

Support comes from AstraZeneca, a leader in oncology research with 3 new FDA approved medicines in the last 3 years. Learn more at astrazeneca-us.com. Welcome to Yale Cancer Answers with doctors Howard Hochster, Anees Chagpar and Steven Gore. I am Bruce Barber. Yale Cancer Answers is our way of providing you with the most up-to-date 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 the early detection of esophageal cancer with Dr. Cary Caldwell and Mr. Joseph Gordon. Dr. Caldwell is an Associate Clinical Professor of Internal Medicine and Digestive Diseases at Yale School of Medicine, and Mr. Gordon is a patient.

Hochster Dr. Caldwell, can you review some of the early warning signs and symptoms of esophageal cancer.

Caldwell Yes, certainly. Esophageal cancer is in fact one of the more devastating GI cancers that we see as gastroenterologists and unfortunately sometimes there can be no symptoms at all, but in those who are symptomatic, there is a presentation of dysphagia or so-called difficulty swallowing, principally to solids, there may be a sense of increased gastroesophageal reflux or heartburn, weight loss in advanced cases and then laboratory findings of iron-deficiency anemia. But again, the presenting symptoms are chiefly dysphagia to solids, eventually to solids and liquids. And the dysphagia may be referred to in the upper esophagus or the throat but nonspecifically oriented when the culprit lesion may be in the distal esophagus where Barrett's esophagitis originates.

Hochster So, what you are saying is that, if people are having food sticking when it goes down, maybe a sensation of trouble swallowing that persists for a week, a couple of weeks or start to lose weight, they should really get it checked out.

Caldwell Absolutely, but even earlier than that with reflux symptoms that have worsened over time. For example, a patient who has heartburn occurring weekly or acid regurgitation weekly and that it may be increasing in frequency or refractory to therapies such as with proton pump inhibitors, omeprazole, lansoprazole, etc. So, symptoms are refractory to treatment. Then, generally speaking, after a vetting by internist, they come to the attention of a gastroenterologist.

Hochster So, if you have heartburn, you got the pills from your internist and things are getting worse and not getting better, you better go back and tell him.

Caldwell That is correct. And even in patients whose symptoms are not getting worse, if they are dependent on proton pump inhibitors that is the trigger point for an endoscopic evaluation. In other words, we do not want to mask the symptoms without an endoscopic intervention.

Hochster Dependent means like for a certain time period if it does not get better?

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Caldwell Absolutely.

Hochster How long?

Caldwell So, generally speaking, if the symptoms are not better within several weeks on proton pump inhibitors, we will see the patient in our gastroenterology evaluations.

Hochster And how common is esophageal cancer.

Caldwell Esophageal cancer is actually increasing in its incidence in United States. There may be an incidence now of approximately 16-18,000. The incidence is probably increased by 300-500 fold since the mid 1900s. This varies between genders. There is an increased incidence in men versus women. There is an increased risk in people who are overweight. So, obesity is another risk for this as well; tobacco usage; ethnicity. So, we see this unfortunately in older white men more than in other populations.

Hochster I see. And you kind of earlier said something about if it is in the proximal or high up in the esophagus, you might feel it more in your throat and then you contrasted that to the distal esophagus, which is more at the bottom of the esophagus where it goes into the stomach. What is the distinction there?

Caldwell Well, there is nonspecific locality or localization I mean. In other words, Barrett's esophagitis is a condition of damage to the distal esophagus, and so that is in the bottom third of the esophagus, and if esophageal cancer has appeared, it is generally in the distal esophagus for adenocarcinoma, that is the kind of cancer, esophageal cancer, that has increased several hundred fold in the last 50 years. So, the symptoms may be referred in the upper esophagus, but in fact the tumor itself or disease is in the distal esophagus, so it is nonspecific.

Hochster And you mentioned two things as Barrett's and something we call – GERD, gastroesophageal reflux disease. Can you tell us a little bit more about what those are and their relationship to esophageal cancer?

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Caldwell Yes. So, gastroesophageal reflux is a risk for Barrett's esophagitis and I mentioned that gastroesophageal reflux is the symptom of heartburn, it is also the symptom of a burning or regurgitation sensation in the upper esophagus or mouth. The experience of either one of these or both of these symptoms on a weekly basis is clinically diagnosed or defined as gastroesophageal reflux. Depending on how that is defined, we see this incidence in the population of 15% of adults. Endoscopically defined, it is the appearance of damage to the distal esophagus, erosions, inflammation, and so we may see up to 20% to 25% incidence of gastroesophageal reflux. Barrett's esophagitis is a microscopic diagnosis, under the microscope in other words, with distortion of the cells of the inner lining under the esophagus. In other words, the appearance of intestinal epithelium, which are gastric-like cells whereas normally in the esophagus, we

see flatter or squamous cells. And so, this change in the esophageal mucosa is defined as Barrett's esophagitis when these biopsies are taken the junction between the stomach and the esophagus.

Hochster So, due to the effect of this acid coming along all the time, the normal appearance of the esophagus turns into look more like stomach.

Caldwell Exactly. So, we call it gastric-like mucosa or intestinal epithelium, sometimes... this is getting into more details, but the presence of goblet cells in the intestinal epithelia, and that itself is a precursor to esophageal cancer. Hochster So that is like a premalignant change that can eventually lead to esophageal cancer? Caldwell Yes. And so, precisely, the annual risk of developing esophageal cancer from Barrett's without dysplasia is approximately 0.1-0.5%. Now, when the mucosa actually becomes dysplastic, low grade or high grade, then incidence of cancer is higher – 10-15% cumulative risk. And it is the precise reason that we perform endoscopic surveillance on a patient with Barrett's.

Hochster Well, that is very interesting. So, Mr. Gordon, can you tell us a little bit about your situation and what happened with you and how you came to be diagnosed?

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Gordon Okay. When I turned 60, I am 75 now, I knew it was time to have an endoscopic exam, a colonoscopy, and I made an appointment with Dr. Caldwell, and before the procedure, he spent quite a long time talking to me about my overall health and other issues – took blood pressure and discussed in detail what would be involved in this endoscopic exam of my colon. And I was very interested because I am engineer and one of my jobs that I have had in the past was working for a company that made endoscopes. So, I knew what they can do and was very interested to hear what he was capable of looking me. So, in the process of interviewing me, he said are there any other health issues and I said, "well I have got chronic heartburn. I have had duodenal ulcer as a young teenager and I have been taking antacids for a long time, and now I take them regularly for heartburn." So, he suggested that while I was undergoing this anesthesia process that I should probably have my upper GI system scoped as well. So, I said "okay, fine." And he found at that time when I was roughly 60 that I had Barrett's esophagus and explained with pictures the difference in the cellular structure caused by that, and he prescribed a different antacid and the heartburn went completely away, so I felt cured. But he pointed out to me that this was a precursor of possible cancer and I should be screened yearly. And so, we basically set it up on a yearly basis for about 12 years, and after that time, he called me into his office after the exam and there was evidence of a tumor in my esophagus just as he had predicted could happen. And then, he outlined to me what the appropriate next process would be to surgically remove that tumor. And also, which was very gratifying that he felt that it could be

it was diagnosed early enough to eliminate and maybe not need radiation or chemotherapy, which was the case. I was then transferred under the care of Dr. Anthony Kim at Smilow who, very smooth transition of continuity of care, explained to me what to expect with the surgery and I spent about 2 weeks or 17 days actually in Smilow and the surgery was surprisingly without pain. I had not one minute of pain in the whole process and I think I was also well prepared for the fact that I would not be able to eat for a while after the surgery and it was done laparoscopically, so there was very little, the size of the opening for my operation where they completely removed my esophagus was like an inch scar, which basically was very good for my comfort, I will put it that way.

Hochster So, you basically decided to go for a colonoscopy when you are 60, I just want to plan it to our listeners the recommendation is to start screening colonoscopy at age 50 and then Dr. Caldwell talked to you and he said, "well, we should take a look in your esophagus because you are having these ongoing heartburn symptoms," and that is how it came to life and then you had yearly endoscopies?

Gordon Yes. It was a life saving diagnosis by Dr. Caldwell for to whom I very grateful. Hochster Okay. Well, we are going to take a short break for a medical minute, and please stay tuned to learn more information about esophageal cancer and we will hear more from Mr. Gordon on his journey with this disease.

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This is Dr. Howard Hochster and my guests Dr. Cary Caldwell and Mr. Joseph Gordon join me tonight to discuss early detection of esophageal cancer. So, Mr. Gordon, you were kind of talking about laparoscopic surgery and it was painless and you said you could not swallow for a while?

Gordon That is correct, right.

Hochster How long did that take before you could start eating normally eating again.

Gordon Well, I had a feeding tube right after the surgery, so that is how I received all my nourishment for a while and then I was transferred to Gaylord Hospital for a rehabilitation for another 2-1/2 weeks, and in that time, I was treated by speech therapist. In addition to regular exercise and dieticians talking to me about what I could need and how to go from basically eating nothing but liquids and then gradually progressing to mashed potatoes, mashed vegetables and also going with speech therapists into exercises so that I could begin to learn how to swallow without difficulty because what they had done is take the stomach and pull it up right up to my throat and then staple it so that the mechanism of swallowing was like a new experience. And there was quite a lot of attention paid to the epiglottis, which would make sure the food would go down my digestive tract rather than into my lungs. And then, later that was followed up by Dr. Caldwell was an active, and he I am sure probably can explain it better, but he could actually watch while the epiglottis would function and it was functioning fine after that point in time. So, again, I feel very fortunate and very grateful.

Hochster So, in the immediate postop period, you had a lot of training to learn to swallow again or swallow differently?

Gordon Yes, that is correct.

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Hochster And now you are back to eating normal diet?

Gordon I feel like I haven't lost any satisfaction from eating. I'm at a better weight, I feel great. I have cut back on my employment, I work only mornings now.

Hochster You are not retired, you are 75 and going strong.

Gordon Well, I am not going as strong as I did. You have to face your mortality and I thought I have a business that might end up in the dumpster if something were to happen and I trained a young man to take it over, who has done a marvelous job and in the total treatment, I was out of work for close to 2 months and he ran place better than I did, so I am very lucky to have been able to preserve my business and live a normal life. I'm anxious to tell people who have Barrett's, I have friends that have Barrett's that how important it is to have a yearly endoscopic exam.

Hochster Well, thank you and thank you for sharing your story with us. So, Dr. Caldwell, the Barrett's leads to one kind of esophageal cancer. There are other risk factors for esophageal cancer that our listeners should be aware of, especially for this squamous type, do you like to discuss that at all.

Caldwell Yes. Two chief kinds of cancer of the esophagus as you mentioned, squamous cell and adenocarcinoma. And whereas squamous cell was the most common esophageal cancer decades ago, now adenocarcinoma is the leading cause. Squamous cell carcinoma is clearly linked to smoking and alcohol, also toxin ingestions - lye for instance, intentional or otherwise, ingestion. And in certain other parts of the world, the squamous cell cancer is still the leading cause, but in the United States, adenocarcinoma is the leading cause of esophageal cancer, and Barrett's is one of the risk factors, obesity is as well. There is clearly a link obesity - high BMIs, several-fold risk over the general population, I mentioned earlier to older age, gender as well. And we do see a decreased incidence of esophageal cancer, and I want to point this out, that taking proton pump inhibitors is clearly associated with decreased Barrett's, decreased adenocarcinoma and increased survival. There may be an inverse association with helicobacter infection, which is a bacterium that invades the gastric mucosa, so-called the lining of the stomach and we do see in some cases of helicobacter gastritis, particularly throughout the stomach, decreased incidence of Barrett's.

Hochster Some people may be aware of that by the name of H. pylori.

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Caldwell One of the things that I wanted to mention is the followup and management of such a patient with Barrett's, and we did hear that yearly endoscopic surveillance is what led to this early diagnosis, but lest the listeners believe that that is the absolute recommendation of all gastroenterologists. Generally speaking now, we suggest endoscopic surveillance every 2-3 years for Barrett's. It was in Mr. Gordon's case that I chose to do yearly endoscopic surveillance because 1 year he did have what is called low-grade dysplasia in a few of the biopsies, and what I mean by dysplasia, think of it as disordered mucosa and dysplasia is a precursor of cancer or early cancer if you will. So, low-grade dysplasia warrants close followup and we that within 6 months and then yearly afterwards and did not see any further dysplasia. Dysplasia again is an indicator for more frequent endoscopic surveillance, which then led to his diagnosis fortunately early, and I will say that because esophageal cancer unfortunately at the time of diagnosis is a limited disease that is confined to the esophagus in only 25% of the patients, so Mr. Gordon was one of the fortunate ones who had the disease confined to the esophagus. By tumor criteria, he was so-called T1b and it was for that reason plus the fact that his Barrett's esophagitis was defined as long segment, in other words longer than 3 cm in his esophagus that we felt that surgical outcome was the best. There are options -- for example, with somebody who has a T1a lesion and short-segment Barrett's esophagus, who might be better suited to endoscopic mucosal resection or EMR and this is done by some of our endoscopic ultrasound colleagues at Yale.

Hochster So, just want to emphasize that, in Mr. Gordon's case, because of the amount of the esophagus, the length, he needed surgery, but some people with smaller areas of involvement can have surgery done endoscopically, they do not

need to have major surgery and it can be done like the same way that they have the regular endoscopic look-see, they can also resect it?

Caldwell That's exactly right. And generally speaking, endoscopic therapy is easily tolerated. There are some peri-procedure risks of stricture, bleeding or rarely, perforation - meaning penetration through the wall of the esophagus, and then there is even a syndrome of subepithelial or submucosal disease and/or hidden Barrett's and dysplasia. In other words, because of treatment with another form of endoscopic therapy such as radiofrequency ablation, whereby the dysplastic tissue could be possibly covered up by scar tissue, and that happens in about 5% of patients treatment with radiofrequency ablation or RFA.

Hochster So, one of the real keys or key messages is that if you go for surveillance and they find this early and it is relatively confined, you might not even need surgery and it can be treated and cured without a big surgery with just this endoscopic procedure?

Caldwell That is right. Hochster That is very encouraging news today for our patients, and I guess because of the risks you talk about including perforation which is basically a hole in the esophagus, people should be sure to go to physicians who are well experienced with these endoscopic techniques.

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Caldwell That is correct. So, the long-term management of such a patient with Barrett's and by whom and where, generally speaking, GERD and Barrett's is a common diagnosis and is managed by the majority of the gastroenterologists, and the frequency of surveillance is really a contingent on what is the underlying histology is as I mentioned earlier low-grade dysplasia or higher. When it comes to the point of possibly needing endoscopic mucosal resection or EMR or the other alternative RFA, then we will use the endoscopic experience of people who use endoscopic ultrasound and will refer patients appropriately for that procedure when it is applicable to people like Mr. Gordon - in his case again, we had him see an endoscopic ultrasonographer not for treatment but really for diagnosis. So, I wanted to make that point that in the workup of the patient, there is a newly found nodule that by biopsy shows esophageal cancer, we will always use endoscopic ultrasound as a determinant of extent of disease. The endoscopic ultrasound probe on the end of the endoscope allows visualization within the walls of the esophagus to find out how far the tumor has progressed.

Hochster So, everybody I think is somewhat familiar with ultrasound from women who are pregnant. The endoscope people can actually have a little scope with that kind of device on it and then they can see how big the tumor is and how deep it goes into the wall of the esophagus. That is kind of an important part of the staging?

Caldwell That is absolutely correct.

Hochster So, for the people who are smokers and drinkers and are worried about

this, we recently had a discussion on Yale Cancer Answers about the lung cancer screening program with CAT scans, what is the recommendation for screening for esophageal cancer?

Caldwell So, for esophageal cancer, once it is diagnosed, in addition to the EUS, the endoscopic ultrasound, we also suggest a CAT scan or a PET scan to make sure there is localized disease.

Hochster And pre that screening for, should people be talking to their doctors about going for endoscopies? Caldwell Absolutely, if they are having symptoms of chronic GERD that is getting worse or is refractory to treatment of the so-called PPIs, proton pump inhibitors.

Dr. Cary Caldwell is an Associate Clinical Professor of Internal Medicine and Digestive Diseases at Yale School of Medicine and Mr. Joseph Gordon is a patient. If you have questions, the address is canceranswers@yale.edu, and past editions of the program are available in audio and written form at YaleCancer-Center.org. I am Bruce Barber reminding you to tune in each week to learn more about the fight against cancer. You are on WNPR, Connecticut's public media source for news and ideas.