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O' Keefe SJ, Li JV, Lahti L, et al. Fat, fibre and cancer risk in African Americans and rural Africans. Nat Commun. 2015;6:6342.

What We Know, Think We Know, or Are Starting to Know

Despite its lack of digestibility in humans, we know, definitively, that dietary fibre is an essential dietary constituent. In fact, it is precisely because fibre is indigestible that it confers health benefits; due to their chemical structure of these carbohydrates, enzymes in the small intestine that breakdown starches and sugars are unable to hydrolyse fibres.

As a result, these carbohydrate structures pass undigested to the large intestine, where they are welcomed by groups of bacteria that specialise in degrading these complex structures [(1)]. Different bacteria are specialised in the fermentation of different dietary substrates, be they carbohydrates, proteins, or fats, and therefore dietary choices and patterns influence the selective growth of specific species [(1)].

The microbiota* of populations consuming diets rich in indigestible carbohydrates display greater bacterial diversity than Western diets, which corresponds to the diversity of complex carbohydrate structures, including resistant starch [RS], prebiotic fibres and other non-starch polysaccharides [NSP], in traditional diets [(2)].

High intake of fibre/NSP results in a shift to increased populations of short-chain fatty acid [SCFA] producing microbes [(3,4)]. SCFA' s, in particular butyrate, exert anti-inflammatory effects in the colon, and are associated with inhibition of neoplastic activity [neoplasms = abnormal tissue growth], carcinogenic detoxification, and tumour inhibition (5). Fibre-rich diets are associated with increased levels of Bacteroidetes, in particular the Prevotella species and other bacterial species required for metabolism of indigestible carbohydrates.

Conversely, a high fat diet drives increased production of bile acids in the liver, which pass through to the colon where they are metabolised by bile acid tolerant bacteria into secondary bile acid metabolites, which are implicated in colon cancer [(5,6)]. Western diets are associated with increased levels of Firmicutes and lower Bacteroidetes, and had significantly lower levels of SCFA [(4)]. This profile is associated with increased levels of pro-inflammatory bacteria.

The rate of colorectal cancer incidence in the Western industrialised world is greater by orders of magnitude than incidence in pre-industrialised cultures. However, within the West, African-Americans are at significantly increased risk of colon cancer: incidence rates in African-Americans stand at 65 per 100,000, while rural Africans have an incidence rate of <5 per 100,000 [(5)].

The present study investigated the relationship with dietary intake a colon cancer risk, with particular focus on dietary fibre and fat, in a group of African-American participants and rural African participants from Kwazulu, South Africa.

*Geek Box: The 'Bacterial Core'

In the course of our evolution, human beings have colonised every corner of the planet, adopting diverse diets in radically different natural environments and climates. Our gastrointestinal tract is one of the largest interfaces with our external environment [other than the skin], providing for both the digestion and absorption of essential nutrients and the first line of immune defence. Within our GI system, particularly the colon, is a dynamic ecosystem of bacteria. At the broadest level, there are 4 main divisions, known as 'phyla': Firmicutes, Bacteroidetes, Actinobacteria and Proteobacteria. These phyla are considered our "bacterial core", with the majority of bacterial types belonging to two major phyla, the Firmicutes and Bacteroidetes, and significant contributions from Actinobacteria and Proteobacteria. Within each phylum, there are a multitude of different genus, and within the genus individual species. For example, the phylum Bacteroidetes contains the genus Prevotella, which contains different species, for example Prevotella copri [P.copri]. It is within the composition of each phyla – at the genus and species level – that significant inter-individual variability is observed. Diversity in the human gut thus reflects the depth and breadth of variability within each major phylum. The exceptional diversity in our gut microbiota reflects diversity of environment, food sources, and consequent adaptations influencing host health.

The Study

Healthy African-American volunteers aged 50-65yrs were randomly selected from the greater Pittsburgh area, and were age-matched with African volunteers from Kwazulu-Natal, South Africa.

The study used a within-person design*. Each subject consumed their own habitual diet for 2-weeks in their home environment, before entering a 2-week residency intervention phase where the diet was swapped: African-American participants consumed a diet reflecting the traditional rural African diet, while African participants consumed a diet reflecting a Western diet.

Diet was controlled for food intake, energy requirements [weight maintenance], and macronutrient composition.

Faecal samples were taken at three time points during the 2-week home run-in, and three times during the 2-week intervention phase [Days 0, 7, and 14, then Days 15, 22, and 29].

Colonoscopy was performed to identify the presence of polyps [small clump of cells on the lining of the colon, which may develop into cancer], biomarkers of cancer risk, colonic evacuates [including SCFA and bile acid metabolites], and take mucosal biopsies.

The primary hypothesis was that swapping African-American participants to a high-fibre, low-fat diet, would result in increased bacterial fermentation and production of short-chain fatty acids, while suppressing secondary bile acid production, while the reverse would occur from swapping African participants to a Western diet. It was hypothesised that these changes would be mediated by dietary effects on the microbiota.

The baseline dietary intake in African-American participants was 35% fat, 47% carbohydrate, and 15% protein, with 14g/d fibre. Baseline intake in the African participants was 16% fat, 72% carbohydrate, and 14% protein, with 66g/d fibre.

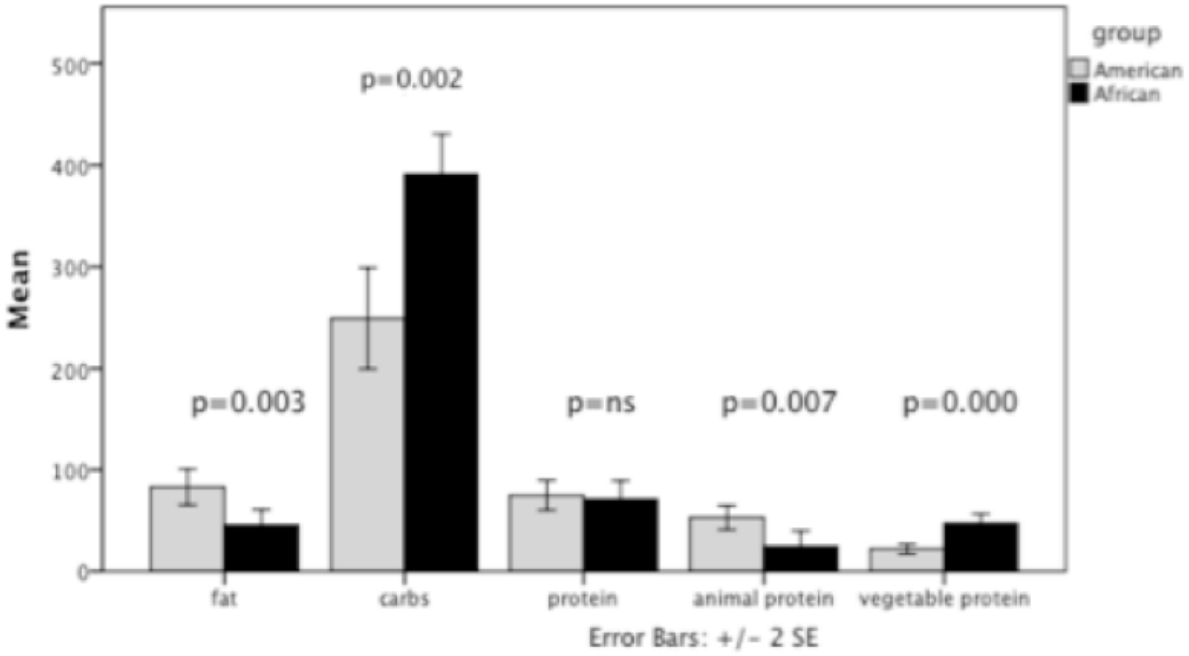

Figure *from Supplementary Data: Baseline differences in dietary intake between the African-American and African participants. Of note is that while total protein was largely similar, the composition of the dietary protein differed significantly, reflecting the wider dietary choices [and reflective of the dietary fat and carbohydrate differences, accordingly].*

*Geek Box: Within-Person Design

In a within-person design, all participants will be exposed to every intervention or treatment. This may often be achieved by a cross-over study, where participants will undergo Intervention A before Intervention B [or B before A, to minimise an effect of treatment order]. In a within-person study, each participant serves as their own control. This is important where there may be significant individual differences which may influence the results, in particular by resulting in measurement errors. For example, we know that the composition of bacteria in the microbiota of one person differs significantly from person to person; thus, comparing two groups of people against each could result in distorted averages. By comparing the effects of an exposure in one person to another exposure in the same person, this potential error is accounted for, because the changes are relative to that persons baseline. This minimises the potential for individual differences to generate misleading results. For nutrition studies, there are a number of attractions to within-person designs. First, responses to diet, and dietary intake generally, varies from person to person: comparing each person against themselves may thus provide more insight into the effect of an intervention. Secondly, in between-person studies where participants in one group are compared to another [often a placebo], double the number of participants are required. For example, if a power calculation indicates that for a between-person study 40 participants would be required for the intervention and 40 for the control - 80 participants total - then by having each subject serve as their own control in a within-person design would mean the study could be conducted with 40 people. The main potential issue with within-person designs is the effect of treatment order; there may be a carryover effect of undergoing treatment A before treatment B. To overcome this, a good design can randomise participants to a treatment order [A, then B vs. B, then A].

Results: The intervention diet in African-American participants consisted of 16% fat, 70% carbohydrate, and 14% protein, with 55g/d fibre.

The intervention diet in African participants consisted of 52% fat, 21% carbohydrate, and 27% protein, with 12g/d fibre.

The diet swap was tolerated and weight-stability was maintained in participants. Nine African-American participants were found to have polyps, but none of the African participants.

Large-intestine biopsies revealed that cell proliferation rates, indicative of abnormal tissue growth and biomarker for cancer, increased significantly in the African participants during the intervention, while decreasing significantly in the African-American participants.

Inflammatory markers were significantly elevated on swapping the African participants to a Western diet, while significantly decreased in the African-Americans on the high-fibre, low-fat diet. The production of the SCFA butyrate was significantly associated with lower mucosal cell proliferation. During the intervention diets, butyrate concentrations decreased by half in the African participants, while increasing by 2.5 times in the African-American participants.

The concentrations of butyrate-producing bacteria increased in response to the high-fibre, low-fat diet. In addition, the diversity of the bacterial compositions altered, with greater expression of protein-degrading bacteria and bile-acid metabolising enzymes, and increased concentrations of secondary bile acids, during the Western diet.

The Critical Breakdown

Pros: The dietary intervention was controlled and supervised. Weight was maintained, an important factor given weight loss may result in compositional changes in gut bacteria. The participants were drawn from population groups which exhibit significantly increased risk of colon cancer [African-Americans] and substantially low risk [Africans]. Thus, the effect of diet change could be expected to be pronounced. The within-person design was appropriate given the substantial inter-individual variance in composition of the microbiota.

Cons: Diet content was not very reflective of a 'Western' diet, and in resembled more a low-carb, high-fat [LCHF] diet: 20% carbs, 51% fat, and 27% protein vs. the 35% fat, 47% carbohydrate, and 15% protein which the African-American participants averaged in the run-in.

The baseline composition is typical of dietary intake in both the US and UK. Thus, the 'Western' diet in the intervention is not reflective of habitual population diets.

Total fat intake was 145g/d in the African participants during the Western diet phase; however, total fat intake in the African-Americans during baseline was 96g/d. Given that bile acids and secondary bile acid metabolites were important outcomes, 145g/d fat content in the 'Western' intervention likely influenced the magnitude of effect.

Key Characteristic

The actual level of dietary fibre intake is instructive, both in the habitual diet of African participants, and in the intervention diet which African-American participants consumed. Habitual intake in the African participants was in the region of 66g/d; of this, 28g fits our current definition of fibre, while the remaining 38g/d was attributable to resistant starch* generated from cooking a maize porridge.

During the intervention, African-Americans consumed 53g/d fibre, of which 9g/d was resistant starch. Resistant starch may be particularly important for the generation of the SCFA, butyrate; however, the findings of this study indicate that butyrate quantities increased 2.5-fold when African-Americans switched to the high-fibre diet.

What this appears to suggest is a threshold effect at which many of the most pronounced benefits of fibre are observed: but this is nothing new. Dennis Burkitt' s famous research in the epidemiology of colon and rectal cancer, and dietary studies in Africa, showed a near-absence of the disease in the studied populations associated with a fibre intake of >50g/d consistent in traditional diets [(7)].

A recent intervention examined the effects of 300g/d red meat with or without 40g maize starch added: while meat alone increased the formation of carcinogens, high levels of butyrate achieved from supplementing 40g maize starch [(8)]. The achieved fibre intake in the intervention diet in the present study suggests that the most protective effects of dietary fibre against carcinogenic processes may occur with a minimum of 40-50g/d fibre.

*Geek Box: Resistant Starch

In simple terms, resistant starches are starches that are resistant to amylase enzymes in the small intestine. Such starches pass through the colon and are fermented by bacteria specialising in the fermentation of non-digestible carbohydrates, but the classification of resistant starch is broad, reflecting diverse structural differences. Currently, there are 5 types of resistant starch: RS1 is within the structure of whole-grain kernels, protected in the cell wall from digestive enzymes, and largely passes to the colon. RS2 is high-amylose maize starch, food in underripe bananas or green plantains, and raw potatoes. Although this is transformed with cooking, there is some evidence that the start in underripe bananas may be particularly beneficial as a 'contrabiotic', inhibiting pathogenic bacteria adhesion to the intestinal lining. RS3 is produced following cooking, and then cooling, starchy foods; this starch cannot be broken down, and similarly is subject to fermentation. RS4 is chemically modified starch, by of particular interest currently is RS5, which is formed with starch interacts with fats. This starch-lipid complex may reduce the post-prandial blood glucose response to starchy meals. The diverse array of resistant starches, and their respective biological activity, is a microcosm for the diversity of complex carbohydrate structures, including resistant starches, prebiotic fibres, non-starch polysaccharides, and resistant oligosaccharides, which broadly fall under the umbrella term, 'fibre'.

Interesting Finding

The Western diet increased concentrations of secondary bile acids in faecal analysis of the African participants by 400%.

As much as we have talked about fibre, it is important to remember that a stated hypothesis of the study was that dietary fat stimulates bile acid production in the liver, leading to increased secondary bile acid metabolites.

As noted in Cons [above], the 'Western' diet intervention was more akin in composition to a LCHF diet; and the magnitude of effect, a 400% increase in secondary bile acids, may reflect the substantial total fat intake of 145g/d.

Nonetheless, given popularities of LCHF diets, and emerging popularity of Carnivorous Cockology, this finding warrants attention.

Animal fat, in particular saturated fat, results in increased bile acid secretion [3]. High animal fat and protein diets result in a shift in the composition of bacteria in the gut, where fibre-degrading bacteria are inhibited, and populations of bile acid tolerant bacteria increased [3,6]. When bile acids reach the colon, increased activity of enzymes which metabolise bile acids result in conversion to secondary metabolites, which are pro-inflammatory and tumour-promoting [6]. Experimental human studies have shown such a shift can occur in as little as 3-days [3].

Thus, while it may be tempting to myopically focus on fibre in the context of colon cancer prevention, diet is always the sum of its part: the dietary fat composition of Western diets may be a significant factor itself.

Relevance

The strength of evidence suggests that indigestible carbohydrates play a central role in shaping microbial composition to the benefit of human health. The Western diet pattern, largely low in overall fibre and high in animal fat, appears to shift the microbiome to a pro-inflammatory, pathogenic environment, increasing risk for intestinal disease.

While the epidemiology of colon cancer implicates environmental factors, in addition to diet, it is arguable that diet is the most important exposure influencing risk. The findings of the present study benefit from the advanced analytical methods of modern science, but the fundamental finding of protective effects of traditional diets against colon cancer with fibre intakes >50g/d goes back to the 1960' s.

However, what can be added to this observation is the potential role of dietary fat. While we are right to be 'fibre-focused' in our general understanding of gut health, it is clear that dietary fat plays an important role in mediating many of the processes associated with the initiation and progression of colon cancer.

A 6-month study in China comparing diets of 20%, 30%, or 40% fat, but with fibre matched at 14g/d [not very high], found that of faecal butyric acids was increased after the lower-fat diet intervention and decreased after the higher-fat diet intervention [9]. This suggests that either total fat content may be a standalone factor, or that a high dietary carbohydrate intake per se increases butyrate production. The fact that changing one nutrient by default changes levels of intake another means it is difficult to state at this juncture whether it is the combination of high-carb/low-fat which exerts positive influences on the gut microbiota. There remain many unturned stones is this complex area of research.

Application to Practice

Are dietary guidelines for fibre too low? There is a benefit evident from obtaining over the 30g/d threshold. And public health recommendations always require a level of compromise for people to engage with. At an individual level, for population subgroups at high-risk for colorectal cancer, it appears that the protective threshold sits at around 50g/d; but this would be a clinical nutrition issue for management. At a more real-world, practical level, given current population averages, it appears this may be one dietary constituent that we can say: more may indeed be better.

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