Role of Aspirin in Colorectal Cancer Prevention and Treatment

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By Andrew T. Chan, MD, MPH [1]

In this interview we discuss the role of aspirin in colorectal cancer prevention and treatment. Various studies have suggested that a daily aspirin pill can help prevent certain types of cancers. Other studies suggest that there may even be a role for aspirin in treating cancer.

Various studies have suggested that a daily aspirin pill can help prevent certain types of cancers. Other studies suggest that there may even be a role for aspirin in treating cancer. Today we are speaking with Dr. Andrew Chan, associate professor in the department of medicine at Harvard Medical School and Massachusetts General Hospital in Boston, about the role of aspirin in colorectal cancer prevention and treatment. Dr. Chan’s research focuses on ways to prevent colorectal cancer, and part of that is to understand how aspirin may play a role in both preventing and treating the disease.

—Interviewed by Anna Azvolinsky, PhD

Cancer Network: Dr. Chan, what were the initial observations that aspirin may in fact help to prevent colorectal cancer?

Very early on, several decades ago, there had been several different groups that had observed that patient populations that take a lot of aspirin, for example, patients who have rheumatoid arthritis or osteoarthritis, tend to have lower rates of colorectal cancer. This led to a variety of studies in different cohorts of patients and also case-control studies that corroborated the finding that individuals who take higher amounts of aspirin over time tend to have lower incidence of colorectal cancer. This also was, I think, around the same time that many medical groups in experimental studies were showing that aspirin in animal models and cell lines seemed to have a direct anticancer role. We had this confluence of data coming both from human studies and from experimental data that began to illuminate this fascinating observation that aspirin could be a potent chemo-preventative.

Cancer Network: What are the hypotheses for how aspirin exerts its effects in preventing colorectal cancer?

I think we understand that aspirin has very specific pharmacological properties. I think one of the roles that aspirin is known to have is to inhibit the expression of the activity of cyclooxygenase enzymes, such as cyclooxygenase-2 (COX-2). This is the enzyme that is known to be upregulated in colorectal cancer. As a normal colon becomes cancerous, COX-2 expression tends to go up. We also know that COX-2 probably has very specific roles in mediating downstream pathways that are important to cancer. Aspirin is known to inhibit COX-2, and it is also known to inhibit another isozyme of the COX family, COX-1. So, it has been very likely that COX-2 and COX-1 have a role in cancer, and that aspirin operates through this mechanism. At the same time, there has been a lot of data suggesting that aspirin has other roles and other potential mechanisms of action in the prevention or treatment of cancer. And some of these roles have been very well validated, including in...
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experimental models, so we have really been interested in understanding, given all of the roles that aspirin has, which are the ones that are relevant to the human situation and which are the ones that we could potentially exploit in helping us tailor therapy. I think if we know better the type of mechanisms that aspirin actually affects, we can use those mechanisms to our advantage, to understand whether we can target therapy for particular types of patients that we think are developing cancer through those mechanisms.

Cancer Network: You mentioned one of the mechanisms by which aspirin can work. Are all of the mechanisms that are thought to work, do all of these have to do with inflammation or are there other potential ways that aspirin exerts its effects?

Dr. Chan: Many of them are related to inflammatory pathways. I think for example, COX-2 certainly is a pro-inflammatory enzyme. It is a very important enzyme in mediating the body’s response to inflammation. We know that COX-2 is upregulated in the setting of inflammation, so it makes sense that aspirin could really be effective in those cancers that may have a pro-inflammatory basis. But, at the same time, we also know that inflammation is a pretty broad term. There are lots of different types of inflammation and there are lots of different pathways that inflammation may activate that may be related to cancer. We do think that the pathways that aspirin influences probably have some connection with inflammation, but it has become more complicated and more complex than we anticipated because these pathways may not have a very clear inflammatory role, but as you dig deeper and see the connections between those pathways and other pathways, you do get a sense that there are some commonalities with respect to inflammation and how that provokes human disease.

Cancer Network: Recently, you and colleagues published several papers suggesting that certain types of colorectal cancers may be more responsive to aspirin than others. Can you talk about that data briefly and any follow-up research you are currently conducting?

Dr. Chan: One of our early studies examined the effect of aspirin in relation to expression of COX-2 in the tumors. Although COX-2 is an important player in colorectal cancer, not all colorectal cancers overexpress COX-2. About 75% of cancers overexpress COX-2 and about 25% do not overexpress COX-2. And in our original studies, we found actually that in a large prospective cohort of individuals followed over time that individuals who use aspirin had a lower risk of developing a colon cancer that overexpressed COX-2, but the use of aspirin didn’t seem to be associated with a low risk of cancer that didn’t express COX-2. This suggests that aspirin could be a preventative and was active in a preventative way, but mostly among individuals that had cancer development through the COX-2 pathway. For whatever reason, those individuals that tended to get cancer through the COX-2 pathway were the ones that were more sensitive to aspirin. We then followed that up by looking at a study of survival. Among patients that had an established diagnosis of colorectal cancer, we found that after those patients were diagnosed, if they took aspirin, they had a lower risk of dying from colorectal cancer. There was a very specific effect on colorectal cancer-specific mortality. What was really interesting was that it was a subgroup of patients that had overexpression of COX-2 who really benefited from the aspirin. Those initial studies suggested that there was a specific subtype of colorectal cancer that may be signaled by expressing COX-2 that could be more potently prevented or treated by aspirin.

More recently, we have done studies to look at other pathways, because as I mentioned, we don’t think that COX-2 is the only pathway at hand. There are probably other pathways that aspirin has a direct effect on. We also looked specifically at the expression of the PIK3CA or the PI3 kinase mutation in colon cancer because there is emerging literature that suggests there is a lot of connections between PI3 kinase and COX-2. What we found was that it was individuals who had that PIK3CA mutation, which was about 10% or 15% of colon cancers, who really benefited the most from taking aspirin after diagnosis.

Then, most recently, we have been looking at subtypes of cancer defined by the BRAF mutation, because BRAF is also a really important player in oncogenesis. We know that it is involved in the MAP kinase pathway, and so there is a subtype of colon cancer that has a BRAF mutation, about 10% or 15% of colon cancers. In this study, what we found is that individuals who take aspirin have a lower risk of developing colon cancer that was BRAF wild-type (ie, didn’t have the BRAF mutation). But, on the other hand, aspirin didn’t seem to have a significant effect on cancers that had a BRAF mutation. I think these different studies suggest to us that there are pathways that aspirin specifically seems to be related to. These are COX-2 pathways, BRAF pathways, and PIK3CA pathways that aspirin has a direct hand in. I think if we feel like those mechanisms are important, we can then use our understanding of how those mechanisms are expressed in colon cancer to help tailor therapy as to who may benefit from aspirin therapy for prevention or aspirin therapy for treatment.
Are there currently trials that are ongoing that are testing whether aspirin can help prevent colorectal cancer or delay progression in those patients who already have the disease?

Dr. Chan: There is a trial that is going on in Southeast Asia known as the ASCOLT trial that is being performed on patients that have been diagnosed with colon cancer. They are being randomized to aspirin therapy to see if there is a benefit in terms of recurrence. There are also plans underway in the United Kingdom to do a multicenter trial of aspirin in the survival of patients with colon cancer. That trial may also expand into other cancers, like esophageal cancer, breast cancer, and prostate cancer, to see if there is a survival benefit among patients who have these types of tumors. There is emerging literature that aspirin has an effect in preventing not only colon cancer but also other cancer types as well.

Cancer Network: Do clinicians currently prescribe aspirin to certain patients with cancer or as a preventive measure? What is your view on that?

Dr. Chan: At this point there are no broad recommendations for aspirin therapy to prevent cancer or to treat cancer. The literature would be very supportive of that type of approach, but at this point in time, we don’t have the gold-standard clinical trials that are needed to make a blanket recommendation for the general population. There is a growing sense that because aspirin is widely used for a variety of diseases, such as prevention of cardiovascular disease, that conducting such a trial may be very difficult. We may have to look at the data as it stands now to determine whether there is enough data out there to potentially make a recommendation that clinicians at least talk to their patients about the possibility of using aspirin for prevention, because there are certainly risks to taking aspirin that shouldn’t be neglected and shouldn’t be overlooked, such as the development of bleeding, etc. At the same time, the benefits can be very good, especially if we think that aspirin can affect multiple cancers and especially among patients who have established cancer where recurrences are a real concern. In addition, I think we have very strong data from patients with hereditary colon cancer, those who have Lynch syndrome—and for that particular syndrome, there has been a phase III clinical trial that has shown that high doses of aspirin, 600 mg of aspirin, are associated with a lower incidence of colon cancer in the long term and also a lower incidence of developing other related cancers. So, in the setting of someone with a genetic mutation that is known to predispose them to hereditary colorectal cancer, I think that we see more and more that those people should be thinking about aspirin therapy and having that discussion with their providers.

Cancer Network: Thank you so much for joining us today, Dr. Chan.

Dr. Chan: Sure.

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