy with medroxyprogesterone acetate, or megestrol acetate, and so that's a big 600-patient study, which will hopefully show that as we have better supportive care to reduce the risk of thromboembolic or cardiovascular complications, we'll really see hormonal therapy finally come in for those patients who have high risk because of lymph-vascular space invasion stage two disease or stage three disease.

So in terms of treatment, the world has completely changed. And so at the SGO meeting in 2023, we saw plenary presentations of GY018, which is a pembrolizumab study, and the RUBY study, which is a dostarlimab study, and this really has changed the standard of care.

And the two things that were really impressive was that there is, at least in the RUBY study, an overall survival advantage. That is fantastic in terms of being sure that endometrial cancer transforms things. And then for the microsatellite instable high patients, quite extraordinarily the progression-free survival curves became flat at one year. So it was designed for a 3-year treatment, pembrolizumab for two years or three years of dostarlimab, but the patients who are exquisitely sensitive to immunotherapy, the patients were microsatellite instable high disease, the mismatch repair-deficient disease, they do fabulously and really no recurrence beyond one year. And so I'm sure sometime soon we're going to be looking at reducing the duration of treatment because it really feels like concurrent paclitaxel carboplatin with immunotherapy and then maintenance immunotherapy maybe you only need a year to completely change the outcomes for patients, which is very exciting.

Dr. Turck:
Now with all this in mind, Dr. Penson, I have one final question for you before we close. What else needs to be done to increase our options for screening strategies and potential therapies for uterine cancer?

Dr. Penson:
So I really think that when we talk about diseases when there's a genetic predisposition, it's all about getting the word out so that clinicians are aware of the changes in the standard of care, and families at risk can benefit from these interventions. It's always tragic when in patients with BRCA mutations in their families or Lynch syndrome for endometrial cancer, patients don't get access to the latest, greatest advances, so using Lynch syndrome, endometrial and colorectal cancer as the index case for screening is really fabulous. In those patients a prophylactic hysterectomy has been shown to save lives. We are close to but not ready yet for population screening at 50, but I think everybody feels like that is coming, and it may well be that endometrial cancer is the disease where that is shown to be cost-effective before any other.

Dr. Turck:
Well, given the recent remarkable rise in uterine cancer cases, I'd like to thank my guest, Dr. Richard Penson, for joining me to discuss how we can better diagnose and treat our patients.

Dr. Penson, it was a pleasure speaking with you today.

Dr. Penson:
Always. And thank you.

Dr. Turck:
I'm Dr. Charles Turck. To access this and other episodes in our series, visit ReachMD.com/ProjectOncology where you can Be Part of the Knowledge. Thanks for listening.