Introduction

Our modern day problem, essentially deficiencies or under exposure to dirt and animals, and overuse of antibiotics and C-section births, are creating imbalanced microbiotas and immune systems, leading to a host of autoimmune and inflammatory conditions [1,2].

The ancestral perspective is that not living like our hunter-gatherer ancestors has created an imbalance in our microbiota and thus our immune systems. And one of the items you often hear cited is that hunter-gatherers don't have autoimmune or inflammatory conditions [3].

Briefly, the proposed solution, to enhance diversity of our microbiota, is to eat a lot of fiber and prebiotics, test and track our microbiota, be less hygienic, get more time in nature and exposure to dirt, soil, and animals [4]. However, this proposed solution is not without side effects. Too much fiber and prebiotics will make some people have more severe symptoms. Children who experience periodic exposures to animals may experience increased allergy. Episodic trips might not be enough to replicate the ancestral environment. Some research studies indicate that children who only go to a farm occasionally actually see inflammatory and allergic conditions worsen. Children might need a constant saturation of bacteria and fungi and not e.g. at age 6 one strong exposure from going to a farm, which might give the child's immune system an offensive attack leading to a defensive response. Studies indicate that we have a limited window around age 3 through which our microbiota and thus our immune systems can form [5,6]. If individual did not evolve or form in a certain society, but have contact with that society later, e.g. around 30 years of age with hunter-gatherer diet or lifestyle, individual may have a harmful response.

Pitfalls of the Proposed Solution, Examples

Those with less than ideal gastrointestinal immune regulation may attack the resident microbiota or have difficulty regulating their microbiota and thus do better with a minimally fermentative diet with less fiber and prebiotics. Irritable bowel syndrome (IBS) and inflammatory bowel diseases (IBD: ulcerative colitis (UC) and Crohn's disease (CD)), are examples of these conditions [7].

Further, antibiotics (abx), administered earlier in life, increase the incidence of allergy and autoimmune diseases [8]. However, abx can also induce remission of inflammatory bowel disease and improve symptoms in adult IBS [9–12], and early administration of probiotics and prebiotics have greater protective effect [13]. For example in type I diabetes, administration of probiotics before 27 days was protective but after 27 days had no protective effect [14].

Hunter-gatherer Microbiota and Diet

Many studies of diet and microbiota of modern day hunter-gatherers represent only equatorial populations e.g. study of equatorial coprolites (fossilized stool remains) [15].

When populations farther away from the equator are studied, carbohydrate intake decreases, and protein and fat intake increases [16–19]. Study concluded that 73% of worldwide hunter-gatherer societies derived more than 50% of their substrates from animal foods [20]. This indicates that equatorial African diet may not increase quality and length of life in other populations than equatorial, and most hunter-gatherers do not eat diet high in carbohydrates and fiber. Especially, in IBS or IBD patients, high-prebiotic diet increases inflammatory bacteria and disease activity. Main objective of diet of these patients is to reduce symptoms, inflammation and control blood sugar, and then in healthy environment, feed healthy microbiota and starve symptom promoting microbiota. The whole ecosystem might not recalibrate itself with abundant prebiotics and fiber.

Better Solutions

Randomized controlled trial (RCT) of CD patients investigated high-FODMAP (Fermentable, Oligo-, Di-, Mono-saccharides and Polyols) and low-FODMAP diets. FODMAPs are mainly high prebiotic foods, mostly vegetables, some fruits [21]. Symptoms, in high-FODMAP diet crossover trial period, doubled in severity but relative abundance was higher for an anti-inflammatory bacterium, *Akkermansia muciniphila* [22]. This points to that, based on this study and my clinical experience, increasing anti-inflammatory bacteria with prebiotics might not have a clinical benefit to a patient [23].

How Do We Assess if We Have a Problem in the Gut? Testing

We have in clinic reliable tests for screening small intestinal bacterial overgrowth (SIBO), candida, ulcers or IBD. However, assays of phylogenetic maps of microbiota are in academic research, not in clinical use. Studies have shown that microbiota oscillates from month to month and even diurnally within the day [24–26]. Secondly, definition of healthy microbiota is not yet specified. *Methanobrevibacter smithii* has a very high colonization density in Africans. Study implies that *M. smithii* helps Africans probably thrive on the food supply they have access to [27]. However, in SIBO patients, this archaea causes constipation, bloating and may cause weight gain, high blood sugar, and high cholesterol in societies not living in equatorial Africa [28,29]. Another hunter-gatherer bacterium *Prevotella copri* 18205, depending on the person, can worsen rheumatoid arthritis or improve blood sugar [30].

Further, commercial microbiota assays study only colonic luminal microbiota. Small intestine, absent in assays, represents over 50% of gastrointestinal (GI) tract, 90% of caloric absorption, and is the main area that programs immune system with the largest density of immune cells [31,32]. Next, in randomized intervention, women with obesity were treated with prebiotics. Study reported an improvement in blood sugar but no change in weight. They also tracked microbiota. However, the blood sugar improvements did not correlate with changes in the microbiota [33]. This study infers that microbiota tests are important, and clinician's participation in gathering data is needed but clinical utility is still in future.

How to Create a Healthy Environment for a Healthy Microbiota

DOI: 10.15310/2334-3591.1045

Clinicians aim is to optimize the patient's' environment for healthy microbiota. I start with diet and lifestyle. Microbiota supports, in a form of dietary supplements, are added for symptom relief and faster recovery to optimal health for the individual. A microbiota reset with herbal anti-microbials, antibiotics, or liquid elemental or semi-elemental diets are used based on symptom severity. The aim is to have more flexibility in the diet by gradually increasing FODMAPs and decreasing supplements. Final step would be considering to add in some supplemental fiber, prebiotics, or resistant starch without causing side effects.

Specifically, the diets used for gastrointestinal conditions like IBS, IBD, GERD, and reflux are low carbohydrate, moderate-to-low carbohydrate paleo, autoimmune paleo and low FODMAP and/or Specific Carbohydrate Diet. In addition, these diets have been shown with highest quality and clinically relevant research methods to work better than the more traditional higher-carbohydrate, higher-fiber diets for metabolic conditions like diabetes, heart disease [34–42] (Figure).

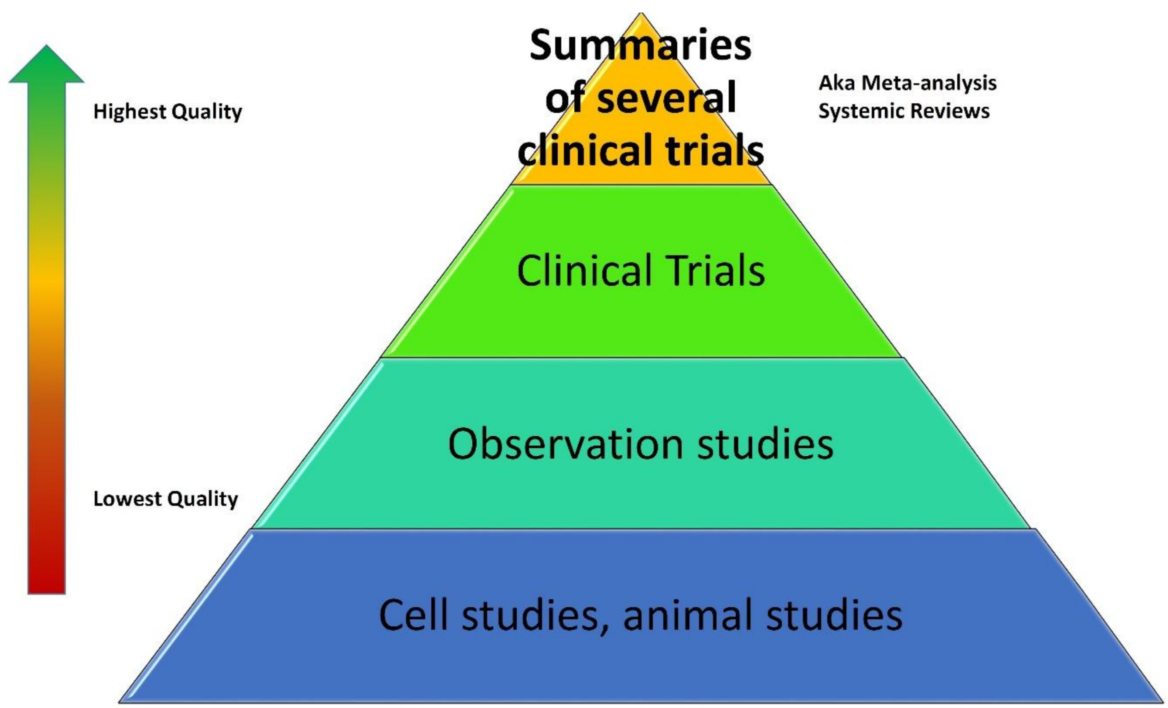

Figure. The evidence pyramid shows the least clinically relevant at the bottom and the most clinically relevant at the top [43].

Expanding lifestyle modifications for increasing microbiota diversity, recommendation is to connect with nature like walking in a forest or by the sea. Other examples are using hand washing instead of dishwashing machine, less abx for children, managing stress, sleep on a natural circadian rhythm, and the appropriate amount of exercise.

Fiber in colorectal cancer prevention

The overall impact of supplemental fiber, including resistant starch, on colorectal cancer risk appears to be minimal at best. Most of the data show no positive impact [44–49].

Some studies of dietary fiber show benefit but an equal number of studies show no effect in systematic reviews or meta-analyses including thousands or tens of thousands of people [50–66].

Conclusion

The evidence points to optimal health at broadest diet tolerated by the individual. Diet may be somewhere between low and high carbohydrate and fiber spectrum and can change overtime. Both low and high carbohydrate and fiber diets are associated with increasing health and quality of life of individual. Future research will be conducted to test the hypotheses that wide variety of diverse diets can be a basis for health promoting microbiota in healthy host.

Disclosure

No conflict of interest.

References

[1] T.T. Hugg, M.S. Jaakkola, R. Ruotsalainen, V. Pushkarev, J.J.K. Jaakkola, Exposure to animals and the risk of allergic asthma: a population-based cross-sectional study in Finnish and Russian children., Environ. Health. 7 (2008) 28. doi:10.1186/1476-069X-7-28.

[2] E. Rutayisire, K. Huang, Y. Liu, F. Tao, The mode of delivery affects the diversity and colonization pattern of the gut microbiota during the first year of infants' life: a systematic review., BMC Gastroenterol. 16 (2016) 86. doi:10.1186/s12876-016-0498-0.

[3] T.W. McDade, Early environments and the ecology of inflammation., Proc. Natl. Acad. Sci. U. S. A. (2012) 17281–8. doi:10.1073/pnas.1202244109.

[4] S.T. Weiss, Eat dirt--the hygiene hypothesis and allergic diseases., N. Engl. J. Med. 347 (2002) 930–1. doi:10.1056/NEJMe020092.

[5] B. Brunekreef, E. Von Mutius, G.K. Wong, J.A. Odhiambo, T.O. Clayton, ISAAC Phase Three Study Group, Early life exposure to farm animals and symptoms of asthma, rhinoconjunctivitis and eczema: an ISAAC Phase Three Study., Int. J. Epidemiol. 41 (2012) 753–61. doi:10.1093/ije/dyr216.

[6] B.J. Apelberg, Y. Aoki, J.J. Jaakkola, Systematic review: Exposure to pets and risk of asthma and asthma-like symptoms., J. Allergy Clin. Immunol. 107 (2001) 455–60. doi:10.1067/mai.2001.113240.

[7] L. Maagaard, D. V Ankersen, Z. Végh, J. Burisch, L. Jensen, N. Pedersen, P. Munkholm, Follow-up of patients with functional bowel symptoms treated with a low FODMAP diet., World J. Gastroenterol. 22 (2016) 4009–19. doi:10.3748/wjg.v22.i15.4009.

[8] S.B. Meropol, A. Edwards, Development of the infant intestinal microbiome: A bird's eye view of a complex process., Birth Defects Res. C. Embryo Today. 105

(2015) 228–39. doi:10.1002/bdrc.21114.
[9] D. Turner, A. Levine, K.-L. Kolho, R. Shaoul, O. Ledder, Combination of oral antibiotics may be effective in severe pediatric ulcerative colitis: a preliminary report., J. Crohns. Colitis. 8 (2014) 1464–70. doi:10.1016/j.crohns.2014.05.010.
[10] A.O. Jigaranu, O. Nedelciuc, A. Blaj, M. Badea, C. Mihai, M. Diculescu, C. Cijevschi-Prelipcean, Is rifaximin effective in maintaining remission in Crohn's disease?, Dig. Dis. 32 (2014) 378–83. doi:10.1159/000358141.
[11] K.J. Khan, T.A. Ullman, A.C. Ford, M.T. Abreu, A. Abadir, A. Abadir, J.K. Marshall, N.J. Talley, P. Moayyedi, Antibiotic therapy in inflammatory bowel disease: a systematic review and meta-analysis., Am. J. Gastroenterol. 106 (2011) 661–73. doi:10.1038/ajg.2011.72.
[12] S.B. Menees, M. Maneerattannaporn, H.M. Kim, W.D. Chey, The efficacy and safety of rifaximin for the irritable bowel syndrome: a systematic review and meta-analysis., Am. J. Gastroenterol. 107 (2012) 28–35; quiz 36. doi:10.1038/ajg.2011.355.
[13] F.K. Videhult, C.E. West, Nutrition, gut microbiota and child health outcomes., Curr. Opin. Clin. Nutr. Metab. Care. 19 (2016) 208–13. doi:10.1097/MCO.0000000000000266.
[14] U. Uusitalo, X. Liu, J. Yang, C.A. Aronsson, S. Hummel, M. Butterworth, Å. Lernmark, M. Rewers, W. Hagopian, J.-X. She, O. Simell, J. Toppari, A.G. Ziegler, B. Akolkar, J. Krischer, J.M. Norris, S.M. Virtanen, TEDDY Study Group, Association of Early Exposure of Probiotics and Islet Autoimmunity in the TEDDY Study., JAMA Pediatr. 170 (2016) 20–8. doi:10.1001/jamapediatrics.2015.2757.
[15] R.Y. Tito, D. Knights, J. Metcalf, A.J. Obregon-Tito, L. Cleeland, F. Najar, B. Roe, K. Reinhard, K. Sobolik, S. Belknap, M. Foster, P. Spicer, R. Knight, C.M. Lewis, Insights from characterizing extinct human gut microbiomes., PLoS One. 7 (2012) e51146. doi:10.1371/journal.pone.0051146.
[16] A. Ströhle, A. Hahn, A. Sebastian, Estimation of the diet-dependent net acid load in 229 worldwide historically studied hunter-gatherer societies., Am. J. Clin. Nutr. 91 (2010) 406–12. doi:10.3945/ajcn.2009.28637.
[17] A. Ströhle, A. Hahn, A. Sebastian, Latitude, local ecology, and hunter-gatherer dietary acid load: implications from evolutionary ecology., Am. J. Clin. Nutr. 92 (2010) 940–5. doi:10.3945/ajcn.2010.29815.
[18] A. Ströhle, A. Hahn, Diets of modern hunter-gatherers vary substantially in their carbohydrate content depending on ecoenvironments: results from an ethnographic analysis., Nutr. Res. 31 (2011) 429–35. doi:10.1016/j.nutres.2011.05.003.
[19] L. Cordain, S.B. Eaton, J.B. Miller, N. Mann, K. Hill, The paradoxical nature of hunter-gatherer diets: meat-based, yet non-atherogenic., Eur. J. Clin. Nutr. 56 Suppl 1 (2002) S42-52. doi:10.1038/sj.ejcn.1601353.
[20] L. Cordain, J.B. Miller, S.B. Eaton, N. Mann, S.H. Holt, J.D. Speth, Plant-animal subsistence ratios and macronutrient energy estimations in worldwide hunter-gatherer diets., Am. J. Clin. Nutr. 71 (2000) 682–92. http://www.ncbi.nlm.nih.gov/pubmed/10702160 (accessed September 7, 2016).
[21] FODMAP, (n.d.). https://en.wikipedia.org/wiki/FODMAP.
[22] E.P. Halmos, C.T. Christophersen, A.R. Bird, S.J. Shepherd, J.G. Muir, P.R.

Gibson, Consistent Prebiotic Effect on Gut Microbiota With Altered FODMAP Intake in Patients with Crohn's Disease: A Randomised, Controlled Cross-Over Trial of Well-Defined Diets., Clin. Transl. Gastroenterol. 7 (2016) e164. doi:10.1038/ctg.2016.22.

[23] Low-FODMAP Diet for Intestinal Inflammation and Autoimmunity, (n.d.). http://drruscio.com/low-fodmap-diet-for-intestinal-inflammation-and-autoimmunity/.

[24] J. Jalanka-Tuovinen, A. Salonen, J. Nikkilä, O. Immonen, R. Kekkonen, L. Lahti, A. Palva, W.M. de Vos, Intestinal microbiota in healthy adults: temporal analysis reveals individual and common core and relation to intestinal symptoms., PLoS One. 6 (2011) e23035. doi:10.1371/journal.pone.0023035.

[25] Y.-D. Nam, M.-J. Jung, S.W. Roh, M.-S. Kim, J.-W. Bae, Comparative analysis of Korean human gut microbiota by barcoded pyrosequencing., PLoS One. 6 (2011) e22109. doi:10.1371/journal.pone.0022109.

[26] C.A. Thaiss, D. Zeevi, M. Levy, G. Zilberman-Schapira, J. Suez, A.C. Tengeler, L. Abramson, M.N. Katz, T. Korem, N. Zmora, Y. Kuperman, I. Biton, S. Gilad, A. Harmelin, H. Shapiro, Z. Halpern, E. Segal, E. Elinav, Transkingdom control of microbiota diurnal oscillations promotes metabolic homeostasis., Cell. 159 (2014) 514–29. doi:10.1016/j.cell.2014.09.048.

[27] M. Million, M. Tidjani Alou, S. Khelaifia, D. Bachar, J.-C. Lagier, N. Dione, S. Brah, P. Hugon, V. Lombard, F. Armougom, J. Fromonot, C. Robert, C. Michelle, A. Diallo, A. Fabre, R. Guieu, C. Sokhna, B. Henrissat, P. Parola, D. Raoult, Increased Gut Redox and Depletion of Anaerobic and Methanogenic Prokaryotes in Severe Acute Malnutrition., Sci. Rep. 6 (2016) 26051. doi:10.1038/srep26051.

[28] U. Ghoshal, R. Shukla, D. Srivastava, U.C. Ghoshal, Irritable Bowel Syndrome, Particularly the Constipation-Predominant Form, Involves an Increase in Methanobrevibacter smithii, Which Is Associated with Higher Methane Production., Gut Liver. (2016). doi:10.5009/gnl15588.

[29] L. Conterno, F. Fava, R. Viola, K.M. Tuohy, Obesity and the gut microbiota: does up-regulating colonic fermentation protect against obesity and metabolic disease?, Genes Nutr. 6 (2011) 241–60. doi:10.1007/s12263-011-0230-1.

[30] Y. Maeda, T. Kurakawa, E. Umemoto, D. Motooka, Y. Ito, K. Gotoh, K. Hirota, M. Matsushita, Y. Furuta, M. Narazaki, N. Sakaguchi, H. Kayama, S. Nakamura, T. Iida, Y. Saeki, A. Kumanogoh, S. Sakaguchi, K. Takeda, Dysbiosis contributes to arthritis development via activation of autoreactive T cells in the intestine., Arthritis Rheumatol. (Hoboken, N.J.). (2016). doi:10.1002/art.39783.

[31] S. El Aidy, B. van den Bogert, M. Kleerebezem, The small intestine microbiota, nutritional modulation and relevance for health., Curr. Opin. Biotechnol. 32 (2015) 14–20. doi:10.1016/j.copbio.2014.09.005.

[32] R. Krajmalnik-Brown, Z.-E. Ilhan, D.-W. Kang, J.K. DiBaise, Effects of gut microbes on nutrient absorption and energy regulation., Nutr. Clin. Pract. 27 (2012) 201–14. doi:10.1177/0884533611436116.

[33] L.K. Brahe, E. Le Chatelier, E. Prifti, N. Pons, S. Kennedy, T. Blædel, J. Håkansson, T.K. Dalsgaard, T. Hansen, O. Pedersen, A. Astrup, S.D. Ehrlich, L.H. Larsen, Dietary modulation of the gut microbiota--a randomised controlled trial in obese postmenopausal women., Br. J. Nutr. 114 (2015) 406–17. doi:10.1017/S0007114515001786.

DOI: 10.15310/2334-3591.1045

[34] R.L. Pastore, J.T. Brooks, J.W. Carbone, Paleolithic nutrition improves plasma lipid concentrations of hypercholesterolemic adults to a greater extent than traditional heart-healthy dietary recommendations., Nutr. Res. 35 (2015) 474–9. doi:10.1016/j.nutres.2015.05.002.

[35] D.K. Tobias, M. Chen, J.E. Manson, D.S. Ludwig, W. Willett, F.B. Hu, Effect of low-fat diet interventions versus other diet interventions on long-term weight change in adults: a systematic review and meta-analysis., Lancet. Diabetes Endocrinol. 3 (2015) 968–79. doi:10.1016/S2213-8587(15)00367-8.

[36] E.W. Manheimer, E.J. van Zuuren, Z. Fedorowicz, H. Pijl, Paleolithic nutrition for metabolic syndrome: systematic review and meta-analysis., Am. J. Clin. Nutr. 102 (2015) 922–32. doi:10.3945/ajcn.115.113613.

[37] T. Jönsson, Y. Granfeldt, B. Ahrén, U.-C. Branell, G. Pålsson, A. Hansson, M. Söderström, S. Lindeberg, Beneficial effects of a Paleolithic diet on cardiovascular risk factors in type 2 diabetes: a randomized cross-over pilot study., Cardiovasc. Diabetol. 8 (2009) 35. doi:10.1186/1475-2840-8-35.

[38] I. Boers, F.A. Muskiet, E. Berkelaar, E. Schut, R. Penders, K. Hoenderdos, H.J. Wichers, M.C. Jong, Favourable effects of consuming a Palaeolithic-type diet on characteristics of the metabolic syndrome: a randomized controlled pilot-study., Lipids Health Dis. 13 (2014) 160. doi:10.1186/1476-511X-13-160.

[39] U. Masharani, P. Sherchan, M. Schloetter, S. Stratford, A. Xiao, A. Sebastian, M. Nolte Kennedy, L. Frassetto, Metabolic and physiologic effects from consuming a hunter-gatherer (Paleolithic)-type diet in type 2 diabetes., Eur. J. Clin. Nutr. 69 (2015) 944–8. doi:10.1038/ejcn.2015.39.

[40] J. Tay, N.D. Luscombe-Marsh, C.H. Thompson, M. Noakes, J.D. Buckley, G.A. Wittert, W.S. Yancy, G.D. Brinkworth, Comparison of low- and high-carbohydrate diets for type 2 diabetes management: a randomized trial., Am. J. Clin. Nutr. 102 (2015) 780–90. doi:10.3945/ajcn.115.112581.

[41] L.R. Saslow, S. Kim, J.J. Daubenmier, J.T. Moskowitz, S.D. Phinney, V. Goldman, E.J. Murphy, R.M. Cox, P. Moran, F.M. Hecht, A randomized pilot trial of a moderate carbohydrate diet compared to a very low carbohydrate diet in overweight or obese individuals with type 2 diabetes mellitus or prediabetes., PLoS One. 9 (2014) e91027. doi:10.1371/journal.pone.0091027.

[42] A.E. Buyken, J. Goletzke, G. Joslowski, A. Felbick, G. Cheng, C. Herder, J.C. Brand-Miller, Association between carbohydrate quality and inflammatory markers: systematic review of observational and interventional studies., Am. J. Clin. Nutr. 99 (2014) 813–33. doi:10.3945/ajcn.113.074252.

[43] Guide to Research Methods, (n.d.). http://library.downstate.edu/EBM2/2100.htm.

[44] M. Principi, A. Di Leo, M. Pricci, M.P. Scavo, R. Guido, S. Tanzi, D. Piscitelli, A. Pisani, E. Ierardi, M.C. Comelli, M. Barone, Phytoestrogens/insoluble fibers and colonic estrogen receptor β: randomized, double-blind, placebo-controlled study., World J. Gastroenterol. 19 (2013) 4325–33. doi:10.3748/wjg.v19.i27.4325.

[45] M.J. Clark, K. Robien, J.L. Slavin, Effect of prebiotics on biomarkers of colorectal cancer in humans: a systematic review., Nutr. Rev. 70 (2012) 436–43. doi:10.1111/j.1753-4887.2012.00495.x.

[46] P.J. Limburg, M.R. Mahoney, K.L.A. Ziegler, S.J. Sontag, R.E. Schoen, R. Benya, M.J. Lawson, D.S. Weinberg, E. Stoffel, M. Chiorean, R. Heigh, J. Levine, G.

Della'Zanna, L. Rodriguez, E. Richmond, C. Gostout, S.J. Mandrekar, T.C. Smyrk, Cancer Prevention Network, Randomized phase II trial of sulindac, atorvastatin, and prebiotic dietary fiber for colorectal cancer chemoprevention., Cancer Prev. Res. (Phila). 4 (2011) 259–69. doi:10.1158/1940-6207.CAPR-10-0215.

[47] M. van Dijk, G.K. Pot, The effects of nutritional interventions on recurrence in survivors of colorectal adenomas and cancer: a systematic review of randomised controlled trials., Eur. J. Clin. Nutr. 70 (2016) 566–73. doi:10.1038/ejcn.2015.210.

[48] M.J. Grubben, C.C. van den Braak, M. Essenberg, M. Olthof, A. Tangerman, M.B. Katan, F.M. Nagengast, Effect of resistant starch on potential biomarkers for colonic cancer risk in patients with colonic adenomas: a controlled trial., Dig. Dis. Sci. 46 (2001) 750–6. http://www.ncbi.nlm.nih.gov/pubmed/11330408 (accessed September 8, 2016).

[49] M.L. Heijnen, J.M. van Amelsvoort, P. Deurenberg, A.C. Beynen, Limited effect of consumption of uncooked (RS2) or retrograded (RS3) resistant starch on putative risk factors for colon cancer in healthy men., Am. J. Clin. Nutr. 67 (1998) 322–31. http://www.ncbi.nlm.nih.gov/pubmed/9459382 (accessed September 8, 2016).

[50] N. Makarem, J.M. Nicholson, E. V Bandera, N.M. McKeown, N. Parekh, Consumption of whole grains and cereal fiber in relation to cancer risk: a systematic review of longitudinal studies., Nutr. Rev. 74 (2016) 353–73. doi:10.1093/nutrit/nuw003.

[51] G.-C. Chen, X. Tong, J.-Y. Xu, S.-F. Han, Z.-X. Wan, J.-B. Qin, L.-Q. Qin, Whole-grain intake and total, cardiovascular, and cancer mortality: a systematic review and meta-analysis of prospective studies., Am. J. Clin. Nutr. 104 (2016) 164–72. doi:10.3945/ajcn.115.122432.

[52] S. Azeem, S.W. Gillani, A. Siddiqui, S.B. Jandrajupalli, V. Poh, S.A. Syed Sulaiman, Diet and Colorectal Cancer Risk in Asia--a Systematic Review., Asian Pac. J. Cancer Prev. 16 (2015) 5389–96. http://www.ncbi.nlm.nih.gov/pubmed/26225683 (accessed September 8, 2016).

[53] F. Turati, M. Rossi, C. Pelucchi, F. Levi, C. La Vecchia, Fruit and vegetables and cancer risk: a review of southern European studies., Br. J. Nutr. (2015) S102-10. doi:10.1017/S0007114515000148.

[54] C.M. Bennett, H.G. Coleman, P.G. Veal, M.M. Cantwell, C.C.L. Lau, L.J. Murray, Lifestyle factors and small intestine adenocarcinoma risk: A systematic review and meta-analysis., Cancer Epidemiol. 39 (2015) 265–73. doi:10.1016/j.canep.2015.02.001.

[55] J. Jiao, J.-Y. Xu, W. Zhang, S. Han, L.-Q. Qin, Effect of dietary fiber on circulating C-reactive protein in overweight and obese adults: a meta-analysis of randomized controlled trials., Int. J. Food Sci. Nutr. 66 (2015) 114–9. doi:10.3109/09637486.2014.959898.

[56] F. Thies, L.F. Masson, P. Boffetta, P. Kris-Etherton, Oats and bowel disease: a systematic literature review., Br. J. Nutr. (2014) S31-43. doi:10.1017/S0007114514002293.

[57] Q. Ben, Y. Sun, R. Chai, A. Qian, B. Xu, Y. Yuan, Dietary fiber intake reduces risk for colorectal adenoma: a meta-analysis., Gastroenterology. 146 (2014) 689–699.e6. doi:10.1053/j.gastro.2013.11.003.

[58] N. Hou, D. Huo, J.J. Dignam, Prevention of colorectal cancer and dietary management., Chinese Clin. Oncol. 2 (2013) 13. doi:10.3978/j.issn.2304-3865.2013.04.03.
[59] D. Aune, D.S.M. Chan, R. Lau, R. Vieira, D.C. Greenwood, E. Kampman, T. Norat, Dietary fibre, whole grains, and risk of colorectal cancer: systematic review and dose-response meta-analysis of prospective studies., BMJ. 343 (2011) d6617. http://www.ncbi.nlm.nih.gov/pubmed/22074852 (accessed September 8, 2016).
[60] K. Uchida, S. Kono, G. Yin, K. Toyomura, J. Nagano, T. Mizoue, R. Mibu, M. Tanaka, Y. Kakeji, Y. Maehara, T. Okamura, K. Ikejiri, K. Futami, T. Maekawa, Y. Yasunami, K. Takenaka, H. Ichimiya, R. Terasaka, Dietary fiber, source foods and colorectal cancer risk: the Fukuoka Colorectal Cancer Study., Scand. J. Gastroenterol. 45 (2010) 1223–31. doi:10.3109/00365521.2010.492528.
[61] P. Haas, M.J. Machado, A.A. Anton, A.S.S. Silva, A. de Francisco, Effectiveness of whole grain consumption in the prevention of colorectal cancer: meta-analysis of cohort studies., Int. J. Food Sci. Nutr. 60 Suppl 6 (2009) 1–13. doi:10.1080/09637480802183380.
[62] A. Schatzkin, Y. Park, M.F. Leitzmann, A.R. Hollenbeck, A.J. Cross, Prospective study of dietary fiber, whole grain foods, and small intestinal cancer., Gastroenterology. 135 (2008) 1163–7. doi:10.1053/j.gastro.2008.07.015.
[63] Y. Park, D.J. Hunter, D. Spiegelman, L. Bergkvist, F. Berrino, P.A. van den Brandt, J.E. Buring, G.A. Colditz, J.L. Freudenheim, C.S. Fuchs, E. Giovannucci, R.A. Goldbohm, S. Graham, L. Harnack, A.M. Hartman, D.R. Jacobs, I. Kato, V. Krogh, M.F. Leitzmann, M.L. McCullough, A.B. Miller, P. Pietinen, T.E. Rohan, A. Schatzkin, W.C. Willett, A. Wolk, A. Zeleniuch-Jacquotte, S.M. Zhang, S.A. Smith-Warner, Dietary fiber intake and risk of colorectal cancer: a pooled analysis of prospective cohort studies., JAMA. 294 (2005) 2849–57. doi:10.1001/jama.294.22.2849.
[64] T. Asano, R.S. McLeod, Dietary fibre for the prevention of colorectal adenomas and carcinomas., Cochrane Database Syst. Rev. (2002) CD003430. doi:10.1002/14651858.CD003430.
[65] C.S. Fuchs, E.L. Giovannucci, G.A. Colditz, D.J. Hunter, M.J. Stampfer, B. Rosner, F.E. Speizer, W.C. Willett, Dietary fiber and the risk of colorectal cancer and adenoma in women., N. Engl. J. Med. 340 (1999) 169–76. doi:10.1056/NEJM199901213400301.
[66] E. Giovannucci, E.B. Rimm, M.J. Stampfer, G.A. Colditz, A. Ascherio, W.C. Willett, Intake of fat, meat, and fiber in relation to risk of colon cancer in men., Cancer Res. 54 (1994) 2390–7. http://www.ncbi.nlm.nih.gov/pubmed/8162586 (accessed June 18, 2016).