REPORT

Defend Against DNA Destruction

By Alex Richter



As each second goes by, your DNA is being attacked by internal and environmental factors that can result in potentially lethal mutations.1

This accumulated DNA damage underlies most of the conditions that kill us, such as atherosclerosis, cancer, and Alzheimer's disease.2-5

Fortunately, there are steps that you can take to protect your DNA from the onslaught of around-the-clock damage.

Scientists have demonstrated that a special group of plant compounds known as *xanthophylls* have shown protective effects against DNA damage.6 These molecules have been researched for their ability to prevent DNA damage and reduce disease risk. Xanthophylls have been shown to not only prevent deadly genomic damage but they simultaneously boost your body's natural DNA repair mechanisms which help it recover from damage that's already occurred.7,8

Widespread Impact of DNA Damage

The DNA molecule is extremely vulnerable to injury from internal and external sources.9,10 Oxygen radicals, toxins, and even sunlight all induce breaks, nicks, and other injuries to the delicate DNA strands.11 Without knowing it, you experience millions of such DNA "accidents" each day. Fortunately, your body has no fewer than five interrelated mechanisms for repairing that damage.9 Those mechanisms are so efficient and accurate that your cells and tissues remain stable and disease-free year after year.9 Periodically, even the most efficient and accurate repair systems make small errors. And these errors add up. Scientists now recognize that the ability to identify and repair DNA damage is the leading discriminator of who does and does not get cancer and probably many of the other diseases of aging.9,10,12

CAROTENOID CONSUMPTION LOWERS CANCER RISK

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Ovarian Cancer	55%56
Non-Hodgkin Lymphoma	46%13
Invasive Breast Cancer	17%57

Lung Cancer	17%16
Estrogen Receptor-Negative (Treatment-Resistant) Breast Cancer	13%58

People with the highest intake of the caroteniods lutein, zeaxanthin, and astaxanthin are protected against developing many different kinds of cancers.

Xanthophylls Fight DNA Damage



Xanthophylls are concentrated in yellow, orange, and deep green leafy vegetables.13,14 Epidemiological studies show that people who consume large amounts of fruit and vegetables have lower rates of cancer and other DNA damage-related diseases.15,16 But studies that take a closer look show that supplying up to **8 servings** of carotenoid-containing fruits and vegetables per day don't demonstrate a reduction in DNA damage or improvement in repair mechanisms.17Eating **12 servings** per day did produce some benefit particularly with regards to reduction of damaging inflammatory molecules, but most people can't sustain that level of vegetable consumption.18 True DNA protection seems to require supplementation to achieve higher levels of these valuable nutrients in your blood.

When human volunteers took capsules containing concentrated xanthophylls, they demonstrated a **40%** reduction in markers of DNA damage in their white blood cells.19 Individually, **lutein**, **zeaxanthin**, and **astaxanthin** supplements each reduce oxidative

stress and DNA destruction in both animal and human studies.20-23 Doses of **4** to **12 mg/day** of xanthophylls, alone or in combination, have been reported to reduce DNA damage in various studies.24,25

Let's turn now to the compelling body of science that demonstrates how these three xanthophylls can work to prevent catastrophic age-related diseases such as cancer and eye disease by protecting DNA from damage.

Xanthophylls Prevent Cancer

Scientists estimate that poor nutrition and lifestyle habits may play a role in up to **80%** of colon, breast, and prostate cancers and **33%** of all other cancers, including inadequate intake of nutrients that prevent DNA damage and promote DNA repair.12,26 Large epidemiological studies consistently show that higher intake of foods rich in lutein, zeaxanthin, and astaxanthin reduce the risk of several different cancer types.16,27

Laboratory studies reveal the reasons for this impressive protection. When tumors are experimentally implanted into mice supplemented with xanthophylls, the rate of tumor growth and the final size of the tumors are reduced by as much as **40%**, compared with unsupplemented animals.28-30 The number of tumors triggered by exposure to a carcinogenic chemical can be

reduced by **55%** in animals supplemented with xanthophylls such as lutein.29 It takes supplemented animals significantly longer to develop those artificial cancers.31-33 How do the xanthophylls exert their powerful anticancer actions?

They do it through a number of mechanisms that strike at different targets throughout the cancer development process:

- They block cancer initiation by limiting DNA damage and strengthening DNA repair mechanisms.12,26
- They suppress genes that promote tumor growth after cancer initiation.34
- They turn on genes that suppress tumor promotion.30
- They reduce inflammation that can promote cancer growth and spread.33-35
- They switch on cancer cells' defective suicide programming (apoptosis), helping to shrink existing cancers and prevent metastatic spread.30
- They slow the development of new blood vessels needed by a rapidly-growing tumor, starving it of its vital nutrient and oxygen supplies.30

Research has shown that supplementation with lutein, zeaxanthin, and astaxanthin boosts the immune system in ways that help it identify and destroy cancerous cells in their earliest stages.29,31 Most scientists today recognize that, after prevention of DNA damage, this kind of "immune-surveillance" is an essential and efficient means of preventing a full-blown cancer from emerging.35 The effects of the xanthophylls on skin cancer, the most common cancer in the United States, are especially prominent. Sunlight, and especially its ultraviolet rays, trigger high rates of DNA damage in skin cells that initiate certain types of skin cancer.36,37 Ultraviolet radiation weakens the immune system's anti-cancer surveillance mechanisms.33

People with the highest intake of lutein and zeaxanthin have a 53% lower risk of developing skin cancer compared to those with the lowest intake levels 38 Studies show that supplementation.

cancer compared to those with the lowest intake levels.38 Studies show that supplementation with xanthophylls reduces skin's unhealthy responses to ultraviolet light and enhances its resistance to cancer development.36,37 Increased survival time in an animal model of skin cancer has been demonstrated as a result of supplementation.37

Interestingly, lutein, zeaxanthin, and astaxanthin supplements reduce light-induced skin aging, again in large part because of their ability to combat age-promoting DNA damage.37 Their unique molecular structure seems to make them especially potent at taming the destructive effects of light bombardment on vulnerable tissues. Nowhere is that protection more essential than in the retina of the eye, as we'll see next.

What You Need to Know DEFEND YOUR DNA WITH CAROTENOIDS

- Damage to DNA, the universal blueprint for life, is a fundamental cause of aging and agerelated chronic disease.
- DNA repair mechanisms begin to fail with advancing age, resulting in accumulation of damaged DNA throughout the body.
- Growing evidence implicates DNA damage and impaired repair mechanisms in the causation not only of cancer, but of the eye disease called age-related macular degeneration (AMD) as well.
- A special group of carotenoid nutrients, the xanthophylls, combat DNA damage and boost DNA repair mechanisms.
- Supplementation with the xanthophyll nutrients lutein, zeaxanthin, and astaxanthin may help to prevent or slow the development of cancer and other age-related disorders such as AMD.

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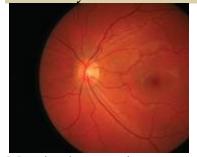
Carotenoids Prevent AMD

WHAT IS AGE-RELATED MACULAR DEGENERATION?

The *macula* is the part of the retina that's most densely packed with vision-producing nerve cells. Despite its tiny size (about **5 mm** in diameter), the macula accounts for the majority of our vision, and virtually all of our "central vision" (what we see when we look directly at something.)

The intense flow of light onto the macula, and the steady production of free radicals by its intensely active mitochondria, imposes massive stresses on the cells in the region. Over time, they can begin to die off, producing a growing "blind spot" directly in the center of our visual field.39 That condition is called age-related macular degeneration, or AMD.

People with early AMD may think they are having trouble focusing, but in fact they simply can't see well in regions directly in front of their eyes. As time goes on, they develop a sort of "donut" vision able to see clearly around the edges but unable to see at all in the center. Because we need our central vision to read, watch television, or do most other vision-requiring tasks, AMD produces a significant reduction in the quality of life, and in fact can leave many people functionally blind.39



Macular degeneration may cause abnormal new blood vessels to grow under the retina and leak fluid an blood. This is one of the most common causes of decreased vision after age 60.

Age-related macular degeneration, or AMD, produces more irreversible loss of vision than any other single cause.39,40 As we've seen, AMD is the result of constant assault on retinal cells by light energy, which damages their mitochondrial DNA. The retina is protected by cells packed with lutein, zeaxanthin, and meso-zeaxanthin (formed from lutein in the retina). These three nutrients produce light-absorbing characteristics that protect the light-sensing cells from damage.41-44

But levels of these three nutrients in retinal tissue decline with age, as does their dietary intake, leaving your retina — and your vision— increasingly vulnerable to damage.43,44 DNA damage and repair are essential in understanding *age-related macular degeneration*. In this case, damage to DNA in mitochondria is the culprit.45,46 Mitochondria generate the power for all

of our cells and they are especially important in tissues with high energy demands, such as the heart muscle, nerve tissue, and cells in the retina.

Mitochondrial DNA is highly vulnerable to damage both by light and by oxidant stress, and it has limited repair mechanisms.45,47 Unrepaired mitochondrial DNA damage causes those cells to become unstable, malfunction, and eventually die, leading to the loss of central vision we identify as age-related macular degeneration.47 And the more severe the DNA damage, the more advanced the damage to the retina in AMD.48

You can replace your dwindling stores of retinal pigment, however, by raising your consumption of these xanthophyll nutrients.

Studies show that people with the highest intake of xanthophylls such as lutein, zeaxanthin, and astaxanthin are at **35%** less risk of developing the most serious form of AMD, so-called "wet," or neo-vascular disease.49 High xanthophyll intake provides up to a **55%** reduction in risk of the less severe, but still disabling, "dry" form of AMD. 49

Unfortunately, you can't get enough of these protective xanthophylls from your diet alone.44 Supplementation at fairly high levels is required in order to restore protective levels of retinal pigment.50

Supplementation studies demonstrate two important and related outcomes of increased xanthophyll consumption. First, people who supplement with these nutrients develop greater concentrations of protective retinal pigments, resulting in improved light protection in their eyes, and lower risk for AMD.41,44,50-52

Second, supplemented people see better. Vision testing shows increased visual acuity in AMD patients taking xanthophyll supplements. One study demonstrated a **5.4 letter** improvement on the standard office eye chart,40 while another showed an incredible **1.5 line** improvement.53 The ability to see visual contrast improves with xanthophyll supplementation, as does overall retinal sensitivity to visual images.40,52 Xanthophyll supplementation produces objective improvements in the intensity of electrical impulses produced by the retina, a direct measure of increased visual functioning.54

These improvements in retinal pigmentation and visual function have been seen with daily doses of lutein, 12 mg, and zeaxanthin, 1 mg, though 10 to 20 mg have been found to be safe daily doses of each nutrient.41,44,50,51,55 Studies using lower doses of lutein (up to 6 mg/day) generally fail to show any effect.52 Products containing free lutein, as opposed to lutein bound up to other molecules, appear to have superior effectiveness.55 You may be able to protect vital eye structures by supplementing with the omega-3 fatty acid DHA, 800 mg/day as well.41 Big Pharma wants to sell expensive drugs that have only limited benefits (and many side effects) in managing AMD, but experts now agree that supplementation with xanthophylls is "a simple, cost-effective public health intervention that might help to decrease the incidence of AMD."39

C3G OFFERS MORE HELP FOR AGING EYES

AMD is the most common cause of major vision loss in older people, but it is far from the only one. Almost everyone suffers from progressive loss of night vision with age. That "night blindness" is the result of slowed regeneration of a pigment called "rhodopsin" that the eye relies on for detection of very low levels of light.

Studies show that a natural plant compound, an anthocyanin called *cyanidin 3-glucoside*, or C3G, can accelerate the regeneration of rhodopsin, potentially restoring dim-light visual sensitivity.59,60 C3G, derived from natural dark berries, is therefore a promising addition to any supplement meant to combat age-related vision changes.

Summary



Damage to DNA is increasingly being understood to underlie many age-related diseases; it may even be one of the primary causes of aging itself.

Prominent conditions in which we understand the role of DNA damage are cancer, and the eye disease called age-related macular degeneration (AMD). Seemingly disparate, these diseases share a common cause, and are showing encouraging signs of responding to a common nutritional supplement.

The xanthophyll molecules, **lutein**, **zeaxanthin**, and **astaxanthin** are powerful preventers of DNA damage. They stimulate DNA repair mechanisms, which fail with advancing age. Studies are showing that these nutrients may slow the development of cancer, and prevent the onset of eye disease. Safe even in high doses, the xanthophylls deserve a place in your age-prevention toolkit.

If you have any questions on the scientific content of this article, please call a Life Extension® Health Advisor at 1-866-864-3027.

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References

- 1. Best BP. Nuclear DNA damage as a direct cause of aging. *Rejuven ation Res.* 2009 Jun;12(3):199-208.
- 2. Malpass K. Alzheimer disease: DNA damage provides novel and powerful biomarkers of Alzheimer disease. *Nat Rev Neurol*. 2012;8(4):178.
- 3. Molenaar JC. DNA damage and aging. *Ned Tijdschr Geneeskd*. Dec 27 2003;147(52):2578-81.
- 4. Tobin DJ, Paus R. Graying: gerontobiology of the hair follicle pigmentary unit. *Exp Gerontol.* Jan 2001;36(1):29-54.
- 5. Warren DT, Shanahan CM. Defective DNA-damage repair induced by nuclear lamina dysfunction is a key mediator of smooth muscle cell aging. *Biochem Soc Trans*. Dec 2011;39(6):1780-85.

- 6. Mein JR, Dolnikowski GG, Ernst H, Russell RM, Wang XD. Enzymatic formation of apocarotenoids from the xanthophyll carotenoids lutein, zeaxanthin and β-cryptoxanthin by ferret carotene-9',10'-monooxygenase. *Arch Biochem Biophys*. 2011 Feb 1;506(1):109-21. Epub 2010 Nov 21.
- 7. Lorenzo Y, Azqueta A, Luna L, Bonilla F, Domínguez G, Collins AR. The carotenoid beta-cryptoxanthin stimulates the repair of DNA oxidation damage in addition to acting as an antioxidant in human cells. *Carcinogenesis*. 2009 Feb;30(2):308-14.
- 8. Santocono M, Zurria M, Berrettini M, Fedeli D, Falcioni G. Influence of astaxanthin, zeaxanthin and lutein on DNA damage and repair in UVA-irradiated cells. *J Photochem Photobiol B*. 2006 Dec 1;85(3):205-15. Epub 2006 Sep 8.
- 9. Mathers JC, Coxhead JM, Tyson J. Nutrition and DNA repair--potential molecular mechanisms of action. *Curr Cancer Drug Targets*. Aug 2007;7(5):425-31.
- 10. Tyson J, Mathers JC. Dietary and genetic modulation of DNA repair in healthy human adults. *Proc Nutr Soc.* Feb 2007; 66(1):42-51.
- 11. Lyons NM, O'Brien NM. Modulatory effects of an algal extract containing astaxanthin on UVA-irradiated cells in culture. *J Dermatol Sci.* Oct 2002;30(1):73-84.
- 12. Mathers JC. The biological revolution towards a mechanistic understanding of the impact of diet on cancer risk. *Mutat Res.* Jul 13 2004;551(1-2):43-49.
- 13. Kelemen LE, Cerhan JR, Lim U, et al. Vegetables, fruit, and antioxidant-related nutrients and risk of non-Hodgkin lymphoma: a National Cancer Institute-Surveillance, Epidemiology, and End Results population-based case-control study. *Am J Clin Nutr.* Jun 2006;83(6):1401-10.
- 14. Serpeloni JM, Grotto D, Mercadante AZ, de Lourdes Pires Bianchi M, Antunes LM. Lutein improves antioxidant defense in vivo and protects against DNA damage and chromosome instability induced by cisplatin. *Arch Toxicol*. Oct 2010;84(10):811-22.
- 15. Astley SB, Elliott RM, Archer DB, Southon S. Increased cellular carotenoid levels reduce the persistence of DNA single-strand breaks after oxidative challenge. *Nutr Cancer*. 2002;43(2):202-13.
- 16. Holick CN, Michaud DS, Stolzenberg-Solomon R, et al. Dietary carotenoids, serum beta-carotene, and retinol and risk of lung cancer in the alpha-tocopherol, beta-carotene cohort study. *Am J Epidemiol*. Sep 15 2002;156(6):536-47.
- 17. Briviba K, Bub A, Moseneder J, et al. No differences in DNA damage and antioxidant capacity between intervention groups of healthy, nonsmoking men receiving 2, 5, or 8 servings/day of vegetables and fruit. *Nutr Cancer*. 2008;60(2):164-70.
- 18. Yeon JY, Kim HS, Sung MK. Diets rich in fruits and vegetables suppress blood biomarkers of metabolic stress in overweight women. *Prev Med.* Dec 29 2011.
- 19. Nantz MP, Rowe CA, Nieves C, Jr., Percival SS. Immunity and antioxidant capacity in humans is enhanced by consumption of a dried, encapsulated fruit and vegetable juice concentrate. *J Nutr.* Oct 2006;136(10):2606-10.
- 20. Kiokias S, Gordon MH. Dietary supplementation with a natural carotenoid mixture decreases oxidative stress. *Eur J Clin Nutr*. Sep 2003;57(9):1135-40.
- 21. Gao S, Qin T, Liu Z, et al. Lutein and zeaxanthin supplementation reduces H2O2-induced oxidative damage in human lens epithelial cells. *Mol Vis.* 2011;17:3180-90.
- 22. Zhao W, Jing X, Chen C, Cui J, Yang M, Zhang Z. Protective effects of astaxanthin against oxidative damage induced by 60Co gamma-ray irradiation. *Wei Sheng Yan Jiu*. Sep 2011;40(5):551-54.

- 23. Serpeloni JM, Barcelos GR, Friedmann Angeli JP, Mercadante AZ, Lourdes Pires Bianchi M, Greggi Antunes LM. Dietary carotenoid lutein protects against DNA damage and alterations of the redox status induced by cisplatin in human derived HepG2 cells. *Toxicol In Vitro*. Mar 2012;26(2):288-94.
- 24. Zhao X, Aldini G, Johnson EJ, et al. Modification of lymphocyte DNA damage by carotenoid supplementation in postmenopausal women. *Am J Clin Nutr.* Jan 2006;83(1):163-9.
- 25. Park JS, Chyun JH, Kim YK, Line LL, Chew BP. Astaxanthin decreased oxidative stress and inflammation and enhanced immune response in humans. *Nutr Metab (Lond)*. 2010;7:18.
- 26. Johnson IT. Micronutrients and cancer. Proc Nutr Soc. Nov 2004;63(4):587-595.
- 27. Tanaka T, Shnimizu M, Moriwaki H. Cancer chemoprevention by carotenoids. *Molecules*. 2012;17(3):3202-42.
- 28. Go VL, Wong DA, Butrum R. Diet, nutrition and cancer prevention: where are we going from here? *J Nutr*. 2001 Nov;131(11 Suppl):3121S-6S.
- 29. Jyonouchi H, Sun S, Iijima K, Gross MD. Antitumor activity of astaxanthin and its mode of action. *Nutr Cancer*. 2000;36(1):59-65.
- 30. Chew BP, Brown CM, Park JS, Mixter PF. Dietary lutein inhibits mouse mammary tumor growth by regulating angiogenesis and apoptosis. *Anticancer Res.* Jul-Aug 2003;23(4):3333-39.
- 31. Nakao R, Nelson OL, Park JS, Mathison BD, Thompson PA, Chew BP. Effect of dietary astaxanthin at different stages of mammary tumor initiation in BALB/c mice. *Anticancer Res.* Jun 2010;30(6):2171-75.
- 32. Firdous AP, Sindhu ER, Ramnath V, Kuttan R. Anti-mutagenic and anti-carcinogenic potential of the carotenoid meso-zeaxanthin. *Asian Pac J Cancer Prev.* 2010;11(6):1795-800.
- 33. Yasui Y, Hosokawa M, Mikami N, Miyashita K, Tanaka T. Dietary astaxanthin inhibits colitis and colitis-associated colon carcinogenesis in mice via modulation of the inflammatory cytokines. *Chem Biol Interact*. Aug 15 2011;193(1):79-87.
- 34. Reynoso-Camacho R, Gonzalez-Jasso E, Ferriz-Martinez R, et al. Dietary supplementation of lutein reduces colon carcinogenesis in DMH-treated rats by modulating K-ras, PKB, and beta-catenin proteins. *Nutr Cancer*. 2011;63(1):39-45.
- 35. Reiman JM, Kmieciak M, Manjili MH, Knutson KL. Tumor immunoediting and immunosculpting pathways to cancer progression. *Semin Cancer Biol.* Aug 2007;17(4):275-87.
- 36. Lee EH, Faulhaber D, Hanson KM, et al. Dietary lutein reduces ultraviolet radiation-induced inflammation and immunosuppression. *J Invest Dermatol*. Feb 2004;122(2):510-17.
- 37. Astner S, Wu A, Chen J, et al. Dietary lutein/zeaxanthin partially reduces photoaging and photocarcinogenesis in chronically UVB-irradiated Skh-1 hairless mice. *Skin Pharmacol Physiol.* 2007;20(6):283-91.
- 38. Heinen MM, Hughes MC, Ibiebele TI, Marks GC, Green AC, van der Pols JC. Intake of antioxidant nutrients and the risk of skin cancer. *Eur J Cancer*. Dec 2007;43(18):2707-16.
- 39. Bernstein PS. Nutritional Interventions against Age-Related Macular Degeneration. *Acta Hortic*. 2009;841:103-12.
- 40. Richer S, Stiles W, Statkute L, et al. Double-masked, placebo-controlled, randomized trial of lutein and antioxidant supplementation in the intervention of atrophic age-related macular degeneration: the Veterans LAST study (Lutein Antioxidant Supplementation Trial). *Optometry*. Apr 2004;75(4):216-30.
- 41. Johnson EJ, Chung HY, Caldarella SM, Snodderly DM. The influence of supplemental lutein and docosahexaenoic acid on serum, lipoproteins, and macular pigmentation. *Am J Clin Nutr.* May 2008;87(5):1521-29.

- 42. Carpentier S, Knaus M, Suh M. Associations between lutein, zeaxanthin, and age-related macular degeneration: an overview. *Crit Rev Food Sci Nutr*. Apr 2009;49(4):313-26.
- 43. Johnson EJ, Maras JE, Rasmussen HM, Tucker KL. Intake of lutein and zeaxanthin differ with age, sex, and ethnicity. *J Am Diet Assoc*. Sep 2010;110(9):1357-62.
- 44. Schweigert FJ, Reimann J. Micronutrients and their relevance for the eye--function of lutein, zeaxanthin and omega-3 fatty acids. *Klin Monbl Augenheilkd*. Jun 2011;228(6):537-43.
- 45. Liang FQ, Godley BF. Oxidative stress-induced mitochondrial DNA damage in human retinal pigment epithelial cells: a possible mechanism for RPE aging and age-related macular degeneration. *Exp Eye Res.* Apr 2003;76(4):397-403.
- 46. Karunadharma PP, Nordgaard CL, Olsen TW, Ferrington DA. Mitochondrial DNA damage as a potential mechanism for age-related macular degeneration. *Invest Ophthalmol Vis Sci.* Nov 2010;51(11):5470-79.
- 47. Jarrett SG, Lin H, Godley BF, Boulton ME. Mitochondrial DNA damage and its potential role in retinal degeneration. *Prog Retin Eye Res.* Nov 2008;27(6):596-607.
- 48. Lau LI, Liu CJ, Wei YH. Increase of 8-hydroxy-2'-deoxyguanosine in aqueous humor of patients with exudative age-related macular degeneration. *Invest Ophthalmol Vis Sci.* Nov 2010;51(11):5486-90.
- 49. SanGiovanni JP, Chew EY, Clemons TE, et al. The relationship of dietary carotenoid and vitamin A, E, and C intake with age-related macular degeneration in a case-control study: AREDS Report No. 22. *Arch Ophthalmol*. Sep 2007;125(9):1225-32.
- 50. Zeimer M, Hense HW, Heimes B, Austermann U, Fobker M, Pauleikhoff D. The macular pigment: short- and intermediate-term changes of macular pigment optical density following supplementation with lutein and zeaxanthin and co-antioxidants. The LUNA Study. *Ophthalmologe*. Jan 2009;106(1):29-36.
- 51. Connolly EE, Beatty S, Thurnham DI, et al. Augmentation of macular pigment following supplementation with all three macular carotenoids: an exploratory study. *Curr Eye Res.* Apr 2010;35(4):335-51.
- 52. Sasamoto Y, Gomi F, Sawa M, Tsujikawa M, Nishida K. Effect of 1-year lutein supplementation on macular pigment optical density and visual function. *Graefes Arch Clin Exp Ophthalmol.* Dec 2011;249(12):1847-54.
- 53. Richer SP, Stiles W, Graham-Hoffman K, et al. Randomized, double-blind, placebo-controlled study of zeaxanthin and visual function in patients with atrophic age-related macular degeneration: the Zeaxanthin and Visual Function Study (ZVF) FDA IND #78, 973. *Optometry*. Nov 2011;82(11):667-80 e666.
- 54. Parisi V, Tedeschi M, Gallinaro G, Varano M, Saviano S, Piermarocchi S. Carotenoids and antioxidants in age-related maculopathy italian study: multifocal electroretinogram modifications after 1 year. *Ophthalmology*. Feb 2008;115(2): 324-33 e322.
- 55. Norkus EP, Norkus KL, Dharmarajan TS, Schierle J, Schalch W. Serum lutein response is greater from free lutein than from esterified lutein during 4 weeks of supplementation in healthy adults. *J Am Coll Nutr.* Dec 2010;29(6):575-85.
- 56. Zhang M, Holman CD, Binns CW. Intake of specific carotenoids and the risk of epithelial ovarian cancer. *Br J Nutr.* Jul 2007;98(1):187-93.
- 57. Mignone LI, Giovannucci E, Newcomb PA, et al. Dietary carotenoids and the risk of invasive breast cancer. *Int J Cancer*. Jun 15 2009;124(12):2929-37.

- 58. Zhang X, Spiegelman D, Baglietto L, et al. Carotenoid intakes and risk of breast cancer defined by estrogen receptor and progesterone receptor status: a pooled analysis of 18 prospective cohort studies. *Am J Clin Nutr.* Mar 2012;95(3):713-25.
- 59. Tirupula KC, Balem F, Yanamala N, Klein-Seetharaman J. pH-dependent interaction of rhodopsin with cyanidin-3-glucoside. 2. Functional aspects. *Photochem Photobiol*. Mar-Apr 2009; 85(2):463-70.
- 60. Yanamala N, Tirupula KC, Balem F, Klein-Seetharaman J. pH-dependent interaction of rhodopsin with cyanidin-3-glucoside. 1. Structural aspects. *Photochem Photobiol*. Mar-Apr 2009; 85(2):454-62.