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Diet and Upper GI Cancers: In Search of Dark Matter

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"Food is an important part of a balanced diet."

-Fran Lebowitz

On that we can probably all agree; the details tend to be more elusive. For over half a century, cancer epidemiologists and other scientists have attempted to understand the role of diet in the etiology of cancer, much of it focused on GI cancers. Haenszel and Kurihara made ground-breaking observations on Japanese migrants to the US, finding that the incidence of colorectal cancer in the migrants and their immediate offspring rose rapidly from the low rates in Japan to approach, and even exceed, the much higher rates in their new home.[1] These large changes (approximately 250% in males[2]) over a short period of time have been interpreted to reflect the importance of environmental exposures later in life in the etiology of colorectal cancer, perhaps via adoption of a more western lifestyle, including dietary patterns.[3, 4] Similarly, studies of esophageal squamous cell carcinoma among migrants from high (e.g., China) to low incidence areas indicate a change in incidence (in this case, reduction) among descendants over time towards that of the host country, with the speed of change depending somewhat on the country of origin and the prevalent risk factors in that country.[2, 5] In contrast, gastric cancer rates, which are quite high in Japan, change only very slowly among migrants in the direction of the new host country, taking multiple subsequent generations, suggesting that for gastric cancer, factors earlier in life (e.g., *H. pylori* infection) and genetics are equally important.[6]

How far have we come since these early studies? A PubMed search reveals over 8,000 publications related to diet and GI cancer, of which almost 2,000 were in the last five years alone. Based on sheer numbers, it would seem that we should already have reached the "promised land," where an individual in the general population or one at high-risk for a specific GI cancer would be offered a simple chemopreventive pill, or a clear dietary recommendation, with the expectation of substantial beneficial results. Society also would be facilitating healthy nutrition choices.[7, 8] Unfortunately we are not in such a land. What is taking so long?

Obviously the topic is extremely complex, even more so when interactions with the microbiome are considered.[9–11] Beyond that, however, an important contributing factor may lie in the choices that have been made over the past decades regarding which aspects of diet to study. Many early studies recognized the potential importance of food groups and patterns of intake, in addition to individual items, as potential determinants of GI cancer incidence. There was an appreciation that the act of eating is more than putting edibles in the mouth – it is, or can be, part of a social/family/community activity, with many potential correlates and interactions related to physical activity and lifestyle that might affect cancer risk.[12–15] However, in a decades-long surge of reductionism, the relationship between cancer incidence patterns across the world and the way individuals in broad social/ethnic groups live and eat, along with the observed changes in eating patterns and cancer incidence that occur upon migration were translated into increasingly narrow hypotheses which were tested by experiments in cell culture and animal models, observational studies, and even randomized clinical trials with the focus on finding a "magic bullet" to be added to (or

eliminated from) the diet that could stand in for a healthy diet that has been defined and refined through thousands of years of evolution. Such studies have investigated associations with individual food items (e.g., tomatoes, red meat); macronutrients (e.g., fat, carbohydrates); vitamins (e.g., folate, Vitamin A) and other micronutrients (e.g., lycopene); specific chemicals or chemical classes (e.g., resveratrol, phytoestrogens); and mineral or specialty supplements (e.g., selenium, glucosamine). From these types of studies it is now unfortunately clear how to increase lung cancer rates in cigarette smokers (beta-carotene)[16, 17], and promote the recurrence of colon adenomas (folic acid).[18] Many other findings, however, have proven quite difficult to replicate, in large part due to different populations, hypotheses, methods of assessing exposure, and analytic approaches.

Fortunately, over the past decade the research pendulum has begun to swing back into a more balanced position, where study of individual molecules is complemented by broader investigations that take into account a more inclusive view of an individual's overall diet and lifestyle. This process might be compared to changes in approaches to understanding the role of constitutive genetic factors in cancer etiology. Early low-throughput studies of variants in candidate genes yielded, in the mid-2000s, to the genomics era, in which agnostic genome-wide association studies (GWAS) focused on a million or more individual SNPs, each analyzed in isolation from the others in its association with a cancer type. While more than one hundred SNPs thus far have been linked with cancer using this approach (probably eventually leading to many fascinating and important biological discoveries), they account for only a small fraction of observed cancer heritability – hence the search for the so-called "missing heritability"[19] – and have yet to make a substantial impact in cancer prevention or prediction at the population level. Recently the "post-GWAS era" has stimulated new approaches to coaxing additional information from the resource-intensive GWAS studies. Many of these take into account previous knowledge about the etiology and pathobiology of a cancer and the specific pathways which may be involved, and test whether multiple variants in multiple genes acting in these pathways or networks may explain more than at an individual level.[20] In the world of nutrition and cancer, the reemphasis on dietary patterns and their correlates in cancer etiology and survival might be termed the "post-micronutrient era" where the broader picture is assessed in searching for the "dietary dark matter" – the factors underlying the presumably large contribution of diet to GI and other cancers that remains unexplained.

This brings us to this issue of CGH, where Li et al. report on their analysis of food frequency questionnaires collected from a large cohort of almost 500,000 men and women participating in the NIH-AARP Diet and Health Study in the US, in relation to incidence of esophageal and gastric cancer during a mean of almost ten years of follow up.[21] Rather than focus on individual food items, macro or micronutrients, or agnostic approaches (e.g., factor analyses or principal component analyses,[22, 23]) which can be difficult to interpret and reproduce, they instead examined pre-defined patterns representing a purported healthy diet, using two related classification schemes: the Healthy Eating Index-2005,[24] and the Alternate Mediterranean Diet Score.[25]

Overall they found that individuals whose diet was most consistent with either of these indices experienced substantially lower risk of esophageal cancer. Reduced risk was particularly strong for squamous cell carcinoma (49% lower in the highest quintile of "healthy diet" versus the lowest), but also 25% lower for esophageal adenocarcinoma. There was less evidence of an association between either of these indices and gastric cancer. It is particularly notable that, in contrast to the marked inverse associations between the healthy diet indices and esophageal cancers, when the individual contributions of the components of the two indices were examined, none were found to be consistently related to reduced risk, with the possible exception of grains.

There are many strengths to the study, including its prospective design, reasonably large number of cancers of each site, the availability of information on major risk factors to minimize confounding, and thorough analyses. The importance of careful collection of potential confounding factors is clearly illustrated in comparisons of the hazard ratios controlling just for age and sex, with the multivariable adjusted hazard ratios, which in all cases were closer to the null (see Tables 2 and 3). However, as pointed out by Martinez, et al.,[12] even prospective studies have their potential weaknesses. In this report diet was assessed only once, likely resulting in increasing misclassification as years of follow up rise; a food frequency questionnaire was used, with its attendant limitations;[26] no information was available on diet earlier in life, which may be more important etiologically, especially for gastric cancer; and there remains potential for residual confounding, possibly exacerbated by factors such as smoking and alcohol use which may have changed since baseline evaluation. In addition, for non-cardia gastric cancers, the lack of information on H. pylori status is an important limitation as, for example, the effects of diet on risk may be quite different depending on H. pylori positivity. Overall, however, the many strengths of the study outweigh its limitations, many of which are conservative in nature and would tend to bias the findings towards the null.

Focusing on the Alternate Mediterranean Diet Score, the better known of the two indices used, a reasonable question is: what does this measure? Does a high score imply one is actually eating a “Mediterranean Diet?” Not according to the United Nations Educational, Scientific and Cultural Organization (UNESCO) (see text box), who define the Mediterranean diet in much broader terms, as much a way of life than a compendium of food items.[27] Nevertheless, for those not residing in smaller cities and towns near Mediterranean shores, the current crude measure, based on 0/1 scores on ten food groups, must suffice. However its relative crudeness is also its strength. With the above in mind, the fact that such a simple measure, taking only a few minutes to administer and assessed only once, significantly predicts risk of esophageal cancer over the following decade might be considered astonishing, especially considering that the confounding effects of smoking and alcohol have largely been eliminated.

The major modifiable risk factors for both types of esophageal cancer and both subsites of gastric cancer, together with estimates of their individual and joint contributions to cases occurring in the US population were described by Engel, et al. in 2003,[28] using data from the US Multicenter Study. A recent report based on the larger Australian Cancer Study reached similar conclusions for adenocarcinomas of the esophagus and gastric cardia.[29] Regarding esophageal squamous cell carcinoma in the US, while cigarette smoking and high alcohol consumption remain key drivers of incidence and should be the major focus of preventive actions,[30] there appears to be abundant room for healthy dietary recommendations, particularly among former smokers and drinkers. Similarly, for esophageal adenocarcinoma, where obesity, gastroesophageal reflux and cigarette smoking are key modifiable risk factors,[31–34] a healthy diet should also be added to the list of candidate preventive actions, especially given the interrelationship among diet, obesity and gastroesophageal reflux. Gastric cancers remain more difficult to address given current knowledge of etiologic factors. Smoking cessation would likely help regarding both sites, but beyond *H. pylori* status, little is known with confidence regarding effective preventive actions.[35] Cancers arising in the gastric cardia or gastroesophageal junction tend to reflect an epidemiology (pattern of incidence and risk factors) roughly midway between those of esophageal adenocarcinomas and non-cardia gastric cancers.[36]

But is the study by Li, et al.,[21] together with other similar observational findings, enough to inform clinical recommendations for persons at high risk for esophageal cancer? In addition to a careful meta-analysis of similar studies, one always hopes for a clinical trial to provide

supporting evidence. However, one might wait a long time for a well-powered long-term trial focused on a Mediterranean diet (or similar) intervention and upper GI cancers. In the meantime, there is new and strong evidence from Spain indicating that a Mediterranean diet type of intervention (in this instance, along with added olive oil or mixed nuts in two different intervention arms) reduces the incidence of cardiovascular events, including death from cardiovascular causes, in a population without prior heart disease by an average of 29% compared to a control diet.[37] Given that persons at high risk for esophageal cancer are also likely candidates for cardiovascular events, which occur with much higher frequency than esophageal cancer, such a recommendation might make sense.

References

1. Haenszel W, Kurihara M. Studies of Japanese migrants I. Mortality from cancer and other diseases among Japanese in the United States. J Natl Cancer Inst. 1968 Jan; 40(1):43–68. [PubMed: 5635018]
2. Kolonel, LN.; Wilkens, LR. Cancer Epidemiology and Prevention. New York, NY: Oxford University Press; 2006. Migrant Studies; p. 189-201.
3. Haenszel W, Berg JW, Segi M, Kurihara M, Locke FB. Large-bowel cancer in Hawaiian Japanese. J Natl Cancer Inst. 1973 Dec; 51(6):1765–1779. [PubMed: 4797262]
4. Le Marchand L, Hankin JH, Pierce LM, Sinha R, Nerurkar PV, Franke AA, Wilkens LR, Kolonel LN, Donlon T, Seifried A, Custer LJ, Lum-Jones A, Chang W. Well-done red meat, metabolic phenotypes and colorectal cancer in Hawaii. Mutat Res. 2002 Sep 30.:506–507. 205–214.
5. King H, Li JY, Locke FB, Pollack ES, Tu JT. Patterns of site-specific displacement in cancer mortality among migrants: the Chinese in the United States. Am J Public Health. 1985 Mar; 75(3): 237–242. [PubMed: 3976947]
6. Kolonel LN, Nomura AM, Hirohata T, Hankin JH, Hinds MW. Association of diet and place of birth with stomach cancer incidence in Hawaii Japanese and Caucasians. Am J Clin Nutr. 1981 Nov; 34(11):2478–2485. [PubMed: 7304487]
7. Larson NI, Story MT, Nelson MC. Neighborhood environments: disparities in access to healthy foods in the U.S. Am J Prev Med. 2009 Jan; 36(1):74–81. [PubMed: 18977112]
8. Auchincloss AH, Mujahid MS, Shen M, Michos ED, Whitt-Glover MC, Diez Roux AV. Neighborhood health-promoting resources and obesity risk (the multi-ethnic study of atherosclerosis). Obes Silver Spring Md. 2013 Mar; 21(3):621–628.
9. Polk DB, Peek RM Jr. Helicobacter pylori: gastric cancer and beyond. Nat Rev Cancer. 2010 Jun; 10(6):403–414. [PubMed: 20495574]
10. Yang L, Francois F, Pei Z. Molecular pathways: pathogenesis and clinical implications of microbiome alteration in esophagitis and Barrett esophagus. Clin Cancer Res Off J Am Assoc Cancer Res. 2012 Apr 15; 18(8):2138–2144.
11. Hajishengallis G, Darveau RP, Curtis MA. The keystone-pathogen hypothesis. Nat Rev Microbiol. 2012 Oct; 10(10):717–725. [PubMed: 22941505]
12. Martínez ME, Marshall JR, Giovannucci E. Diet and cancer prevention: the roles of observation and experimentation. Nat Rev Cancer. 2008 Sep; 8(9):694–703. [PubMed: 19143054]
13. Pollard J, Greenwood D, Kirk S, Cade J. Lifestyle factors affecting fruit and vegetable consumption in the UK Women's Cohort Study. Appetite. 2001 Aug; 37(1):71–79. [PubMed: 11562159]
14. Johansson L, Andersen LF. Who eats 5 a day?: intake of fruits and vegetables among Norwegians in relation to gender and lifestyle. J Am Diet Assoc. 1998 Jun; 98(6):689–691. [PubMed: 9627628]
15. Dehghan M, Akhtar-Danesh N, Merchant AT. Factors associated with fruit and vegetable consumption among adults. J Hum Nutr Diet Off J Br Diet Assoc. 2011 Apr; 24(2):128–134.
16. Albanes D, Heinonen OP, Huttunen JK, Taylor PR, Virtamo J, Edwards BK, Haapakoski J, Rautalahti M, Hartman AM, Palmgren J. Effects of alpha-tocopherol and beta-carotene supplements on cancer incidence in the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study. Am J Clin Nutr. 1995 Dec; 62(6 Suppl):1427S–1430S. [PubMed: 7495243]

17. Omenn GS, Goodman GE, Thornquist MD, Balmes J, Cullen MR, Glass A, Keogh JP, Meyskens FL, Valanis B, Williams JH, Barnhart S, Hammar S. Effects of a combination of beta carotene and vitamin A on lung cancer and cardiovascular disease. N Engl J Med. 1996 May 2; 334(18):1150–1155. [PubMed: 8602180]
18. Cole BF, Baron JA, Sandler RS, Haile RW, Ahnen DJ, Bresalier RS, McKeown-Eyssen G, Summers RW, Rothstein RI, Burke CA, Snover DC, Church TR, Allen JI, Robertson DJ, Beck GJ, Bond JH, Byers T, Mandel JS, Mott LA, Pearson LH, Barry EL, Rees JR, Marcon N, Saibil F, Ueland PM, Greenberg ER. Folic acid for the prevention of colorectal adenomas: a randomized clinical trial. Jama J Am Med Assoc. 2007 Jun 6; 297(21):2351–2359.
19. Yang J, Benyamin B, McEvoy BP, Gordon S, Henders AK, Nyholt DR, Madden PA, Heath AC, Martin NG, Montgomery GW, Goddard ME, Visscher PM. Common SNPs explain a large proportion of the heritability for human height. Nat Genet. 2010 Jul; 42(7):565–569. [PubMed: 20562875]
20. Li W-Q, Hu N, Hyland PL, Gao Y, Wang Z-M, Yu K, Su H, Wang C-Y, Wang L-M, Chanock SJ, Burdett L, Ding T, Qiao Y-L, Fan J-H, Wang Y, Xu Y, Shi J-X, Gu F, Wheeler W, Xiong X-Q, Giffen C, Tucker MA, Dawsey SM, Freedman ND, Abnet CC, Goldstein AM, Taylor PR. Genetic variants in DNA repair pathway genes and risk of esophageal squamous cell carcinoma and gastric adenocarcinoma in a Chinese population. Carcinogenesis. 2013 Apr 5.
21. Li W-Q, Park Y, Wu JW, Ren J-S, Goldstein AM, Taylor PR, Hollenbeck AR, Freedman ND, Abnet CC. Index-Based Dietary Patterns and Risk of Esophageal and Gastric Cancer in a Large Cohort Study. Clin Gastroenterol Hepatol Off Clin Pr J Am Gastroenterol Assoc. 2013 Apr 13.
22. Navarro Silvera SA, Mayne ST, Risch HA, Gammon MD, Vaughan T, Chow W-H, Dubin JA, Dubrow R, Schoenberg J, Stanford JL, West AB, Rotterdam H, Blot WJ. Principal component analysis of dietary and lifestyle patterns in relation to risk of subtypes of esophageal and gastric cancer. Ann Epidemiol. 2011 Jul; 21(7):543–550. [PubMed: 21435900]
23. Bahmanyar S, Ye W. Dietary patterns and risk of squamous-cell carcinoma and adenocarcinoma of the esophagus and adenocarcinoma of the gastric cardia: a population-based case-control study in Sweden. Nutr Cancer. 2006; 54(2):171–178. [PubMed: 16898861]
24. Guenther PM, Reedy J, Krebs-Smith SM. Development of the Healthy Eating Index-2005. J Am Diet Assoc. 2008 Nov; 108(11):1896–1901. [PubMed: 18954580]
25. Fung TT, McCullough ML, Newby PK, Manson JE, Meigs JB, Rifai N, Willett WC, Hu FB. Diet-quality scores and plasma concentrations of markers of inflammation and endothelial dysfunction. Am J Clin Nutr. 2005 Jul; 82(1):163–173. [PubMed: 16002815]
26. Kristal AR, Peters U, Potter JC. Is it time to abandon the food frequency questionnaire? Cancer Epidemiol. Biomarkers Prev. 2005; 14:2826–2828.
27. UNESCO Culture Sector - Intangible Heritage - 2003 Convention_: [Internet]. [cited 2013 Apr 24]; Available from: http://www.unesco.org/culture/ich/en/RL/00394
28. Engel LS, Chow WH, Vaughan TL, Gammon MD, Risch HA, Stanford JL, Schoenberg JB, Mayne ST, Dubrow R, Rotterdam H, West AB, Blaser M, Blot WJ, Gail MH, Fraumeni JF Jr. Population attributable risks of esophageal and gastric cancers. J Natl Cancer Inst. 2003 Sep 17; 95(18):1404–13. [PubMed: 13130116]
29. Olsen CM, Pandeya N, Green AC, Webb PM, Whiteman DC. Population attributable fractions of adenocarcinoma of the esophagus and gastroesophageal junction. Am J Epidemiol. 2011 Sep 1; 174(5):582–590. [PubMed: 21719746]
30. Lubin JH, Cook MB, Pandeya N, Vaughan TL, Abnet CC, Giffen C, Webb PM, Murray LJ, Casson AG, Risch HA, Ye W, Kamangar F, Bernstein L, Sharp L, Nyrén O, Gammon MD, Corley DA, Wu AH, Brown LM, Chow W-H, Ward MH, Freedman ND, Whiteman DC. The importance of exposure rate on odds ratios by cigarette smoking and alcohol consumption for esophageal adenocarcinoma and squamous cell carcinoma in the Barrett's Esophagus and Esophageal Adenocarcinoma Consortium. Cancer Epidemiol. 2012 Jun; 36(3):306–316. [PubMed: 22504051]
31. Cook MB, Kamangar F, Whiteman DC, Freedman ND, Gammon MD, Bernstein L, Brown LM, Risch HA, Ye W, Sharp L, Pandeya N, Webb PM, Wu AH, Ward MH, Giffen C, Casson AG, Abnet CC, Murray LJ, Corley DA, Nyrén O, Vaughan TL, Chow W-H. Cigarette smoking and adenocarcinomas of the esophagus and esophagogastric junction: a pooled analysis from the

international BEACON consortium. J Natl Cancer Inst. 2010 Sep 8; 102(17):1344–1353. [PubMed: 20716718]

32. Hoyo C, Cook MB, Kamangar F, Freedman ND, Whiteman DC, Bernstein L, Brown LM, Risch HA, Ye W, Sharp L, Wu AH, Ward MH, Casson AG, Murray LJ, Corley DA, Nyrén O, Pandeya N, Vaughan TL, Chow W-H, Gammon MD. Body mass index in relation to oesophageal and oesophagogastric junction adenocarcinomas: a pooled analysis from the International BEACON Consortium. Int J Epidemiol. 2012 Nov 12.
33. Farrow DC, Vaughan TL, Sweeney C, Gammon MD, Chow WH, Risch HA, Stanford JL, Hansten PD, Mayne ST, Schoenberg JB, Rotterdam H, Ahsan H, West AB, Dubrow R, FJF, Blot WJ. Gastroesophageal reflux disease, use of H2 receptor antagonists, and risk of esophageal and gastric cancer. Cancer Causes Control. 2000; 11(3):231–8. [PubMed: 10782657]
34. Lagergren J, Bergstrom R, Lindgren A, Nyren O. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. N Engl J Med. 1999 Mar 18; 340(11):825–31. [PubMed: 10080844]
35. De Martel C, Forman D, Plummer M. Gastric cancer: epidemiology and risk factors. Gastroenterol Clin North Am. 2013 Jun; 42(2):219–240. [PubMed: 23639638]
36. Buas MF, Vaughan TL. Epidemiology and risk factors for gastroesophageal junction tumors: understanding the rising incidence of this disease. Semin Radiat Oncol. 2013 Jan; 23(1):3–9. [PubMed: 23207041]
37. Estruch R, Ros E, Salas-Salvadó J, Covas M-I, Corella D, Arós F, Gómez-Gracia E, Ruiz-Gutiérrez V, Fiol M, Lapetra J, Lamuela-Raventos RM, Serra-Majem L, Pintó X, Basora J, Muñoz MA, Sorlí JV, Martínez JA, Martínez-González MA. Primary prevention of cardiovascular disease with a Mediterranean diet. N Engl J Med. 2013 Apr 4; 368(14):1279–1290. [PubMed: 23432189]