AHC Media

Integrative Medicine

Vol. 16, Issue 8, August 2013
www.ahcmedia.com

Evidence-based summaries and critical reviews on the latest developments in integrative therapies [ALERT]

PROSTATE CANCER

ABSTRACT & COMMENTARY

Omega 3s and the Prostate: Good or Bad?

By Luke Fortney, MD

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Dr. Fortney reports no financial relationships relevant to this field of study.

SYNOPSIS: Among men diagnosed with prostate cancer, those with the highest levels of plasma omega-3 fatty acids demonstrated an increased risk for developing prostate cancer, bringing into question various recommendations for increased omega-3 intake.

SOURCE: Brasky TM, et al. Plasma phospholipid fatty acids and prostate cancer risk in the SELECT trial. *J Natl Cancer Inst* 2013; July 10 [Epub ahead of print].

The role of omega-3 fatty acids in prostate cancer risk has been inconsistent and it has been difficult to draw practical and clinically useful conclusions from the research. Previous studies have shown an association with lower prostate-specific antigen (PSA) values and increased intake of omega-3s, to increased prostate cancer incidence in others. The case-cohort study by Brasky et al — a subanalysis of the larger SELECT trial (Selenium and Vitamin E Cancer Prevention Trial) — supports those previous reports that suggest a concern about increased prostate cancer risk and omega-3 fatty acids. In this recent study, researchers evaluated data from 834 men who eventually were diagnosed with prostate cancer, 156 of whom were found to have high-grade cancers. Compared to 1393 age- and race-matched controls, men with the highest levels of plasma omega-3 fatty acids demonstrated an increased risk in developing both low- and high-grade prostate cancers. Using proportional hazards models, the researchers estimated that omega-3s were associated with a 43% increased risk for prostate cancer overall and a 71% increase in aggressive prostate cancer (hazard ratio, 1.43 and 1.71, respectively). However, overall relative risk is small. Given the consistency of these results, the authors concluded that omega-3 fatty acids, in contrast to conventional wisdom, may be associated with prostate tumorigenesis.

COMMENTARY

This study has significant limitations. First, these data do not demonstrate a cause and effect relationship between fish oil intake and prostate cancer incidence

Financial Disclosure: *Integrative Medicine Alert*'s executive editor David Kiefer, MD, peer reviewer J. Adam Rindfleisch, MD, MPhil, AHC Media executive editor Leslie Coplin, and managing editor Neill Kimball report no financial relationships relevant to this field of study.

Integrative Medicine
The Clinician's Evidence-Based Resource on Complementary Therapies [ALERT]

Integrative Medicine Alert,
Integrative Medicine Alert (USPS 017-001) is published monthly by AHC Media, a division of Thompson Media Group LLC, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.
Periodicals Postage Paid at Atlanta, GA, and at additional mailing offices.

GST Registration Number: R128870672.

POSTMASTER: Send address changes to Integrative Medicine Alert, PO. Box 105109, Atlanta, GA 30348.

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$369 per year plus GST (Student/Resident rate: $180 plus GST).

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or severity. Second, because the data were extracted retroactively from a larger, retrospective, case-control study that was not designed to determine if fish oil intake is implicated as either a benefit or risk in prostate cancer risk, controls for other potential factors that may influence risk are lacking. For example, the researchers did not assess any of the participants' dietary intake of omega-3s over time. Other important prostate cancer risk variables — such as smoking status, alcohol use, family history of prostate cancer, and obesity — were not adequately controlled in this study. Additionally, these results are based on only one measure of plasma omega-3 levels taken at one particular moment in time, which can be variable depending on a person's recent dietary habits and other behaviors. A better indicator of long-term omega-3 intake and tissue status is the "omega-3 index," which measures red blood cell levels of eicosapentaenoic acid (EPA) and docosapentaenoic acid (DHA). Although the data presented in this study hint at DHA possibly playing more of a role in prostate cancer risk compared to EPA, this distinction is not clear or definitive.

The story of prostate cancer is a messy one at best. While prostate cancer is the leading diagnosed cancer in men and second leading cause of cancer-related death among men in the United States, only 2.8% of men ultimately die from complications directly related to prostate cancer itself. The lifetime risk for being diagnosed with prostate cancer is 15.9%, while 70% of deaths due to prostate cancer occur after 75 years of age. Even though the majority of men will eventually harbor prostate cancer cells if they live long enough, detection typically will either be elusive with screening or result in morbidity from invasive testing and treatment. This being said, it is still challenging to determine exactly which prostate cancers will go on to be aggressive and life-threatening and which are slow-growing and benign.[1]

Detection is further complicated by the fact that PSA screening is incomplete at best. In its most recent update, the United States Preventative Services Task Force simply recommends against PSA-based screening for prostate cancer (D recommendation). This evaluation is based largely on the fact that approximately 80% of positive PSA tests are actually false-positives. A third of men who eventually undergo prostate biopsy testing report major problems later. Five out of 1000 men will go on to die within 1 month of prostate cancer surgery, while up to three of 10 will experience significant morbidity such as urinary incontinence, bowel dysfunction, persistent pain, and erectile dysfunction. As such, there is convincing evidence that PSA screening leads to significant overdiagnosis and resulting treatment complications.[1]

With this being said, many men and their physicians look toward prevention to avoid this dilemma altogether. Prostate cancer risk is affected variably by age, race, dietary factors, weight, and chronic diseases such as diabetes, obesity, and cardiovascular disease. In general, prostate cancer mortality is significantly lower among Japanese men, but this cultural protection is lost among Japanese men who migrate to the United States and adapt Western habits, including a standard American diet (SAD). For comparison, this effect is also seen in Polish immigrants.[2]

It is easy to see why so much emphasis has been directed toward environmental factors in prostate cancer risk. As such, it has long been supposed that the fatty acid content of varying diets plays a significant role in prostate tumorigenesis. For example, the omega-6 to omega-3 fatty acid ratio of the SAD is 15:1, as opposed to 4:1 in a traditional Japanese diet. It has been proposed that omega-3s slow down tumorigenesis, induce apoptosis, decline proliferation, diminish PSA doubling time, and inhibit androgen-sensitive proliferation of prostate cancer cells as possible mechanisms. Recent studies have even demonstrated that omega-3s were able to prevent progression of laboratory human prostate cancer cell lines, while omega-6s accelerated their growth.[3] Another study went further in showing that a diet rich in omega-3s in mice slowed down prostate tumorigenesis.[4] In a well-done, randomized, controlled study published in 2013 by Safarinejad et

Summary Points

- Among men with prostate cancer, those with the highest short-term and isolated plasma omega-3 fatty acids levels appear to have an increased risk of developing low- and high-grade prostate cancers.
- For prostate cancer mortality prevention, clinicians are advised to encourage patients to adhere to a healthy lifestyle, to exercise regularly, and to avoid tobacco.

al, the case for omega-3s' role in decreasing prostate cancer risk went even further in showing that supplementation with omega-3s actually decreased PSA levels among healthy men. In addition, PSA levels increased significantly over 12 weeks among participants who were given omega-6 fatty acid supplements.[5]

Because lifestyle changes, especially dietary factors, appear to significantly affect the risk for developing prostate cancer, clinicians and patients are in need of guidelines and evidence-based recommendations that may favorably improve their chances. The omega-3 narrative in prostate cancer prevention appeared to be gaining momentum until Brasky et al released their findings showing that omega-3s may actually accelerate prostate cancer among men who have already been diagnosed. If we accept the authors' conclusions, the omega-3 fatty acid and prostate cancer story appears to share similarities with the vitamins and lifestyle (VITAL) study from 2008, which reported higher incidence of lung cancer among smokers who supplemented with vitamin E.[6] In both instances, the trail of evidence appeared to be going in one direction, when the narrative took an abrupt turn among a certain demographic. It has been proposed that high-dose omega-3 supplementation — similar to vitamin E supplementation in smokers — may actually increase oxidative stress, resulting in further DNA damage and thereby increasing the risk for prostate cancer. This mechanism also may be at work in people who have several cardiovascular risk factors, as seen in a recent study in the *New England Journal of Medicine* that showed no improvement in morbidity or mortality when supplemented with 1 g of omega-3 fatty acids daily.[7]

In general, while the evidence overall supports the health and safety claims of omega-3s — particularly through eating a healthful diet[8] — patients diagnosed with prostate cancer or those at high risk for prostate cancer would be well-advised to use some caution with supplementation of high doses of omega-3s in the context of obesity, smoking, or eating a SAD. Nonetheless, the mystery of what lifestyle factors, in what patients, and how various dietary components contribute to prostate cancer continues. For example, one study showed that Yup'ik Eskimos in Alaska, who eat a traditional diet that includes consumption of up to 20 times more omega-3 fatty acids compared to people living in the lower 48 states, have lower rates of diabetes and obesity.[9] In another study of Inuit communities in Canada, where smoking rates are higher than other Canadian region, no increase of prostate cancer incidence was reported.[10] Finally, a similarly designed cohort study found that in a setting of very high fish consumption, no association was found with early or midlife prostate cancer risk, while salted or smoked fish may increase the risk of advanced prostate cancer.[11]

BOTTOM LINES

1) In this study, among men who are eventually diagnosed with prostate cancer, those with the highest short-term and isolated plasma omega-3 fatty acids levels also appeared to have increased risk of developing both low- and high-grade prostate cancers.

2) There are many significant methodological concerns limiting the clinical relevance of the study results.

3) Although there is continuing discrepancy in the medical literature, overall recommendations for patients will largely remain unchanged. For prostate cancer mortality prevention, clinicians are advised to continue encouraging patients adhere to a healthy lifestyle, which means eating a variety of healthy whole foods (including foods high in omega-3 fatty acids such as salmon up to twice a week),[12] getting regular exercise, keeping body mass index < 30, and avoiding tobacco.[13] ■

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ABSTRACT & COMMENTARY

Fish Oil if High Cardiovascular Disease Risk?

By David Kiefer, MD, Editor

SYNOPSIS: In more than 12,000 patients at high risk of cardiovascular events, daily supplementation with 1 g of fish oil (85% eicosapentaenoic acid plus docosahexaenoic acid) did not reduce cardiovascular morbidity nor mortality over approximately 5 years of follow up.

SOURCE: Risk and Prevention Study Collaborative Group. n-3 fatty acids in patients with multiple cardiovascular risk factors. *N Engl J Med* 2013;368:1800-1808.

The authors of this study recruited patients at high risk of cardiovascular (CV) disease from 860 general practitioners in clinical practice throughout Italy. The inclusion criteria for research participants are listed in Table 1. Patients were excluded from this study if they previously had a myocardial infarction, were hypersensitive to omega-3 fatty acids, had poor short-term prognosis, or were unable to provide informed consent.

The 12,513 enrollees in the study were randomly assigned, in a double-blind fashion, to either a 1 g capsule of omega-3 fatty acids (omega-3; n = 6244) or an olive oil placebo (n = 6269) once daily for a median follow-up of 5 years. The omega-3 fatty acid capsule contained the ethyl ester polyunsaturated fatty acids, at least 85% of which were eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in a ratio ranging from 0.9:1 to 1.5:1.

Enrollees had a baseline visit and yearly follow-up visits. These visits were with their general practitioner who collected information about interim health history, CV risk factors, lifestyle, new diagnoses, and changes in medications, in addition to physical examination parameters and laboratory testing. The primary endpoint of this study included time to CV death or first hospitalization for CV causes, both listed as event rates or percentages. Table 2 lists these endpoints and the numerous secondary endpoints of these studies.

The study had an intention-to-treat methodology, in the sense that even patients whose treatment was stopped were followed until the end of the study. This resulted in 12,505 patients being analyzed — 6239 in the omega-3 group and 6266 in the placebo group. Baseline characteristics were similar between the two groups, except for slightly more men and people on calcium channel blockers in the omega-3 group. The most common criteria being met for inclusion in the study was the presence of diabetes mellitus plus one or more CV risks (47.9% of patients).

Summary Points

- The patients in this research study were at high risk for cardiovascular (CV) events.
- Supplementation was with a 1 g fish oil capsule once daily, containing 85% eicosapentaenoic acid plus docosahexaenoic acid.
- The primary endpoints were CV death or hospitalization for CV causes; there were numerous secondary endpoints also analyzed.
- No difference in the primary endpoints were seen for the omega-3 group as compared to the placebo group, though a few minor differences (i.e., heart failure admissions) were seen in some of the measurements.

Table 1: Criteria for Inclusion

"Multiple cardiovascular risk factors" (at least four of the following)

- 65 years old or older
- Male gender
- Hypertension (clinical diagnosis or use of antihypertensive medications)
- Current smoker
- Elevated lipids (clinical diagnosis or use of cholesterol-lowering medications)
- Body mass index (BMI) ≥ 30
- Family history of premature cardiovascular disease (cardiovascular disease < 55 years old in patient's father or a brother, or cardiovascular disease < 65 years old in patient's mother or a sister)

"Clinical evidence of atherosclerotic vascular disease"

- Angina pectoris
- Peripheral artery disease
- Previous cerebral vascular accident (ischemic) or transient ischemic attack
- Previous arterial revascularization treatment

"Any other condition putting the patient at high cardiovascular risk in the opinion of the patient's general practitioner"

- Details not specified

After a median follow up of 5 years, only a few differences were noted in the omega-3 group vs the placebo group (*See Table 3*). No differences were noted for blood pressure, LDL cholesterol, total cholesterol, blood glucose, hemoglobin A1C, nor CV drug prescriptions. The primary event rate occurred in 11.8% of patients: 11.7% in the omega-3 group and 11.9% in the placebo group; this was statistically similar (hazard ratio, 0.97; confidence interval, 0.88-1.08; $P = 0.64$). Similarly, there was no difference between the two groups for any of the secondary endpoints as listed in Table 2.

The most common adverse effects were gastrointestinal, although the incidence was similar between the omega-3 and placebo groups. Two severe cases of epistaxis occurred in the omega-3 groups; both of these people were taking blood-thinning medication. Interestingly, "bleeding" as an adverse event was similar between the two groups (n = 16 in the omega-3 group and n = 12 in the placebo group, $P = 0.44$).

As an aside, the funding for this trial came from Pfizer and two societies, Sigma Tau and an antibiotic production organization, but the authors explicitly stated that these groups had no role whatsoever in the planning nor implementation of the research nor in the analysis of the results.

COMMENTARY

This study advances our knowledge about the use of fish oil supplementation. Common omega-3 recommendations involve the consumption of two servings of fish twice weekly for primary CV prevention, and 1 g of EPA plus DHA daily for secondary CV prevention.[1] This article is one of the first, and largest, to examine fish oil supplementation for primary CV prevention in a high CV risk population. If we believe the veracity and applicability of these results, then it appears that fish oil supplementation does not function in this capacity for this demographic.

The results of this study agree with a recent meta-analysis of any CV outcomes across demographics.[2] This congruence improves its believability. What may detract from its relevance to clinical medicine in the United States is the location of the trial. The Italian patients studied, likely closely approximating the country as a whole given the large number of clinics and geographic locations covered, had a lower than expected rate of "hard endpoints," or CV morbidity and mortality, especially as the trial progressed over the years. The authors comment that there could have been a significant effect of preventive CV measures throughout Italy or dietary habits (the Mediterranean diet). It could be argued the typical diet in the United States

Table 2: Primary and Secondary Endpoints Measured

Primary Endpoints	Secondary Endpoints
Time to cardiovascular disease death	Time to death
Time to first hospitalization for cardiovascular causes	Time to nonfatal myocardial infarction
	Time to nonfatal stroke
	Death from coronary heart disease
	Sudden death from cardiac causes

Table 3: Two Differences Between Omega-3 Group and Placebo Group After 5 Years of Follow Up

Omega-3 Group	Placebo Group	Statistics
Triglycerides lower by 28.2 mg/dL	Triglycerides lower by 20.1 mg/dL	$P < 0.001$
"Slight increase in HDL"		Not provided
96 admissions for heart failure	142 admissions for heart failure	$P = 0.002$
Lower primary event rate for women than for men		HR = 0.82, CI = 0.67-0.99, $P = 0.04$

diverges from that seen in Italy, and that a "nudge" from omega-3 supplementation might make more of a CV difference. A U.S. study of the size and methodological quality as seen in the Italian analysis would be welcome to shed light on this.

Possibly a minor detail, but there are different formulations of omega-3 fatty acids that may affect physiology and, therefore, clinical outcomes. In this study, the product used was an ethyl ester omega-3, whereas other studies have used a triglyceride form. Manufacturers of each product type try to tout the benefits of their particular form of omega-3, but the medical literature is relatively mute on the topic. A not-so-recent review doubted that different omega-3 sources had CV relevance,[3] but the possibility that omega-3 form is important, or not, needs to be clarified at some point. In addition, most experts use much higher doses (2-4 g of DHA plus EPA daily) of omega-3 to have meaningful physiological effects, such as the lowering of serum triglycerides.[1] Therefore, this study may not have documented improvements in the primary outcomes simply due to underdosing.

Omega-3 research does not seem to be waning, but rather more, and more specific, studies are likely to continue to be published in the years to come. All of this should help to clarify the dose, form (supplementation, diet), and demographic for which this intervention is most useful or minimally effective. That said, the current state of the literature still supports the normalization of the omega-6 to omega-3 ratio (through the lowering of omega-6 intake and the increase of omega-3 intake through diet or supplementation) for inflammatory disorders (i.e., arthritis) and fish oil supplementation for hypertriglyceridemia. Intriguing results also exist for many psychological diagnoses — such as mood disorders and attention deficit disorder, and during pregnancy and lactation — that warrant our clinical attention, especially given omega-3's favorable side effect profile. ■

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DEPRESSION

ABSTRACT & COMMENTARY

Positively Old: MBSR and the Elderly

By Russell H. Greenfield, MD

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Dr. Greenfield reports no financial relationships relevant to this field of study.

SYNOPSIS: Elderly patients with mild-to-moderate depressive symptoms may experience improvement in affect with the practice of mindfulness-based stress reduction.

SOURCE: Gallegos AM, et al. Emotional benefits of mindfulness-based stress reduction in older adults: The moderating roles of age and depressive symptom severity. *Aging Ment Health* 2013; May 22 [Epub ahead of print].

Regular practice of mindfulness-based stress reduction (MBSR) benefits a wide variety of patients in disparate health circumstances, yet one patient population where the impact of MBSR training has yet to be explored indepth is the elderly. Old age is often accompanied by harsh realities that may include a decline in physical health as well as emotional stressors. While many weather these developments, they are nonetheless challenging for even the most optimistic and resilient of elderly patients, in large part because of a perceived, and, often real, sudden and increasing lack of control. The authors of the current study previously explored this realm and developed what they call the Motivational Theory of Life-Span Development.[1] Using this theory as a framework, they sought to examine the effects of age and depressive symptom severity on changes in positive affect among older (≥ 65 years), community-dwelling adults (n = 200) randomized to either an 8-week MBSR program or a waitlist control group.

The theory developed by the investigators suggests that all people, especially the elderly, best maintain control and adapt to changing opportunities by developing strategies for replacing unattainable goals with more appropriate ones. Primary control is important to everyone and can be thought of as directed at changing the environment to bring it in line with an achievable desired outcome. Adults lose much of their capacity for primary control with increasing age, and depression worsens this circumstance; but older adults might compensate by employing secondary control processes, defined as changing oneself so as to be better aligned with environmental forces, even when those forces restrict available options.[2] Interventions that augment secondary control provide emotional benefits in uncontrollable circumstances and are important for promoting optimal emotional aging. In this context, MBSR helps teach participants to increase nonjudgmental awareness of their momentary emotional and physical experiences and improve regulation of affect by increasing attention, awareness, and acceptance of emotions as they arise moment-to-moment.

Subjects were recruited through newspaper advertisements and flyers posted at primary care offices. Exclusion criteria included potential cognitive or uncorrected sensory impairment, major depression with psychotic features, bipolar disorder, and substance abuse within the past year. Once enrolled, subjects were randomized to active (MBSR) and control (waitlist) groups. The eight-week MBSR program consisted of nine group sessions (15-20 members), seven of which were 2 hours in duration and one, at mid-treatment, that was 7 hours long.

Summary Points

- All people, including the elderly, adapt best to changing circumstances by appropriately adjusting their goals.
- Mindfulness-based stress reduction training may help the aged maintain a healthy sense of control, provided they are not severely depressed, through cultivation of nonjudgmental acceptance.

Practices emphasized during these meetings included yoga (mindful movement), sitting meditation (mindful awareness of one's experience while sitting), informal meditation (while walking or engaged in other activities), and the body scan (serial attention to the sensations of different regions of the body). Activities were adapted on an individual basis to accommodate the presence of limitations, including physical and sensory impairments (the authors give the example of sitting yoga for those using wheelchairs).

Participants were administered the Center for Epidemiologic Studies Depression Scale, Revised (CESD-R), the Hamilton Rating Scale for Depression (HAM-D), and the Positive Affect (PA) scale of the Positive and Negative Affect Schedule (PANAS) at baseline, at the end of treatment (8 weeks), and 6 months thereafter by one of three masters-level research assistants. Potential confounders including gender, comorbidity, and level of education were controlled for, and subjects 70 years or older were compared to younger participants. Regression was used to determine whether age, depressive symptom severity, or their interaction over time were associated with changes in the positive affect.

The groups were similar at baseline save for slightly greater depressive symptom severity in those receiving MBSR. After 8 weeks, 54% of participants in the MBSR group experienced improvements in positive affect (average $d = 0.12$) compared to 46% in the waitlist control group (average $d = 0.00$). Analysis of positive affect outcomes at the 6-month follow-up revealed significant group by baseline depressive symptom severity (ß = -0.17, $P = 0.02$) and group by baseline depressive symptom severity by age (ß = -0.14, $P = 0.05$) interactions; as a result, analyses examining the contributions of age and baseline depressive symptom severity to changes in positive affect were conducted separately for both the MBSR and waitlist control groups. The findings are noteworthy: Older MBSR group members who had more severe baseline depressive symptoms

experienced less improvement in positive affect at treatment completion (ß = -0.21, *P* = 0.02) and at 6-month follow up (ß = -0.30, *P* = 0.003) than age-matched subjects who were happier at baseline. Effects related to age (ß = 0.05, *P* = 0.66) and the depressive symptom severity by age interaction (ß = -0.03, *P* = 0.75) were not significant. MBSR group members ≥ 70 years with low baseline depressive symptom severity had the greatest improvement in positive affect at the 6-month follow-up, whereas those ≥ 70 years with worse baseline depression had the poorest outcomes (ß = -0.25, *P* = 0.01). Age and depressive symptom severity were not associated with changes in affect in the waitlist control group. The authors conclude that MBSR improves positive affect for older adults in the absence of severe depression.

COMMENTARY

MBSR helps cultivate nonjudgmental acceptance of one's circumstances. Based on this study's findings, by extension it also enhances secondary control provided that severe depression is not present, where MBSR has the potential to worsen affect.
The authors frequently promote their previously published Motivational Theory of Life-Span Development, but it seems appropriate as the theory is convincing and functions well as a backdrop to help explain the potential advantages of MBSR for older adults. Limitations of the trial are few and include potential for bias (voluntary sign-ups), unequal randomization (slightly worse baseline depression in the MBSR group), and limited ethnic diversity, but overall the study was well done.

Practitioners in the trenches know that some elderly patients manage the situational changes associated with aging better than others. Those who by nature are more optimistic may not need any specific interventions to gird their inner resilience, but for those for whom the burdens of life have become increasingly challenging MBSR may prove a valuable tool. Old dogs can learn new "tricks" — MBSR seems a good one to consider sharing with select elderly patients. ■

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Epigenetics and Integrative Medicine

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Dr. Pantuso reports no financial relationships relevant to this field of study.

A popular field that is being discussed in medical research, in popular science, and by the media, epigenetics is broadly defined as the study of the changes in gene expression that occur on the DNA sequence and are heritable. These changes, or epigenetic marks, occur as modifications on the DNA sequence itself or to associated proteins that affect the transcription of the genome during normal development and in response to environmental factors.[1,2] Part of the excitement of epigenetics is that it followed in the steps of genome-wide association studies (GWAS). There have been numerous GWAS investigating the relationships between DNA variants and diseases.[2] The results of these GWAS have not been very fruitful in identifying gene variants as the causes of disease; however, epigenetic studies are yielding more results along these lines.[2]

Epigenetic marks have been demonstrated to be involved in a wide variety of biological processes from X-chromosome inactivation and imprinting to the state of health and disease in humans.[3] With epigenetic regulation being involved in diabetes, cancer, cardiovascular disease (CVD), schizophrenia, autism, and numerous other illnesses, it is no wonder that it is an important field and a "hot topic."[2-6]

It has long been recognized that there is an association between fetal nutrition and chronic diseases in later life, and epigenetics is beginning to shed some light on this relationship. Epigenetic mechanisms also have been able to demonstrate effects of the environment (including diet) on gene expression in animal models and humans.[4]

Due to the rapidly expanding field of epigenetics, information overload is a common phenomenon. A basic understanding of both the history of the field and the mechanisms of regulation are required to fully understand the magnitude of the discoveries in epigenetics.

This article will review fundamental epigenetic concepts, relevant research (especially regarding nutrition), and the implications for the field of integrative medicine.

BACKGROUND

There is confusion in the field of epigenetics, both from the definition of epigenetics itself and from the sheer volume of data. The term *epigenetics* traces back to the 1940s when C.H. Waddington, a British embryologist, first used the word to describe how a cell is able to maintain the same observable characteristics or phenotype through cell division.[7] It is interesting to note that DNA was not identified as the transforming particle until 1943, through the Avery-Macleod-McCarty experiment, and was not discovered to be a hereditary unit until the Hershey-Chase experiment in 1952.[8] Waddington's term epigenetics was not widely used until the discovery of DNA methylation in 1975 by Holliday and Pugh.[9] Holliday and Pugh proposed that DNA methylation was a molecular mechanism that explained Waddington's epigenetic concept.

The explosion of studies focusing on epigenetic regulation appears to have started in the early 2000s. Prior to that time, there were less than 100 published articles with epigenetics in the title, compared to 1300 articles by 2010.[9] Much of this increase in epigenetic research occurred with the advent of Next Generation Sequencing, which allows for more samples to be sequenced in a shorter period of time at a decreased cost. The first commercial device was available in 2005.[2]

EPIGENETIC MECHANISMS

Currently, epigenetics encompasses the mechanisms of DNA methylation, histone modifications, and regulation by noncoding RNAs in DNA transcription. Researchers are using these epigenetic mechanisms, or marks, to understand the effects of both the fetal and adult environment on gene expression. The most discussed and researched type of epigenetic mark is known as DNA methylation.[10] Although DNA methylation is the classic example of epigenetics, many other post-translational mechanisms regulate transcription, such as modifications to the histone proteins that keep the DNA tightly wound into chromatin and noncoding RNAs.

DNA METHYLATION

DNA methylation is the process where methyl groups are added to a cytosine preceding a guanine at the 5' end of the DNA; these are called CpG sites. The methyl groups are covalently attached to the cytosine by the enzyme DNA methyltransferase (DNMT) from the methyl donor SAM. Although a number of enzymes are involved in DNA methylation, DNMTs are the best studied. CpG islands are regions of DNA that are rich in CpG sites and occur near gene promoters. Currently, it is understood that methylations at CpG islands will turn off gene transcription by preventing the transcription machinery from binding to the promoter region of the gene.[10]

Summary Points

- Epigenetics encompasses the mechanisms of DNA methylation, histone modifications, and regulation by non-coding RNAs in DNA transcription.
- Clinical applications of epigenetics involve the effects of diet and environment on disease processes, mediated by changes in gene expression.
- Some of the best epigenetic research resulted from isolated nutrients, such as folate, or the adult disease effects of malnutrition during early life or fetal development.

Between 70-80% of the cytosines in DNA are methylated in the healthy human genome. Changes in the percentages of DNA methylation are associated with both health and disease.[2] Decreased methylation of the genome (hypomethylation) is associated with increasing age and increased cancer risk.[11,12] However, there is also evidence to suggest hypermethylation at tumor suppressor gene promoter sites also may lead to increased carcinogenesis. It is becoming more clear that the particular gene promoter affected by the methylation status may be more important than the global methylation status of the genome. There is controversy over whether there is an enzyme that actively removes methyl groups from the DNA or if hypomethylation is the result of decreased methyl donors or decreased activity of DNMTs when DNA replication occurs.[10,11]

The preeminent studies demonstrating the importance of DNA methylation were performed in mice; these studies demonstrated that offspring from mothers supplemented with methyl donors were brown in color and lean (Agouti phenotype) compared to non-supplemented mothers who produced offspring that were yellow in color, obese, and had increased incidence of diabetes and tumors.[2]

HISTONE MODIFICATIONS

DNA is tightly packed into the nucleus as chromatin, which consists of 147 base pairs of DNA wrapped around a histone octamer. When DNA transcription occurs, the histones have to open to allow access to the DNA. Modifications are made to histone proteins to control transcription

through phosphorylation, acetylation, sumoylation, methylation, ubiquitylation, prolyl-isomeryzation, and ADP-ribosylation, and these enzymes rely on a number of cofactors and metabolites (*see Table 1*).[13,14] In general, increased histone tail acetylation signifies areas of active transcription while decreased acetylation is associated with less activity.[14] In contrast to DNA methylation, histone tail methylation can signify increased or decreased transcription. Due to the number of different modifications that can occur on histones regulating DNA transcription, a lot of research still remains to be done to determine clinical relevance.

NONCODING RNAS

Noncoding RNAs (ncRNA) are characterized by size as micro-RNAs, piwi-interacting RNAs (piRNAs), small nucleolar RNAs (snoRNA), and long ncRNAs (lncRNAs), and have numerous regulatory functions in transcription. This is a broad topic beyond the scope of this review article.[2,15]

PATHWAY INTERACTION

The communication between all of these epigenetic pathways is still being elucidated. For example, the enzymes that catalyze histone and DNA methylation are supplied with methyl donors by related pathways and may be in competition.[14] In addition, there are data supporting that modifications to histones may increase DNMT enzyme activity, further repressing transcription. Relevant to the dietary and supplement effects on these interactions, there is active in vitro cell research investigating dietary compounds involved in histone modifications.[4,16]

HUMAN RESEARCH

Epigenetic research relevant to the field of integrative medicine is mostly centered on the effects of the environment on DNA expression. One example is the effect of diet on gene expression. One hypothesis is that DNA methylation patterns are established early in development but that alterations, such as from diet, lead to diseases in adulthood; this has actually been documented in animal and human models. One interesting observation is that identical twins have similar epigenetic patterns in childhood, but DNA methylation and histone acetylation differences are noted in later life.[2,4,17]

Fetal nutrition. The concept of the fetal nutritional environment having long-term effects on the adult is now being referred to as the Developmental Origins of Health and Disease Hypothesis, which is based on the pivotal work of a few research groups that demonstrated low birth weight is associated with CVD, insulin resistance, and hypertension.[17] Other epidemiological studies also have demonstrated the link between low birth weight and CVD, insulin resistance, cancer, obesity, and some behavioral disorders.[2,4,17] There may be an epigenetic basis for these findings.

The Dutch Cohort Study is one of the classic research trials supporting the concept that epigenetic changes occurring during fetal development are responsible for long-term health and disease. The Dutch Cohort study investigated the effects of a 6-month famine (Dutch Hunger Winter) on pregnant mothers and fetuses who suffered malnutrition from the World War II Nazi blockade. The adult children of mothers pregnant during this episode show increased incidence of CVD, metabolic disorders, obesity, and breast cancer, as well as alterations in epigenetic marks. It is widely accepted that these genetic changes and diseases were the result of nutritional imbalances in utero. Specifically,

Table 1. Epigenetic Modification and Sources of Cofactors[13,14]

Modification	Cofactor Required	Sources of Cofactors
DNA methylation	SAM	Folate, choline, B-group vitamins, methionine
5-methyl-cytosine oxidation	Oxygen, α-ketoglutarate, Fe(II)	Glutamic acid, Fe
Histone methylation	SAM	Folate, choline, B-group vitamins
Histone demethylation	Oxygen, α-ketoglutarate, Fe(II) FADH	Glutamic acid, Fe, vitamin B2
Histone O-linked glycosylation	UDP-GlcNAc	
Histone acetylation	Acetyl-CoA	
Histone deacetylation	NAD+	Dietary tryptophan, niacin
Histone ubiquitylation	ATP	Adenosine
Histone sumoylation	ATP	Adenosine
Histone ADP-ribosylation	NAD+	Dietary tryptophan, niacin
Histone deamination	Ca2+	Calcium
Histone isomerization	None identified	
Histone phosphorylation	ATP	Adenosine
Histone crotonylation	Crotonyl-CoA	

the Dutch Cohort Study demonstrated lower methylation status of genes involved in growth, metabolism, and CVD; some of the genes involved are IGF2, IL10, GNAsAS, INSIGF, LEP, ABCA1, and MEG3.[18]

According to other research, dietary factors influence the epigenome during both "critical windows" and "dietary transitions." Critical windows are identified as periods of fetal or neonatal development, while dietary transitions occur over longer time periods in adults.[4]

NUTRIENTS

A number of different nutrients, including folate, choline, betaine, and vitamins B2, B6 and B12, have been shown to be important in epigenetic regulatory pathways. The most well-studied nutrient is folate, which has a role in the one-carbon metabolism pathway. Vitamins B2, B6, and B12 are used as cofactors in the one-carbon metabolism, which maintains the cellular methyl donor SAM used in DNA methylation and histone methylation.[17-19] Many of the enzymes responsible for the epigenetic marks in DNA methylation, histone modification, and noncoding RNAs also are required as dietary cofactors (*see Table 1*). Also, in vitro cell culture studies have demonstrated that botanical extracts and phytochemicals have epigenetic effects on DNA transcription.[4,17]

Folate. The folate story is both fascinating and complicated. Some data show that DNA hypomethylation may be the result of low folate status and is associated with increased cancer risk; this points to the importance of dietary folate. Also, well known is the necessity of folate during pregnancy to prevent neural tube defects. Furthermore, folate is required to prevent homocysteinemia, a complex mechanism of action. Briefly, folate's role in homocysteine metabolism starts with the reduction of folate to tetrahydrofolate (THF), then a conversion to 5,10-methylene THF, and on to 5-methyl THF via the enzyme methyltetrahydrofolate reductase (encoded by the MTHFR gene). Methyl groups from 5-methyl THF are dontated to homocysteine, which coverts it to methionine in the one-carbon metabolism pathway. The one-carbon pathway uses the cofactors vitamins B2, B6, and B12 as mentioned above. With the discovery of the MTHFR gene and its numerous variants, which have varying degrees of methyltetrahydrofolate reductase activity, methylated folate has become a popular supplement. However, the effects on specific gene expression of these supplements or additional folate supplementation in folate-replete populations are unclear and require further investigation.[18-21] Hopefully, further research will identify how and why a particular gene promoter is selected to be methylated. Until then, many experts caution about supplementing with too much folate.

Choline and betaine. Dietary choline is oxidized to betaine, which is a methyl group donor in the conversion of homocysteine to methionine. Animal studies have demonstrated a complex relationship between choline/betaine supplementation; there appears to be methylation that occurs at specific gene regions compared to non-supplementation.[4]

Amino acids. Methionine is the precursor to SAM and is one of the essential amino acids, in that it is required through dietary intake. Data suggest that methionine supplementation causes hypermethylation at specific gene regions. Research studies on methionine supplementation demonstrate that there is an alteration in the one-carbon metabolism; however, it is unclear how methionine effects DNA methylation. Diets low in homocysteine, which is the precursor to methionine, may lead to hypomethylation.[2]

Botanicals. In vitro cell line studies investigating the effects of *Allium tuberosum* L. and *Artemisia dracunuculus* L. reduced DNMT expression.[4,16] Epigallocatechin-3-gallate (EGCG), found in green tea and soybeans, inhibits DNMT activity in a cell line. Genistein also has been found to have effects on DNA methylation in mice; however, more research is needed to further unravel the effects on the epigenome.

IMPLICATIONS FOR THE FIELD OF INTEGRATIVE MEDICINE

Epigenetic research is still expanding and much research needs to occur to detail the interconnectedness of epigenetic regulation. Despite the promise of being able to theoretically manipulate epigenetic mechanisms to treat disease in humans, there are still many unanswered questions. For example, how do individual nutrients (i.e., folic acid) affect the global methylation status as well as the methylation of single target genes? Some experts point out that until more is known about the interconnectedness of these pathways, simply supplementing everyone above-and-beyond a nutritionally sound diet may be contraindicated because the dietary cofactors could affect the epigenome in unknown ways.

Epigenetic research may help show the mechanism of action of integrative therapeutics and the interactions between diet and gene expression. This area of research, known as nutrigenomics and metabolomics, may be able not only to offer patients

knowledge about their nutritional and metabolic gene expression but also to identify potential targets for mechanisms of action for diet, lifestyle, and other integrative medicine treatments. With a basic understanding of the field of epigenetics, providers eventually may be better able to guide patients through this advancing field and apply diagnostic and treatment approaches appropriately. ■

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CME QUESTIONS

1. Increased prostate cancer risk is associated with all of the following *except*:
a. obesity.
b. standard American diet.
c. diagnosis of benign prostatic hypertrophy.
d. advanced age.

2. The results of a recent research trial show that 1 g of fish oil supplementation:
a. reduces recurrence of nonfatal myocardial infarction.
b. does not affect cardiovascular morbidity nor mortality in high cardiovascular risk people.
c. significantly affects secondary cardiovascular disease prevention.
d. slightly increases the risk of fatal stroke.

3. In the context of the Motivational Theory of Life-Span Development, mindfulness-based stress reduction can be considered an effective tool to:
a. increase primary control.
b. increase secondary control.
c. improve affect in severely depressed elderly patients.
d. distract patients from thinking about unhappy personal circumstances.

4. DNA is methylated by which of the following?
a. DNMT
b. mi-RNA
c. Histone acetylase
d. SAM

[IN FUTURE ISSUES]

Vitamin D supplementation and Parkinson's disease

Telomere length and supplements

Anthocyanin intake and MI in women