American Institute of Integrative Oncology
RESEARCH & EDUCATION

Foundations of Integrative Oncology
COURSE

GRAND ROUNDS CALL
With Dr. Nalini Chilkov
August 8th, 2018
Second Wednesday of Every Month
5:30 PM Pacific / 6:30 PM Mountain / 7:30 PM Central / 8:30 PM Eastern

Clinical Pearl: Phytochemicals that Reverse Inhibition of Apoptosis: PART ONE Bcl-2 Protein

See the included slides.

SUMMARY

PHYTOCHEMICALS THAT REVERSE INHIBITION OF APOPTOSIS
PART ONE Bcl-2 Protein

EVASION OF CELL DEATH
APOPTOSIS RESISTANCE: A HALLMARK OF CANCER

- Escape from Programmed Cell Death is a Hallmark of Cancer
- The initiation of apoptosis directly determines the fate of the cell
- Cancer cells have hyper-polarized mitochondrial membranes compared to normal cells
- Hyper-polarization prevents inhibition of apoptosis in cancer cells
- Induction of apoptosis is the key for successful tumor regression or elimination of abnormal premalignant cells
- A majority of tumors develop drug resistance
- Leading to the failure of apoptosis to be induced by chemotherapy

Bcl-2 Protein

- Mitochondrial Membrane Bound Protein (A regulatory protein)
- Bcl-2 protein inhibits apoptosis prolonging the life of cells
- High levels of Bcl-2 prevent efflux of Cytochrome C from the mitochondria and the initiation of apoptosis
- Tumor cell escape apoptosis by downregulating pro-apoptotic Bcl-2 and/or upregulating anti-apoptotic BAX protein

Foods that That Promote Normal Apoptosis and inhibit Bcl-2

- Garlic
- Parsley
- Celery
- Broccoli
- Kale
- Turmeric
- Ginger
- Rosemary
- Oregano
- Cayenne
- Red & Purple grapes
- Red Onions Red Apples Pomegranate
- Red Berries

- Blackberries
- Blueberries
- Green Tea
- Soybeans

Phytochemicals that That Promote Normal Apoptosis and Inhibit Bcl2

- Alicillin
- Apigenin
- Carnosol
- Sulphoraphanes
- I3C
- Curcumin
- Gingerol
- Chrysin
- EGCG
- Resveratrol
- Pterostilbene
- Quercetin
- Genestein
- Capsaicin
- Gallic acid

Botanicals That Promote Normal Apoptosis and Inhibit Bcl2 3-6g/day

- Rhizoma Curcuma longa
- Rdx Panax ginseng
- Polygonum cuspidatum
- Rabdosia rubescens
- Camelia sinensis
- Cortex Magnoila
- Andrographis paniculatus
- Ctx-Tips Taxus brevifolia
- Rdx Scutellaria baicensis
- Rdx Salvia milthiorrhiza
- Rdx Dioscorea spp
- Rdx Salvia milthiorrhiza
- Ganoderma lucidum
- Pleurotus pulmonaris
- Inontus obliqus
- Rosmarinus officinalis
- Tanacetum parthenium
- Tababueia spp.
- Rz Zingiber off,
- Withania somnifera
- Berberis vulgaris
- Coptis chinensis
- Viscum album

Nutraceutical Supplements that Promote Apoptosis and Inhibit Bcl2. 1-3g/day

- Curcumin
- EGCG
- Resveratrol
- Pterostilbene

- Honokiol
- Indole-3-Carbinol
- Quercetin
- Berberine
- Tanshinone
- Reishi mushroom
- Chaga mushroom

Chrysin (bioflavinoid) 200-400mg/day
- Induces cancer cell apoptosis
- Activates caspases 3 and 9
- Increases the BAX:Bcl-2 ratio

Honokiol from Cortex Magnolia off (Hou Po) (500-2000 mg/day)
- Triggers apoptosis
- Interferes with mitochondrial respiration and redox status
- Checkpoint inhibitor
- Reduces Proliferation and tumorigenesis

Indole-3-Carbinol (I3C) 500-1000mg/day
Promotes Apoptosis
- Upregulates BAX causing mitochondrial membrane depolarization
- Activates caspases
- Inhibits inflammation
- Inhibits angiogenesis
- Inhibits histone de-acetylase (HDAC)
- Inhibits proliferation
- Interferes with Tamoxifen
- Cruciferous vegetables: cabbage, cauliflower, kale, broccoli, broccoli sprouts, Brussels sprouts, collard greens, bok choy

Polygonatum odoratum rhizome, Yu Zhu, Solomon's Seal
- Down regulates Bcl2
- Upregulates BAX
- Increases ratio of apoptotic malignant cells

Oldenlandia diffusa flos (Bai Hua She She Cao),
- A source of Ursolic acid
- Causes depolarization of the mitochondrial membrane potential
- Promotes cell cycle arrest
- Promotes apoptosis
- Promotes necrosis
- Promotes autophagy

References:
Amin, A. R., Haque, A., Rahman, M. A., Chen, Z. G., Khuri, F. R., & Shin, D. M. (2015). Curcumin Induces Apoptosis of Upper Aerodigestive Tract Cancer Cells by Targeting Multiple Pathways. Plos One, 10(4). doi:10.1371/journal.pone.0124218

Bostan, M., Mihaila, M., Hotnog, C., Bleotu, C., Anton, G., Roman, V., & Brasoveanu, L. I. (2016). Modulation of Apoptosis in Colon Cancer Cells by Bioactive Compounds. Colorectal Cancer - From Pathogenesis to Treatment. doi:10.5772/63382

Gibellini, L., Bianchini, E., De Biasi, S., Nasi, M., Cossarizza, A., & Pinti, M. (2015). Natural compounds modulating mitochondrial functions. Evidence-Based Complementary and Alternative Medicine, 2015.

Lemasters, J. J., & Holmuhamedov, E. (2006). Voltage-dependent anion channel (VDAC) as mitochondrial governator—Thinking outside the box. Biochimica Et Biophysica Acta (BBA) - Molecular Basis of Disease, 1762(2), 181-190. doi:10.1016/j.bbadis.2005.10.006

Tai, Y., Sun, Y., Zou, X., Pan, Q., Lan, Y., Huo, Q., . . . Liu, H. (2016). Effect of Polygonatum odoratum extract on human breast cancer MDA-MB-231 cell proliferation and apoptosis. Experimental and Therapeutic Medicine, 12(4), 2681-2687. doi:10.3892/etm.2016.3630

Yang, J. (1997). Prevention of Apoptosis by Bcl-2: Release of Cytochrome c from Mitochondria Blocked. Science, 275(5303), 1129-1132. doi:10.1126/science.275.5303.1129

Case Study: 51yo F Recurrent Pancreatic Cancer

Submitted by: Stacy D'Andre

Overview: Post Whipple Post CT recurrent Pancreatic CA

Core Questions:
1.What is significance of low Homocysteine? Methylation defects, low SAMe, Low Glutathione ‘

2. Nutraceuticals and Interventions to support QOL and decrease risk of recurrence?

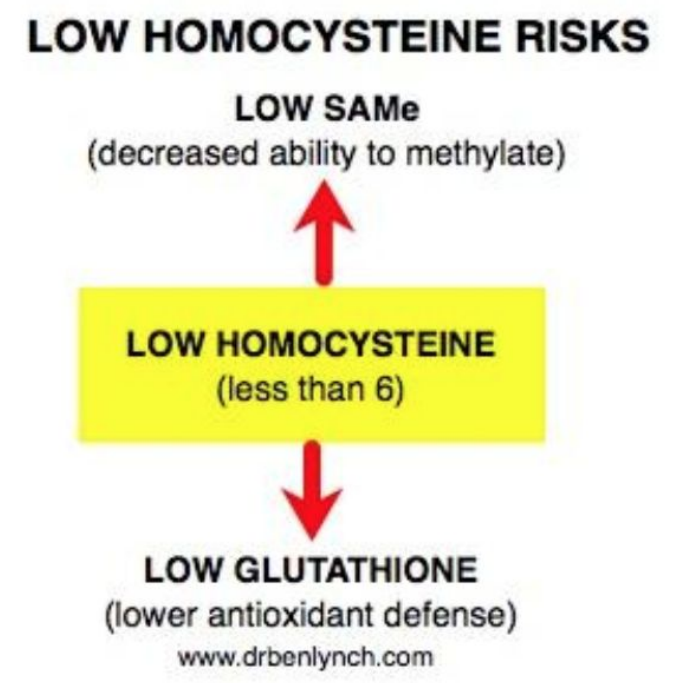
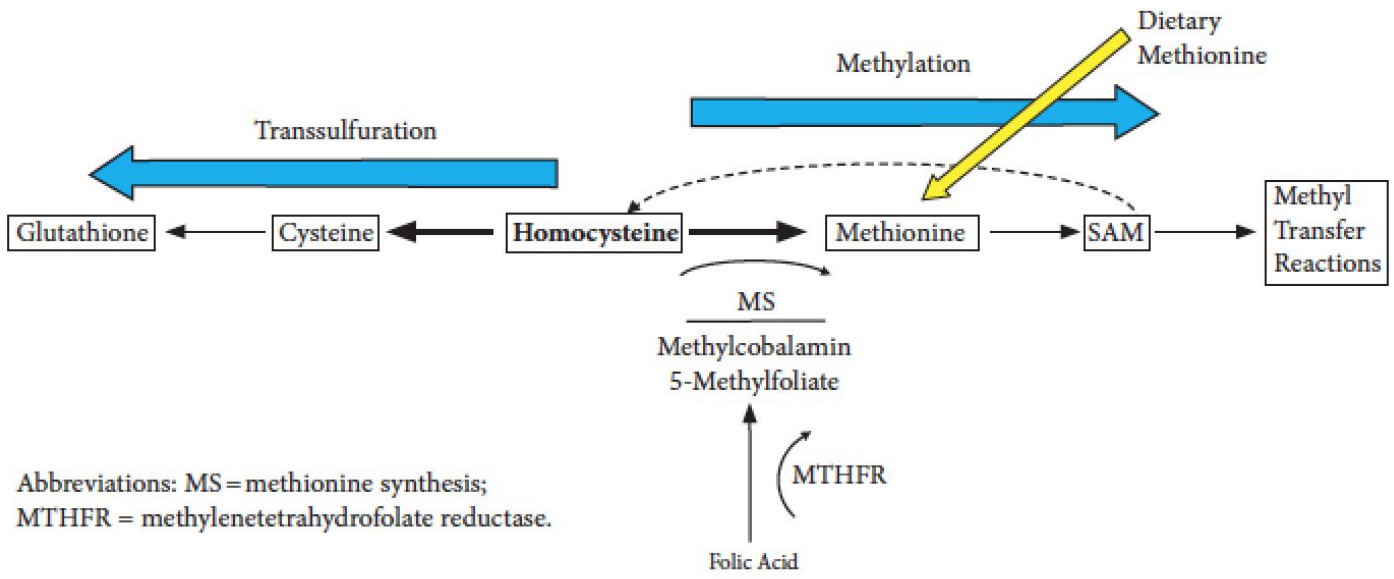


Figure 2. Homocysteine as Storage for Sulfur and Transfer for Methyl Molecules



J Pizzorno ND *Homocysteine Friend or Foe?*

Recommendations: Increase sulfur: N - AcetylCysteine, Taurine, Sulforaphanes
Dietary methionine: Brazil Nuts, Soy, White Beans, Animal Proteins (Meats, Fish, Eggs, Dairy)

References

Low Homocysteine? Not Good https://www.drbenlynch.com/low-homocysteine/

Pizzorno, J. (2014). Homocysteine: Friend or Foe?. Integrative Medicine: A Clinician's Journal, 13(4), 8.

Patient Update (from Stacy D'Andre):

- Shake has been introduced and is well tolerated
- Peritoneal involvement revealed in recent scans - patient does not want to pursue chemotherapy but is open to targeted therapies
- Oily stool - Dr. Chilkov reinforces introducing lipase to help with fatty acid absorption

Questions & Answers

Bob Nesbitt: **I noticed that Dr. Chilkov seems to favor Designs For Health (DFH), is there any particular reason?**

Dr. Chilkov:
There are very few brands that I feel meet the highest standards. Currently I recommend Designs for Health, Integrative Therapeutics and Thorne, primarily. These companies maintain a commitment to verified uncontaminated raw materials, good manufacturing practices, proper control of heat and light, and update their formulas when new research becomes available. I have vetted these companies. I know Jonathan Lizotte, CEO and Founder of DFH who started the company 25 years ago. He is one of the few owners left in the industry which such a strong commitment to quality raw materials.

Bob Nesbitt: **I see Dr Nalini uses these products in her 5 Daily Essentials Kit**
https://www.purebodysystems.com/five-daily-essentials-kit-designs-for-health.html

But when I try to find these TWO products from DFH it seems they don't exist??
https://www.purebodysystems.com/calcium-malate-chelate-120-caps-designs-for-health.html

https://www.purebodysystems.com/magnesium-malate-chelate-120-caps-designs-for-health.html

Are these products OLD formulas? I like the forms being used in these formulas so would like to continue this practice, but maybe DFH doesn't carry these any longer…

Dr. Chilkov:
These products are available via Designs for Health directly or Emerson Ecologics. Search Calcium Malate and Magnesium Malate.

My online store Pure Body Systems carries only a limited inventory of products. I also recommend you explore WELLEVATE.me for an online personal dispensary. Fullscript does not carry the entire inventory of the companies on its platform. Wellevate has a bigger more diverse and more consistently in stock inventory and a more reliable fulfillment system.

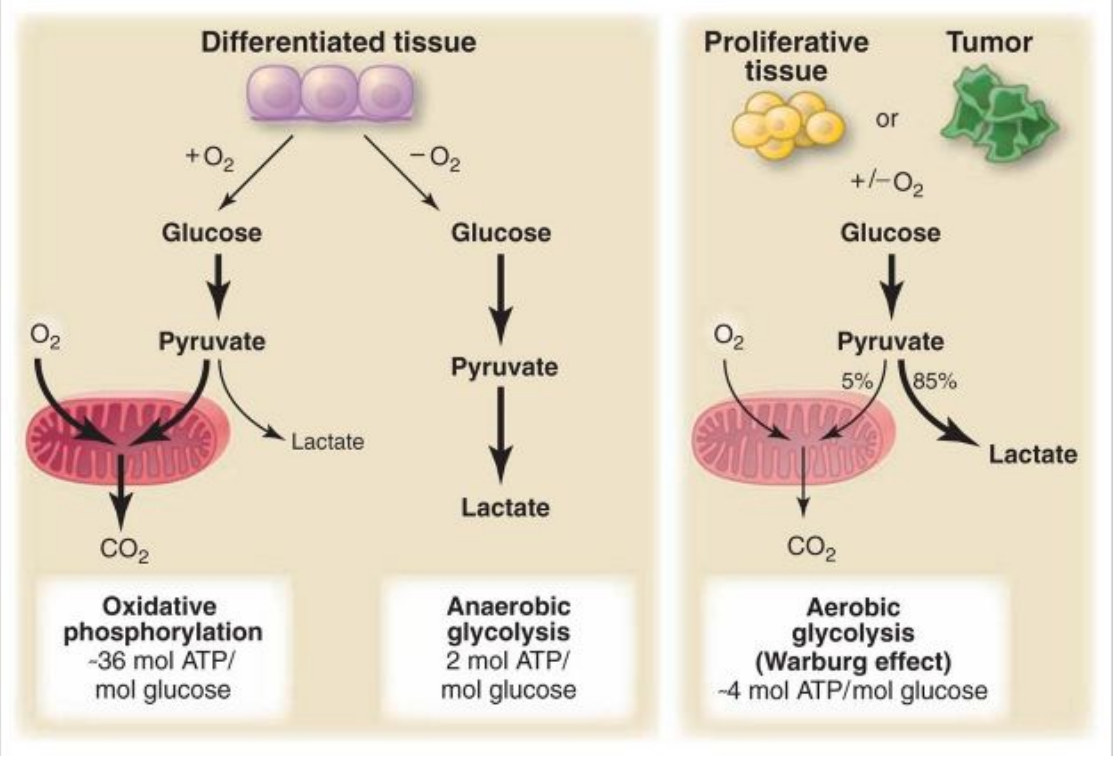
Bob Nesbitt: **Presence of heavy metals and how to deal with them for a cancer patient?**

Dr. Chilkov:
Briefly: I follow the protocols of Walter Crinnion ND, Joseph Pizzorno ND and some of Chris Shade's work in terms of analysis, assessment and treatment.

Cancer patients undergoing treatment cannot use chelating agents concurrently with their therapies. There are too many interactions. And cancer patients tend to be depleted and have mitochondrial dysfunction. Both nutrient repletion and robust mitochondrial function are required for any successful detox program.

Gently Detox Antiox, NAcetyl Cysteine, and Sulforaphanes can be used judiciously. The primary sequelae of heavy metal body burden is mitochondropathies, immuno-disruption, endocrine disruption, neuro-disruption. IV Chelation and Oral Chelation protocols can be used once the patient has recovered from the most adverse effects of their treatments.

CC Raeside: **Can you provide clarification on the Warburg effect and net mitochondrial energy (ATP) production?**



LISTEN TO GRAND ROUNDS CALL APRIL 2018 for a review of Warburg Effect

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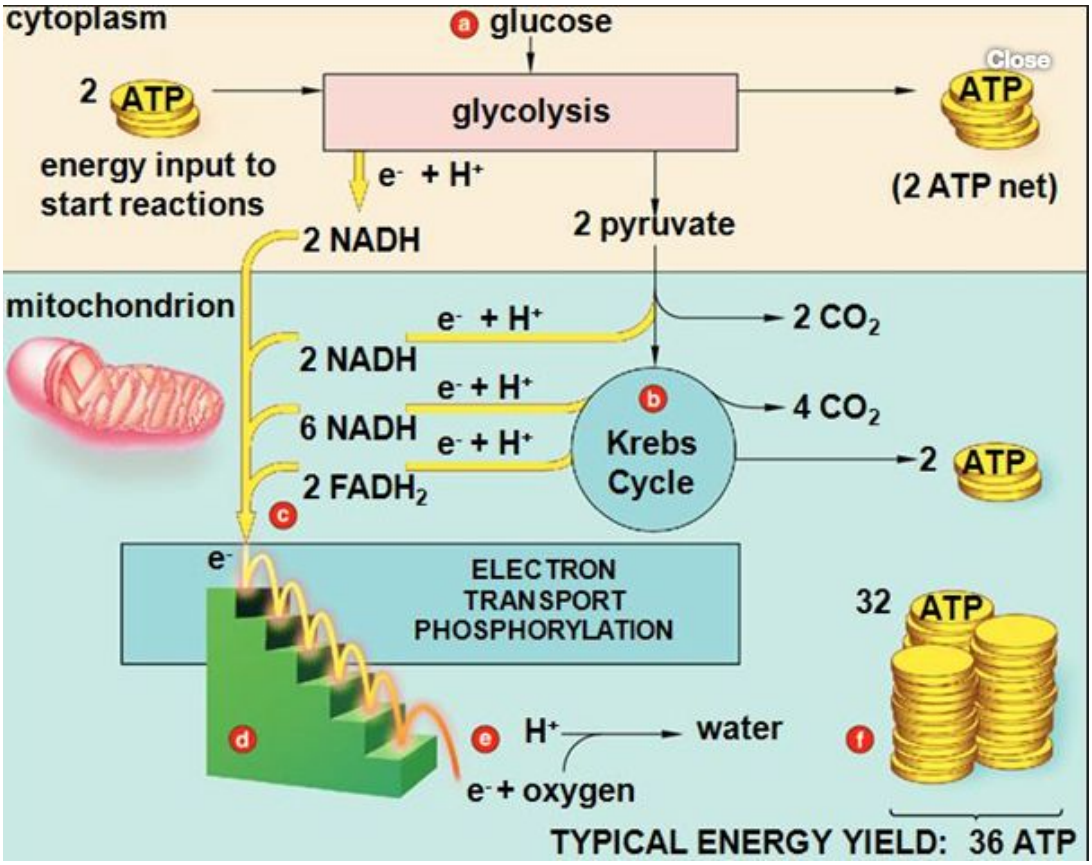
https://www.quora.com/How-is-36-ATP-produced-in-cellular-respiration



Dr. Chilkov: A great slide share review can be found here
https://www.slideshare.net/sadiqpa/glycolysis-54592219

Research: How To Manage GastroIntestinal Side Effects of Irinotecan

Michael, M., Brittain, M., Nagai, J., Feld, R., Hedley, D., Oza, A., ... & Moore, M. J. (2004). Phase II study of activated charcoal to prevent irinotecan-induced diarrhea. Journal of Clinical Oncology, 22(21), 4410-4417.

Abstract

PURPOSE: The dose-limiting toxicity of irinotecan (CPT-11; Camptosar) is delayed-onset diarrhea, with an incidence at the grade 3 to 4 level of 20% to 35%. SN38, its active moiety, is responsible by a direct effect on mucosal topoisomerase-I. The aim of this study was to assess whether activated charcoal (AC), possibly by adsorbing free lumenal SN38, can reduce irinotecan-induced diarrhea (CID) and optimize its dose-intensity.

PATIENTS AND METHODS: Patients with advanced colorectal cancer receiving irinotecan 125 mg/m(2) intravenously once a week for 4 weeks every 6 weeks were studied. In cycle 1, patients received irinotecan plus AC (5 mL aqueous Charcodote [**1,000 mg AC] plus 25 mL water) given the evening before the irinotecan dose and then tid for 48 hours after the dose**. In cycle 2, no AC was given. National Cancer Institute Common Toxicity Criteria diarrhea grade, irinotecan dose-intensity, and loperamide consumption were recorded prospectively in both cycles.

RESULTS: Twenty-eight patients had completed cycle 1 with AC; 24 subsequently completed cycle 2 without AC. **Grade 3 to 4 diarrhea was 7.1% v 25%, and grade 0 diarrhea was 46.4% v 20.8%** in cycles 1 and 2, respectively. Median percent planned dose delivered was 98% v 70% in cycles 1 and 2, respectively. In cycles 1 and 2, respectively, 25% v 54% patients took more than 10 loperamide tablets. AC was well tolerated with excellent compliance.

CONCLUSION: The administration of AC with irinotecan reduced the incidence of grade 3 to 4 diarrhea and antidiarrheal medication consumption and increased irinotecan dose-intensity. Prophylactic AC may have a role in reducing dose-limiting CID and optimizing irinotecan therapy.

PMID:15514383

Research: Effects of Acupuncture on Cancer-Related Cognitive Impairment in Chinese Gynecological Cancer Patients: A Pilot Cohort Study

Zeng, Y., Cheng, A. S., Song, T., Sheng, X., Wang, S., Xie, J., & Chan, C. C. (2018). Effects of Acupuncture on Cancer-Related Cognitive Impairment in Chinese Gynecological Cancer Patients: A Pilot Cohort Study. Integrative cancer therapies, 1534735418777109.

Background: Among women in China, gynecological cancers are the second most common cancers after breast cancer. **Cancer-related cognitive impairment (CRCI) has emerged as a significant problem affecting gynecological cancer survivors.** While acupuncture has been used in different aspects of cancer care, the possible positive effects of acupuncture on cognitive impairment have received little attention. This study hypothesized that patients would demonstrate lower neurocognitive performance and lower structural connectivity compared to healthy controls. This pilot study also hypothesized that **acupuncture may potentially be effective in treating CRCI of cancer patients by increasing brain structural connectivity and integrity**. **Methods:** This prospective cohort study consisted of 3 stages: the

first stage included a group of gynecological cancer patients and a group of age-matched healthy controls. This baseline stage used a core set of neurocognitive tests to screen patients with cognitive impairment and used a multimodal approach of brain magnetic resonance imaging (MRI) to explore the possible neurobiological mechanism of cognitive impairment in cancer patients, comparing the results with a group of noncancer controls. The second stage involved assigning CRCI patients into the acupuncture intervention group, while patients without CRCI were assigned into the cancer control group. The third stage was a post-intervention assessment of neurocognitive function by the same set of neurocognitive tests at baseline. To explore the possible neurobiological basis of acupuncture for treating CRCI, this study also used a multimodal MRI approach to assess changes in brain structural connectivity, and neurochemical properties in patients at pre- and post-acupuncture intervention. **Results: This study found that the prevalence of cognitive impairment in Chinese gynecological cancer patients at diagnosis was 26.67%.** When investigating the microstructural white matter in the brain, diffusion tensor imaging data in this study indicated that **premorbid cognitive functioning (before clinical manifestations become evident) has already existed,** as the global and local connectome properties in the entire patient group were lower than in the healthy control group. Using magnetic resonance spectroscopy, this study indicated there was a **significant reduction of relative concentration of NAA (*N*-acetyl aspartate) in the left hippocampus,** comparing these results with healthy controls. **Regarding the effects of acupuncture on reducing CRCI, patients in the acupuncture group reported better neurocognitive test performance after matching for age, menopausal status, cancer stage, and chemotherapy regimen dosage**. On a microstructural level, acupuncture's ability to reduce CRCI may be attributed to a reduction in demyelination and an **enhancement of the neuronal viability of white matter in the hippocampus. Conclusion: This pilot study indicates that acupuncture is a promising intervention in treating CRCI in gynecological cancer patients undergoing chemotherapy;** however, it requires evaluation in larger randomized controlled studies to definitively assess its benefit. By using a multimodal imaging approach, this pilot study also provides novel insights into the neurobiological basis of cognitive impairment on the human brain that has been induced by cancer and/or its treatment.

http://journals.sagepub.com/doi/full/10.1177/1534735418777109

Research: Meriva® enhances gemcitabine's effectiveness against advanced pancreatic cancer

Pastorelli D, Fabricio A, Giovanis P, et al. Phytosome complex of curcumin as complementary therapy of advanced pancreatic cancer improves safety and efficacy of gemcitabine: Results of a prospective phase II trial. Pharmacol Res 2018;132:72-79.

https://www.researchgate.net/publication/51403371_Phase_II_Trial_of_Curcumin_in_Patients_with_Advanced_Pancreatic_Cancer

Curcumin is commonly used in complementary medicine strategies for cancer trials and therapeutic protocols. One reason for doing so is because **curcumin activates Nrf2, which has cytoprotective properties as an activator of the cellular antioxidant response. Nrf2 has also been shown to have paradoxical effects as an oncogene – potentially rescuing cancer cells as well.** This understandably raises concerns that the concomitant use of curcumin might reduce the efficacy of certain chemotherapy or radiotherapy regimens. To address this issue in the context of advanced pancreatic cancer, a **phase II trial involving 44 patients was conducted to assess the effectiveness and toxicity of a combination of gemcitabine and Meriva (a phospholipid-complexed form of curcumin with enhanced bioavailability). While receiving standard gemcitabine treatments on a 28-day cycle (3 treatments per cycle), patients also received 2,000 mg Meriva daily.**

Average overall survival with gemcitabine treatment alone is 5.7-6.7 months. A new standard using nanoparticle albumin-bound paclitaxel and gemcitabine offers improved survival, extending it to 8.5-10.7

months, although it has higher toxicity that adversely impacts quality of life. **In the present study, combining gemcitabine with Meriva extended median overall survival to 10.2 months, which is comparable to the newer combination chemotherapy, but with lower toxicity and no adverse impact on quality of life during treatment. This study achieved 61.3-percent disease control rate (27.3% response rate plus 34% stable disease).**

Gemcitabine is a pyrimidine antimetabolite inhibiting DNA synthesis

Research: Efficacy of Acupuncture Therapy for Chemotherapy-Related Cognitive Impairment in Breast Cancer Patients

Tong, T., Pei, C., Chen, J., Lv, Q., Zhang, F., & Cheng, Z. (2018). Efficacy of Acupuncture Therapy for Chemotherapy-Related Cognitive Impairment in Breast Cancer Patients. Medical science monitor: international medical journal of experimental and clinical research, 24, 2919.

Abstract

BACKGROUND Chemotherapy can cause adverse effects such as chemotherapy-related cognitive impairment (CRCI). In this prospective study, **the efficacy of traditional Chinese medicine acupuncture therapy in relieving CRCI and its impact on serum brain-derived neurotrophic factor (BDNF) are evaluated.**

MATERIAL AND METHODS Eighty patients were randomly divided into a treatment group and a control group with 40 patients in each group. The treatment group was treated at the following acupuncture points: **Baihui (DU20), Sishencong (EX-HN1), Shenting (DU24), Zusanli (ST36), Taixi (K13), Dazhong (K14), and Juegu (GB39)**. Cognitive function was assessed using the functional assessment of cancer treatment cognition test (FACT-COG, version 3), the auditory-verbal learning test (AVLT), the verbal fluency test (VFT), the symbol digit modality test (SDMT), the clock-drawing test (CDT), and the trail-making test part B (TMT-B). In addition, blood serum levels of BDNF were measured before and after treatment. Correlations between change in BDNF levels and cognitive function were also analyzed.

RESULTS CRCI was ameliorated in the acupuncture treatment group, with scores on FACT-COG, AVLT-recognition and CDT assessments all significantly increased ($P<0.05$ in all cases). In addition, **serum BDNF levels after acupuncture treatment were significantly higher than before treatment** ([i]t[/i]=3.242, [i]P[/i]<0.01). Moreover, the level of BDNF was positively correlated with the total score of FACT-COG, AVLT-recognition, and CDT ([i]r[/i]=0.694, 0.628, and 0.532, respectively; all $P<0.05$). The control group showed no statistically significant difference in any measures over the same period.

CONCLUSIONS Acupuncture therapy is effective in the treatment of CRCI in breast cancer patients through a mechanism that may be related to an increase of BDNF.

PHYTOCHEMICALS THAT REVERSE INHIBITION OF APOPTOSIS

PART ONE
Bcl-2 Protein

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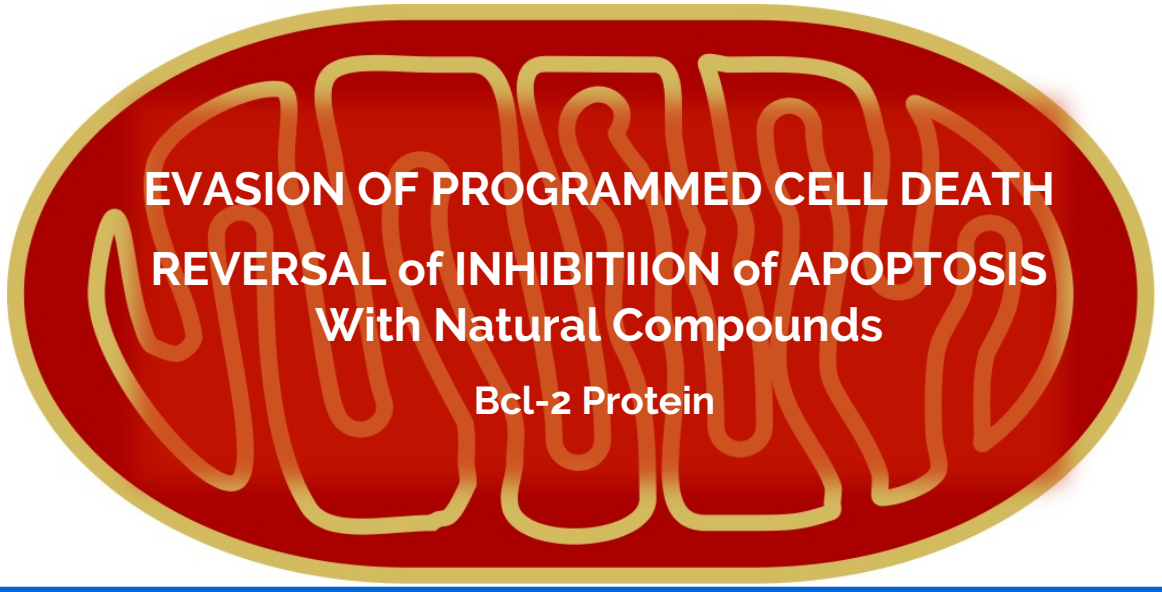

EVASION OF PROGRAMMED CELL DEATH

REVERSAL of INHIBITIION of APOPTOSIS With Natural Compounds

Bcl-2 Protein

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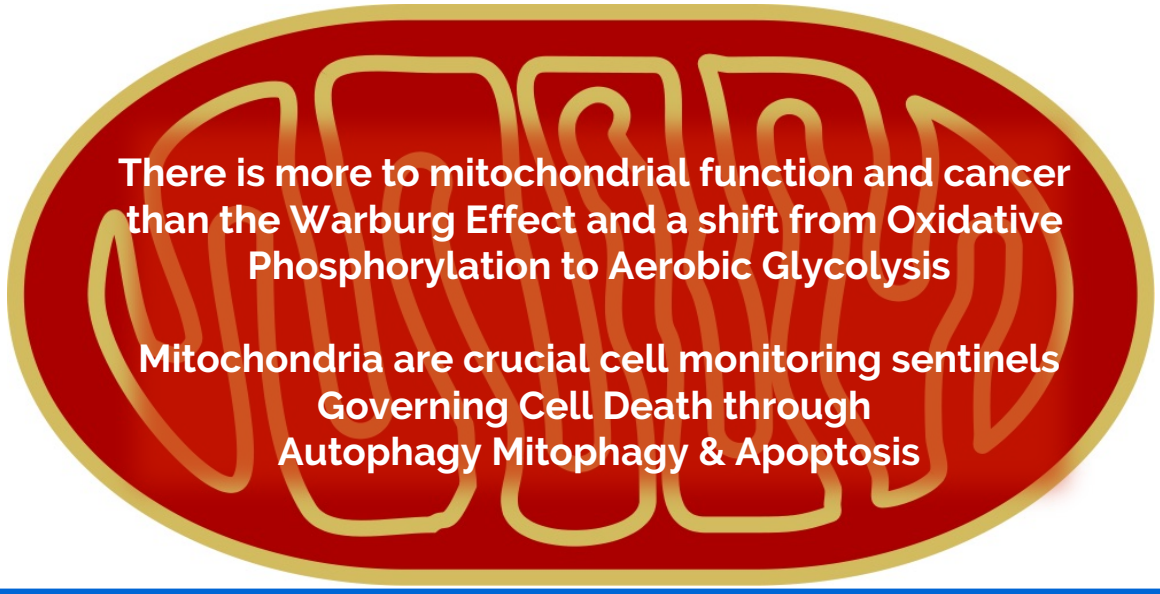

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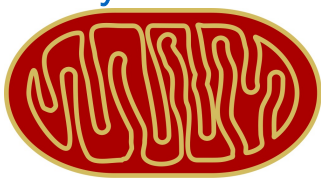
Chemoprevention by Promotion of Apoptosis



Bcl-2

p53

Induction of apoptosis is the key for successful tumor regression or elimination of abnormal premalignant cells

HK-2

miRNA

Curcumin Induces Apoptosis of Upper Aerodigestive Tract Cancer Cells by Targeting Multiple Pathways
A. R. M. Ruhul Amin et al PLoS One. 2015; 10(4): e0124218.

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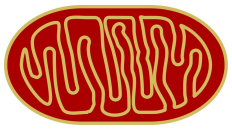
Chemoprevention by Promotion of Apoptosis



The initiation of the apoptotic process directly determines the 'fate' of the cell

Cancer cells have hyperpolarized mitochondrial membranes compared to normal cells, preventing them from throwing the apoptotic off-switch no matter how old or mutated they become.

Lemasters JJ, et al E. Voltage-dependent anion channel (VDAC) as mitochondrial governator—thinking outside the box. Biochim Biophys Acta. 2006 Feb;1762(2):181-90.

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HALLMARK OF CANCER: APOPTOSIS RESISTANCE

ESCAPE of PROGRAMMED CELL DEATH

OVEREXPRESSION of ANTI-APOPTOTIC PROTEIN Bcl-2

The initiation of the apoptotic process directly determines the 'fate' of the cell

In 371 cases of breast cancer a positive expression of Bcl-2 is as high as 79.3%

Normal cells undergo a spontaneous death process known as apoptosis, which includes mitochondrial regulation.

This process is active, highly ordered, signal-dependent, and controlled by genes and a series of enzymes.

A high expression of the Bcl-2 gene maintains cell survival.

The main physiological function of the Bcl-2 protein is inhibition of apoptosis, thereby prolonging the life of cells

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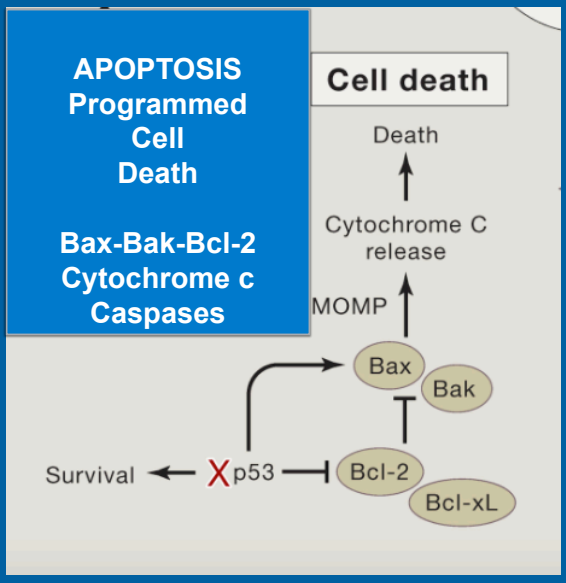
A Hallmark of Cancers is their ability to Evade Cell Death, a phenomenon tightly linked to mitochondria.

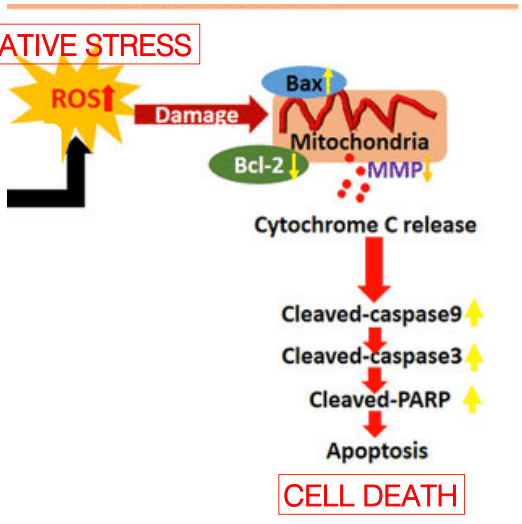
The pro-apoptotic Bcl-2 family members Bax and Bak are recruited to the OMM and oligomerize to mediate
Mitochondrial Outer Membrane Permeabilization (MOMP)

resulting in Pore Formation and
Cytochrome *c* Release from mitochondria into the cytosol to Activate Caspases, the executors of programmed cell death.

Tumor cells escape apoptosis by downregulating pro-apoptotic Bcl-2 genes and/or upregulating anti-apoptotic Bcl-2 genes



NORMAL APOPTOTIC SIGNALLING in response to INCREASED OXIDATIVE STRESS



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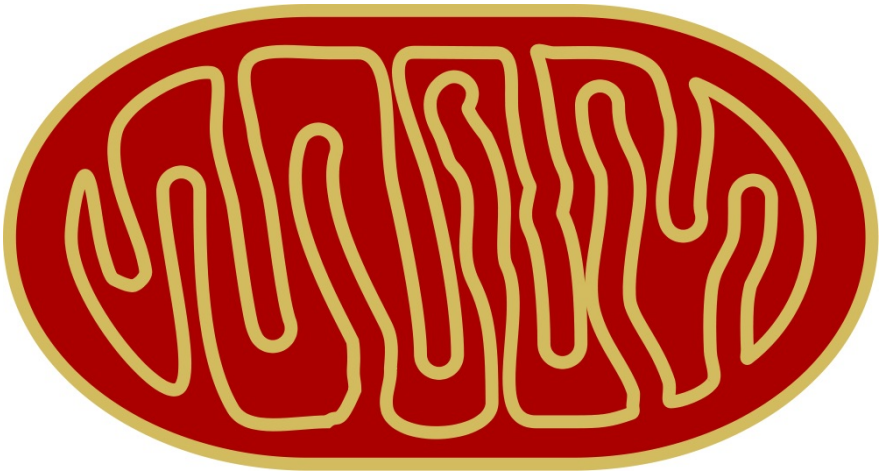
MODULATION OF MITOCHONDRIAL-DEPENDENT BCL2 APOPTOSIS PATHWAYS BY NATURAL COMPOUNDS



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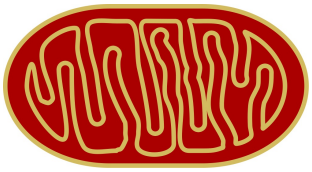

High levels of mutated Bcl-2 are associated with most types of human cancer

Overexpression of Bcl-2 prevents efflux of cytochrome c from the mitochondria and the initiation of apoptosis.

Prevention of Apoptosis by Bcl-2: Release of Cytochrome c from Mitochondria Blocked
Jie Yang, et al *Science* 21 Feb 1997: Vol. 275, Issue 5303, pp. 1129-1132

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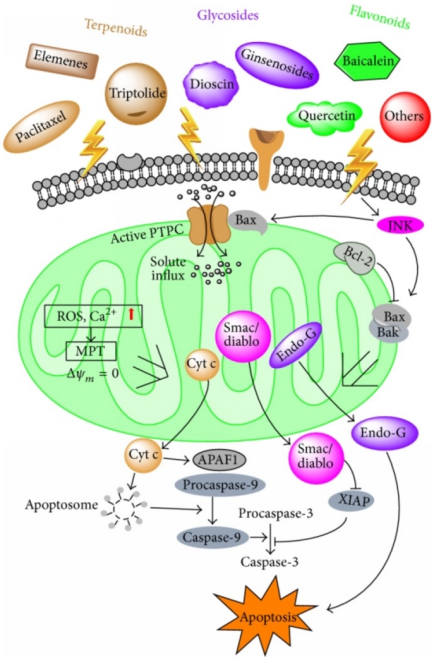
Modulation of mitochondrial-dependent apoptosis pathways by natural compounds

Bioactive compounds can act on mitochondria to trigger the permeabilization of the mitochondrial outer membrane and lead to the impairment of the mitochondria, including the alteration of electron transport, the loss of mitochondrial transmembrane potential, and the cytosolic release of apoptotic proteins such as cytochrome c

Evidence-based Complementary and Alternative Medicine 2015(5):1-14 · November 2015



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Phytochemicals in Foods and Spices that Promote Normal Apoptosis by inhibition of Bcl-2

Garlic
Parsley
Celery
Brocolli
Kale
Tumeric
Ginger
Rosemary
Oregano
Cayenne

Red & Purple grapes
Red Onions
Red Apples
Pomegranate
Red Berries
Blackberries
Blueberries
Green Tea
Soybeans

Modulation of Apoptosis in Colon Cancer Cells by Bioactive Compounds
http://dx.doi.org/10.5772/63382

Alicillin
Apigenin
Carnosol
Sulphoraphanes
I3C
Curcumin
Gingerol
Chrysin

EGCG
Resveratrol
Pterostilbene
Quercetin
Genestein
Capsaicin
Gallic acid

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Botanicals that Promote Normal Apoptosis by inhibition of Bcl-2

Rhizoma Curcuma longa	Rdx Scutellaria baicensis	Tanacetum parthenium
Rdx Panax ginseng	Rdx Salvia milthiorrhiza	Tababueia spp.
Polygonum cuspidatum	Rdx Dioscorea spp	Rz Zingiber off,
Rabdosia rubescens	Rdx Salvia milthiorrhiza	Withania somnifera
Camelia sinensis	Ganoderma lucidum	Berberis vulgaris
Cortex Magnoila	Pleurotus pulmonaris	Coptis chinensis
Andrographis paniculatus	Inontus obliqus	Viscum album
Ctx-Tips Taxus brevifolia	Rosmarinus officinalis.	





Nutriceutical Supplements that Promote Normal Apoptosis by inhibition of Bcl-2

Curcumin			
EGCG		Quercetin	
Resveratrol		Berberine	
Pterostilbene		Tanshinone	
Honokiol		Reishi mushroom	
Indole-3-Carbinol		Chaga mushroom	

500-1000mg tid








Polygonatum odoratum and apoptosis
Solomon's Seal 1-3g tid

- Downregulation of Bcl-2 and upregulation of Bax
- Increase in the ratio of apoptotic breast cancer cells

The majority of tumors develop drug resistance
Adequately sensitive apoptosis cannot be induced by chemotherapy.

Effect of *Polygonatum odoratum* extract on human breast cancer MDA-MB-231 cell proliferation and apoptosis EXPERIMENTAL AND THERAPEUTIC MEDICINE 12: 2681-2687, 2016 YU TAI et al

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Anticancer Agents Med Chem. 2014;14(6):901-9.

Role of caspases, Bax and Bcl-2 in chrysin-induced apoptosis in the A549 human lung adenocarcinoma epithelial cells.

Samarghandian S et al

- Chrysin treatment resulted in the activation of caspase-3 and - 9 and an increase in the Bax/Bcl-2 ratio ($p<0.01$).
- Bax protein expression was increased but Bcl-2 protein expression decreased in chrysin-treated cells
- Chrysin inhibits the growth of the lung cancer cells by **inducing cancer cell apoptosis via the regulation of the Bcl-2 family and also activation of caspase-3 and -9**, which may, in part, explain its anticancer activity.

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Proportion and Number of Cancer Cases and Deaths Attributable to Potentially Modifiable Risk Factors in the United States

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Additional supporting information may be found in the online version of this article.

DISCLOSURES: The authors report no conflicts of interest.

We acknowledge Dr. Kevin W. Dodd (National Cancer Institute [NCI]), Ruth Parsons (Information Management Services, Inc. [IMS]), and Dr. Amy F. Subar (NCI) for their guidance with regards to the exposure analysis of dietary factors, and Dr. Eric J. Feuer (NCI) and Andy Lake (IMS) for providing delay adjustment factors for incident cancer cases.

doi: 10.3322/caac.21440. Available online at cacancerjournal.com

Abstract: Contemporary information on the fraction of cancers that potentially could be prevented is useful for priority setting in cancer prevention and control. Herein, the authors estimate the proportion and number of invasive cancer cases and deaths, overall (excluding nonmelanoma skin cancers) and for 26 cancer types, in adults aged 30 years and older in the United States in 2014, that were attributable to major, potentially modifiable exposures (cigarette smoking; secondhand smoke; excess body weight; alcohol intake; consumption of red and processed meat; low consumption of fruits/vegetables, dietary fiber, and dietary calcium; physical inactivity; ultraviolet radiation; and 6 cancer-associated infections). The numbers of cancer cases were obtained from the Centers for Disease Control and Prevention (CDC) and the National Cancer Institute; the numbers of deaths were obtained from the CDC; risk factor prevalence estimates were obtained from nationally representative surveys; and associated relative risks of cancer were obtained from published, large-scale pooled analyses or meta-analyses. In the United States in 2014, an estimated 42.0% of all incident cancers (659,640 of 1570,975 cancers, excluding nonmelanoma skin cancers) and 45.1% of cancer deaths (265,150 of 587,521 deaths) were attributable to evaluated risk factors. Cigarette smoking accounted for the highest proportion of cancer cases (19.0%; 298,970 cases) and deaths (28.8%; 169,180 deaths), followed by excess body weight (7.8% and 6.5%, respectively) and alcohol intake (5.6% and 4.0%, respectively). Lung cancer had the highest number of cancers (184,970 cases) and deaths (132,960 deaths) attributable to evaluated risk factors, followed by colorectal cancer (76,910 cases and 28,290 deaths). These results, however, may underestimate the overall proportion of cancers attributable to modifiable factors, because the impact of all established risk factors could not be quantified, and many likely modifiable risk factors are not yet firmly established as causal. Nevertheless, these findings underscore the vast potential for reducing cancer morbidity and mortality through broad and equitable implementation of known preventive measures. **CA Cancer J Clin 2018;68:31-54. © 2017 American Cancer Society.**

Keywords: cancer, prevention, population-attributable fraction, risk factor

Introduction

Much progress against cancer has been made in the United States over the past several decades, as evidenced by the 25% decline in the cancer mortality rate since 1991.[1] However, the cancer burden remains substantial, with more than 1.6 million newly diagnosed cases and 600,000 deaths estimated to occur in 2017.[1] The costs associated with cancer morbidity and premature mortality are staggering, with approximately $88 to $124 billion per year for direct medical costs alone.[2,3]

Many cancers are causally related to potentially modifiable risk factors,[4,5] and contemporary estimates of this proportion in a population (ie, the population-attributable fraction [PAF]) are a valuable tool for setting priorities for cancer

prevention and control. Several previous studies provided estimates of PAFs in the United States, but they included a limited number of risk factors or cancer types, used data sources that may not be nationally representative, or are outdated.[4-11] Herein, we estimate the PAF of cases and deaths overall (excluding nonmelanoma skin cancers) and for 26 cancer types, in adults aged 30 years and older in 2014, attributable to potentially modifiable risk factors using nationally representative data on exposure prevalence and cancer occurrence. These risk factors include cigarette smoking; secondhand smoke (SHS); excess body weight; alcohol intake; consumption of red and processed meat; low consumption of fruits and vegetables, dietary fiber, and dietary calcium; physical inactivity; ultraviolet (UV) radiation exposure; and infection with *Helicobacter pylori*, hepatitis B virus (HBV), hepatitis C virus (HCV), human herpes virus type 8 (HHV8), human immunodeficiency virus (HIV), or human papillomavirus (HPV).

Materials and Methods

Data Sources

Risk factors and cancer types

We used reports published by the International Agency for Research on Cancer (IARC) and the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) to identify potentially modifiable risk factors with sufficient[12-17] or strong (either convincing or probable)[18-29] evidence for causing cancer in humans and for which risk factor exposure and cancer outcome data were available (Table 1). When a risk factor was evaluated more than once, we prioritized the more recent evaluation. A list of potentially modifiable risk factors that were not considered in this analysis is provided in Supporting Information Table 1.

Cancer occurrence

Numbers of new invasive cancer cases in 2014 in the United States by sex and age group (ages 30-79 years in 5-year increments and 80 years and older) were obtained from the Centers for Disease Control and Prevention's (CDC's) National Program of Cancer Registries (NPCR) and the National Cancer Institute's (NCI's) Surveillance, Epidemiology, and End Results (SEER) program, which collectively provided complete coverage of the US population in 2014.[30] The corresponding numbers of cancer deaths were obtained from the CDC's National Center for Health Statistics.[31]

Cancer cases from the NPCR/SEER were adjusted for delays in reporting to central cancer registries, which have been shown to occur in the most recent data years, using composite, age-specific, delay adjustment factors derived from the North American Association of Central Cancer Registries (NAACCR) 2016 December submission (personal communication, Andy Lake [Information Management Services Inc. on behalf of NAACCR] and Eric Feuer [NCI]). The methodology for delay adjustment is described elsewhere.[32,33] Both cases and deaths were accessed via the NCI's SEER*Stat software program (version 8.3.4; NCI, Bethesda, MD) and were classified according to the *International Classification of Diseases for Oncology, third edition*[34] and the *International Classification of Diseases, 10th revision*, respectively. Because of high levels of misclassification and/or missing information on histologic and anatomic subtypes for mortality data, we used the corresponding proportions from incidence data to estimate the number of deaths from esophageal squamous cell carcinoma and adenocarcinoma, gastric cardia and noncardia cancers, and colon cancer (excluding rectal cancer).

Prevalence of exposures

Exposure data used in this analysis were based on sex-specific and age-specific (ages 30-79 years in 5-year increments and 80 years and older) prevalence estimates from nationally representative surveys and were weighted to account for the appropriate complex sample design using SAS (version 9.4; SAS Institute, Inc, Cary, North Carolina) and SAS-callable SUDAAN (release 11.0.1; RTI International, Research Triangle Park, North Carolina). Exposure definitions and data sources are summarized in Supporting Information Table 2.

Data on cigarette smoking status (current, former, and never) and alcohol intake (number of drinks per day) were obtained from averaging results from the 2013 and 2014 National Health Interview Surveys to ensure more stable subgroup estimates.[35] The number of alcoholic drinks per day was calculated for current drinkers only; former drinkers and lifetime abstainers were combined for this analysis and were considered to have consumed 0 drinks per day in the year before the survey. Because alcohol intake is generally highly underreported in surveys, we adjusted National Health Interview Survey alcohol intake using per-capita alcohol sales according to a method previously suggested by Rey et al (see Supporting Information).[36]

National Health and Nutrition Examination Survey (NHANES) data were used to calculate estimates for other exposures. NHANES does not collect data on the same items every survey cycle; therefore, we included data from the most recent years available. Survey years were also combined to provide stable subgroup estimates for SHS exposure (based on serum cotinine levels; survey years 2007-2010); body mass index (BMI), in kg/m^2 (as an indicator of excess body weight; survey years 2011-2014); red meat, processed meat, fruit, vegetable, and dietary fiber and calcium consumption (all in grams per day, except calcium, which was in milligrams per day; survey years 2007-2010); and physical activity (recreational activity in metabolic equivalent of task minutes per week; survey years 2011-2014).[37] We considered only

TABLE 1. Factors Associated With Increased Cancer Risk (by Cancer Type) Considered in This Analysis

RISK FACTOR (STUDY)	CANCER TYPE (ICD-10)[a]
Smoking (Secretan 2009[14])	Oral cavity, pharynx (C00-C14); esophagus (C15); stomach (C16); colorectum (C18-C20, C26.0); liver (C22.0, C22.2-C22.4, C22.7, C22.9); pancreas (C25); nasal cavity/paranasal sinus (C30-C31); larynx (C32); lung, bronchus, trachea (C33-C34); cervix (C53); kidney, renal pelvis, ureter (C64-C66); urinary bladder (C67); acute myeloid leukemia (C92.0, C92.4-C92.5, C94.0, C94.2)
Exposure to secondhand smoke (Secretan 2009[14])	Lung, bronchus, trachea (C33-C34; only among never-smokers and former-smokers)
Excess body weight (Lauby-Secretan 2016[17])	Esophagus (C15; adenocarcinoma only); stomach (C16.0; cardia only); colorectum (C18-C20, C26.0); liver (C22.0, C22.2-C22.4, C22.7, C22.9); gallbladder (C23); pancreas (C25); female breast (C50; postmenopausal cancers only[b]); corpus uteri (C54-C55); ovary (C56); kidney, renal pelvis (C64-C65); thyroid (C73); multiple myeloma (C90.0, C90.2)
Alcohol intake (Secretan 2009[14])	Lip, oral cavity, pharynx (C00-C14); esophagus (C15; squamous cell carcinoma only); colorectum (C18-C20, C26.0); liver (C22.0, C22.2-C22.4, C22.7, C22.9); larynx (C32); female breast (C50)
Poor diet	
Red meat consumption (WCRF/AICR 2017[28])	Colorectum (C18-C20, C26.0)
Processed meat consumption (WCRF/AICR 2016,[26] WCRF/AICR 2017[28])	Colorectum (C18-C20, C26.0); stomach (C16.1-C16.6; noncardia only)
Low fruit/vegetable consumption (WCRF/AICR 2007[19])	Oral cavity, pharynx, larynx (C00-C14, C32; associated with low consumption of both fruits and vegetables); lung, bronchus, trachea (C33-C34, associated with low fruit consumption only)
Low dietary fiber consumption (WCRF/AICR 2017[28])	Colorectum (C18-C20, C26.0)
Low dietary calcium consumption (WCRF/AICR 2017[28])	Colorectum (C18-C20, C26.0)
Physical inactivity (WCRF/AICR 2013,[21] WCRF/AICR 2017[28,29])	Colon, excluding rectum (C18, C26.0); female breast (C50; premenopausal cancers inversely associated with vigorous activity only, postmenopausal cancers inversely associated with all types of physical activity[b]); corpus uteri (C54-C55)
Ultraviolet radiation (El Ghissassi 2009[15])	Melanoma of the skin (C43)
Infections	
Helicobacter pylori (Bouvard 2009[13])	Stomach (C16.1-C16.6; noncardia only)
Hepatitis B virus (Bouvard 2009[13])	Liver (C22.0, C22.2-C22.4, C22.7, C22.9)
Hepatitis C virus (Bouvard 2009[13])	Liver (C22.0, C22.2-C22.4, C22.7, C22.9); non-Hodgkin lymphoma (C82-C85, C96.3)
Human herpes virus type 8: Kaposi sarcoma herpes virus (Bouvard 2009[13])	Kaposi sarcoma (C46)
Human immunodeficiency virus (Bouvard 2009[13])	Anus (C21); Kaposi sarcoma (C46); cervix (C53); Hodgkin lymphoma (C81); non-Hodgkin lymphoma (C82-C85, C96.3)
Human papillomavirus (Bouvard 2009[13])	Oral cavity (C02-C06); oropharynx, tonsils and base of tongue (C01, C09-C10); anus (C21); cervix (C53); vulva (C51); vagina (C52); penis (C60)

Abbreviations: ICD-10, International Classification of Diseases, 10th revision; ICD-O-3, International Classification of Diseases for Oncology, third edition; WCRF/AICR, World Cancer Research Fund/American Institute for Cancer Research. [a]ICD-O-3 morphology codes for incidence data for acute myeloid leukemia, Hodgkin lymphoma, non-Hodgkin lymphoma, multiple myeloma, and Kaposi sarcoma were defined per Surveillance, Epidemiology, and End Results (SEER) site recode ICD-O-3/World Health Organization 2008 definitions. Esophageal adenocarcinoma includes histologies 8050, 8140-8147, 8160-8162, 8180-8221, 8250-8507, 8514, 8520-8551, 8560, 8570-8574, 8576, and 8940-8941. Esophageal squamous cell carcinoma includes histologies 8070-8078 and 8083-8084. [b]In this analysis, women aged younger than 50 years were considered as premenopausal (and were not included in calculation of breast cancers attributable to excess body weight); and women aged 50 years or older were considered as postmenopausal.

recreational activity for the association between physical inactivity and cancer, because guidelines generally pertain to recreational activity, and most studies have investigated this type of activity.[38,39] SHS exposure was defined as having a serum cotinine level of 0.05 ng/mL or greater among never-smokers and former-smokers, according to definitions used for the 2014 US Surgeon General's report.[40,41] Anthropomorphic measurements for BMI estimates were collected in person by trained personnel. The NCI method[42,43] was implemented to estimate usual daily consumption of dietary factors using data from the two 24-hour recalls of NHANES (see Supporting Information).

Laboratory data from NHANES were used to calculate prevalence estimates for infections with HBV and HIV (survey years 2011-2014), HCV (survey years 2009-2012), *H. pylori* (survey years 1999-2000), oral HPV (survey years

2011-2014), and genital HPV (survey years 2013-2014). Because HIV tests were done and swab samples for HPV were only collected from younger age groups (younger than 60 years for HIV and vaginal and penile swabs; younger than 70 years for oral swabs), combined HIV or HPV prevalence from the 2 oldest 5-year age groups with available data were applied as the prevalence for older age groups without data. Equivocal tests for infections were considered as missing values, unless additional tests were performed (eg, HCV-RNA after an anti-HCV test).

Relative risks

We used relative risks (RRs) from large-scale pooled analyses or meta-analyses of studies in the United States when available. Otherwise, we used RRs from pooled or meta-analyses of studies conducted in North America and/or Europe or, tertiarily, from studies worldwide (see Supporting Information Table 3). For nonsex-specific cancers (except breast), we used the overall RRs for men and women. When multiple risk estimates were available, we selected the RR adjusted for the greatest number of confounders.

Statistical Analysis

We applied a simulation method[44] in which numbers from repeated draws were generated for all RRs, exposure levels, and numbers of cancer cases and deaths, allowing for uncertainty in the data. The simulation process was replicated 1000 times for each sex and age-group stratum. We used numbers from repeated draws to calculate the proportion and number of attributable cancer cases and deaths and their 95% confidence intervals. By using exposure prevalence (Pi) at the exposure category i and the corresponding RR (RRi), PAFs for categorical exposure variables for each stratum of sex and age group were calculated using the following approximate formula:

$$PAF = \frac{\sum P_i(RR_i - 1)}{\sum P_i(RR_i - 1) + 1}$$

The number of cancer cases and deaths attributable to each risk factor by sex was calculated by multiplying the number of cancer cases or deaths in each sex and age group by the PAF in that sex and age group, and summing the results over age.[45]

The above approximate formula was used for all associations, with a few exceptions. Similar to previous studies, we attributed all cervical cancers to HPV infection and all Kaposi sarcomas to HHV8 infection.[10] Because of the lack of data on anal HPV infection, we attributed 88% of anal cancers to HPV[10] before applying the simulation method. We estimated PAFs for excess UV radiation-associated melanomas using the difference between observed melanoma incidence rates by sex and age group in the general population and the rates in blacks during 2010 through 2014, as applied in previous studies.[46] Melanoma occurrence in blacks can be considered a proxy for rates in people with minimal UV exposure, because UV radiation (through sun exposure and indoor tanning) is a much less important risk factor for melanoma among blacks compared with whites in the United States.[47]

To calculate the overall attributable proportion and number of cancer cases or deaths for a given cancer type when there were several risk factors, we assumed that the risk factors had no interactions. We also calculated proportions and numbers of cancer cases and deaths attributable to 4 risk factor groups: 1) tobacco smoking (cigarette and secondhand); 2) excess body weight, alcohol intake, poor diet (consumption of red and processed meat and low consumption of fruits/vegetables, dietary fiber, and dietary calcium), and physical inactivity; 3) UV radiation; and 4) 6 cancer-associated infections. It is believed that HIV only increases the risk of cancers associated with other carcinogenic viruses (several of which were considered in this analysis) indirectly and through immunosuppression.[10,13] Thus, for estimates of all infections and all evaluated risk factors combined, we excluded HIV-related cancers from the calculations, except for HIV-related Hodgkin and non-Hodgkin lymphomas, because the infection causally associated with these 2 cancer types (Epstein-Barr virus)[13] was not considered in our analysis.

Numbers of attributable cancer cases and deaths overall and by sex and individual cancer type were obtained from separate simulation models and rounded to the nearest 10. Thus, numbers of cancer cases or deaths by sex or for individual cancer types may not sum to the totals. All statistical analyses to calculate proportions and numbers of cancers attributable to evaluated risk factors were conducted using Stata statistical software (version 13; Stata Corporation LP, College Station, Texas). Detailed information on statistical analysis is provided in the Supporting Information.

Results

Incidence

In 2014, an estimated 42.0% of all incident cancers in adults aged 30 years and older (659,640 of 1570,975 incident cancers) were attributable to the potentially modifiable risk factors evaluated (Fig. 1). Cigarette smoking had by far the highest PAF (19.0% of all cases), accounting for 55.5% of all potentially preventable cancers in men (184,400 of 332,320 cancers) and 35.0% in women (114,520 of 327,240 cancers). Excess body weight had the second highest PAF (7.8%), followed by alcohol intake (5.6%), UV radiation (4.7%), and physical inactivity (2.9%). Excess body weight caused twice as many cancers in women as in men in terms of both the PAF (10.9% vs 4.8%) and case numbers (85,680 vs 37,670 cases).

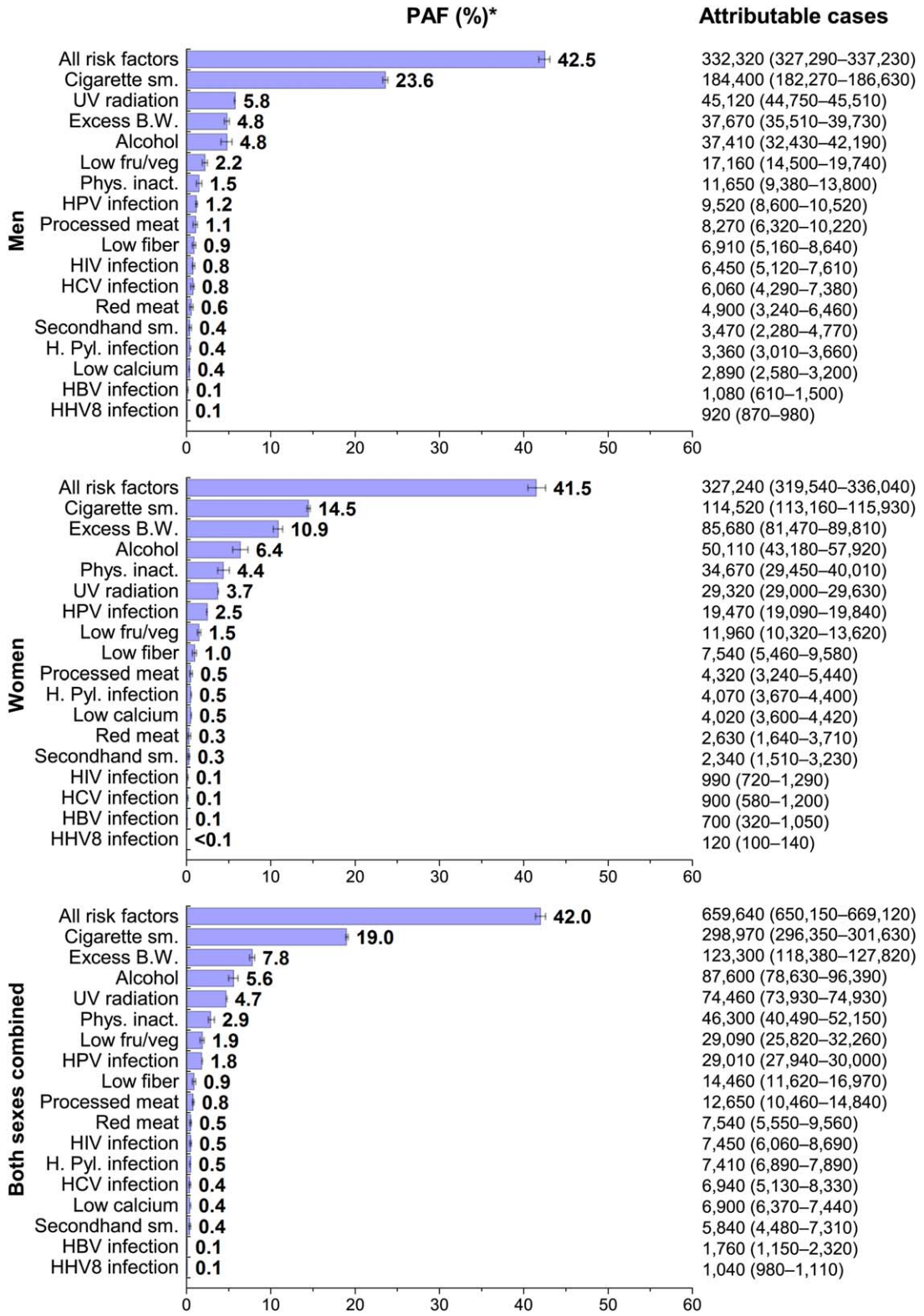

FIGURE 1. Estimated Proportion and Number of Incident Cancer Cases Attributable to Evaluated Risk Factors in Adults Aged 30 Years and Older in the United States in 2014, by Sex.

B.W. indicates body weight; CI, confidence interval; fru/veg, fruit and vegetable consumption; H. Pyl., *Helicobacter pylori*; HBV, hepatitis B virus; HCV, hepatitis C virus; HHV8, human herpes virus type 8; HPV, human papillomavirus; PAF, population-attributable fraction; Phys. inact., physical inactivity; sm., smoking; UV, ultraviolet radiation. PAFs are the percentages of all incident cancer cases in the United States in 2014. The total number of all incident cancer cases (excluding nonmelanoma skin cancer cases) in adults aged 30 years and older was 782,210 among men, 788,765 among women, and 1570,975 for both sexes combined. The bars in the figure and numbers in parentheses represent 95% confidence intervals. Numbers of attributable cancer cases and deaths are rounded to the nearest 10.

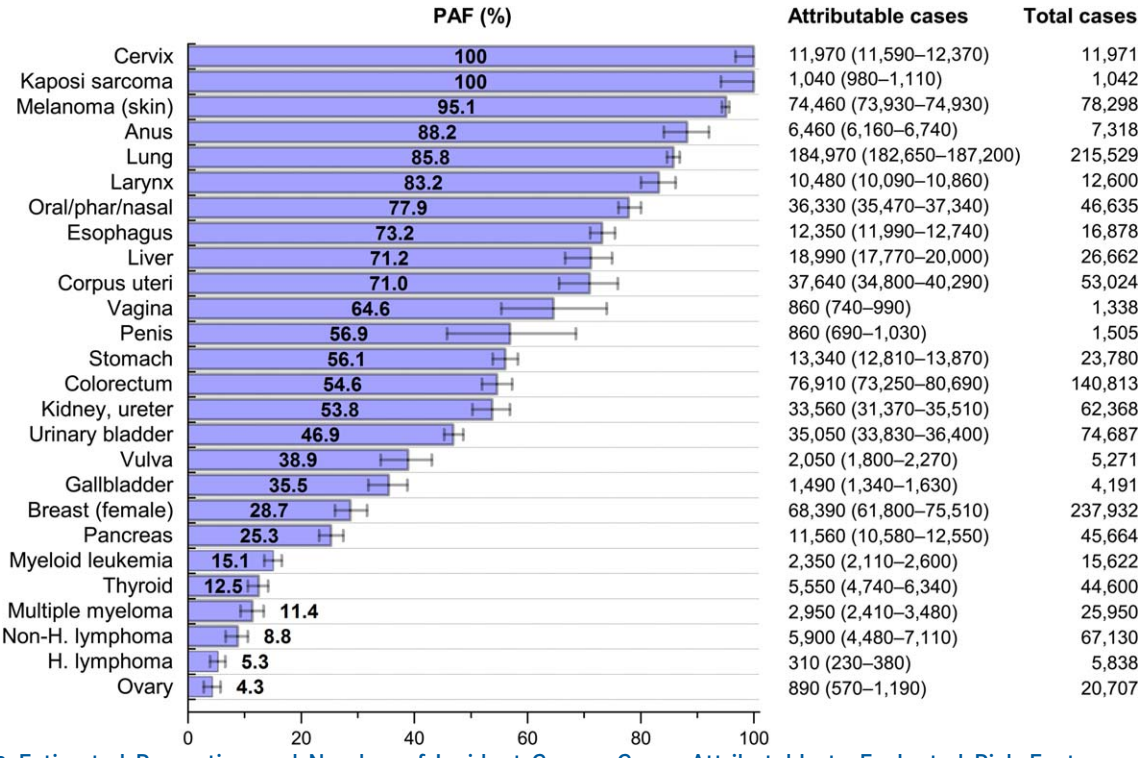

FIGURE 2. Estimated Proportion and Number of Incident Cancer Cases Attributable to Evaluated Risk Factors and Number of Total Cases in Adults Aged 30 Years and Older in the United States in 2014, by Cancer Type.

H. lymphoma indicates Hodgkin lymphoma; N-H. lymphoma, non-Hodgkin lymphoma. Here, kidney also includes renal pelvis and ureter, and lung includes bronchus and trachea. Population-attributable fractions (PAFs) are the percentages of total cases for each cancer type (both sexes combined). The bars in the figure and numbers in parentheses represent 95% confidence intervals. Numbers of attributable cancer cases are rounded to the nearest 10.

Similarly, physical inactivity accounted for 4.4% of cancers in women compared with 1.5% in men.

The proportion of cases caused by potentially modifiable risk factors ranged from 100% for cervical cancer and Kaposi sarcoma to 4.3% for ovarian cancer and was greater than 50% for 15 of the 26 cancer types (Fig. 2). In addition to cervical cancer and Kaposi sarcoma, more than three-quarters of all melanomas of the skin (95.1%) and cancers of the anus (88.2%), lung (85.8%), larynx (83.2%), and oral cavity/pharynx/nasal cavity/paranasal sinus (77.9%) were attributable to evaluated risk factors. Lung cancer had the highest number of cases attributable to evaluated risk factors in both men (99,860 cases) and women (85,050 cases), followed by skin melanoma (45,120 cases), colorectal cancer (43,080 cases), and urinary bladder cancer (28,050 cases) among men and cancers of the breast (68,390 cases), corpus uteri (37,640 cases), and colorectum (33,980 cases) among women (Table 2).

Cigarette and secondhand smoking

Cigarette smoking accounted for the highest proportion and number of cancer cases of all risk factors evaluated (23.6% of all cases in men and 14.5% in women), about three-fourths of which occurred in current smokers. Lung cancer had the highest proportion of smoking-attributable cases (81.7%), followed by cancers of the upper aerodigestive tract (larynx, 73.8%; esophagus, 50.0%; and oral and nasal cavity, pharynx, and paranasal sinuses, 49.2%), and the urinary bladder (46.9%) (Table 3). Lung cancer also had the highest burden of smoking-related cancer (176,190 cases), followed by urinary bladder cancer (35,050 cases), oral cavity/pharynx/nasal cavity/paranasal sinus cancers (22,960 cases), and colorectal cancer (16,510 cases). SHS exposure contributed an additional 5840 cases of lung cancer (2.7%).

Excess body weight

Excess body weight was associated with 4.8% of all cancers (37,670 cases) in men and 10.9% of all cancers (85,680 cases) in women (Fig. 1). However, it accounted for more than one-half of all cancers of the corpus uteri (60.3%) and one-third of gallbladder (35.5%), liver (33.9%), and kidney/renal pelvis (33.2%) cancers (Table 3). The case burden because of excess body weight was largest for cancers of the kidney/renal pelvis (12,250 cases), liver (6680 cases), and esophagus (4640 cases) among men and for cancers of the corpus uteri (31,950 cases), breast (26,780 cases), and kidney/renal pelvis (7740 cases) among women. Excess body weight accounted for a higher percentage of esophageal and gastric cancers in men than in women.

Alcohol intake

Alcohol intake was the third largest contributor to all cancer cases among women (6.4%; 50,110 cases) and the fourth largest contributor among men (4.8%; 37,410 cases). Almost one-half of oral cavity and pharyngeal cancers in

TABLE 2. Estimated Proportion and Number of Incident Cancer Cases Attributable to All Evaluated Risk Factors and Estimated Total Number of Cancer Cases in Adults Aged 30 Years and Older in the United States in 2014, by Sex and Cancer Type

CANCER	PAF (95% CI), %	ATTRIBUTABLE CASES, NO. (95% CI)	TOTAL NO. OF CASES
Men			
Kaposi sarcoma	100 (93.9-100)	920 (870-980)	921
Melanoma (skin)	96.0 (95.2-96.8)	45,120 (44,750-45,510)	47,021
Lung, bronchus, trachea	88.5 (87.0-90.0)	99,860 (98,150-101,570)	112,831
Anus	88.1 (81.5-94.8)	2310 (2130-2480)	2619
Larynx	84.4 (80.7-87.8)	8430 (8060-8780)	9997
Oral cavity, pharynx, nasal cavity, paranasal sinus	82.3 (80.0-84.9)	27,220 (26,460-28,060)	33,064
Esophagus	74.7 (72.3-77.1)	9940 (9620-10,270)	13,308
Liver	74.1 (68.1-78.7)	14,800 (13,620-15,730)	19,979
Colorectum	58.2 (54.0-61.9)	43,080 (39,980-45,810)	73,978
Penis	56.9 (45.8-68.6)	860 (690-1030)	1505
Stomach	53.6 (50.5-56.5)	7950 (7490-8380)	14,838
Kidney, renal pelvis, ureter	52.4 (47.2-56.5)	20,710 (18,670-22,350)	39,550
Urinary bladder	49.4 (47.2-51.6)	28,050 (26,800-29,290)	56,773
Gallbladder	32.9 (28.1-38.1)	430 (370-500)	1311
Pancreas	26.0 (23.2-29.0)	6160 (5480-6850)	23,633
Myeloid leukemia	17.1 (14.8-19.6)	1490 (1290-1710)	8718
Non-Hodgkin lymphoma	14.1 (10.6-17.3)	5190 (3880-6340)	36,732
Thyroid	11.5 (9.4-13.8)	1340 (1100-1600)	11,604
Multiple myeloma	10.9 (8.1-14.2)	1590 (1180-2060)	14,547
Hodgkin lymphoma	8.0 (5.7-10.3)	270 (190-350)	3364
Women			
Cervix	100 (96.8-100)	11,970 (11,590-12,370)	11,971
Kaposi sarcoma	100 (83.5-100)	120 (100-140)	121
Melanoma (skin)	93.7 (92.7-94.7)	29,320 (29,000-29,630)	31,277
Anus	88.3 (83.4-93.1)	4150 (3920-4370)	4699
Lung, bronchus, trachea	82.8 (81.4-84.3)	85,050 (83,580-86,550)	102,698
Larynx	78.5 (72.8-85.1)	2040 (1900-2220)	2603
Corpus uteri	71.0 (65.6-76.0)	37,640 (34,800-40,290)	53,024
Esophagus	67.5 (63.2-72.0)	2410 (2250-2570)	3570
Oral cavity, pharynx, nasal cavity, paranasal sinus	65.7 (62.7-68.7)	8920 (8510-9330)	13,571
Vagina	64.6 (55.4-74.0)	860 (740-990)	1338
Liver	62.6 (56.9-68.0)	4180 (3810-4540)	6683
Stomach	60.6 (56.8-64.0)	5420 (5080-5730)	8942
Kidney, renal pelvis, ureter	56.4 (51.7-61.1)	12,870 (11,790-13,930)	22,818
Colorectum	50.8 (47.4-54.1)	33,980 (31,650-36,130)	66,835
Urinary bladder	39.1 (37.1-41.2)	7010 (6640-7390)	17,914
Vulva	38.9 (34.1-43.1)	2050 (1800-2270)	5271
Gallbladder	36.5 (31.8-41.1)	1050 (920-1180)	2880
Breast	28.7 (26.0-31.7)	68,390 (61,800-75,510)	237,932
Pancreas	24.5 (21.6-27.8)	5390 (4750-6120)	22,031
Thyroid	12.8 (10.4-14.9)	4220 (3430-4930)	32,996
Myeloid leukemia	12.5 (10.7-14.3)	860 (740-990)	6904
Multiple myeloma	11.8 (8.9-15.0)	1350 (1010-1710)	11,403
Ovary	4.3 (2.8-5.8)	890 (570-1,190)	20,707
Non-Hodgkin lymphoma	2.4 (1.5-3.3)	720 (460-1,000)	30,398
Hodgkin lymphoma	1.5 (0.9-2.3)	40 (20-60)	2474

Abbreviations: CI, confidence interval; PAF, population attributable fraction. Cancer types are ordered by PAF, and numbers of attributable cancer cases are rounded to the nearest 10.

TABLE 3. Estimated Cancer Cases in Adults Aged 30 Years and Older in the United States in 2014 Attributable to Potentially Modifiable Risk Factors, by Sex, Risk Factor, and Cancer Type

	MEN		WOMEN		BOTH SEXES COMBINED	
CANCER	ATTRIBUTABLE CASES, NO. (95% CI)	PAF (95% CI), %	ATTRIBUTABLE CASES, NO. (95% CI)	PAF (95% CI), %	ATTRIBUTABLE CASES, NO. (95% CI)	PAF (95% CI), %
Cigarette smoking						
Lung	95,180 (94,380-95,950)	84.4 (83.6-85.0)	81,010 (79,980-81,950)	78.9 (77.9-79.8)	176,190 (174,910-177,390)	81.7 (81.2-82.3)
Larynx	7490 (7120-7810)	74.9 (71.2-78.1)	1810 (1700-1930)	69.5 (65.4-74.0)	9300 (8920-9650)	73.8 (70.8-76.6)
Esophagus	6940 (6680-7220)	52.1 (50.2-54.2)	1510 (1430-1590)	42.2 (40.0-44.6)	8450 (8180-8740)	50.0 (48.5-51.8)
Oral cavity, pharynx, nasal cavity, paranasal sinus	17,160 (16,260-18,000)	51.9 (49.2-54.4)	5810 (5480-6160)	42.8 (40.4-45.4)	22,960 (22,000-23,880)	49.2 (47.2-51.2)
Urinary bladder	28,050 (26,800-29,290)	49.4 (47.2-51.6)	7010 (6640-7390)	39.1 (37.1-41.2)	35,050 (33,830-36,400)	46.9 (45.4-48.6)
Liver	4950 (4460-5420)	24.8 (22.3-27.1)	1230 (1110-1350)	18.4 (16.6-20.1)	6180 (5700-6670)	23.2 (21.4-25.0)
Cervix	—	—	2380 (2040-2730)	19.9 (17.0-22.8)	2380 (2040-2730)	19.9 (17.0-22.8)
Kidney, renal pelvis, ureter	7580 (6860-8320)	19.2 (17.3-21.0)	3250 (2920-3590)	14.2 (12.8-15.8)	10,830 (10,040-11,660)	17.4 (16.1-18.7)
Stomach	2880 (2480-3260)	19.4 (16.7-22.0)	1280 (1110-1470)	14.3 (12.4-16.4)	4150 (3710-4570)	17.4 (15.6-19.2)
Myeloid leukemia	1490 (1290-1710)	17.1 (14.8-19.6)	860 (740-990)	12.5 (10.7-14.3)	2350 (2110-2600)	15.1 (13.5-16.6)
Colorectum	10,000 (9180-10,820)	13.5 (12.4-14.6)	6510 (5990-7040)	9.7 (9.0-10.5)	16,510 (15,550-17,540)	11.7 (11.0-12.5)
Pancreas	2770 (2430-3120)	11.7 (10.3-13.2)	1880 (1650-2090)	8.5 (7.5-9.5)	4640 (4230-5070)	10.2 (9.3-11.1)
Secondhand smoke						
Lung	3470 (2280-4770)	3.1 (2.0-4.2)	2340 (1510-3230)	2.3 (1.5-3.1)	5840 (4480-7310)	2.7 (2.1-3.4)
Excess body weight						
Corpus uteri	—	—	31,950 (29,190-34,840)	60.3 (55.1-65.7)	31,950 (29,190-34,840)	60.3 (55.1-65.7)
Gallbladder	430 (370-500)	32.9 (28.1-38.1)	1050 (920-1180)	36.5 (31.8-41.1)	1490 (1340-1630)	35.5 (31.9-38.8)
Liver	6680 (5460-7760)	33.4 (27.3-38.8)	2380 (2000-2770)	35.6 (30.0-41.4)	9050 (7800-10,230)	33.9 (29.2-38.4)
Kidney, renal pelvis	12,250 (10,830-13,450)	32.1 (28.3-35.2)	7740 (6980-8570)	35.2 (31.7-39.0)	19,980 (18,360-21,410)	33.2 (30.5-35.6)
Esophagus	4640 (4210-5050)	34.9 (31.7-38.0)	800 (710-880)	22.3 (20.0-24.6)	5440 (4990-5850)	32.2 (29.6-34.7)
Stomach	3210 (2760-3650)	21.7 (18.6-24.6)	960 (830-1090)	10.7 (9.3-12.2)	4170 (3700-4630)	17.5 (15.6-19.5)
Pancreas	3840 (3210-4560)	16.3 (13.6-19.3)	3860 (3210-4590)	17.5 (14.6-20.8)	7710 (6730-8750)	16.9 (14.7-19.2)
Thyroid	1340 (1100-1600)	11.5 (9.4-13.8)	4220 (3430-4930)	12.5 (10.7-14.3)	5550 (4740-6340)	12.5 (10.6-14.2)
Multiple myeloma	1590 (1180-2060)	10.9 (8.1-14.2)	1350 (1010-1710)	11.8 (8.9-15.0)	2950 (2410-3480)	11.4 (9.3-13.4)
Breast	—	—	26,780 (24,280-29,340)	11.3 (10.2-12.3)	26,780 (24,280-29,340)	11.3 (10.2-12.3)
Colorectum	3740 (3070-4400)	5.1 (4.1-6.0)	3600 (2970-4260)	5.4 (4.4-6.4)	7340 (6380-8290)	5.2 (4.5-5.9)
Ovary	—	—	890 (570-1190)	4.3 (2.8-5.8)	890 (570-1190)	4.3 (2.8-5.8)
Alcohol intake						
Oral cavity, pharynx	14,670 (13,880-15,450)	46.3 (43.8-48.8)	3450 (3210-3700)	27.4 (25.4-29.3)	18,130 (17,320-18,910)	40.9 (39.1-42.7)
Larynx	2560 (2290-2840)	25.6 (22.9-28.4)	370 (320-420)	14.0 (12.3-16.0)	2930 (2660-3200)	23.2 (21.1-25.4)

TABLE 3. *Continued*

CANCER	MEN		WOMEN		BOTH SEXES COMBINED	
	ATTRIBUTABLE CASES, NO. (95% CI)	PAF (95% CI), %	ATTRIBUTABLE CASES, NO. (95% CI)	PAF (95% CI), %	ATTRIBUTABLE CASES, NO. (95% CI)	PAF (95% CI), %
Alcohol intake [*Continued*]						
Liver	4960 (2920-7340)	24.8 (14.6-36.7)	800 (460-1180)	11.9 (6.9-17.7)	5750 (3740-8230)	21.6 (14.0-30.9)
Esophagus	2530 (2160-2840)	19.0 (16.2-21.4)	1010 (780-1250)	28.4 (21.9-35.1)	3540 (3120-3930)	21.0 (18.5-23.3)
Breast	—	—	39,060 (32,250-46,380)	16.4 (13.6-19.5)	39,060 (32,250-46,380)	16.4 (13.6-19.5)
Colorectum	12,670 (8250-17,150)	17.1 (11.1-23.2)	5380 (3630-7520)	8.1 (5.4-11.3)	18,090 (13,260-23,230)	12.8 (9.4-16.5)
Red meat consumption						
Colorectum	4900 (3240-6460)	6.6 (4.4-8.7)	2630 (1640-3710)	3.9 (2.5-5.5)	7540 (5550-9560)	5.4 (3.9-6.8)
Processed meat consumption						
Colorectum	7630 (5700-9560)	10.3 (7.7-12.9)	3850 (2780-4980)	5.8 (4.2-7.5)	11,530 (9340-13,770)	8.2 (6.6-9.8)
Stomach	660 (410-910)	4.4 (2.8-6.1)	470 (310-660)	5.3 (3.5-7.4)	1130 (840-1430)	4.8 (3.6-6.0)
Low fruit and vegetable consumption						
Oral cavity, pharynx	5400 (3710-7210)	17.1 (11.7-22.8)	2330 (1610-3030)	18.5 (12.8-24.0)	7770 (5810-9630)	17.6 (13.1-21.7)
Larynx	1700 (1130-2290)	17.0 (11.3-22.9)	480 (330-640)	18.3 (12.7-24.4)	2190 (1600-2780)	17.4 (12.7-22.1)
Lung	10,010 (8310-11,740)	8.9 (7.4-10.4)	9170 (7660-10,620)	8.9 (7.5-10.3)	19,150 (16,760-21,520)	8.9 (7.8-10.0)
Low dietary fiber consumption						
Colorectum	6910 (5160-8640)	9.3 (7.0-11.7)	7540 (5460-9580)	11.3 (8.2-14.3)	14,460 (11,620-16,970)	10.3 (8.3-12.1)
Low dietary calcium consumption						
Colorectum	2890 (2580-3200)	3.9 (3.5-4.3)	4020 (3600-4420)	6.0 (5.4-6.6)	6900 (6370-7440)	4.9 (4.5-5.3)
Physical inactivity						
Corpus uteri	—	—	14,140 (9940-17,890)	26.7 (18.8-33.7)	14,140 (9940-17,890)	26.7 (18.8-33.7)
Colon, excluding rectum[a]	11,650 (9380-13,800)	15.7 (12.7-18.6)	11,250 (9020-13,440)	16.8 (13.5-20.1)	22,930 (19,720-25,880)	16.3 (14.0-18.4)
Breast	—	—	9290 (6520-12,150)	3.9 (2.7-5.1)	9290 (6520-12,150)	3.9 (2.7-5.1)
Ultraviolet radiation						
Melanoma (skin)	45,120 (44,750-45,510)	96.0 (95.2-96.8)	29,320 (29,000-29,630)	93.7 (92.7-94.7)	74,460 (73,930-74,930)	95.1 (94.4-95.7)
H. pylori infection						
Stomach	3360 (3010-3660)	22.6 (20.3-24.7)	4070 (3670-4400)	45.5 (41.1-49.2)	7410 (6890-7890)	31.2 (29.0-33.2)
HBV infection						
Liver	1080 (610-1500)	5.4 (3.1-7.5)	700 (320-1050)	10.5 (4.8-15.7)	1760 (1150-2320)	6.6 (4.3-8.7)
HCV infection						
Liver	5670 (3920-7000)	28.4 (19.6-35.0)	780 (450-1070)	11.6 (6.8-15.9)	6450 (4660-7800)	24.2 (17.5-29.3)
Non-Hodgkin lymphoma	380 (250-570)	1.0 (0.7-1.5)	120 (60-200)	0.4 (0.2-0.6)	510 (370-700)	0.8 (0.5-1.0)

TABLE 3. *Continued*

CANCER	MEN		WOMEN		BOTH SEXES COMBINED	
	ATTRIBUTABLE CASES, NO. (95% CI)	PAF (95% CI), %	ATTRIBUTABLE CASES, NO. (95% CI)	PAF (95% CI), %	ATTRIBUTABLE CASES, NO. (95% CI)	PAF (95% CI), %
HHV8 infection						
Kaposi sarcoma	920 (870-980)	100 (93.9-100)	120 (100-140)	100 (83.5-100)	1040 (980-1110)	100 (94.2-100)
HIV infection						
Kaposi sarcoma	730 (590-790)	78.8 (64.5-86.0)	70 (40-100)	60.7 (30.6-80.6)	800 (660-870)	76.5 (63.6-83.3)
Anus	640 (450-770)	24.2 (17.1-29.5)	200 (120-290)	4.3 (2.5-6.3)	830 (650-1010)	11.4 (8.8-13.8)
Non-Hodgkin lymphoma	4850 (3520-5980)	13.2 (9.6-16.3)	590 (340-870)	1.9 (1.1-2.9)	5440 (4010-6640)	8.1 (6.0-9.9)
Hodgkin lymphoma	270 (190-350)	8.0 (5.7-10.3)	40 (20-60)	1.5 (0.9-2.3)	310 (230-380)	5.3 (3.9-6.6)
Cervix	—	—	80 (40-130)	0.7 (0.4-1.1)	80 (40-130)	0.7 (0.4-1.1)
HPV infection						
Cervix	—	—	11,970 (11,750-12,190)	100 (98.2-100)	11,970 (11,750-12,190)	100 (98.2-100)
Anus	2310 (2130-2480)	88.1 (81.5-94.8)	4150 (3920-4370)	88.3 (83.4-93.1)	6460 (6160-6740)	88.2 (84.1-92.1)
Vagina	—	—	860 (740-990)	64.6 (55.4-4.0)	860 (740-990)	64.6 (55.4-74.0)
Penis	860 (690-1030)	56.9 (45.8-68.6)	—	—	860 (690-1030)	56.9 (45.8-68.6)
Vulva	—		2050 (1800-2270)	38.9 (34.1-43.1)	2050 (1800-2270)	38.9 (34.1-43.1)
Oropharynx	5730 (4900-6690)	37.9 (32.4-44.2)	360 (260-480)	11.2 (8.0-14.9)	6100 (5240-7060)	33.2 (28.5-38.5)
Oral cavity	630 (380-940)	7.4 (4.5-11.1)	90 (50-160)	1.6 (0.9-2.7)	730 (480-1050)	5.1 (3.4-7.3)

Abbreviations: CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; HHV8, human herpes virus type 8; HIV, human immunodeficiency virus; HPV, human papillomavirus; H. pylori, *Helicobacter pylori*; PAF, population-attributable fraction. Numbers of attributable cancer cases are rounded to the nearest 10, and cancer types associated with each risk factor are ordered by PAF for both sexes combined. [a]PAF values are the percentages of all colorectal cancers.

men (46.3%; 14,670 cases) and one-fourth of esophageal (28.4%; 1010 cases) and oral cavity and pharyngeal (27.4%, 3450 cases) cancers in women were associated with alcohol; however, the largest burden by far was for female breast cancer (39,060 cases). In general, the proportions of cases attributable to alcohol intake by cancer type were higher in men than in women, except for esophageal cancer.

Poor diet

The proportion of all cancers attributed to poor diet ranged from 0.4% for low dietary calcium consumption to 1.9% for low fruit and vegetable consumption. However, for colorectal cancer specifically, the PAFs ranged from 4.9% (6900 cases) for low dietary calcium to 10.3% (14,460 cases) for low dietary fiber. Red and processed meat consumption accounted for 5.4% and 8.2% of colorectal cancers, respectively, with higher PAFs in men than in women. Low fruit and vegetable consumption was associated with 17.6% of oral cavity/pharyngeal cancers, 17.4% of laryngeal cancers, and 8.9% of lung cancers, and the highest number of attributable cases was from lung cancer (19,150 cases). There were no substantial differences between men and women in the PAFs for low fruit and vegetable or dietary fiber, while the PAF for low dietary calcium consumption was slightly higher in women.

Physical inactivity

Physical inactivity accounted for 2.9% of all cancers, with the highest proportion for cancer of the corpus uteri (26.7%; 14,140 cases), but the largest number of cases were for colon cancer (22,930; 16.3% of all colorectal cancer cases); 3.9% of female breast cancers (9290 cases) were attributable to physical inactivity.

The combination of excess body weight, alcohol intake, poor diet, and physical inactivity accounted for 13.9% of cancer cases in men (second to tobacco smoking, 24.0%), but it accounted for the highest proportion of cancer cases

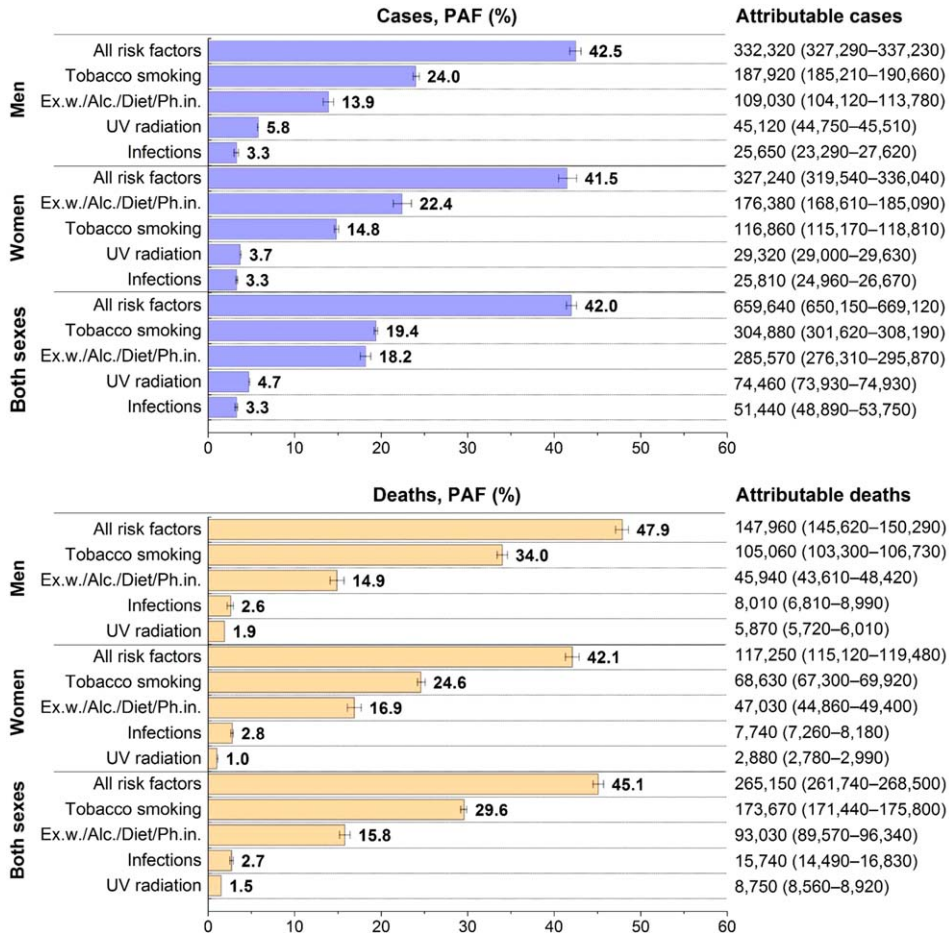

FIGURE 3. Estimated Proportion and Number of Incident Cancer Cases and Cancer Deaths Attributable to Risk Factor Groups in Adults Aged 30 Years and Older in the United States in 2014, by Sex.

Population-attributable fractions (PAFs) are the percentages of all incident cancer cases or cancer deaths (excluding nonmelanoma skin cancers). The bars in the figure and numbers in parentheses represent 95% confidence intervals. Numbers of attributable cancer cases and deaths are rounded to the nearest 10. Risk factor groups include tobacco smoking (cigarette and secondhand); excess body weight (Ex.w.), alcohol intake (Alc.), poor diet (Diet [consumption of red and processed meat; and low consumption of fruits/vegetables, dietary fiber, and dietary calcium]), and physical inactivity (Ph.in.); ultraviolet (UV) radiation (from any source); and infections (*Helicobacter pylori*; hepatitis B virus; hepatitis C virus; human herpes virus type 8; human immunodeficiency virus [only associated Hodgkin lymphoma and non-Hodgkin lymphoma], and human papillomavirus). The proportion of cancer cases attributable to poor diet only was 4.8% (37,810 cases) in men, 3.7% (28,880 cases) in women, and 4.2% (66,640 cases) in both sexes combined; the corresponding proportion for cancer deaths was 5.4% (16,630 deaths) in men, 4.7% (13,230 deaths) in women, and 5.1% (29,850 deaths) in both sexes combined.

in women (22.4%), followed by tobacco smoking (14.8%) (Fig. 3).

UV radiation

Despite an association with only one cancer, UV radiation was the second largest contributor to total cancer cases in men (5.8%; 45,120 cases) and the fifth largest contributor to total cancer cases in women (3.7%; 29,320 cases). Approximately 95% of skin melanoma cases were attributable to UV radiation exposure, with comparable PAFs in men and women.

Infections

Overall, 3.3% of all cancer cases were attributable to evaluated infections (Fig. 3). By infection type, the attributable fraction for all cases combined ranged from 0.1% to 1.2% in men and from less than 0.1% to 2.5% in women (Fig. 1). Although the number of gastric cancer cases attributable to *H. pylori* infection was similar in men (3360 cases) and women (4070 cases), the PAF in women (45.5%) was twice that in men (22.6%). While liver cancer in women was equally attributable to HBV infection (10.5%) and HCV infection (11.6%), in men, the PAF for HCV infection (28.4%) was 5 times that for HBV (5.4%). All cases of Kaposi sarcoma were attributed to HHV8. Non-Hodgkin lymphoma had the highest number of cancers (5440 cases) attributable to HIV infection.

All cervical cancers (11,970 cases) and 88.2% of anal cancers (6460 cases) were attributed to HPV infection. HPV infection also accounted for large fractions of cancers of the vagina (64.6%; 860 cases) and penis (56.9%; 860 cases). The proportion of HPV-attributable cases was higher in men than in women for cancers of the oropharynx (37.9% vs 11.2%) and oral cavity (7.4% vs 1.6%).

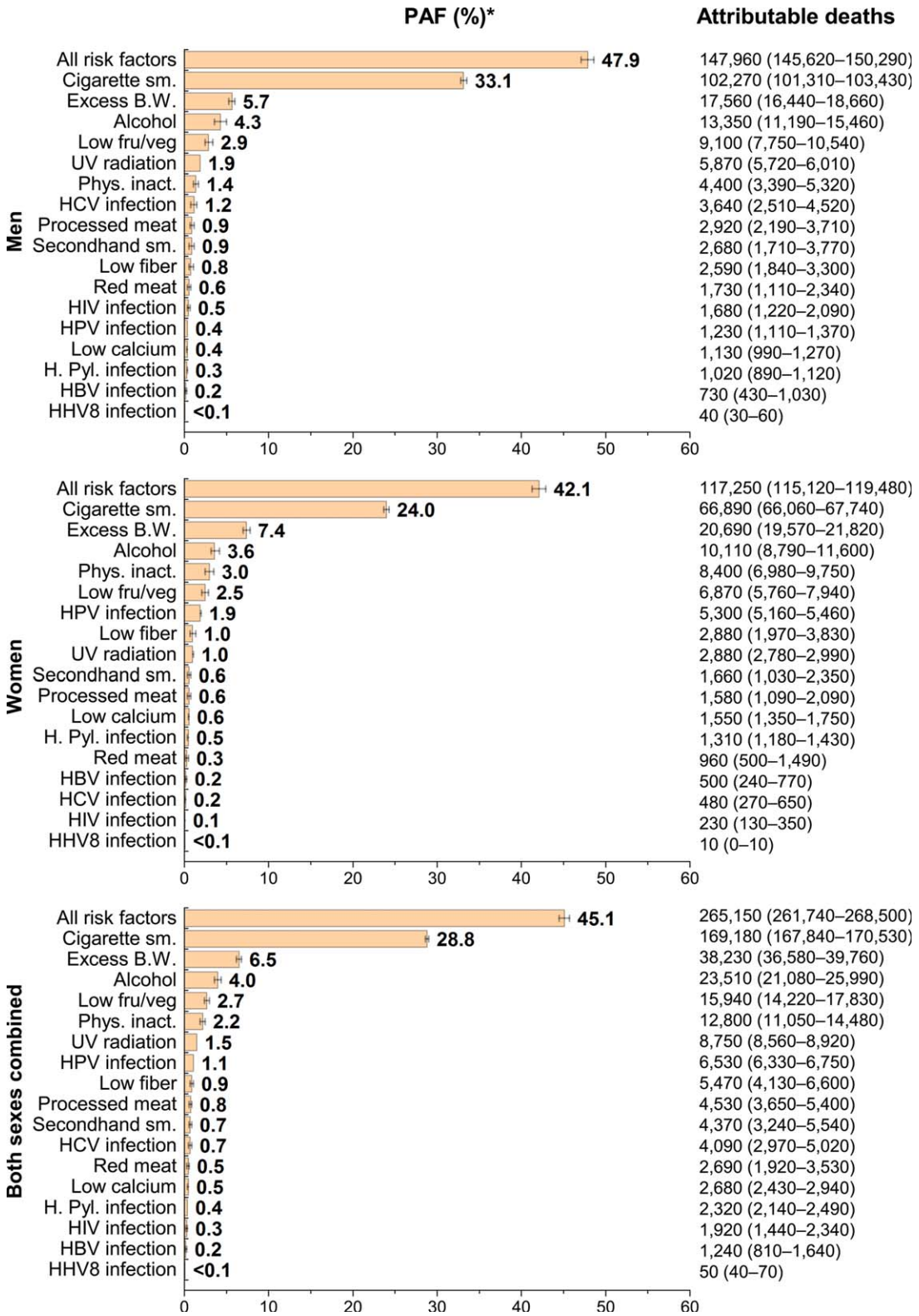

FIGURE 4. Estimated Proportion and Number of Cancer Deaths Attributable to Evaluated Risk Factors in Adults Aged 30 Years and Older in the United States in 2014, by Sex.

B.W. indicates body weight; CI, confidence interval; fru/veg, fruit and vegetable consumption; H. Pyl., *Helicobacter pylori*; HBV, hepatitis B virus; HCV, hepatitis C virus; HHV8, human herpes virus type 8; HPV, human papillomavirus; PAF, population-attributable fraction; Phys. inact., physical inactivity; sm., smoking; UV, ultraviolet. PAFs are the percentages of all cancer deaths in the United States in 2014. The total number of all cancer deaths (excluding nonmelanoma skin cancer deaths) in adults aged 30 years and older was 308,915 among men, 278,606 among women, and 587,521 in both sexes combined. The bars in the figure and numbers in parentheses represent 95% confidence intervals. Numbers of attributable cancer deaths are rounded to the nearest 10.

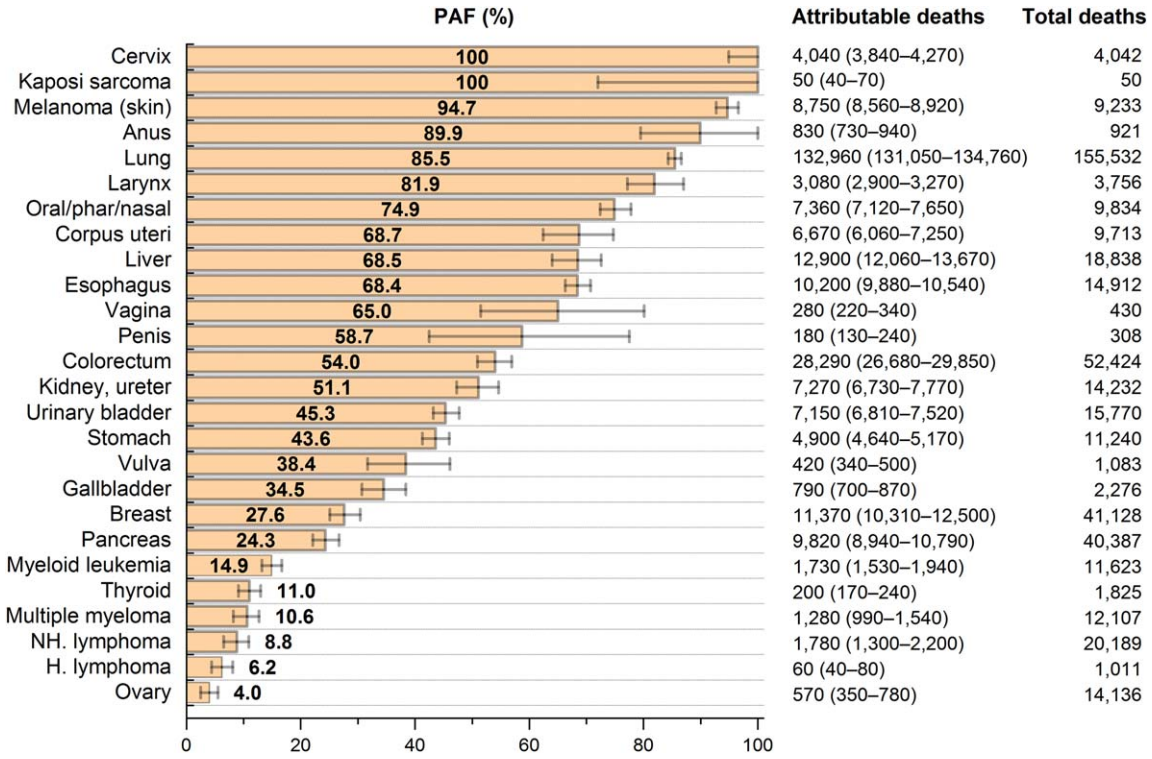

FIGURE 5. Estimated Proportion and Number of Cancer Deaths Attributable to Evaluated Risk Factors and Number of Total Cancer Deaths in Adults Aged 30 Years and Older in the United States in 2014, by Cancer Type.

H. lymphoma indicates Hodgkin lymphoma; NH. Lymphoma, non-Hodgkin lymphoma. Here, kidney also includes renal pelvis and ureter, and lung includes bronchus and trachea. Population-attributable fractions (PAFs) are the percentages of total deaths for each cancer type (both sexes combined). The bars in the figure and numbers in parentheses represent 95% confidence intervals. Numbers of attributable cancer deaths are rounded to the nearest 10.

Mortality

The PAF patterns for mortality were similar to those for incidence (Fig. 4). The proportion of all cancer deaths attributable to evaluated risk factors in 2014 was 47.9% (147,960 of 308,915 deaths) in men, 42.1% (117,250 of 278,606 deaths) in women, and 45.1% in both sexes combined (265,150 of 587,521 deaths). The risk factors considered in this analysis contributed to more than one-half of cancer deaths in 14 of the 26 cancer types (Fig. 5). By cancer type, lung cancer had the largest number of deaths attributable to evaluated risk factors in both men (74,990 deaths) and women (57,980 deaths), followed by colorectal cancer in both men (15,740 deaths) and women (12,570 deaths), liver cancer in men (9860 deaths), and breast cancer in women (11,370 deaths) (Table 4).

Cigarette smoking accounted for the greatest number (169,180 deaths) and proportion (28.8%) of overall cancer deaths, including 33.1% of deaths in men and 24.0% of deaths in women. In contrast to incidence, the fractions and numbers of cancer deaths because of excess body weight were similar in men (5.7%; 17,560 deaths) and women (7.4%; 20,690 deaths) (Fig. 4). Alcohol intake was the third largest contributor to overall cancer deaths in both men (13,350; 4.3% of all cancer deaths) and women (10,110; 3.6% of all cancer deaths). The combination of excess body weight, alcohol intake, poor diet, and physical inactivity accounted for 14.9% of cancer deaths in men and 16.9% in women (Fig. 3). The proportion of cancer deaths attributable to infections was 2.6% in men and 2.8% in women, which was slightly higher than that for UV radiation (1.9% and 1.0%, respectively). The proportions and numbers of cancer deaths attributable to evaluated risk factors by cancer type are shown in Table 5.

Discussion

We found that 42% of all incident cancer cases and almost one-half of all cancer deaths, representing 659,640 cancer cases and 265,150 deaths, were attributable to evaluated risk factors in the United States in 2014. Cigarette smoking was associated with far more cancer cases and deaths than any other single risk factor, accounting for nearly 20% of all cancer cases and 30% of all cancer deaths, followed by excess body weight. Lung cancer had the highest number of cancer cases or deaths attributable to potentially modifiable risk factors, followed by colorectal cancer.

The proportions of all cancer cases and deaths attributable to smoking, red and processed meat consumption, HCV infection, UV radiation, and HIV infection were higher in men compared with women, reflecting historically higher prevalence of these risk factors in men.[48-53] In contrast, the

TABLE 4. Estimated Proportion and Number of Cancer Deaths Attributable to All Evaluated Risk Factors and Estimated Total Number of Cancer Deaths in Adults Aged 30 Years and Older in the United States in 2014, by Sex and Cancer Type

CANCER	PAF (95% CI), %	ATTRIBUTABLE DEATHS, NO. (95% CI)	TOTAL NO. OF DEATHS
Men			
Kaposi sarcoma	100 (70.5-100)	40 (30-60)	44
Melanoma (skin)	96.0 (93.5-98.4)	5870 (5720-6010)	6113
Anus	90.1 (72.9-100)	320 (260-390)	351
Lung, bronchus, trachea	88.4 (86.7-90.0)	74,990 (73,570-76,350)	84,859
Larynx	83.1 (77.6-88.7)	2530 (2360-2700)	3045
Oral cavity, pharynx, nasal cavity, paranasal sinus	79.2 (76.3-82.7)	5570 (5360-5810)	7032
Liver	72.4 (66.3-77.7)	9860 (9020-10,570)	13,608
Esophagus	70.8 (68.3-73.3)	8450 (8150-8750)	11,936
Penis	58.7 (42.5-77.5)	180 (130-240)	308
Colorectum	57.5 (52.9-61.3)	15,740 (14,480-16,800)	27,393
Kidney, renal pelvis, ureter	50.5 (45.3-55.2)	4730 (4240-5170)	9369
Urinary bladder	48.7 (45.9-51.9)	5500 (5180-5860)	11,290
Stomach	44.0 (40.5-47.2)	2970 (2730-3180)	6742
Gallbladder	32.8 (27.1-39.5)	240 (190-280)	718
Pancreas	25.3 (22.3-28.6)	5240 (4620-5940)	20,737
Myeloid leukemia	17.1 (14.4-19.9)	1130 (950-1310)	6604
Non-Hodgkin lymphoma	14.2 (10.2-17.7)	1580 (1140-1980)	11,155
Thyroid	10.6 (8.0-13.7)	80 (60-110)	793
Multiple myeloma	10.3 (7.3-13.5)	680 (480-890)	6586
Hodgkin lymphoma	9.4 (6.5-12.5)	60 (40-70)	598
Women			
Cervix	100 (94.9-100)	4040 (3840-4270)	4042
Kaposi sarcoma	100 (33.3-100)	10 (0-10)	6
Melanoma (skin)	92.3 (89.2-95.8)	2880 (2780-2990)	3120
Anus	89.5 (75.9-100)	510 (430-590)	570
Lung, bronchus, trachea	82.0 (80.4-83.7)	57,980 (56,820-59,170)	70,673
Larynx	76.2 (66.6-86.8)	540 (470-620)	711
Corpus uteri	68.7 (62.4-74.7)	6670 (6060-7250)	9713
Vagina	65.0 (51.5-80.1)	280 (220-340)	430
Oral cavity, pharynx, nasal cavity, paranasal sinus	62.5 (57.9-68.0)	1750 (1620-1910)	2802
Esophagus	58.8 (54.6-63.3)	1750 (1620-1880)	2976
Liver	58.3 (52.6-64.4)	3050 (2750-3370)	5230
Kidney, renal pelvis, ureter	52.1 (46.0-58.0)	2540 (2240-2820)	4863
Colorectum	50.2 (45.8-54.5)	12,570 (11,470-13,650)	25,031
Stomach	43.1 (39.7-46.3)	1940 (1780-2080)	4498
Vulva	38.4 (31.7-46.1)	420 (340-500)	1083
Urinary bladder	36.9 (33.8-40.2)	1660 (1520-1800)	4480
Gallbladder	35.2 (30.5-40.2)	550 (480-630)	1558
Breast	27.6 (25.1-30.4)	11,370 (10,310-12,500)	41,128
Pancreas	23.2 (20.2-26.8)	4570 (3970-5270)	19,650
Myeloid leukemia	12.0 (10.1-14.1)	600 (510-710)	5019
Thyroid	11.2 (8.4-14.2)	120 (90-150)	1032
Multiple myeloma	10.7 (7.6-14.1)	590 (420-780)	5521
Ovary	4.0 (2.5-5.5)	570 (350-780)	14,136
Non-Hodgkin lymphoma	2.1 (1.0-3.4)	190 (90-310)	9034
Hodgkin lymphoma	1.4 (0.5-2.4)	10 (0-10)	413

Abbreviations: CI, confidence interval; PAF, population-attributable fraction. Cancer types are ordered by PAF, and numbers of attributable cancer deaths are rounded to the nearest 10.

TABLE 5. Estimated Cancer Deaths in Adults Aged ≥30 Years in the United States in 2014 Attributable to Potentially Modifiable Risk Factors, by Sex, Risk Factor, and Cancer Type

	MEN		WOMEN		BOTH SEXES COMBINED	
CANCER	ATTRIBUTABLE DEATHS, NO. (95% CI)	PAF (95% CI), %	ATTRIBUTABLE DEATHS, NO. (95% CI)	PAF (95% CI), %	ATTRIBUTABLE DEATHS, NO. (95% CI)	PAF (95% CI), %
Cigarette smoking						
Lung	71,300 (70,630-71,940)	84.0 (83.2-84.8)	55,070 (54,330-55,820)	77.9 (76.9-79.0)	126,410 (125,360-127,370)	81.3 (80.6-81.9)
Larynx	2230 (2100-2370)	73.2 (68.8-77.8)	470 (430-510)	66.4 (60.5-72.4)	2700 (2570-2840)	72.0 (68.3-75.7)
Esophagus	6220 (5980-6460)	52.1 (50.1-54.1)	1230 (1150-1310)	41.2 (38.6-43.9)	7440 (7190-7690)	49.9 (48.2-51.6)
Oral cavity, pharynx, nasal cavity, paranasal sinus	3530 (3330-3740)	50.2 (47.3-53.2)	1100 (1010-1200)	39.4 (36.2-42.7)	4640 (4400-4870)	47.1 (44.7-49.5)
Urinary bladder	5500 (5180-5860)	48.7 (45.9-51.9)	1660 (1520-1800)	36.9 (33.8-40.2)	7150 (6810-7520)	45.3 (43.2-47.7)
Liver	3320 (3010-3630)	24.4 (22.1-26.7)	900 (800-990)	17.2 (15.4-18.9)	4220 (3890-4540)	22.4 (20.7-24.1)
Cervix	—	—	790 (680-920)	19.6 (16.7-22.8)	790 (680-920)	19.6 (16.7-22.8)
Kidney, renal pelvis, ureter	1820 (1620-2030)	19.4 (17.3-21.6)	650 (570-740)	13.4 (11.7-15.2)	2470 (2250-2700)	17.4 (15.8-18.9)
Stomach	1290 (1090-1470)	19.1 (16.2-21.8)	610 (510-710)	13.6 (11.3-15.7)	1900 (1680-2100)	16.9 (14.9-18.7)
Myeloid leukemia	1130 (950-1310)	17.1 (14.4-19.9)	600 (510-710)	12.0 (10.1-14.1)	1730 (1530-1940)	14.9 (13.2-16.7)
Colorectum	3630 (3290-3960)	13.3 (12.0-14.4)	2270 (2040-2510)	9.1 (8.2-10.0)	5890 (5480-6310)	11.2 (10.5-12.0)
Pancreas	2320 (2010-2660)	11.2 (9.7-12.8)	1540 (1310-1750)	7.8 (6.7-8.9)	3860 (3480-4270)	9.6 (8.6-10.6)
Secondhand smoke						
Lung	2680 (1710-3770)	3.2 (2.0-4.4)	1660 (1030-2350)	2.3 (1.5-3.3)	4370 (3240-5540)	2.8 (2.1-3.6)
Excess body weight						
Corpus uteri	—	—	5500 (4960-6070)	56.7 (51.1-62.4)	5500 (4960-6070)	56.7 (51.1-62.4)
Gallbladder	240 (190-280)	32.8 (27.1-39.5)	550 (480-630)	35.2 (30.5-40.2)	790 (700-870)	34.5 (30.7-38.4)
Liver	4450 (3670-5120)	32.7 (26.9-37.6)	1750 (1450-2050)	33.4 (27.8-39.2)	6210 (5390-6960)	32.9 (28.6-36.9)
Kidney, renal pelvis	2780 (2450-3080)	30.4 (26.8-33.7)	1490 (1300-1700)	31.9 (27.7-36.3)	4270 (3920-4620)	30.9 (28.3-33.4)
Esophagus	3540 (3190-3880)	29.7 (26.7-32.5)	480 (430-530)	16.1 (14.3-17.9)	4010 (3670-4380)	26.9 (24.6-29.4)
Pancreas	3300 (2740-3930)	15.9 (13.2-19.0)	3290 (2720-3990)	16.8 (13.8-20.3)	6610 (5810-7560)	16.4 (14.4-18.7)
Stomach	1180 (1010-1360)	17.5 (15.0-20.2)	340 (290-390)	7.5 (6.4-8.6)	1520 (1340-1700)	13.5 (11.9-15.1)
Breast	—	—	4710 (4260-5140)	11.4 (10.3-12.5)	4710 (4260-5140)	11.4 (10.3-12.5)
Thyroid	80 (60-110)	10.6 (8.0-13.7)	120 (90-150)	11.2 (8.4-14.2)	200 (170-240)	11.0 (9.1-13.0)
Multiple myeloma	680 (480-890)	10.3 (7.3-13.5)	590 (420-780)	10.7 (7.6-14.1)	1280 (990-1540)	10.6 (8.2-12.7)
Colorectum	1330 (1080-1570)	4.8 (3.9-5.7)	1250 (1000-1530)	5.0 (4.0-6.1)	2590 (2210-2940)	4.9 (4.2-5.6)
Ovary	—	—	570 (350-780)	4.0 (2.5-5.5)	570 (350-780)	4.0 (2.5-5.5)

TABLE 5. *Continued*

CANCER	MEN		WOMEN		BOTH SEXES COMBINED	
	ATTRIBUTABLE DEATHS, NO. (95% CI)	PAF (95% CI), %	ATTRIBUTABLE DEATHS, NO. (95% CI)	PAF (95% CI), %	ATTRIBUTABLE DEATHS, NO. (95% CI)	PAF (95% CI), %
Alcohol intake						
Oral cavity, pharynx	3000 (2830-3180)	44.4 (41.9-47.2)	650 (590-710)	24.6 (22.5-27.1)	3640 (3460-3830)	38.9 (36.9-40.9)
Larynx	750 (660-830)	24.5 (21.7-27.3)	90 (80-110)	12.8 (11.1-14.9)	840 (750-920)	22.3 (20.1-24.6)
Liver	3270 (1970-4840)	24.0 (14.5-35.6)	570 (340-860)	10.9 (6.4-16.4)	3840 (2540-5420)	20.4 (13.5-28.8)
Esophagus	1900 (1620-2130)	15.9 (13.6-17.8)	610 (450-750)	20.6 (15.2-25.2)	2510 (2180-2780)	16.8 (14.6-18.6)
Breast	—		6350 (5250-7570)	15.4 (12.8-18.4)	6350 (5250-7570)	15.4 (12.8-18.4)
Colorectum	4460 (2870-6150)	16.3 (10.5-22.4)	1810 (1160-2660)	7.2 (4.6-10.6)	6290 (4590-8100)	12.0 (8.8-15.5)
Red meat consumption						
Colorectum	1730 (1110-2340)	6.3 (4.1-8.5)	960 (500-1490)	3.8 (2.0-5.9)	2690 (1920-3530)	5.1 (3.7-6.7)
Processed meat consumption						
Colorectum	2700 (1970-3490)	9.9 (7.2-12.7)	1430 (940-1940)	5.7 (3.7-7.7)	4160 (3310-5060)	7.9 (6.3-9.7)
Stomach	220 (140-310)	3.2 (2.0-4.6)	150 (100-210)	3.4 (2.2-4.6)	370 (270-480)	3.3 (2.4-4.2)
Low fruit and vegetable consumption						
Oral cavity, pharynx	1140 (790-1540)	17.0 (11.8-22.8)	480 (290-670)	18.5 (10.9-25.4)	1640 (1190-2060)	17.5 (12.7-22.0)
Larynx	520 (340-690)	17.0 (11.2-22.6)	130 (90-180)	18.4 (12.2-25.2)	650 (470-830)	17.3 (12.4-22.1)
Lung	7440 (6120-8740)	8.8 (7.2-10.3)	6250 (5150-7340)	8.8 (7.3-10.4)	13,660 (11,910-15,400)	8.8 (7.7-9.9)
Low dietary fiber consumption						
Colorectum	2590 (1840-3300)	9.5 (6.7-12.0)	2880 (1970-3830)	11.5 (7.9-15.3)	5470 (4130-6600)	10.4 (7.9-12.6)
Low dietary calcium consumption						
Colorectum	1130 (990-1270)	4.1 (3.6-4.6)	1550 (1350-1750)	6.2 (5.4-7.0)	2,680 (2430-2940)	5.1 (4.6-5.6)
Physical inactivity						
Corpus uteri	—	—	2670 (1840-3470)	27.5 (18.9-35.7)	2670 (1840-3470)	27.5 (18.9-35.7)
Colon, excluding rectum[a]	4400 (3390-5320)	16.0 (12.4-19.4)	4340 (3260-5350)	17.3 (13.0-21.4)	8740 (7220-10,130)	16.7 (13.8-19.3)
Breast	—	—	1410 (1080-1740)	3.4 (2.6-4.2)	1410 (1080-1740)	3.4 (2.6-4.2)
Ultraviolet radiation						
Melanoma (skin)	5870 (5720-6010)	96.0 (93.5-98.4)	2880 (2780-2990)	92.3 (89.2-95.8)	8750 (8560-8920)	94.7 (92.7-96.6)
H. pylori infection						
Stomach	1020 (890-1120)	15.1 (13.2-16.6)	1310 (1180-1430)	29.1 (26.2-31.8)	2320 (2140-2490)	20.6 (19.1-22.1)
HBV infection						
Liver	730 (430-1030)	5.4 (3.1-7.6)	500 (240-770)	9.6 (4.5-14.6)	1240 (810-1640)	6.6 (4.3-8.7)

TABLE 5. *Continued*

CANCER	MEN		WOMEN		BOTH SEXES COMBINED	
	ATTRIBUTABLE DEATHS, NO. (95% CI)	PAF (95% CI), %	ATTRIBUTABLE DEATHS, NO. (95% CI)	PAF (95% CI), %	ATTRIBUTABLE DEATHS, NO. (95% CI)	PAF (95% CI), %
HCV infection						
Liver	3550 (2420-4420)	26.1 (17.8-32.5)	450 (260-630)	8.7 (4.9-12.1)	3990 (2860-4900)	21.2 (15.2-26.0)
Non-Hodgkin lymphoma	90 (50-150)	0.8 (0.5-1.3)	20 (10-30)	0.2 (0.1-0.4)	110 (70-170)	0.6 (0.4-0.8)
HHV8 infection						
Kaposi sarcoma	40 (30-60)	100 (70.5-100)	10 (0-10)	100 (33.3-100)	50 (40-70)	100 (72.0-100)
HIV infection						
Kaposi sarcoma	40 (30-50)	88.6 (61.4-100)	0 (0-10)	50.0 (16.7-100)	40 (30-60)	86.0 (60.0-100)
Anus	90 (60-110)	25.1 (17.2-31.6)	20 (10-40)	4.0 (2.3-6.3)	110 (80-140)	12.1 (9.1-14.9)
Non-Hodgkin lymphoma	1500 (1040-1900)	13.5 (9.3-17.0)	170 (70-290)	1.9 (0.8-3.2)	1670 (1210-2090)	8.3 (6.0-10.4)
Hodgkin lymphoma	60 (40-70)	9.4 (6.5-12.5)	10 (0-10)	1.4 (0.5-2.4)	60 (40-80)	6.2 (4.4-8.1)
Cervix	—	—	30 (20-40)	0.6 (0.4-0.9)	30 (20-40)	0.6 (0.4-0.9)
HPV infection						
Cervix	—	—	4040 (3920-4170)	100 (97.1-100)	4040 (3920-4170)	100 (97.1-100)
Anus	320 (260-390)	90.1 (72.9-100)	510 (430-590)	89.5 (75.9-100)	830 (730-940)	89.9 (79.5-100)
Vagina	—	—	280 (220-340)	65.0 (51.5-80.1)	280 (220-340)	65.0 (51.5-80.1)
Penis	180 (130-240)	58.7 (42.5-77.5)	—	—	180 (130-240)	58.7 (42.5-77.5)
Vulva	—	—	420 (340-500)	38.4 (31.7-46.1)	420 (340-500)	38.4 (31.7-46.1)
Oropharynx	570 (480-660)	37.5 (31.8-43.9)	50 (30-70)	10.9 (7.7-15.0)	620 (530-710)	31.5 (27.0-36.5)
Oral cavity	180 (110-270)	7.3 (4.5-11.1)	20 (10-40)	1.5 (0.8-3.0)	200 (120-290)	5.4 (3.4-7.9)

Abbreviations: CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; HHV8, human herpes virus type 8; HIV, human immunodeficiency virus; HPV, human papilloma virus; H. pylori, *Helicobacter pylori*; PAF, population-attributable fraction. Cancer types associated with each risk factor are ordered by PAF in both sexes combined, and the numbers of attributable cancer deaths are rounded to the nearest 10. [a]PAF values are the percentages of all colorectal cancers.

proportions were higher in women for excess body weight, alcohol intake, physical inactivity, and HPV infection, largely driven by the high burden of breast, endometrial, and cervical cancers attributable to these risk factors.

Our overall PAFs are generally comparable to those from recent studies that used similar methods.[5-11] However, there are some notable differences, mainly in the proportion of specific cancer types attributable to a given risk factor. For example, previous studies reported larger proportions of HCV-associated liver cancer in women (26%-28%) than in men (18%-19%),[8,54] whereas we found the reverse (28% in men vs 12% in women), consistent with higher HCV infection prevalence in men.[51] A previous estimate of the PAF for cancer mortality specifically because of excess weight reported a slightly lower PAF for men (4% vs 6% in our study) and a higher PAF for women (14% vs 7%).[55] However, these estimates were based on exposure data for a relatively narrow age group and used risk estimates for all cancers combined without taking into account the distribution of deaths and RRs by cancer type.

Several previous studies reported on the proportion of cancers attributable to various risk factors in the United States using cohort data,[56,57] and the findings from some of those studies differ slightly from ours. For example, compared with our study, the PAFs for cancer incidence within cohort studies of health professionals reported by Song and Giovannucci[56]

were lower than those in our study for both men (33% vs 43% in our study) and women (25% vs 42%), whereas the PAF for mortality was slightly lower in men (44% vs 48%) and higher in women (48% vs 42%). The lower PAFs in that study may be related in part to the lower numbers of risk factors considered and the inclusion of moderate alcohol drinkers and some former smokers in the low-risk group. In general, however, PAFs within cohort studies may not be directly generalizable to the entire US population, mainly because of potential differences in exposure prevalence between the general population and cohort study participants.[58,59]

Smoking

Despite substantial declines in overall smoking prevalence over the past 5 decades,[41,48,60] cigarette smoking remains the leading contributor to cancer cases and deaths in both men and women, accounting for 19% of all cancer cases and 29% of all cancer deaths. These estimates are comparable to findings from previous studies.[5,9] Our results reemphasize that expanding comprehensive tobacco-control programs could have the greatest impact on reducing the overall cancer burden in the United States. It is noteworthy that we did not include the use of tobacco products other than cigarettes[14,61] and only considered smoking for cancer types with an established causal association according to IARC reports, although there is accumulating evidence for causal associations between smoking and additional cancers (eg, breast cancer).[62] In an earlier study that also considered these cancer types, the proportion of cancer deaths attributable to cigarette smoking was about 32%.[63] Furthermore, a considerable proportion of cancer deaths categorized as unknown site actually may be caused by smoking-attributable cancers.[62] Thus, the burden of cancer attributable to smoking is likely higher than we have estimated.

Proven measures to reduce smoking include taxation, smoke-free laws, assistance with smoking cessation, warning labels and media campaigns, and marketing bans.[48] In the United States, taxation appears to have the strongest effect, followed by smoke-free laws, which can also substantially reduce exposure to SHS and related health issues.[48,64,65] Tobacco taxation has a higher impact on lower income people, who also have a higher smoking prevalence, and on youth, because taxation may prevent them from initiating smoking.[48,65,66] However, there is wide variation across states in the number and intensity of implemented measures.[9,64,66] For example, the state-level tax per cigarette pack as of April 2017 ranged from $0.17 in Missouri to $4.35 in New York (with an additional $1.50 in New York City).[67] In addition, as of July 2017, only 25 states and the District of Columbia had implemented comprehensive smoke-free laws in all 3 recommended locations (worksite, restaurants, and bars).[68] Currently, no state has fully implemented the CDC's recommended comprehensive tobacco-control measures.[69]

It is also important to integrate tobacco initiation prevention and support for cessation into the health care system,[70] but these services are generally underused, especially in low-income and uninsured individuals.[71] Moreover, only less than 4% of eligible current or former smokers received the recommended lung cancer screening in the United States in 2015.[72] Overall, broad implementation of effective cancer prevention and control interventions, including tobacco-control policies, has been challenging in the United States.[73] There is a need for increasing awareness about the health hazards of smoking to discourage initiation and promote cessation; for equitable access to cessation services; and, more important, for further political commitment to tobacco control (including securing financial resources) at the local, state, and federal levels to substantially reduce the burden of smoking-related diseases.[69,74]

Excess Body Weight, Alcohol Intake, Poor Diet, and Physical Inactivity

We estimated that nearly 7% to 8% of all cancer cases and deaths in the United States were attributable to excess body weight and 4% to 6% of cases and deaths were due to alcohol intake, respectively, similar to other recent estimates.[6,7,11,75] Previous PAFs for poor diet included variable dietary factors and criteria,[76] but more recent PAFs are comparable to our estimates (4% to 5% of all cancer cases and deaths).[77] Our estimated PAF for physical inactivity (2% to 3% of all cancer cases and deaths) is slightly higher than earlier PAFs.[4]

The combination of excess body weight, alcohol intake, poor diet, and physical inactivity accounted for the highest proportion of all cancer cases in women and was second only to tobacco smoking in men. These 4 combined risk factors also accounted for the second highest proportion of cancer deaths in both men and women. These findings underscore the importance of adherence to comprehensive guidelines on weight control, alcohol, diet, and physical activity. Indeed, large, prospective epidemiologic studies have demonstrated that adherence to a lifestyle consistent with the American Cancer Society's cancer prevention guidelines for maintaining a healthy body weight, limiting alcohol intake (for those who drink), consuming a healthy diet, and being physically active[38] is associated with a reduced risk of developing and dying from cancer.[78,79] Currently, nearly three-fourth of adults and one-third of children and adolescents aged 2 to 19 years are overweight or obese.[80,81] Furthermore, many Americans regularly drink alcohol and do not meet other dietary recommendations.[49,60,82] Despite a modest decrease in physical inactivity prevalence over the past few decades, it remains substantially high in the United States (see Supporting Information Table 2).[83]

For many children, excess body weight extends into adulthood and increases the risk of adverse health conditions and death,[84,85] so weight control in childhood should be a major focus of any strategy to control the obesity epidemic.[86,87] School-based interventions can provide an opportunity for promoting healthy diet, physical activity, and weight control, as well as family-based interventions.[88-90] Several studies have demonstrated that intensive lifestyle interventions to promote healthy eating and physical activity are effective among adults,[91,92] although long-term effects of such interventions at the population level have generally been modest at best.[83,88,89] Studies of behavioral interventions for reducing alcohol intake have focused primarily on alcohol use disorders and have produced mixed results,[93] whereas information on more commonly consumed levels is much more limited.

Effective implementation of preventive measures (consultation, screening, and treatment) in the health care system and increasing awareness through education campaigns may help to reduce excess body weight and alcohol intake and promote healthier diet and physical activity.[84,92,94-98] Some regulations may be highly beneficial, such as taxation and reducing marketing of nonessential high-calorie foods, sugary beverages, and alcohol; regulating alcohol outlet density and the days and hours of alcohol sale; and improving civil structure (eg, increasing public transportation and safe sidewalks).[99-103] For example, similar to the effect of taxation on tobacco smoking, higher excise taxes on alcohol have been associated with a substantial reduction in alcohol intake.[104] However, more research is still needed to identify tailored, more efficient interventions, particularly those that could be successfully applied at the community level.

UV Radiation

We estimated that nearly 95% of all skin melanoma cases and deaths in the United States are attributable to UV radiation, comparable to earlier studies.[46] Moreover, UV radiation from sun exposure and indoor tanning can increase the risk of nonmelanoma skin cancers (4.3 million individuals are treated annually in the United States), which are less fatal but associated with substantial financial burden.[105] Both melanoma and nonmelanoma skin cancers are increasing in the United States, making skin cancer prevention increasingly important.[105-107]

Sun-protection measures, including limiting excessive sun exposure; wearing protective clothing, hat, and sunglasses; and using broad-spectrum sunscreens, have been recommended to reduce skin cancer risk.[108] Although more research on the effectiveness of sunscreen use at the population level is needed,[109] several studies have either shown a direct decrease in melanoma risk after regular application of approved products[110,111] or have suggested a reduction in melanoma incidence rates in areas where sunscreens are freely available.[112] However, the uptake of sun-protection measures in the United States is far from optimal, but it may improve through multicomponent interventions at the community level.[108,113]

Reducing indoor tanning is particularly important among adolescents, because exposure at younger ages is associated with a higher risk of skin cancer up to at least age 50 years.[114,115] Federal- and state-level interventions to restrict access to indoor tanning or educate youth about the harms are likely to have contributed to a decrease in the overall indoor tanning prevalence among youth in the United States in recent years.[116-118] However, because of wide variations in regulation strictness (including the defined age limit) or compliance across states, high numbers of adolescents in the United States still engage in indoor tanning (eg, 1.2 million [7% of] high school students in 2015).[118]

Infections

Approximately 3% of all cancer cases in our study were attributable to infections, similar to 4% in an earlier study that also included less common infections (for which exposure prevalence could only be estimated).[10] *H. pylori* infection prevalence in the United States has decreased in the past century, probably because of improvements in sanitation and living conditions and more widespread antibiotic use.[119] This trend was followed by a decrease in gastric noncardia cancer incidence rates in the country.[120] Currently, screening for *H. pylori* and subsequent treatment is only recommended for people with certain conditions, and there is no evidence to support routine screening in other individuals.[121,122]

In contrast to *H. pylori* infection, chronic HCV infection prevalence in the United States increased in the last one-half of the 20th century (mainly among Baby Boomers),[51] which contributed in part to rising liver cancer rates.[123] Interventions to reduce HCV and HBV burden include increasing awareness; HBV vaccination; screening; treatment to cure HCV infection; and comprehensive programs to reduce transmission through high-risk behaviors (eg, using shared syringes); however, the uptake of many of these interventions is suboptimal in the United States.[123-127] For example, one-time HCV testing is recommended for Baby Boomers, but only 14% report HCV testing.[128] HBV vaccination coverage is only 65% among health care personnel and is even lower in other high-risk adults for whom HBV vaccination is recommended (eg, 27% among those with chronic liver conditions).[127]

Among people with HIV infection, highly active antiretroviral therapy reduces the risk of cancers that define the onset of acquired immunodeficiency syndrome (AIDS), ie, Kaposi sarcoma, non-Hodgkin lymphoma, and cervical cancer.[129,130] At the same time, however, increasing rates of

successful highly active antiretroviral therapy have also increased the number of HIV-infected individuals who are aging, leading to increased number of non–AIDS-defining cancers in this population.[129,130] As most carcinogenic infections (because of shared transmission routes with HIV) and smoking are more common in people with HIV infection,[131] receiving recommended vaccines (including HPV vaccine through age 26 years and HBV vaccine at any age),[132] screenings (eg, for HCV infection), and smoking-cessation services is even more important in this group.

Some cancer types that are highly associated with HPV infection have shown contradictory incidence rate trends in the United States in recent decades. Cervical cancer incidence and death rates have been decreasing since the mid-20th century, mainly because of the widespread use of cervical cancer screening.[133] Conversely, incidence rates for cancers of the tongue base and tonsil among younger men and anal cancer in both sexes have been increasing, in part because of changes in sexual behavior.[134-136] Although HPV vaccination can prevent anogenital cancer and is recommended at ages 11 and 12 years (but can be given up to age 26 years),[137] only 50% of females and 38% of males ages 13 to 17 years in the United States were up to date with HPV vaccination as of 2016.[138] Furthermore, the cervical cancer screening rate for uninsured women, among whom HPV infection is more common, is much lower than that for insured women (61% vs 84%, respectively).[60]

Strengths and Limitations

We have provided contemporary estimates of the PAFs of cancer cases and deaths for several potentially modifiable risk factors (including some risk factors that were not included in previous studies) in the United States using contemporary, nationally representative data on exposure, occurrence (accounting for delayed reporting), and RRs. Furthermore, we used a systematic approach, as well as exposure and outcome data largely from the same period, to compute PAFs; thus, our estimates are comparable across risk factors and cancer types.

However, there are several inherent limitations in studies that estimate the PAF of cancer caused by specific exposures. The selected RRs may not be homogenous across sexes and age groups. In addition, we used the same RRs in calculations for both cancer deaths and cases, because RRs were generally available only for cases, with some exceptions. However, some risk factors may affect the survival of patients with cancer and, thus, have an impact on cancer mortality beyond that for incidence. Similarly, survival for some cancer subtypes for which we estimated death counts using case-based proportions is known to be different from survival for other subtypes within the overall cancer type (eg, for colon cancer, 5-year relative survival is slightly lower than that for rectal cancer). Furthermore, in general, we used the most recent exposure data rather than historical data; because, for most risk factors, the latency from exposure to cancer occurrence is not well defined.[139,140] Therefore, our PAF estimates for exposures with declining or increasing prevalence in recent years could be underestimated or overestimated, respectively.

Finally, when calculating PAFs, we assumed that the risk factors were independent, and no robust, comprehensive information was available on the nature or magnitude of the amount of overlap among risk factors at the population level. Therefore, some PAFs may be slightly overestimated. Conversely, we did not include several other potentially modifiable risk factors, such as breastfeeding, because of a lack of representative exposure data (see Supporting Information Table 1), and we did not consider some other likely associations that had less than sufficient or strong evidence for a causal association with cancer according to the IARC or the WCRF/AICR, notably for smoking,[62] despite accumulating evidence for a causal association. Thus, we likely underestimated the actual proportions of cancers attributable to some individual risk factors and all potentially modifiable factors combined. Furthermore, some risk factors may be more important when exposure occurs in adolescence or earlier,[141] such as excess body weight and colorectal cancer,[142] which are likely unaccounted for by RRs from studies of mostly older adults. More research is needed on earlier life exposures that can increase the risk of cancer in adulthood.

Conclusions

An estimated 42% of all cancer cases and nearly one-half of all cancer deaths in the United States in 2014 were attributable to evaluated risk factors, many of which could have been mitigated by effective preventive strategies, such as excise taxes on cigarettes to reduce smoking and vaccinations against HPV and HBV infections. Our findings emphasize the continued need for widespread implementation of known preventive measures in the country to reduce the morbidity and premature mortality from cancers associated with potentially modifiable risk factors. Increasing access to preventive health care and awareness about preventive measures should be part of any comprehensive strategy for broad and equitable implementation of interventions to accelerate progress against cancer. However, for some of the risk factors considered in the current analysis, such as unhealthy diet, further implementation research is needed for widespread application of known interventions, particularly for populations at a higher risk. Further research is also needed on the etiology of cancer, particularly cancers for which avoidable risk factors with substantial PAFs are not well known (eg, prostate and pancreas cancers) or where the evidence is considered insufficient for causality in humans. ■

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Homocysteine: Friend or Foe?

Joseph Pizzorno, ND, Editor in Chief

We are all well aware that high levels of homocysteine are associated with a wide range of diseases, as shown in Table 1. This would tend to imply that homocysteine is a toxic molecule, and the less the better.

I have watched with interest as the recommended maximum "safe" levels have dropped several times through the past 2 decades as research has progressed. Several months ago, one of the thought leaders in nutritional medicine recommended, at a lecture I attended, that homocysteine should be less than 6 mg/L. I found this intriguing and likely very difficult to attain. Then as I was studying the biochemistry of glutathione for my editorial in February 2014,[1] I couldn't help but notice the homocysteine/methylation cycle, right in the middle of a lot of metabolism. It got me to wondering if, like cholesterol (see my editorial from June 2014),[2] perhaps we were inappropriately vilifying a molecule important for health.

Initially, it looked to me like homocysteine might be an important storage/transfer molecule and the factors that cause its elevation are the actual problem, not the homocysteine itself. So this led me to ask 4 questions:

(1) Does homocysteine play an important role in metabolism?
(2) Is homocysteine itself toxic?
(3) What causes homocysteine to increase?
(4) What is the optimal level of homocysteine in the blood?

Table 1. Diseases and Conditions Associated With Hyperhomocysteinemia

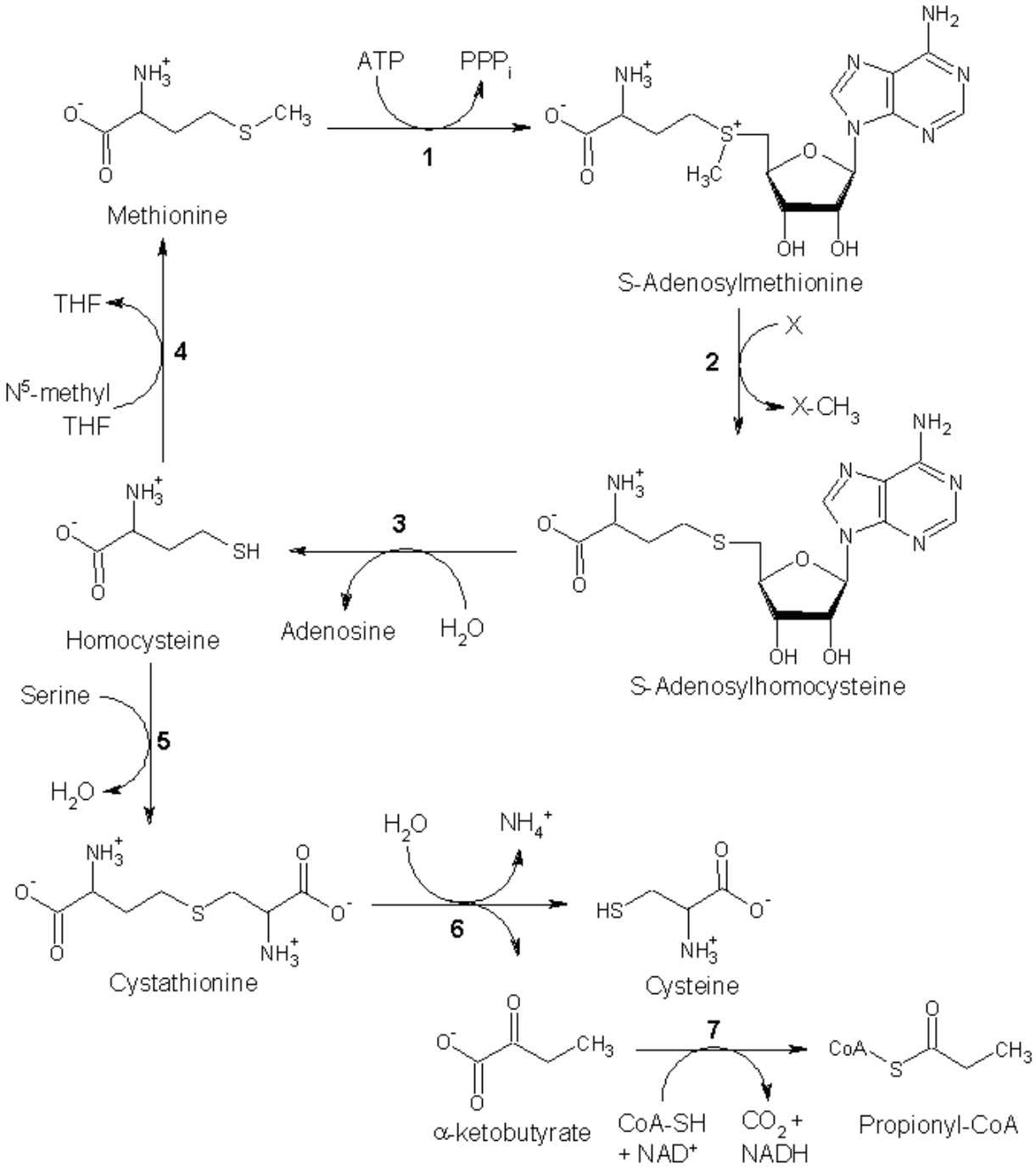
Alzheimer's disease
Birth defects
Blood clots
Cancer
Coronary artery disease
Dementia
Endothelial damage
Miscarriage
Myocardial infarction
Parkinson's disease
Pre-eclampsia
Stroke

Following is what I found in the research. As a PubMed search of homocysteine produces more than 13 000 hits, there is obviously much more than I can cover here.

Metabolic Role

Does homocysteine play an important role in metabolism? Homocysteine is not obtained from the diet. Rather, it is synthesized from methionine via a multistep process. The first clue that homocysteine plays an important role in the body is that this synthesis requires energy. Homocysteine is a nonprotein α-amino acid homologue of cysteine, which, as can be seen in Figure 1, differs from cysteine by an additional methylene bridge ($-CH_2-$). It is biosynthesized from methionine by the removal of a terminal methyl group.

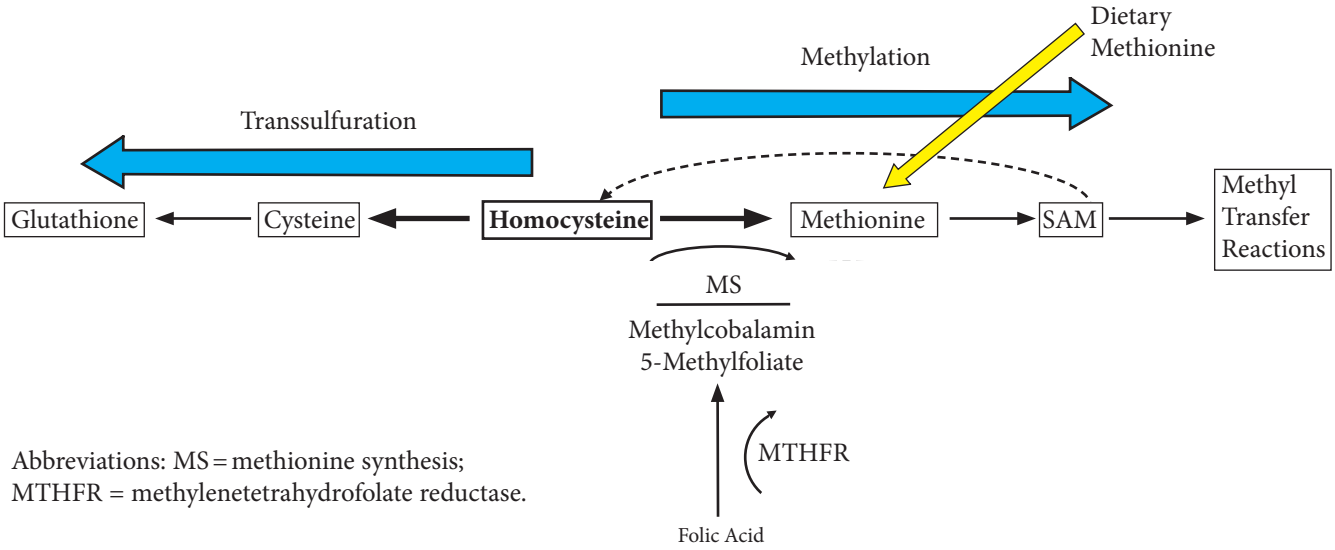
Figure 1. Methionine Cycle[3]



Stating the question differently: Is hypohomocysteinemia associated with metabolic dysfunction or disease?

Turns out the answer is yes: Low homocysteine levels do indeed have disease correlations. For example, low homocysteine has been shown to have a strong association with peripheral neuropathy. A surprising 41% of patients with idiopathic peripheral neuropathy have hypohomocysteinemia.[4] As can be seen in Figure 2, homocysteine can be considered a storage molecule for sulfur and a transfer molecule for methyl metabolism. For example, homocysteine is clearly a storage molecule for cysteine, the rate limiting amino acid for glutathione production.

Figure 2. Homocysteine as Storage for Sulfur and Transfer for Methyl Molecules



Abbreviations: MS = methionine synthesis; MTHFR = methylenetetrahydrofolate reductase.

Homocysteine enables single carbon units to be shuttled from the reduced folate pool to the principal methyl donor in the cell. Hypohomocysteinemia—defined as less than 6.0 mmol/L—is not common, occurring in only 0.5% to 1.0% of the population.[4]

Low homocysteine may also be indicative of excessive conversion to cystathione for use in the transsulfuration pathways (see Figure 2) for production of glutathione, taurine, and sulfate. Low homocysteine would suggest impaired ability for de novo production of glutathione and thus increased susceptibility to oxidative stress.

Is Homocysteine Itself Toxic?

We can thank Kilmer McCully, MD, (Winner of the Linus Pauling Award from Institute for Functional Medicine in 1999) for first discovering that elevated levels of homocysteine are associated with cardiovascular disease. Since then, as shown in Table 1, many more disease associations have been found. The question arises: Is homocysteine itself toxic or is it an indirect measure of the actual causative factors? It looks like the answer is a bit of both.

In cell cultures, homocysteine induces programmed cell death in human vascular endothelial cells by interfering in protein syntheses.[5] Because of its similarity to methionine, homocysteine can enter the protein biosynthetic apparatus. However, it cannot complete the protein biosynthetic pathway, resulting in abnormal proteins and adducts that are toxic to cells.[6] These abnormal proteins can also initiate an immune response as they are now foreign to normal body tissues. As can be seen in Figure 3, in addition to impairing protein synthesis, homocysteine is also directly toxic to the endoplasmic reticulum, activates glutamate receptors, and damages DNA.

Equally important, homocysteine elevation is clearly a marker of dysfunctional metabolism.[7] The many nutritional, hormonal, and genetic factors that raise homocysteine levels are also associated with common pathological conditions, such as cancer, autoimmune diseases, endothelial dysfunction, and neurodegenerative disease.

There are 3 pathways for reducing homocysteine levels: 2 are for homocysteine remethylation to methionine and the third through conversion into cystathione for transsulfuration, as can be seen in Figure 4. The first is dependent on the folate coenzyme 5-methyltetrahydrofolate that can donate a methyl group to homocysteine in a reaction catalyzed by the vitamin B_{12}–dependent enzyme methionine synthase. The supply of 5-methyltetrahydrofolate depends on vitamin B_6 and the catalytic activity of MTHFR where single nucleotide polymorphisms of MTHFR (C677T) are common, thus impairing folate-dependent remethylation of homocysteine. The second route for homocysteine remethylation is independent of the 1-carbon pool, using betaine, derived from diet or the oxidation of choline, as a methyl group source in a reaction catalyzed by betaine-homocysteine methyltransferase (BHMT). Although folate-dependent remethylation is found in all tissues, the betaine pathway is only found in the liver and kidneys.

Somewhat surprising, most of the research looking at the correlation between hyperhomocysteinemia and a wide range of diseases—cardiovascular disease (eg, atherosclerosis and thrombosis), autoimmune disease (eg, type 1 and type 2 diabetes), gastrointestinal disorders (eg, constipation, inflammatory bowel disease, Crohn's disease, and colorectal cancer), bone density, and neurodegenerative disease (eg, Alzheimer's disease, depression, and Parkinson's disease)—actually find significantly stronger associations with aberrant methylation and folate metabolism abnormalities.[5] This

Figure 3. Homocysteine Metabolism[8]

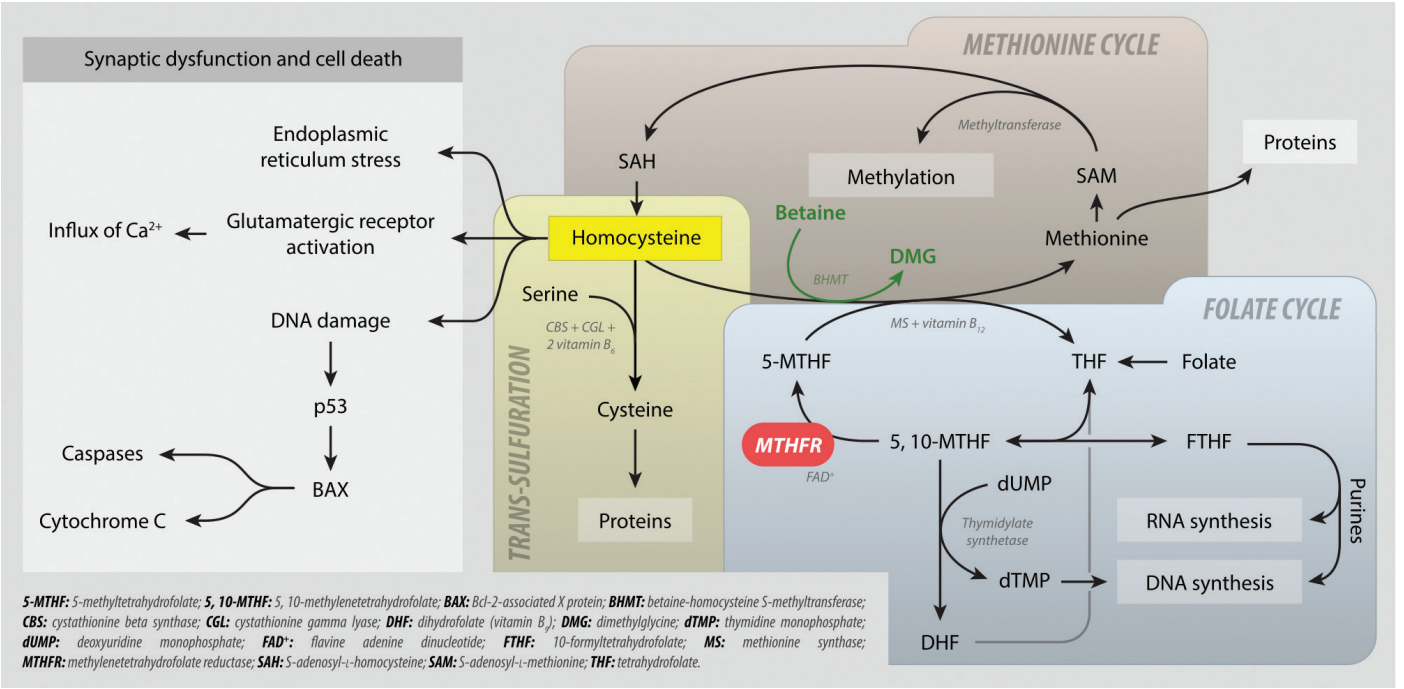
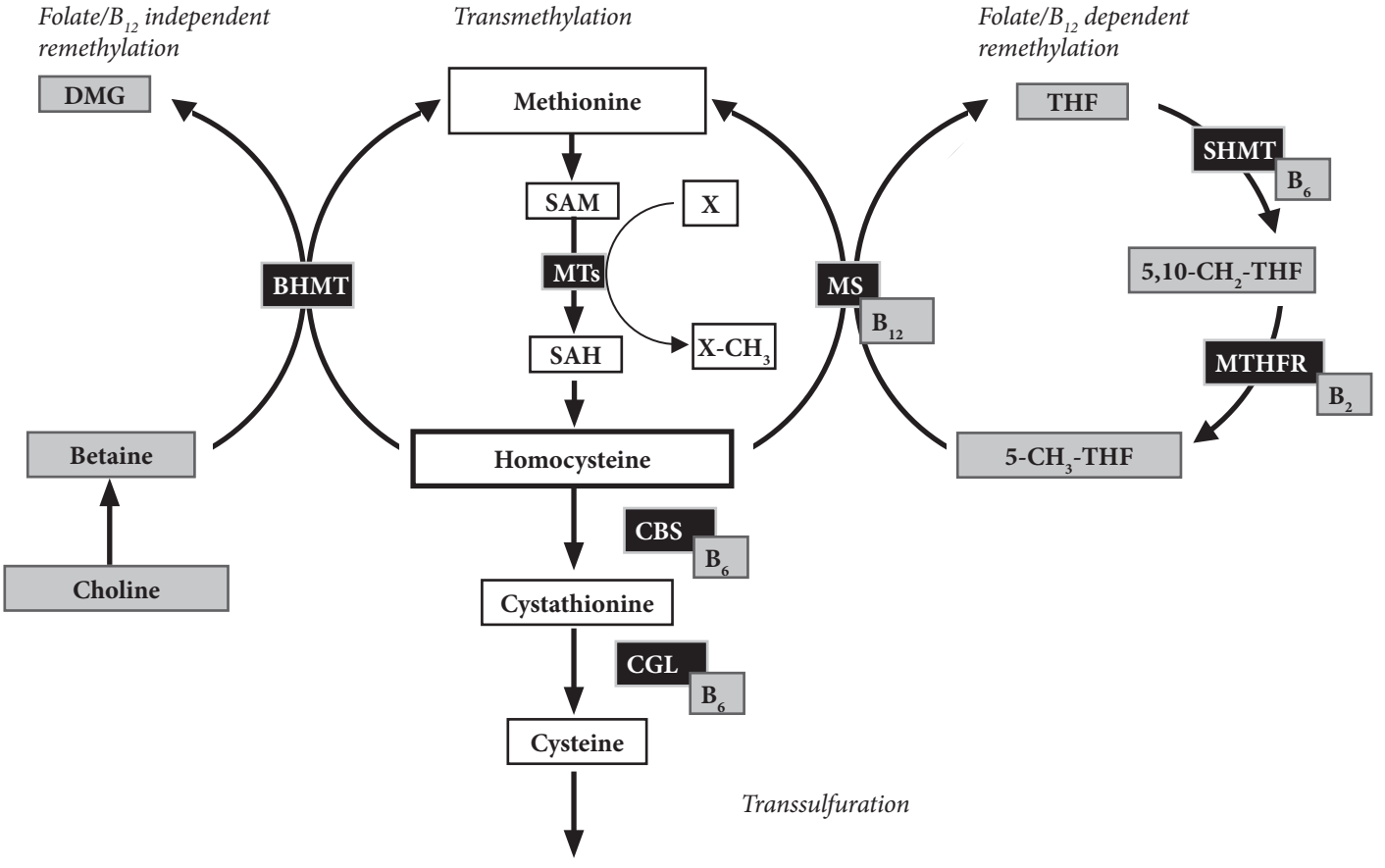


Figure 4. Pathways for Reducing Homocysteine Levels



seems to substantiate the perspective that although homocysteine is directly toxic, more important is that hyperhomocysteinemia is a marker of metabolic dysfunction, primarily methylation disruption.

What Causes Homocysteine to Increase?

Now this is where it gets clinically interesting, as in many ways serum levels of homocysteine can be seen as an indirect measure of other factors known to be critical to health.

What Is the Optimal Blood Level of Homocysteine?

In the final analysis, homocysteine is somewhat like glucose: It plays an important metabolic role, but too much is toxic and too little results in metabolic problems. This seems true of so many metabolites in the body. They play key roles in physiological function—but when outside of a typically narrow range, problems arise. I think it important that we refrain from the current habit of so many clinicians and patients of defining any molecules in the body as bad. Although there are certainly a few that appear toxic at any level, such as lead, there are others, even arsenic, that at some level are beneficial. The problem is not the molecule, but what happens when the molecule is damaged—such as oxidized cholesterol—or at such a high level in the body—such as blood sugar higher than 200—that it alters physiology. These are typically not the result of ingestion of the molecule, but rather all the physiology around them that is dysfunctional. For homocysteine, my best estimate is that the ideal range is 5.0 to 7.0 mmol/L. What do you think?

If homocysteine is low, supplementation with methionine, *N*-acetylcysteine, and taurine is indicated. If homocysteine is high, the many factors listed in Table 3 need to be addressed as well as supplementation with the activated forms of $B_{6,}$ folate (not folic acid) and B_{12}. If unresponsive, betaine should also be used.

Although supplementation with folate, B_6 and B_{12} does normalize homocysteine levels, the clinical outcomes have been disappointedly mixed. This seems to further support the idea of elevated homocysteine as an indirect measure of disturbed metabolism.

I find very revealing that the Mediterranean diet, with so much research showing that it reduces almost every chronic disease, is associated with lower homocysteine levels. The same is true of a nutrient and fiber rich diet: 19% decrease in homocysteine after only 2 weeks.[12]

Table 2. Causes of Elevated Homocysteine[9,10]

Enzyme deficiencies
- Cystathione-β-synthase
- Methionine synthase
- 5-Methyltetrahydrofolate reductase

Genetic polymorphisms (worst)
- MTHFR 677CT (TT)
- MTHFR 1298A>C (AA, CC)
- MTR 2756A>G (AA)
- MTRR 66A>G (AG)
- CBS 884ins68 (WW, WI)
- (See Table 3 for a complete list of genes involved in homocysteine metabolism. Polymorphisms have been detected in many of them.)

Vitamin deficiencies
- Folate
- Vitamin B_6
- Vitamin B_{12}

Demographics
- Increasing age
- Male
- Tobacco use
- Solid organ transplant recipients

Chronic diseases
- Renal dysfunction
- Systemic lupus erythematosus
- Malignant neoplasm
- Psoriasis
- Osteoporosis

Acute-phase response to systemic disease
- Prescription drugs
- Colestipol
- Methotrexate
- Nitrous oxide
- Niacin
- Thiazide diuretics

Table 3. Genes Directly and Indirectly Involved in Homocysteine Metabolism[11]

Symbol	Gene Name	Function
MTHFR	Methylenetetrahydrofolate reductase	Conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate
CBS	Cystathionine-β-synthase	Condensation of homocysteine and serine to form cystathionine
MTR	Methyltetrahydrofolatehomocysteine methyltransferase	Remethylation of homocysteine to methionine
MTRR	Methionine synthase reductase	Reductive regeneration of cob(I)alamin cofactor required for the maintenance of MTR in a functional state
RFC1	Reduced-folate carrier	5-methyltetrahydrofolate internalization in cell
GCP2/FOLH1	Glutamate carboxypeptidase II	Polyglutamate converted to monoglutamate folate by action of the enzyme folylpoly-γ-glutamate-carboxy-peptidase (FGCPI), an enzyme expressed by GCP2
ENOS	Endothelial nitric oxide synthase	Conversion of L-arginine to L-citrulline and nitric oxide synthase (NO)
TC2	Transcobalamine II	Transport of vitamin B_{12}
SHMT1	Serine hydroxymethyltransferase I	Reversible conversion of serine and tetrahydrofolate to glycine and 5,10-methylenetetrahydrofolate
TYMS	Thymidylate synthase	5,10-methylenetetrahydrofolate and deoxyuridylate to form dihydrofolate and thymidylate
CTH	Cystathionine-γ-lyase	Hydrolysis of cystathionine to cysteine and α-ketoglutarate
MTHFD	Methylenetetrahydrofolate dehydrogenase	Conversion of 5,10-methylenetetrahydrofolate to 5,10-methenyltetrahydrofolate
MTHFS	Methenyltetrahydrofolate synthetase	Conversion of 5-formyltetrahydrofolate to 5,10-methenyltetrahydrofolate
APOE	Apolipoproteine E	Mediates the binding, internalization, and catabolism of lipoprotein particles
VEGF	Vascular endothelial growth factor	Growth factor active in angiogenesis, vasculogenesis and endothelial cell growth
PON1	Paraoxonase I	Hydrolyzes the toxic organophosphorus. It also mediates an enzymatic protection of LDL against oxidative modification
BHMT	Betaine-homocysteine methyltransferase	In liver and kidney, it catalyses the conversion of betaine to dimethylglycine (DMG)
MAT1A	Methionine adenosyltransferase IA	Methionine to SAM by transfer of the adenosyl-moiety of ATP to the sulfur atom of methionine
AHCY	*S*-adenosy-L-homocysteine hydrolase	Hydrolysis of *S*-adenosy-L-homocysteine to adenosine and homocysteine
CBL	Cystathionine-β-lyase	Conversion of cystathionine to homocysteine
F5	Coagulation factor V	Cofactor for the factor Xa-catalyzed activation of prothrombin to the clotting enzyme thrombin
PAI1	Prothrombin activator inhibitor I	Inhibition of fibrinolysis by inhibiting the plasminogen-activator and t-PA

In This Issue

I write this editorial with great sadness; Sandi Cutler, who played a foundational role in the success of Bastyr University and the advancement of natural medicine, suddenly passed away July 1. I have the honor of his eulogy, which we will publish in the next issue of *IMCJ*. He was my closest friend, and I am devastated by his untimely loss.

One of the most compelling books on environmental medicine I have seen is *Slow Death By Rubber Duck*, written by Rick Smith and Bruce Lourie. Managing Editor, Craig Gustafson, interviews Mr Smith. This is a must-read story and an entertaining resource for educating your patients about environmental toxins.

Because we focus on being a resource for clinicians, we would normally not publish an academic article on education. However, I was struck by the very interesting presentation by Michael Tims, PhD, on how challenging it is to change a student's worldviews. As more and more conventionally trained health care professionals enter integrative medicine, they are seriously challenged to think differently about their patients. Moving from a disease-centric to patient-focused approach requires transformative thinking and experiences. Unlearning is indeed every bit as important as learning.

We have 2 articles on mitochondria, which complement well my editorial in the April issue of *IMCJ*.[13] An excellent commentary article by Alex Vasquez, DC, ND, DO, FACN, where he brings up the compelling idea of leaky mitochondrial membranes. If you have not heard Alex speak or read his work, you are in for a real treat. His grasp of health and nutrition is remarkable. I know of no one else to achieve degrees in 3 different health care professions. I have been harassing him for several years now on an article comparing the schools … Garth L. Nicolson, PhD, provides great guidance on the use of nutritional supplements to promote mitochondrial energy production and protect from oxidative stress. Very encouraging to see the growing number of positive clinical trials.

I appreciate how well John Weeks keeps us abreast of developing public policy in integrative medicine. I find of particular interest the proposed change of name of the National Center for Complementary and Alternative Medicine to the National Center for Research in Complementary and Integrative Health. Far more important than the name is what is being researched. We must study whole systems of healing, not isolated therapies. Otherwise, the model will not change and the health care crisis will continue to worsen.

A very different BackTalk from Bill Benda, MD. A good reminder of what is important in the world.

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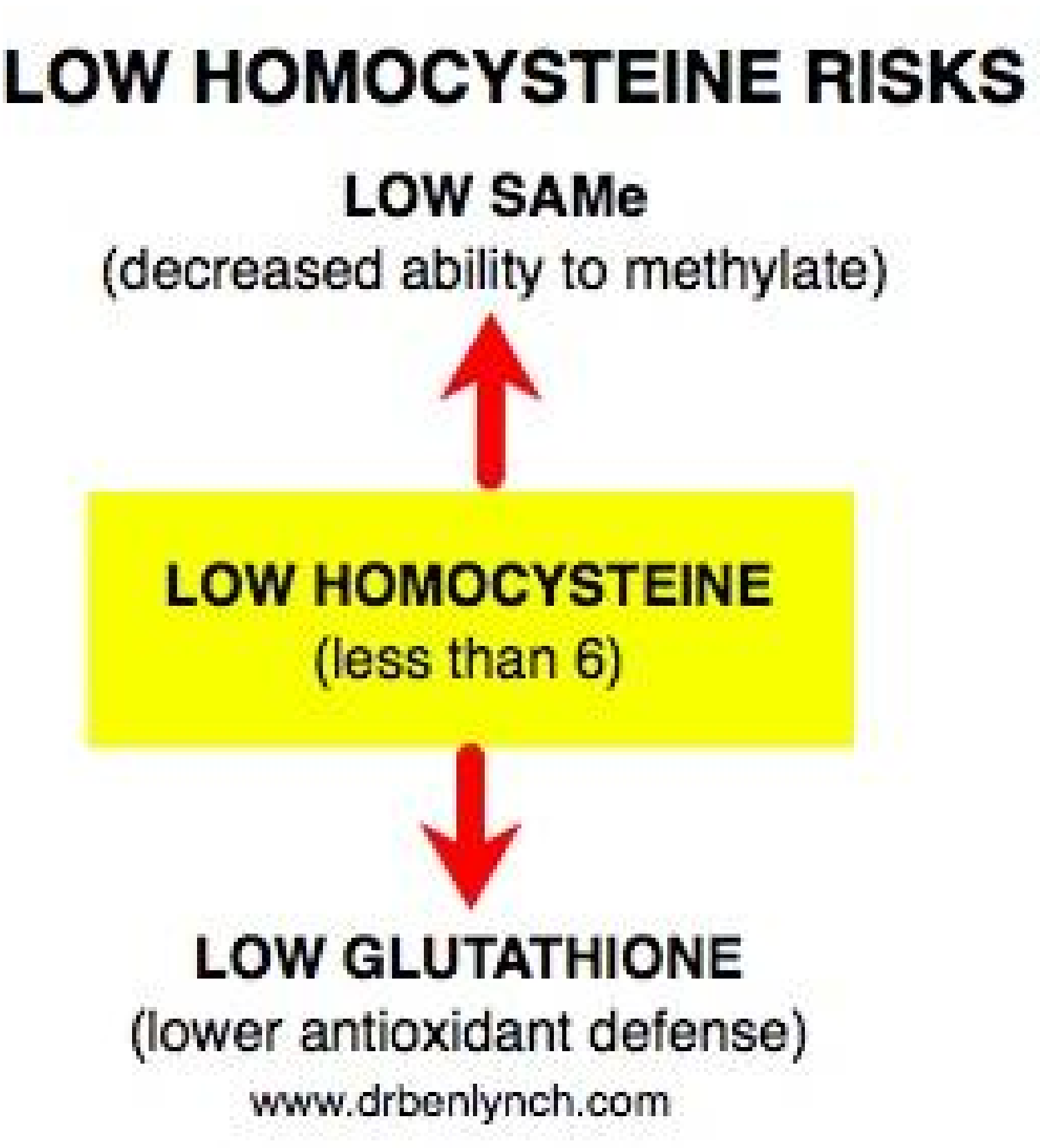
Low Homocysteine? Not Good.

5/5 (5)



What do you think of when you hear the word – homocysteine?

Bad. Cardiovascular disease. High blood pressure. Toxic. Lower the better.

I am challenging this thinking right now.

When I think of homocysteine, I think of this:

> The body has to make homocysteine. It's an important building block for two very important compounds in our body. It must be balanced. Too low homocysteine is bad and too high homocysteine is bad.

When was the last time a health professional said, “Hmm. You have *low homocysteine* levels. We need to increase your homocysteine to help you feel better!”

This is a very rare occurrence.

If your health professional has said this to you, my hat is off to them!

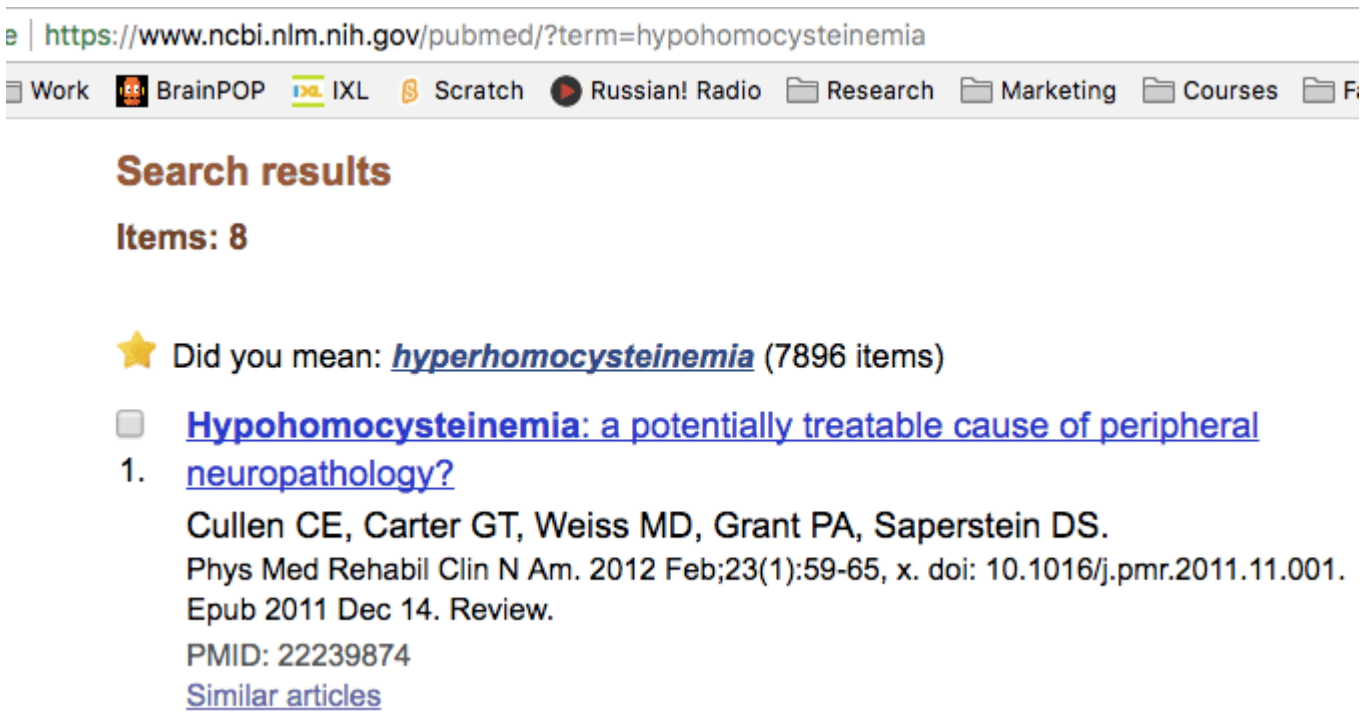
Most research and, as a result most health practitioners and patients, focus on normal to high homocysteine.

Low homocysteine isn’t even on their radar.

Medically speaking, low homocysteine doesn’t really even exist.

I used the medical term for low homocsyteine, hypohomocysteinemia, in the National Library of Medicine to search for published papers on low homocysteine.

Here is what I got: (they wondered if I meant something else!)



Only 8 results for hypohomocysteinemia (low homocysteine) compared to nearly 8,000 for hyperhomocysteinemia (high homocysteine).

I reviewed the one and only abstract on low homocysteine. Here is what they found:

“There is a striking relationship between hypohomocysteinemia and the incidence of idiopathic peripheral neuropathy.”(2)

This makes total sense.

If one has low homocysteine, then how can they make glutathione?

If they cannot make glutathione well, then their nerves are very susceptible to oxidative stress and damage.

There it is.

We need a lot more research on the impact of low homocysteine on human biochemistry and physiology.

When research does publish findings on low homocysteine, they are confused or misinterpret it:

“Children with diabetes, in view of their higher future risk of cardiovascular disease, are characterized by a higher concentration of protective adiponectin and paradoxically lower blood concentrations of some other possible risk markers of atherosclerosis, i.e. ADMA and homocysteine compared to healthy children.”(1)

To me, children with diabetes have higher reactive oxygen species which requires glutathione to neutralize them. Thus, a lower homocysteine level in a person with high free radical / reactive oxygen species tells me that their body is trying to fight it by producing glutathione.

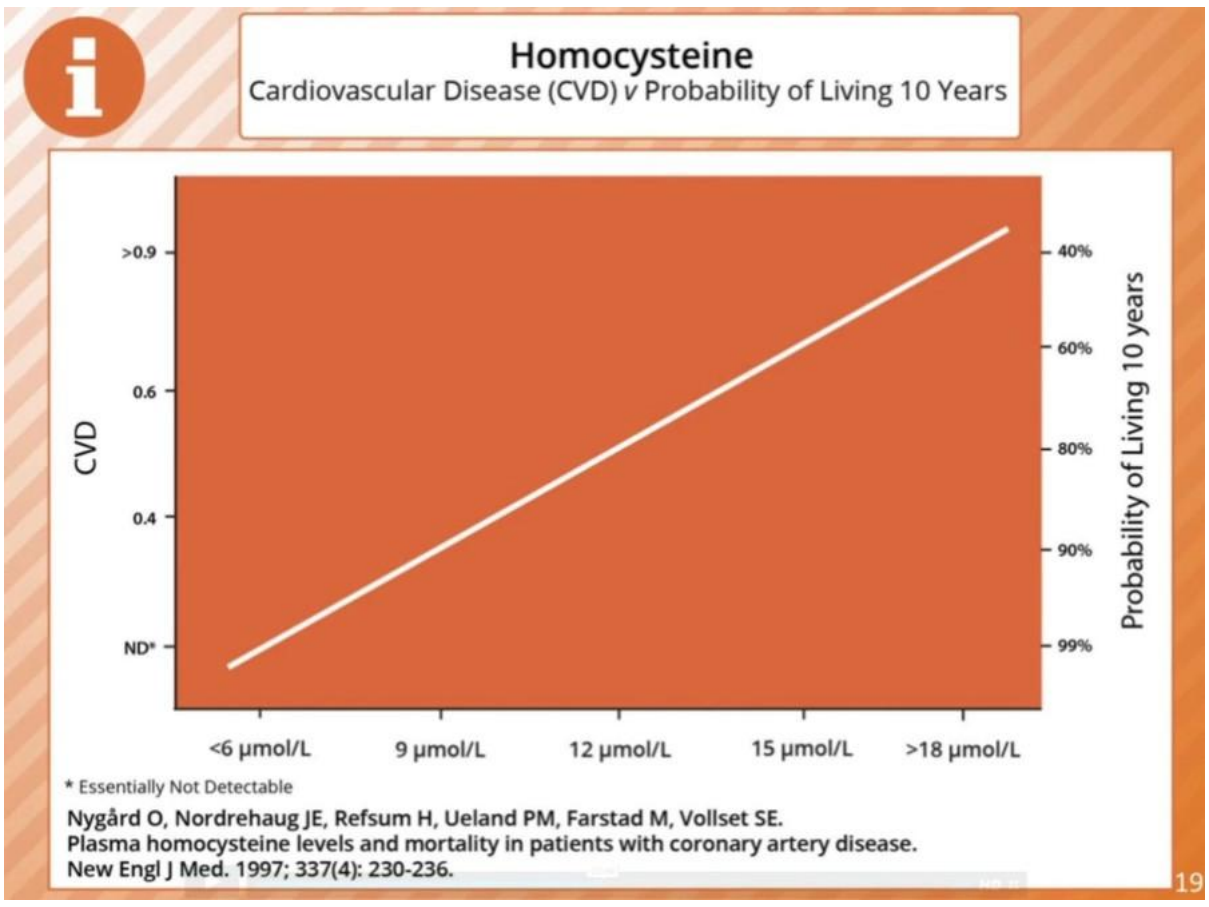
Simple steps:

High free radical / reactive oxygen species -> increases demand for glutathione -> increases utilization of homocysteine especially in low sulfur diets

A Low Homocysteine is NOT Good.

First we have to define a ‘low homocysteine’.

There are many papers which demonstrate that homocysteine around 6 or 7 is quite healthy for lowering cardiovascular risk.



Is homocysteine only related to cardiovascular risk?

No.

Homocysteine is needed to help produce our body's *primary*:

- methyl donor, SAMe.
- antioxidant, Glutathione.

Hmmm.

So why is it ok to have no homocysteine as shown here?

It's not!

Who comes up with these things?

It is common sense that if we are low in a specific ingredient, we cannot make something.

If you're trying to make a romaine salad and the recipe calls for romaine, yet you don't have any romain lettuce, can you make it?

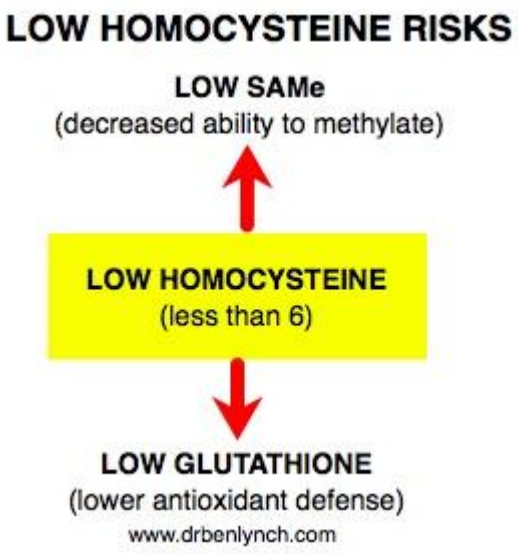
No.

You need to make a different type of salad or just go without it.

In the case of producing your body's *primary* methyl donor, SAMe – you need homocysteine.

In the case of producing your body's *primary* antioxidant, glutathione – you need homocysteine.

In short:

> **No to low homocysteine translates to . . .**
>
> 
>

Causes of Low Homocysteine and How to Increase It

1. **Low protein intake**: need to make sure you are eating adequate protein. Approximately 1 gram per 2 pounds of body weight is a rough guideline.
2. **Low sulfur intake**: if one does not consume enough sulfur-containing foods, homocysteine will break down in order to provide much needed cysteine for the body. Cysteine is very important for many reactions. If cysteine levels are low, the body will break down glutathione in order to provide it! So not only does one become low in homocysteine, but also glutathione. Eating your cruciferous vegetables is very important as they contain sulfur. You can also support with MSM (https://www.seekinghealth.com/optimal-msm-plus-molybdenum-100-capsules) or NAC (https://www.seekinghealth.com/nac-n-acetyl-l-cysteine-90-capsules). If you don't do well with sulfur-containing vegetables or other foods – or sulfur-containing supplements, then you may have a molybdenum deficiency for various reasons. Molybdenum is the mineral needed to breakdown sulfites. Consider taking a molybdenum supplement (https://www.seekinghealth.com/molybdenum-90-capsules) and also determine why you need to. I prefer liposomal glutathione (https://www.seekinghealth.com/optimal-liposomal-glutathione-plus-30-servings) most the time to replenish lost sulfur levels. This is for many reasons.
3. **Poor digestion and absorption of protein:** eating protein is step one. Being able to digest it and absorb it is important. Consider chewing your food (shocker), reducing stress before and during eating (shocker), not drinking a ton during meals as it may dilute your digestive powers. You can support your digestive enzymes with a digestive enzyme supplement (https://www.seekinghealth.com/pro-digestion-intensive-120-capsules) and increase stomach acid with a HCL supplement (https://www.seekinghealth.com/pregestion-100-capsules). If taking antacids, your stomach acid is lower and that is going to impact your protein and nutrient absorption. Fix your gastritis and acid reflux. (https://www.youtube.com/watch?v=pdTxzURDbUk)
4. **High demand for glutathione:** if you are struggling with high amounts of inflammation, stress or free radicals, you are going to require a high amount of glutathione. Producing glutathione requires homocysteine. One can minimize their need of glutathione by reducing or minimizing stress with adaptogens (https://www.seekinghealth.com/optimal-adrenal-90-capsules), improving deep sleep (https://www.drbenlynch.com/melatonin-for-sleep/), reducing inflammation and reducing exposure to chemicals (http://mthfr.net/toxic/2014/12/09/). One can also reduce their demand for glutathione production indirectly by taking liposomal glutathione. Taking liposomal glutathione is helpful for many but if they are deficient in selenium, riboflavin or molybdenum or have high oxidative stress, it may backfire. This is why I formulated a liposomal glutathione with needed cofactors. (https://www.seekinghealth.com/optimal-liposomal-glutathione-plus-30-servings)
5. **Too much methylation support**. I'm a fan of methylation support. However, when it is not needed, it can lower your homocysteine levels too much. Maybe this is yet another reason why some people do not feel good from taking methyl donors? If your homocysteine level is too low, talk with your health professional about reducing your methylation support. You can use a multivitamin without any folate or B12 – called Optimal Start (https://www.seekinghealth.com/optimal-start-120-capsules). Or you can use a multivitamin without any methyl donors yet contains folinic acid and hydroxocobalamin – called Optimal Multivitamin Minus One (https://www.seekinghealth.com/optimal-multivitamin-minus-one-45-capsules). If you are taking a B Complex with methylfolate and methylcobalamin, you should consider switching to one without these for a bit or just stop if possible. I formulated a B complex without folate and without B12 – called B Minus (https://www.seekinghealth.com/b-minus-100-capsules).

Who else is thinking the same way I am about low homocysteine?

I scoured the research again to see if anyone else is thinking that low homocysteine is a problem.

It turns out that the only other one that I see out there is another naturopathic physician – and a well known one at that. Dr Joseph Pizzorno, one of the founders of Bastyr University, wrote a paper called: Homocysteine: Friend or Foe? (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4566450/pdf/8-14.pdf)

Brilliant!!

It's a must read.

Do you have low homocysteine?

Is your homocysteine lower than 6?

Share your story below.

Did your doctor say anything?

Work with you to correct it?

References:

1. https://www.ncbi.nlm.nih.gov/pubmed/18830896
2. https://www.ncbi.nlm.nih.gov/pubmed/22239874

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GLUTATHIONE (HTTPS://WWW.DRBENLYNCH.COM/TAG/GLUTATHIONE/)

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METHYLATION (HTTPS://WWW.DRBENLYNCH.COM/TAG/METHYLATION/)

Comments 115

Eliza Drake

OCTOBER 30, 2017 AT 1:06 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-92546)

Hi Dr! I'm homozygous c677T in September my homocysteine level was 8.6. Do you still recommend supplementing with Glutathione & if so how often?

Reply

post author

Dr Lynch (http://seekinghealth.org)

OCTOBER 30, 2017 AT 1:24 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-92584)

Eliza – fantastic question.

Yes. This is because methylation can be SLOWED by hydrogen peroxide. Hydrogen peroxide is neutralized to water by glutathione.

If one takes liposomal glutathione (preferred over just reduced capsule of glutathione), then the body will just push out the homocysteine as cysteine and pee out the excess cysteine as sulfate. This requires vitamin B6 and molybdenum to happen.

I actually recommend liposomal glutathione to people with stubborn high homocysteine and it does seem to help some.

Reply

Katy

OCTOBER 30, 2017 AT 1:06 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-92563)

Very interesting, I'm homozygous MTHFR C766T and docs tested me for high homocystein, which I don't have. Are there any other symptoms.you know of? I get pins and needles down the pinky edge of each hand pretty much every time I lay down or sit down for a while. Pinky fingers can go totally numb. Thanks again Dr Lynch.

Reply

post author

Dr Lynch (http://seekinghealth.org)

OCTOBER 30, 2017 AT 1:25 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-92585)

Katy –

That sounds more like nerve compression to me – thoracic outlet syndrome or disc compression. Please get evaluated by a chiropractor or one who understands physical medicine.

Reply

Emily

OCTOBER 30, 2017 AT 1:15 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-92579)

Is SamE supplementation something you've seen be helpful for low homocysteine?

Reply

post author

Dr Lynch (http://seekinghealth.org)

OCTOBER 30, 2017 AT 1:21 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-92582)

Hi Emily –

Great question. It can be yes. The trick though is identifying why homocysteine is low in the first place. I suspect most common reason are those mentioned in the article.

Instead of taking SAMe, I'd consider: liposomal glutathione, eating more protein, absorbing protein better, reducing stress –

SAMe can get stuck and not be used – thus staying as SAMe and not really converting to homocysteine. However, SAMe does increase the speed of the CBS enzyme so it may indirectly – but not as fast as liposomal glutathione or protein intake.

I'm unsure positively here – so bouncing thoughts around while writing.

In short – yes a SAMe supplement (https://www.seekinghealth.com/same-30-capsules) could raise homocysteine. 😉 – in some people and others it may take awhile.

Reply

Nicole

OCTOBER 30, 2017 AT 1:17 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-92580)

Hello Dr. Lynch,

My husband and I are 36 and preparing for conception. I have two mutations, one copy C677T and one copy A1298C. I am taking your exact recommended prenatal supplements as I've read and followed your other work. I've been taking methylfolate for 3 years now (usually about 3-4 mg a day, along with the other recommended B-vitamins in HomocysteX Plus or MethylGuard Plus.) I haven't felt much of a difference with them.

My homocysteine labs just came back at 4.5 and still chronic EBV this month.

Genova Micronutrient testing also showed continued microbiome dysbiosis and recommended 50 billion probiotics and pancreatic enzymes. I've been working with gut health, probiotics, etc for years. The only symptom I have is persistent acne.

I read in one of your articles that low homocysteine could be related to Downs Syndrome.

What should I do to prepare for a baby or do you think we're ready now?

Thank you so much!

Reply

post author

Dr Lynch (http://seekinghealth.org)

OCTOBER 30, 2017 AT 1:36 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-92642)

Hi Nicole –

I'm impressed you're working so hard preparing yourself for a healthy pregnancy!

I would hold off a bit until you are feeling good and healthier.

Persistent acne can be many issues:
– liver
– microbiome
– stress
– hormones
– low digestive enzymes / acid
– combination of all the above

Taking that much methylfolate is likely not that beneficial – especially if you are not feeling much different.

I'd work with a doc to get those chronic infections under control.

Lack of deep restorative sleep, stress, nutrient deficiencies – all can increase risk of infections.

Consider a vacation as well once you get a treatment plan in place 😉

Infections are typically causing many of your underlying issues – or an environmental exposure – such as household chemicals, new construction, mold..

Reply

Keri

OCTOBER 30, 2017 AT 1:19 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-92581)

This sounds like me. I have been low glutathione for about 10 years and do not tolerate glutathione supplements in any form. I am not able to eat much in the way of cruciferous vegetables as I have low tolerance for oxalate. Am I understanding correctly that the way to increase homosycystein is to reduce the demand for it or is there a way to directly increase homosycystein itself. I'm wondering because at one time or another I have taken NAC, reduced stress, taken Same, adaptigens, molybdenum, eaten cruciferous veggies, Epsom salt, antioxidants etc many at the same time and still can't get glutathione to rise or my symptoms to improve.

Reply

post author

Dr Lynch (http://seekinghealth.org)

OCTOBER 30, 2017 AT 1:31 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-92622)

Hi Keri –

I'd consider looking into molybdenum and also your gut health. If your GI health is not right, you'll be using up a lot of glutathione plus not tolerating sulfur or oxalates.

You can try a molybdenum supplement (https://www.seekinghealth.com/molybdenum-90-capsules) by itself for a week or so and see how your symptoms improve. It's only a band-aide though as you need to find out why your sulfites are high.

Then after you do this, you can try a liposomal glutathione that has added cofactors to it so it gets used and recycled and limits sulfite production. Optimal Liposomal Glutathione Plus (https://www.seekinghealth.com/optimal-liposomal-glutathione-plus-30-servings) offers these.

Evaluate your GI, liver, gallbladder,etc – with a good health professional. Infections should be sussed out, too.

Reply

MB

OCTOBER 30, 2017 AT 1:31 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-92616)

Hi thank you for all your writing and answers and your "out of the box" thinking! I so wish you would practice in Canada and could review my medical file. I will keep on reading and bringing new path of ideas to my practice era (conventional and natural).

Reply

Alyson

OCTOBER 30, 2017 AT 1:35 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-92640)

I have a homocysteine of 5.

I have lots of inflammation ad just diagnosed with Polymyalgia Rheumatica.

LDN and turmeric seem to be keeping it unde4 control.

Think i will try your glutathione product, if it delivers to UK

Reply

post author

Dr Lynch (http://seekinghealth.org)

OCTOBER 30, 2017 AT 1:38 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-92643)

Hi Alyson – I'd look into your microbiome and digestion – and underlying infections and environmental exposures.

We have Seeking Health for sale in the UK – via Detox Doctors and Amazon UK.

Seeking Health also ships worldwide.

Glad you have it under control – now let's have it go away 🙂

Reply

Romilly Hodges

OCTOBER 30, 2017 AT 1:35 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-92641)

Dear Dr. Lynch,

Appreciate you bringing up the importance of balanced homocysteine. Dr. Fitzgerald has been writing about it too, for a while: https://www.drkarafitzgerald.com/2017/04/04/low-homocysteine-concern/ (https://www.drkarafitzgerald.com/2017/04/04/low-homocysteine-concern/).

Keep doing what you do! We appreciate your work.

Reply

Mary

OCTOBER 30, 2017 AT 1:46 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-92644)

Thanks for a great article Dr Lynch. I'm curious if a homocysteine level of 6.8 might be borderline low – or is it ideal as per your article & Dr Pizzorno.
I am in the initial stages of advising a lady (in her mid 40s, has had 12 miscarriages in less than 5 years!) – she has been through the mill and yes has been dosed to the eyeballs with folic acid etc. On my advice she got her genetic profile – shes hetero 677T, CBS & COMT; Homo – PEMT, MTHFD etc – so I advised her to get homocysteine levels checked and was surprised that its 6.8 (I was expecting it would be high) – this result only last week.
I wonder if low(ish) homocysteine can also be a factor in a history of pregnancy loss. No doubt removing folic acid was the absolute biggest 1st step for her, Shes starting to take seeking health prenatal, plus other dietary / nutrient changes etc
Thanks for your work
Mary

Reply

post author

Dr Lynch (http://seekinghealth.org)

OCTOBER 30, 2017 AT 2:31 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-92670)

Hi Mary –

I'd say 6.8 is pretty good for homocysteine.

However, I'd like to see:
– lipid peroxides
– RBC fatty acids
– amino acids
– organic acids

Her homocysteine isn't elevated likely as it is busy burning it up for methylation support (cell membrane production, creatine synthesis) and glutathione production.

She also may not be eating that much protein – so a methionine loading test may push her homocysteine up quite high. Not saying that's needed – but could be a way to check how her system is doing.

I've seen many recurrent miscarriages resolve with using extensive nutrition – as I've outlined here in my prenatal supplementation and MTHFR (http://mthfr.net/prenatal-supplementation-optimizing-your-future-child/2012/01/20/) article.

Yes – low-ish homocysteine is definitely a risk factor for pregnancy loss – and also having increased risk for the newborn developing autism (along with low vitamin D)

here is a paper on glutathione and pregnancy issues (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4712587/pdf/jkms-31-98.pdf) –

Reply

Mary

OCTOBER 31, 2017 AT 3:22 AM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-93010)

Fantastic – thank you so much.
Mary

Reply

Amy

OCTOBER 30, 2017 AT 1:55 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-92646)

My sons homocystiene was undetected in his amino acid labs. But did not indicate it was a problem. The range stated 0-2 umol/L. I don't understand why 6 is good if lab stated 0-2?
What lab do I need to ask for to have this checked again

Reply

post author

Dr Lynch (http://seekinghealth.org)

OCTOBER 30, 2017 AT 2:25 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-92668)

Amy – kids have a lower homocysteine than adults because they are using it so much faster. All the more important to make sure they are eating enough protein and getting liposomal glutathione.

Support with these first – and then recheck in a month.

Reply

Nicole

OCTOBER 30, 2017 AT 1:59 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-92647)

Thank you, Doctor. I appreciate your response. I'm a little heartbroken but I know it's the right answer. EBV has been chronic for me since I got mono 7 years ago. I've tried different anti-viral and immune-boosting approaches with my Naturopath but to little improvement. I'll start again… 😕

Since you're no longer taking patients and I'm in the Seattle area, is there a local doctor you'd recommend for EBV/mthfr/gut dysbiosis/prenatal care?

Thank you again.

Reply

post author

Dr Lynch (http://seekinghealth.org)

OCTOBER 30, 2017 AT 2:24 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-92667)

Nicole –

I hear you – truly.

The way to combat an infection is not to kill it.

The way is to nourish yourself – mentally, emotionally and physically.

Find out what is blocking you from this and replenish.

🙂

Forget the fighting infections for now – and focus on restoring on a deeper level.

If the deeper level has to do with having a beautiful pregnancy and lovely child so you can be an incredible mother, know that this will come when you are stronger mentally, physically and emotionally.

I'm absolutely confident in you to take this to heart.

I've seen many struggle with fighting infections – only to realize that it was something deeper that was missing.

Meditate on this – even if for a few moments a day.

That will drive clarity for you – as it likely is buried.

Reply

Amanda

OCTOBER 30, 2017 AT 2:01 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-92648)

Should those of us trying to raise our low homocysteine avoid taking methyl folate? Are there other supplements that should be avoided for those with low homocysteine?

Reply

post author

Dr Lynch (http://seekinghealth.org)

OCTOBER 30, 2017 AT 2:20 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-92666)

Amanda – great question. I'd say yes to limiting methylfolate when trying to raise homocysteine. Avoid it – no – that wouldn't be good.

If taking a methylfolate supplement, then consider reducing or stopping it. Only use a multivitamin that has it in it. I have multivitamins that contain non-methylated nutrients – such as Optimal Multivitamin Minus One (https://www.seekinghealth.com/optimal-multivitamin-minus-one-45-capsules). It's a one capsule a day – easy to take and only has folinic acid and hydroxocobalamin.

If you want to avoid folate and B12 completely – you can do that with Optimal Start (https://www.seekinghealth.com/optimal-start-120-capsules).

I also formulated a B complex without folate and B12 – called B Minus (https://www.seekinghealth.com/b-minus-100-capsules).

Instead of worrying too much about what to avoid, I'd focus more on what to add.

However, you are very correct one should reduce their methylated nutrients in order to raise their homocysteine back up to a healthy level – say 7 umol.

Reply

jennyfmurphy

OCTOBER 30, 2017 AT 2:09 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-92664)

Hello Dr Lynch,

I am homozygous C677T and slow COMT. My homocysteine is at 4. I have continuous low ferritin. So tired all the time. Just found out I have acid reflux AND mild sleep apnea which is causing my nightly heart palpitations. I was told after wearing a take home sleep monitor twice that I had no sleep apnea. I got a question through to you on your recent FB live and you said get checked for sleep apnea so I requested an overnight study this time. I have it! Thank you! An answer.

I take your Hydroxy B12/Folinic Acid and eat higher protein amounts as of recently. I just ordered liposomal glutathione. I'm working on a real food only lifestyle change and feeling better already.
Should my homocysteine levels improve with all these changes?
Thank you!

Reply

Dr Lynch (http://seekinghealth.org)

post author

OCTOBER 30, 2017 AT 2:34 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-92671)

Hi Jenny –

Awesome!! You rock! Well done and taking action and figuring this out! Huge find 😉

Now – how are you addressing the sleep apnea?

For your homocysteine – you appear to doing the right things and taking the right nutrients. I would not recommend MTHF and methylcobalamin.

You could likely check your homocysteine in a month since you're really making some changes.

High 5! 🙂

Reply

Patricia C Tice

OCTOBER 30, 2017 AT 2:18 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-92665)

I had high homocystine until I started taking metanx and deplin. Now it's low and I was ok with that. Not sure now. Homozygous C677T and I need every bit of both the supplements along with 100 mg pristiq to maintain mood and function in fibro/ME/CFS. Adding LDN this week and exploring lowering oxalates. I usually eat a whey protein isolate bar for breakfast and am heavy on protein overall but not afraid of good fats (saturated, long chain omega 3s and mct) but also not terrified of sugar. Thoughts?

Reply

post author

Dr Lynch (http://seekinghealth.org)

OCTOBER 30, 2017 AT 2:38 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-92672)

Hi Patricia –

When you say you have 'low homocysteine' – what do you mean? Lower than 6 umol?

If so, then I'd say I'm with you on re-evaluating your intake of Metanx and Deplin.

That's a ton of methylfolate.

Maybe you can add in folinic acid and reduce the use of methylfolate.

Using liposomal glutathione (https://www.seekinghealth.com/optimal-liposomal-glutathione-plus-30-servings) could be a boon -but make sure you use the one with the cofactors so you reduce the potential of side effects – and start low – few drops.

Reply

Robin Amundson

OCTOBER 30, 2017 AT 2:31 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-92669)

Should people with peripheral neuropathy have their homocysteine tested? Can it be reversed with dietary adjustments recommended in this article?

Reply

post author

Dr Lynch (http://seekinghealth.org)

OCTOBER 30, 2017 AT 2:41 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-92673)

Hi Robin –

I say most people should have their homocysteine checked – yes.

Peripheral neuropathy has many causes – some improve a lot with:
– chiropractic adjustments – if compression or impingement
– vitamin B12 – especially methylcobalamin
– L-methylfolate
– vitamin B6
– vitamin B1
– liposomal glutathione
– alpha r lipoic acid

These are all available at http://www.seekinghealth.com (http://www.seekinghealth.com) – well – not the chiropractor 🙂

Also reducing carbohydrate intake is important – replace it with vegetables or healthy fats / protein.

Also limit snacking – only eat a few meals a day ideally. This isn't easy –

Acetyl-L-Carnitine, Biotin, Niacin and 5-HTP may help support your healthy eating choices and being able to burn fat.

Reply

Kristin

OCTOBER 30, 2017 AT 2:57 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-92676)

Last time my homocysteine level was checked it was 5.The doc said she thought that wasn't right and could mean methylation issues. I'm the one who lives in the Midwest. Functional medicine practitioners are hard to come by and they just don't have the experience because many people in the Midwest only know conventional medicine. I keep my health to myself – most of my friends think I a looney health nut…I have searched for info on low homocysteine and found nothing helpful for me. I have Hashimoto's and have been working with a practitioner for almost 4 years and I still don't feel very good. I've been doing many of the things you talk about. Food, air, water, environment – reducing stress, and on. I have been taking liposomal glutathione. I plan on sending this article to my doc and have her help me know how to proceed. I know you gave suggestions – some are counter to what they say is good for Hashi patients- like cruciferous veggies, but I'm going to start eating them.. And you suggested three supplements. With my history I have to start slowly, one at a time or I won't know which one is causing problems, if something causes a problem. I know every body is different so it's hard to say where to start but if you had to…where would you tell a person to start? Molybdenum? Thank for this article. Appreciate all you do.

Reply

post author

Dr Lynch (https://www.drbenlynch.com)

OCTOBER 30, 2017 AT 8:08 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-92951)

Hi Kristin –

First place I have people start is fundaments – like the Dirty Genes Course (https://www.drbenlynch.com/product/dirty-genes-bundle-b/)

Sounds like you have been doing those which is great.

Only then do supplements actually seem to work as they should – or least a much higher chance of it.

Supplementing too early will be frustrating, expensive and worthless.

One supplement I recommend right out of the gate though for most people is Optimal Electrolyte (https://www.seekinghealth.com/optimal-electrolyte). Most are deficient in all the ingredients listed and they feel much better right away.

I would then look into why your homocysteine is low and consider adding in more protein. Using the Optimal Prenatal Protein Powder (https://www.seekinghealth.com/optimal-prenatal-protein-powder) may be a wise addition because it is so comprehensive. I use it most mornings -and you can adjust the serving easily – say 1/2 scoop etc.

These three – prenatal protein powder, electrolytes and glutathione – are pretty solid.

The other one would be ProBiota HistaminX – but it's not out yet – soon – very soon.

Molybdenum is pretty solid recommendation as well – especially if intolerant to sulfur, sulfites or have gas / bloating.

Reply

Gal

OCTOBER 30, 2017 AT 3:02 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-92681)

Dr Lynch,
I suspect my son has low stomach acid as he doesn't really absorb nutrients. Can apple cider vinegar help or you would recommend Betaine HCL supplement?
Thank you very much!

Reply

post author

Dr Lynch (https://www.drbenlynch.com)

OCTOBER 30, 2017 AT 3:18 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-92696)

Hi Gal –

Apple cider vinegar diluted with warm filtered water can be great! So can a bit of lemon juice in water as well. He needs to chew…chew…chew. Make a game out of it.

Reply

Keri

OCTOBER 30, 2017 AT 3:03 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-92684)

Thanks Dr. Lynch,

I've got great health professionals on my team using innovative and integrative methods. What I really was looking for was double checking that I'm understanding correctly. Is there a way to directly raise homocystein or is it done only as you mentioned by reducing the demand for it?

Reply

post author

Dr Lynch (https://www.drbenlynch.com)

OCTOBER 30, 2017 AT 3:20 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-92697)

You can directly raise homocysteine by the methods I mentioned in the article.
– eat more protein
– supplement with liposomal glutathione
– exercise will also help

Reply

info97

OCTOBER 30, 2017 AT 3:13 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-92695)

Hi Dr Lynch, I'm just starting to explore my own situation so please bear with me! I've been feeling rubbish for a while so had standard blood tests and I was found to have low folate. I have PCOS but have had no fertility issues, I've had 3 healthy children. I've sent off samples for MTHFR testing as I'm suspicious something may be going on there. What is causing the low folate and what is the impact of this? I'm now supplementing with L-methylfolate, calcium d-glucarate, vit c, k2, fermented cod liver oil, kelp, methylcobalamin, gluthione, zinc/copper, Vit A and magnesium following the test results. I'm just trying to work out what's going on?
I'm suspicious Estrogen dominance is at play too? I'm a yoga teacher and my diet is along the lines of keto. I feel much better when I'm strict with this!!! Thank you 🙂

Reply

post author

Dr Lynch (https://www.drbenlynch.com)

OCTOBER 30, 2017 AT 3:22 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-92698)

Hi there – not sure beyond there is a demand for folate in your body. Needs to be evaluated. It is tough being strict with a diet – I, too, go on and off fat adapted – it's very easy to do – just one day of poor choices and it takes a week or two to get back! 😉

Reply

info97

OCTOBER 30, 2017 AT 3:30 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-92702)

Thank you 🙂 yes it is tough! I wondered if the low folate was being caused by a faulty mechanism somewhere? I will keep exploring. Looking forward to getting my MTHFR results back and reading your book!!

Reply

post author

Dr Lynch (https://www.drbenlynch.com)

OCTOBER 30, 2017 AT 3:34 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-92704)

It could be – I know of someone who has to take folinic acid daily in order to keep her MCV and MCH levels down. It could be a genetic thing but it could easily be high demand – such as leaky gut, infections, inflammation

Reply

Gal

OCTOBER 30, 2017 AT 3:32 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-92703)

Dr Lynch,
Thanks a lot! Most of the time My son is tube fed:(i put some lemon juice in his water but i don't see any difference. Please see my first question.

Thanks a lot!

Reply

Melissa

OCTOBER 30, 2017 AT 3:35 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-92705)

Thank you, Dr. Lynch!!! perfect article I have been in dire need of, puts together so many pieces for me as I have peripheral neuropathy (sudden onset) with 4 range of homocysteine. It has been a very debilitating long year process (walking is a struggle) this makes a lot of since to me along with your dirty genes course. again thank you!

Reply

Gal

OCTOBER 30, 2017 AT 3:41 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-92706)

Dear Dr Lynch,
Please, excuse me for repeating my questuon!
Thank you so much for your brilliant work and for sharing your knowledge with us!
I have a 2 years old son suffering from severe genetic epilepsy. He has Homozygous MTHFR A1298C, Homozygous VDR, Homozygous GSTP1 and a heterozygous COMT.
He has a stubborn Candida infection which so far i couldn't eliminate with botanicals. He gets about 300 mg of Niacinamide because of other issues. We tested his homocysteine and it's just 4.5, so low. He is on the ketogenic diet but lower ratio (2:1).
I started giving him methylfolate 200 mcg and hydroxy B12 about 1000 mcg. I don't see any improvement:(his gluthathione levels are fine (he gets lyposomial gluthatione and before starting him on it his levels were very low) and i supplement him with electrolytes. Am i on a good way?
I plan giving him some medication to eliminate his Candida issue. Does it mean that because of his Candida infection and the fact that he gets Niacinamide he has reduced (blocked) methylation? Can i do anything to help him? He is non verbal so it's not that easy to get a feedback from him. We have a holistic practitioner but i feel that he doesn't have enough knowledge to lead us through this complicated situation…
Thank you from the bottom of my heart!
Gal

Reply

post author

Dr Lynch (https://www.drbenlynch.com)

OCTOBER 30, 2017 AT 8:16 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-92954)

Hi Gal –

It seems you are doing a pretty thorough job with your son – well done.

Yes – I would consider using a medication to eliminate his candida. There is also a product called Biocidin which is pretty effective – just tastes quite badly. Candida medications are typically pretty safe – just start low and work up so the die-off doesn't make him sick.

I see a lot of results from treating yeast overgrowth.

I would also consider ProBiota HistaminX when it becomes available – which is any day now. That will help restore his microbiome and reduce histamine.

Consider a urinary organic acids test (OAT) to spot other deficiencies.

Thiamine has been seen at times to be low in those with seizures.

Do you know which genetics he has for his epilepsy? There are genes associated with sulfites, folate, thiamine, B6, glutamate…ammonia..

So many things to evaluate and consider.

Reply

Jessica

OCTOBER 30, 2017 AT 3:46 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-92707)

This explains a lot. My GP said my homocysteine was perfect, 0,7! My feeling is that it's really low. And it would explain why I felt good taking methyl B12 for a while but now I do not anymore and started to feel really weird, headaches, heart racing...I now switched to folinic acid and hydroxo B12 but so far doesnt help much either with feeling bad. Should I use other supplements? Try Sam-e? I am also COMT +/+
Thank you dr Lynch for this article!

Reply

Dr Lynch (https://www.drbenlynch.com)

post author

OCTOBER 30, 2017 AT 7:48 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-92936)

Hi Jessica – that does seem pretty low 🙂

This is why I always recommend pulsing supplements – starting, stopping and using only when needed vs all the time. I never take a supplement continuously – start / stop all the time.

I'm all for lifestyle changes first prior to supplementing. I am not sure what fundamentals you're doing / not doing. I highly recommend the Dirty Genes Course Bundle (https://www.drbenlynch.com/product/dirty-genes-bundle-b/) – and then proceed with the courses.

SAMe can help to raise homocysteine – but if glutathione is low, SAMe won't help much. Need to replenish with liposomal glutathione first. If you do want to try supplements, the key is to start with electrolytes (https://www.seekinghealth.com/optimal-electrolyte). Most are deficient in them – I'd say everyone frankly.

Reply

Melissa

OCTOBER 30, 2017 AT 3:47 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-92708)

Also to share my doctors have done nothing with the homocysteine level (or neuropathy for that matter), said oh your homocysteine is low that's really good with MTHFR. Here is Metanx and Gabapentin, don't need to change your diet after specifically asking about Folic Acid.

Reply

Alina

OCTOBER 30, 2017 AT 3:53 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-92709)

Hi Dr. Lynch

Thank you so much for all your great work, you are amazing. A few years ago I did my genetic testing and did both your online courses (the long ones I believe you get acreditation throuh bastyr). There's lot of questions that I had for you and one of them was with regards to low homocyteine. My test results indicated it was 5. I am also

compound heterozygous for MTHFR and have slow COMT, slow MAOA, and fast CBS. I always thought that that the CBS upregulation was what was draining my homocysteine. Would that be correct? And would taking the optimal glutathione be helpful in this case?

I have made all the lifestyle changes you recommended in your course prior to getting pregnant (through IVF due to endometriosis). Still take your optimum prenatal but can only take btwn 4-6 capsules a day, otherwise I don't feel good. CBS i feel plays a role in that as well. Unfortunately I am unable to take most of the test you recommend as I live in Canada. In addition I am unable to find a practioner in the area familiar with all these pathways. My background is in biochemistry so I love how detailed you get into things. Really looking forward to your new book. Hopefully it could help me answer more questions. Please don't mind my being all over the place as I have baby brain right now.

Reply

post author

Dr Lynch (https://www.drbenlynch.com)

OCTOBER 30, 2017 AT 7:54 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-92937)

Hi Alina –

Great to hear you love biochemistry and have taken those courses!

It's hard to say what is draining your homocysteine – possibly a faster CBS – but why is it faster? A SNP is not the only cause. I'd say evaluate your glutathione levels if possible.

– lipid peroxides
– RBC fatty acids

Or you can just supplement with liposomal glutathione along with molybdenum to help offset the increased sulfite load.

4-6 capsules of Optimal Prenatal is plenty especially for those who are quite healthy already. Always take what makes you feel good – not what the bottle serving size is.

With a slow MAOA and slow COMT and slow MTHFR, you're at risk for anxiety and irritability with a higher protein intake. So consider a higher protein breakfast, some at lunch and less at dinner.

The Optimal Prenatal Protein Powder (https://www.seekinghealth.com/optimal-prenatal-protein-powder) would be perfect if you can get it – as it provides the most comprehensive amount of nutrients and bioavailable protein. You can also adjust the serving size. This morning I used about 2/3rds serving as I felt I didn't need all those nutrients this morning.

I'd highly consider adding in electrolytes (https://www.seekinghealth.com/optimal-electrolyte) too if you can access them.

Reply

Jeri

OCTOBER 30, 2017 AT 3:55 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-92710)

My homocysteine was 5.8. My doctor was very pleased with that number. Since the test I added in electrolytes and a multi with methyl b's. I feel a little better, a bit more energy and clarity of thought even though my latest labs show my iron levels are in the toilet and thyroid ft3/rt3 of 10. I've been working for years to clean up my environment, diet, improve digestion and such but I'm obviously missing something. I'm compound hetero mthfr. I was relieved when my homocysteine levels weren't high or really low but I'm concerned that adding the methylated multi will drop it lower.

Reply

post author

Dr Lynch (https://www.drbenlynch.com)

OCTOBER 30, 2017 AT 4:22 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-92713)

As long as you eat sufficient protein and walk about / exercise a bit, your homocysteine should be good to go.

Reply

Jeri

OCTOBER 30, 2017 AT 4:34 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-92727)

Thanks! Protein intake isn't an issue but the walking/exercise is since I am in a wheelchair 🙁

Reply

post author

Dr Lynch (https://www.drbenlynch.com)

OCTOBER 30, 2017 AT 8:01 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-92939)

Hi Jeri – can you use your arms to buzz around a bit or just back and forth up a ramp perhaps? Or lift weights while seated? Or pull on elastic bands?

Reply

Alyssa Tait (http://www.equilibriahealth.com.au)

OCTOBER 30, 2017 AT 4:27 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-92715)

What a fantastic article, Dr Lynch. I have shared it on my professional FB pages (including Functional Nutrition Australia). I test serum homocysteine routinely – where Medicare and/or budget allows! – and see low homocysteine, albeit less commonly than high. I have two questions. One: why don't you recommend N-acetyl cysteine, for its ability to increase glutathione levels – why only liposomal glutathione? Two: children! I do find kids with low homocysteine more challenging, especially when they are not good at taking tablets like SAM-e, which can't be cut or crushed. I have trialled L-methionine as a powder, crossing my fingers but compliance is poor as it tastes terrible. Even digestive support is tricky – betaine HCl tablets are huge and herbal bitters and ACV are heartily rejected. I take your point about chewing, but the early teen age group is particularly challenging as they don't want to be told, or treated like a child. Upregulated CBS seems to make homocysteine more resistant to rising. (Can we assume that low Hcy in upregulated CBS means glutathione production will be impaired? I must admit, I had wondered whether actually fast CBS would preferentially promote the transsulfuration pathway, thereby producing adequate GSH. But I take your point that inadequate substrate -> inadequate product.) What would your key recommendations be to promote a healthier Hcy level in kids or teens at levels of 4-5, especially when they have upregulated CBS? Thanks a heap.

Reply

post author

Dr Lynch (https://www.drbenlynch.com)

OCTOBER 30, 2017 AT 8:00 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-92938)

Hi Alyssa –

Great – thank you!

1) NAC – I used to LOVE NAC – until I realized how DRYING it makes people – eyes (dry eyes), gut (constipation, dries out mucous membranes), nose (nosebleeds).

Also – NAC is only one step in making glutathione. There are other steps involved too – using vitamin B6, glycine, glutamine and epigenetic controls of these genes. Mold actually inhibits a gene which has a major involvement in producing glutathione.

So – yes – I recommend liposomal glutathione because I want to make sure people get it vs thinking they are.

Then the cysteine that is conserved upstream will go towards taurine, sulfate and other things as needed.

2) Kids have a naturally lower homocysteine than adults – because they are growing so fast (using more methylation) and burning up homocysteine. I give liposomal glutathione to my three boys about 3x a week – with grumbling. They don't like it but I tell them – hey – you want to be smart, good looking, fast and healthy? Ughh – they open their mouths and take a shot. Kids tend to like the tropical flavor of our Optimal Glutathione. Personally, I like the mint flavor.

You know you have sulfate issues in people when they smell like sulfur – gas, armpits, breath, skin. There are bacteria which produce hydrogen sulfide – and they also can tend to looser stools. If this is the case, have to limit sulfur containing foods and supplements, use molybdenum and also kill the hydrogen sulfide bacteria and replace with other bacterial strains like bifidobacter.

I'd use more protein in kids – again – as they are growing. Many chow on carbs.

Reply

Alyssa Tait (http://www.equilibriahealth.com.au)

OCTOBER 31, 2017 AT 8:16 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-93579)

Thanks very much for your reply. Yes, I imagine that would be the mucolytic effect of NAC. I will look out for this side effect more closely. I did have a patient recently where we used NAC to try to prevent the detox headache she would get when using acetaminophen by providing her with some more sulfur to make up for what she was using up, and unfortunately she had to stop the NAC after a little while as it made her gastritis worse. I'm sure it was compromising the mucus lining of the stomach. Thank you, this gives me some justification for the use of liposomal glutathione instead. Your kids are tough 🙂

Reply

COLETTE

OCTOBER 30, 2017 AT 5:06 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-92838)

YI have small fiber peripheral neuropathy-etiology unknown 😐. Getting results from homocysteine levels next week. Will be interesting to see.

Reply

post author

Dr Lynch (https://www.drbenlynch.com)

OCTOBER 30, 2017 AT 8:02 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-92940)

let me know – post a follow up!

Reply

Lacey Akridge

OCTOBER 30, 2017 AT 5:07 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-92839)

NAILED IT. Can't believe someone other than a chiropractor just nailed TOS.

Reply

post author

Dr Lynch (https://www.drbenlynch.com)

OCTOBER 30, 2017 AT 7:44 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-92935)

ha 😉 – I was trained heavily in physical medicine and thought about specializing in it as well. Love it.

Reply

Monique

OCTOBER 30, 2017 AT 5:13 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-92850)

I've had homocysteine levels around 5.2 if I remember right. They were under 6 so the doctor automatically said it was good but as with cholesterol I knew that anything too low wasn't always good. I've also tested significantly low for niacin, and way higher than normal b6. When I have taken methylfolate or methylcobalamin, I've reacted poorly feeling extremely irritable and anxious. I'm like the exact opposite of usual problems low cholesterol, low blood pressure, and low homocysteine. I'm currently pregnant and have removed alcohol and caffeine from my diet, and I'm currently taking your optimal prenatal.

Reply

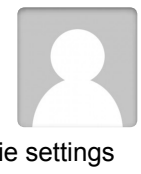
post author

Dr Lynch (https://www.drbenlynch.com)

OCTOBER 30, 2017 AT 7:43 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-92933)

Hi Monique – if your homocysteine is low, please consider adding more protein. The Optimal Prenatal Protein Powder (https://www.seekinghealth.com/optimal-prenatal-protein-powder) – vanilla is what I take most mornings to get started. It will help keep your protein intake higher which is tough while pregnant.

Reply



Miia

OCTOBER 30, 2017 AT 5:24 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-92860)

Thank you Dr Lynch, great article and replies.

Could MSM also help to raise/support bioavailable sulfur levels while improving digestion of protein/addressing gut issues?

Reply

post author

Dr Lynch (https://www.drbenlynch.com)

OCTOBER 30, 2017 AT 7:41 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-92932)

Hi Mila – possibly yes as sulfur is needed to provide cysteine. Sometimes low homocysteine is associated with low sulfur intake. Anytime one takes MSM or sulfur, molybdenum should be nearby to reduce sulfite load. MSM Plus Molybdenum (https://www.seekinghealth.com/optimal-msm-plus-molybdenum-100-capsules) provides both.

Reply

CC

OCTOBER 30, 2017 AT 6:39 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-92925)

I was treating pyroluria for about three years and then something shifted. Checked my homocysteine levels and it was down to 3. I stopped taking supplements and tested for pyroluria. I didn't have pyroluria anymore. Thankfully my homocysteine went back up to a normal range.

Reply

Jasmine

OCTOBER 30, 2017 AT 6:50 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-92926)

Would taking NAC help with no homocysteine?

Reply

post author

Dr Lynch (https://www.drbenlynch.com)

OCTOBER 30, 2017 AT 7:40 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-92931)

Yes it would. You may find NAC supplement (https://www.seekinghealth.com/nac-n-acetyl-l-cysteine-90-capsules) here in 500 mg capsules.

Reply

Candace

OCTOBER 30, 2017 AT 7:43 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-92934)

My homocysteine levels last year (while pregnant) were 3.1. I was taking a prenatal from NeuroBiologix with methyl folate and wonder if that lowered them? I do know they made me extremely anxious and I developed a painful, visible lump in my armpit that stayed for over a month. When I tried a glutathione cream on my feet by the same company, my feet were on fire and I was up til 3 or 4 AM with my mind racing. What in the world?? I was told to use it on our special needs child, but after that, I was concerned, esp. since they have no way of telling me if it makes them feel that crazy.

After delivery, I scanned for sulfur, so started taking a supplement and felt MUCH better. Nails got stronger and my hands looked human again (eczema). I tried the prenatal again as well and guess what, another lump under my arm. I stopped within a week this time and it disappeared quickly.

Maybe I should have it checked again sometime to see if it's still low… I couldn't find any info last year about low levels and any concerns. Thank you!

Reply

post author

Dr Lynch (https://www.drbenlynch.com)

OCTOBER 30, 2017 AT 8:03 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-92942)

Interesting – thanks for sharing. So the sulfur helped you a lot while the prenatal with methylfolate got you irritated? Did you take MSM or NAC or ?

Reply

Megan

OCTOBER 30, 2017 AT 9:28 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-92981)

Thanks for sharing. I am compound heterozygous and my hymociestine is only 4.2 i am overwhelmed with health, gut and fatigue issues that started after miscarriages (I've had 4 in a row) and had no idea they could be associated with these levels. Working on folate levels, mythelation cycle, thyroid, iron and vitamin D. Also suspected liver issues (low ceruolplasmin). The list goes on. I will continue trial and error with your products! Thank you for publishing your knowledge!

Reply

post author

Dr Lynch (https://www.drbenlynch.com)

OCTOBER 30, 2017 AT 9:47 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-92982)

Hi Megan –

Sorry about your recurrent miscarriages. Let's get you feeling optimal again!

Vacation? Can you just walk away for a bit – say a week or two? Seriously – vacation. Beach. Nice weather. Great people, food, nature…

This article is great on prenatal supplementation and MTHFR (http://mthfr.net/prenatal-supplementation-optimizing-your-future-child/2012/01/20/). It has helped many women with recurrent miscarriages – many many. I wish I kept a running list.

Reply

Gal

OCTOBER 31, 2017 AT 5:55 AM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-93063)

Dear Dr Lynch,

Thank you so much for replying! We run regular OAT and supplement as needed. There we discovered his Candida overgrowth, very high oxalates, very low glutathione levels, very low serotonine, high ammonia, other nutritional deficiencies,etc… and we started targeted supplimentation. Since then the “only” issues left are high Arabinose level (Candida) and high oxalates. I know about Biocidin but it contains grapefruit seed extract which can excarbate seizures:(and can intetfere with AEDs…we have tried Candex, Allimax, Caprilic acid, probiotics, etc with no effect. He is on low oxalate diet too. I guess our final choice will be medication. Do you recommend Nystatin or Difulcan please?
Do you think that the Candida issue could be the blockage of seeing good results with all other supplements especially with the addition of methyl folate and hydroxy b12?

I saw your comments for kids having notmally lower homocysteine than adults. Is 4.5 mmol/l a good value or is it low?

He has a deletion of 28 genes in total but the ones related to his refractory epilepsy are SCN1A, SCN2A and possibly SCN3a. Do you have any idea if they are related to other issues?

Thank you so much!

Reply

post author

Dr Lynch (https://www.drbenlynch.com)

OCTOBER 31, 2017 AT 10:22 AM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-93268)

I cannot recommend medications. I do believe candida to be significant if he actually has an overgrowth. Organic acid testing for yeast overgrowth is not the best way to detect – a stool test is. I question the yeast markers in OAT testing.

Homocysteine of 4.5 in a child seems pretty good to me.

Not sure about SCN1,2,3 genes. I haven’t looked into them.

Reply

Margie

OCTOBER 31, 2017 AT 6:29 AM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-93095)

Dr. Lynch, my homocysteine was 5.8 last year. I haven’t had it checked recently because I thought that was normal but will ask for the labs again. At the time, I was having a lot of problems from too much B6 in my blood serum and lowish SpectraCell B6, and low glutathione- yet P-5-P flared up my symptoms. I just cannot take anything with B6 in it, so now I get my B6 from high B6 foods. I used what you had said a while ago about clearing SUOX with B1 and molybdenum (I already have highish selenium) and taking N-A-C to raise glutathione. I did this because I suspected that a possible issue with SUOX might have been slowing down my CBS- hence the low glutathione and build up of B6. (I was also having symptoms of B1 deficiency at the time even though I had normal serum and SpectraCell B1). I tried this approach, and bingo! My serum B6 went down, my functional SpectraCell B6 went up, and my glutathione went up (although that and my cysteine are still borderline low), and my nystagmus, POTS symptoms, and peripheral neuropathy improved. I know this is off topic but might be somehow related, but although my neuro symptoms are better, I’m still fatigued- I think due in part to my SpectraCell B12 being low despite taking plenty of good sublingual methyl B12. My SpectraCell folate level is really good. Are cyanocobalamin injections ever

okay, as they are the only thing that has raised my B12 levels in the past, and I'm afraid that methyl B12 injections might be too strong. Note: I have a connective tissue disorder (Ehlers-Danlos syndrome), which I'm pretty sure increases my oxidative stress and need for antioxidants. Another side note: I need carbs, B5, and magnesium before bed to sleep through the night, probably because the constant physical stress from the EDS steals away my B5 and magnesium.

Reply

Tiffany

OCTOBER 31, 2017 AT 1:32 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-93369)

I am so grateful for your work! I have had low homocysteine, low inflammation and low liver enzymes for quite a long time and my doc has never been concerned, even though I have had significant health challenges. After having my genetics done, MTHFR C677t and MTHFR A1298C, as well as CBS, BHMT, CYP2D6 and others are present. I am enjoying learning about all this so much. It has helped me greatly understand the multiple organ failures that I have had over the years, as well as other health issues. Thank you for your tireless work. I, for one, am truly grateful. I honestly cannot understand how any practitioner would not utilize genetic information when designing healing plans for their patients. Genetics has confirmed the fact that there is no such thing as an optimal broad blanket protocol (or supplement) for such unique individuals.

Reply

Donna Girard

NOVEMBER 1, 2017 AT 2:54 AM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-93611)

This information is very consistent and important for the Down syndrome population. My 7 year old grandson reacts strongly negatively to methyl donors particularly folate, has a 1298c variation, low homocysteine, and practically non-existent glutathione. He sleeps poorly, is so tiny he needs human growth hormone, but eats like a 250 pound adult. He is frequently agitated (lack of restorative sleep?) . Doctors are working on zinc/copper balance but not homocysteine. What are your recommendations?

Reply

Laura Burns

NOVEMBER 1, 2017 AT 5:05 AM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-93651)

Yes. My homocysteine is low at 4.7. My dad passed at 67 from a first time heart attack. I got very concerned and looked at his health record. I knew he was type 2 diabetic. But I didn't know he had been anemic the month before he died. He had also been on thyroid medication for a while but my mom doesn't know why. My sons and I are both MTHFR, anemic, struggle with vitamin D, and have hashimotos. I measured my homocysteine thinking at least I got that under control at 4.7. But reading this looks like I have more work to do. I'm taking 5MTHF daily and getting by B12 shots quarterly. I just started liposomal glutathione.

Reply

Susan Sentilles

NOVEMBER 1, 2017 AT 6:22 AM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-93665)

Hi Dr Lynch.
I'm enjoying your Dirty Genes course and videos. This post has struck a chord with me. My husband started with peripheral neuropathy in his feet. He isn't diabetic. The cause seems to be a mystery to his doctors. After a few years of this he developed a tremor in his hand. They diagnosed him with Parkinson's. I always felt it was connected in some way to the neuropathy but his neurologist dismissed my suggestion in a condescending way. "Stay off of the Internet". I've been researching more ever since. There was no treatment effective for his foot pain and the Parkinson's treatment is just not improving his tremor and general condition. I have been trying to clean up our diet and air and water with very little results. I'm not even sure if a homocysteine level was ever done on him. This is so frustrating when you have nuggets of information and no doctor who will help you explore it.
So do you think low homocysteine could be his problem and could this treat and or reverse his symptoms?

Reply

post author

Dr Lynch (https://www.drbenlynch.com)

NOVEMBER 1, 2017 AT 2:00 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-93946)

Hi Susan –

The low homocysteine is not causal for neuropathy – it's a result.

Homocysteine may be low because there is a higher need for glutathione production – to help offset the oxidative stress he may have.

Supporting with liposomal glutathione, ensuring sufficient protein but not excessive, deep sleep (measure it using OURA ring) and limiting carbohydrates (refined ones) are great starts.

Reply

Chris

NOVEMBER 1, 2017 AT 8:07 AM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-93679)

Hi Dr Lynch. This is a very interesting article for me as my homocysteine level is somewhere between 0 and 4. I believe this is because of 5 years of supplementing with sublingual methylcobalamin most days, and eating foods containing a good amount of the other b vitamins. I have been unwell for over 18 months now (mainly daily headaches and fatigue) following some toxin exposure (mercury and concentrated diesel emissions), and given my homocysteine result, I suspect it is the effects of a SAMe and glutathione deficiency that I am feeling (though liposomal glutathione hasn't helped). My question is, given that I eat plenty of protein (80-100g daily), don't seem to have digestive problems (I've tried betaine hcl and apple cider vinegar), exercise a good amount and don't have stresses or known ongoing toxin problems, where would the methionine I eat daily be going other than being turned into SAMe/ glutathione which I appear to be needing? And how can someone really be deficient in SAMe/ glutathione when they eat their building blocks and have methylation working well? Shouldn't I have rapid daily doses of SAMe/ glutathione when I eat methionine?

Reply

post author

Dr Lynch (https://www.drbenlynch.com)

NOVEMBER 3, 2017 AT 12:53 AM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-94658)

Hi Chris –

Producing SAMe from methionine is not simple. Your body could be diverting it down a pathway called dcSAM. This is commonly occurring during chronic infections or autoimmunity. You could consider the combination of SAMe and liposomal glutathione. I am not sure which company you are using to supplement but these two

nutrients require specific packaging and preparation or they are worthless. I highly recommend you consider Seeking Health as we put care into how we source and package our SAMe (https://www.seekinghealth.com/same-30-capsules) and our liposomal glutathione (https://www.seekinghealth.com/optimal-liposomal-glutathione-plus-30-servings) has won an award for best antioxidant at a major supplement conference. Not easy making effective supplementation – you could have been using 'duds'.

Perhaps you are exercising too hard? Maybe reduce a bit – need to evaluate your training and sleep / rest / recovery.

Reply

Jeanne

NOVEMBER 2, 2017 AT 10:41 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-94649)

Dr. Ben,

Appreciate you making finally a post about low homocysteine. My blood test results just came out, and it is at 3.4 umol/L. I am based in Australia, just as a reference because I don't know if it is different measurement in the US.

I have been supplementing with SAM-e for maybe 3-4 years now. I take magnesium supplements, experiment on different vit B (Thorne brand).

I have heterozygous C677T. Hubby is homozygous A1298C. Prior to seeing a naturopath, our homocysteine levels hover around 5-6. Stopped seeing the naturopath as, homocysteine kept going lower. And, we did not achieve what we want, which is a pregnancy.

Any assistance would be appreciated. Thanks.

Reply

post author

Dr Lynch (https://www.drbenlynch.com)

NOVEMBER 3, 2017 AT 12:40 AM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-94654)

Hi Jeanne –

That is the same units as in USA. That is quite low and likely contributing to your pregnancy difficulties.

I would highly consider:
– liposomal glutathione
– Optimal Prenatal Protein Powder – this is the best formulation out there by far and provides additional protein which you absolutely need. Plus it has additional carnitine, carnosine, taurine, choline – which are never found in other prenatals.

Watch the video and read the article in full – prenatal supplementation and MTHFR (http://mthfr.net/prenatal-supplementation-optimizing-your-future-child/2012/01/20/) – – pls do also consider the must consider supplements. I know they seem like a lot but you definitely need them during this time.

Your husband needs to take the exact same things as you – seriously.

– liposomal glutathione
– prenatal protein powder
– fish oil
– liposomal vitamin c
– probiota histaminX
– optimal iron plus cofactors

those are the key ones

I take the prenatal protein powder nearly every morning – it's been my breakfast smoothie base for over 3 years now.

Let's get you both super healthy and proud parents!

Reply

Jeanne

NOVEMBER 3, 2017 AT 2:37 AM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-94660)

Thank you for your response Dr Ben. Sadly our dreams of becoming parents are over. I am over 40 now and, having gone through multiple miscarriages and IVF, hubby and I needed to put that behind us. 🙁

Now, the aim is to become healthy again. Apologies if I had not made it clear earlier. It is still a difficult topic to share.

What modifications would we need for the supplements you indicated, plus how long for?

Thank you.

Reply

post author

Dr Lynch (https://www.drbenlynch.com)

NOVEMBER 3, 2017 AT 11:22 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-95157)

Hi Jeanne –

I hear you. Let's get you healthy 😉

Regarding supplements – based on the limited information you shared with me, I'd say you could likely benefit from those but I would rather you start at the foundations and work this way and forward.

The Dirty Genes Course Bundle (https://www.drbenlynch.com/product/dirty-genes-bundle-b/) is where you should start – it sets you up for long term success.

Start there and then you'll have more insight to know what to do next. 😉

Reply

Jeanne

NOVEMBER 5, 2017 AT 1:53 AM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-95446)

Hi Dr Ben,

I've already purchased the bundle 🙂
I think the book is due around early next year? I have not logged on to any of the courses tho.

Thank you for taking the time out to respond.

Cheers,
Jeanne

Nicole

NOVEMBER 3, 2017 AT 12:31 AM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-94651)

Hi Dr Lynch
You mention that low homocystein in children is ok. Wondering if 3.4 & 3.7 is too low for my 8 & 11 year olds?
Thanking you.

Reply

post author

Dr Lynch (https://www.drbenlynch.com)

NOVEMBER 3, 2017 AT 12:35 AM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-94652)

I'm still learning about this range for kids – just make sure they are eating enough protein and support with liposomal glutathione as well. We lose a lot of homocysteine to glutathione production.

Reply

karenwillingham

NOVEMBER 3, 2017 AT 10:44 AM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-94859)

Hi, Dr. Lynch,
My Dr. had me test my sulfates and sulfites on test strips. I also tested my two boys. We were all in the very high range for both. (they were hard to read but near the top of the measured range) I am borderline low homocysteine, I believe it was about 5. My SAMe level was fine. My biggest problem is sleep. I have added Moly-b and liposomal glutathione. I eat plenty of protein, fat, and mostly low carb diet. Other than the Moly-b glutathione, and diet, is there anything else I should do to decrease the sulfites and sulfates?

Even if you don't get to reply, I am so thankful for all of the information you have made available!

Reply

post author

Dr Lynch (https://www.drbenlynch.com)

NOVEMBER 3, 2017 AT 11:15 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-95155)

Hi Karen –

I am not a fan of testing urinary sulfate. This is natural by the body to eliminate. If sulfites were high – than that is an issue. Which strips are you using? Please provide a link.

Boys will have a lower homocysteine such as 5 – that is pretty normal for kids.

Sleep has many factors – can be slow COMT, slow MAOA or fast MAOA or a dirty DAO or MTHFR. Depends. I'd reduce your protein in the evening a bit and add in some healthy carbohydrate.

Many do well with Optimal Sleep (https://www.seekinghealth.com/optimal-sleep-90-capsules) – I typically just use 1 capsule most evenings or I will also use SAMe at times also if I am wired. It helps me calm down.

Have you ordered the Dirty Genes Course Bundle (https://www.drbenlynch.com/product/dirty-genes-bundle-b/)? That may help you a lot with your sleep.

Supplements are useful – but they will not address the underlying problem if the fundamentals are not in check.

This article on sleep and melatonin (https://www.drbenlynch.com/melatonin-for-sleep/) is also useful.

For the sulfites, be careful with liposomal glutathione as it can increase sulfites and sulfate. Be sure to use a liposomal glutathione with molybdenum built into it like Optimal Liposomal Glutathione Plus (https://www.seekinghealth.com/optimal-liposomal-glutathione-plus-30-servings).

To reduce sulfate, one would need to evaluate how much protein is being consumed and how much sulfur-containing veggies and foods and supplements.

Reply

karenwillingham

NOVEMBER 7, 2017 AT 10:42 AM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-96309)

Sulfite and sulfate strips…..from Amazon
SEOH Indicator to Detect Sulfite Quantofix 100 Analytical Strips
SEOH Indicator to Detect Sulfate Quantofix 100 Analytical Strips

I'm a little afraid of the Optimal Sleep, it is similar to a glutamate scavenger my doctor had me try. It ZAPED my desire to do anything. (you responded to my comment on miscarriages and birth defects…Niacin) But I will, and pulse.

Melatonin only works for 4-5 hours. I will read that artilce

Drinking my electrolytes now….. delicious!

yes… Glutathione with moly-b. learned that the hard way at my sons expense. Had horrible detox reaction! Nasty rash. Pulsing 1every 4 days now

I have purchased the bundle. Love it!! It has really helped me step back to take a look at all of the things that are in my control. And make good choices because I can CHOOSE to make the time to exercise and take care of myself. Ordered the book Essentialists too.

You rock! Thank you.

Reply

Sandra

NOVEMBER 3, 2017 AT 9:17 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-95101)

Dr. Carolyn Ledowsky also writes about low homocysteine.

Reply

Bea Löw

NOVEMBER 10, 2017 AT 1:40 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-98082)

Hi Dr. Lynch, I am writing to you from Germany, glad that I found your site! Since three years my daughter (now 19) deals with heath issue problems, skin, fatigue, hormones, organ problems (lung, stomach, heard, head, muscels and joints etc.), her lab tests showed elevatated ANA (1:640) and low Leucocytes. We discovered by hazard that Sulforaphane immediadly stops her symptoms and the Lab results after six weeks taking it, came out without any ANA!
From that point I started a lot of research on PubMed and the internet. I assumed that her detoxification system and her methylation doesn't work well enough. I remembered that without Sulforaphane her homocysteine was below 4! We checked again and with sulforaphane she got 5 – still low, but higher than without. It makes sense to me as the S. helps with methylation and detoxification of phase II.

The question, I still don't understand, is: what might be the reason(s) for the low homocysteine? It may be due to high oxidative stress and a high need for gluthatione. What other reasons could be and how can we find that out? What kind of tests would you recommend (gluthation? what else?) We don't find a physician who knows about these things – we looked and tried in whole Germany. I hope to get an answer with some ideas from you as you

got so much expertise in this field.
Should we try to give s-gluthation and SAMe (Methionin itself made heard problems to her after taking it for a week)?

Btw: by starting with Sulforaphane her usually high levels of Selenium and Molybdaen fell down and her long term deficites in Phosphat came up to a normal level, that was interesting for me to. It seems that the Sulforaphane made the detoxification work (so selenium was able to be used) and the molybdaen also maybe for the sulfur breakdown of the sulforaphne itself. Why the low phosphat came up – no idea.

Sorry for my long text and my mistakes in the English language! Thank you for your ideas on our problem! Bea

Reply

post author

Dr Lynch (https://www.drbenlynch.com)

NOVEMBER 10, 2017 AT 2:11 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-98111)

Bea –

You are sharp 😉 Well done. Love your thinking – you're right on.

Regarding other causes of low homocysteine – they are mentioned in the article. Please refer back to it.

I do not like using SAMe in people if they are not responding well to it.

It seems she needs more antioxidant support – so I'd actually consider **Optimal Liposomal Glutathione** (https://www.seekinghealth.com/optimal-liposomal-glutathione)

We also have a liposomal glutathione with added cofactors of molybdenum, selenium, PQQ and riboflavin – but she seems already high in those so I wouldn't use this.

I'd also consider **PQQ** (https://www.seekinghealth.com/pqq-lozenge-30-lozenges) as it is a potent antioxidant. Use only 1/4 lozenge to start with as it is potent.

The low phosphate coming up – that is interesting.

Perhaps vitamin D was working better and was able to increase her phosphate? Did you supplement her with more vitamin D?

I just took a moment to look into this and appears I may be right:
"In vivo, cysteine supplementation increased glutathione and protein and mRNA expression of vitamin D binding protein and vitamin D 25-hydroxylase (CYP2R1) in the liver, and simultaneously resulted in elevated blood levels of cysteine and glutathione, as well as increases in VDBP and 25(OH) vitamin D levels, and decreased inflammatory biomarkers in ZDF rats compared with those in placebo-supplemented ZDF rats consuming a similar diet."
source (https://www.ncbi.nlm.nih.gov/pubmed/26778482)

If this happens – then by giving glutathione, you are increasing vitamin D transport, binding and levels which then increase phosphate levels.

Plus – indirectly:
'The present study demonstrates that VDR inactivation has a negative effect on sulfate status; sulfate wasting as a result of increased sulfate excretion leads to sulfate deficiency. Given the roles that sulfate plays, the physiological impact of sulfate deficiency can be multiple. Here we showed that VDR deficiency causes a dramatic reduction in sulfated proteoglycan synthesis in the skeleton and a moderate decrease in hepatic glutathione levels. The former may represent a direct effect of a decreased inorganic sulfate pool, inasmuch as decreased availability of sulfate may affect intracellular sulfation of cellular components such as proteoglycans. It has been reported that proteoglycan sulfation in articular cartilage is dependent on the inorganic sulfate concentration in the media (42). The latter finding suggests that chronic sulfate wasting may ultimately cause a reduction in the organic sulfate pool, because methionine and cysteine can be metabolized to glutathione, taurine, or inorganic sulfate (21). Glutathione is an

antioxidant critically involved in cellular detoxification and reduction-oxidation processes (11, 34), and the consequence of its diminution remains to be determined.'

'A hallmark of vitamin D deficiency is the development of rickets and osteomalacia. A typical characteristic of rachitic bones is disorganization and expansion of the chondrocyte columns in the growth plate and accumulation of unmineralized bones. These phenotypes are commonly attributed to abnormal calcium and phosphate metabolism caused by impaired vitamin D function (2). Because sulfation is essential for the formation and biological properties of proteoglycans, the major extracellular component of cartilage, it was argued that abnormal sulfate metabolism in vitamin D-deficient animals may contribute to development of rickets and osteomalacia (14). However, our observation that serum sulfate and skeletal proteoglycan levels in normocalcemic VDR/ mice remained reduced, even in the absence of rickets and osteomalacia, argues against the above notion. That is, the role of sulfate in the development of rickets and osteomalacia is minimal, if any. Certainly, this does not exclude the possibility that the reduction in sulfated proteoglycans may contribute to other, more subtle, bone abnormalities. Further investigations are needed to elucidate the exact role of sulfate in bone growth and remodeling.'

source (http://ajpendo.physiology.org/content/ajpendo/287/4/E744.full.pdf)

Reply

Laura

NOVEMBER 25, 2017 AT 9:19 AM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-105452)

My combination of A1298C and C677T reduces my MTHFR activity 53%. I am also homozygous for a mutation in the enzyme that precedes MTHFR called MTHFD1 that reduces its activity by 34%. Theoretically, these add together to lead to an 87% reduction in methylfolate production.

I've been told this might be one of the worst possible combinations for methylfolate production. I did start taking methylfolate last month where my homocysteine was 8. Had it recently tested last week at it's at 6.6.

My main problem is insomnia so getting a good night's sleep is difficult and I assume cranks up my need for glutathione? However, a serum amino acids analysis came back abnormal–high ornithine, high aspartate, and borderline low arginine (could be consistent with decreased ammonia disposal) and high leucine and isoleucine could reflect an impairment in branched chain amino acid metabolism that could cause an impairment in ammonia disposal. I'm waiting on the ammonia lab.

Could glutathione provide me any help in the sleep arena?

Reply

post author

Dr Lynch (https://www.drbenlynch.com)

NOVEMBER 29, 2017 AT 3:11 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-108974)

Hi Laura –

MAY.. May reduce – not does.

It is not the worst combination – and statements like that are not supportive. They are scary and do no good.

Nonsense I say.

Glutathione could help yes – as liposomal form. And so could SAMe. I'd also reduce down on the methylfolate.

Reply

Sonja

NOVEMBER 27, 2017 AT 10:54 AM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-106142)

Hi Dr. Lynch,
I'm also writing from Germany. I got tested by my OBgyn after 3 miscarriages. My homocysteine was 13 and then they tested for MTHFR. I'm homozygous c677t, and also have low COMT variants.
Unfortunately the recommendation from the geneticists was to take 5mg Folic Acid and from the hematologist to take just 150 picograms Folic acid.
I didn't follow their adviced and started with 400 mcg Methylfolate, active B6, B2, B12 and TMG. I have been doing terrible tolerating the Methyl forms, I didn't do well either with TMG, Glutathione and Choline. All give me terrible headaches and tiredness. Even just 1-2 pills of the Optimal prenatal daily is too much.
I've tried and keep trying everything possible to tolerate it.
I got pregnant again and my homocysteine was 5,4, reduced mostly with Folinic Acid, Hydroxy B12, B6, B2 and eating plenty of beets. But I miscarriaged again.

Is it possible to reduce the homocysteine so much within Methylfolate?

If so, should I completely avoid B9?

I'm also worried that just taking Folinic alone is not enough for a pregnancy being homo c677t.

Thank you!

Reply

post author

Dr Lynch (https://www.drbenlynch.com)

NOVEMBER 29, 2017 AT 3:09 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-108973)

Hi Sonja –

If you are eating leafy green vegetables, salads and your homocysteine levels are down, then you may be doing ok with folinic acid.

However, since you miscarried again, it does seem to be insufficient.

I'm sorry you are struggling with this.

Are you taking electrolytes?

Having MTHFR and slow COMT is a tricky combination and methylfolate/choline will push more neurotransmitter formation – and thus excitation – leading to headaches.

Please read this on reducing methylfolate side effects (http://mthfr.net/preventing-methylfolate-side-effects/2014/11/26/).

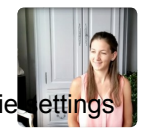
I'd seriously consider the electrolytes and the other steps I discuss in that article.

Then try the Optimal Prenatal Protein Powder – in a smoothie with frozen berries, milk of your choice (almond, goat, etc).

Yes, you can really lower homocysteine levels with too much methylfolate and B6.

I'd also consider liposomal glutathione – as discussed in the article.

Reply



Melissa Sklepetas (https://www.instagram.com/melswellnesspage/)

DECEMBER 4, 2017 AT 9:47 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-114340)

Hello from Canada 🙂

What is the range one should shoot for then? Of course not feasible to keep taking blood tests, for homocysteine levels but to base off the efficacy of supplementation with the symptoms going away/new ones coming up…

I haven't tried a methylated form of anything before, but will be taking it once it comes in (ordering from pure encapsulations)…also will be going to my doctor and hopefully he agrees to run a test just to see where I'm at…

The reason I'm commenting is that I've been starting to detox/got rid of my candida overgrowth (using timed release oregano capsules from ADP (that's the brand) and trying to support methylation by getting my leafy greens in (uncooked) and taking phosphatidylcholine….but this is what's happening:

My hormonal acne actually went away! I didn't breakout at the usual time in my menstrual cycle (used homeopathics to help get rid of estrogen and of course the candida cleanse helped as well) however, the cystic acne is still there….and the brain fog, that's a big big big issue with me.
Over the past 5-7 years I feel like I've just been getting stupid, feel like my brain isn't as sharp as it used to be. Since my health journey and discovering my mutations, I'm trying to fix things (i.e. candida cleanse, soon a parasite cleanse – confirmed I have them) but the brain function is getting worse and really freaking me out….
I'm having weird neuro symptoms as in messing up spelling (never happened before) and memory issues….
to revisit brain fog, its more associated with SOD2 I'm finding through research which I'm homozygous for…I know supporting the mitochondria is crucial here as that mutation is related to ALS which really freaks me out…and brain fog is a big sign of oxidative stress…yes I know not to treat the SNP – obviously! in this regard I'm paying attention to the symptom, so the brain fog and decreasing cognition….
also, I'm using as clean natural health products as possible to avoid xenoestrogens etc, eating organic and grass fed meat when I can, using DIY washing machine 'detergent' etc so I don't think that's an issue…but here are the allergies that seem to be popping up:
ASA and caffeine will give me an ulcer caffeine makes me jittery and I can feel my heart racing/beating harder
right shoulder pain (I know this is associated with gallbladder and liver issues)
persistent cystic acne that I thought would go away with candida cleanse

And I think I'll stop there because I'm pretty sure I'm leaving the longest comment on here….feeling lost and a bit scared and honestly can't wait to get your book in the new year I feel like I really need help, want to learn and use my new nutrition education to help people….but I'm reaching out to you because I need to help/heal myself before I can move on to others

Best Wishes,
Melissa

Reply

Miranda Habalou

DECEMBER 16, 2017 AT 6:29 AM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-121650)

Hi there , I have been having strange problems lately .. feeling as if I will pass out randomly .. numbness in my nose, hands and feet that comes and goes . My homocysteine levels were at 3 in 2013 after I thought I experienced a mini stroke , the Dr. Just told me "well this is something that may affect you or you could live a long healthy life with " whatever that means !!! So now I am wondering if these new strange symptoms have to do with low levels .

Reply

Aubrey Johnson

DECEMBER 19, 2017 AT 3:19 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-123560)

Hi Dr.,

I am 4 weeks pregnant. (i know so early) I did some testing and I have a copy of C677t mthfr. My homocysteine was 3.5. My dr said it was great but looks like its not so much. My vitamin B levels she said were way too high at 1889 and to stop taking my methyl b 12. Should I? Vitamin D she said was way too low at 22 so I am going to start taking 3000 iu of vitamin D. Does that sound optimal? My prenatal has 800 mcg of methyl folate. Let me know how this all sounds please. I want to ensure I have a healthy pregnancy and baby and my dr doesnt seem to know much about this kinda stuff...

Reply

post author

Dr Lynch (https://www.drbenlynch.com)

DECEMBER 20, 2017 AT 2:07 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-124094)

Hi Aubrey –

You're correct that your homocysteine is too low. High vitamin B levels can be for many reasons. I suspect you may have low glutathione levels. It is not proven to be safe during pregnancy but if my wife had a low glutathione level, I would recommend she take liposomal glutathione – 1/4 teaspoon upon waking in the morning.

Vitamin D – I think 3,000 iu is too low. I'd consider 6,000 units.

Pregnancy requires more than just l-methylfolate. The focus is on folate during pregnancy but it is wholly inaccurate.

I highly highly recommend you switch to Optimal Prenatal Protein Powder (https://www.seekinghealth.com/optimal-prenatal-protein-powder) and make morning smoothies with it. You can also use the Optimal Prenatal capsules as well but the powder is the most comprehensive and easiest to take. It also provides additional protein which is much needed for those with low homocysteine and pregnancy.

I'd also add in ProBiota HistaminX (https://www.seekinghealth.com/probiota-histaminx-60-capsules) as high histamine levels are associated with pre-term infants and pregnancy complications. Consider 1 capsule after dinner.

If you are nervous about the liposomal glutathione, then use the Optimal Liposomal Vitamin C (https://www.seekinghealth.com/optimal-liposomal-vitamin-c-30-servings) at 1 teaspoon a day with breakfast.

Also make sure you are taking fish oil and sleeping well 😉

Have a fantastic pregnancy!

Reply

Breanna

DECEMBER 20, 2017 AT 9:50 AM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-123854)

Hello Dr. Lynch,
I'm compound hetero MTHFR. My homocysteine is 5.4, has been that exact same number over two measures 6 months apart. I started seeing a functional medicine doctor 7 months ago after having a miscarriage (went on to have a 2nd miscarriage). I would like to try to conceive again & wondering if my homocysteine is too low. I've been taking 2.4-4 mg of methylfolate a day. Is that too much? I handle them very well. No symptoms of being unwell, but functional med doctor did discover mild hypothyroid & possible hashimotos as I do have some antibodies. I'm on NDT now. We are now trying to figure out why my oxidative stress is high. Suspect some sort of underlying infection. We are at the point where we need to TTC soon or give up on the dream.

Reply

post author

Dr Lynch (https://www.drbenlynch.com)

DECEMBER 20, 2017 AT 4:32 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-124206)

Hi Breanna –

I think that is a lot of methylfolate. Many people – docs included – think that pregnancy has to do with folate only. It's not.

Please read this article fully – and share with your doctor – about NADH/NAD ratio and pregnancy (https://www.drbenlynch.com/miscarriages-birth-defect-prevention/)

This article is also useful about folic acid and pregnancy (https://www.drbenlynch.com/resource/folic-acid-pregnancy-case-study/).

I really dive deep here and give you a lot of information regarding prenatal supplementation (http://mthfr.net/prenatal-supplementation-optimizing-your-future-child/2012/01/20/).

I highly encourage you to switch to Optimal Prenatal Protein Powder along with other supportive nutrients like Optimal Liposomal Vitamin C, Optimal Iron Plus Cofactors (if needed), fish oil, vitamin D and also ProBiota HistaminX. Optimal Liposomal Glutathione is also needed prior to pregnancy. These nutrients will greatly support your oxidative stress. I do agree looking for infections is important – but so is environmental causes (air, food, water, shelter).

The Dirty Genes Course (https://www.drbenlynch.com/product/dirty-genes-bundle-b/) will give you deeper insights as well.

I've helped many women nutritionally and with lifestyle recommendations – and they've carried to term and have healthy babies 😉 – dedicate some time to read and watch these videos.

Reply

Lucinda

JANUARY 1, 2018 AT 3:08 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-129504)

Hello Dr. Lynch,

My son has just turned 2 and has dysbiosis/SIBO, hypothyroidism, poor appetite, failure to thrive, and is on a severely restricted diet due to his many non-ige mediated food allergies. We're really struggling to find a doctor with experience treating these issues in a child his age. Would you consider his homocysteine, at 3.6, to be low, given his age?

Thank you

Reply

post author

Dr Lynch (https://www.drbenlynch.com)

JANUARY 1, 2018 AT 11:17 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-129784)

Hi Lucinda –

Given his age, I'd consider that level to be decent.

I'd look at consulting with Barry Smeltzer, Eric Potter, MD or David Berger, MD.

These are great practitioners who understand my work very well and think outside the box.

Reply

Daniel

JANUARY 9, 2018 AT 6:07 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-136652)

Hello Dr. Lynch,

My son (3 year old) had a test result of homocysteine of 3.7. His doctor prescribed him MB12 injections every 3 days to improve his methylation.

One concern has been that a recent test of the homocysteine showed a value of <1 (is this equivalent to undetectable?)

What does this imply from your perspective? Thank you

Reply

Brandi Rodenburg

JANUARY 20, 2018 AT 2:52 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-150168)

Hi Dr. Lynch, I have heard you on so many podcasts and love reading your website. It has definitaly enlightened me and this article really was mind blowing. My dr. said nothing and probably had literally no idea AND he is a respected integrative dr in his 60s who continues to learn constantly. of course no one can know it all. I appreciate your work he often downplays Mthfr snps and I don't appreciate that. I was born with spina bifida and tethered cord syndrome, and also have chronic lymphedema, fibromyalgia very severely, biomechanical birth defects feet worst, severe chronic fatigue syndrome, hypothyroidism, childhood obesity (i had a nutrition snps test done this summer and I had nearly ALL the current identified snps that code for childhood and adult obesity, my score was 8.5 out of 10 for obesity,,,which I am and am always craving and always hungry, and cannot really exercise at all. I also have a terribly difficult time losing weight unless I go completely to one monofood, ie. cucumbers, white rice, grapefruit. Not exaggerating. Need to lose over 70 lbs. I have homozygous MTHFR a1298c and homozygous COMT gg rs4680. I also have heterozygous ag of BDNF rs6265. Prior I have had very difficult time with B vits. This july I discovered Thorne's methylgaurd plus and finally can take one. I did experience a much better outcome the first week, than I do now. I am on hydroxycobalamin injections .8ml every other day. I have very low levels of ALL nuerotransmitters and have been trying to do the CHK nutrition amino acids, but every time i bump up the mucuna I throw up and am so nauseous I cannot function. I tried and tried the cysreplete and it felt like the l cysteine was eating my throat away, and increased the nausea. I have felt the mucuna very much aid my dopamine but was so miserable I had to remove the l cysteine and go back to low dose NAC and decrease the mucuna. I increased the neuroreplete. I have felt my cravings and binge eating get worse since lowering the mucuna dose, and slightly less energy and happiness. I don't understand this very well, dr says need to keep balacncing but I told him I just couldn't keep increasing anymore I was too miserable. And i really really wanted to get high high doses. I have had depression since I was a little girl. with periods of severe severe depression. I also have been trying vyvanse for binge eating disorder, and it has helped very little compared to when I took adderall. This article has me wondering if you could provide me any insight, I just had the boston heart panel done and found out my homocysteine level is 5.9. I have a great deal of inflammation and take TONS of supplements to try to reduce my pain without taking narcotics. I thought this was why it was low. but now I am not so sure. 12/22 I had a nerve conduction and EMG on my arms and legs and it was found I have carpal tunnel on my right arm, and widespread polyneuropathy. (i must add that since I was 21 I have been on and off vegetarian and am currently 33. I have only added some fish and meat recently. though I much prefer fatty fish like mackeral and red meat to chicken which is what i have been eating.) Could this neuropathy be due to my homocysteine, birth defects, mutations, and/or diet? Are there any other actions I can be taking, I try a lot of things and always want to get better. my diet is a severe downfall, especially sugar and desserts. I eat mostly organic though and no gluten/dairy/tree nuts (allergy)/shellfish. Any help is much appreciated.

Reply

Brandi Rodenburg

JANUARY 20, 2018 AT 2:57 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-150187)

I also forgot to mention I have high arsenic levels, over the upper limit, and very very very high levels of uranium due to uranium in my groundwater, meaning so far off the charts it would probably be like the 200% or soemthing. I understand how these affect my mitochondria as I have been researching them, and that not a lot can detox very much of the uranium, dr confirms.

Reply

Brandi Rodenburg

JANUARY 20, 2018 AT 3:12 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-150253)

I am currently taking fisetin, quercetin and bromelian, and vitamin c that contains rutin, green tea extract, and the neuroreplete contains tyrosine, and occasionally chocolate and resveratrol to lower COMT levels. but I don't fully understand how to balance COMT and MAO, it is over my head.

Reply

post author

Dr Lynch (https://www.drbenlynch.com)

JANUARY 21, 2018 AT 1:02 AM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-150968)

Hi Brandi –

Balancing genes is learned by reading Dirty Genes – it reads easily and you'll get understand! you may get your copy of Dirty Genes here: http://amzn.to/2mUYe4G (http://amzn.to/2mUYe4G)

Reply

Michelle

JANUARY 23, 2018 AT 10:35 AM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-163313)

Dr. Lynch,
Thank you and bless you for helping and providing all this on such a little known area! I could not find much when i got my result back of my homocystiene of 4.2 I am 32 yo female, I have tried so many things and so many of them do not work, I got so sick and anxious from SAMe, and b vitamins in their bioavailable form make me VERY angry and irritated, stressed to the max. i am starting to lose hope because I just dont understand, I hear one thing then I get hopeful, but then it doesn't work not only do they not work, it makes things harder, then I miss work etc because I will be so panicy and cannot sleep. Currently on .25 clonazpam twice per day, lunesta 2 mg at night along with 15 mg benedryl and two does of 5htp, i was put on remeron for sleep and weight gain as i am underweight, and had to stop it, it was making things worse too, now they think something with comt and want me to try lamictal, but i am so worried that it will make my life worse again! I also had low cortisol (adrenal something) if you cant make sense of this that is okay! nobody else can either! But i figured it was worth a shot! Thanks again so much for all the great work you do!

Reply

verst2

JANUARY 26, 2018 AT 8:23 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-173700)

I have the C677t mutation homozygous. My homocysteine is 5. Doctor wanted to make sure it was not elevated but didn't say anything about it being low. I have brain fog, mental fatigue, exercise intolerance where it makes me feel a lot worse, depression and anxiety. Poor memory and focus. Hyper-reflexes and skin sensitivity. The only labs that have come back positive are b12 off the charts, d-lactate off the chart, cortisol low, vitamin d low, and thyroid antibodies. Have elevated LFTs at times and gallbladder pain at times. I'm reading and trying to watch your videos because I am trying to figure out what the heck is going on!!!!! Got a lot worse after pregnancy.

Reply

Elizabeth

JANUARY 27, 2018 AT 10:14 AM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-174554)

Hi Dr Lynch,

My pre-verbal ASD son 6 years old is positive for C677t heterozygous. His recent Homocysteine results are 4.7. He is also low in glutathione. Results were 433 um. Currently he is taking NAC, Leucovorin Calcium, and B12 injections every 3 days. He seems to be a non-responder to anything we try. I'd appreciate any recommendations. I was recently told he may never be independent. He has so much knowledge there has to be a way to recover him.

Thanks in advance!!

Reply

Julia

FEBRUARY 10, 2018 AT 1:28 PM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-208316)

Hi DOCTOR!I've been doing myers coctail IVs with B12 and mthfr in it, because i have hetherosigous mutation mthfr. After one months I went to ER with symptoms of my heart was beating too slow and i felt breathless. ER found nothing. I suspected it might be because of b vitamins and stopped them.
Resently I started again IM injections of b 12, mthfr,and other Bs, after 2 weeks,I had the same symptoms with heart! Cardiologist found nothing! Yesterday came my bloodwork and i have B12 over 2000 ,very very high, max.is 1000,
And homocysteine is 4!
Should I do glutathione IV? To get rid of B12 faster? I also developed stomach ulcer recently, and probably oral form of glutathione will not help me. I also suspect an ulcer is a result of too much b12, because I already treated h-pylory and my stomach is still hearting.
Please advise.
Thank you!

Reply

Abbe

MAY 19, 2018 AT 2:45 AM (HTTPS://WWW.DRBENLYNCH.COM/LOW-HOMOCYSTEINE/#COMMENT-245523)

Hi Dr Lynch, thanks for this information, I have recently had homocysteine result of 3.7 , coagulation screen all normal and fbc all normal, I am 24 weeks pregnant, my obstetric consultant was concerned I may be at risk of clotting and homocystinuria due to family history and homozygous A1298C and one of the CBS which increases homocysteine, she wanted me to have clexane (enoxoparin) from week 28 as a precaution, I was not keen and requested the blood tests first to assess if there really was a need .
I have been following an Autoimmune protocol diet for quite some time so plenty of meat, fish, fruit and vegetables; I have been supplementing with methylated B complex along with a good quality methylated prenatal, fish oil, pycnogenol nattokinase, betaine pepsin, and 5mthf.

I have been supplementing for over a year and increased gradually, along with improving lifestyle, I have had massive improvements, having been diagnosed with M.E. (chronic fatigue syndrome) back in 2010 and being bed bound for over two years, I now feel I am functioning at a good 85-90% of my originalcapacity. I sleep plenty, I am happier, fitter and exercise and meditate regularly and had no issues conceiving, all tests have been fine, all scans good. The only issue I have is rosacea and a low grade recurrent eye infection, which has flared with pregnancy and a bit of sciatica which the Chiropractor is helping.
I am considering reducing the extra 5mthf to improve my homocysteine levels, any other advice you may have on this would be greatly appreciated.

P.S. I have recently purchased your Dirty genes book and look forward to learning more.

Reply

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MEDICAL SCIENCE MONITOR

CLINICAL RESEARCH

e-ISSN 1643-3750
© Med Sci Monit, 2018; 24: 2919-2927
DOI: 10.12659/MSM.909712

Received: 2018.03.01
Accepted: 2018.04.03
Published: 2018.05.08

Efficacy of Acupuncture Therapy for Chemotherapy-Related Cognitive Impairment in Breast Cancer Patients

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Source of support: Departmental sources

Background: Chemotherapy can cause adverse effects such as chemotherapy-related cognitive impairment (CRCI). In this prospective study, the efficacy of traditional Chinese medicine acupuncture therapy in relieving CRCI and its impact on serum brain-derived neurotrophic factor (BDNF) are evaluated.

Material/Methods: Eighty patients were randomly divided into a treatment group and a control group with 40 patients in each group. The treatment group was treated at the following acupuncture points: Baihui (DU20), Sishencong (EX-HN1), Shenting (DU24), Zusanli (ST36), Taixi (K13), Dazhong (K14), and Juegu (GB39). Cognitive function was assessed using the functional assessment of cancer treatment cognition test (FACT-COG, version 3), the auditory-verbal learning test (AVLT), the verbal fluency test (VFT), the symbol digit modality test (SDMT), the clock-drawing test (CDT), and the trail-making test part B (TMT-B). In addition, blood serum levels of BDNF were measured before and after treatment. Correlations between change in BDNF levels and cognitive function were also analyzed.

Results: CRCI was ameliorated in the acupuncture treatment group, with scores on FACT-COG, AVLT-recognition and CDT assessments all significantly increased ($P<0.05$ in all cases). In addition, serum BDNF levels after acupuncture treatment were significantly higher than before treatment ($t=3.242$, $P<0.01$). Moreover, the level of BDNF was positively correlated with the total score of FACT-COG, AVLT-recognition, and CDT ($r=0.694$, 0.628, and 0.532, respectively; all $P<0.05$). The control group showed no statistically significant difference in any measures over the same period.

Conclusions: Acupuncture therapy is effective in the treatment of CRCI in breast cancer patients through a mechanism that may be related to an increase of BDNF.

MeSH Keywords: Acupuncture – Methods • Breast • Brain-Derived Neurotrophic Factor – Chemical Synthesis • Mild Cognitive Impairment

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/909712

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

Background

Breast cancer (BC) is a common malignant disease in women. When treated with chemotherapy, patients often complain of memory loss; this symptom is referred to as chemotherapy-related cognitive impairment (CRCI) or "chemotherapy brain" [1]. It is widely recognized as one of the adverse effects of chemotherapy used to treat malignant tumors. CRCI is defined as a cognitive decline in memory, learning, attention, reasoning, visual-spatial functioning, and information processing during and after discontinuation of chemotherapy in cancer patients [2,3]. A recent nationwide, multicenter, prospective, longitudinal study noted that chemotherapy can cause CRCI and affect quality of life [4]; however, CRCI treatment methods are limited. Therefore, an effective rehabilitation approach to CRCI is desirable. A randomized controlled trial has established that traditional Chinese medicine acupuncture is safe, well-tolerated, and effective in treating mild cognitive impairment in people with Alzheimer's disease [5]. Acupuncture has been widely used to treat other diseases and shown to be safe and effective, with little risk and no complication, in many studies [6–8]. Acupuncture has a history of over 2000 years and is important in traditional Chinese medicine [9]. The philosophy behind acupuncture is the balance between yin and yang energies, similar to the need for sympathetic and parasympathetic activity to be balanced [10]. In the clinic, hair-thin needles are inserted deep into the skin at specific sites known as acupuncture points by skilled practitioners, followed by stimulation to those points through different methods, including manual stimulation (acupressure), heat (moxibustion), electrical pulses (electro-acupuncture), or laser light (laser acupuncture) [9]. Acupuncture is widely used in cancer patients for its ability to relieve pain, fatigue, xerostomia, and other symptoms [11,12]. This study evaluated the effect of acupuncture on CRCI in breast cancer patients who received chemotherapy and assessed changes in BDNF levels in these patients.

Material and Methods

Participants

Breast cancer patients treated with chemotherapy were recruited from the local hospital from May 2017 to October 2017. Patients were diagnosed with early breast cancer (stage 0–II) and received chemotherapy. Inclusion criteria were: (1) age 21–55 years (i.e., premenopausal); (2) newly diagnosed with breast cancer after surgery and treated with common standard-dose chemotherapy regimens; (3) a chief complaint of memory impairment that was confirmed by a family member; (4) a level of education sufficient to understand the information content of the Mini-Mental State Examination (MMSE); (5) expected to survive >1 year. Exclusion criteria were: metastatic breast cancer, prior cancer, substance abuse, brain injury, a history of neurological or psychiatric disorders, or currently taking psychoactive medications that might affect brain structure and function.

Patients were recruited according to the above criteria and were treated with acupuncture therapy (n=40) or not treated with acupuncture (control, n=40). All subjects were right-handed. No demographic differences were found between groups ($P>0.05$).

All assessments were completed twice: before acupuncture therapy (time 1) and after completion of acupuncture therapy (time 2). The control group completed assessments at the same time points. Data collectors were blind to the study participants' treatment group.

This study was approved by the Ethics Committee of the Affiliated Hospital of Jiangnan University. All participants provided informed written consent.

Chemotherapy

Based on the current guidelines for the treatment of breast cancer, we chose the 3 most commonly used chemotherapy schemes. Specific regimens were as follows: (1) TC chemotherapy: 5 mg/m^2 docetaxel + 600 mg/m^2 cyclophosphamide by intravenous (IV) on day1; cycled every 21 days for 4 cycles; (2) TCb chemotherapy: 75 mg/m^2 docetaxel + AUC 6 dose of carboplatin by IV on day 1; cycled every 21 days for 4 cycles; and, 3) AC followed by docetaxel chemotherapy: 60 mg/m^2 doxorubicin + 600 mg/m^2 cyclophosphamide by IV on day 1; cycled every 21 days for 4 cycles and followed by 100 mg/m^2 docetaxel by IV on day 1; cycled every 21 days for 4 cycles. The total duration of chemotherapy lasted 3–6 months. Adjuvant drugs included antacids (lansoprazole and omeprazole), antiemetics (ondansetron and palonosetron) and anti-allergy medicine (dexamethasone). Granulocyte colony-stimulating factor was used when complications such as anemia and bone marrow suppression occurred.

Neuropsychological assessment

Neuropsychological assessment, including self-report measures and neuropsychological tests, were performed within 14 days of the final chemotherapy treatment. Self-report measures were: (1) health information and medical history and (2) functional assessment of cancer treatment cognition (FACT-COG, version 3). FACT-COG is the cancer patient's own cognitive function assessment; it includes 4 aspects: perceived cognitive impairments (PCI), impact on quality of life (QOL), comments from others (OTH), and perceived cognitive abilities (PCA). Neuropsychological tests performed were: (1)

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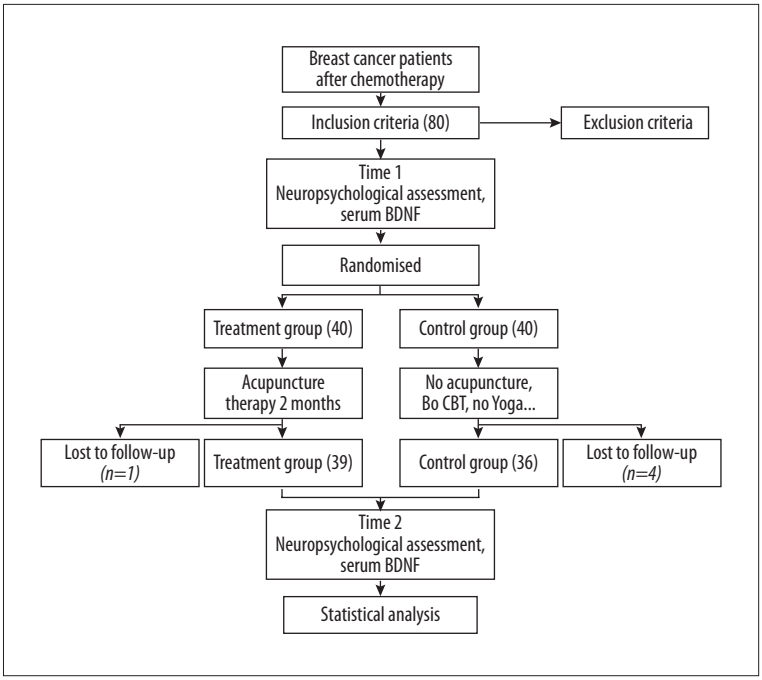

Figure 1. Flow chart of the study. BT: cognitive-behavior therapy.

the auditory-verbal learning test (AVLT); (2) the verbal fluency test (VFT); (3) the symbol digit modality test (SDMT); (4) the clock-drawing test (CDT); and, (5) the trail-making test part B (TMT-B). AVLT is to assess memory, including short-term memory (AVLT1), delayed recall (AVLT2), and recognition (AVLT3). The verbal fluency test (semantic categories "animals/minute") aims to verify language, semantic memory, and executive functions by evaluating word retrieval ability established in long-term memory. The symbol digit modality test (SDMT) is a measure of attention (perception and coding), cognitive processing speed, and visual working memory. The clock-drawing test (CDT) is a visual (non-verbal) screening instrument for measuring mild-to-moderate cognitive impairment. The trail-making test part B (TMT-B) is used to evaluate driving abilities and includes testing for executive functions. All participants were also required to complete the MMSE, State Anxiety Inventory (S-AI) and Beck Depression Inventory (BDI). S-AI was used to exclude patients with anxiety disorder and was measured as baseline values. BDI was used to exclude depressive disorder and was measured for inclusion as covariates in analyses.

Serum BDNF detection

On the mornings before and after acupuncture treatment, 5 ml of venous blood was drawn from each subject on the same day as the neuropsychological assessment. Blood samples were centrifuged at 3000 rpm for 10 min after standing for 15 min, and then kept at –80°C after separation. An enzyme-linked immunosorbent assay (ELISA) kit was used to measure expression levels of BDNF in the serum twice, and the mean value was used in analysis.

Acupuncture therapy

Acupuncture therapy was performed by 2 skilled acupuncturists with >5 years' experience in neurological rehabilitation with acupuncture. Sterile, disposable needles 40 mm long and 0.25 mm in diameter (Huatuo, Suzhou Medical Instruments Factory, China) were used by acupuncturists. Basic acupuncture formulas Baihui (DU20), Sishencong (EX-HN1), and Taixi (KI3) were used. Based on symptoms and tongue manifestation, other acupoints could also be stimulated as follows. The angle insertion of Baihui, Shenting (DU24), and Sishencong are approximately 10–20° (between needle and scalp), with 10–15 mm as the best insertion depth. Taixi, Dazhong (KI4), and Juegu (GB39) were inserted 15–20 mm deep with a 0.25×25 mm acupuncture needle. Zusanli (ST36) was inserted 25–35 mm deep with a 0.25×40 mm acupuncture needle. Effective needling was accompanied by needling feelings of numbness, tingling, swelling, or muscle weakness, known as "de qi" in acupuncture; the needle was kept *in situ* for 30 min after stimulation. Patients received two 4-week courses of acupuncture with a 3-day rest between the 2 courses. Every week, patients were treated once a day for 5 days, followed by 2 days of rest.

Statistical analysis

SPSS v. 19.0 (SPSS Inc., IL, USA) was used for statistical analysis. Paired *t* tests were used to assess changes in neuropsychological test performance between time 1 (t1) and time 2 (t2) within each treatment group. Differences in cognitive tests and subjective measures were assessed using an ANCOVA with age, radiotherapy, tamoxifen, S-AI, and BDI scores initially

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Table 1. Demographic and clinical characteristics.

	Treatment group (n=39)	Control group (n=36)	Paired *t* test	P
Age, mean (SD), years	43.11±4.23	42.26±4.42	0.70	0.50
TNM stage, No (%)				
0	0 (0.0)	0 (0.0)	–	–
I	24 (61.5)	22 (61.1)	–	–
II	15 (38.5)	14 (38.9)	–	–
Surgery method, No (%)				
Conservative surgery	8 (20.5)	7 (19.4)	–	–
Mastectomy + SLNB	20 (51.3)	18 (50.0)	–	
Modify mastectomy	11 (28.2)	11 (30.6)	–	–
Subtype, No (%)				
Luminal A (HR/HER2-)	0 (0.0)	0 (0.0)	–	–
Luminal B (HR/HER2)	20 (51.3)	19 (52.8)	–	–
Erb-B2 (HR-/HER2)	9 (23.1)	8 (22.2)	–	–
Basal-like (HR-/HER2-)	10 (25.6)	9 (25.0)	–	–
Radiotherapy, No (%)	12 (30.8)	11 (30.6)	–	–
Hormonal therapy, No (%)	21 (53.8)	20 (55.6)	–	–
Chemotherapy regimen, No (%)				
TC	19 (48.7)	18 (50.0)	–	–
TP	9 (23.1)	7 (19.4)	–	–
ECx4→Tx4	11 (28.2)	11 (30.6)	–	–
T1 to T2, mean (SD), days	58.94±5.73	55.85±4.86	1.76	0.09
Depression BDI, mean (SD)	7.81±4.35	7.33±4.47	0.56	0.58
Anxiety S-AI, mean (SD)	34.91±7.20	33.95±6.27	2.01	0.06
Education, mean (SD), years	14.26±2.06	13.87±2.58	0.28	0.78
MMSE, mean (SD)	24.81±1.48	25.19±1.72	0.84	0.41

N/A – not applicable; SD – standard deviation; SLNB – sentinel lymph node biopsy; TC – Docetaxel + cyclophosphamide; TP – Paclitaxel + Carboplatin; ECx4→Tx4 – (Epirubicin + Cyclophosphamide)×4+Docetaxel×4; BDI – Beck Depression Inventory; S-AI – State Anxiety Inventory; MMSE – Mini-Mental State Examination. P-values are the result of t tests for continuous variables, or Fisher's Exact test for categorical variables * Statistically significant (p<.05).

included as covariates (and removed from the model if p>0.05). Relationships between change in BDNF and change in neuropsychological measures (scores that changed from t1 to t2) were explored within each group separately using a two-tailed Pearson or Spearman correlation, as appropriate.

Results

Demographic characteristics and clinical data

A total of 80 subjects were initially enrolled in the study. Figure 1 show the flow of patients through the study. One treatment subject and 3 control subjects were excluded from analysis because they were unable to finish the neuropsychological

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Table 2. Summary of neuropsychologic assessment.

Metabolites	Treatment (n=39)			Control (n=36)			Repeated measures ANOVA	
	T1	T2	T value	T1	T2	T value	F	P
	Mean ±SD	Mean ±SD		Mean ±SD	Mean ±SD			
FACT-COG	98.75±12.94	102.38±13.78	4.840**	99.60±11.05	99.80±10.77	1.489	5.77	0.001
PCI	55.42±10.95	56.29±11.49	3.494**	57.55±8.43	57.35±8.99	0.721	3.21	0.027
QOL	11.33±3.42	11.75±3.38	2.632*	11.70±2.41	11.55±2.24	0.326	1.30	0.279
OTH	11.63±2.89	12.54±3.31	2.991**	11.10±2.65	11.30±1.92	1.189	0.48	0.697
PCA	20.38±4.19	21.79±4.40	2.298*	19.25±3.31	19.60±3.33	1.285	3.75	0.014
AVLT1	9.13±1.48	9.17±1.55	0.440	9.25±1.55	9.50±1.82	1.561	0.23	0.873
AVLT2	9.42±1.61	9.63±1.50	2.005	9.45±1.36	9.65±1.50	1.453	0.14	0.936
AVLT3	10.92±1.44	11.42±1.18	2.202*	10.75±1.59	10.70±1.49	0.357	5.21	0.002
VFT	17.88±3.33	18.21±3.74	1.163	18.50±3.38	19.15±2.83	1.412	0.56	0.642
SDMT	34.75±5.15	35.71±5.54	1.558	36.70±5.50	38.05±6.62	2.077	1.33	0.269
CDT	8.08±1.50	8.54±1.14	2.696*	8.10±1.21	8.05±1.36	0.438	5.50	0.002
TMT-B	95.58±26.67	95.46±26.80	0.901	92.35±27.06	90.40±26.19	1.698	0.19	0.901

ANOVA – analysis of variance; FACT-COG – Functional Assessment of Cancer Therapy-Cognitive Function; PCI – perceived cognitive impairments; QOL – impact of perceived impairments on quality of life; OTH – comments from others; PCA – perceived cognitive abilities; AVLT1 – Auditory-Verbal Learning Test – Immediately recall; AVLT2 – Auditory-Verbal Learning Test – Delayed Recall; AVLT3 – Auditory-Verbal Learning Test – recognition; VFT – Verbal Fluency Test; SDMT – Symbol digit modality test; CDT – Clock-Drawing Test; TMT-B – Trail-Making Test part B. Statistically significant * (p<.05, ** p<.01).

assessment or acupuncture therapy. One control subject was diagnosed with brain metastases in the second assessment and was also dropped from the analysis. Therefore, n=39 for the treatment group and n=36 for the control group.

Patients in the treatment and control groups did not differ in terms of age, education, MMSE, or depression or anxiety symptoms at time 1 (Table 1). S-AI and BDI scores were initially included as covariates, but none had significant effects and they were thus removed from the final model. The second neuropsychological assessment was conducted, on average, 2 months after time 1; inter-scan intervals did not differ significantly between the 2 groups.

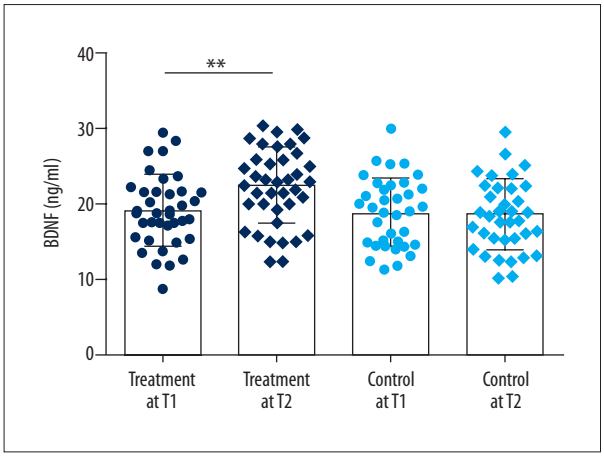

Figure 2. Levels of BDNF in serum. ** p<.01.

Neuropsychological assessment

Treatment and control groups did not differ in self-report measures or neuropsychological tests at baseline (Table 2). The treatment group had significantly higher scores after acupuncture therapy on FACT-COG, AVLT3, and CDT compared with baseline (paired *t* test, *P*<0.05). In contrast, the control group showed no significant differences in performance at time 2 compared to baseline. Moreover, a repeated-measures ANOVA revealed significant interactions between groups and performance change over time for self-report measures (FACT-COG), CDT, and AVLT3.

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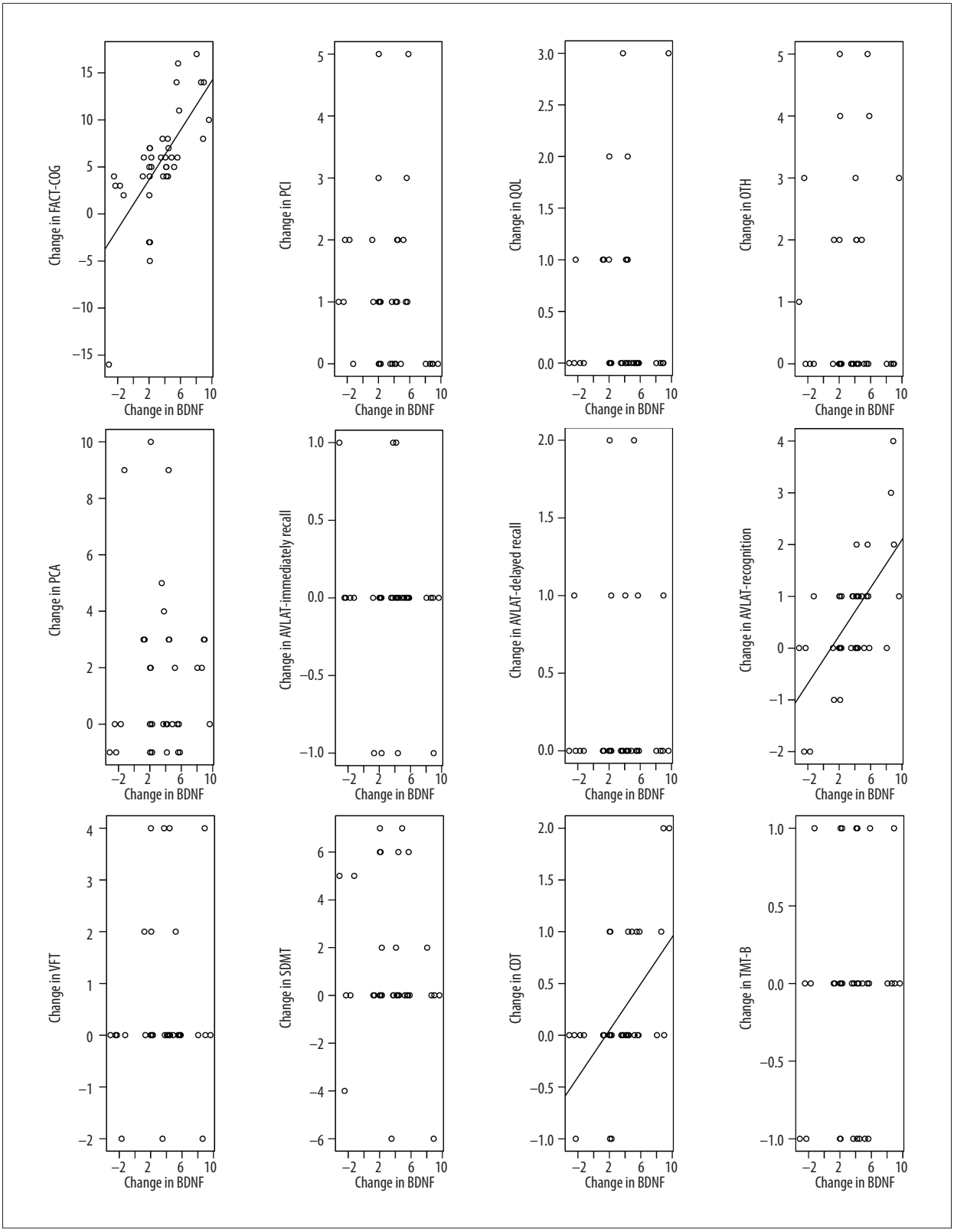

Figure 3. Correlation in BDNF changes and cognitive changes (treatment group).

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BDNF change

The expression of BDNF significantly increased after acupuncture treatment (BDNF Mean ±SD, before treatment (t1): 19.17±4.63 ng/ml; after treatment (t2): 22.52±4.99 ng/ml; t=3.242, P<0.01). No significant difference was observed in the control group (BDNF Mean ±SD, t1: 18.97±4.52 ng/ml; t2: 18.67±4.61 ng/ml) (Figure 2).

Correlation analysis

BDNF levels were positively correlated with cognitive scores (Figure 3). Change in FACT-COG, AVLT3, and CDT scores were positively correlated with BDNF levels in the treatment group (r=0.694, 0.628, and 0.532, respectively, all P<0.05). No other cognitive score changes were correlated with BDNF change and no significant correlations were observed in the control group.

Discussion

This study on the efficacy of acupuncture treatment to CRCI showed, using neurocognitive assessments, that acupuncture can improve the cognitive ability of breast cancer patients who receive chemotherapy. Both subjective and objective cognitive function tests were performed, and the results of the objective AVLT3 and CDT tests were consistent with the subjective FACT-COG test, showing that the CRCI is ameliorated after acupuncture treatment.

Although acupuncture has a long history of, and is widely accepted in, clinical use, the mechanism by which it works remains elusive. Recent studies on acupuncture have provided some possible insights into its mechanism. For example, through neuroimaging, researchers studying Alzheimer disease have shown that acupuncture increases hippocampal connectivity, activates certain cognitive-related areas, and adjusts default network activity patterns [13]. In a cognitively-impaired rat model, stimulating Shenmen (HT7) with laser acupuncture inhibits the expression of acetylcholinesterase in the hippocampus [14].

In the expresses mutated amyloid precursor protein (APP) and presenilin-1 mouse model, electro-acupuncturing Baihui can reduce the abnormally high expression of β-amyloid-42, inhibit the apoptosis of nerve cells, enhance BDNF level, and relieve cognitive impairment [15]. Moreover, experiments have shown that acupuncture on aging mice can: induce cell proliferation and improve learning and memory in different brain regions [16]; upregulate the activity of phospho-isomerase in the hippocampus [17]; and regulate the function of cytoskeletal-related synapses, induce neurotransmitter secretion, and promote the recovery of neuroplasticity [18,19].

In the present study, sham acupuncture was not used in the control group because the acupuncture control method is not yet mature and should not be considered as a standard model of acupuncture research [20,21]. The so-called "sham acupuncture control trial" may simply be a comparative study of different acupuncture methods [22]. Scholars hold differing views on whether sham acupuncture has a placebo effect or a therapeutic effect [23]. The commonly used sham acupuncture methods include adjacent sham acupuncture control, non-condition-related acupoint control, shallow needling acupoint control, minimal stimuli acupuncture control, and soothing acupuncture control. All of these have obvious defects and may cause infection if not done properly. Researchers have no standard method to follow when conducting clinical trials [21] and can only minimize the therapeutic effect of the placebo through a rational and rigorous design to better verify the therapeutic effect of acupuncture. The 2 groups were not allowed to receive cognitive therapy, yoga, or other physical therapy throughout the present study. Many factors can influence CRCI, making it difficult to isolate any one aspect; we controlled other factors to the best of our ability by assigning patients to treatment groups at random and taking baseline measures for all patients to control for individual differences.

The Chinese version of FACT-COG is clinically convenient and makes it easy to diagnose patients with cognitive function difficulties [24]. In the objective test, the Auditory-Verbal Learning Test (AVLT) was used for cognitive dysfunction among cancer survivors with chemotherapy. In fact, the AVLT, the California Verbal Learning Test (CVLT), and the Hopkins Verbal Learning Test – Revised (HVLT-R) are equivalent to the memory tests and are similar in structure [25], but the HVLT-R is shorter. There is no standard procedure for selection of a scale in cognitive function research; HVLT and AVLT are both commonly used in published literature. The AVLT is easier to use and a revised version for Chinese has been created. The results of AVLT3 and CDT after acupuncture were significantly higher than those before acupuncture treatment. Given that AVLT reflects word memory function and CDT reflects executive function and visual space structure ability, we speculate that acupuncture can significantly improve memory and executive function.

In further analysis, the type of surgical technique did not affect the overall quality of life and sexual satisfaction [26]. Problems with memory and attention are not directly correlated with surgical adverse effects [26], but breast reconstruction has a negative effect on the cognitive function of breast cancer survivors [27]. In this study, we selected premenopausal patients to exclude the effect of hormonal changes at menopause, with an average age of 43 years. A mastectomy was done in 50% of patients. However, according to the current Chinese national data, breast reconstruction occurs in less than 1% of the all

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breast cancers patients. Thus, regrettably, no analysis on this can occur because of the lack of data.

BDNF in peripheral serum can reflect the level of central BDNF [28]. BDNF is related to cognition [29, 30]. After acupuncture treatment, BDNF significantly changes and correlates positively with improved cognitive function. We speculate that acupuncture relieves "chemotherapy brain" through a mechanism mediated by BDNF. Acupuncture treatment may promote the physiological formation of BDNF, increasing levels of BDNF, which, in turn, accelerates recovery of the central nervous system from chemotherapy damage [19] affecting attention, memory and executive function, and other cognitive tasks. We found acupuncture effective in reducing CRCI without any report of adverse effects. Acupuncture treatment may also provide other benefits, such as improved mood [31], reduced pain [32], and improved quality of life; thus, it warrants further study as part of cancer patient care.

There are some limitations to our research. First, the small sample size is not sufficient to provide strong support to the conclusion and further studies are warranted in multicenter, large-sample trials. Second, patients willing to participate in studies like this tend to be positive, and thus participants may represent a biased sample. Third, subjective and memory-learning effects occur when using cognitive function scales, and more convincing results can be achieved if combined with neuroimaging technology. In addition, there was no follow-up observation. The effect of chemotherapy-related cognitive dysfunction is obvious in the short term [33,34], especially within 6 months. Subjective complaints of cognitive impairment are most often reported 1 month after chemotherapy; some are reported perennially, while others partially recover. Many factors affect the rehabilitation of cognitive impairment after chemotherapy [35]. This study focused on short-term chemotherapy-related cognition impairment; if an appropriate experimental control design method can be found, long-term cognitive effects warrant further study.

Conclusions

Acupuncture therapy is effective in the treatment of chemotherapy-related cognitive impairment in breast cancer patients through a mechanism that may be related to the observed concomitant increase of BDNF.

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Integrative Cancer Therapies
1–10

DOI: 10.1177/1534735418777109
journals.sagepub.com/home/ict
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Effects of Acupuncture on Cancer-Related Cognitive Impairment in Chinese Gynecological Cancer Patients: A Pilot Cohort Study

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Abstract

Background: Among women in China, gynecological cancers are the second most common cancers after breast cancer. Cancer-related cognitive impairment (CRCI) has emerged as a significant problem affecting gynecological cancer survivors. While acupuncture has been used in different aspects of cancer care, the possible positive effects of acupuncture on cognitive impairment have received little attention. This study hypothesized that patients would demonstrate lower neurocognitive performance and lower structural connectivity compared to healthy controls. This pilot study also hypothesized that acupuncture may potentially be effective in treating CRCI of cancer patients by increasing brain structural connectivity and integrity. **Methods:** This prospective cohort study consisted of 3 stages: the first stage included a group of gynecological cancer patients and a group of age-matched healthy controls. This baseline stage used a core set of neurocognitive tests to screen patients with cognitive impairment and used a multimodal approach of brain magnetic resonance imaging (MRI) to explore the possible neurobiological mechanism of cognitive impairment in cancer patients, comparing the results with a group of noncancer controls. The second stage involved assigning CRCI patients into the acupuncture intervention group, while patients without CRCI were assigned into the cancer control group. The third stage was a postintervention assessment of neurocognitive function by the same set of neurocognitive tests at baseline. To explore the possible neurobiological basis of acupuncture for treating CRCI, this study also used a multimodal MRI approach to assess changes in brain structural connectivity, and neurochemical properties in patients at pre- and postacupuncture intervention. **Results:** This study found that the prevalence of cognitive impairment in Chinese gynecological cancer patients at diagnosis was 26.67%. When investigating the microstructural white matter in the brain, diffusion tensor imaging data in this study indicated that premorbid cognitive functioning (before clinical manifestations become evident) has already existed, as the global and local connectome properties in the entire patient group were lower than in the healthy control group. Using magnetic resonance spectroscopy, this study indicated there was a significant reduction of relative concentration of NAA (*N*-acetyl aspartate) in the left hippocampus, comparing these results with healthy controls. Regarding the effects of acupuncture on reducing CRCI, patients in the acupuncture group reported better neurocognitive test performance after matching for age, menopausal status, cancer stage, and chemotherapy regimen dosage. On a microstructural level, acupuncture's ability to reduce CRCI may be attributed to a reduction in demyelination and an enhancement of the neuronal viability of white matter in the hippocampus. **Conclusion:** This pilot study indicates that acupuncture is a promising intervention in treating CRCI in gynecological cancer patients undergoing chemotherapy; however, it requires evaluation in larger randomized controlled studies to definitively assess its benefit. By using a multimodal imaging approach, this pilot study also provides novel insights into the neurobiological basis of cognitive impairment on the human brain that has been induced by cancer and/or its treatment.

Keywords

cancer-related cognitive impairment, acupuncture, neurobiological mechanism, gynecological cancer, Chinese women

Submitted December 4, 2017; revised February 25, 2018; accepted February 28, 2018

Introduction

Among women in China, gynecological cancers as a group of cervical, uterine, ovarian, vaginal, and vulvar cancers are the second most common cancers after breast cancer.[1] Because of medical technology advancements, bringing more potentially curative treatments such as surgery, radiotherapy, chemotherapy, and targeted therapies,[2] the current 5-year relative survival rate of patients with gynecological cancer ranges from 46% to 82%.[3] As more patients with gynecological cancer are living longer after curative treatment, long-term or late effects of cancer and its treatment are becoming more common in cancer survivors.[4] One such long-term and late effect is neurocognitive change, which has emerged as a significant problem affecting gynecological cancer survivors.[5,6]

Gynecological cancer and its treatment can have neurotoxic effects which are associated with brain injury, resulting in cognitive impairment.[5] Cancer-related cognitive impairment (CRCI) is often described colloquially as chemo brain or chemofog.[7,8] CRCI has the potential to significantly affect social and occupational functioning, interfering with the ability to carry out normal daily activities, all of which in turn contribute to lower quality of life in cancer survivors.[5,9] The domain of cognitive impairment may affect memory, concentration, information processing speed, and executive function.[10] These types of cognitive impairment could exert a significant impact on social and occupational functioning, interfering with the ability to carry out normal daily activities, all of which in turn contributes to lower quality of life for cancer survivors.[5,9]

Advanced neuroimaging studies in cancer patients provide a better understanding of CRCI, and there is accumulating evidence to support the assertion that CRCI is a pathophysiologic process.[5,11,12] In recent years, diffusion tensor imaging (DTI) has been able to characterize water diffusion and microstructure in biological tissues, especially for white matter integrity and diffusivity.[13,14] Using DTI could also identify degradation of neural structures, and determine whether axonal death and/or deterioration of the myelin sheath are involved.[14] While DTI is becoming a promising technique to assess whether cancer and its therapy-induced subtle white matter changes could explain CRCI in cancer patients,[15] DTI could not provide information about the underlying biological mechanism of neural degeneration.[14] Magnetic resonance spectroscopy (MRS) is an imaging technique that can provide further insight regarding the biochemical properties of the brain, and whether white matter changes represent inflammation or axonal death by detecting changes in brain metabolites.[9,13,14,16] As axonal death is irreversible, it may be unlikely that cognitive impairment in cancer survivors can be restored.[14] Thus, there is a need for intervention strategies in preventing and managing CRCI.

There are limited pharmacological treatment approaches for the management of CRCI, and it is noted that pharmacological treatments often have side effects.[11,17] A large body of evidence confirms that acupuncture is effective in reducing anticancer treatment–caused side effects, including pain, nausea, hot flashes, fatigue, anxiety, depression, and sleep disturbances.[18,19] A number of other studies have shown the effectiveness of acupuncture therapy in improving the cognitive function of patients with cancer.[19-21] The reduced severity of cognitive symptoms is associated with neuroimaging improvement in brain regions relevant to learning and memory processes.[13-15] In various animal studies, acupuncture has also been shown to ameliorate cognitive impairment.[22] While acupuncture has been a part of traditional Chinese medicine for thousands of years and has been used in different aspects of cancer care, the possible positive effects of acupuncture on cognitive impairment have received little attention. Hence, we hypothesized that patients would demonstrate lower neurocognitive performance and lower structural connectivity compared with healthy controls. We also hypothesized that acupuncture may potentially be effective in treating CRCI of cancer patients by increasing brain structural connectivity and integrity.

Aims

This pilot study aimed to assess cognitive outcomes of gynecological cancer patients compared to healthy controls, and to examine the possible effects of acupuncture on patient cognitive outcomes, as well as acupuncture's possible underlying neurobiological mechanisms of mitigating cognitive impairment in cancer patients.

Methods

This pilot, prospective cohort study was conducted to assess cancer patients' neurocognition, brain structural connectiv-

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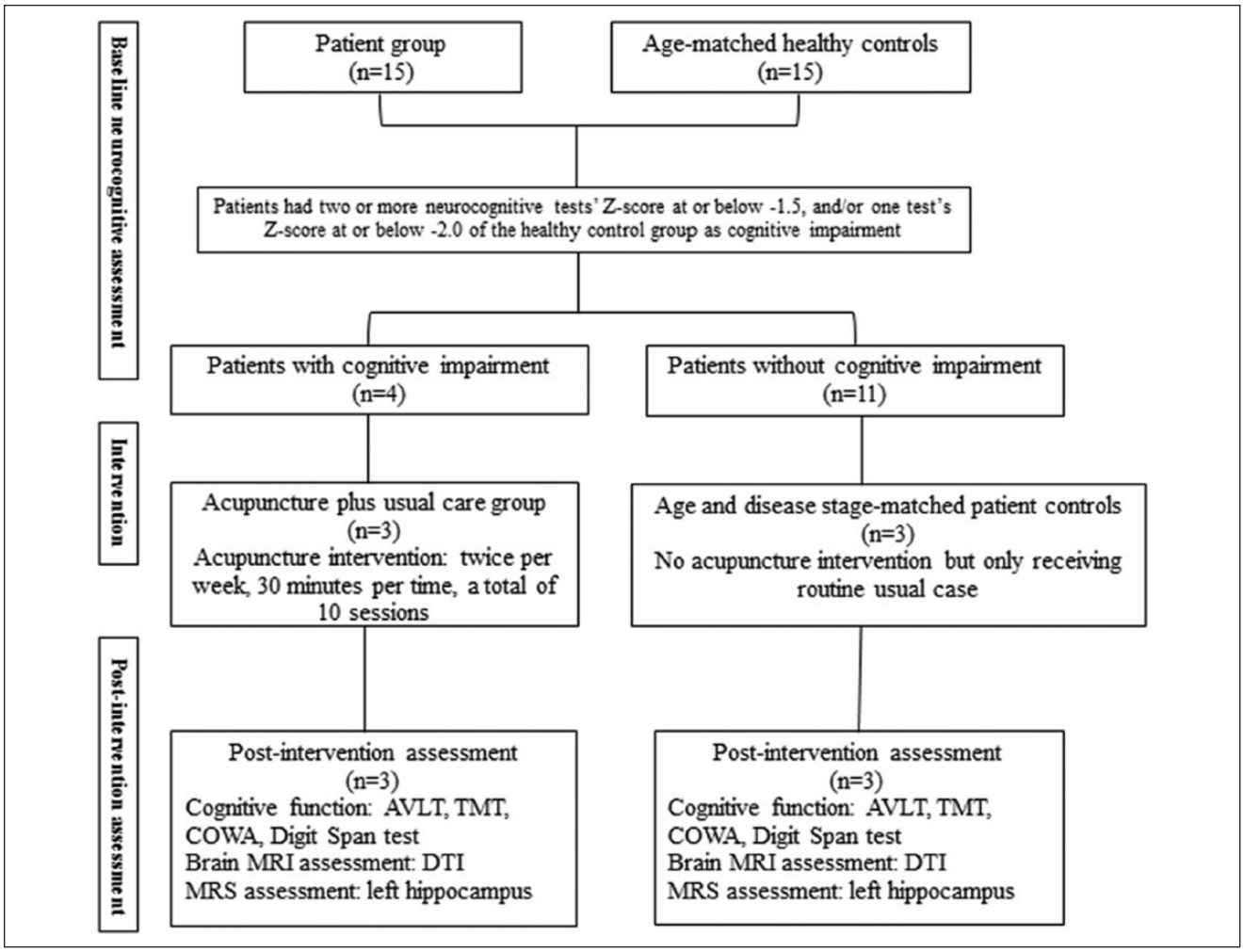

Figure 1. Study procedure.[1]

ity, and neurochemical properties at pre- and postacupuncture intervention.

Subjects and Study Procedure

All subjects were recruited in the Unit of Gynecological Oncology at a general teaching hospital. Ethical approval was obtained from the ethics committees at both The Hong Kong Polytechnic University and The Third Affiliated Hospital of Guangzhou Medical University. Subjects were Chinese females aged 18 to 65 years; with a primary diagnosis of stage I-III gynecological cancer; and who were ready for adjuvant chemotherapy after surgical treatment. Exclusion criteria were women with a previous history of cancer (not a primary diagnosis of cancer), and/or who were in a terminal stage of cancer, and/or had a severe needle phobia. Inclusion criteria for healthy controls included women within 1 year of age and same menopausal status as the patient group. Exclusion criteria for both patient and healthy control groups included potential psychiatric disorders, such as depression and anxiety, a history of any neurological condition, traumatic brain injury, intellectual disability, and the use of psychotropic medication. The entire study procedure is shown in Figure 1.

Acupuncture Interventions

Patients with cognitive impairment at the time of diagnosis were invited to receive manual acupuncture, which was provided by a single acupuncturist trained in traditional Chinese medicine. Sterile, disposable, stainless steel needles (0.25 mm in diameter and 40 mm in length, Huanqiu brand, made in China) were inserted at the following forehead acupuncture points: EX-HN1 (left and right, anterior and posterior Sishencong), EX-HN3 (Yintang), EX-HN5 (bilateral Taiyang), GB8 (bilateral Shuaigu), GB15 (Toulinqi), GB20 (Fengchi), GV20 (Baihui), and ST8 (bilateral Touwei), unilaterally or bilaterally, depending on each woman's traditional diagnosis

(constitution) as determined by the acupuncturist. All selected acupuncture points were related to cognitive function.[23] The duration of needling was 30 minutes, and the frequency of interventions was 2 times per week. As the total number of chemotherapy cycles for gynecological cancer patients ranges from 4 to 6 cycles, so the average total number of interventions was 10 sessions per patient. The depth of needling varied between 25 and 40 mm, depending on the individual point.

Neurocognitive Function Assessment

As suggested by Joly et al,[10] the most common domains of cognitive impairment in cancer survivors include learning and memory, information processing speed, and executive function. The International Cognition and Cancer Task Force (ICCTF) recommends that the following measures (at minimum) be included in assessing cognitive function in cancer patients: the Hopkins Verbal Learning Test–Revised (HVLT-R), the Trail Making Test (TMT), and the Controlled Oral Word Association Test (COWA).[24] This study administered the Chinese version of the Auditory Verbal Learning Test–Revised version (AVLT-R) to measure the domains of learning and memory[25]; the TMT-A, to measure information processing speed, and the TMT-B, to measure executive function.[26] According to Zeng et al,[27] attention, working memory, and language/verbal comprehension problems were the most common cognitive complaints among Chinese cancer patients. This study also included the WAIS-III (Wechsler Adult Intelligence Scale–III) Digit Span test for measuring attention and working memory,[28] and the COWA for assessing the verbal fluency and language comprehension of Chinese gynecological cancer patients.[26]

MRI and MRS Data Acquisition

The MRI data were acquired using a Philips 3T Achieva MRI/MRS scanner with an 8-channel head coil. Neurocognition evaluation and MRI scans took place on the same day. DTI and MRS were used to investigate changes in subjects' brain structural connectivity, and changes in brain metabolites, respectively. DTI, high-resolution structural T1-weighted brain scans were obtained using single-shot echo-planar imaging (EPI) (acquisition matrix = 128 × 128; TE (echo time) = minimum; TR (repetition time) = 16 000 ms; field of view = 256 mm × 256 mm; slice thickness/gap = 2.0 mm/0 mm; scanning time = 6 minutes 56 seconds) with 32 distributed isotropic orientations for the diffusion-sensitizing gradients at a *b*-value of 1000 s/mm^2 and a *b*-value of 0. T1-weighted imaging was achieved for morphometric (gray matter volume, cortical thickness, and surface area) analysis using 3-dimensional fast spoiled-gradient recalled acquisition in steady state (3D-FSPGR) in 166 coronal slices (acquisition matrix = 128 × 128; TE = 3.9 ms; TR = 9.6 ms; field of view = 256 mm × 256 mm; slice thickness/gap = 2 mm/0 mm; scanning time approximately 7 minutes).

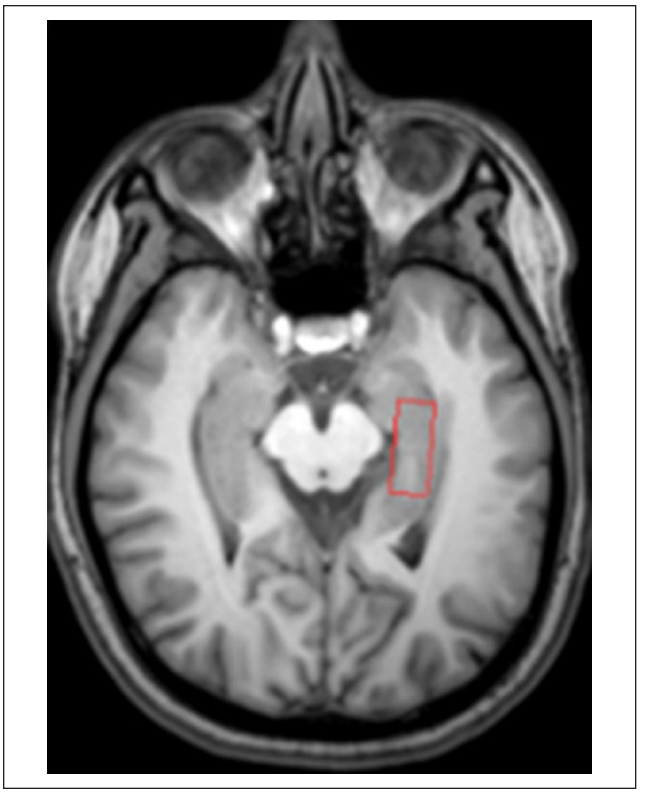

Figure 2. Left hippocampus volume of interest (VOI).

As the hippocampus is an important brain structure due to its well-known function in the maintenance of memory, especially on the left side of the brain,[29] 1H-MRS data were located in the region of the left hippocampus. Single voxel proton MRS was acquired in the left hippocampus to assess the neurochemical properties of white matter. The region of interest is 2.5 × 1 × 1 cm^3, and voxels contained the head, body, and tail of the hippocampus. Fully automated PRESS (point-resolved spectroscopy), including global shimming (TR/TE = 2000/35 ms, number of signal averages [NSA] = 16) was acquired in the red box area of the left hippocampus (Figure 2).

MRI and MRS Data Processing and Analyses

The DTI images were preprocessed using PANDA: a pipeline toolbox for analyzing brain diffusion images (https://www.nitrc.org/projects/panda/). Each individual's DTI data set was registered to the same individual's high-resolution structural image and then into the standard Montreal Neurological Institute (MNI) space using affine transformations. Fractional anisotropy (FA) images were created from the preprocessed DTI data of all subjects. All FA images were then non-linearly aligned to a common space. The mean FA image was used to represent the center of all tracts common to the group. Then, all subjects' aligned FA data were projected onto the skeleton, and the resulting data were subjected to voxel wise cross-subject statistics. Whole brain tractography was then performed

Table 1. Demographic and Clinical Characteristics of Subjects.

Variables	Cancer Patients (n = 15), n (%)	Healthy Controls (n = 15), n (%)
Age, years mean ± SD (range)	49.33 ± 9.14 (28-60)	49.60 ± 8.27 (29-59)
Highest education		
Primary school or below	12 (80.0)	14 (93.3)
High school	2 (13.3)	1 (6.7)
University and above	1 (6.7)	
Employment status		
Employed	2 (13.3)	15 (100)
Unemployed	13 (86.7)	
Marital status		
Never married	1 (13.3)	1 (6.7)
Married	14 (93.3)	13 (86.7)
Divorced		1 (6.7)
Menopausal status		
Premenopausal	8 (53.3)	8 (53.3)
Perimenopausal	1 (6.7)	1 (6.7)
Postmenopausal	6 (40.0)	6 (40.0)
Cancer type		
Cervical cancer	8 (53.3)	
Ovarian cancer	1 (6.7)	
Uterine cancer	6 (40.0)	
Disease stage		
Early stage (stage I-IIa)	9 (60.0)	
Middle stage (stage IIb-IIIa)	3 (20.0)	
Advanced stage (stage IIIb)	3 (20.0)	
Treatment type		
Surgery + chemotherapy	13 (86.7)	
Surgery + chemotherapy + radiation	2 (13.3)	

in the patient's native space for each subject at each time point using a deterministic streamlined approach,[30,31] in which fiber pathways were reconstructed by following the main diffusion tensor direction as indicated by the principal eigenvector, until an FA value of 0.20 or lower was reached, or until an angular turn of 45 degrees or more was made.[30,31] The DTI data were used to construct the large-scale connectivity of the brain network and to assess network outcome measures using PANDA. MRS data were analyzed using MRS software integrated into the MR scanner. The experimentally measured spectra included *N*-acetyl aspartate (NAA), creatine (Cr), and choline (Cho). Metabolites were expressed in relative concentrations. The ratios of NAA/Cr, NAA/Cho, Cho/Cr, and Cho/NAA were automatically determined by this integrated software.

Statistical Analysis

Preliminary descriptive statistics and correlation analyses were conducted using SPSS for Windows (version 21; IBM SPSS Statistics, Armonk, NY, USA). The threshold for statistical significance was set at $P < .05$. Descriptive statistics are presented as mean, standard deviation (SD), and range. Cancer patients were rated as cognitively impaired "if two or more neurocognitive tests (AVLT, TMT, COWA and Digit Span test) had a Z-score at or below −1.5, and/or one test had a *Z* score at or below −2.0 of the healthy control group."[24] Transformation of *Z* scores was computed as subjects' raw score minus the mean group score and divided by standard deviation. Correlations of neurocognitive outcomes with brain structural connectivity and neurochemical properties were made using Pearson correlation coefficients.

Results

Research Participant Characteristics

A total 18 potentially eligible women with gynecological cancer were approached, with 15 agreeing to take part. Three patients were refused, as they felt the MRI scans and neurocognition assessment would be too burdensome. There were 15 healthy control subjects who were matched in terms of age and menopausal status. The mean age of healthy controls was 49.6 years (range 29-59 years). All healthy controls were employed at the time of assessment. Detailed information on the characteristics of all research participants is shown in Table 1. In the patient group, more than half of all subjects (n = 8, 53.3%) had been diagnosed with cervical cancer. All patients had taken chemotherapy as an adjuvant cancer treatment (Table 1).

Table 2. Mean Scores of Objective Cognitive Tests at Baseline.

Variables	Cancer Patients (n = 15), Mean (SD)	Healthy Controls (n = 15), Mean (SD)
Attention and working memory		
Digit span forward	6.23 (2.73)	7.46 (1.99)
Digit span backward	2.26 (1.27)	2.92 (2.20)
Verbal memory		
AVLT immediate recall	11.60 (4.76)	13.33 (3.65)
AVLT delayed recall	3.86 (2.38)	4.46 (2.29)
AVLT recognition	9.53 (2.61)	10.73 (0.96)
Psychomotor speed		
TMT-A	53.13 (25.48)	58.80 (24.86)
Executive function		
TMT-B	72.33 (36.07)	75.13 (29.55)
Language		
COWA	31.06 (6.48)	32.93 (8.89)

Abbreviations: AVLT, Auditory Verbal Learning Test; COWA, Controlled Oral Word Association; TMT, Trail Making Test.

Neurocognitive Function of Cancer Patients Compared With Healthy Controls

All research participants in this study were right-handed. Four out of 15 patients could be categorized as cognitively impaired, with a CRCI rate of 26.67%. From Table 2, mean neurocognitive test scores in the patient group were lower than in the healthy control group, especially in the domain of working memory and verbal memory scores.

DTI Data and Correlations With Neurocognitive Test Performance

As shown in Figure 3, both groups had a small-worldness index greater than 1 across network densities. According to Humphries and Gurney,[32] a small-worldness index greater than 1 across network densities demonstrates as small-world connectome organization. But the patient group had a lower small-worldness index compared with healthy controls (Figure 3). In terms of regional connectome properties, this study calculated the mean node degree of structural connectivity. The patient group also demonstrated lower mean node degree across 90 brain regions, based on the template from the AAL (Automated Anatomical Labeling) atlas, than did the healthy control group (Figure 4). For correlations of DTI parameters with cognitive test performance, FA values in the patient group had positive significant correlations with AVLT-immediate scores (r = 0.654, P = .018) among 15 patients, although other DTI parameters of mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD) had no significant correlations with neurocognitive test performance.

^{1}H-MRS Data and Correlations With Neurocognitive Test Performance

From Table 2, memory scores in the patient group were significantly lower than in the healthy controls.[33] While there were no significant differences in absolute concentrations of the main metabolites of NAA, Cho or Cr between groups, differences between the groups in metabolite ratios relative to NAA (NAA/Cr and NAA/Cho) were significantly lower for the patient group than for the healthy controls (Table 3). Only in the patient group (n = 15), there were significant positive correlations of NAA/Cr with total digit span test scores (r = 0.701, P = .005).

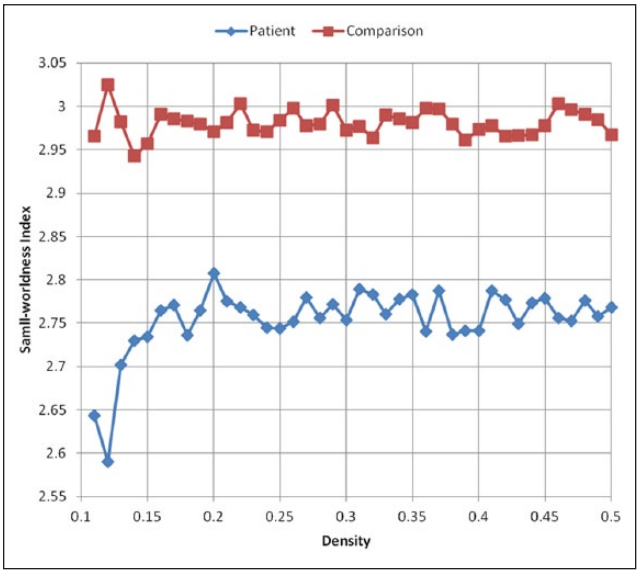

Figure 3. Global structural connectome properties (N = 30).

Effects of Acupuncture on Neurocognitive Test Performance

During chemotherapy, 3 cancer patients received a total of 10 sessions of acupuncture interventions, respectively. Compared with age-matched cancer controls, patients with acupuncture interventions achieved a better neurocognitive

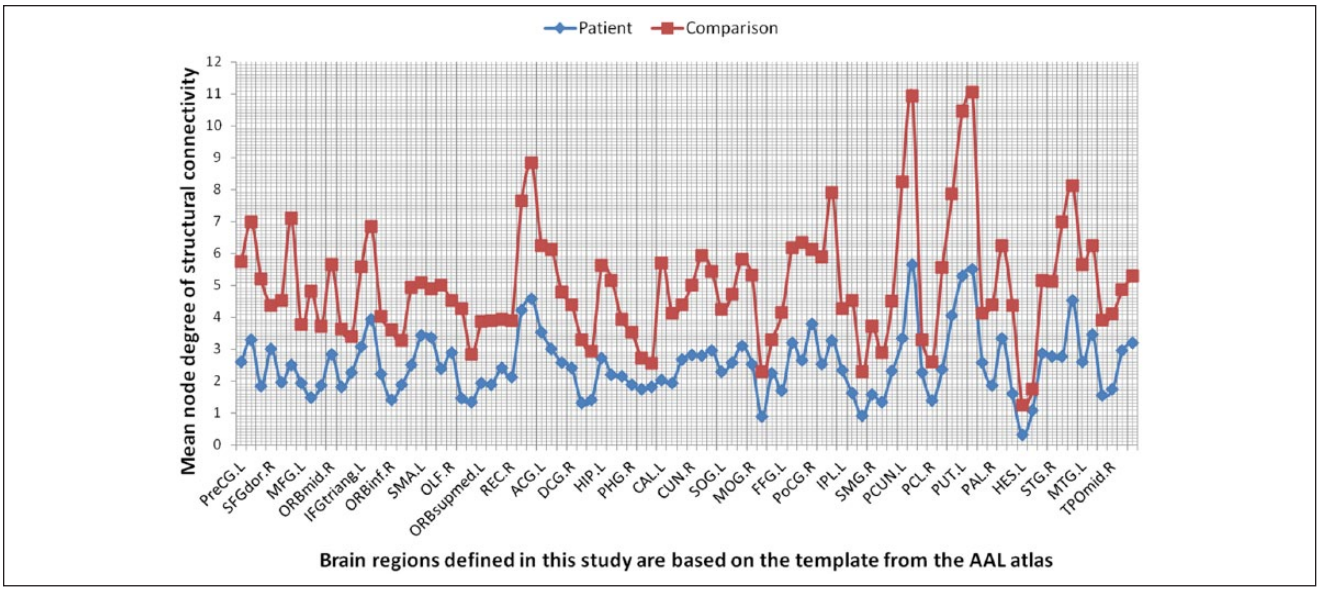

Figure 4. Regional structural connectome properties (N = 30).

Table 3. Comparison ^{1}H-MRS of Parameters in the Left Hippocampus at Baseline.

	Intervention Group (n = 15)	Healthy Controls (n = 15)
NAA/Cr	1.42 (0.23)	1.89 (0.12)
NAA/Cho	1.28 (0.08)	1.62 (0.19)
Cho/Cr	0.96 (0.11)	0.82 (0.07)
Cho/NAA	0.71 (0.07)	0.62 (0.24)

Abbreviations: MRS, magnetic resonance spectroscopy; NAA, *N*-acetyl aspartate; Cr, creatine; Cho, choline.

Table 4. Mean Scores of Objective Cognitive Tests at Postintervention.

Variables	Intervention Group (n = 3), Mean (SD)	Cancer Controls (n = 3), Mean (SD)
Attention and working memory		
Digit span forward	6.76 (1.94)	6.57 (2.87)
Digit span backward	2.11 (1.41)	1.85 (1.57)
Verbal memory		
AVLT immediate recall	16.65 (6.45)	16.28 (3.65)
AVLT delayed recall	5.86 (1.73)	5.42 (3.64)
AVLT recognition	10.53 (2.98)	10.78 (1.96)
Psychomotor speed		
TMT-A	57.13 (27.48)	53.80 (21.86)
Executive function		
TMT-B	75.33 (36.07)	74.17 (29.55)
Language		
COWA	27.42 (6.89)	26.76 (9.48)

Abbreviations: AVLT, Auditory Verbal Learning Test; COWA, Controlled Oral Word Association; TMT, Trail Making Test.

test performance (Table 4). Differences between the groups in terms of DTI parameters are shown in Table 5. Within the left hippocampus, FA values decreased more in the cancer control group, and MD values increased more in the cancer control group (Table 5), indicating that acupuncture therapy may have positive effects in maintaining white matter integrity. As shown in Table 6, the changes in NAA/Cr and NAA/Cho ratios were found to have significantly decreased in the cancer control group, compared with the acupuncture intervention group.

Discussion

This pilot cohort study aimed to describe the prevalence of CRCI and explore the neurobiological mechanism of cognitive impairment in cancer patients on a microscopic level by using DTI and MRS. This study found that the prevalence of cognitive impairment in Chinese gynecological cancer patients at diagnosis was 26.67%, which was lower than the 40% reported in previous research.[9] Based on the mean score of the neurocognitive tests, only working memory and immediate verbal memory scores in the patient group were statistically significantly lower than in the age-matched healthy controls. But when investigating the microstructural white matter in the brain, DTI data in this study indicated that premorbid cognitive functioning (before clinical manifestations became evident) already existed at cancer diagnosis, as the global and local connectome properties in

Table 5. Changes in DTI Parameters for White Matter in Left Hippocampus Between Pre- and Postintervention.

	Intervention Group (n = 3)		Cancer Controls (n = 3)	
FA	0.456 (0.012)	0.454 (0.015)	0.581 (0.036)	0.572 (0.034)
MD ($\mu m/s^2$)	0.426 (0.040)	0.433 (0.027)	0.770 (0.018)	0.785 (0.021)
AD ($\mu m/s^2$)	0.734 (0.023)	0.751 (0.028)	0.765 (0.034)	0.745 (0.027)
RD ($\mu m/s^2$)	0.273 (0.049)	0.274 (0.039)	0.262 (0.034)	0.274 (0.037)

Abbreviations: DTI, diffusion tensor imaging; FA, fractional anisotropy; MD, mean diffusivity; AD, axial diffusivity; RD, radial diffusivity.

Table 6. Changes of ^{1}H-MRS of Parameters in the Left Hippocampus Between Pre- and Postintervention.

	Acupuncture Group (n = 3)		Cancer Controls (n = 3)	
NAA/Cr	1.39 (0.10)	1.37 (0.10)	1.41 (0.08)	1.21 (0.01)
NAA/Cho	1.35 (0.16)	1.37 (0.17)	1.45 (0.11)	1.30 (0.07)
Cho/Cr	0.98 (0.13)	0.94 (0.05)	1.02 (0.12)	1.01 (0.17)
Cho/NAA	0.75 (0.09)	0.76 (0.15)	0.69 (0.05)	0.77 (0.04)

Abbreviations: MRS, magnetic resonance spectroscopy; NAA, *N*-acetyl aspartate; Cr, creatine; Cho, choline.

the entire patient group were lower than in the healthy control group. "Group differences in nodal degree and global network efficiency of the brain can help identify specific brain regions that show altered integration within the network, which could help find specific neural circuits may be at high risk for loss of response plasticity."[34(p333)]

Although one of the essential DTI parameters, FA, had a statistically significant association with immediate verbal memory score, this study did not find any significant correlation between global and local connectome properties, and neurocognitive test scores. Consistent with previous research, Bruno et al[34] also found that breast cancer patients displayed alterations in global and regional network characteristics, but these network alterations had no significant correlation with cognitive performance. However, a cross-sectional study found that breast cancer survivors had reduced brain structural network efficiency, which was associated with a simulated neurodegeneration in these patients compared with healthy controls.[35] Another cross-sectional study also indicated that poorer network organization was found to be associated with greater cognitive impairment.[36] Furthermore, recent longitudinal research reported that decreased small-worldness and local efficiency was related to poorer overall cognitive performance across time in a group of male cancer patients.[37] This study failed to find either small-worldness or nodal degree associated with neurocognitive test scores, which may be due to the small sample size, as supporting the optimal level of cognitive processes depends on an effective network organization and integration across brain regions.[38]

By using multimodal neuroimaging of MRS, this study investigated absolute and relative concentrations of NAA, Cr, and Cho in the left hippocampus. Although the absence of absolute concentrations of NAA, Cr, and Cho abnormalities in the patient group may be due to the mild degree of cognitive impairment in these patients before chemotherapy, the findings of the present study indicated a statistically significant reduction of NAA/Cr in the left hippocampus. As NAA is localized almost exclusively in neurons, the reduction in relative NAA in the left hippocampus suggests that axonal degeneration contributed to the observed diffusion abnormalities.[13] In addition, this study found that the reduction of NAA/Cr was associated with lower mean digit span score (lower working memory functioning). Previous research also found that neurochemical properties were associated with cognitive deficits.[13] Perhaps abnormalities in both the metabolic-level and network-level changes in the brain may appear before the alterations in clinical performance of a neurocognitive test.[39] Thus, detecting alterations in structural connectivity networks and brain metabolic properties might provide a potential earlier biomarker of CRCI, which could be used for the relevant development of prevention strategies.

This is the first pilot study to investigate the effects of acupuncture in preventing and reducing cognitive impairment. Compared with the cancer control group, the results showed that acupuncture improved neurocognitive performance over the chemotherapy period. While patients in the acupuncture group reported a mild degree of cognitive impairment at baseline, after receiving 10 sessions of acupuncture treatment, patients in the intervention group had higher mean neurocognitive test scores than the cancer control group. As both groups were matched for age, menopause status, cancer stage, and dosage of chemotherapy regimen (all had a standard-dose regimen), better neurocognitive test performance in the intervention group may be due to the positive effects of acupuncture. Admittedly, this pilot cohort study had a small number of patients and the lack of any randomization, which may account for the

possibility of residual confounding. Although patients in both groups after chemotherapy had impairment of white matter integrity (reduced FA values and increased MD values), changes in DTI parameters in the cancer control group were higher than in the acupuncture intervention group. Previous research has indicated that changes in FA and MD values could be due to demyelination.[13] Preclinical research evidence specifically indicates that the possible mechanism of decreased white matter integrity may be attributed to incoherence of myelin basic protein fiber.[40] Thus, findings of this pilot study suggest that acupuncture may mitigate cognitive impairment by reducing demyelination.

Additional positive effects of acupuncture on CRCI included a lower reduction in relative concentrations of NAA for patients in the acupuncture group. Previous research also indicated that the ratio of NAA/Cr was obtained by measuring the level of NAA and Cr to evaluate neuronal activity in the hippocampus.[41] A review suggested that lower levels of NAA may reflect inefficient neuronal viability.[42] Therefore, on a microstructural level, acupuncture preventing or reducing CRCI may be attributed to its reducing demyelination and enhancing neuronal viability of white matter in the hippocampus. Monitoring structural alterations of white matter connections and concentrations of NAA can be potential markers for acupuncture interventions for preventing or reducing CRCI in patients with gynecological cancer.

The strength of this study lies in the fact that this was a pilot cohort study exploring the effects of acupuncture on preventing cognitive impairment in cancer patients during chemotherapy. The study also examined the neurobiological mechanism of CRCI by multimodal MRI of structural brain connectivity and brain metabolite properties. The main study limitation was the small cohort size, although there were similar demographic characteristics between the intervention group and the control group. In addition, the intrinsic clinical differences between cancer patients (eg, types of cancer, disease stage) resulted in different chemotherapy regimens assigned to each patient. Therefore, future studies using a larger cohort size and including homogeneous cancer patients, preferably with identical chemotherapy regimens, should be conducted to replicate these study findings.

Conclusions

This pilot study indicates that acupuncture is a promising intervention in preventing CRCI in gynecological cancer patients undergoing chemotherapy. However, it requires evaluation in larger randomized controlled studies to definitively assess its benefit. By using a multimodality imaging approach, this pilot study also provides novel insights into the neurobiological basis of cognitive impairment on the human brain, induced by cancer and/or its treatment. Information from this study could potentially serve as a guide in future treatment and rehabilitation strategy development for this vulnerable population.

Acknowledgments

The authors thank all the subjects for participating in this study.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was supported by the Guangzhou Medical University Fund for Overseas Returners (No. 2013C57).

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AIIORE CASE STUDY SUBMISSION. AUGUST 2018
(notes in italic are added by Dr. Nalini Chilkov)

Submitted by Stacy D'Andre MD. dandrs1@sutterhealth.org

Recurrent Pancreatic Cancer
Initially T2N2 high grade AdenoCA, now recurrent at tumor bed
51 yo female, caucasian. thin. *(Sarcopenia/Cachexia?)*

GOALS Quality of life, prolongation of life

HISTORY SUMMARY
Patient had Whipple 7/17 followed by 6 cycles of adjuvant gemzar and abraxane.
She then developed recurrence as seen on PET scan in the tumor bed and completed SBRT to the tumor bed 5/18.

- Whipple 7/17 followed by 6 cycles of gemzar/abraxane
- Local recurrence detected on PET scan,
- Treated 5/18 with 6 treatments of SBRT.
- On observation currently

Self Rx

- melatonin 5 mg qhs,
- unknown amount curcumin,
- store bought probiotic

PMH sig for **autoimmune thyroid disease**;
FH also significant for AI disease
Has very supportive husband and family, church
Does yoga, good control of stress.

RECENT LABS
HgbA1c high, *(Common in PanCa). Berberine Low Glycemic Paleo-Keto Diet*
VIT D 31 L. *replete*
Homocysteine very low(<6). *Sulfur containing supplements*
Mid iron deficiency *replete and monitor*
Stool cultures negative for C diff
NLR is less than 3-monitor
No Hypercoagulation-monitor
No elevated Cu or Cp Improve Zinc Copper Ratio.

2 Core Questions

1. **What is the meaning of such a low homocysteine and what can we do to balance that?**
   Poor ability to methylate and quench oxidative stress Sulfur containing nutrients: N AcetylCysteine 2-3g/day, L Taurine 1-2g/day, Glutathione (oral liposomal or IV). Quicksilver and DFH make Liposomal Glutathione. 4 pumps under tongue x 2 min bid-qid . ITI Cytoredoxin 2 bid
2. **What are some anticancer foods and nutraceuticals we can add to help keep her cancer in remission after therapy?** *See below*

ADVERSE EFFECTS

- ***Persistent diarrhea****. (neg for C diff).*
  - *Huang Qin Tang 3 - 6 g/day,*
    - *Scutellaria baicalensis,*
    - *Paeonia Alba,*
    - *Glycyrriza cooked,*
    - *Fr. Zizyphus*
  - *Acupuncture/Moxabustion 1-3x/week*

  - *PreBiotics*
  - *Probiotics*
  - *Glutamine 3-10 g/day*
  - *Colostrum 1 bid*

- ***Fatigue. (Combine herbs: 3-6 g/day)***
- *DFH Adrenotone (adaptogens) 3 bid*
- *or*
- *Natura Power Adapt 2 tsp bid*
- *or*
  - *Astragalus*
  - *Panax Ginseng*
  - *Rhodiola*
  - *Ashwaganda*
  - *Ganoderma*

  - *Acupuncture /Moxabustion 1-3x/week*

- ***Insomnia. (MPX?)***
  - *Magnesium glycinate 150mg qid (spread out due to diarrhea) last dose hs*
  - *L Theanine hs 200mg*
  - *Pure Honokiol 500mg (2 caps) hs*
  - *Acupuncture*
  -
- ***Menopausal symptoms*** *(caution HRT- first check for ER+receptors)*
  - *Acupuncture*
  - *Yin Tonics (not estrogenic)*
    - *Schizandra*
    - *Lycium*
    - *Ziziphus*
    - *Asparagus root*
- ***Low libido*** *Adaptogenic herbs above, Acupuncture, Moxabustion, Regulate Sleep cycle*

Focus of Interventions

NUTRIENT and CALORIE REPLETION

Must focus on Nutrient Repletion and Restoration of Digestive Function with PANC CA patients…not TIME…cannot WAIT to rebuild their gut

ASAP: Start delivering calories…these patients rapidly develop sarcopenia and cachexia

Modified KETO Diet and Shake is essential (1-2 shakes daily)
VIT D Vit D Supreme (w/Vit K) 1 bid
Fe DFH FERROCHEL monitor 1 bid

GLYCEMIC CONTROL. *HgbA1c (modified-Keto-Paleo)*
Berberine 3g/day
Panax Ginseng 2 g /day

SUPPORT GI FUNCTION *as above 90% cooked food*
Pancreatic Enz + Oxbile, questran, creon

SUPPORT MICROBIOME *as above*

MANAGE INFLAMMATION.
O3FA 3-4g/day+
Curcumevail 4 g/day
Boswellia AKBA 2 g/day

ADAPTOGENIC and QI TONIFYING *as above*

TUMOR CONTROL (TUMOR MICROENVIRONMENT + CYTOTOXIC) *see below*

Dr. D'Andre PROPOSED TREATMENT PLAN

Foundation Nutrition Supplements:

Added: melatonin 10 mg qhs, *(can go up to 20mg)*

omega 3 FA 2g/d, added (suggest 4-6g with lipase or Creon))

questran

VSL #3 for diarrhea. *(prefer Klaire Therbiotic Complete and Targetgbx)*

Add DFH Twice Daily Multi or ITI ProThriver Wellness Multi 1 bid

THC for sleep; *(see Mg, Theanine and Acup above)*

consider topical HRT for menopausal sx; *caution check ER+*

consider some colostrum/glutamine for gut repair

Targeted Supplements:

once gut improved add in some *(cannot really wait in PaCa pts)*

*R*esveratrol *2 g/d*

ECGC *2-4 g/d*

Curcumin (cont) , *Curcumevail 2 bid 4 g daily*

Quercitin*+Bromelain combo (Thorne Quercenase 4 tid away from food)*

(Dr Nick Gonzalez recommended Wobenzyme 8-10 caps qid)

ADD

CS Modified Citrus Pectin 5 grams tid. (Angiogenesis-Metastasis)

ARG Super Artemesinin one week on, one week off 2 tid (cytotoxic)

*******Specific to PaCa********

Anvirzel: *Nerium (per Keith Block MD)*

PI3K, AKT, mTOR

877-822-7908 and ask for Liz.

0.5 cc every 5 hours 4 times daily.

3 minutes under tongue then swallow.

Replete Zinc: Zinc Supreme 60-90mg/day (contains molybdenum)

Tocotrienols 2 grams/day

Nigella sativa seed oil (thymoquinone) 2 tsp daily

Honokiol 2g daily (Pure Honokiol)

Scutellaria baicalensis Huang Qin
Salvia miltiorrhiza Dan Shen
Oldenlandia (Heydotis) diffusa Bai Hua She She Cao (Ursolic Acid)
Matricaria chamomilla (Apigenin-also found in celery, parsley)

Add Digestive Herbs
Dried Ginger, Dried Tangerine Peel

Add
Traditional Chinese Formula :
Pinellia and Magnolia (Ban Xia Hou Po Tang) 3-6 g/day

Functional Foods and/or Therapeutic Shake may need medical foods with more enzymes given gut dysfunction

Need to add CALORIES, PROTEIN (60g+/day), FATS

Add Medium Chain Triglycerides to shake

Add CS Myoceutics Mushroom Immune Max (combo) 1-2 scoops

Add Carnitine Tartrate powder 1.5-2.0 g

Dietary Guidelines

cut out all processed sugar; eat the rainbow, limit meat (fish ok), recommend elim dairy she may need elim diet if bowel issues do not resolve

Lifestyle Guidelines increase exercise and meditation daily

increasing muscle workload improves insulin resistance (yoga, weights, bands, walking)

Recommended Diagnostics Ubiome, labs ordered

ESR, CRP, Fibrinogen activity, D Dimer, Transforming Growth Factor b1, Serum VEGF,

SNP: COMT, MTHFR, APOE (Quest, Labcorp)

Methylation SNPS : 23 and me + GeneticGenie.org

Naturopathic Oncology Considerations

High dose Proteolytic Enzymes on empty stomach
Infla-zyme or Wobenzyme 8 tabs qid

IV Vitamin C
IV Lipoic Acid
IV NAD
IV Phosphatidyl Choline
IV or SubQ Mistletoe

Botanical CytoToxic Therapies (oral)
Anvirzel sublingual
Super Artemesin (Allergy Research Group)
Phyto Cyto (Natural Health Products)
Polygonatum odoratum
Taxus brevifolia (tips) (Taxanes source)
Catharanthus roseus (Vinca spp)
Camptotheca (Irinotecan source)

Off Label use of Rx
Low Dose Naltrexone
COX2 Inhibitors
Cimetidine

Conventional Oncology -Tumor Cell Sensitivity
If fresh tissue available: Weisenthal or Rational Therapeutics Cancer Labs
If frozen tissue available: ER+, EGFR+? Ras? Foundation One? Caris Life Sciences Molecular Profile?

EGFR inhibitors. Erbitux, Iressa, Gefitinib, Erlotinib
Pi3K/mTOR Inhibitors
CAR T cell therapy if fails other tx

Serge Jurasunas MD
Holitherapias
Rue da Misericordia 137-1
1200-272 Lisbon Portugal
info@sergejurasunas.com. 351-21-3471-1117

Description: 51 year old female

Progress Notes Encounter Date: 6/27/2018

support@aiiore.com

D'Andre, Stacy D, MD
Hematology/Oncology

a 51 year old female seen in consultation from Dr. Koon for second opinion/integrative oncology visit

Chief Complaint: pancreatic cancer

History of Present Illness:

Pt has hx pancreatic cancer sp Whipple 8/4/17 followed by adjuvant chemotherapy, treated at UCD as summarized below:

" Patient with Graves disease and Hashimoto's thyroiditis who developed epigastric pain for approximately six weeks. The pain was initially intermittent and mostly at night but later progressed to postprandial and throughout the day. Other associated symptoms include itching, generalized jaundice, and 20 lb weight loss. The ultrasound performed on 6/23/17 at Sutter demonstrated a heterogeneously hypoechoic 2.7 cm mass lesion in the pancreatic head with associated main pancreatic duct and biliary duct dilatation. CT of abdomen and pelvis on 6/27/17 revealed an ill-defined slightly hypoattenuated mass in pancreatic head measuring 3.2 x 2.7 cm. There was extrahepatic biliary obstruction noted. No evidence of any liver lesions or any regional adenopathy identified. Patient subsequently underwent an endoscopic ultrasound with fine needle aspiration of pancreatic head mass on 7/7/17 and confirmed adenocarcinoma. CA 19-9 was normal at 33 on 7/17/17. PET/CT on 7/19/17 at Sutter revealed mild to moderate increased uptake in the known adenocarcinoma in the pancreatic head but otherwise no definite evidence of metastasis.

Patient was referred to UCDMC and seen by Dr. Bold on 7/24/17. She underwent the Whipple resection and cholecystectomy by Dr. Bold on 8/4/17. Pathology reveals grade 3 poorly differentiated invasive ducal adenocarcinoma of pancreatic head. Five out of twenty one lymph nodes (5/21) are involved. Positive for lymphovascular invasion and perineural invasion. All margins are uninvolved by invasive carcinoma, although the closest margin is <1 mm from pancreatic neck margin, 0.3 mm from vascular groove, and 0.6 mm from the uncinate process margin. Overall stage pT2N2.

Other medical illnesses:
Graves disease/Hashiomoto's thyroiditis - been followed by endocrinology at Sutter

DISEASE STATUS: pT2N2 disease s/p whipple resection and adjuvant chemotherapy with gem/xeloda

SUMMARY OF HEMATOLOGIC/ONCOLOGIC THERAPY, RESPONSE & SIDE EFFECTS
1. Whipple resection on 8/4/17
Pathology reveals grade 3 poorly differentiated invasive ducal adenocarcinoma of pancreatic head. The tumor invades peripancreatic soft tissues. Five out of twenty one lymph nodes (5/21) are involved. Positive for lymphovascular invasion and perineural invasion. All margins are uninvolved by invasive carcinoma, however the closest margin is <1 mm from pancreatic neck margin, 0.3 mm from vascular groove, and 0.6 mm from the uncinate process margin.

Overall stage pT2N2. Note, there is evidence of chronic pancreatitis.

2. Adjuvant therapy with gem/xeloda 9/15/17-2/27/18
Completed 6 cycles of gemcitabine and xeloda
Gemcitabine at 1000 mg/m2 D1,8,15
Xeloda at 1,660 mg/m2/day (in 2 divided doses) D1 to 21 [BSA 1.61 roughly equivalent to 1330 mg bid]
For every 28 day cycle
-tolerated fair with nausea, abdominal pain, reflux
-self-discontinued xeloda starting week 2 of cycle 6

Tumor recurrence
CT abdomen and pelvis on 3/19/18 shows increasing soft tissue density surrounding the portal vein confluence with stricturing concerning for tumor recurrence.
PET/CT on 4/10/18 shows focal FDG activity near the Whipple anastomosis site consistent with residual/recurrent disease. The hypodense hypermetabolic right thyroid nodule likely related to Graves' disease. No overt evidence of metastasis."

She was treated with 6 fx SBRT 5/18. Some fatigue with treatment but overall tolerated well.

She would like to incorporate some integrative treatment into her care. She does not want any further standard chemotherapy.

Her current diet is pretty healthy although she does like sweets at times. Has some sugar cravings. She does eat meat daily and dairy. She does eat fair amount of veges. Her current exercise is yoga. She also meditates occasionally. She is not particularly stressed.

Current issues include:

Diarrhea- on creon. Not floating or greasy but bilious and foul smelling. Some upper abd pain. No GERD. On probiotics.
Insomnia- falls asleep OK but wakes up. Maybe sleeping 5-6 hrs. Using prn ativan and melatonin 5 mg.
Fatigue- some persisting after treatments
Menopausal sx- hot flashes, low libido. Used to be on topical HRT but not for awhile.

Review of patient's past medical history indicates:
Nontoxic multinodular goiter
HASHIMOTO'S THYROIDITIS
Graves disease
Malignant neoplasm of breast (female) (HCC)

Review of patient's past surgical history indicates:
ENLARGE BREAST WITH IMPLANT
US THYROID BIOPSY
US THYROID BIOPSY
MAMMO GUIDED NEEDLE PLACEMENT LEFT
PR MASTECTOMY PARTIAL (EG LUMPECTOMY) W/AXILLA LYMPHADENECT
HX COLONOSCOPY

HX UPPER GI ENDOSCOPY,EXAM
HX PANCREATECTOMY WHIPPLE PROCEDURE

Social History

Substance and Sexuality
Tobacco Use: Never
Alcohol Use: No
Drug Use: No
Sexual Activity: Yes Partners with: Male
Birth Control/Protection: Sterilization male
Comment: Pt is married.

Social Documentation
The patient resides locally
She is married
She is a homemaker
She has five children, 3 in house still
She enjoys spending time with her family, baking, gardening, reading

Socioeconomic
Marital Status: Married

Family History

Problem	Relation	Age of Onset
• Alzheimer's Disease *alive 73 alzheimers, fibromyalgia, CFS*	Mother	
• Hypertension *alive 78 HTN, myasthenia gravvos. vitiligo, ess tremor, heart rhythm*	Father	
• Depression *alive 53*	Sister	
• Depression *alive 52*	Brother	
• Depression *alive 50 ess tremor, depression*	Brother	
• Thyroid Disease *alive 45 Grave's, depression*	Sister	
• No Current problems or disability *alive 32*	Brother	
• Other *died young farm accident*	Paternal Grandfather	
• Other *died 80s pneumonia*	Paternal Grandmother	
• Diabetes type II *died 80s natural causes*	Maternal Grandfather	
• Cancer *died 80s leukemia*	Maternal Grandmother	
• Hypothyroidism *two nieces*	Other	
• Breast cancer	No Significant Family History	
• Ovarian Cancer	No Significant Family History	

• Melanoma	No Significant Family History
• Colon Cancer	No Significant Family History
• Colonic Polyps	No Significant Family History

Family Status

Relation	Status
• Mother	Alive
• Father	Alive
• Sister	Alive
• Sister	Alive
• Brother	Alive
• Brother	Alive
• Brother	Alive
• Sister	(Not Specified)
• Brother	(Not Specified)
• Brother	(Not Specified)
• Sister	(Not Specified)
• Brother	(Not Specified)
• PGFa	(Not Specified)
• PGMo	(Not Specified)
• MGFa	(Not Specified)
• MGMo	(Not Specified)
• OTHER	(Not Specified)
• NSFH	(Not Specified)

Allergies: Sulfa Antibiotics

Current Outpatient Prescriptions

Medication	Sig
• Probiotic Product (PROBIOTIC DAILY PO)	Take by mouth
• TURMERIC CURCUMIN PO	Take by mouth
• Multiple Vitamins-Minerals (MULTIVITAMIN ADULT PO)	Take by mouth
• Pancrelipase, Lip-Prot-Amyl, (CREON PO)	Take 1 Cap by mouth three times daily
• LORazepam (ATIVAN) 1mg Tab	Take 1 mg by mouth at bedtime as needed for Anxiety/Restlessness
• cholestyramine (QUESTRAN) 4g Packet	Start with once a day, can increase to twice as day if needed for diarrhea

No current facility-administered medications for this visit.

Review of Systems

General : Denies fever, chills, night sweats, anorexia, +fatigue/weakness, weight loss.
Eyes: Denies blurring, diplopia, vision loss, eye pain.
ENT: Denies earache, tinnitus, decreased hearing, nasal congestion, sore throat, and hoarseness.
CV: Denies chest pains, palpitations, syncope, dyspnea on exertion, orthopnea, PND, and peripheral edema.

Resp: Denies cough, hemoptysis, wheezing, and pleurisy.
GI: Denies nausea, vomiting,++ diarrhea, constipation, +abdominal pain, melena, hematochezia.
GU: Denies dysuria, hematuria, urinary frequency, urinary hesitancy, nocturia, incontinence.
MS: Denies joint stiffness or pain/ swelling, muscle cramps, lower extremity edema and muscle wasting.
Derm: Denies rash, itching, dryness, suspicious lesions, change in color, and abnormal hair or nail growth.
Neuro: Denies headaches, syncope, seizures, weakness, numbness, loss of feeling, tremor, involuntary movements, memory loss, frequent falls and difficulty walking.
Psych: Denies depression, anxiety, memory loss, mood changes, and sleep disturbance.
Heme: Denies anemia, easy bruising, prolonged bleeding, blood transfusion, and blood clots.
Allergy: Denies dermatitis, hay fever, positive skin testing, allergy shots, allergic rash, and recurrent infections.

Physical Exam:

BP 103/62 | Pulse 67 | Temp (Src) 98.2 °F (36.8 °C) (Temp Artery) | Ht 1.702 m (5' 7") | Wt 54.6 kg (120 lb 6.4 oz) | SpO2 99% | LMP 02/14/2017

General: Well Developed, well nourished, in no acute distress.
Eyes: PERRLA/EOM intact; conjunctiva and sclera clear.
Skin: intact without lesions or rashes
Psych: alert and cooperative; normal mood and affect; normal attention span and concentration.

Assessment and Plan:

a 51 year old female
(C25.9) Pancreatic adenocarcinoma (HCC) (primary encounter diagnosis): SP Whipple/adjuvant chemo and recent SBRT (5/18) for local recurrence.

Reviewed all OSR, detailed questionnaire scanned in.

Reviewed integrative approach to health including diet, lifestyle and other areas as detailed below. She is interested in other possible alternative therapies to help treat cancer but at this time I think she needs to focus on her gut issues and a few other key things.

Will get some baseline labs done.

GUT: She will do UBIOME testing. She likely has severe dysbiosis due to treatment. Recommend starting VSL #3 probiotic. She clinically also has possible bile acid diarrhea (bilious foul smelling stools, on high dose creon, past cx negative). Will do trial of cholestyramine. Recommend making some dietary changes as outlined below. Cannot add in fiber yet until bowel issues have improved or she will have worsened sx.

SLEEP: Can increase melatonin to 10 mg at bedtime (also an antioxidant). Can add in some THC low dose indica strain PRN. Prefer that over ativan.

HORMONES: consider restarting topical HRT given menopausal sx

TOXINS: Reviewed importance of avoiding toxins, ie. Cleaners/beauty products/pesticides. She is filtering water. Check EWG website.

EXERCISE: Rec increase aerobic and add in some weight resistance slowly.

STRESS: Rec meditation daily

DIET: Would decrease carbohydrates esp sugars/sweets. Eat mostly plant based, fish ok. I am not a fan of dairy in cancer patients. Eat the rainbow of veges/fruits- many colors/phytonutrients. Berries are best.

SUPPLEMENTS: Fish oil (if not eating much fish), continue tumeric, will add in VIT D once I have her blood tests done.

Will see her back in about 4 weeks after testing done to review.

Reviewed plans and answered all questions.

Plan: CBC WITH AUTOMATED DIFFERENTIAL, COMPREHENSIVE METABOLIC PANEL W GFR, INSULIN, HEMOGLOBIN A1C, GGT, GAMMA GLUTAMYLTRANSFERASE, COPPER, CERULOPLASMIN, ZINC, PLASMA, SELENIUM, VITAMIN D (25 HYDROXY), HOMOCYSTEINE, FIBRINOGEN, CLOTTABLE, IRON & IRON BINDING CAPACITY, cholestyramine (QUESTRAN) 4g Packet

> 65 minutes were spent face to face in consultation with patient/family regarding treatment options, over 50% of which was spent in counselling and/or coordinating of the medical care.

Office Visit on 6/27/2018 Note shared with patient

IRON & IRON BINDING CAPACITY (ExtID# F1750611_FETIBC_20180629092100) (Order 918530359)

Results

Status: Final result (Collected: 6/29/2018 9:35 AM)

Specimen Source

Type: Serum
Blood

Result Information

Collected Date and Time	Lab Received Date and Time	Filed in EpicCare Date and Time
6/29/2018 9:35 AM	6/29/2018 9:37 AM	6/29/2018 1:47 PM

6/29/2018 1:47 PM - Ifc, Ehr Ss Amb Sunquest Lab Results In

Component Results

Component	Value	Ref Range & Units	Status	Collected	Lab
Iron	52	35 - 150 ug/dL	Final	06/29/2018 9:35 AM	RVML
Iron Binding	400	250 - 450 ug/dL	Final	06/29/2018 9:35 AM	RVML
Iron % Saturation	13	15 - 50 %	Final	06/29/2018 9:35 AM	RVML

Testing Performed By

Lab - Abbreviation	Name	Director	Address	Valid Date Range
59-RVML	SUTTER ROSEVILLE MEDICAL CENTER LABORATORY	Ronald Rowberry, MD	1 Medical Plaza ROSEVILLE CA 95661	06/27/18 1437-Present

Lab and Collection

IRON & IRON BINDING CAPACITY (Order #918530359) on 6/29/2018 - Lab and Collection Information

Patient Demographics

Patient Name	Sex	DOB	Address	Phone
	Female			

Patient Release Status:

This result is viewable by the patient in MHO.

Last viewed in MHO:

7/3/2018 8:22 AM

HOMOCYSTEINE (ExtID# F1750606_HCYS_20180629092100) (Order 918530357)

Results

Status: Final result (Collected: 6/29/2018 9:35 AM)

Specimen Source

Type: Serum
Blood

Result Information

Collected Date and Time	Lab Received Date and Time	Filed in EpicCare Date and Time
6/29/2018 9:35 AM	6/29/2018 9:36 AM	6/29/2018 9:38 PM

6/29/2018 9:38 PM - Ifc, Ehr Ss Amb Sunquest Lab Results In

Component Results

Component	Value	Ref Range & Units	Status	Collected	Lab
Homocysteine	0.6	3.7 - 13.9 umol/L	Final	06/29/2018 9:35 AM	LV1

Testing Performed By

Lab - Abbreviation	Name	Director	Address	Valid Date Range
30013300-LV1	SUTTER HEALTH SHARED LABORATORY	Joan Etzell, MD	2950 Collier Canyon Road Livermore CA 94551	12/17/13 1635-Present

Lab and Collection

HOMOCYSTEINE (Order #918530357) on 6/29/2018 - Lab and Collection Information

Patient Demographics

Patient Name	Sex	DOB	Address	Phone
	Female			

Patient Release Status:

This result is viewable by the patient in MHO.

Last viewed in MHO:

7/3/2018 8:22 AM

By:

Release Information

VITAMIN D (25 HYDROXY) (ExtID# F1750608_VITD_20180629092100) (Order 918530356)

Results

Status: Final result (Collected: 6/29/2018 9:35 AM)

Specimen Source

Type: Serum
Blood

Result Information

Collected Date and Time	Lab Received Date and Time	Filed in EpicCare Date and Time
6/29/2018 9:35 AM	6/29/2018 9:37 AM	6/29/2018 8:13 PM

6/29/2018 8:13 PM - Ifc, Ehr Ss Amb Sunquest Lab Results In

Component Results

Component	Value	Ref Range & Units	Status	Collected	Lab
VitD,25-Hydroxy Tot	31	20 - 80 ng/mL	Final	06/29/2018 9:35 AM	LV1

Comment:

This Total 25-OHD assay measures the sum of 25-hydroxy vitamin D metabolites
(D2 and D3)
All ages: 20-50 ng/mL*
There is no known benefit of values > 50 ng/mL
Values > 80 ng/mL may be associated with toxicity

*In patients with risk factors such as bone disease, values between 20-29 ng/mL may be insufficient, and values greater than 30 ng/mL may be more appropriate.

Testing Performed By

Lab Abbreviation	Name	Director	Address	Valid Date Range
30013300-LV1	SUTTER HEALTH SHARED LABORATORY	Joan Etzell, MD	2950 Collier Canyon Road Livermore CA 94551	12/17/13 1635-Present

Lab and Collection

VITAMIN D (25 HYDROXY) (Order #918530356) on 6/29/2018 - Lab and Collection Information

Patient Demographics

Patient Name	Sex	DOB	Address	Phone
	Female			

Patient Release Status:

CERULOPLASMIN (ExtID# F1750606_CERULO_20180629092100) (Order 917849662)

Results

Status: Final result (Collected: 6/29/2018 9:35 AM)

Specimen Source

Type: Serum
Blood

Result Information

Collected Date and Time	Lab Received Date and Time	Filed in EpicCare Date and Time
6/29/2018 9:35 AM	6/29/2018 9:36 AM	6/29/2018 7:51 PM

6/29/2018 7:51 PM - Ifc, Ehr Ss Amb Sunquest Lab Results In

Component Results

Component	Value	Ref Range & Units	Status	Collected	Lab
Ceruloplasmin	23.1	20 - 60 mg/dL	Final	06/29/2018 9:35 AM	LV1

Testing Performed By

Lab - Abbreviation	Name	Director	Address	Valid Date Range
30013300-LV1	SUTTER HEALTH SHARED LABORATORY	Joan Etzell, MD	2950 Collier Canyon Road Livermore CA 94551	12/17/13 1635-Present

Lab and Collection

CERULOPLASMIN (Order #917849662) on 6/29/2018 - Lab and Collection Information

Patient Demographics

Patient Name	Sex	DOB	Address	Phone
	Female			

Patient Release Status:

This result is viewable by the patient in MHO.

Last viewed in MHO:

6/30/2018 7:22 AM

By:

Release Information

GGT, GAMMA GLUTAMYLTRANSFERASE (ExtID# F1750606_GGT_20180629092100) (Order 917849660)

Results

Status: Final result (Collected: 6/29/2018 9:35 AM)

Specimen Source

Type: Serum
Blood

Result Information

Collected Date and Time	Lab Received Date and Time	Filed in EpicCare Date and Time
6/29/2018 9:35 AM	6/29/2018 9:36 AM	6/29/2018 3:26 PM

6/29/2018 3:27 PM - Ifc, Ehr Ss Amb Sunquest Lab Results In

Component Results

Component	Value	Ref Range & Units	Status	Collected	Lab
GGT	5	5 - 55 U/L	Final	06/29/2018 9:35 AM	RVML

Testing Performed By

Lab Abbreviation	Name	Director	Address	Valid Date Range
59-RVML	SUTTER ROSEVILLE MEDICAL CENTER LABORATORY	Ronald Rowberry, MD	1 Medical Plaza ROSEVILLE CA 95661	06/27/18 1437-Present

Lab and Collection

GGT, GAMMA GLUTAMYLTRANSFERASE (Order #917849660) on 6/29/2018 - Lab and Collection Information

Patient Demographics

Patient Name	Sex	DOB	Address	Phone
	Female			

Patient Release Status:

This result is viewable by the patient in MHO.

Last viewed in MHO:

7/3/2018 8:17 AM

By:

Release Information

HEMOGLOBIN A1C (ExtID# F1750606_A1CB_20180629092100) (Order 917849659)

Results

Status: Final result (Collected: 6/29/2018 9:35 AM)

Specimen Source

Type: Blood
Blood

Result Information

Collected Date and Time	Lab Received Date and Time	Filed in EpicCare Date and Time
6/29/2018 9:35 AM	6/29/2018 9:36 AM	6/29/2018 3:19 PM

6/29/2018 3:19 PM - Ifc, Ehr Ss Amb Sunquest Lab Results In

Component Results

Component	Value	Ref Range & Units	Status	Collected	Lab
Hemoglobin A1c	6.0 ^	4.8 - 5.6 %	Final	06/29/2018 9:35 AM	SMF Lab
Average Glucose	126	mg/dL	Final	06/29/2018 9:35 AM	SMF Lab

Comment:

INSULIN (ExtID# F1750606_INSU_20180629092100) (Order 917849658)

Results

Status: Final result (Collected: 6/29/2018 9:35 AM)

Specimen Source

Type: Serum
Blood

Result Information

Collected Date and Time	Lab Received Date and Time	Filed in EpicCare Date and Time
6/29/2018 9:35 AM	6/29/2018 9:36 AM	6/29/2018 9:56 PM

6/29/2018 9:56 PM - Ifc, Ehr Ss Amb Sunquest Lab Results In

Component Results

Component	Value	Ref Range & Units	Status	Collected	Lab
INSULIN, FASTING	<2	<17 uIU/mL	Final	06/29/2018 9:35 AM	LV1

Testing Performed By

Lab - Abbreviation	Name	Director	Address	Valid Date Range
30013300-LV1	SUTTER HEALTH SHARED LABORATORY	Joan Etzell, MD	2950 Collier Canyon Road Livermore CA 94551	12/17/13 1635-Present

Lab and Collection

INSULIN (Order #917849658) on 6/29/2018 - Lab and Collection Information

Patient Demographics

Patient Name	Sex	DOB	Address	Phone
	Female			

Patient Release Status:

This result is viewable by the patient in MHO.

Last viewed in MHO:

6/30/2018 7:22 AM

By:

Release Information

Instant	Action
Sat Jun 30, 2018 6:06 AM	Release

COMPREHENSIVE METABOLIC PANEL W GFR (ExtID# F1750606_CMPG_20180629092100) (Order 917849657)

Results

Status: Final result (Collected: 6/29/2018 9:35 AM)

Specimen Source

Type: Serum
Blood

Result Information

Collected Date and Time	Lab Received Date and Time	Filed in EpicCare Date and Time
6/29/2018 9:35 AM	6/29/2018 9:36 AM	6/29/2018 3:26 PM

6/29/2018 3:27 PM - Ifc, Ehr Ss Amb Sunquest Lab Results In

Component Results

Component	Value	Ref Range & Units	Status	Collected	Lab
Sodium	141	136 - 145 mmol/L	Final	06/29/2018 9:35 AM	RVML
Potassium	4.3	3.5 - 5.1 mmol/L	Final	06/29/2018 9:35 AM	RVML
Chloride	109 ^	98 - 107 mmol/L	Final	06/29/2018 9:35 AM	RVML
CO2 (Bicarbonate)	29	21 - 32 mmol/L	Final	06/29/2018 9:35 AM	RVML
Glucose	81	70 - 100 mg/dL	Final	06/29/2018 9:35 AM	RVML
BUN	13	6 - 25 mg/dL	Final	06/29/2018 9:35 AM	RVML
Creatinine	0.63	0.40 - 1.00 mg/dL	Final	06/29/2018 9:35 AM	RVML
Comment: Note New Normal Range IDMS-traceable method					
GFR Est-Other	104	>60 See Cmnt	Final	06/29/2018 9:35 AM	RVML
GFR Est-African American	120	>60 See Cmnt	Final	06/29/2018 9:35 AM	RVML
Comment: Units: mL/min/1.73 m2. Estimated glomerular filtration rate values are calculated using the CKD-EPI equation					
Calcium	9.2	8.2 - 10.2 mg/dL	Final	06/29/2018 9:35 AM	RVML

Component	Value	Ref Range & Units	Status	Collected	Lab
Total Protein	7.3	6.4 - 8.2 g/dL	Final	06/29/2018 9:35 AM	RVML
Albumin	3.9	3.2 - 4.7 g/dL	Final	06/29/2018 9:35 AM	RVML
Total Bilirubin	0.4	<1.1 mg/dL	Final	06/29/2018 9:35 AM	RVML
Alkaline Phosphatase	108	26 - 137 U/L	Final	06/29/2018 9:35 AM	RVML
AST	36	0 - 37 U/L	Final	06/29/2018 9:35 AM	RVML
ALT	74	12 - 78 U/L	Final	06/29/2018 9:35 AM	RVML

Testing Performed By

Lab - Abbreviation	Name	Director	Address	Valid Date Range
59-RVML	SUTTER ROSEVILLE MEDICAL CENTER LABORATORY	Ronald Rowberry, MD	1 Medical Plaza ROSEVILLE CA 95661	06/27/18 1437-Present

Lab and Collection

COMPREHENSIVE METABOLIC PANEL W GFR (Order #917849657) on 6/29/2018 - Lab and Collection Information

Patient Demographics

Patient Name	Sex	DOB	Address	Phone
	Female			

Patient Release Status:

This result is viewable by the patient in MHO.

Last viewed in MHO:

7/2/2018 7:46 PM

By:

Release Information

Instant	Action	Who
Fri Jun 29, 2018 3:40 PM	Release	

Result History

COMPREHENSIVE METABOLIC PANEL W GFR (Order #917849657) on 6/29/2018 - Order Result History Report

Order Providers

CBC WITH AUTOMATED DIFFERENTIAL (ExtID# F1750606_CBCA_20180629092100) (Order 917849656)

Results

Status: Final result (Collected: 6/29/2018 9:35 AM)

Specimen Source

Type: Blood
Blood

Result Information

Collected Date and Time	Lab Received Date and Time	Filed in EpicCare Date and Time
6/29/2018 9:35 AM	6/29/2018 9:36 AM	6/29/2018 2:06 PM

6/29/2018 2:07 PM - Ifc, Ehr Ss Amb Sunquest Lab Results In

Component Results

Component	Value	Ref Range & Units	Status	Collected	Lab
White Blood Cell Count	4.3	4.0 - 11.0 K/uL	Final	06/29/2018 9:35 AM	RVML
Red Blood Cell Count	4.12	3.9 - 5.4 M/uL	Final	06/29/2018 9:35 AM	RVML
Hemoglobin	11.9 ↓	12.0 - 15.5 g/dL	Final	06/29/2018 9:35 AM	RVML
Hematocrit	35.9	35.0 - 47.0 %	Final	06/29/2018 9:35 AM	RVML
MCV	87	80.0 - 100.0 fL	Final	06/29/2018 9:35 AM	RVML
MCH	28.9	27.0 - 33.0 pg	Final	06/29/2018 9:35 AM	RVML
MCHC	33.1	31.0 - 36.0 g/dL	Final	06/29/2018 9:35 AM	RVML
RDW	13.3	<16.4 %	Final	06/29/2018 9:35 AM	RVML
Platelet Count	200	150 - 400 K/uL	Final	06/29/2018 9:35 AM	RVML
Differential Type	Automated		Final	06/29/2018 9:35 AM	RVML
Neutrophil %	68	49.0 - 74.0 %	Final	06/29/2018 9:35 AM	RVML
Lymphocyte %	23 ↓	26.0 - 46.0 %	Final	06/29/2018 9:35 AM	RVML
Monocyte %	7	2.0 - 12.0 %	Final	06/29/2018 9:35 AM	RVML

Component	Value	Ref Range & Units	Status	Collected	Lab
Eosinophil %	1	0.0 - 5.0 %	Final	06/29/2018 9:35 AM	RVML
Basophil %	1	0.0 - 2.0 %	Final	06/29/2018 9:35 AM	RVML
Abs. Neutrophil	2.9	2.0 - 8.0 K/uL	Final	06/29/2018 9:35 AM	RVML
Abs. Lymphocyte	1.0	1.0 - 5.1 K/uL	Final	06/29/2018 9:35 AM	RVML
Abs. Monocyte	0.3	0.0 - 0.8 K/uL	Final	06/29/2018 9:35 AM	RVML
Abs. Eosinophil	0.1	0.0 - 0.5 K/uL	Final	06/29/2018 9:35 AM	RVML
Abs. Basophil	0.1	0.0 - 0.2 K/uL	Final	06/29/2018 9:35 AM	RVML

Testing Performed By

Lab - Abbreviation	Name	Director	Address	Valid Date Range
59-RVML	SUTTER ROSEVILLE MEDICAL CENTER LABORATORY	Ronald Rowberry, MD	1 Medical Plaza ROSEVILLE CA 95661	06/27/18 1437-Present

Lab and Collection

CBC WITH AUTOMATED DIFFERENTIAL (Order #917849656) on 6/29/2018 - Lab and Collection Information

Patient Demographics

Patient Name	Sex	DOB	Address	Phone
	Female			

Patient Release Status:

This result is viewable by the patient in MHO.

Last viewed in MHO:

7/2/2018 7:46 PM

By:

Release Information

Instant	Action	Who
Fri Jun 29, 2018 2:22 PM	Release	

Result History

CBC WITH AUTOMATED DIFFERENTIAL (Order #917849656) on 6/29/2018 - Order Result History Report

FIBRINOGEN, CLOTTABLE (ExtID# F1750606_FIB_20180629092100) (Order 918530358)

Results

Status: Final result (Collected: 6/29/2018 9:35 AM)

Specimen Source

Type: Plasma
Blood

Result Information

Collected Date and Time	Lab Received Date and Time	Filed in EpicCare Date and Time
6/29/2018 9:35 AM	6/29/2018 9:36 AM	6/29/2018 2:11 PM

6/29/2018 2:11 PM - Ifc, Ehr Ss Amb Sunquest Lab Results In

Component Results

Component	Value	Ref Range & Units	Status	Collected	Lab
Fibrinogen	308	245 - 488 mg/dL	Final	06/29/2018 9:35 AM	RVML

Testing Performed By

Lab - Abbreviation	Name	Director	Address	Valid Date Range
59-RVML	SUTTER ROSEVILLE MEDICAL CENTER LABORATORY	Ronald Rowberry, MD	1 Medical Plaza ROSEVILLE CA 95661	06/27/18 1437-Present

Lab and Collection

FIBRINOGEN, CLOTTABLE (Order #918530358) on 6/29/2018 - Lab and Collection Information

Patient Demographics

Patient Name	Sex	DOB	Address	Phone
	Female			

Patient Release Status:

This result is viewable by the patient in MHO.

Last viewed in MHO:

6/29/2018 4:44 PM

By:

Release Information

Instant	Action	Who

SELENIUM (ExtID# F1750606_RSELEN_20180629092100) (Order 918530355)

Results

Status: In process (Collected: 6/29/2018 9:35 AM)

Specimen Source

Blood

Result Information

Collected Date and Time	Lab Received Date and Time	Filed in EpicCare Date and Time
6/29/2018 9:35 AM		6/29/2018 9:36 AM

6/29/2018 9:37 AM - Ifc, Ehr Ss Amb Sunquest Lab Results In

Lab and Collection

SELENIUM (Order #918530355) on 6/29/2018 - Lab and Collection Information

Patient Demographics

Patient Name	Sex	DOB	Address	Phone
	Female			

Patient Release Status:

This result is not viewable by the patient.

Order Providers

Authorizing Provider	Encounter Provider
(ID # 106976) D'Andre, Stacy D, MD	(ID # 15004304) SSOA LAB-ROSEVILLE MOB3 PROVIDER

Order Diagnosis

	ICD-10-CM	ICD-9-CM
Pancreatic adenocarcinoma (HCC)	C25.9	157.9

Detailed Information

Priority and Order Details

Collection Information

Original Encounter

View Parent Encounter

Results Encounter

View Encounter

ZINC, PLASMA (ExtID# F1750606_RZINC_20180629092100) (Order 918530354)

Results

Status: Final result (Collected: 6/29/2018 9:35 AM)

Specimen Source

Type: **Blood**
Blood

Result Information

Collected Date and Time	Lab Received Date and Time	Filed in EpicCare Date and Time
6/29/2018 9:35 AM	6/29/2018 9:36 AM	7/2/2018 6:55 PM

7/2/2018 6:55 PM - Ifc, Ehr Ss Amb Sunquest Lab Results In

Component Results

Component	Value	Ref Range & Units	Status	Collected	Lab
Zinc	66	60 - 130 ug/dL	Final	06/29/2018 9:35 AM	SLI

Comment:

Note

This test was developed and its analytical performance characteristics have been determined by Quest Diagnostics Nichols Institute Valencia. It has not been cleared or approved by the US Food and Drug Administration. This assay has been validated pursuant to the CLIA regulations and is used for clinical purposes.

Testing Performed By

Lab - Abbreviation	Name	Director	Address	Valid Date Range
803-SLI	QUEST DIAGNOSTICS-NICHOLS VALENCIA	B Kashlan MD FCAP	27027 Tourney Road Valencia CA 91355	04/28/15 1332-Present

Lab and Collection

ZINC, PLASMA (Order #918530354) on 6/29/2018 - Lab and Collection Information

Patient Demographics

Patient Name	Sex	DOB	Address	Phone
	Female			

Patient Release Status:

COPPER (ExtID# F1750606_RCOPS_20180629092100) (Order 917849661)

Results

Status: Final result (Collected: 6/29/2018 9:35 AM)

Specimen Source

Type: Serum
Blood

Result Information

Collected Date and Time	Lab Received Date and Time	Filed in EpicCare Date and Time
6/29/2018 9:35 AM	6/29/2018 9:36 AM	7/2/2018 6:55 PM

7/2/2018 6:55 PM - Ifc, Ehr Ss Amb Sunquest Lab Results In

Component Results

Component	Value	Ref Range & Units	Status	Collected	Lab
Copper, Serum	97	70 - 175 ug/dL	Final	06/29/2018 9:35 AM	SLI

Comments

Note
This test was developed and its analytical performance characteristics have been determined by Quest Diagnostics Nichols Institute Valencia. It has not been cleared or approved by the US Food and Drug Administration. This assay has been validated pursuant to the CLIA regulations and is used for clinical purposes.

Testing Performed By

Lab Abbreviation	Name	Director	Address	Valid Date Range
803-SLI	QUEST DIAGNOSTICS-NICHOLS VALENCIA	B Kashlan MD FCAP	27027 Tourney Road Valencia CA 91355	04/28/15 1332-Present

Lab and Collection

COPPER (Order #917849661) on 6/29/2018 - Lab and Collection Information

Patient Demographics

Patient Name	Sex	DOB	Address	Phone
	Female			

Patient Release Status:

This result is viewable by the patient in MHO.

Last viewed in MHO: