Colorectal Cancer Screening and Therapeutics

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My name is David Rubin. I'm an Assistant Professor at the University of Chicago. Colon cancer remains a significant cause of morbidity and mortality in the United States. As I always say to patients and colleagues, it is, in my mind, the most tragic of the GI diseases. Tragic because as this audience probably understands, colon cancer is one of the most preventable human cancers, not only because of the biology of the disease that we understand so well, but also because of existing screening technologies. It remains tragic that it's the second leading cause of cancer death in the United States and it's scandalous that 50% of our population remains unscreened. Clearly, there is a tremendous need in the United States for improved access to screening technologies and improved ability to understand who is at increased risk of colon cancer and to understand why people are not getting screened. The primary reasons that have been identified on the patient side is a lack of understanding of who is at risk and when they are at risk, combined with a fear of existing procedures like colonoscopy or as we've seen frequently in our practice, a fear of the diagnosis of bowel cancer. A combination of ignorance and fear contribute to a population of people who I call vulnerable. A vulnerable population that is afraid and misinformed of tests and afraid of the diagnosis and therefore are potentially at greater risk for misinterpretation of guidelines and misinterpretation of what physicians may try to tell them and offer to them. After extensive review, I did choose our twelve abstracts from the categories of risk factors, detection and prevention, although I recognize that some of the abstracts I am going to present actually overlap in those different categories. Let's start by talking about risk factors.

Abstract 222622: "Risk for adenoma recurrence at the second surveillance exam"

This abstract, by Douglas Robertson and colleagues, asks the question, "What is the risk for a second or future adenoma after the second surveillance colonoscopy?" The study reviewed two adenoma chemoprevention trials and the data from the polyp prevention group. These two adenoma chemoprevention trials were designed slightly differently, but the main outcome of interest was the development of an advanced adenoma, which they defined as a tubulovillous or villous histology, high grade dysplasia or a polyp that was ≥ 1 centimeter or multiple adenomas at the second follow-up colonoscopy after baseline. Seven hundred and ninety three subjects who underwent these procedures as part of the predesigned studies were looked at for outcomes at the second follow-up exam. Investigators found that outcomes were significantly influenced by the findings on the first exam. In this particular abstract, what they shared in their table was that a patient who had an advanced adenoma at their initial exam was two times more likely to have advanced adenomas on their second follow up exam than somebody who did not have that advanced adenoma at the first exam. What is this implication for our

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understanding in practice? The idea is that it is the cumulative number of adenomas that a patient has in their lifetime that can influence what we should be recommending for follow up in those individuals, rather than just looking at a cross section in time and an individual's findings on a colonoscopy to determine what we might do for their follow up.

Some of the abstracts I have chosen this morning will help us understand better which patients are at risk more than just looking at our standard approach using age and family history.

***Abstract 226377*: "Patients with diabetes more than 15 years have increased odds of colorectal cancer"**

This was submitted by Donald Garrow and colleagues. This abstract expands on work that others have shown, that increased insulin levels, increased blood sugar and increased levels of insulin growth factor–1 (IGF-1) are associated with promotion of cancer growth both *in vitro* and *in vivo*. They wished to expand on our understanding of who is at risk for colon cancer, so they asked a very important question which is, "Is diabetes a significant risk factor and if so how might we factor that into our screening and stratification schemes?" They used the National Health Interview Survey (NHIS) which was collected from 1997 to 2003. The NHIS is a comprehensive nationally representative survey that was weighted to represent the U.S. adult population. There were 226,953 subjects in this database. They looked at those who had diabetes and grouped them based on duration of diabetes, asking if over the cumulative exposure to diabetes, was there a relationship between duration of disease and the cancer risk; a so-called "dose effect." They grouped people into 0-5, 5-10, 10-15 and greater than 15 years with diabetes and did multiple logistic regression to control for age, race, gender, obesity, alcohol use, tobacco use, and the treatment for diabetes (insulin, pills, both or diet only). What appears missing in their control was a family history of colon cancer and aspirin or statin therapies. Unlike another abstract that we will discuss later, they did not control for those two variables. Nonetheless they found that having diabetes for more than 15 years had a modest increased risk of colon cancer (OR=1.76) with statistically significant confidence intervals. They also found (validating their design) that age over 50 and a history of tobacco and alcohol use increased risk as well. This information would suggest that in our clinical practice we should be looking carefully at those who have long standing diabetes as a group that is at modestly increased risk for colon cancer compared to their age-matched cohorts in the population.

***Abstract 224103*: "IL-6, TNF-a and CRP gene polymorphisms are associated with increased colon cancer risk in African Americans compared to whites in the North Carolina Colon Cancer Study"**

This was submitted by Temitope O. Keku and colleagues at the University of North Carolina in Chapel Hill. It remains quite important that in the United States, African Americans have an increased risk of colon cancer as well as an increased risk of dying from colon cancer. It was suggested that this might be a health access issue, but more recently it has been shown that there are some biological differences in the cancers that African Americans get and the concept of ethnic and/or genetic differences has become an important issue in disease control. Better ways to understand why African Americans might be at greater risk in our population and how we might stratify screening strategies in the future is therefore very important. The study also suggested some novel genetic polymorphisms that might be related to the development of cancer. They evaluated 528 incident colon cancer cases (231 African Americans, 297 whites) and 836 controls (306 African Americans, 530 whites) from a large population-based case control study in North Carolina, which has previously been described and validated in a variety of ways. They looked at the polymorphisms and frequent genetic variance of IL-6, TNF-α and CRP (C-reactive protein) variants and found that IL-6 and TNF-α variant genotypes were significantly associated with an increased risk of colon cancer among African Americans compared to wild-type, and also found that those variants were increased among whites with colon cancer but it was greater among African Americans. The odds ratio was modestly increased for the IL-6 variant (OR=1.7) and for the TNF-α variant in African

Americans (OR=1.6), but when they looked at the risk for African Americans compared to whites it was not statistically significant. In addition, and possibly of biological significance, the odds ratio for having greater than median waist to hip ratio plus one or more of these genetic variants of cytokines was 2.2 compared to persons below median waist-to-hip ratio. More work is needed in this area but it suggests some novel potential mechanisms and explanations for either cause or associations with molecular measures of colon cancer risk in different races.

***Abstract 224660*: "Colorectal adenomatous polyposis linked to MYH gene mutations: Genotype and phenotype characteristics in a French series of 56 patients"**

This was submitted by Guillaume Bouguen and colleagues from France. This group studied the frequency of MYH Gene mutations in a population with no detectable APC mutations. MYH is a germ line mutation in a gene that is related to the repair of base excision DNA that was first described a number of years ago. This has now been described and recognized as an autosomal recessive risk for colon cancer. When we see polyposis that is not otherwise explained by either attenuated adenomatous polyposis, classic polyposis, and in some cases when we suspect it might be hereditary non-polyposis colorectal cancer, we think of MYH. In this French study, they were trying to define among their patients who had polyposis, what the risk factors were to identify individuals who might be at risk for MYH. In this study, 56 French patients had undergone testing for MYH germline mutations. They found it in 11/56 patients (19.6%) and the prevalence of the mutation was 34% in the subgroup who had 10 or more adenomatous polyps. What we have been discussing and debating is how many polyps are necessary before you consider a genetic syndrome such as attenuated familial adenomatous polyposis (FAP) or MYH? Among the 10 patients who had biallelic MYH mutations, two were homozygotes, and the other eight were compound heterozygotes and only one patient had a monoallelic mutation. This supports the idea that this is probably a complex recessive mutation and that it is likely required to have two abnormalities in order to have disease expression. There was no vertical transmission noted in their review. In other words, they could not easily identify a first-degree family member who also had polyposis or colon cancer to explain these findings. This is a very important clinical take home, which is that the patients who have polyposis syndromes associated with MYH abnormalities are unlikely to have an obvious family history. One patient in this series had gastric and duodenal adenomas with high-grade dysplasia. The reason I chose this abstract was because I feel as though my colleagues are not as aware of MYH and its contribution to polyposis that we are now seeing and we believe that this probably is more prevalent then we are acknowledging.

Moving on to detection, let's review a number of abstracts related to detection of colon cancer.

***Abstract 221219*: "Impact of initial polypectomy versus follow-up surveillance colonoscopy on colorectal cancer incidence in post-polypectomy patients"**

This was submitted by Ann Zauber and Sid Winawer from Sloan-Kettering Cancer Center**.** This study was a modeling study looking at the data from the National Polyp Study to ask "Why is colon cancer risk decreased after polypectomy?" What was previously shown is that when you remove polyps at a colonoscopy and in subsequent surveillance exams you are decreasing the incidence of colorectal cancer. The model asked the question, "Is it the first colonoscopy when the polypectomy occurs, or is it the surveillance exam? They divided patients into three groups in which they hypothetically said number one, "What if they never had the colonoscopy?" Number two, "What if they had the initial colonoscopy but no follow up surveillance exam that is responsible?" And number three, "They had, as was designed in the studies, an initial colonoscopy with polypectomy and a surveillance follow up exam?" In the model, they looked at predicting subsequent number of polyps and their size and what they found was that 90% of the impact of colonoscopic intervention is due to the initial colonoscopic polypectomy. This is not

necessarily a surprise to us. We know that the incident exam is often the one that has the most impact. More importantly and what we want to understand better is, "What is the impact of subsequent exams?" In other words, can we space out subsequent exams, can we stratify patients for follow-up in different ways, and based on this model, what they concluded is that for those with one or two adenomas even if they were slightly larger in size, there was only a very small risk reduction for that follow-up surveillance exam. They suggested, based on this model, that those patients can be followed up at five or ten years, which is consistent with what guidelines are now suggesting. I thought the model was interesting because it provides additional statistical support for delaying our surveillance follow-up longer than many physicians are currently doing.

***Abstract 216047*: "Accuracy of computed tomographic colonography for colorectal cancer (CRC) screening in asymptomatic individuals"**

This abstract by Brooks Cash and colleagues is related to CT colonography, and although none of the United States healthcare societies are endorsing CT colonography as a screening test yet, there still remains great interest by patients and by our colleagues in what is going to happen with this technology. Recall that three major virtual colonoscopy or CT colonography studies have been published in the last number of years. In 2003 in the *New England Journal of Medicine*, Pickhardt, a radiologist, found a sensitivity for polyps, large polyps, that was similar to what colonoscopy has reported, but in his study, he beat colonoscopy, as many of you may recall, and colonoscopy in his study also missed one large polyp that harbored a cancer, and that is what I have called "the cancer heard around the world." He used a three-dimensional fly-through technique, and tagged the stool using a small amount of diluted oral contrast. He had tremendous results in this study of patients who were asymptomatic presenting for screening. The subsequent CT colonography studies published have not shown the same results but have used two-dimensional axial slice reading with three-dimensional problem solving only for difficult-to-discern lesions. There was Peter Cotton's trial published in *JAMA* in 2004 which showed that CT colonography had an abysmal sensitivity for large lesions compared to colonoscopy. Then Don Rockey's study published in *Lancet* in 2005 in which patients who were at increased risk (an enriched population) underwent three tests including barium enema. It was the largest study ever to compare barium enema to CT colonography to colonoscopy. The Rockey trial was designed to be a four-year trial recruiting a large number of patients, but it had as its predefined interval analysis a two year statistical review and at two years they found that colonoscopy was so far superior to barium enema and CT colonography that continuing the study for an additional two years would not have changed the result. So we have two studies where the principal investigator was a gastroenterologist; one study was a radiologist - different techniques.

What Brooks Cash and his colleagues asked is. "If we used Pickhardt's technique, would we have similar results to what he saw," and in fact they almost did. In this study of asymptomatic average risk individuals at the Naval Medical Hospital, they performed CT colography using endoluminal fly-through and with dilute contrast agent in the bowel, they found a sensitivity for 10 mm polyps that was on par with colonoscopy in the 90 +% with high specificity and for 6 to 9 mm polyps, the sensitivity and specificity were 65.6% and 92% which is higher than the other studies (except Pickhardt's), but still inferior to optical colonoscopy. They concluded that this approach may be a better way to proceed with further evaluations of CT colonography. What remains of concern and interest to everybody who looks at this is we do not necessarily have a problem at all with 10 mm or greater polyps or masses, but rather what to do with these smaller polyps. If you see them do you go after them and if you see them (or you miss them) and you do not go after them, what is the outcome?

The next abstract is related to that specific question.

<u>Abstract 216292</u>: "The management of small (6-9 mm) polyps found by virtual colonoscopy: Results of a decision analysis"

This was submitted by Chin Hur, David Chung and their colleagues at Massachusetts General Hospital. They were specifically asking "What happens to small (6-9 mm) polyps if we don't resect them?" If we look back historically at the barium enema literature, small polyps were ignored by radiologists. There was never a very large formal study of what happened to those polyps, but it was out of necessity when we did not have very good therapeutic techniques. The small lesions were left in. Now we know more about the natural history of small lesions and the sensitivity and specificity of colonoscopy as well as the complication rate for colonoscopy. These investigators performed a Markov decision-analysis to ask the questions, "If patients had small polyps on a screening CT colonography, if they underwent an immediate colonoscopy for polypectomy, what was the risk to benefit analysis including the possibility of complications from the colonoscopy? What if they wait three years for a repeat exam using the existing sensitivity and specificity of CT colonography? What is the likelihood of the outcome in these different scenarios?" Given a hypothetical 100,000 patients, the overall number of cancers in the CT colonography group was 1,168 compared to 58 in the colonoscopy group. In other words, polypectomy cured the majority of cancers in the colonoscopy group. All the deaths in the virtual colonoscopy group would be to subsequent colon cancer metastasis and death. The deaths in the colonoscopy group were from complications as well as from cancers. They concluded that following a small polyp on CT colonography for three years will result in greater number of cancers and deaths and therefore said that this needs to be factored into any widespread utilization of CT colonography. What was not mentioned in this abstract that is a very important issue in relationship to follow-up is that if you are going to follow patients with CT colonography more frequently, you have the issue of radiation exposure and cost. I think that cost-effectiveness of CT colonography remains unproven with existing models and sensitivities and specificities. More work clearly needs to be done.

<u>Abstract 218598</u>: "Risk stratification for colonic neoplasia through enhanced backscattering spectroscopy analysis of the endoscopically-normal rectal mucosa"

Submitted by Hemant Roy and colleagues at Evanston-Northwestern Healthcare, this is a novel detection technique that they have been studying for a number of years. It uses a technology that they are calling "enhanced backscattering spectroscopy" which gives a unique signal which correlates to the nano structure of cells. They have been able to predict cancer, polyps and precancerous findings with a great deal of sensitivity and specificity. Their question in this particular study was what does the rectum look like with using this technology and can it predict proximal neoplasia? They obtained two rectal biopsies from the endoscopically normal rectal mucosa in 88 patients who were undergoing colonoscopic evaluation and they performed their enhanced backscattering spectroscopy analysis using their apparatus and looked at the signals from these biopsies to see how it correlated to the findings on that colonoscopy. What they found was that there were highly significant differences between the values from patients who had neoplasia and those who had no polyps found on their colonoscopy, or cancers. They said the magnitude of the alteration progressively increased with the significance of the colonoscopic findings. In other words how many polyps, how large were they, or whether it was a cancer, and with their panel of markers and with looking at some different fine tuning of these markers, they describe that this might be a future technology to predict who might need colonoscopy earlier, and they imagine developing some additional techniques to approach patients in this regard. I will be interested to see what happens with that in the future.

***Abstract 225215*: "Loss of imprinting of the insulin growth factor 2 (IGF2) gene in buccal cells: Correlation with risk of colorectal cancer"**

Submitted by Enrique Quintero and colleagues from Spain, this is a study that looked at the loss of imprinting at the IGF2 gene which is thought to be an epigenetic change that is present in colonic tissue in some people who have colon cancer. They wanted to know whether they could determine if IGF2 gene in the buccal mucosa could predict colon cancer risk. They had 34 patients who had known colon cancer, 60 with adenomas and 62 controls, where they obtained the buccal cells and assessed for the loss of imprinting by studying the methylation status of a key marker in these individuals. They looked at hypomethylation as a surrogate marker for the loss of imprinting, which has been studied and described before. They found that the loss of imprinting of the IGF2 was detected in 5 of 62 controls, 10 of 60 patients who had polyps and 12 of 34 patients with cancer. Clearly not a signal that is strong enough to determine cancer from polyps or in this case even polyps from controls. However, they did show that there was an odds ratio of 6.21 to separate cancers from controls and it led to a conclusion that perhaps sampling these cells might again be a way to stratify people or know who might be at increased risk. If this type of tissue sampling can predict risk in the future, it would clearly be valuable.

***Abstract 226280*: "Colon cancer specific antigen-3 and -4 (CCSA-3 and CCSA-4): Novel serum based markers for detection of colorectal cancer (CRC)"**

Robert Schoen and colleagues from both Hopkins and Pittsburgh used a previously described proteomic approach on nuclear matrix proteins specific to colon cancer to develop an ELISA assay to determine circulating CCSA-3 and CCSA-4 on serum samples. The hope would be to identify a marker that could be measured in blood, circulating serum and use that as another way to stratify or to follow-up patients who had colon cancer (similar to what we do already with CEA [carcinoembryonic antigen]) but perhaps with a higher sensitivity as a screening or stratification test. In this small pilot study, the mean levels for both the CCSA-3 and CCSA-4 were higher in the patients with colorectal cancer than in the benign conditions and they concluded that they detected with 100% sensitivity the cancers and they suggested that this serum based assay would be of interest. Of course our marker and our goal in cancer prevention is not looking for cancers, it is looking for polyps. What would need to happen is either refinement of this approach or maybe addition in a panel approach, or even using this for people with known cancer for follow-up and clinical response to disease and remission from their cancer, which I think would be of interest.

***Abstract 225762*: "Long-term aspirin use and mortality: Implications for chemoprevention"**

Submitted by Andrew Chan and colleagues from Massachusetts General Hospital and the Dana-Farber Cancer Institute, this was a question of the effect of aspirin on mortality of all causes and specifically in mortality related to colon cancer. This was a prospective, nested case-control study of 75,816 women in the Nurses' Health Study to assess the use of aspirin, the dose of aspirin and mortality from all causes. Over 24 years they showed 9,477 total deaths and among women who reported current use of aspirin, the multivariate relative risk of death from all causes was 0.75 which was statistically significant suggesting aspirin use was protective. The risk reduction was more apparent for death due to cardiovascular disease as we would fully expect given the data and understanding of aspirin's role in those diseases. They also observed a significant linear relationship between increasing duration of use and decreasing all cause mortality. They suggested that the longer you used aspirin, the more likely you were to have a benefit. The strongest effective long-term aspirin use was observed with colon cancer death with a relative risk of 0.60 for greater than 20 years of use. This is an important study using a very large database to suggest that the aspirin effect may be in fact related to duration and longer use may have a greater benefit to people who are at risk for polyps and colorectal cancer. What is not reported in this study, which is

obviously of interest to all of us, are the potential complications of aspirin use, particularly GI toxicity. I think that will be defined further as we consider future prevention strategies.

***Abstract 214435*: "Ace inhibitor therapy is associated with a decreased incidence of colorectal cancer"**

Submitted by George Makar, Jim Lewis and colleagues at the University of Pennsylvania, this was a study that came from laboratory data that suggest increased angiotensin II may promote growth of colorectal cancer (CRC) through mechanisms that have been previously described such as neovascularization and IGF-1 receptor expression. They asked the question, are people who are on ACE inhibitors less likely to develop colorectal cancer? They conducted a nested case control study using the General Practice Research Database from the United Kingdom which captures diagnoses and therapies. Cases were subjects who had a new diagnosis of colon cancer and up to 10 controls per case were selected, matched for age, sex, calendar year, and duration of follow-up. They excluded patients who had a diagnosis within a year, but the primary exposure duration of interest was being on an ACE inhibitor for more than three years. They also assessed the effect of escalating durations of exposure and found when they controlled for potential confounders including BMI, smoking, aspirin, and NSAID use, hormone replacement therapy, folate, calcium, statins and insulin exposure, that greater than three years of ACE inhibitor therapy was associated with a reduction in the colon cancer risk which was significant at 0.79. A significant duration response effect was also present and they suggested that long-term ACE inhibitor therapy was associated with a decreased risk of colon cancer in this cohort.

I think the underlying message in all the work that is coming out, whether it is looking more carefully at African-American cancer incidence and rates or the increased risk of cancer in those who have diabetes who are on certain therapies or who are obese, is that we should not be treating all of our patients the same, and as clinicians, we need to be thinking carefully about stratifying them and approaching them in different ways. The other major message from the abstracts at this meeting has to do with follow-up of small adenomas. Although not novel, the work at this meeting support existing guidelines that two or less adenomas can have a five-year follow-up. However, additional work supports the important concept that we should not just look at those two adenomas in a cross sectional way, but we should be thinking about the lifetime history of adenomas in individual patients and their cumulative adenomas, that we should be aware of these other potentially recessive genetic causes for polyposis, and we should be thinking about getting our patients into better screening and prevention schemes in their future management.

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Abstracts Discussed

222622: Risk For Adenoma Recurrence At The Second Surveillance Exam. *Douglas Robertson, Carol A Burke,Leila A Mott, John A Baron*

Background: Current guidelines for post-polypectomy colonoscopic surveillance are based only on the most recent exam findings. Aim: We determined adenoma recurrence risk over time in the context of an individual's entire lifetime adenoma history. Methods: Subjects were drawn from 2 adenoma chemoprevention trials. At enrollment, all subjects had one or more adenoma and had undergone clearing colonoscopy. For this analysis, we only included subjects whose qualifying adenoma(s) were their first lifetime adenoma(s). 'First follow up exam' was defined as the protocol exam occurring either three or four years after the baseline exam (varied by trial). Any exam ≥ 2 years after the 'first follow up exam' was defined as the 'second follow up exam'. The main outcome of interest was development of an advanced adenoma (tubulovillous or villous histology, high grade dysplasia, or ≥ 1cm) or multiple (>2) adenomas (AdvMult) at the second follow up exam after baseline. Statistical significance was assessed by $\chi2$. Results: 793 subjects (mean age, 58 years) were identified; 62% were male. Mean time from baseline to first follow up exam was 3.4 years, and from first to second follow up exam, 4.2 years. 82 (10%) subjects developed AdvMult at the second follow up exam. When separately considering high and low risk populations at baseline, outcomes at second follow up exam were significantly influenced by both prior colonoscopy results (see table). For example, those with high risk findings (AdvMult) at both baseline and first follow up exams had a 30% risk of AdvMult on the second follow up exam. This was significantly higher than the 15% risk of AdvMult at 2nd follow-up in those with high risk findings at baseline but no adenomas on the first follow up exam(p=.03). Similarly, in a low risk group at baseline (< 3 small tubular adenomas), findings at the second follow up exam were significantly influenced by the first follow up exam. In the low risk group at baseline,those with AdvMult at the first follow-up exam were at much higher risk for AdvMult at 2nd follow-up (15%) compared to those with no adenomas at the first follow-up (3.6%) (p=.01). Conclusion: An individual's entire adenoma history is useful in determining adenoma recurrence risk. Based on findings from both colonoscopies, high and low risk groups can be identified that may lead to more effective surveillance recommendations.

Subjects (%) With Advanced or Multiple Adenomas on 2nd Follow Up Exam

	1st Follow Up Exam Findings		
Baseline Findings	No Adenomas	Non Advanced and 2 adenomas	Advanced or > 2 adenomas
Non Advanced and 2 adenomas (n = 482)	3.6%	8.0%	15.0%
Advanced or >2 adenomas (n = 311)	15.2%	14.3%	30.0%

226377: Patients with Diabetes more than 15 years have Increased Odds of Colorectal Cancer. *Donald Garrow, Brenda Hoffman, Leonard Egede*

OBJECTIVE: To assess the effect of duration of diabetes mellitus on the odds of colorectal cancer within a nationally representative population. BACKGROUND: Previous studies have yielded evidence that diabetes mellitus may be a risk factor for colon cancer. Both hyperinsulinemia and hyperglycemia have been noted in vitro to be promoters of colon cancer growth. Furthermore, insulin and insulin-like growth factor-1 (IGF-1) receptors have been found on colon cancer tissue. Also, high levels of circulating IGF-1 are associated with an elevated risk of colorectal adenomas and cancer. This study seeks to assess the effect of duration of diabetes on the risk of colorectal cancer. METHODS: Data collected by the 1997-2003 National Health Interview Survey (NHIS) was analyzed to assess the risk of colorectal cancer among individuals with diabetes. The NHIS is a comprehensive nationally representative survey weighted to represent the U.S. adult population. There were 226,953 subjects represented in the combined seven years of the NHIS. Duration of diabetes was divided into four groups; 0-5 years, 5-10 years, 10-15 years, and > 15 years. Multiple logistic regression was performed probing the relationship between duration of diabetes and colorectal cancer while adjusting for age, race, gender, obesity, alcohol use, tobacco use, and treatment for diabetes (insulin, pill, both, or diet only). NHIS data from 1997 - 2003 was merged with SAS v. 9.1.3. Analyses performed with STATA v. 8.0, which accounted for the complex survey design of the NHIS and generated population estimates. Multiple logistic regression was used to determine independent correlates of colorectal cancer among individuals with diabetes. RESULTS: Among the 226.953 subjects in this study, 13,399 (5.9%) revealed a history of diabetes mellitus. Adjusted for potential confounders, individuals with diabetes > 15 years were significantly more likely to have colorectal cancer than persons without diabetes (Odds Ratio (OR) = 1.76, 95% Confidence Interval (CI) = 1.03 to 3.00). Other independent correlates with significant findings included age > 50, history of tobacco use, and history of alcohol use. CONCLUSIONS: Individuals with diabetes more than 15 years were noted to have an increased likelihood of colorectal cancer. If this association remains positive in prospective trials, people with diabetes may require earlier and more aggressive screening for colorectal cancer than the general population.

Research should be directed at understanding the pathophysiologic reasons why duration of diabetes is associated with increased odds of colorectal cancer.

224103: IL-6, TNF-a and CRP Gene Polymorphisms Are Associated with Increased Colon Cancer Risk in African Americans Compared to Whites in the North Carolina Colon Cancer Study. *Temitope O Keku, Joseph Galanko, Seun Omofoye, Rachel Holston, Janie Peacock, Jeffrey Barnes, Chris Martin, Robert S Sandler*

Background: Among major US ethnic groups, African Americans have the highest incidence and mortality of colon cancer. However, critical questions remain unanswered about genetic susceptibility to colon cancer in African Americans. Cytokines mediate immune and inflammatory responses, which may act in neoplastic pathways. Genetic variants that influence cytokines levels may thus affect colon cancer risk. Aim: To evaluate IL-6 (G -174 C), TNF-a (G -308 A), CRP (G -1081 A) genetic polymorphisms among African Americans and Caucasian Whites in relation to the risk of colon cancer and assess interactions with lifestyle-dietary factors. Methods: We analyzed 528 incident colon cancer cases (231 African Americans, 297 Whites) and 836 controls (306 African Americans, 530 Whites) from a large population-based case control study in North Carolina. Controls were frequency matched to cases on age, race and sex. Consenting subjects provided blood specimens, information about lifestyle and diet histories, and anthropometric measurements. IL-6, TNF-a, CRP genotypes were determined by the TaqMan assay. Logistic regression was used to calculate odds ratio (OR) and 95% confidence intervals (CI) for variant genotypes while controlling for potential confounders such as age, sex, non-steroidal anti inflammatory drugs (NSAIDs), and body mass index (BMI). Results: IL-6 and TNF-a variant genotypes were significantly associated with increased risk of colon cancer among African Americans, compared to wildtype genotypes (IL-6 GC+CC, OR 1.7, 95% CI 1.0-2.8; TNF-a GA+AA, OR 1.6, 95% CI 1.0-2.4), but not in Whites. However, the CRP GA+AA variant genotype showed a modest association with colon cancer in Whites compared to wildtype (OR 1.3, 95% CI 1.0-1.8). Interestingly, in a combined analysis with all three genes, using common wildtypes as referent, having one or more variants was significantly related to colon cancer risk in both African Americans and Whites (OR 1.3, 95% CI 1.0-1.6) but this association was stronger for African Americans (OR 1.4, 95% CI 0.9-2.0; Whites OR 1.2, 95% CI 0.9-1.7). No interactions were observed with BMI and NSAIDs use. However, the risk of variant genotypes was greater among persons with elevated waist-to-hip ratios (WHRs). The OR for having greater-than-median WHR plus 1 or more variants was 2.2 (95% CI 1.6-3.2), compared to persons below median WHR having no variants. Conclusion: These results suggest that genetic polymorphisms in IL-6, TNF and CRP strongly contribute to colon cancer susceptibility, particularly in African Americans. Supported by grants from NIH K01CA093654, P30DK34987 and P50CA106991

224660: Colorectal Adenomatous Polyposis Linked to MYH Gene Mutations: Genotype And Phenotype Characteristics in a French Series of 56 Patients. *Guillaume Bouguen, Sylvain Manfredi, Martine Blayau, Catherine Dugast, Bruno Buecher, Dominique Bonneau, Laurent Siproudhis, Veronique David, Jean-Francois Bretagne*

Aim: Recent literature reports that a subgroup of patients with attenuated and classic polyposis as well as with young-onset colorectal cancer (CCR) is associated with mutations in the base excision repair gene MYH. The aim of this study was to establish the prevalence of germ-line MYH mutations in a French series of 56 consecutive patients with no detectable APC mutation and to describe the phenotype of those with MYH mutations. Methods: MYH mutations were screened by DNA sequencing after PCR amplification of each exon. Clinical and endoscopic characteristics (age, sex, family history, extra-colonic manifestations, number and types of polyps, associated cancer) and surgical data have been collected for tested patients. Results: MYH germ-line mutations were identified in 11 (19.6%) of the 56 tested patients. The prevalence of MYH mutations was 34.4% in the subgroup of 32 patients having 10 or more adenomatous polyps. No mutation was found among patients with mixed polyposis (n=2) and with CCR (n=13). Among 10 patients with biallelic MYH mutations, 2 proved to be homozygotes and the other 8 were compound heterozygotes. Only one patient had a monoallelic mutation. At least one of the two mutational hot spots (Y165C and G382D) was identified in all cases, except one patient. There were 9 males and two females aged of 47 years old (ranged 36-57). Three patients presented a family history of adenomatous polyposis in siblings, but no vertical transmission was noted. The median number of colorectal adenomatous polyps was 53 (11-100) without preferential localization. A CCR was associated to polyposis in 7 of the 11 patients (63.6%); 2 cancers were stage I, 3 stage II and 2 stage III. Gastric and duodenal adenomas with high grade dysplasia were diagnosed in one case. Ten of the 11 patients were operated on: restorative proctocolectomy was performed in 4 cases, a subtotal colectomy with rectal preservation in 5 cases and a left colectomy in 1 case. In the latter case, polyposis was diagnosed two years after the left colectomy and total colectomy is planned at this time. Rectal adenomas were diagnosed during the follow-up in 3 patients with preserved rectum. Conclusions: 1) MYH mutations, mainly corresponding to biallelic mutations have been observed in one third of French patients who had more than 10 colorectal adenomatous polyps without APC mutation. 2) The phenotype of the disease is similar to attenuated FAP, but its transmission shows evidence on recessive or more complex inheritance. 3) The high risk of CCR suggests that prophylactic colectomy is recommended. 4) Upper GI endoscopy should be also recommended.

221219: Impact of Initial Polypectomy versus Follow-up Surveillance Colonoscopy on Colorectal Cancer Incidence in Post-Polypectomy Patients *Ann G Zauber, Iris Vogelaar, Marjolein van Ballegooijen, Rob Boer, Deborah Schrag, Dik Habbema, Sidney J Winawer*

INTRODUCTION. The National Polyp Study (NPS) demonstrated that detection and removal of adenomatous polyps reduced subsequent colorectal cancer (CRC) by 76% to 90%. This overall incidence reduction was achieved with initial polypectomy together with surveillance colonoscopy (SC) for patients with adenomas in a RCT comparing surveillance intervals at 1, 3 and 6 years versus 3 and 6 years post polypectomy. Of importance is how much the incidence reduction was due to the initial vs the SC and which patients may benefit from SC. METHODS. The MISCAN-Colon micro-simulation model was used to assess the separate effects of initial and SC by the patient's adenoma characteristics. A population of adenoma patients of the same age, sex and baseline adenoma characteristics of the NPS followed over 10 years was simulated for three scenarios - 1) no initial colonoscopy and no SC 2) initial colonoscopy but no SC and 3) initial colonoscopy and SC. The surveillance effect was the difference in the percent developing CRC with and without SC and assessed by the patient characteristics of multiplicity (1 or 2 versus 3 or more) and size (<=0.5 cm (small), 0.6-0.9 cm (medium), or >=1.0 cm (large)) of the adenomas at initial colonoscopy. RESULTS. 90% of the impact of colonoscopic intervention is due to the initial colonoscopic polypectomy rather than to SC for the 10 years post polypectomy. SC provides the largest benefit for the 20% of NPS patients with 3 or more adenomas where SC reduces the CRC rate by 1.3%. SC has a smaller effect for those with 1 or 2 adenomas regardless of size with 0.4% to 0.7% reduction. CONCLUSIONS. The initial colonoscopy rather than SC provides the largest impact on CRC incidence in the 10 years following initial polypectomy. For those with 3 or more adenomas, SC at 3 year intervals shows a benefit. Based on these results the surveillance interval for those with only 1 or 2 adenomas could be extended to 5 to 10 years. Tailoring subsequent surveillance recommendations to the baseline colonoscopy findings can achieve the benefits of colonoscopic polypectomy and a reduction in the number of surveillance colonoscopies required with their associated risks.

216047: Accuracy of Computed Tomographic Colonography for Colorectal Cancer (CRC) Screening in Asymptomatic Individuals. *Brooks D Cash, Cecilia Kim, Priscilla Cullen, Myra Kim, Cathy A Dykes, Donald W Jensen, Duncan S Barlow,Mark H Johnston, James W Kikendall, Peter W Soballe*

Background: Pickhardt demonstrated that computed tomographic colonography (CTC) was comparable to optical colonoscopy (OC) for the accurate detection of adenomas. Our study seeks to validate Pickhardt's findings using the same technique for CTC. Methods: Participants are asymptomatic, average-risk patients referred for colorectal cancer screening who undergo CTC with subsequent care based on CTC interpretation. Patients with polyps >10 mm or >3 polyps exceeding 6 mm proceed to same day OC in which all polyps identified by CTC or OC are removed (Category A). Patients with 1 or 2 polyps measuring 6-9 mm undergo CTC and clearing OC at 1 year (Category B) and patients without any polyps >6 mm have OC in 5 years (Category C). Fleets Phosphosoda prep is used with oral contrast to tag fluid and stool for digital subtraction. CO2 is used for colon insufflation and a 3-D flythrough serves as the primary mode of assessment by an experienced (>500 CTC) radiologist. Polyp matching adheres to Pickhardt's method of segmental unblinding during OC. Data is presented on a per patient basis and is not histology specific. Results: 666 patients have undergone CTC since inception (mean age 56.0 years; 33.6% female; 78.5% Caucasian). 16.1% (107/666) patients have proceeded to OC; 35.5% (38/107) for significant CTC findings (category A) and 44.9% (48/107) randomly selected (categories B/C). For lesions >10 mm, CTC polyp detection sensitivity and specificity are 94.1% (95% CI: 80.3% to 99.3%) and 93.2% (95% CI: 84.7% to 97.7%), respectively, with positive predictive value (PPV) and negative predictive value (NPV) of 86.5% (95% CI: 71.2% to 95.5%) and 97.1% (95% CI: 90.1% to 99.7%). The 93.6% accuracy of CTC is comparable to OC (p= 0.10, McNemar's Test). For 6-9 mm polyps, the sensitivity, specificity, PPV and NPV of CTC are 65.6% (95% CI: 46.8% to 81.4%), 92% (95% CI: 83.4% to 97%), 77.8% (95% CI: 57.7% to 91.4%), 86.3% (95% CI: 76.7% to 92.9%), respectively, with an accuracy of 84.1% (p=0.001). There are too few patients in group B with evaluable outcomes to comment on the observational history of intermediate sized polyps at this time. Conclusions: These results indicate that CTC and OC have similar accuracy for the detection of polyps > 10 mm and validate the previous findings of Pickhardt. CTC accuracy is significantly less than OC for polyps 6-9 mm, however the observed accuracy of CTC for these polyps is superior to previous studies. The natural history of intermediate sized polyps remains unclear, but CTC may be a valuable tool in elaborating this information in future longitudinal outcomes analyses.

216292: The Management of Small (6-9mm) Polyps Found by Virtual Colonoscopy: Results of a Decision Analysis. *Chin Hur, Daniel C Chung,Robert E Schoen, Amy B Knudsen, G. Scott Gazelle*

Background: Although there is a firm consensus that larger (>9mm) colonic polyps should be removed, the necessity of polypectomy for smaller polyps is controversial. The majority of polypoid lesions found by VC will be less than 9mm in size. Furthermore, recently published VC reporting guidelines suggest that it may be reasonable to manage a 6-9mm polypoid lesion discovered on VC with another VC study 3 years later. The aim of this study was to compare the outcomes of two management strategies for smaller polyps discovered by VC. Methods: A Markov decision-analytic model was constructed to analyze the outcomes of patients with a small polyp on a screening VC. These hypothetical patients were simulated to either: 1) undergo

immediate colonoscopy for polypectomy (COLO); or 2) wait 3 years for a repeat VC examination (VC). The time horizon (f/u period) for the model analysis was 3 years and endpoints compared included # of deaths, # of cancers (CAs) and CA stage (SEER Summary Staging). Model input (parameter estimates) values were derived from and calibrated to SEER data and published estimates and included: VC false positive rate=31.9%; POLYPS- Hyperplastic=39.3%, Adenomas (Low Risk=94.1%, High Risk=5.0%, Cancer=0.9%); ANNUAL CANCER MORTALITY RATES- Local=2%, Regional=7.5%, Distant (metastatic)=37%; COLONOSCOPY- Complication rate=0.1%, Complication Death Rate=0.01%, Inability to find polyp=5%. Results: The results (see Table 1) are 3 years after the initial VC and the #s presented are out of 100,000 patients in each strategy. The overall number of CAs in the VC group was 1168 (1.168%) compared to 58 (0.058%) in the COLO group (polypectomy cured the majority of CAs in the polyp). All the deaths in the VC group were from CA (111) vs 6 CA and 10 colonoscopy complications deaths in the COLO group. The stage distribution of the CAs is also presented as they significantly impact both prognosis and treatment. Conclusions: Following a small polyp found on VC for 3 years will result in a greater number of CAs and more deaths than immediate COLO.

Table 1. Results (# out of 100,000 pts)

	COLO	VC	Difference*
Total CA	58	1168	-1110
Localized	21	416	-395
Regional	8	163	-155
Distant	3	63	-60
Total Deaths	16	111	-95
CA Deaths	6	111	-105
CC** Deaths	10	0	10
CC	100	0	100

*Neg value=VC greater **CC=COLO complication

218598: **Risk Stratification for Colonic Neoplasia through Enhanced Backscattering Spectroscopy Analysis of The Endocopically-Normal Rectal Mucosa**. *Hemant Roy, Young Kim, Yang Liu, Michael Goldberg, Nahla Hasabou, Vladimir Turzhitsky, Mohammed Jameel, Eric Elton, Vadim Backman*

Background: Risk stratification is critical for designing an efficacious, cost-effective colon cancer screening program. Examination of the rectal mucosa for markers of the "field effect" (e.g. aberrant crypt foci, epithelial proliferation, apoptosis etc.) can reliably predict the occurrence of proximal neoplasia; however, their performance characteristics have been suboptimal for clinical practice. Working with some of the pioneers of light scattering technology (Nature 2000, Nature Med 2001, Gastroenterology 2004, Gut 2005), our group has developed a new generation of optics technology, enhanced backscattering spectroscopy (EBS). EBS can provide heretofore unattainable depth-selective quantitative assessment of the nanoscale architecture of the cell (reflecting subtle genetic/epigenetic events). We have previously reported outstanding sensitivity for the “field effect” in the azoxymethane-treated rat and MIN mouse models of colon carcinogensis (Clin Cancer Res in press). In this study, we assess the ability of novel EBS markers obtained from the rectum to predict colonic neoplasia in humans. Methods: Two rectal biopsies from endoscopically normal mucosa were taken from 88 patients undergoing colonoscopic evaluation at our institution. The fresh tissue was subjected to EBS analysis using an advanced light scattering apparatus. Five spectral markers were chosen that span the spectrum of EBS parameters and values were calculated by an investigator blinded to colonoscopic findings. Results: Spectral markers from histologically normal rectum are detailed in the table below. In general, there were highly significant differences between the values from patients harboring neoplasia when compared to those who were neoplasia free. Importantly, the magnitude of alteration progressively increased with importance of colonoscopic findings (i.e. advanced adenomas> adenomas). With this panel of 5 markers, it was possible to approach 100% sensitivity for predicting advanced adenomas. Conclusions: We report, for the first time, that novel EBS markers assessed from the rectum were able to accurately predict neoplasia throughout the colon. Our long term goals would be to develop a rectal probe that could be used by the primary care physicians to decide upon timing of colonoscopic screening.

Correlation of EBS Markers from normal rectal mucosa to findings on colonoscopy

	Spectral Slope	EBS Auto-correlation	Enhancement factor	Principle component 1	EBS Width
No Neoplasia (control)	0.0045	22005	1.103	-0.007	0.459
Adenoma	0.0036 ($p<0.0001$)	22245 (p=0.31)	1.098 (p=0.027)	0.016 (p=0.002)	0.469 (p=0.26)

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Advanced Adenoma	0.0031 (p<0.0001)	23899 (p=0.006)	1.093 (p=0.041)	0.023 (p=0.013)	0.56 (p=0.008)

p values compare control versus adenoma or control versus advanced adenoma, respectively

225215: Loss of Imprinting of the Insulin Growth Factor 2 (IGF2) Gene in Buccal Cells: Correlation with Risk of Colorectal Cancer. *Enrique Quintero, Daniel Deniz, Cristina Paz-Cabrera, Alejandro Jimenez, Antonio Z Gimeno, Adolfo Parra-Blanco, David Nicolas, Eduardo Salido*

Introduction: Loss of imprinting at the IGF2 gene (IGF2-LOI) is an epigenetic change present in colonic tissue of about 40% of colorectal cancer (CRC) patients. Aim: to investigate whether IGF2-LOI in the epithelial cells of buccal samples is a surrogate marker that could predict the risk of CRC. Methods: 34 patients with CRC, 60 with colonic adenomas and 62 controls (colonoscopy without pathological findings) were included. LOI was assessed by studying the methylation status of a key CpG island at the IGF2 promoter, using PCR-RFLP after bisulfite treatment of DNA (COBRA method). Hypomethylation was taken as a surrogate marker for LOI, which was investigated in DNA from buccal cells, tumor samples, non-neoplastic adjacent mucosal samples, and peripheral blood cells. Results: In buccal cells, IGF2-LOI was detected in 5/62 (8%) controls, 10/60 (17%) patients with colonic adenoma and 12/34 (35%) patients with colorectal carcinoma. In neoplastic tissue, IGF2 LOI was observed in 9/43 (21%) samples of carcinoma and 13/50 (26%) samples of adenomas. No differences in IGF2-LOI were observed in the DNA from peripheral blood cells among the various study groups. Buccal samples of patients with colorectal carcinoma presented a higher relative risk to show IGF2-LOI than the controls (OR 6,21; IC 1,96-19,70, p<0.01). Conclusion: IGF2-LOI in the DNA from buccal cells could be a non-invasive surrogate marker useful for the screening of colorectal cancer in the average-risk population.

226280: Colon Cancer Specific Antigen-3 and -4 (CCSA-3 and CCSA-4): Novel Serum Based Markers for Detection of Colorectal Cancer (CRC). *Eddy Lehman, Robert E Schoen, Grant W Cannon, Robert H Getzenberg*

A blood test for CRC screening would represent a major advance because of the relative ease of implementation and potential to markedly increase patient participation. Using a proteomic approach focused on nuclear matrix proteins specific to colorectal cancer, we developed an ELISA based assay to CCSA-3 and CCSA-4, two novel proteins. Aim: To assess the sensitivity and specificity of these markers. Methods: Serum samples were collected prospectively from patients undergoing colonoscopy, and from subjects with CRC and benign colon conditions prior to surgery. Based on histologic results, subjects were classified into the following categories: normal colonoscopy (N=30), hyperplastic polyp (N=23), benign surgical condition (N=9), and cancer (N=28). A pilot study was performed to establish cut off points for test positivity (CCSA-3 (2 µg/ml) and CCSA-4 (0.3 µg/ml)). Results: Mean levels for both CCSA-3 and CCSA-4, respectively, were higher in colorectal cancer (3.2 ± 1.1; .72 ± .29) than in the benign conditions: normal colon (.66 ± .3; .13 ± .05); hyperplastic polyps (1.08 ± .48; .13 ± .76); pre-surgical benign (.58 ±.13; .26 ± .10). At the specified cut off points, CCSA-3 and CCSA-4 each detected 100% (95%CI 88-100) of the cancers. The specificity for normal colon, hyperplastic polyps, and benign colon was 98% (95%CI 88-100) for CCSA-3 and 97% (95%CI 86-99) for CCSA-4. Conclusions: This is the first report of a serum based assay able to distinguish subjects with cancer from subjects with a benign colon. Studies in subjects with advanced and non-advanced adenoma are ongoing. If substantiated, this would represent a major advance in colorectal cancer screening.

225762: Long-term Aspirin Use and Mortality: Implications for Chemoprevention. *Andrew T Chan, JoAnn E Manson, Diane Feskanich, Meir J Stampfer, Graham A Colditz, Charles S Fuchs*

Randomized trials have shown that aspirin reduces risk of colorectal adenoma. However, the use of aspirin for widespread chemoprevention has been hindered by uncertainty over its risk-benefit profile. One measure of the overall benefit of aspirin is the relation between long-term aspirin use and total mortality. Methods: We conducted a prospective, nested case-control study of 75,816 women enrolled in the Nurses' Health Study to determine the association between aspirin use and mortality. Women provided data biennially since 1980 and were followed through 2004. Each participant who died was matched with 7 controls alive at the time of her death. For each death, aspirin use was assessed prior to initial diagnosis of cardiovascular disease (CVD) or cancer and during the corresponding time period for matched controls. Results: Over 24 years, we documented 9,477 total deaths. Among women who reported current use of aspirin, the multivariate relative risk (RR) of death from all causes was 0.75 (95% CI, 0.71-0.81) compared to women who never used. The risk reduction was more apparent for CVD death (RR 0.62; CI, 0.54-0.71) than for cancer death (RR 0.88; CI, 0.81-0.96). The lower risk of cancer death among current users was significant only for colorectal cancer death (RR 0.72; CI, 0.56-0.92). We observed a significant linear relationship between increasing duration of use and decreasing all-cause mortality (Ptrend<.0001). However, for CVD death, much of the benefit was achieved within the first 5 years of use (Ptrend=0.14). In contrast, for all cancer-related mortality, significant risk reduction was not apparent until at least 10 years of use (Ptrend=0.005). The strongest effect of long-term use was observed with colorectal cancer death, with a RR of 0.60 (CI, 0.41-0.90) for >20 years (Ptrend=0.02). The benefit associated with aspirin was confined to low and moderate doses. However, we did observe a relationship between increasing dose and lower risk of colorectal cancer death among women who used aspirin >10 years (P trend = 0.02). Of note, we documented only 41 cases of death related primarily to

gastrointestinal bleeding or peptic ulcer disease over the 24 years of follow-up. Conclusions: Aspirin use, at low to moderate doses, is associated with a reduced risk of all-cause mortality, largely due to death from cardiovascular disease. Although aspirin did appear to have a modest benefit against death from cancer, the effect was primarily confined to death from colorectal cancer, and required at least 10 years of use. These data support a need for continued study into long-term use of aspirin in prevention of chronic diseases.

214435: ACE Inhibitor Therapy Is Associated with a Decreased Incidence of Colorectal Cancer. *George Makar, James D Lewis, Yu-Xiao Yang*

BACKGROUND Laboratory data suggest that increased angiotensin II may promote the growth of colorectal cancer (CRC) by inducing neovascularization and IGF-1 receptor expression, while angiotensin converting enzyme inhibitors (ACE-I) enhance the antitumor effect of COX-2 inhibition through inhibition of the IGF-1 pathway. Based on these observations, we sought to determine whether ACE-I therapy reduced the risk of CRC in a population-based cohort. METHODS We conducted a nested case-control study within a cohort of hypertensive patients in the General Practice Research Database (United Kingdom). Cases were subjects with a new diagnosis of CRC. Using incidence density sampling, up to 10 controls per case were selected, matched on age, sex, calendar year and duration of follow-up. Patients with <1 yr of CRC-free follow-up after diagnosis of hypertension and CRC patients with <1 yr of ACE-I therapy before their cancer diagnosis were excluded. Conditional logistic regression was used to calculate Odds Ratio's (ORs) for CRC associated with exposure to ACE-I therapy. The primary exposure duration of interest was ≥3 years. We also assessed the effect of escalating durations of exposure. *A priori* potential confounders adjusted in the model included duration of follow-up after hypertension, number of physician visits within 1 year of index date, BMI, smoking, aspirin/NSAIDs, hormone replacement therapy, folate, calcium, statins, and insulin. *A priori* testing for effect modification among diabetics was performed, since hyperinsulinemia among diabetics has been shown to increase the risk of colorectal cancer primarily via the IGF-1 system. RESULTS(Table) 1,988 cases were matched with 18,131 controls. Greater than 3 years of ACE-I therapy was associated with a reduction in CRC risk (OR 0.79 (95% CI, 0.64 -0.96)); a significant duration-response effect was present (Test for trend: p=0.02). Larger effects were observed among patients with diabetes (LR test for interaction: p=0.06). CONCLUSION Long-term ACE-I therapy was associated with a decreased risk of CRC in this cohort. The magnitude of this effect was greater in diabetics.

Duration of ACE-I Therapy and OR of CRC

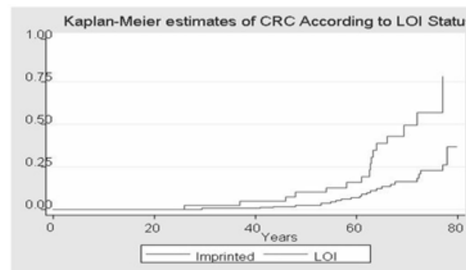
ALL PATIENTS(n=20,119)	ADJUSTED OR
1-3yrs	0.99 (0.85-1.16)
3-5yrs	0.87 (0.70-1.10)
≥5yrs	0.60 (0.41-0.87)
DIABETICS(n=771)	
1-3 yrs	0.72 (0.38-1.37)
≥3 yrs	0.28 (0.10-0.81)
NONDIABETICS(n=19,348)	
1-3 yrs	1.01 (0.87-1.19)
≥3 yrs	0.83 (0.68-1.02)

Additional Reading: Colorectal Cancer Screening and Therapeutics

215930: Increased Life-time Risk for Colorectal Cancer in Patients with Loss of Genomic Imprinting of Insulin-like Growth Factor 2: A Survival Analysis. *Marcia Cruz-Correa, Ronghua Zhao, Dana Sands, Eric Weiss, Juan Nogueras, Steven Wexner, Francis M Giardiello*

Background: Loss of genomic imprinting (LOI) of the IGF2 gene is independently associated with colorectal cancer (CRC), but underlying carcinogenic mechanisms remain unclear. Whether LOI-positive individuals have a higher life-time risk for CRC than LOI-negative individuals is unknown. This study investigated the incidence rate and life-time risk of developing CRC in patients whose LOI-status was known. Methods: We performed PCR on gDNA and RT-PCR on RNA extracted from normal peripheral blood lymphocytes (PBL) of prospectively recruited individuals. After digestion by Apa I, the PCR and RT-PCR products were run on 2% agarose gel and the gel photos were quantitatively analyzed to determine the informative status and IGF2 imprinting status, respectively. Incidence rates of CRC were calculated by person-year analysis using Kaplan-Meier survival estimates and cox regression as appropriate. Results: A total of 245 informative patients were recruited including 130

normal individuals (73 males; mean age 60.0 ± 12.6 years), 71 patients with colorectal polyps (33 males; age 62.8 ± 7.7 years) and 44 with CRC (18 males; age 61.9 ± 12.3 years). The incidence rates for CRC were 2.3 and 6.0 per 1000 person-years for LOI-negative and LOI-positive patients, respectively (Hazard Risk 3.03, 95% CI 1.62-5.7). Using age-at-diagnosis as a time variable in a gender-adjusted cox regression model, LOI-positive patients presented with CRC at earlier age compared to LOI-negative patients ($p = 0.001$). Conclusion: Individuals with LOI of IGF2 as noted in PBL had an increased life-time risk for and earlier age of diagnosis of CRC, compared to LOI-negative patients. These findings suggest a distinct carcinogenic pathway for LOI-positive patients, which may have implications in screening and risk assessment. Support: NIH grants K07 CA092445 and P50 CA-62924-10, The John G. Rangos, Sr. Charitable Foundation, The Cancer Research and Prevention Foundation, The Clayton Fund.



223691: Detection of Aberrant Fecal DNA Methylation May be a Useful Screening Strategy for Asymptomatic Gastrointestinal Neoplasia. *Nagahide Matsubara, Takeshi Nagasaka, Hiromi Sasamoto, Takuyuki Uchida, Ajay Goel, Richard C Boland, Noriaki Tanaka*

BACKGROUND Current noninvasive screening tools for colorectal neoplasia remain ineffective because of poor sensitivity and specificity. The aim of this study was to develop a more sensitive and accurate screening strategy for detecting gastrointestinal neoplasia through analysis of fecal DNA methylation. METHODS We used six genes as potential markers and investigated the methylation status of the promoters in 755 gastrointestinal specimens, including neoplastic tissues and normal epithelium of the colorectum and stomach by using a simplified assay that does not require the pre-extraction of DNA from the stool samples. We examined the methylation status of the six genes in 166 stool samples; 33 samples came from patients with adenocarcinoma, 30 with advanced polyps, 39 with minor polyps, and 64 without neoplasia using a newly developed bisulphite modification technique. RESULTS Promoter methylation was observed in all the gastrointestinal specimens and was a gradual increase in the number of genes methylated from normal to cancer, both in the large intestine and stomach. As similar trend was observed in the stool samples, these findings provide proof of principal that gene methylation in stool can be used to detect gastrointestinal neoplasia. Receiver-operating-characteristic (ROC) curves obtained from the fecal DNA methylation assay offered various cut-off values using six methylated genes to differentiate between the presence or absence of carcinoma, of carcinoma and advanced polyps, or of carcinoma, advanced and minor polyps. CONCLUSIONS The detection of early, asymptomatic gastrointestinal neoplasia can be facilitated by the analysis of fecal DNA methylation status.

220444: RNA-Based Stool Assay Is Superior to a Single Immunochemical Fecal Occult Blood Test for Detecting Early Colorectal Cancer and Adenoma. *Shigeru Kanaoka, Tetsunari Takai, Ken-ichi Yoshida, Mutsuhiro Ikuma, Masayoshi Kajimura, Naoyuki Miura, Haruhiko Sugimura, Akira Hishida*

Background and Aims: It has been reported that fecal occult blood test (FOBT) is less sensitive for early colorectal cancer (CRC) and adenoma. We reported that Fecal COX-2 assay, one of RNA-based stool assays, is useful for detecting CRC (Gastroenterology 2004; 127: 422-427). It is reported that Snail is a repressor of both E-cadherin and vitamin D receptor gene expression, which is involved in colon carcinogenesis (Nature Cell Biol 2000; 2: 84-89, Nature Med 2004; 10: 917-919). We aimed to perform a study of whether RNA-based stool assay, combination of Snail and COX-2 as targets, allows us to improve further sensitivity for colorectal cancers and advanced adenomas compared the results with those of a single immunochemical FOBT (IFOBT). Methods: Standard histological techniques were used to classify adenoma or malignancy at I to IV stages according to TNM classification. We purified RNA from routinely collected stool samples and screened mRNA using COX-2 and Snail specific nested RT-PCR as previously described, consequently compared the results with those of a single immunochemical FOBT (Magstream 1000/HemSp; FUJIREBIO, Inc., Tokyo, Japan) on same stool samples. Results: Stool samples from 65 patients with CRC, 13 patients with advanced adenoma, and 32 control patients without neoplastic disease were studied. The specificity of Fecal Snail assay as well as Fecal COX-2 assay was 100% (95% confidence interval [CI], 89.1-100%), while that of IFOBT was 87.5% (95% CI, 71.0-96.5%). The sensitivity of RNA-based stool assay was 87.7% (95% CI, 76.6-94.5%) for CRC, and 76.9% (95% CI, 46.2-95.0%) for advanced adenoma, while that of IFOBT was 73.0% (95% CI, 60.2-83.5%) and 30.8% (95% CI, 9.1-61.4%), respectively. COX-2 and/or Snail mRNA was detected in 84.6% of stage I (n=13), 93.5% of stage II (n=31), 81.0% of stage III or IV (n=21), while IFOBT was positive in 41.7% of stage I, 80.0% of

stage II, 81.0% of stage III or IV. Snail mRNA was detected in 2 of 5 stool samples from patients with advanced adenoma who had negative Fecal COX-2 assay and IFOBT. Noteworthy, COX-2 and/or Snail mRNA was detected in 17 of 22 stool samples from patients with early cancer or advanced adenoma who had negative IFOBT. Finally, the sensitivity of this assay was 87.7% (95% CI, 76.2-94.9%) for advanced adenoma to stage II cancer, while that of IFOBT was 60.0% (95% CI, 45.6-73.1%). Conclusions: We could improve further sensitivity to add Snail as a target to RNA-based stool assay, which is superior to a single IFOBT in term of detecting curable colorectal cancer and advanced adenoma. These results strongly suggest that this assay would be useful for CRC screening.

215248: Flexible Sigmoidoscopy Is Associated with a Reduced Incidence of Distal But Not Proximal Colorectal Cancer (CRC): A Population-Based Cohort Study. *Linda Rabeneck, James D Lewis, Lawrence Paszat, Refik Saskin, Therese A Stukel*

Background: Flexible sigmoidoscopy (FS) is used to triage those with distal colon polyps to colonoscopy and those without polyps to repeat FS screening in 5 yr. However, it is unclear whether those with a negative FS (without polyps) have a reduced incidence of cancer proximal to the rectosigmoid colon. Objectives: In a population-based cohort study of persons with a negative FS to: 1) estimate the annual incidence of CRC; and (2) identify factors associated with incident CRC. Methods: We identified all individuals 50-80 yr who had a negative FS between 1/1/1996 and 12/31/1998 in Ontario and followed them through 12/31/2002. We computed the annual age- and sex- standardized incidence rates (SIRs) for colon (ICD-9 codes 153.0-153.4, 153.6-153.9) and rectum or rectosigmoid (154.0-154.1) cancers for the study cohort and for the remaining Ontario population. We compared the annual incidence of CRC between the study cohort and the remaining Ontario population. Cox proportional hazards models were used to examine patient (age, sex), physician (type, procedure volume) and procedure setting (office, hospital) factors associated with incident cancers among those with a negative FS. Data were obtained from the: 1) Ontario Cancer Registry; 2) Canadian Institute for Health Information database, which has information on all patients discharged from hospitals; 3) Ontario Health Insurance Plan (OHIP), which has information on all claims for physician services; and 4) Registered Persons Database, which is a roster of all permanent residents who are covered under OHIP. Results: Between 1996 and 1998 we identified 45,304 persons who had a negative FS, of whom 58.3% were women. During follow-up 324 cancers (269 colon, 58 rectum/rectosigmoid) were observed in these patients. For rectum/rectosigmoid cancers the annual SIRs following negative FS were significantly lower than in the Ontario population. For example, at 4 yr, the SIR following negative FS was 0.24 cancers/1000 persons (95% CI: 0.11-0.45) vs 0.54/1000 (0.51-0.57) in the Ontario population (RR=0.44, 95% CI: 0.16-0.73). For colon cancers, the annual SIRs following negative FS were not significantly different than in the Ontario population. For example, at 4 yr, the SIR following negative FS was 1.32 cancers/1000 persons (1.00-1.72) compared with 1.34/1000 (1.29-1.39) in the Ontario population (RR=0.99, 95% CI: 0.72-1.25). Only age was significantly associated with incident CRC following negative FS. Conclusions: Following negative FS the incidence of rectum/rectosigmoid cancers - but not colon cancers - is reduced for up to 4 years. Age, but not sex, is associated with incident CRC following negative FS.

212894: Type 2 Diabetes Mellitus: The Impact on Colorectal Adenoma Risk in Women. *Jill E Elwing, Feng Gao, Nicholas O Davidson, Dayna S Early*

Background & Aims: Increased risk for colorectal cancer (CRC) has been associated with type 2 diabetes. Despite several studies linking insulin resistance to increased CRC risk, there is limited data on colorectal adenoma risk in diabetic women. We hypothesized that diabetic women would have increased rates of colorectal adenomas relative to a group of non-diabetic women. Methods: 100 women with type 2 diabetes mellitus (60.0±9.5yr, 41% Caucasian, 10% with a first degree relative with CRC, BMI 34.4±8.0, 29% on insulin therapy) and 500 non-diabetic, hormone status matched controls (59.0±9.2yr, 68% Caucasian, 7% with a first degree relative with CRC, BMI 28.5±7.1) were selected consecutively from women undergoing screening colonoscopy at an outpatient university endoscopy center. Adenomas were defined as any adenoma, or advanced adenoma (villous or tubulovillous features, size>1cm or high grade dysplasia). A multivariate model was used to determine the independent effects of diabetes on colorectal adenoma incidence. Results: Diabetic as compared with non-diabetics had increased rates of any adenoma (37% vs. 24%; OR1.8, 95%CI: 1.2-2.9; p=0.009) and advanced adenomas (14% vs. 6%; OR 2.4, 95%CI: 1.2-4.7; p=0.009). 245 obese compared with 321 non-obese subjects had increased rates of any adenoma (32% vs. 22%; OR 1.8, 95%CI: 1.3-2.6; p=0.001). Obese diabetics compared with non-obese, non-diabetics had increased rates of any adenoma (42% vs. 23%, OR 2.6, 95%CI: 1.5-4.6; p=<0.001) and advanced adenomas (19% vs. 7%; OR 3.5, 95%CI: 1.7-7.4; p=<0.001). Multivariate analysis (including age, race, diabetes, hypertension, hypercholesterolemia, and BMI) showed that adenomas and advanced adenomas were independently predicted by diabetes (OR 1.8, 95%CI: 1.1-2.9 and OR 2.2, 95%CI: 1.004-4.6 respectively; p<0.05) and adenomas by age (p=0.08). Discussion: Women with type 2 diabetes mellitus had higher rates of colorectal adenomas as compared with lean and non-diabetic women. This finding adds to the evidence that type 2 diabetes is an important factor in the progression of the adenoma-carcinoma sequence.

212899: Endometrial Cancer: The Impact on Colorectal Adenoma Risk in Women. *Jill E Elwing, Feng Gao, Dayna S Early, Nicholas O Davidson*

Background & Aims: Colorectal cancer (CRC) and endometrial cancer occur in the same individual more frequently than by chance alone. We hypothesized that patients with endometrial cancer would have increased rates of colorectal adenomas compared to a control group without previous gynecologic malignancy. Methods: 60 endometrial cancer patients (61±9.0yr, 97% Caucasian, 3% with a first degree relative with CRC, 18% diabetic, BMI 32.4±9.1) and 600 hormone status matched controls without a history of gynecologic malignancy (59.1±9.6yr, 66% Caucasian, 7% with a first degree relative with CRC, 17% diabetic, BMI 29.4±7.5) were selected consecutively from women undergoing screening colonoscopy at an outpatient university endoscopy center. Adenomas were defined as any adenoma or advanced adenoma (villous or tubulovillous features, size>1cm or high grade dysplasia). A multivariate model was used to predict the independent effect of endometrial cancer on colorectal adenomas. Results: Increased rates of colorectal adenomas (42% vs. 26%; OR 2.0, 95%CI: 1.2-3.5; p=0.01) and advanced colorectal adenomas (17% vs. 8%; OR 2.5, 95% CI:1.2-5.2 p=0.02) were found in women with a history of endometrial cancer as compared to controls. Subjects with both endometrial cancer and diabetes or with both endometrial cancer and obesity, had highly significant increased rates of adenomas (OR 5.4, 95% CI 1.6-18.9; p=0.007 and OR 3.2, 95%CI: 1.6-6.4; p=0.001, respectively) and advanced adenomas (OR 8.4, 95%CI: 2.3-30.1; p=0.005 and OR 3.8, 95%CI: 1.5-9.6, p=0.009, respectively). Multivariate analysis (including age, race, diabetes, hypertension, hypercholesterolemia, BMI and endometrial cancer) showed that colorectal adenomas and advanced adenomas were independently predicted by endometrial cancer (OR 1.8, 95%CI: 1.04-3.3; p=0.04 and OR 2.2, 95% CI: 0.99-4.9 p=0.05, respectively) as well as diabetes (p=0.03, p=0.007) and age (p=0.04, p=0.05). Discussion: Women with a history of endometrial cancer had higher rates of colorectal adenomas as compared with controls. Women with both endometrial cancer and diabetes or obesity had higher rates of colorectal adenomas than did subjects with each risk factor alone. An association between adenomas and endometrial cancer could have an impact on CRC screening recommendations.

221480: Smokers Have a Higher Risk for Significant Colorectal Neoplasia and at a Younger Age Than Those Who Never Smoked: Implications for Screening Guidelines. *Joseph C Anderson, Brendan J Wiggins, Zvi A Alpern, Carol A Martin, Patricia Hubbard-Ells*

Background: Age and family history are the main risk factors considered when stratifying for colorectal cancer screening. In a screening population, smoking and age were the most predictive factors for colorectal neoplasia (Anderson et al AJG 98:2777-83,2003). One expert has suggested that smokers should be considered a high risk group but also stated sufficient data did not exist to justify earlier screening for smokers (Giovannucci et al, Dig Liv Dis 36:643-5, 2004). The goal of our study was to determine if smokers are at risk for colorectal neoplasia at a younger age. **Methods**:Asymptomatic patients (>40 years old) undergoing screening colonoscopy are queried with respect to age, gender,BMI, family history, smoking history (pack years and year quit), medications, alcohol use, aspirin/NSAID use, exercise, fruit/vegetable and red meat intake. Endoscopic findings and pathology are entered into the database. Subjects were divided:1)Never smokers 2)Current smokers or patients with > 10 pack-years, still smoking or having quit recently 3)Low exposure smokers: < 10 pack years or who having quit over 10 years ago. Significant colorectal neoplasia (SCN) = villous tissue, high grade dysplasia, large tubular adenomas or > 2 adenomas. **Results:** 2466 patients were screened. Current smokers had a higher prevalence (67/478;14%) for SCN than never smokers (115/1385; 8.3%)(p<0.001) or low exposure smokers (44/566; 7.8%)(p<0.01). Current smokers had a higher risk than never smokers for SCN(OR=1.84;95%CI=1.35-2.49;p<0.001).The average age for smokers with SCN (58.1;95% CI: 55.5-60.6) was lower than never smokers with SCN (62.2;95% CI:60.0-64.5)(p=0.04). There was no difference other than age between these two groups,including gender, BMI, family history and alcohol use. Smoking is a risk factor for SCN in younger (most who are not eligible for screening) subjects as well(see Table). **Conclusions:** 1)Current smokers have a higher risk and prevalence of SCN than in never smokers. 2)SCN occurs in current smokers 4 years earlier than in those who never smoked suggesting an etiological association between smoking and colorectal neoplasia. 3)Our results strongly support the notion current smokers are at high risk for colorectal neoplasia at a younger age and probably should be screened at an earlier age than non-smokers.

Prevalence and Risk of Significant Neoplasia in the 40 to 55 Age Group

Smoking Status	Prevalence (%)	OR	95% CI
Never smokers	32/576 (5.6%)	1.0	1.0
Current smokers	25/205 (12.2%)	2.36	1.36-4.09

p<0.003;OR, after controlling for BMI, Fam Hx, gender

216007: Risk Factors for Advanced Colorectal Neoplasia in Women: Comparison of the CONCeRN and VA 380 Populations. *Brooks D Cash, Andrew Flood, David Weiss, Arthur Schatzkin, David Lieberman, Philip S Schoenfeld*

Background: VA Cooperative Study 380 data identified several important risk factors for advanced colorectal neoplasia (i.e., adenomas > 10 mm, villous adenomas, adenomas with high-grade dysplasia or carcinoma), including family history of colorectal cancer, current smoking or current alcohol use. However, generalizability of these findings is limited since 97% of the study population was male. The CONCeRN study of asymptomatic, average-risk women who underwent screening colonoscopy identified significant differences between men and women in the anatomic distribution of colorectal neoplasia. The current analysis examines risk factors for advanced neoplasia in women and contrasts these results to men from VA 380. This is the first study to report risk factors for advanced neoplasia and risk factors for proximal and distal adenomas for women undergoing screening colonoscopy. Methods: Prior to colonoscopy in both studies, patients completed standardized, validated questionnaires to assess potential risk factors for advanced neoplasia. Responses were evaluated using univariate and multivariate logistic regression models to identify associations between risk factors and advanced neoplasia and adenomas (any size). Results: Among 1463 women, 4.9% had advanced neoplasia and 20.4% had adenomas (any size). Women in the CONCeRN study demonstrated significant associations between advanced neoplasia and African-American race (OR = 2.06; 95% CI: 1.07-3.94), current or past regular tobacco use (OR = 1.64; 95% CI: 1.01-2.66), BMI > 35 kg/m2 (OR = 2.73; 95% CI: 1.18-6.31), and NSAID use (OR = 0.48; 95% CI: 0.28-0.85) while men from VA 380 did not demonstrate these associations. Conclusions: Several risk factors appear to be associated with an increased risk of advanced colonic neoplasia in women including a family history of CRC, African American race, a history of current or past regular tobacco use, and BMI > 35 kg/m2, while a history of regular NSAID use appears to be protective in women. Several of these risk factors appear to be more important for women than men.

Risk Factor Associations in CONCeRN and VA 380

Risk Factor (OR;95% CI)	Any adenoma CONCeRN	Advanced adenoma CONCeRN	Any adenoma VA 380	Advanced adenoma VA 380
Family history CRC	1.67;1.19-2.33	1.96;1.08-3.55	1.40;1.12-1.76	1.63;1.17-2.28
African American	1.38;0.89-2.15	2.06;1.07-3.94	1.16;0.89-1.51	0.81;0.51-1.31
Current or past regular tobacco use	1.22;0.94-1.58	1.64;1.01-2.66	1.37;1.14-1.65	1.27;0.96-1.69
Regular NSAID use	0.65;0.49-0.87	0.48;0.28-0.85	0.85;0.72-0.99	0.80;0.62-1.04
BMI > 35 kg/m2	1.76;1.08-2.86	2.73;1.18-6.31	1.36;1.00-1.82	1.13;0.72-1.78
HRT	0.75;0.58-.098	0.68;0.42-1.10	na	na

220912: Aspirin for the Prevention of Recurrent Colorectal Adenomas - Results of the ukCAP Trial. *Richard F Logan, Kenneth R Muir, Matthew J Grainge, Nicholas C Armitage, Vic C Shepherd, ukCAP Trial Group and Epidemiology and Public Health*

Background: Many observational studies have found regular aspirin use is associated with a reduced risk of colorectal (CR) cancer and 2 randomised trials have shown that aspirin reduces risk of recurrent CR adenomas, although results were not wholly consistent (Baron et al., *N Engl J Med*, 2003; Benamouzig et al., *Gastroenterology*, 2003). We report the preliminary aspirin results of a large factorial trial of aspirin (enteric 300 mg/day) and folate supplements in patients under surveillance for recurrent CR adenomas. **Methods:** A double-blind, placebo-controlled randomised trial was carried out in 10 centres (9 in the UK and 1 in Denmark). Patients who had one or more adenomas (≥0.5cm) removed by colonoscopy in the 6 months prior to enrolment were randomised to receive either aspirin (enteric 300 mg/day) or placebo. All participants were followed-up at intervals of 4 months to assess compliance, with a second colonoscopy arranged for 3 years after the date of trial entry. The primary outcome measure was a histologically confirmed CR adenoma or cancer either at the end examination or during the course of the trial. **Results:** 945 patients were recruited into the study, of which 853 (434 receiving aspirin and 419 placebo) underwent a second colonoscopy and were included in an intention to treat analysis. 56.9% of randomised patients were male and the mean age at recruitment was 57.8 years. Full compliance with trial medication was reported by 700 patients . In total, 101 (23.3%) patients receiving aspirin had a recurrent adenoma compared with 120 (28.6%) patients who received placebo (Relative Risk = 0.81; 95% CI, 0.65 to 1.02). 103 advanced CR adenomas were observed (on the basis of villous/tubulovillous features, size ≥1cm, evidence of severe dysplasia, or CR cancer diagnosis); 39 (9.0%) of these were in the aspirin group and 64 (15.3%) in the placebo group (Relative Risk = 0.59; 95% CI, 0.40 to 0.86). This advanced group included 11 patients with CR cancers (3 aspirin and 8 placebo). **Conclusion:** Aspirin use (300 mg/day) resulted in a 19% reduction in risk of any colorectal adenoma recurrence and a marked, statistically significant, 41% reduction in risk of advanced adenoma development.

218385: Daily Soluble Aspirin and Prevention of Colorectal Adenoma Recurrence : Four Years Results of the APACC Trial. *Robert Benamouzig, Jacques Deyra, Antoine Martin, Baktiar Bejou, Jean-Jacques Raynaud, Bernard Girard,Stanislas Chaussade*

Aspirin is one of the most promising candidate drugs for colorectal cancer chemoprevention. Many case control, cohort and two prospective studies suggested an aspirin protective effect. To clarify this effect, we conducted a prospective, randomized, double-blind, placebo-controlled, multicenter trial (the APACC Study) involving 49 centers in France to compare the efficacy of aspirin as lysine acetylsalicylate 160 or 300 mg/d vs. placebo on the recurrence of the colorectal adenomas at one and 4 years. A protective effect was previously showed at one year. However the optimal dose and the duration of this chemoprevention remain discussed. We report here the final results at 4 years. Subjects were aged between 18 to 75 years and had undergone a complete colonoscopy with removal of at least one adenoma of more than 6 mm or at least 3 adenomas irrespective of size. Patients with an history of colorectal cancer, FAP, inflammatory bowel disease and the women likely to be pregnant were excluded. In order to evaluate the tolerance and compliance with the treatment, the 291 eligible patients received 300 mg of lysine acetylsalicylate daily during a 4-week run-in period. After this period, 272 patients were randomized: 188 men and 84 women, 58 years, with at least one adenoma of more than 10 mm in 180 cases and more than 3 adenomas in 90 cases, a personal history of adenoma in 64 cases and a family history of colorectal cancer in 94 cases. After one and 4 years of treatment, 238 and 176 subjects (90 and 65% of randomized) underwent colonoscopy respectively. The presence of at least one recurrent adenoma at 1 or 4 years was noted in 94 (53%) of the 176 patients. Aspirin was associated with a reduction in the risk of recurrent adenomas at one year in term of subjects with at least one adenoma of more than 5 mm or multiple adenomas (>3) ($p<0,005$). Aspirin was associated only with lower multiplicity (RR of 0,28, $p<0,02$) at 4 years. This lower effect observed at 4 years was not related to a lower statistical power related to lost of follow-up. The effect at one year seems more important with the 300-mg dose while the effect at 4 years seems more important with the lower dose suggesting different transduction pathways according to the aspirin dose. One possible hypothesis could be that the high dose had a direct anti-tumor effect, observed on the polyps left in place, and that low dose would be the "preventive" dose associated with an observed after several years of treatment as suggested by observational studies.