ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

Section Editor: Eugene R. Schiff, MD

Genomics in the Early Detection of Cholangiocarcinoma

Emmanuel Thomas, MD, PhD
Assistant Professor
Sylvester Comprehensive Cancer Center
Schiff Center for Liver Diseases
University of Miami
Miami, Florida

G&H What are some important facts about cholangiocarcinoma that merit increased efforts to improve early detection?

ET Cholangiocarcinoma (CCA) is a rare liver cancer that occurs in 1 or 2 individuals per 100,000 in developed regions. Approximately 2500 new cases are diagnosed in the United States each year. The greatest risk factor for developing this cancer is a diagnosis of primary sclerosing cholangitis (PSC). Among patients with this diagnosis, CCA rates may be as high as 30%. Although its overall incidence is low, CCA is one of the few cancers whose incidence is increasing. In addition, CCA is a deadly tumor, with a 5-year survival rate that can be less than 15%.

G&H Why is the incidence of CCA increasing?

ET We do not have a clear picture of exactly why CCA is on the rise. Several liver conditions may contribute, but a definitive link has not been established. These potential contributors include progressive liver fibrosis and cirrhosis in aging patients infected with hepatitis B virus or hepatitis C virus. The link between PSC and CCA supports the belief that as PSC rates rise, the same will be true for CCA. There is a well-defined link between progressive liver fibrosis and nonalcoholic steatohepatitis (NASH) and hepatocellular carcinoma, but whether these conditions are proven risk factors for CCA is not certain. In the United States, the incidence of many liver diseases is increasing because of the aging population of people with hepatitis C virus infection, along with the increasing rate of obesity, which subsequently contributes to the incidence of NASH. All of these factors may play a role in the development of CCA, but we do not know how much.

G&H Why is the survival rate so low?

ET One reason for the poor outcomes is the lack of effective early detection tools. Usually, this cancer is detected late, when it is difficult to treat. We need better methods to find CCA early on in its development.

Individuals with risk factors for any type of liver cancer should undergo some type of surveillance. For CCA, surveillance is an active area of research. One sophisticated approach utilizes brush cytology, conducted during endoscopic retrograde cholangiopancreatography (ERCP), to sample the biliary tract and obtain epithelial cells. An analysis of these cells can determine whether the individual has basic cellular indicators of established or developing CCA. However, this procedure is quite invasive and can cause significant complications, including pancreatitis.

Less invasive approaches include magnetic resonance imaging cholangiopancreatography (MRCP) and ultrasound. These methods may be less sensitive and specific than ERCP-based approaches. However, combining these noninvasive approaches with a test for a serum biomarker, including cancer antigen–9 or carcinoembryonic antigen, improves the detection of CCA. The field is evolving, and we do not yet have good evidence to establish the most effective combination.

G&H In general, what is the status of using genomics to detect cancer?

ET The sequencing of the human genome generated a lot of excitement. At that time, many people envisioned that we would carry around our genetic information on some type of medical credit card, and physicians would be able to read our sequences and predict our susceptibility to various diseases. However, the technology has not yet translated into clinical advancement for most patients. We have isolated cases in which this information has been very useful, but in general, the science has not yet turned out to be as effective as we had hoped in the direct clinical management of patients.

After the publishing of the human genome, the field soon turned its focus to genome-wide association studies, where we examine differences among specific patient cohorts to identify links between genes and polymorphisms and specific diseases. The creation of the Cancer Genome Atlas is an example of a more specific approach to targeting cancer that has recently been initiated. In addition, the new Precision Medicine Initiative that is supported by President Obama will increase efforts toward utilizing genomics to detect cancer.

G&H Have such links been established for CCA and genomics?

ET We have evidence for genetic predispositions to CCA. No specific link is firmly established, but studies thus far provide the impetus for further research. In addition, it is easy to obtain DNA from blood samples for analysis. Developing this area would enable us to avoid invasive procedures, such as ERCP with brush cytology for the early detection of CCA. Pursuing this line of research is very worthwhile from that standpoint alone.

G&H What links have been identified with CCA?

ET The most striking finding is the strong association between PSC and CCA. Up to 30% of patients with PSC may develop CCA. Studies examining this link found that some patients first diagnosed with PSC were subsequently diagnosed with CCA within a year. This finding led to the hypothesis that specific genetic mutations may contribute to the rapid progression of CCA in some patients, and identifying these patients through genetic analyses would aid in early detection. These specific genetic alterations would not be present in patients with PSC who develop CCA many years later.

G&H How would genomics contribute to the current approaches for CCA surveillance?

ET Genomics could potentially be used to determine the frequency of surveillance visits. For example, if a physician has decided to perform noninvasive imaging with ultrasound or MRCP every 8 months, based on an approximated growth rate of a specific liver cancer, the frequency could be adjusted based on additional evaluation of risk as determined by evidence from genetic markers. For example, if the patient has a much higher probability of developing CCA based on genetic information, the physician can be more aggressive with surveillance.

However, we need to identify and characterize these genetic variants that predispose people to CCA. After diagnostic genomic tests have been developed, testing could be performed just once. If an individual has any other clinical risk factors for developing liver cancer, this information could be used in conjunction with the genetic tests to develop a patient-specific program for surveillance. We do not currently have any such genetic tests approved for CCA by the US Food and Drug Administration (FDA), but we do have such tests for other cancers, such as breast, ovarian, and colorectal.

G&H Could any of these tests be useful for CCA detection?

ET Interestingly, there is an association between colorectal cancer and CCA through PSC. Patients with PSC are more likely to develop inflammatory bowel disease (IBD), and patients with IBD are more likely to develop colorectal cancer. It may be useful to look at the risk for other cancers and apply what we know about genetic susceptibility to those cancers to CCA.

G&H In considering testing for genetic variants potentially associated with CCA, would these be inherited variants only or spontaneous mutations?

ET Diagnostically, the most useful variants are hereditary/germline because they are better characterized and because they have an established link to cancer risk. Specific hereditary/germline mutations can be strong predictors of cancer development. With spontaneous/somatic mutations, the link is not as strong, but they can be very informative, especially for prognostication and for prediction of treatment efficacy when CCA has been diagnosed in a patient.

G&H What genes have been linked, even in a preliminary way, to CCA?

ET Variants in several genes have been identified, including *TP53, KRAS,* and *SMAD4*. However, we do not know whether these are driver mutations that cause the develop-

ment of cancer cells, or secondary gene mutations that promote tumor progression once the cancer is already established. In general, determining whether a variant is a driver mutation or not is difficult, and driver mutations are the ones we want to find for early detection purposes.

G&H What have recent studies in this area found?

ET One interesting study looked at the development of CCA from liver flukes, which are pathogens associated with the development of this cancer. In an Asian cohort, mutations in several genes were identified, including *MLL3, ROBO2, RNF43, PEG3,* and *GNAS*. These genes may be useful in detecting all forms of CCA, not just that associated with liver fluke pathogenesis.

G&H Could this finding lead to a test for early detection of CCA?

ET We are years away from having a routine genetic test for early detection of CCA, but we have the tools to generate a comprehensive mutational landscape in patients to identify somatic and germline mutations that can be useful for prediction. Several technologies now in development could eventually translate into an FDA-approved test. Another approach focuses on gene expression, which refers to the levels of RNA transcripts that are generated from a genome, as opposed to directly identifying genomic mutations. The levels of transcripts of a specific set of genes could possibly correlate with the development of CCA. This approach has been used to create a gene expression signature test for breast cancer and could potentially be the basis for a CCA test. If we identified 20 genes for which the RNA levels were found to correlate with CCA, such as from blood cells, then we could easily assay just those 20 genes and determine which patients are most likely to develop CCA based on the RNA levels.

Another, more established approach of utilizing information from nucleic acids and genomes entails identifying abnormalities in the DNA content per cell, which is referred to as aneuploidy. This test can be performed once cells are obtained through brush cytology and may be useful as a diagnostic marker to detect early dysplasia that may be missed with routine cytology. Cells obtained through brush cytology can also be used to detect chromosomal alterations, including polysomy as determined by fluorescence in situ hybridization. Genome-wide association studies using single nucleotide polymorphisms also offer an exciting opportunity for the discovery of mutations associated with CCA, but studies identifying new mutations through this methodology have yet to be published. Overall, new sequencing technologies and data analysis platforms will allow us to identify somatic/germline mutations, changes in gene expression, gene copy number alterations (including amplifications/deletions), and finally gene fusions/translocations that can be used for the early detection of CCA. In addition, in the future, this new information could be used by "precision medicine" tumor boards to guide treatment strategies that could improve the survival rate for this deadly cancer.

Dr Thomas has no relevant conflicts of interest to disclose.

Suggested Reading

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