American Institute of Integrative Oncology
RESEARCH & EDUCATION

Foundations of Integrative Oncology
COURSE

GRAND ROUNDS CALL
With Dr. Nalini Chilkov
September 26th, 2018
Second Wednesday of Every Month
5:30 PM Pacific / 6:30 PM Mountain / 7:30 PM Central / 8:30 PM Eastern

Clinical Pearl: Natural Compounds that Influence Apoptosis and p53 Gene Expression

See the attached slides.

Case Study: 47yo F CRC Adenocarcinoma

Submitted by: *Ana Komazec* (Canada)

Overview: CRC Adenocarcinoma pT3N0, resection, chemotoxicity (Capcetabine+Oxaliplatin) colitis and neuropathy

Core Questions: QOL, Decrease Risk of Recurrence, Which Biomarkers to track, Tx plan guidance

1. The initial health plan below forms the foundation, what would be in priority (additional) nutraceuticals recommended by your expertise? (thus far patient is compliant and determined to improve QOL)
2. With this high risk for CRC recurrence, what would be suggested blood biomarkers for inactive tumor environment? (In Canada, we have trouble getting robust blood work through Universal care, unless specialist requested which we can wait months for)

Recommendations: See separate treatment plan notes

Resource: Excellent Review Paper:
Contemp Oncol (Pozn). 2014;18(4):222-6. doi: 10.5114/wo.2014.44296. Epub 2014 Aug 20.
The effects of selected drugs and dietary compounds on proliferation and apoptosis in colorectal carcinoma. Kiedrowski M1, Mroz A2.

https://www.ncbi.nlm.nih.gov/pubmed/25258577

Questions & Answers

Ana Komazec: **With the popular influx of wide options of IV therapies for cancer patients offered by multiple clinics, have you found that not providing IV therapy has limited the options for your patients, has influenced the therapeutic plan of action, and has limited the efficacy of art and science of cancer care?**

In other words, how important is the IV therapy in today's cancer care programs? Do you collaborate with the clinics who do offer IV therapy, and send your patients for sessions there?

Dr. Chilkov's Response:

I highly recommend IV therapies
Aggressive, high dose, cytotoxic, immune modulation

Considerations:
CYTOTOXIC
IV Vitamin C
IV Curcumin
IV Artesunate

Non Specific Immune Modulation
IV or Sub Q Mistletoe
UltraViolet Blood Irradiation UBI

Other
IV NAD+ CAUTION
Review Article: J Clin Exp Oncol Vol: 5 Issue: 4
NAD+ in Cancer Prevention and Treatment: Pros and Cons (Borut Poljsak)

IV Repletion of vitamin-mineral nutrients Post CT
Myer's: vitamin C, vitamin B5, vitamin B6, vitamin B complex, magnesium, and calcium.
Omega 3 FA
Glutathione

Expert Instructor on IV Therapies-Naturopathic Oncology:
Brendan Cochran ND, practices in Seattle area
Teaches worldwide

Stacy D'Andre: **Can you please discuss the possible anti-cancer properties and other benefits as well as your thoughts on fucoidan supplements as adjunct/treatment for certain cancers?**

Dr. Chilkov's Response:
FUCOIDAN Polysaccharide - Dose 88.5-350 mg daily
CAUTION: high in K+, anticoagulant properties

Summary notes and references from
https://www.mskcc.org/cancer-care/integrative-medicine/herbs/fucoidan

Fucoidan is a sulfated polysaccharide found in the cell walls of many species of brown seaweed, *Undaria pinnatifida*, *Saccharina cichorioides, Laminaria japonica, Fucus vesiculosis, Macrocystis pyrifera*

- Antitumor, Antiangiogenic (VEGF inhibition), Pro-apoptotic
- Anti-T, *Macrocystis pyrifera* thrombotic modulates platelet aggregation
- Anti-metastatic Reduces cell adhesion to ECM, Blocks fibronectin cell binding domain
- Relieves chemotherapy-related gastroenteritis: relieve cyclophosphamide-induced intestinal mucosal injury by altering gut flora, resulting in reduced inflammation and increased expression of tight junction proteins
- Regulates chemotherapy cancer treatment related fatigue

- Reduces the levels of pro-inflammatory cytokines in advanced cancer patients (NFkb, COX 2, TNFa, IFNg, MMP 1, 3, 9)
- Reduces tumor-promoting M2 macrophages
- Stimulates Natural Killer Cells
- Downregulates IGF-IR signaling through PI3K/AKT pathway

CAUTION with concurrent use of anticoagulants-has anti-thrombotic properties

References:
Summary from Sloan Kettering see:
https://www.mskcc.org/cancer-care/integrative-medicine/herbs/fucoidan

Atashrazm, F., Lowenthal, R. M., Woods, G. M., Holloway, A. F., & Dickinson, J. L. (2015). ***Fucoidan and cancer: a multifunctional molecule with anti-tumor potential****. Marine drugs, 13(4), 2327-2346. doi: 10.3390/md13042327*

Chen, S., Zhao, Y., Zhang, Y., & Zhang, D. (2014). ***Fucoidan induces cancer cell apoptosis by modulating the endoplasmic reticulum stress cascades****. PloS one, 9(9), e108157. https://doi.org/10.1371/journal.pone.0108157*

Stacy D'Andre: **What is the dose of astragalus and marrow plus that you find helps most with cytopenias?**

Dr. Chilkov's Response:
Health Concerns Marrow Plus 3 tid

Astragalus: I usually give as a liquid botanical extract (more shelf stable) 2 teaspoons qd up to 2 teaspoons bid. As freeze dried granules 3g bid.

Stacy D'Andre: **Can you please discuss artenimol use in advanced disease?**

Dr. Chilkov's Response:

Artenimol = Dihydroartemisinin is a drug used to treat malaria. Dihydroartemisinin is the active metabolite of all artemisinin compounds and is also available as a drug in itself It is the active metabolite of other artemesia drugs (artesunate, arthemeter)

Sesquiterpenoid derived from Seeds of Artemesia annua (Qing Hao, Sweet Wormwood, Sweet Annie)

Mechanism of action:

Binds to Fe and increases oxidative stress in the cell, damaging mitochondria and DNA (cleavage of endoperoxide bridges by iron, producing free radicals (hypervalent iron-oxo species, epoxides, aldehydes, and dicarbonyl compounds) which damage biological macromolecules causing oxidative stress in the cells)

Alkylating Agent: artemisinin targets a broad spectrum of proteins in the human cancer cell proteome through heme-activated radical alkylation leading to ferropoptosis.

Promotes Ferroptosis, Apoptosis, Cell Cycle Arrest, Decreases Angiogenesis via inhibition of VEGF, Inhibits NFkB

Immune Modulation: Enhances T Cell Proliferation

Cabello, C. M., Lamore, S. D., Bair, W. B., Qiao, S., Azimian, S., Lesson, J. L., & Wondrak, G. T. (2012). ***The redox antimalarial dihydroartemisinin targets human metastatic melanoma cells but not primary melanocytes with induction of NOXA-dependent apoptosis.*** *Investigational new drugs, 30(4), 1289-1301. doi:10.1007/s10637-011-9676-7. PMC 3203350 . PMID 21547369.*

Administered IV as Artesunate

ORALLY as ARTEMESININ (mildly toxic)

Allergy Research Group Super Artemesinin 2 caps tid one week on one week off

180mg artemesinin +20mg Sweet Annie (whole herb) per cap (total daily dose 1080mg)

From Donnie Yance: Recommends taking Artemesinin with Grapefruit Juice and O3FA to enhance absorption and metabolism

From Jonathan Treasure: Adding Butyrate

A recent development is the synergistic combination of butyrate with artemisinin. Butyrate is active against cancer (histone deacetylase inhibition) but also synergizes with artemisinin, increasing its anticancer effects supra-additively. Butyrate is non-toxic and available in supplemental form in 630 mg capsules from Pharmax as “Butyrate Complex”. Unfortunately due to its rapid metabolism, high does of butyrate are requitred to attain effective plasma levels. The standard dose for buyrate is around 10 grams (10,000 mgm) per day which is 5 Pharmax capsules three times a day with meals. Butyrate is only taken with the artemisinin and not during the off week. Side effects of this quantity of butyrate are minimal, although some stomach discomfort, breath or body odor may be noticeable.

Singh, N. P., & Lai, H. C. (2005). ***Synergistic cytotoxicity of artemisinin and sodium butyrate on human cancer cells.*** *Anticancer research, 25(6B), 4325-4331.*

Artemisinin Toxicity

Although artemisinin is cytotoxic (kills cancer cells), as a botanical agent it is much milder than most regular cancer chemotherapy drugs. For this reason, it can be taken continuously over a six-month period. The following is based on our own patients’ experiences.

Symptoms: Symptoms of mild artemisinin toxicity can include cold extremities, numbness, ringing in the ears (tinnitus), or headache. In addition, there may be some gastric discomfort, anorexia and occasional diarrhea. At times, the diarrhea may be moderate to severe. In this case, do not stop the artemisinin, but see if the situation persists. If the diarrhea lasts more than a few days, and involves more than moderate fluid loss, contact your care provider for instructions. All of these mild toxicities are a sign that the artemisinin is

acting effectively and they usually disappear once the body is accustomed to the dosage.

Signs - Slight elevations of liver enzymes (AST and ALT) may be expected. These rises should level off, possibly to a marginally supra-normal baseline during ART. Persistent and increasing elevations have not been associated with artemisinin and should be investigated if present. Bilirubin levels should not be affected. If abnormal reticulocyte counts appear in association with higher doses, this is likely an artemisinin effect. The office will automatically contact individuals whose labs show abnormalities that may be related to ART. *(You are responsible for assuring that lab work is faxed to us in a timely manner).*

Supplements:

- Allergy Research Group Super Artemesinin 180mg/cap
- Natura Health Products Artemis Plus 150mg/cap
- IV Artesunate

Dr. Paul Anderson ND comments on Artesunate IV:

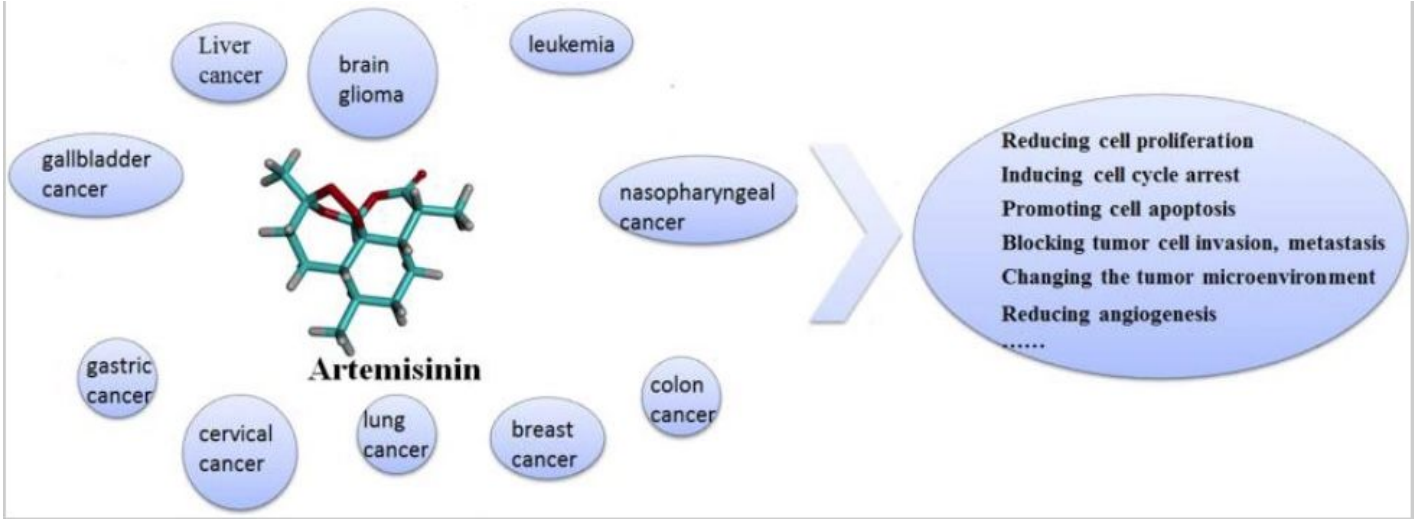
https://www.consultdranderson.com/iv-artesunate-considerations-cont/

1. Artesunate IV (ART) has a t1/2 between 2.5 and 15 min depending on the source read.
2. **It has synergy with the constituents of FOLFOX (as does ascorbate)**
3. In hundreds of co-administrations (in my research and clinical work in and out of hospital settings) of FOLFOX / FOLFIRI / FOLFIRINOX and HDIVC/ART we have seen only synergy and improved patient outcomes.
4. There are no practical, pharmacologic or realistic concerns with concurrent use.
5. **Regarding IV Artesunate administration:** In reality I never (or almost never) do an oral trial for this purpose. Of all the things I have infused into people I have had the safest and least adverse event profile with ART. That said I do sometimes co-administer it with an oral dose, and certainly if a person has a Type-1 allergy to ART I wouldn't use it. I use the Quicksilver brand (no affil) of liposomal ART and dose 5 to 15 mL a day 3 days in a row with 4 days off in cancers of most types as this is the only form that absorbs well. In GI cancers I will use 5 mL of the liposomal ART with a less absorbable form (I like the Allergy Research (no affil) wormwood oil/Artemisinin caps) dosed at 3-4 caps a day (again 3 on and 4 days off).
6. **Liver Enzymes** may go up and down and are almost never of any consequence. They often indicate collateral immune activity in hepatocytes which may have nothing to do with the CA (like HHV viri) or may be related to mets or potential mets. I simply watch them over time and make note. Of course if the patient has preexisting biliary obstruction then you may need further assessment.
7. **Iron** – everyone worries about iron and ART. Part of the MOA is to flip electrons with Fe (and Cu) similar to IVC. ART patients may have some drop in iron studies over time so watch it (in my experience it is 10-20% of people) but you almost never need to give iron to compensate. The ART works even in significant anemia. This(need for iron compensation) is a fallacy based on inaccurate extrapolation of ART MOA. In cancer patients the rules for iron administration are clinically guided and I have written about them in other papers.
8. Otherwise we see very good tolerance to IV ART. We normally do the ART-IVC twice a week

with the same IVC escalation and formulas (unless they have been doing IVC and are set at a dose already, then you don't need to re-escalate.) We will try for 16-20 total tx at twice a week and reassess.

RECENT PAPER (2018)

Zhang, Y., Xu, G., Zhang, S., Wang, D., Prabha, P. S., & Zuo, Z. (2018). ***Antitumor Research on Artemisinin and Its Bioactive Derivatives.*** *Natural products and bioprospecting, 1-17.* http://doi.org/10.1007/s13659-018-0162-1 (168 references)



- Artemisia annua. (2015). cam-cancer.org/The-Summaries/Herbal-products/Artemisia-annua/(merge)
- Artemisia annua. (2015). mskcc.org/cancer-care/integrative-medicine/herbs/artemisia-annua
- Artemisia annua L. (n.d.). powo.science.kew.org/taxon/urn:lsid:ipni.org:names:304416-2
- Bhaw-Luximon A, et al. (2017). Artemisinin and its derivatives in cancer therapy: Status of progress, mechanism of action, and future perspectives. DOI: 10.1007/s00280-017-3251-7
- Das AK. (2015). Anticancer effect of antimalarial artemisinin compounds [Abstract]. DOI: 10.4103/2141-9248.153609
- Lai H, et al. (2005). Targeted treatment of cancer with artemisinin and artemisinin-tagged iron-carrying compounds [Abstract]. DOI: 10.1517/14728222.9.5.995
- Meshnick SR. (2002). Artemisinin: Mechanisms of action, resistance and toxicity. DOI: 10.1016/S0020-7519(02)00194-7
- National Cancer Institute. (n.d.). Antioxidants and cancer prevention [Fact sheet]. cancer.gov/about-cancer/causes-prevention/risk/diet/antioxidants-fact-sheet
- Tompa R. (2008). Scientists develop new cancer-killing compound from salad plant. washington.edu/news/2008/10/13/scientists-develop-new-cancer-killing-compound-from-salad-plant/

Stacy D'Andre: **Do you have any experience with ellagic acid for neutropenia in patients on therapy?**

Dr. Chilkov's Response:
Ellagic acid is a phytophenol found in red berries (highest in raspberries, strawberries) and pomegranates. It is not possible to ingest enough ellagic acid to exert a pharmacologic effect on neutropenia. Not easily absorbed. It does act as a potent antioxidant and positively influences the Estrobolome. A healthy microbiome is required to increase bioavailablity ellagic acid.

Ellagic acid and Ellagitannins are widely studied for their antioxidant and antiproliferative effects. Also antagonizes growth promoting effects of 17-*b*-Estradiol via its metabolite Urolithins A & B.

I could not find any studies on ellagic acid and neutropenia.

For myelosuppression and especially neutropenia and leukopenia:
I primarily use

- Health Concerns Marrow Plus
- Natura Health Products Immucare One
- Astragalus Extract
- Acu Point Su San Li Stomach 36

Ismail, T., Calcabrini, C., Diaz, A. R., Fimognari, C., Turrini, E., Catanzaro, E., ... & Sestili, P. (2016). ***Ellagitannins in cancer chemoprevention and therapy. T****oxins, 8(5), 151. doi: 10.3390/toxins8050151*

Research: NCI: Annual Report to the Nation on the Status of Cancer

https://www.cancer.gov/research/progress/annual-report-nation

The most recent Annual Report to the Nation on the Status of Cancer was released on **May 22, 2018.**

According to the report:

- Overall cancer death rates continue to decrease in men, women, and children for all major racial and ethnic groups.
- Overall cancer incidence rates, or rates of new cancers, have decreased in men and remained stable in women.
- Overall prostate cancer incidence rates declined. Incidence of distant disease increased, and after decades of decline, prostate cancer mortality leveled off.

Between 2010 and 2014, seven of the 17 most common cancers in men showed decreases in incidence: prostate, lung and bronchus, colon/rectum, bladder, esophagus, brain and other nervous system, and larynx. Prostate cancer had the greatest decrease in incidence. Leukemia, melanoma, myeloma, and cancers of the kidney, liver, oral cavity, pancreas, and thyroid in men showed increases in incidence between 2010 and 2014, with liver cancer having the greatest increase. On average, the overall cancer incidence rate in men decreased 2.2 percent per year.

Between 2010 and 2014, seven of the 18 most common cancers in women showed decreases in incidence: non-Hodgkin lymphoma, bladder, brain and other nervous system, cervix, colon/rectum, lung and bronchus, and ovary. Colorectal cancer had the greatest decrease in incidence. Leukemia, melanoma, myeloma, and cancers of the breast, uterus, kidney, liver, oral cavity and pharynx, pancreas, and thyroid showed increases in incidence among women between 2010 and 2014. Liver cancer had the greatest increase. The overall cancer incidence rate in women on average did not change year by year between 2010 and 2014.

Female Breast Cancer

- **Estimated New Cases 2018:** 268,670 *
- **Estimated Deaths 2018:** 41,400 *
- **5 year survival varied by stage at diagnosis from 26.5% (stage IV) to 100% (stage I) for cases diagnosed between 2007 and 2013.**

- **Overall incidence rate increased from 2010-2014:** rising for all races highest in whites lowest among Asian or Pacific Islanders
- **Overall mortality rate decreased from 2011-2015**: decreasing for all races except American Indian/Alaskan Natives and API highest in blacks lowest among API

Research: Proportion and number of cancer cases and deaths attributable to potentially modifiable risk factors in the United States

Islami, F., Goding Sauer, A., Miller, K. D., Siegel, R. L., Fedewa, S. A., Jacobs, E. J., ... & Flanders, W. D. (2018). ***Proportion and number of cancer cases and deaths attributable to potentially modifiable risk factors in the United States.*** *CA: a cancer journal for clinicians, 68(1), 31-54. doi: 10.3322/caac.21440.*

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**.

FACTORS
Highest incidence of cancers and deaths

- cigarette smoking
- secondhand smoke
- excess body weight
- alcohol intake

Other Attributable Factors

- consumption of red and processed meat
- low consumption of fruits/vegetables
- low consumption of dietary fiber
- low consumption of dietary calcium
- physical inactivity
- ultraviolet radiation
- cancer-associated infections HCV, HBV, HPV, EBV, HTLV-1, H.pylori, HIV-1, Kaposi sarcoma herpes virus, Helminths: Schistosomes, Liver Flukes

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).

Molecular mechanisms of the preventable causes of cancer in the United States.

Golemis EA, Scheet P, Beck TN, Scolnick EM, Hunter DJ, Hawk E, Hopkins N.
Genes Dev. 2018 Jul 1;32(13-14):868-902. doi: 10.1101/gad.314849.118. Epub 2018 Jun 26. Review.

Modifiable Lifestyle Factors: Opportunities for (Hereditary) Breast Cancer Prevention - a Narrative Review.

Lammert J, Grill S, Kiechle M.
Breast Care (Basel). 2018 Apr;13(2):109-114. doi: 10.1159/000488995. Epub 2018 Apr 20. Review.

Annual Report to the Nation on the Status of Cancer, part I: National cancer statistics.

Cronin KA, Lake AJ, Scott S, Sherman RL, Noone AM, Howlader N, Henley SJ, Anderson RN, Firth AU, Ma

J, Kohler BA, Jemal A.
Cancer. 2018 Jul 1;124(13):2785-2800. doi: 10.1002/cncr.31551. Epub 2018 May 22.

Population attributable fractions continue to unmask the power of prevention.
Bray F, Soerjomataram I.
Br J Cancer. 2018 Apr;118(8):1031-1032. doi: 10.1038/s41416-018-0062-5. Epub 2018 Mar 23.

PHYTOCHEMICALS THAT REVERSE INHIBITION OF APOPTOSIS

PART ONE
Bcl-2 Protein

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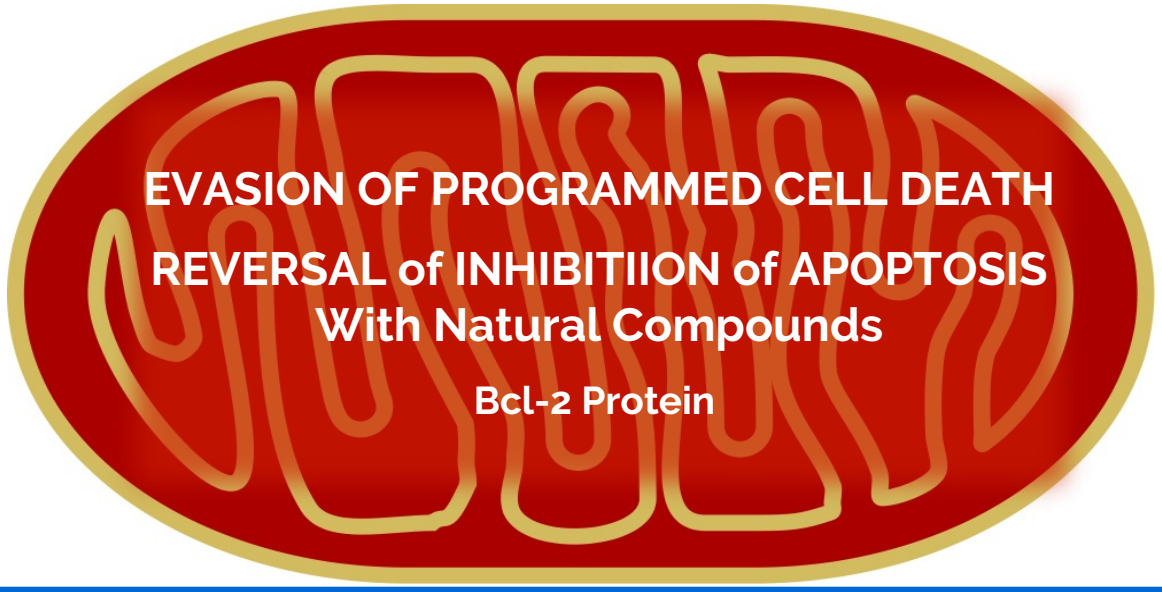

EVASION OF PROGRAMMED CELL DEATH

REVERSAL of INHIBITIION of APOPTOSIS With Natural Compounds

Bcl-2 Protein

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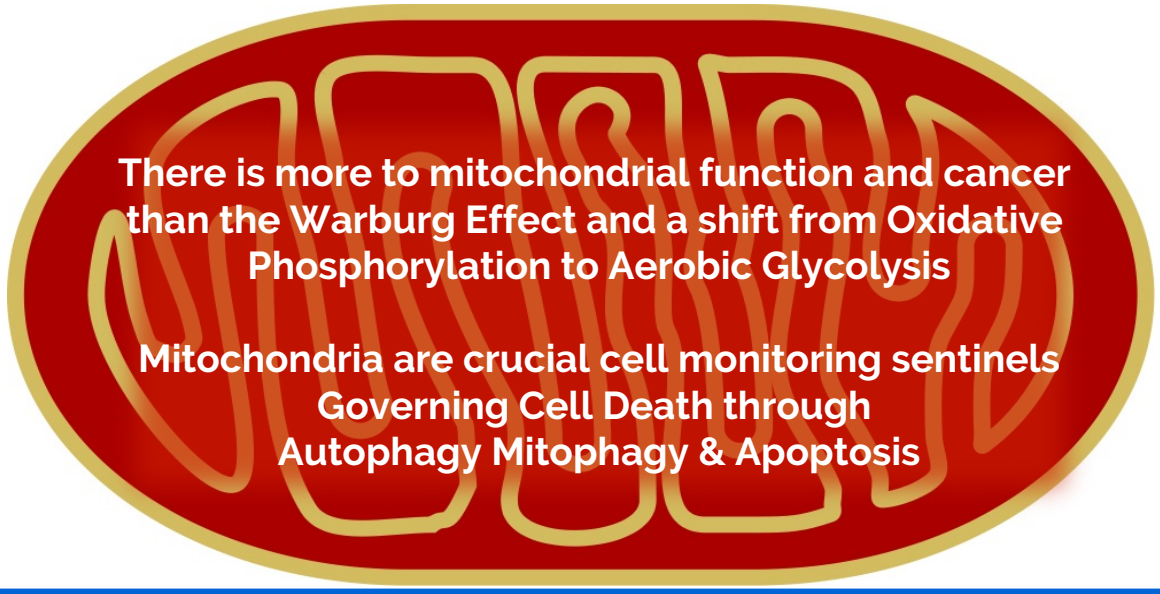

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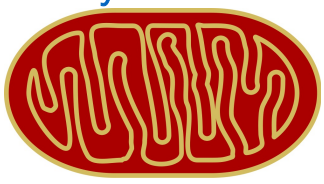
Chemoprevention by Promotion of Apoptosis



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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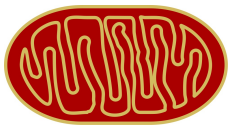
Chemoprevention by Promotion of Apoptosis



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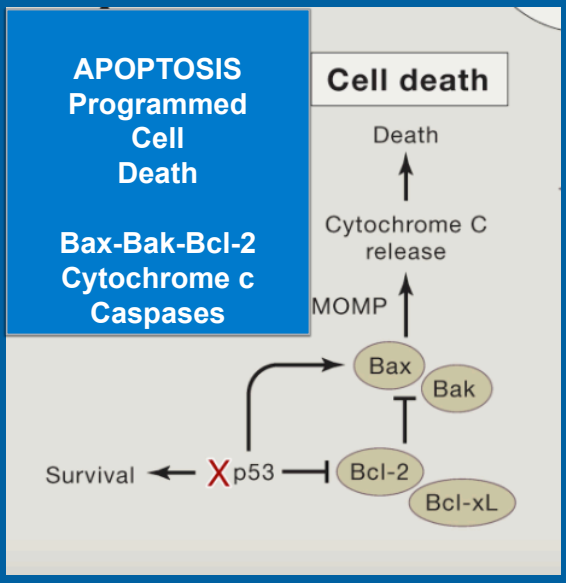
A Hallmark of Cancers is their ability to Evade Cell Death, a phenomenon tightly linked to mitochondria.

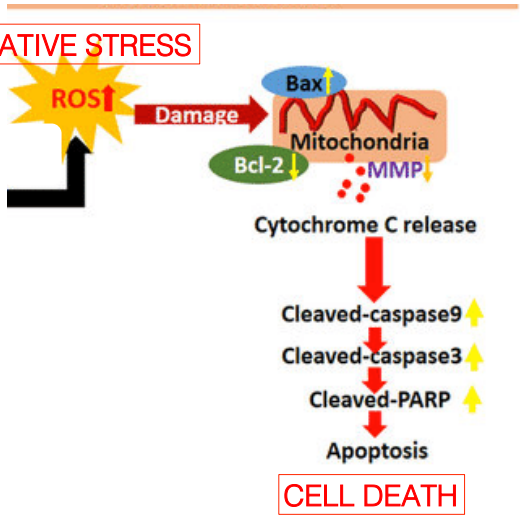
The pro-apoptotic Bcl-2 family members Bax and Bak are recruited to the OMM and oligomerize to mediate
Mitochondrial Outer Membrane Permeabilization (MOMP)

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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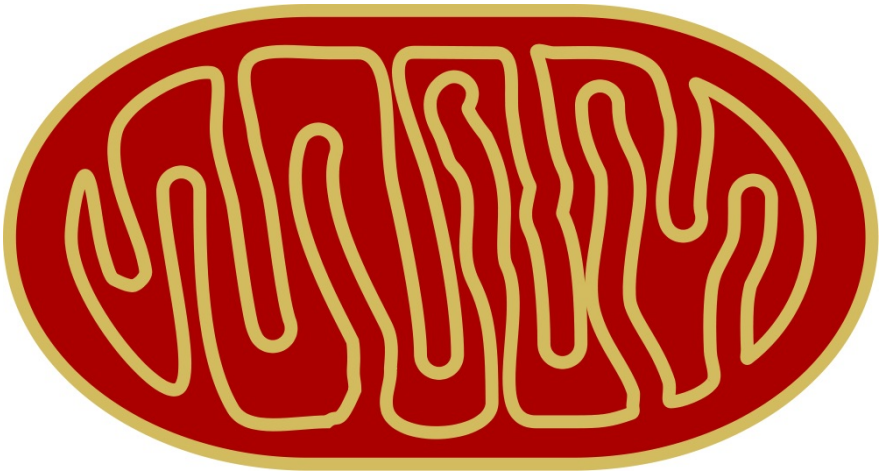
MODULATION OF MITOCHONDRIAL-DEPENDENT BCL2 APOPTOSIS PATHWAYS BY NATURAL COMPOUNDS



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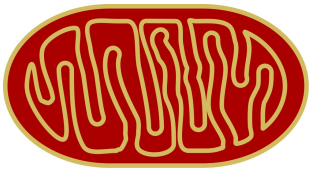

High levels of mutated Bcl-2 are associated with most types of human cancer

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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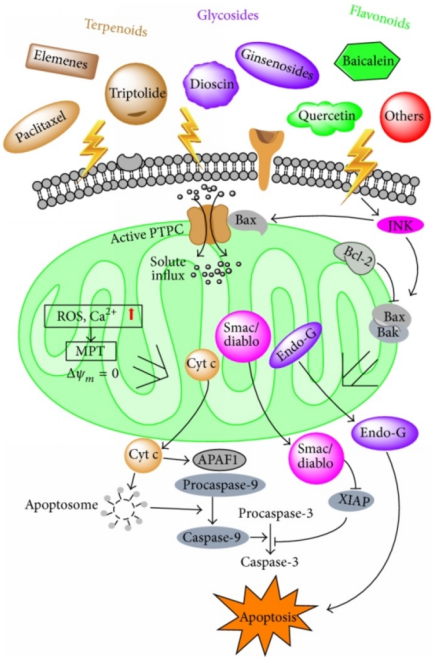
Modulation of mitochondrial-dependent apoptosis pathways by natural compounds

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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CASE STUDY SUBMISSION

Important: In observance of HIPAA and the sacred trust between care giver and patient, absolutely no patient names or identifying information is to be disclosed. Patient privacy is to be preserved. If you attach any medical records, pathology, surgical or laboratory reports, all names are to be removed.

Date	August 08, 2018
Clinician Name & Credentials	Komazec, Ana HBSc DHMHS RNCP/ROHP CFMP MSc (c)
Email	akomazec@gmail.com

Describe Your Patient (Please SUMMARIZE and use economy of words. You will have 15 minutes to present)

Age, Gender & Ethnicity	47yo Female, Married, Croatian Ethnicity , Occupation: Taxi owner/driver
Body Type	Slim (lack in musculature) , 173 cm, 64kg, BMI: 21.4 (July 6 2018 BIA Test); Pulse:66 O2sa:99%
Values *What is most important to this patient? (Quality of Life, Decision Making, Side Effects?)*	To reduce reocurrance, To improve and implement a nutrition and lifestyle plan, Improving quality of life. She comes with an overall positive outlook of her recent diagnosis. She is aware of the worst case scenario, and her high risk for reoccurance. She is also aware of how her current lack of nutrition is imperative to be modified as primary foundational platform.
Stress Resilience	Work mild stress. Adequate and content support from husband and friends. Positive mindset.
Other	Multiple dental bridges, Hg fillings removed in past. Hx Smoking. Currently 3 cigs per day (with desire to quit) Negates traumas, health history clean. Mild synovitis of 2nd MTP joint 2017,
Primary Diagnosis & Date *(ex. Breast Cancer L, T3 N1 M0, BRCA1 positive, grade 3, Ki67 > 45%)*	April 2018: Stage II Colon Cancer , MSS stable , T3, Positive LVI, Negative PNI, Margins clear, 0 out ot 31 lymph nodes, high risk features: LVI, larger tumor with some obstructive symptoms at presentation
Secondary Diagnosis *(ex. Diabetes Type 2, Obesity)*	Chronic Rhinitis over 20 years, Allergies (hayfever)

Patient Status

☐ New Diagnosis ☐ Recurrence ☑ In Treatment ☑ In Recovery ☐ In Remission ☑ At Risk

Concomitant and/or Complicating Factors *(ex: poorly controlled diabetes, insomnia, poor support system)*	Resected Stage II Colon Cancer, Status post resection Intolerance to adjuvant chemo Capecitabine and Oxaliplatin (had 2 cycles neuropathy)--> Capecitabine induced colitis.
Adverse Effects of Cancer or Cancer Treatments *(ex. anxiety-depression, diarrhea, peripheral neuropathy)*	Neuropathy (oxaliplatin sensitivity) Anticipatory nausea with intake of Capecitabine, Capecitabine induced colitis, Cold sensitivity Metalic taste , Short term memory, GERD
Relevant Laboratory, Pathology & Medical Reports *(attach a PDF with patient identifying information removed or summarize)*	Hospital oncology lab work most recent July 9th 2018 without CEA marker. Overall: Liver enzymes ALT 60 U/L, AST 38H U/L, LD 596 U/L (higher normal), WBC 3.9 L X10(9)L, RDW 20.2%,

Brief Summary of Recent History

January 2018: Sudden abdominal pain LLQ radiated to RLQ, CT scan narrowing inflamamtion at descending colon proximal to sigmoid colon junction, Treated as diverticulitis with antibiotics (Abx). Blood in stool thereafter Abx. Colonoscopy February 2018: adenocarcinoma multiple biopsies from circumferential mass at 40 cm. No evidence of Metastasis. April pathology report revealed low grade adenocarcionoma 6cm. Large vessel invasion and obstructive symptoms as high risk features. CT scan showed renal hepatic cysts incompletely assessed. Preoperative CEA 3.
Past medical history non significant no prior surgeries, no previous complaints.No family history of cancer. No alcohol intake. History of smoking, quit 10 years ago 30 pack /year, now consumes 3 cigarettes per day .

Brief Summary of Additional Relevant Health, Medical, Psycho-Social and/or Family History

Childhood Birth Jaundice. Hx of multiple antibiotics, Hx of Anemia, Hx of chronic rhitnitis since her 20's allergic hayfevers,
Mother left her at 6 months, brought up by grandparents (paternal) , Father death at her age of 20 in car accident, Grief unresolved (her view she could not change the outcome). Her outlook: what is point of suffering if you can not change something ,usually issues ignored. Good marriage, supportive husband, content with her life thus far. Lovely woman to work with.

Other Relevant Information

Such as Chinese or Ayurvedic diagnosis, Naturopathic/Homeopathic Information, etc. *(ex. Liver Qi Stagnation, Dysbiosis)*

Unconfirmed dysbiosis due to history of use of antiobitics, most recent use of fluorobionoles (aware of its toxicity), (GI MAP, GPL OAT)

Brief Summary of Relevant Past Oncology or Medical Treatments

(ex. surgery, radiotherapy, chemotherapy, immunotherapy, hormone therapy, drug therapy)

May 2018 to begin: 4 cycles of Capecitabine and Oxaliplatin
Rx June 29 2018 ER discharged with Dx capecitabine induced colitis, nonneutropenic with symptoms of nausea, vomitting, fever, abdominal pain, abnormal adenopathy on ultrasound: Ciprofloxacin (fluoroquinolone) 500 mg p.o BID until July1 2018. Flagyl 500 mg po BID until July 1 2018. Pantoprazole 40 mg , Ranitidine 150 mg BID for 5 days, Imodium 2 mg QID for diarrhea.

Summary of Recent and Current Treatments

Medical Oncology Care *(surgery, radiotherapy, chemotherapy, immunotherapy, hormone therapy, drug therapy)*

April 10, 2018: Left hemicolectomy
May 2018: Adjuvant chemotherapy with Capecitabine and Oxaliplatin 4 cycles (tolerated to completion only 2 cycles)

Integrative Oncology Care *(nutraceutical, botanical, phytochemical, acupuncture, energy medicine, other)*

None to report from diagnosis until our initial consult.

Your 2 Core Questions (stated clearly and succinctly)

1. The initial health plan below forms the foundation, what would be in priority (additional) nutraceuticals recommended by your expertise? (thus far patient is compliant and determined to improve QOL)
2. With this highrisk for CRC reoccurance case, what would be suggested blood biomarkers list for not active tumor environment? (In Canada we have trouble getting robust blood work through Universal care, unless specialist requested which we can wait months for)

Attached Medical Records for Reference (with patient identifying information removed)

Recent July 9 2018 Lab, Pathology April 2018

PROPOSED TREATMENT PLAN Your case will not be reviewed without a completed proposed treatment plan

Nutriceutical, Phytochemical and Botanical Supplements (name of supplement, dosing)

Foundation Nutrition Supplements:

DFH OmegaAvail 2Tdaily with meal; Solray Liposomal Vit D3/K2 (PE) 8 000 IU per day divided (monitor/adjust serum 25 OH Vit D every 3 months), GALT Fortifier 2c TID (PE), Hypozymase 2 c TID before meal (PE digestives enzymes), Methyl B 12 Liposomal (after 2 months of opening up drainage pathways, working on nutrient uptake, pH balance, enzyme and colon health, and hydration, rassess and see if methylation restoration is to proceed by using correct absorbable formula methyl/adnenosyl/hydroxy); Probiotics (starting with Ultimate Flora critical care by Renew Life 1 c BID meal, then will move to Klaire Labs broad spectrum and rotate every 4 months, Sacc Boul if GI MAP results call for normalization of flora); Lymph 2 (PE 30 drops TID); Nat Colon 2c at night (PE)

Targeted Supplements:

Formulated Herbals: Viriditas Herbs : Hepato Pure Formula (Taraxum off. radix, Silybum ma., Bupleurum spp, Chionanthus virginicus, Glycerrhiza gl., Berberis vul., Schizandra ch., Androgaphis Pann.) 1 tspn TID for 30 day= 500 ml ; Deep Immune Activation Formula (Astragalus mem., Bupleurum spp., Ganoderma luc., Agaricus Bla., Ganoderma applanatum, Lentinus edodes, Glycerrhiza gla.,Eleutherococcuss senti., Inonotus ob., Grifola frondosa, Trametes vers., Ascorbic acid, Phellinus ignarius) 1 tspn TID for 30 day= 500 ml
JHS Coriouls versicolor, 3 g/day ; Melatonin iIposomal (PE) adjust to goal depending on stage dx, 10 g,
Heart Song Millieu (Body Mind heart Tonic, Homeopathic tonifier , PE) ; Bio A Curcumin 3.5 g per day

Functional Foods and/or Therapeutic Shake

Renew Food Plan with Pescatarian focus increasing fibre to 35g per day (adjust to sx as increasing g) Protein start 60 g per day
Therapeutic Shake: Sunwarrior Protein (25g p), Hepatagest Powder (Liver detox 1 and 2 Physica Energetics PE) 1scoop, VIta LF 1 scoop (Greens Physica energetics PE), L Glutamine 1 scoop (10 g), 14 strains of mushrooms (harmonic arts 2 tbspn), 3 tbspn Hemp seed, Probiotics, MCT oil 2 teaspoon, Maqui berry 1 tspn (harmonic arts) ,Flaxseed 2 tbspn (ground fresh), 1/2 avocado, 1c blueberries, coconut water/ almond milk.
Hydration: 2. 5 L of filtered H2O with Spectralyte 20 drops per 1 oz H2O (ionic trace minerals, electrolytes PE)

Dietary Guidelines

Reduce exposure to copper in suppx
Bone marrow (organic sourced local farm Leapple) bone broth adding Astragauls, Shitake mushrooms, sea vegetables (remineralization, collagen, glutamine)
DGL if GERD persists
If pt decides to return to adjuvant chemo; oxaliplatin (for neuropathy), Suggest IV Ca/Mg before and after infusion, Acetyl L carnitine 1500-2000 mg/d, Increase l- glutamine to 20 -30 g/d,

Lifestyle Guidelines

She has been living an active lifestyle, prior to diagnosis, continues to go to gym 3-4 x per week, 45 minutes per session. Suggested to incorporate yoga, meditative exercises, swimming, and use of available sauna to detox to tolerance. Prior to use of sauna she was advised to use tailored supplement program to improve detoxification and support the pathways of elimination.

Recommended Diagnostics

Gi MAP (based on results after the foundational work above, anti microbial program will be applied to reduce toxic vir/bac/par/fung load)
GPL OAT (nutrient def, mitochondrial, neurotransmitter profile, krebs cycle, not priority as GI MAP)

Referrals to specialists

Chiropractor , NSA technique (CNS focus); TCM trained Accupuncturist; Local ND for IV vit C (1x per week), test G6PD

Other Notes (please do not include additional notes in your email – notate them here within the case study)

Dr.Chilkov, We have a self motivated individual who is keen to reduce her chances for reocurrance, and has deep desire to improve her lifestyle, we have a platform where we can practice preventative measures and monitor over the years while working on the pieces of systems biology primary causes, starting with gut flora and GALT. Would you be kind to help me with what lab parametes to look for over the years that would help us monitor her progress with regards to tumor resurgance. Respectfully ,Ana.

Colorectal Cancer. Female age 47 Croatian (toxic exposures???)
Low Grade Invasive Adenocarcinoma pT3N0
Resection
And 2 of 4 rounds of CT
CHEMOTOXICITY RELATED COLITIS D/C CAPECETABINE (THYMIDILATE SYNTHASE?) AND D/C OXALIPLATIN

Moderate Risk of Recurrence. (large tumor mass, low grade, no + nodes)

Naturopathic Oncology
Victoria BC. Neil McKinney ND. Vital Victoria Naturopathic Clinic (888) 722-6401
Toronto Akbar Khan ND. Medicor Cancer Centre. 1.888.622.6644

Lynch Syndrome ruled out (MisMatch Repair) Genetic analysis??
Hereditary nonpolyposis colorectal cancer (HNPCC) or Lynch syndrome is an autosomal dominant genetic condition that has a high risk of colon cancer as well as other cancers including endometrial cancer (second most common), ovary, stomach, small intestine, hepatobiliary tract, upper urinary tract, brain, and skin. Usually CA dx under 50yo.

Any additional tumor analysis?
Expression of Sialyl Lewis Antigens (Cimetidine v effective)

<u>Additions to Your Treatment Plan</u>
***Baby aspirin dailly**
***Cimetidine (OTC Tagamet) daily 800mg daily (many studies on CRC and Cimetidine)**
***COX 2 Inhibition** (ASA, Omega 3 FA, Curcumin, Tocotrienols, Boswellia)
(Simvastatin-lipophilic- associated with lowered risk of CRC)
Natural Statin also impacts CRC control **Red Yeast Rice. 4 caps at bedtime**

Tocotrienols. 250 mg bid
Pure Honokiol 500mg bid and at Bedtime
Broccoprotect 1 bid. (sulphoraphane)
Boswellia AKBA (Tx related Colitis, CRC)
Curcumevail 2 bid 2 grams Curcumin twice daily
EGCG 1 gram twice daily
Omegavail TG 1000 2 2x/day. 2g day
Berberine 1000 mg bid
Oil of Oregano 1 bid
Allergy Research Group Super Artemesinin one week one one week off. 2/2x/dY

L-Glutamine 5 g bid (colitis)

Impaired Detoxification
Detox Anti Ox 2 bid
N Acetyl Cysteine 900mg 1 bid
Milk Thistle 3 grams daily

BEDTIME
Red Yeast Rice 4 caps (1200mg) (CRC)
Melatonin 10-20 mg (CRC)

Important Probiotics
Lactobacillus Reuteri
Lactobacillus acidophilus
Bifido bacterium longum
Streptococcus thermophilus
Lactobacillus salivarius
Pedioccus pentosceus

Prebiotics:
Saccharomyces boulardii
PaleoFiber 1-2 heaping teaspoons

******Hx of C Difficile: BIO-K live probiotic 1 container daily**

CUSTOM HERBAL TONIC

Tumor Control, Immune Modulation, Inflammation Control

Digestive Support

2 teaspoons daily with food or shake

Shake Well

Dilute in warm water or ginger tea

480 ml	240ml	
60	30	Astragalus and Ganoderma Formula
30	15	Minor Bupleurum Formula
40	20	Polygonatum Solomon's Seal
60	30	Salvia Milthiorrhiza Dan Shen
70	35	Heydotis-Oldenlandia Bai Hua She She Cao (Ursolic Acid)
60	30	Scutellaria baicalensis Huang Qin
60	30	Cameila sinensis Cha Ye (Green Tea)
40	20	Magnolia Bark Hou Po (Ursolic Acid)
40	20	Fu Ling Pi. Poria cocos
10	5	Tangerine Peel Chen Pi
10	5	Licorice root Gan cao

IV THERAPIES

IVC to be cytotoxic and exert control needs to be high dose 2-3x week x 8-12 weeks

Consider
IV or sub Q mistletoe
IV Artesunate
IV Curcumin
Oral Cimetidine
Low Dose Naltrexone. 4.5mg hs
TCH CBD (available in Canada?)

Biomarkers
Get a baseline and watch trend
CBC. Watch NLR. (CURRENT 1.0. POSITIVE PROGNOSIS)
CMP
CEA
CA-19.19
hsCRP
LDH
GGPT
LFT
Serum Cu. *If Cu and Cp are not in lower quartile of nl consider oral Cu Chelation Rx*
Serum Zn. *Cu:Zn 1:1*
Ceruloplasmin
Ferritin
Serum Fe, IBC % Sat
D Dimer
FIbrinogen
Hgb A1c
IGF-1

GENOMICS
Check her Methylation and Detoxification SNPS

Stool, Digestive and Microbiome Analysis. (must have high butyrate in gut for cancer resistance)

Intermittent Fasting 13+ hours no calories. (dinner>>>next breakfast)

OutSmart Cancer Diet-Modified Paleo-Keto, no red meat, very little animal protein, pescatarian, vegan is best

Low Carb, Low Sugar, Low Starch, Anti-Inflammatory, Gluten Free (Dairy free?)
Healthy Fats and Oils
Rainbow of colors: vegetables that grow above ground,

Limit fruit to 1 cup berries daily 60 grams+ protein daily

LIFESTYLE
Exercise: Minimum 30 min+ moderate exercise daily (Sweat)
Sleep 7-9 hours nightly
Meditation, Prayer, Visualization
Skin Dry Brushing to stimulate lymphatic drainage

CYTOTOXIC SEASONAL HERBAL THERAPY PLUS IV THERAPY

Combine protocol below concurrently with IV Vit C or IV Artesunate. (a cytotoxic therapy)
10-14 days once every three months
(every solstice and equinox is a simple way to remember)

CytoToxic Compound- for 10 days only once per season
1/2 teaspoon 3x/day diluted in warm water or tea with food or shake
(Suspend regular tonic during this time)

40 ml Polygonatum (Solomon's seal) root
20 ml Taxus brevifolia (Yew) tips
20 ml Catharanthus (Madagascar Periwinkle) Leaf
40 Phyto Cyto (Asimina triloba, Taxus brevifolia, Catharanthus rosea, Viscum album, Phytolacca americana, Podophyllum pelatum)

PLUS
ARG Super Artemesinin 3 caps twice daily for 10 days once per season

If possible also add Hyperbaric Oxygen Therapy during this cycle

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Review

Fucoidan and Cancer: A Multifunctional Molecule with Anti-Tumor Potential

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Abstract: There is a wide variety of cancer types yet, all share some common cellular and molecular behaviors. Most of the chemotherapeutic agents used in cancer treatment are designed to target common deregulated mechanisms within cancer cells. Many healthy tissues are also affected by the cytotoxic effects of these chemical agents. Fucoidan, a natural component of brown seaweed, has anti-cancer activity against various cancer types by targeting key apoptotic molecules. It also has beneficial effects as it can protect against toxicity associated with chemotherapeutic agents and radiation. Thus the synergistic effect of fucoidan with current anti-cancer agents is of considerable interest. This review discusses the mechanisms by which fucoidan retards tumor development, eradicates tumor cells and synergizes with anti-cancer chemotherapeutic agents. Challenges to the development of fucoidan as an anti-cancer agent will also be discussed.

Keywords: fucoidan; cancer; apoptosis; synergy

1. Introduction to Cancer

Cancers are multifactorial diseases of various etiologies. They arise largely as a result of acquired genetic changes that alter cell function leading neoplastic cells to gain survival or growth advantages [1]. For cancer cells to survive, the generation of new blood vessels (angiogenesis) is required. Cancer leads to death mostly through tumor cell spread to distal organs (metastasis). Various pathways are disrupted in tumor development, which result from unbalanced programmed cell death, disordered signaling pathways, angiogenesis and poor immune response against cancer. Most of the chemotherapeutic agents used in cancer treatment target these major deregulated pathways. Unfortunately, as many of these therapies cause severe side effects, the toxicities limit the dose and thus the efficacy of treatment. Therefore, there is strong interest in developing better-tolerated anti-cancer agents.

2. A Role for Natural Products for Cancer Treatment

Chemotherapy has been a cornerstone of the standard cancer treatment regimens since the 1960s. A variety of chemicals ranging from traditional agents such as methotrexate and folic acid analogues to novel chemicals such as anthracyclines have been used in cancer treatment [2]. Despite promising tumor growth-inhibitory effects in pre-clinical tests, many fail in clinical trials when adverse unexpected side effects are revealed. Traditionally anti-cancer chemotherapy targets rapidly dividing and proliferating cells. Therefore, normal cells which have high-proliferating potential are also affected.

Novel therapeutic agents are designed to target specific molecules (targeted therapy). However, these targeted therapies are not always completely free of side effects either. For instance, vemurafenib, a B-Raf enzyme inhibitor, is specific for oncogenic mutant V600E B-Raf positive melanoma cells. This drug was the first targeted molecular therapy, which was approved for use in advanced stages of melanoma. Although vemurafenib has shown significant beneficial anti-cancer effects, several studies have reported the rapid emergence of acquired resistance and adverse dermatological effects. It also stimulates B-Raf expression in V600E B-Raf negative patients promoting melanoma growth [3,4]. Monoclonal antibodies are another example of targeted therapy and are designed to specifically target the cancer antigens located on tumor cells. Monoclonal antibodies are generally safer than chemotherapy and the side effects caused by them include mild allergic reactions such as urticaria. But they can also cause severe reactions such as infusion reactions and serum sickness. As an example, rituximab (anti-CD20), which is widely used in treating B-cell lymphoma, generally causes only mild toxicities, however, reports have described occasional cases with severe complications such as anaphylactic reactions and myocardial infarction as well as high risk of tumor lysis syndrome in patients who have a high burden of tumor cells in their circulation [5].

Concerns over toxicity, tumor cell resistance and development of secondary cancers from chemotherapeutic chemicals have generated interest in exploiting natural products for cancer treatment. Flavopiridol is a flavonoid derived from the indigenous Indian plant *Dysoxylum binectariferum*, which inhibits cell cycle progression. It is the first cyclin-dependent kinase (CDK) inhibitor to be approved for use in clinical trials [6]. Natural products are also being tested as adjuvants for use in synergy with chemotherapeutic agents. For example those with immunomodulatory effects can reduce immune

suppression and the associated increased risk of infection. In George *et al.* [7] study, *Indukantha Ghritha* (IG), a polyherbal preparation consisting of 17 plant components, was used as an adjuvant to cyclophosphamide cancer chemotherapy and shown to stimulate the hematopoietic system and induce leukopoiesis in tumor-bearing mice. When administrated in combination with cyclophosphamide, it reversed myelosuppression induced by cyclophosphamide suggesting its potential to minimize or reverse chemotherapy-induced leukopenia.

Polysaccharides include a large family of diverse biopolymers. They are constituted by monosaccharide residues linked together by *O*-glycosidic bonds that are found in natural and semi-synthetic structures [8]. Due to structural diversity, polysaccharides display the highest biological properties among macromolecules. Many natural polysaccharides obtained from natural sources such as plants and algae have anti-cancer properties. The multifunctional structure of natural polysaccharides also allows them to be used in conjugation with anti-cancer agents that lack physiochemical and biopharmaceutical properties [8,9].

3. Fucoidan

Fucoidan is a natural sulfated polysaccharide that exists mainly in the cell wall matrix of various species of brown seaweed such as mozuku, kombu, limumoui, bladderwrack and wakame [10]. Various forms of fucoidan have also been recognized in some marine invertebrates such as sea urchins [11] and sea cucumbers [12]. The brown seaweeds containing fucoidan are widely consumed as part of the normal diet in East Asia, particularly Japan, China and Korea.

3.1. Fucoidan's Anti-Cancer Potential

The anti-cancer property of fucoidan has been demonstrated *in vivo* and *in vitro* in different types of cancers. Nevertheless, it has been rarely investigated for its anti-cancer properties in clinical trials. Fucoidan mediates its activity through various mechanisms such as induction of cell cycle arrest, apoptosis and immune system activation. Additional activities of fucoidan have been reported that may be linked to the observed anti-cancer properties and these include induction of inflammation through immune system, oxidative stress and stem cell mobilization. These activities have been reviewed by Kwak [13].

3.1.1. Fucoidan and Cell Cycle

Fucoidan treatment results in sub G0/G1 cell accumulation (suggestive of dead cells/apoptotic cells) in a variety of cell types [14,15]. It can also induce cell cycle arrest in other phases; Riou *et al.* [16] and Mourea *et al.* [17] reported arrest in G1 phase in a chemo-resistant non-small-cell bronchopulmonary carcinoma line by fucoidan from *Ascophyllum nodosum* and *Bifurcaria bifurcate*, respectively.

In an investigation of the mechanism of the action, fucoidan demonstrated significant down regulation of cyclin D1, cyclin D2 and CDK4 in cancer cells [18–20]. The crude fucoidan from *Fucus vesiculosus* increased the level of p21/WAF1/CIP1 in PC3 cells and down-regulated E2F; a transcription factor that controls progression of cells from G1 to S phase [18].

Table 1. Effects of fucoidan on cell cycle and apoptosis molecules.

Ref	Cell Type	Fucoidan Source	Dose (μg/mL)	Effects on Cell Cycle	Effects on Apoptosis Pathways Extrinsic	Intrinsic	Common
[15]	Human lymphoma HS-sultan cells	*F. vesiculosus*	100	• ↑ sub G0/G1 • No G0/G1 or G2/M arrest	-	• ↓ MMP	• Caspase 3 activation
[20]	HTLV-1 infected T-cell HUT-102- cells	*C. okamurans*	3000	• G1 arrest • ↓ cyclin D2, c-myc • No changes in p21,p53	Apoptosis was reversed by caspase 8 inhibitor	• Caspase 9 activation • No changes in Bcl-2 and Bcl-XL • ↓ survivin, cIAP-2	• Apoptosis was reversed by caspase 3 inhibitor
[21]	Human hepatocellular carcinoma cells	*Okinawa mozuku*	22.5	• ↑ G2/M phase in HAK-1A, KYN-2, KYN-3 cell lines	-	• No clear caspase 9 activation in HAK-1B cell line	• No clear caspase 3 activation in HAK-1B cells
[22]	Human breast cancer MCF7 cells	Not mentioned	1000	• ↑ sub-G1 fraction	• Caspase 8 activation • Caspase inhibitors blocked apoptosis completely	• Caspase 9 activation • ↓ Bid, cytosolic Bax • ↑ whole lysate Bax, cytosolic cytochrome C	• Caspase 7 activation • PARP cleavage
[23]	Human acute leukemia NB4 and HL-60 cells	*F. vesiculosus*	150	• ↑ sub-G1 fraction	• Caspase 8 activation	• caspase 9 activation • No changes in Bcl-2 or Bax • ↓ Mcl-1, ↑ cytochrome C	• PARP cleavage • Caspase 3 activation
[24]	Human colon cancer HT-29 and HCT116 cells	*F. vesiculosus*		-	• Caspase 8 activation • ↑ Fas, DR5, TRAIL • No significant effects on FasL and DR4	• Caspase 9 activation • ↑ cytochrome C, Smac/Diablo, Bak, t-Bid • No changes in Bcl-2, Bcl-xL, Bax, Bad, Bim, Bik • ↓ XIAP, survivin	• PARP cleavage • Caspase 3 and 7 activation
[25]	Human lung cancer A549 cells	*U. pinnatifida*	50, 100, 200	• ↑ Sub-G1frction	-	• Caspase-9 activation • ↓ Bcl-2, ↑ Bax	• ↓ procaspase-3 • PARP cleavage
[14]	Human breast cancer MCF-7 cells	*Cladosiphon novae-caledoniae*	82, 410, 820	• ↑ Sub-G1 • No significant changes in cell cycle distribution	• No changes in caspase-8	• Mitochondrial dysfunction • AIF and cytochrome C release • No cleavage of caspase-9 and Bid. • ↓ Bcl-2, Bcl-xl ,↑ Bax, Bad	• No activation of PARP and caspase-7 • All caspase inhibitors failed to attenuate FE-induced apoptosis
[26]	Hela cells	*Sargassum filipendula*	1500	-	-	• No effect on caspase 9 activation • ↑ cytosol AIF	• No effect on caspase 3 (Caspase independent)
[19]	Human breast cancer MCF-7 cells	*F. vesiculosus*	400, 800, 1000	• G1 phase arrest • ↑ Sub G0/G1 ↓ cyclin D1 and CDK-4 gene expression	• Caspase-8 activation	• ↓ Bcl-2 • ↑ Bax • Release of cytochrome C and APAf-1	• Caspase-dependent pathway

Table 1. *Cont.*

Ref	Cell Type	Fucoidan Source	Dose (µg/mL)	Effects on Cell Cycle	Effects on Apoptosis Pathways Extrinsic	Intrinsic	Common
[18]	Human prostate cancer PC-3 cells	*U. pinnatifida*	100	• G0/G1 phase arrest • ↓ E2F-1 • ↑ p21Cip1/Waf	• DR5, caspase-8 activation	• ↓ Bcl-2 • ↑ Bax, • Caspase 9 activation	• Caspase-3 activation • PARP cleavage
[27]	Human Hepatocellular Carcinoma SMMC-7721 cells	*U. pinnatifida*	1000	• Non-significant accumulation in S-phase	• Caspase-8 activation	• Caspase-9 activation • MMP dissipation, Cytochrome C release • ↓ Bcl-2, ↑ Bax • ↓ *XIAP*, livin mRNA expression	• Caspase-3 activation
[28]	Human bladder carcinoma 5637 and T-24 cells	*F. vesiculosus*	100	• ↑ G1-phase, p21WAF1 • ↓ Cyclin E, D1, DK2, CDK4 • No change in p27KIP,p53 • ↑ p21WAF1 and CDK4 binding	-	-	-

In a recent study, fucoidan down-regulated cyclin E, CDK2, CDK4 resulting in G0/G1 arrest in human bladder cancer 5637 cells. Furthermore, immunoprecipitation assays revealed a significant increase in the binding of p21/WAF1/CIP1 to CDK2 and CDK4 in cells treated with fucoidan, suggesting that the induced G0/G1 arrest is due to suppression of CDK activity following direct binding of this CDK inhibitor to CDKs 2 and 4 [28]. Table 1 summarizes findings of studies examining the effects of fucoidan on cell cycle.

3.1.2. Fucoidan and the Apoptosis Pathway

Apoptosis characterized by cytoplasmic shrinkage and chromatin condensation facilitates the removal of cells without inducing inflammation [29]. Apoptosis occurs through either the extrinsic (cytoplasmic) pathway whereby death receptors trigger the apoptosis, or the intrinsic (mitochondrial) pathway in which changes in mitochondrial membrane potential (MMP) lead to cytochrome C release and death signal activation. Both pathways activate executive caspases that cleave regulatory and structural molecules [30]. Several studies examining a variety of cancers such as hematopoietic, lung, breast and colon cancers have shown that fucoidan-mediated cell death occurs through triggering apoptosis (Table 1) [14,22,24]. A very low dose of fucoidan from *F. vesiculosus* (20 μg/mL) activated common caspases 3 and 7 in human colon cancer cells [24], whereas it induced the same activity in T-cell leukemia at a much higher concentration (3 mg/mL) [20]. Caspase 8 and 9, two of the best characterized molecules of the extrinsic and intrinsic pathways respectively are activated by fucoidan [24]. Yamasaki-Miyamoto *et al.* showed that pre-treatment with caspase 8 inhibitor completely blocked fucoidan mediated apoptosis in MCF-7 breast cancer cell line [22]. In contrast, in Zhang *et al.* [14] study, the mediated apoptosis by fucoidan from *Cladosiphon okamuranus* in MCF-7 human breast cancer cell line was shown to be caspase independent. As cytochrome C and apoptosis inducing factor (AIF) increased in the cytosol, it was concluded that fucoidan performed its activity through mechanisms altering mitochondrial function.

Fucoidan also affects other components of extrinsic and intrinsic pathways. Analyzing the extrinsic pathway, 20 μg/mL crude fucoidan from *F. vesiculosus* increased the levels of the death receptors Fas, DR5 and TRAIL but not FasL and DR4 in human colon cancer cell lines [24]. Bcl-2 family members include anti-apoptotic, pro-apoptotic and regulatory proteins, which are mainly involved in the apoptosis intrinsic pathway. Contradictory results have been described in the expression of these regulatory molecules in response to fucoidan (Table 1). Treatment of MDA-MB231 breast cancer cells with 820 μg/mL of low molecular weight (LMW) fucoidan resulted in a significant decrease in anti-apoptotic proteins Bcl-2, Bcl-xl and Mcl-1 [31]. In contrast, no changes in expression of Bcl-2, Bcl-xl, Bad, Bim and Bik were observed in colon cancer cells when they were treated with 20 μg/mL fucoidan from *Fucus vesiculosus* [24]. Taken together, the results suggest that fucoidan may interact with several components of the apoptosis pathway.

3.1.3. Fucoidan and Angiogenesis

Fucoidan inhibits the formation of new vessels by which tumor cells receive their oxygen and required nutrients. Fucoidan has been found to inhibit the binding of VEGF, a key angiogenesis promoting molecule, to its cell membrane receptor [32]. Xue *et al.* examined the anti-angiogenic properties of

fucoidan in 4T1 mouse breast cancer cells both *in vitro* and *in vivo* and observed a significant dose-dependent decrease in VEGF expression in cells treated with fucoidan. Further, in a mouse breast cancer model using 4T1 cells, intraperitoneal injections of 10 mg/kg body weight fucoidan from *F. vesiculosus* for 20 days markedly reduced the number of microvessels. Using immunohistochemistry, fucoidan was shown to reduce VEGF expression compared to the control group [33]. In contrast, Zhu *et al.* reported that fucoidan did not suppress angiogenesis and VEGF expression in human hepatocarcinoma cell lines treated with 10 to 200 μg/mL of a commercial fucoidan purified from *Sargassum* spp. Similarly no changes in VEGF expression were observed in xenograft tumors developed in nude mice following 20 to 200 mg/kg/body weight fucoidan injected intraperitoneally once a day over 25 days [34]. It is postulated that different effects are observed with fucoidans of various MWs and molecular structures and this is reviewed by Kwak [13].

3.1.4. Fucoidan and Metastasis

In 1987, Coombe *et al.* demonstrated that fucoidan significantly decreased tumor cells metastasis to the lungs in animals that were intravenously injected with rat mammary adenocarcinoma 13762 MAT cells [35]. It was first reported that fucoidan inhibits cell invasion through competing with tumor cell binding with laminin in the basement membrane [36]. Subsequent studies then revealed that fucoidan binds to fibronectin with high affinity and prevent attachment of tumor cells. In agreement with this study, fucoidan reduced the spread of human breast adenocarcinoma cells plated on a surface containing fibronectin [37].

Selectin inhibition by fucoidan interferes with tumor cell–platelet interaction. In Cumashi *et al.* study [38], highly metastatic MDA-MB-231 breast cancer cells were plated in platelet-coated plates in the presence or absence of 100 μg/mL fucoidan. The number of cells attached to the platelets decreased by 80% in the presence of fucoidan. Interaction of tumor cells with platelets is one of the key factors in facilitating the early steps of tumor cell migration. During tumor cell migration, most circulating tumor cells do not survive attack from immune cells or the shear forces of the blood stream. However, they can attach to platelets to induce platelet aggregation allowing the tumor cell cluster to survive in the micro-vascular system. It was concluded that fucoidan inhibited P-selectin residing on the platelet surface and led to reduced number of attached tumor cells. Fucoidan can also inhibit other adhesion molecules such as integrins residing on the tumor cell surface and can modify distribution of their subunits.

Tumor invasion requires the secretion of proteolytic enzymes by tumor cells to break down the extracellular matrix (ECM) proteins (e.g., collagen, fibronectin and laminin), with the matrix metalloproteinases (MMPs) MMP-2 and MMP-9 playing a major role. Fucoidan attenuates both expression and activity of these enzymes [39].

3.1.5. Fucoidan and Signaling Pathways

The extracellular signal-regulated kinase (ERK) pathway (or Ras/Raf/MAPK pathway) is often hyperphosphorylated and upregulated in a variety of human cancers. The potential for developing anticancer agents that cause ERK's dephosphorylation and pathway blockade have been explored. Various studies have shown that fucoidan inhibits tumor cell proliferation by decreasing ERKs activity

through reduction of its phosphorylation [15,40] while several studies have proposed that fucoidan causes ERK activation rather than inactivation [41,42]. To explain these contradictions, it should be noted that the ERK signaling pathway is highly complex. It induces a range of different responses including cell proliferation, differentiation, migration and apoptosis depending on cell type, the type of stimulus and duration of activation [43]. Therefore, some of the contradictory results of the aforementioned studies can be explained by different fucoidan extracts with different molecular structures being used on different tumor cell types. Another complication is that different studies have examined ERK phosphorylation over different time periods ranging from 10 min to 48 h. Jin *et al.* reported increased ERK1/2 phosphorylation in HL-60 leukemic cell line 10–15 min after fucoidan treatment. The phosphorylation returned to the basal level after 1 h [23]. In Lee *et al.* study, crude fucoidan progressively diminished phosphorylation of ERK1/2 from 1 h to 9 h after treatment [39].

JNK and p38 are other MAPK superfamily members whose activity is altered by fucoidan. Fucoidan induced cell death in breast cancer cells through phosphorylation and activation of JNK and p38 after 30 min. The fucoidan-induced apoptosis significantly annulled in the presence of JNK inhibitor, indicating critical role of JNK in fucoidan-mediated apoptosis [14].

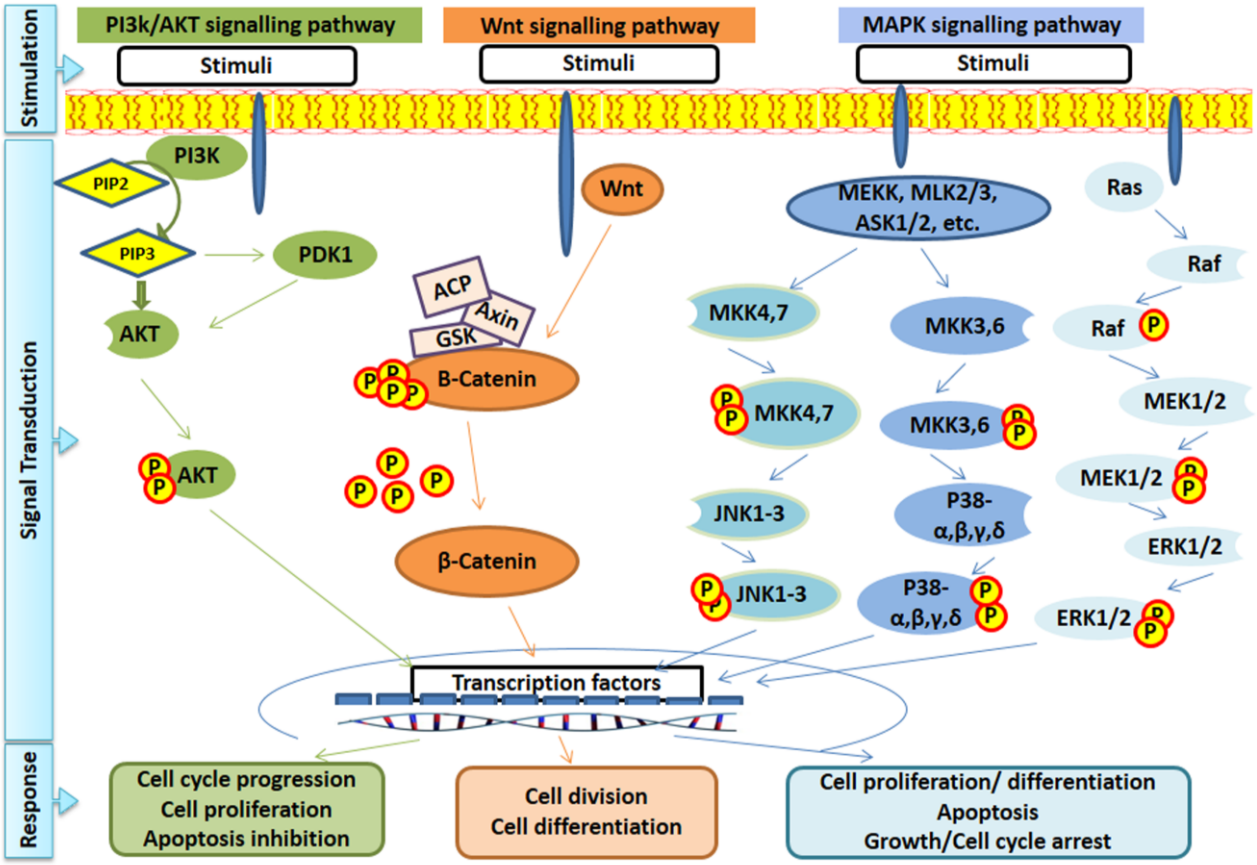

Figure 1. Overview of main signal transduction pathways involved in cell proliferation and apoptosis.

Similarly, the PI3K/AKT, GSK and Wnt pathways have been shown to be triggered by fucoidan. PI3K/AKT pathway generally inhibits apoptosis. AKT over-activation is also associated with drug resistance and tumor cell survival. As a result, deactivating this pathway could be another potential target for anti-cancer drug development. Most of the studies have reported inactivation of AKT by

fucoidan. PI3k, an upstream molecule of AKT, is also inhibited by fucoidan [39]. Upregulation of the Wnt signaling pathway is believed to have a critical role in prostate cancer development, survival and progression. Fucoidan from *F. vesiculosus* activated GSK-3β in PC3 human prostate cancer cells resulting in hypo-phosphorylation and inactivation of β-catenin, a critical component of the Wnt pathway (Figure 1) [18]. Figure 1 represents an overview of the mentioned signaling pathways.

3.1.6. Fucoidan and the Immune System

The effects of fucoidan on molecules of the immune system have been studied both *in vitro* and *in vivo* and effects on both cellular and humoral elements have been described. Fucoidan increases both activity and number of natural killer (NK) cells *in vivo* [44,45]. Increase in the number of cytotoxic T-cells (CTLs) has also been reported. A high-molecular-weight (HMW) fucoidan from *Cladosiphon okamuranus* (200–300 kDa) induced a large increase in the proportion of murine cytotoxic T cells [46]. Investigation of the role of fucoidan on dendritic cell (DC)-mediated T-cell cytotoxicity has revealed that the stimulation of CTLs was more effective in fucoidan-treated DCs as CTLs co-cultured with fucoidan-treated DCs exerted a high level of specific lysis of breast cancer cells [47].

In a recent study, the role of fucoidan in DCs function and its adjuvant effect have been examined *in vivo*. Fucoidan was systemically administrated to mice by intraperitoneal injection. Examination of the spleen DCs revealed up-regulation of maturation markers as well as production of IL-6, IL-12 and TNF-α. Fucoidan was then used as an adjuvant *in vivo* with ovalbumin antigen and induced Th1 mediated immune response and CTL activation [48].

3.1.7. Fucoidan and Malignant Transformation *in Vitro* and *in Vivo*

Few studies have reported the potential of fucoidan to inhibit neoplastic transformation. Teas *et al.* fed rats with dietary seaweed (*Laminira*) for 55 days and administrated the carcinogen 7,12-dimethylbenz(a) anthracene intragastrically. Following 26 weeks monitoring, experimental rats showed a significant delay in the median time for tumor appearance (19 *vs.* 11 weeks in the control group) [49].

Transforming growth factor β1 (TGFβ1) is believed to promote tumor development and metastasis through epithelial to mesenchymal transition (EMT), a process that enables epithelial cells migrate to distant areas during late stages of breast cancer development [50]. To trigger tumor progression, TGFβ1 recruits TGF receptors (TGFR) residing on the cell surface. The investigations of effects of fucoidan on TGFβ1-promoted carcinogenesis in MDA-MB-231 breast cancer cells have indicated that fucoidan decreased the expression of TGFRs and affected the downstream signaling molecules, which are involved in TGFβ1-mediated EMT [41].

Epidermal growth factor (EGF) is another carcinogenesis promoter, which induces tumor transformation through overexpression and activation of EGF receptor (EGFR). EGFR has a key role in cell proliferation and differentiation and many carcinomas arise from its mutations [51]. Lee *et al.* examined the role of fucoidan on the activation of EGFR and EGF-mediated neoplastic transformation [52]. They utilized murine JB6 Cl41 epidermal cells and induced cell transformation by EGF in the presence of fucoidan from *L. guryanovae*. Fucoidan markedly reduced the EGFR activation through hypo-phosphorylation. It also inhibited EGF-tumorigenic activity through inhibition of AP-1, a transcription factor responsible for cell proliferation regulation.

3.2. Fucoidan Metabolism

Fucoidanase, the enzyme responsible for fucoidan hydrolysis, has only been found in brown seaweed and marine microorganisms such as some marine bacteria and fungi [53] and not in humans. It is possible that the acidic conditions in the stomach could degrade fucoidan, but it has been reported that the low gastric pH does have restricted effects on fucoidan [54].

Small amounts of dietary fucoidan can be endocytosed and cross the intestinal wall directly without breaking down [54]. In Tokita *et al.* study, 10 volunteers were given oral fucoidan and the concentrations of fucoidan in the serum and urine were analyzed. Fucoidan was detectable 3 h after administration and increased to 100 ng/mL in serum and 1000 ng/mL in urine. However the rate of absorption in the small intestine was highly variable among the participants. The MW of fucoidan in serum was similar to administered fucoidan indicating that fucoidan was not hydrolyzed by digestive enzymes [55]. However, the MW of the fucoidan detected in urine was significantly smaller than the ingested fucoidan suggesting that fucoidan is degraded in the excretory system and possibly the kidney and not by intestinal enzymes or normal flora.

To evaluate the fucoidan uptake process by cells, the internalization of LMW fucoidan into rabbit smooth muscle cells (SMCs) was analyzed. Fucoidan was shown to be internalized by endocytosis at 6 h. The number of vesicles containing fucoidan increased in the peri-nuclear region at 24 h, but nuclear internalization was not observed at any time during the study [56]. However, examining the transport of a native fucoidan from *Cladosiphon okamuranus* with MW of 80 kDa revealed a poor permeation of fucoidan across the human colon adenocarcinoma Caco-2 cell monolayer [57].

Regarding the specific ligands by which fucoidan binds to the cells surface, several molecules have been implicated including class A macrophage scavenger receptors for fucoidan attachment to macrophages [58] as well as adhesion molecules such as L-selectin and P-selectin [59] and integrins [60]. However, some reports have shown fucoidan mediates apoptosis through selectin-independent mechanisms [15].

3.3. Fucoidan as a Synergistic Anti-Cancer Agent

The ability of fucoidan to synergize with standard anti-cancer agents and/or reduce toxicity has recently been investigated. Ikeguchi *et al.* examined the synergistic effect of a HMW fucoidan with colorectal cancer chemotherapy agents; oxaliplatin plus 5-fluorouracil/leucovorin (FOLFOX) or irinotecan plus 5-fluorouracil/leucovorin (FOLFIRI). The test patients received 150 mL/day for 6 months of liquid that contained 4.05 g fucoidan. From the commencement of chemotherapy, toxicities and chemotherapy efficiency were compared. Fucoidan showed no side effects such as allergic dermatitis. Diarrhea, neurotoxicity and myelosuppression were not suppressed by fucoidan, whereas general fatigue was significantly decreased from 60% to 10%. The patients were followed for approximately 15 months and the survival rate of the patients who received fucoidan was longer than that of the control participants; however the difference was not significant, probably due to the small numbers [61].

Fucoidan affects the migration and invasion of multiple myeloma (MM) cells treated with chemotherapy drug cytarabine. The human myeloma cell lines RPMI8226 and U266 were treated with crude fucoidan from *F. vesiculosus* for 72 h and then cytarabine for 6 h. Fucoidan reduced cell migration

through a Boyden chamber and down-regulated expression of CXCR4 and MMP-9 [62]. Fucoidan from *Saccharina cichorioides* has been reported to synergize with the anti-tumor activity of low dose resveratrol (a natural polyphenol extracted from foods and beverages) on invasive and highly motile HCT 116 colon cancer cell line [63]. In the colony formation assay, fucoidan plus resveratrol reduced the colony number by 60% compared to 34% and 27% in resveratrol alone or fucoidan alone, respectively.

Zhang *et al.* studied the combinatory effect of fucoidan and three commonly used anti-cancer agents; cis-platin (CDDP), tamoxifen (TAM) and paclitaxel (Taxol) on signal transduction pathways. Fucoidan from *Cladosiphon navae-caledoniae* plus anti-cancer agents reduced the ERK phosphorylation in MDA-MB-231 breast cancer cells compared to untreated control or fucoidan alone [64]. Dietary fucoidan synergistically reduced cell growth in the OE33 cell line when it was combined with lapatinib, a targeted therapy that acts as a tyrosine kinase inhibitor in advanced HER2-positive breast cancer cells [65].

In a xenograft transplantation study, the effect of fucoidan alone or in combination with cyclophosphamide was examined on tumor growth. Nine days after the injection of Lewis lung carcinoma cells into mice, fucoidan from *Fucus evanescens* was administered to animals alone or combined with cyclophosphamide. The fucoidan group showed marked antitumor (33% tumor growth inhibition) and anti-metastatic (29% reduction of the number of metastases) activities. However, fucoidan did not exhibit a synergistic effect with cyclophosphamide on tumor growth, but significantly decreased the lung cancer cells metastasis [66].

3.4. Why Fucoidan Usage is Complicated?

Despite the promising results about the anti-cancer effect of fucoidan, there are still challenges impeding utilization of fucoidan in the clinic. Variable and contradictory results being influenced by endogenous and exogenous factors in fucoidan usage are of the main concerns. In this section we will summarize important conditions, which have been undertaken in different experiments and have led to such variable results in reported studies.

3.4.1. Structure and Molecular Weight Variation

Fucoidan is composed of α-(1-2) or α-(1-3)-linked L-fucose with a fucose content of 34-44%. It also contains various amounts of other monosaccharaides such as galactose, mannose, xylose and uronic acid all of which make up less than 10% of the total fucoidan structure [67,68]. The sulfate groups in fucoidan structure are mainly at position 4 but they can also occupy position C_2 and occasionally C_3 [53]. The fucoidan structure and monosaccharide composition vary depending on different factors such as the source of fucoidan, the time and location of harvesting and the extraction method, which can affect the fucoidan's bioactivities. Most anti-cancer studies of fucoidan have used a commercially available crude fucoidan extracted from *Fucus vesiculosus* (Sigma Co. St. Louis, MO, USA). Some groups have extracted and purified fucoidan in their own laboratories. *Okinawa mozuku*, *C. Okamuranus* tokida, *Sargassum* sp. and *Undaria pinnatifida* are the most common fucoidans examined in cancer studies.

Cumashi *et al.* studied different biological aspects of fucoidan from nine different species of brown seaweed in rats [38]. Analysis of P-selectin-mediated neutrophil adhesion to platelets revealed that

extracted fucoidans from only some sources like *F. evanescens* and *A. nodosum* could serve as more efficient P-selectin inhibitors. Furthermore, in contrast to other sources, fucoidan from *C. okamuranus* did not exert anti-coagulant activity, which was suggested to be due to high content of 2-O-a-D-glucuronyl substituent in the polysaccharide chain of fucoidan from *C. okamuranus*.

Sulfation is another key factor in fucoidan bioactivity. More sulfation is linked with greater bioactivity and thus researchers have produced over-sulfated fucoidans to enhance its biological properties [36]. It has been suggested that over-sulfation causes higher negative charge in the molecule which can facilitate formation of fucoidan-protein complexes involved in cell proliferation [69].

Molecular weight is another crucial factor in fucoidan activity. Cho *et al.* produced three fucoidan fractions with molecular weights of <5, 5–30 and >30 kDa and reported that the $F_{5\text{-}30K}$ showed the most tumor growth inhibitory effect despite the sulfate amount in $F_{<5K}$ being greater than in the two other fractions [70].

The extraction method can also affect fucoidan's bio-properties. Fucoidan from *Undaria pinnatifida* was hydrolyzed using different hydrolysis conditions and their anti-cancer activity was compared *in vitro*. The native fucoidan showed 37% anti-cancer activity; hydrolyzed fucoidan generated under mild conditions (in boiling water with HCl for 5 min) exhibited 75.9% anti-tumor activity; whereas hydrolyzed fucoidan generated under harsh conditions (microwave for more than 90 s) slightly enhanced the anti-cancer effect [71].

3.4.2. Fucoidan Dose and Route of Administration

As fucoidan is a large highly branched molecule, the dosage for *in vitro* studies mostly resides in the range of μg/mL and not ng/mL. However, there is a large variation in the doses. Vischchuk *et al.* treated HCT-116 colon cancer cells with 100–800 μg/mL fucoidan from the brown alga *Saccharina cichorioides* Miyabe and observed that fucoidan exerted a low cytotoxicity and there was less than 15% reduction in cell number with the high dose of 800 μg/ml after 24 h [63]. In contrast, Kim *et al.* demonstrated that 20 μg/mL fucoidan from *F. vesiculosus* caused 37% growth inhibition in the same cell line after 72 h [24]. Though the difference between incubation times (24 h *vs.* 72 h) should be considered, the dose difference (800 μg/mL *vs.* 20 μg/mL) was substantial. The source of fucoidan appears to be the main factor leading to variation in results. Though most researchers have utilized dosages of less than 1 mg/mL, there are reports of use of up to 3 mg/mL fucoidan.

Regarding the *in vivo* studies, both dose and the route of administration can affect outcome. To select the most effective dose, mice were treated with various doses of fucoidan (10–400 mg/kg body weight) followed by total-body irradiation. The mice injected with 100 mg/kg body weight fucoidan showed the best survival rate at 30 days post-irradiation [72]. Other studies have used various doses ranging from 5 mg/kg to 100 mg/kg and occasionally doses up to 500 mg/kg/body weight of different fucoidan extracts. The amount and number of doses of fucoidan administration has also been shown to be important for *in vivo* studies. Alekseyenko *et al.* studied mice with lung carcinoma that were treated with fucoidan from *Fucus evanescence*. They found that a single injection of 25 mg/kg/body weight of fucoidan did not inhibit tumor cell proliferation, while three-time injections of 10 mg/kg/body weight significantly reduced tumor growth and metastasis [66]. Most *in vivo* studies of anti-tumor activity have selected intraperitoneal (IP) injections, but subcutaneous (SC) or intravenous (IV) routes of

administration have also been used. Oral fucoidan is another route for *in vivo* delivery either for its anti-tumor properties following tumor induction or as a neoplastic transformation inhibitor administered prior to cancer induction. Taken together, these studies indicate that different delivery routes can affect the fucoidan metabolism *in vivo* and lead to variable outcomes.

3.5. Fucoidan Toxicity

Whilst fucoidan consumed in food in the form of 4% of the total dry weight of brown seaweeds is generally regarded as safe, the fucoidan used for research is a highly purified extract. For *in vitro* studies, researchers have utilized normal cells such as normal fibroblasts alongside tumor cell lines and reported that fucoidan did not induce apoptosis within normal cells at the doses which were toxic for cancer cell lines. A very high dose of 3 mg/mL fucoidan suppressed the viability of peripheral blood mononuclear cells from healthy donors by 25% compared to 60%–90% in five different leukemic T-cells [20]. *In vivo*, oral administration of up to 1 g/mL/body weight *Undaria pinnatifida* fucoidan was non-toxic in mice but higher doses (2 g/mL/body weight) induced changes in thyroid weight and altered levels of triglyceride and alanine transaminase activity [73]. In another study, daily administration of 300 mg/kg/body weight fucoidan from *Laminaria japonica* in Wister rats over 6 months did not induce any adverse side effects, but higher doses (900–2500 mg/mL) resulted in coagulopathy and markedly elevated clotting time [74].

Toxicity has also been examined in the context of fucoidan use as adjuvant. Oh *et al.* examined the combinatory effect of fucoidan with the standard anti-Her2 inhibitor lapatinib in different breast cancer cell lines *in vitro* [65] and found that fucoidan decreased the efficiency of lapitinib and exerted antagonistic effects on cell proliferation in a few cell lines. Examining the effect of combination of fucoidan from *Fucus evanescence* with cyclophosphamide, 7 out of 10 mice that were injected with 25 mg/kg/body weight fucoidan plus cyclophosphamide died whereas of the mice that were treated with fucoidan alone, 3 out of 10 died [66].

Fucoidan has been examined in several clinical trials mainly for its anti-coagulant and anti-viral properties. Administration of capsules containing 560 mg fucoidan from *Undaria pinnatifida* for up to 24 months did not induce any side effect when the participants took 4 capsules a day [75]. In Mori *et al.* [76] and Irhimeh *et al.* [77] studies, daily consumption of 5 capsules contained 166 mg fucoidan from *C okamuranus* Tokida for over one year and 3 g HMW fucoidan from *Undaria pinnatifida* for up to 12 days, respectively, were revealed to be safe. However, Irhimeh *et al.* demonstrated that orally administered fucoidan affected coagulation tests and prolonged the aPTT, thrombin time and AT-III. Other studies have also shown the potential of bleeding complication development due to fucoidan's anti-thrombotic property [78]. Diarrhea is another reported side effect, which was seen in 4 out of 17 participants within 1 month of daily administration of 6 g fucoidan [79].

When a blend of three different extracts (from *Fucus vesiculosis* (85% w/w), *Macrocystis pyrifera* (10% w/w), and *Laminaria japonica* (5% w/w)) in capsules containing up to 187.5 mg were daily given to volunteers, a statistically significant change in the potassium level was seen after 28 days. Although, the change was minor and within the clinical reference range [80].

4. Conclusions

The goal of cancer treatment is eradication of tumor cells ideally with minimal damage to healthy tissues. Because of the side-effects of many current treatments, the use of natural substances of low toxicity is of interest. A number of *in vitro* and *in vivo* studies have indicated that fucoidan contains strong anti-cancer bioactivity. Since fucoidan also possesses immunomodulatory effects, it is postulated that it may have protective effects against development of side effects when it is co-administered with chemotherapeutic agents and radiation.

In this report, we reviewed the underlying cellular mechanisms by which fucoidan induces cell death within tumor cells and increases the survival rate of tumor-bearing animal models by suppression of metastasis and angiogenesis. However despite numerous promising pre-clinical reports, there are few reported clinical studies so far [61]. In this review we also discussed the challenges impeding utilization of fucoidan in the clinic which include the complex heterogeneous structure of fucoidan, highly variable doses, different administration routes and possible negative interactions with chemotherapy. Due to the wide variation of fucoidan structure and to make future experiments reproducible, it is recommended that the critical bioactivity factors such as fucoidan content, sulfate content, monosaccharide constituents and molecular weight be reported. Attention to these factors will be likely to lead to more consistent reports and ultimately produce the required evidence to underpin clinical studies in near future.

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Authors Contribution

FA conducted the literature research and drafted the manuscript. RML carried out the supervision and edited the manuscript. GMW carried out the supervision and edited the manuscript. AFH carried out the supervision and edited the manuscript. JLD carried out the supervision and edited the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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Synergistic cytotoxicity of artemisinin and sodium butyrate on human cancer cells.

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BACKGROUND: Butyric acid is a short chain fatty acid produced by large bowel bacterial flora. It serves as an antiinflammatory agent and nutrient for normal colon cells. Butyric acid has also been shown to induce apoptosis in colon and many other cancer cells. Artemisinin is a compound extracted from the wormwood Artemisia annua L. It has been shown to selectively kill cancer cells in vitro and to be effective in treating animal and human cancer. We and others have found that the artemisinin analog, dihydroartemisinin (DHA), kills cancer cells by apoptosis. In the present study, the efficacy of a combined treatment of DHA and butyric acid at low doses in killing cancer cells was investigated. MATERIALS AND METHODS: Molt-4 cells (a human lymphoblastoid leukemia cell line) and freshly isolated human lymphocytes, cultured in complete RPMI-1640 medium, were first incubated with 12 microM of human holotransferrin at 37 degrees C in a humid atmosphere of 5% CO2 for one hour to enhance the iron concentration in the cells. Cells from each cell type were then divided into 20 flasks. These flasks were grouped into four sets of five cultures each. Zero, 5, 10 or 20 microM of DHA was added, respectively, to these sets and the cells were incubated at 37 degrees C for one hour. Zero, 1, 5, 10, or 20 mM of sodium butyrate was then added to the five cultures of each set, respectively. Thus, the treatments involved a combination of 4 doses of DHA and 5 doses of sodium butyrate. The cells were counted immediately before the addition of DHA, and at 24 and 48 hours after the addition of sodium butyrate. RESULTS: DHA alone at the 24-hour time-point and 20 microM concentration significantly reduced the number of Molt-4 cells in the culture by approximately 40% ($p < 0.001$, compared to non-treated control), whereas it did not significantly affect the number of normal human lymphocytes. Similarly, 1 mM sodium butyrate alone at 24 hours reduced the number of Molt-4 cells by approximately 32% ($p < 0.001$, compared to non-treated control), without significantly affecting normal human lymphocytes. The combination of 20

microM DHA and 1 mM sodium butyrate killed all Molt-4 cells at the 24-hour time-point and did not significantly affect lymphocytes. CONCLUSION: DHA in combination with butyric acid acts synergistically at low doses. The combination may provide a less toxic, inexpensive and effective cancer chemotherapy.

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Review

Ellagitannins in Cancer Chemoprevention and Therapy

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Abstract: It is universally accepted that diets rich in fruit and vegetables lead to reduction in the risk of common forms of cancer and are useful in cancer prevention. Indeed edible vegetables and fruits contain a wide variety of phytochemicals with proven antioxidant, anti-carcinogenic, and chemopreventive activity; moreover, some of these phytochemicals also display direct antiproliferative activity towards tumor cells, with the additional advantage of high tolerability and low toxicity. The most important dietary phytochemicals are isothiocyanates, ellagitannins (ET), polyphenols, indoles, flavonoids, retinoids, tocopherols. Among this very wide panel of compounds, ET represent an important class of phytochemicals which are being increasingly investigated for their chemopreventive and anticancer activities. This article reviews the chemistry, the dietary sources, the pharmacokinetics, the evidence on chemopreventive efficacy and the anticancer activity of ET with regard to the most sensitive tumors, as well as the mechanisms underlying their clinically-valuable properties.

Keywords: ellagitannins; phytochemicals; cancer; chemoprevention; cancer therapy; safety

1. Introduction

Despite the enormous efforts of the scientific and medical community, cancer still represents the second leading cause of death and is nearly becoming the leading one in the elderly [1]. It is estimated that, due to demographic changes alone, in the next 15 years the number of new cancer cases will increase by 70% worldwide [2].

The lack of effective diagnostic tools for early detection of several tumors, the limited treatment options for patients with advanced stages of cancer, and the onset of multiple drug resistance favor poor prognosis and high mortality rates. The significant, but still unsatisfactory, improvement of survival, the severe toxicity profile, and the high costs characterizing many current anticancer therapies clearly show that a threshold in terms of clinical benefit and patients' tolerance has been reached. Thus, the identification and development of innovative, preventive as well as therapeutic strategies to contrast cancer-associated morbidity and mortality are urgently needed.

Epidemiological, preclinical, and clinical studies have generally concluded that a diet rich in phytochemicals can reduce the risk of cancer [2,3]. Due to their pleiotropism which includes

antioxidant, anti-inflammatory, and antiproliferative activities as well as modulatory effects on subcellular signaling pathways, phytochemicals from edible fruits and vegetables are recognized as an effective option to counteract cancer incidence and mortality [3–5]. Plants constitute a primary and large source of various chemical compounds including alkaloids, flavonoids, phenolics, tannins, tocopherols, triterpenes, and isothiocyanates. Ellagitannins (ET) are an important class of phytochemicals contained in a number of edible plants and fruits recommended by the traditional medicine of a variety of cultures, both in the developing and developed countries, to treat common health problems. ET biological and nutraceutical potential has received increasing attention over the last several decades. ET exert multiple and clinically-valuable activities [4], and among them the chemopreventive, anticarcinogenic, and antiproliferative activities are being receiving growing interest and attention (Figure 1).

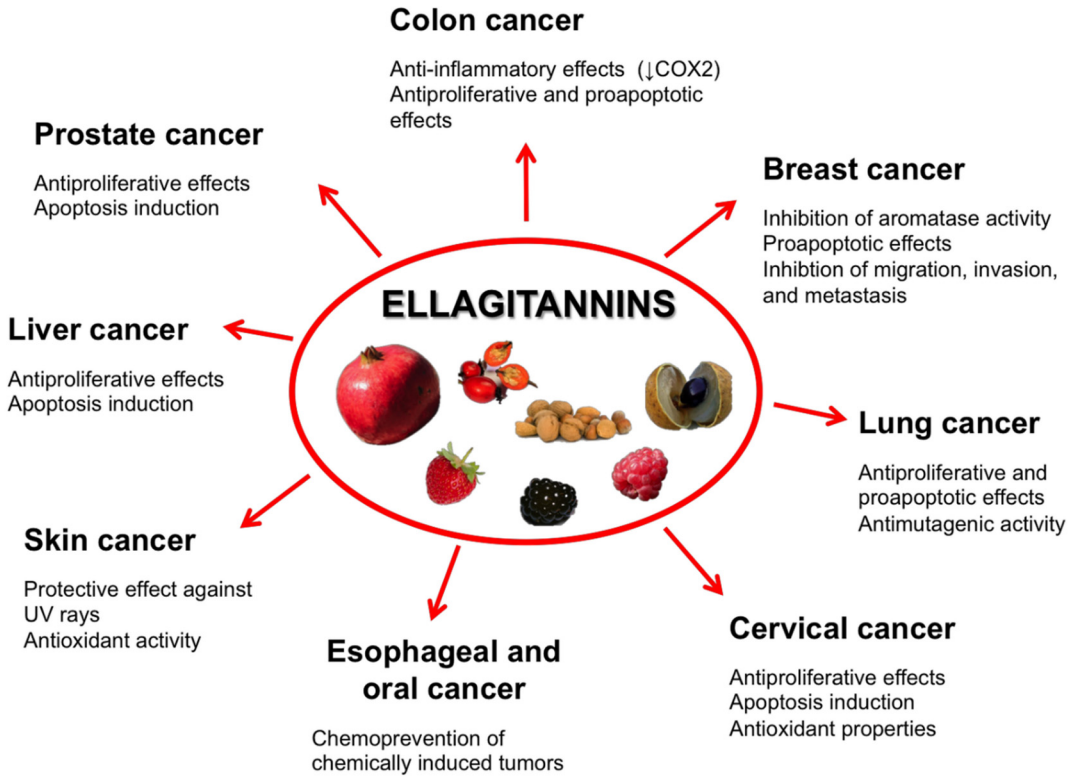

Figure 1. Fruits containing ET with chemopreventive, anticarcinogenic, and antiproliferative activities.

2. Dietary Sources, Types, and Occurrence

ET and their derivatives are noticeably contained in edible seeds, nuts, and various fruits of nutritional interests. The structures of relevant ETs and of ellagic acid are shown in Figure 2. A wide variety of fresh fruits including berries, like raspberries, black raspberries, strawberries, pomegranate, longan, and dried nuts, are renowned for their ample polyphenols concentration in the form of ET [5]. Five species of berries including raspberry, strawberry, cloudberry, rose hip, and sea buckthorn were identified by Koponen *et al.*, [6] as significant carrier of ET in a range of 1–330 mg per 100 g of fruit. Sanguiin H-6 and lambertianin C were reported from Glen Ample raspberries and Scottish-grown red raspberries, along with some trace levels of ellagic acid [7,8]. Blackberries (fruit and seeds) have been reported for a range of ET including pedunculagin, casuarictin, sanguiin H-6 (lambertianin A), and lambertianin (C and D) [9–11]. Pomegranate and various fractions of the fruit are known for their cancer chemopreventive properties owing to their unique phenolics composition in the form of ET, which include punicalagin, punicalin, granatin A, granatin B, tellimagrandin I, pedunculagin, corilagin, gallagic acid, ellagic acid, and casuarinin [12].

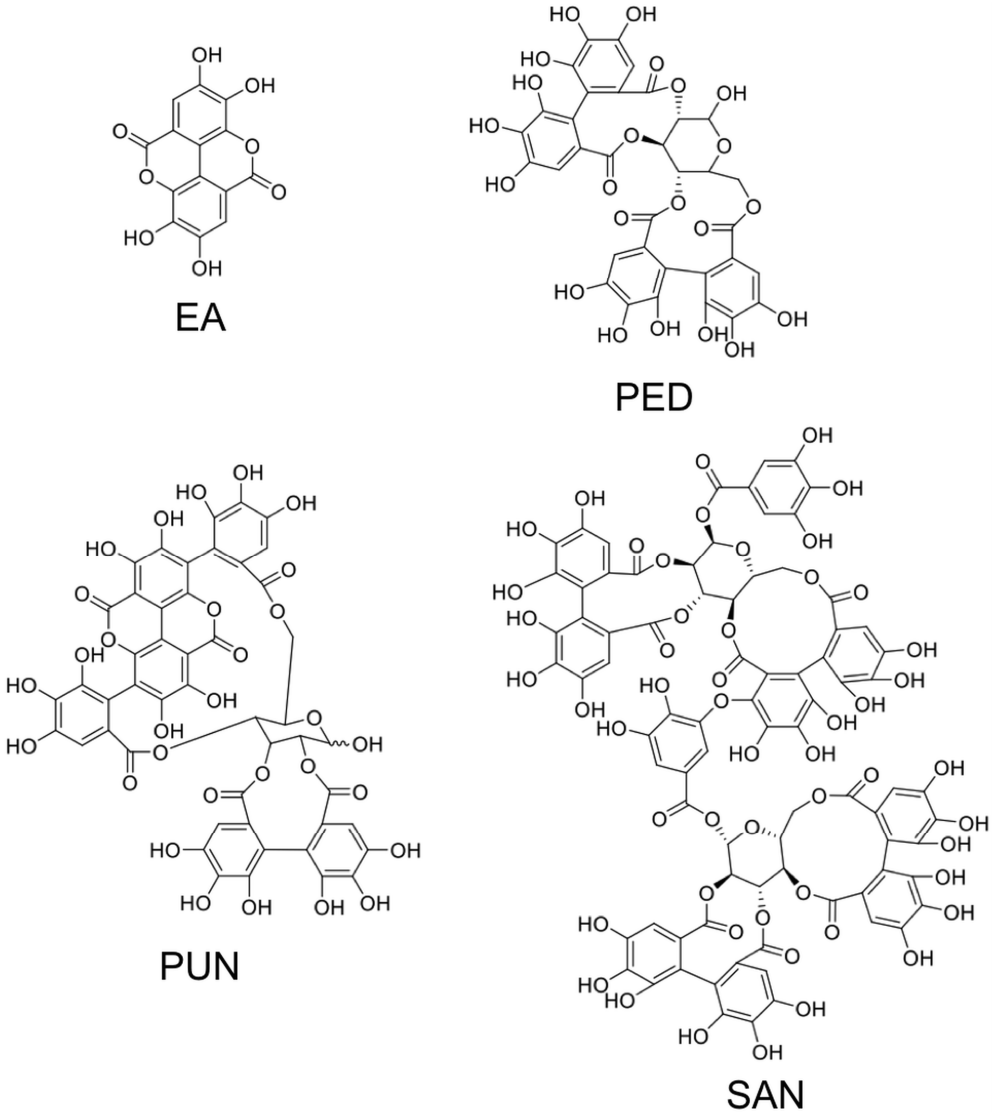

Figure 2. Structures of ellagic acid and of three major and representative ellagitannins. EA, ellagic acid; PED, pedunculagin; PUN, punicalagin; SAN, sanguiin H-6.

ET, predominately those isolated from pomegranate (e.g., punicalagin), have gained a wide popularity as preventive and therapeutic ethnopharmacological approaches for cancer treatment. However, a lot more has been added to this class of compounds from fruits other than pomegranate, including raspberries, blueberries, strawberries, muscadine grapes, and longan [7,13–18]. Major phenolic fractions recovered from longan include gallic acid, ellagic acid, and corilagin, much more concentrated in the seed segment as compared to the fruit pulp and peel [17]. Good essential fatty acid composition of nuts and fairly high concentrations of ET and their derived fractions, such as ellagic acid and its glycosidic derivatives have been associated with the potential cardioprotective properties of nuts. Ellagic acid (free and total) has been reported in a range of 0.37–823 mg per 100 g of dried nuts [19]. High concentrations of a variety of ET (ellagic acid, sanguiin H2 and 6, lambertianin C, castalagin/vescalagin, galloyl-bis-HHDP glucose, pedunculagin) can be found in blackberries (*Rubus* sp.) [20]. Shi *et al.*, [21] identified agrimoniin as the second highest phenolic compound of strawberries.

Irrespective of the edible fractions of fruiting plants, some inedible fractions like fruit peels, bark and foliage have also been reported as good source of hydrolysable tannins including bioactive ET [4,22]. Leaves extracts of *Shepherdia argentea*—a deciduous shrub commonly known as silver

buffaloberry—were reported as a good reserve of gluconic acid core carrying the potential anti-HIV novel ET, such as hippophaenin A, shephagenin A and shephagenin B [23].

3. Ellagitannins—Classification and Chemistry

Tannins are unique secondary metabolites of plant phenolics with relatively higher molecular weight (300–30,000 Da) and bear the ability to generate complexes with some macromolecules, like proteins and carbohydrates [24]. Chemistry and nomenclature of the tannins is complicated by virtue of the frequent changes which parallel the advancement in this very specific field [25]. Taking into account different definitions of tannins [26,27], these compounds may be referred as either galloyl esters and their derivatives (ET, gallotannins, and complex tannins), or the oligomeric and polymeric proanthocyanidins (condensed tannins). In a broader perspective, tannins may be classified most satisfactorily and unambiguously on the basis of structural configuration and/or solubility [28]. C–C coupling of galloyl units in absence of glycosidically-linked catechin make ETs structurally different from the condensed tannins that are characterized by monomeric catechin linkages (C4–C8 or C4–C6) to generate oligomeric likewise polymeric proanthocyanidins [27]. Gallotannins and ETs constitute a major group of tannins *i.e.*, hydrolysable tannins that are well known for their properties to hydrolyze into hexahydroxydiphenol (HHDP) or gallic acid moieties. Gallotannins are the gallic acid derivatives carrying $\geqslant$ six gallyol groups and might further be characterized on account of one or more than one digalloyl group [29].

ETs (hydrolysable tannins) on their hydrolysis yield gallic acid and ellagic acid from the compounds carrying gallyol groups and HHDP groups, respectively [28]. *In vitro* digestion models declare ETs to remain stable under the normal physiological condition of the stomach [30]. However, ETs hydrolysis to free ellagic acid or their degradation may proceed in the small intestine at neutral to alkaline pH [31]. Biologically, condensed tannins and gallotannins are thought to deliver relatively higher protein precipitation properties as compare to the ETs and hence are considered potential antinutritional compounds from the class of plants polyphenolics [32]. Gallotannins and condensed tannins have also been reported as oxidatively least active tannins as compared to the ETs and on the same time gallotannins and condensed tannins have also been found to reduce pro-oxidant properties of ETs [33,34].

3.1. Simple Ellagitannins

ET (M.W. 300–20,000 Da) are non-nitrogenous compounds with at least two C–C coupled galloyl units with no glycosidically-bonded catechin unit [3,35]. ET are derivatives of 1,2,3,4,6-penta-*O*-galloyl-β-D-glucopyranose (PGG). Structurally, ET are esters of carbohydrates and or cyclitols and also include metabolic compounds derived from oxidative cleavage of either condensed or hydrolysable tannins [27,35,36]. The presence of hexahydroxydiphenol (HHDP) in a glucopyranose ring in addition to acyl units and certain HHDP metabolites such as dehydrohexahydroxydiphenol (DHHDP), valoneoyl and chebuloyl groups constitute simple ET. Tellimagrandin I and II, pedunulagin, casuarictin, and chebulagic acid originate from the specific orientation and number of acyl groups on glucose units. Variation in HHDP group originates by linking (C–C or C–O) one or more galloyl groups to HHDP unit.

Structural diversity of ET has been reported to correlate with their carrier-plants' taxonomy and evolutionary hierarchy [37]. More often, monomeric ET or oligomeric ET constitute the major tannic component of plant species. The monomeric compounds of the group include tellimagrandins I and II, pedunculagin, casuarictin, and potentillin. Type I hydrolysable tannins (*i.e.*, gallotannins) carrying HHDP in stable conformation at either the 2,3 or 4,6 position on a D-glucopyranose may be referred to as a simple ET [38–40]. Geraniin, a type III ET, is another example of monomeric simple ET carrying a DHHDP unit linked to D-gluopyranose of HHDP unit via $^{1}C_{4}$ conformation. Dimers of ET are generated by intermolecular oxidative coupling/condensation of simple ET.

3.2. Glycosidic Ellagitannins

Chemically, the *C*-glycosidic linkage of ET is established via intermolecular bonds between two monomeric units, one carrying anomeric carbon while the second one galloyl or HHDP group [3,35,41]. Most recently *C*-glycosidic ET including granadinin, vescalagin, methylvescalagin, castalagin, stachyurin, and casuarinin have been reported from the peel and seed fraction of camu-camu, a fruiting tree of Amazon rainforest [42]. Woody fractions of various fruits, particularly the nuts and berries, have also been observed to hold novel *C*-glycosidic ET (e.g., castalagin and vescalagin). Castacrenins D and F are two other forms of *C*-glycosidic ET isolated from the woody fraction of Japanese chestnut and carry gallic acid/ellagic acid moieties [43]. Treating vescalagin with *Lentinula edodes* generates quercusnins A and B that may be referred as fungal metabolites of *C*-glycosidic ET [44]. Castacrenins D and F isolated from chestnut wood may generate oxidative metabolites, namely castacrenins E and G, by replacing pyrogallol rings of *C*-glycosidic ET with cyclopentone rings [43]. Rhoipteleanins H, I, and J were reported as novel *C*-glycosidic ET isolated from the fruit and bark fractions of *Rhoiptelea chiliantha*. Structural configuration of rhoipteleanins H revealed the presence of cyclopentenone carboxy moieties that are generated by oxidation and rearrangement of *C*-glycosidic ET aromatic ring [45].

Condensate of *C*-glycosidic ET is another subclass of hydrolysable tannins, which includes rhoipteleanin J produced by the intermolecular condensation (C–C or C–O) of monomeric *C*-glycosidic ET followed by oxidation of aromatic rings of ET [45]. Wine aged in oak wood barrels is often reported to carry oak ET, particularly the condensation products of monomeric *C*-glycosidic ET. The studies infer *C*-glycosidic ET to play a significant role in modulation of organoleptic features of wine aged in oak wood barrels [46].

4. Ellagitannins Pharmacokinetics

A precise knowledge of phytochemicals' pharmacokinetics is very important to exploit their health benefits, as well as the effects of their metabolites [47]. *In vivo*, ET, instead of being absorbed directly into the blood stream, are physiologically hydrolyzed to ellagic acid, which is further metabolized to biologically-active and bioavailable derivatives, *i.e.*, urolithins, by the activity of microbiota in gastrointestinal (GI) tract [5,48]. The biological properties of ET, such as free radical scavenging, further depend on their metabolic transformation inside gut. ET recovered from pomegranate juice may be metabolically converted by gut microbiota to urolithin A, B, C, D, 8-*O*-methylurolithin A, 8,9-di-*O*-methylurolithin C, and 8,9-di-*O*-methylurolithin D, and some of these metabolites display higher antioxidant activity than the parental tannins themselves. For instance, urolithin C and D show an antioxidant capacity—as determined in a cell-based assay—which is 10- to 50-fold higher as compared to punicalagin, punicalin, ellagic acid, and gallic acid [49]. This finding suggests that intestinal transformation products of ET are likely to play a central role for the antioxidant properties at least inside the GI tract. Significant differences in urolithins' profiles in individual human subjects feed on raspberries—a renowned source of ET—have been attributed to gut microflora, whose variations on an inter-individual basis affect their capacity of hydrolyzing ET and subsequent metabolite synthesis [48,50]. The interaction of gut microbiota composition and the host endogenous excretory system is also likely to play a further role in the observed inter-individual variability [51]. ET are highly stable under the acidic environment of stomach, and retain their composition without being hydrolyzed to simpler compounds when exposed to various gastric enzymes. Consequently the complex structure of ET impedes their gastric absorption: however, the stomach might serve as the first site of absorption of free ellagic acid and pre-hydrolyzed forms of ET.

Contrary to stomach, the neutral or alkaline environments of duodenum and small intestines, characterized by pH values ranging from 7.1 to 8.4, allow ET hydrolyzation [31,41]. In humans, ET are rapidly absorbed and metabolized, as documented by [18,52]: following ingestion of pomegranate juice (at a dose containing 25 mg of ellagic acid and 318 mg of ET), ellagic acid can be found in plasma for up to 4 h while, at later times, it is no more detectable. In contrast, another study reported that no ellagic

acid could be detected in plasma during the 4 h following the juice intake [53], a discrepancy which has been attributed to inter-individual variability [54]. Ellagic acid is converted by catechol-*O*-methyl transferase to dimethylellagic acid, which is then glucuronidated and excreted [52].

Finally, the microbiologically metabolized fraction of ET, *i.e.*, urolithins, is further incorporated to enterohepatic circulation system [18,53,55,56].

5. Ellagitannins for Tumor Chemoprevention and Therapy

The development of novel mechanism-based chemopreventive and antitumor approaches to fight cancer through the use of dietary substances which humans can easily accept has become an important goal. Along this line, ET have received increasing attention over the last two decades.

Similarly to other anticancer phytochemicals, ET display chemopreventive and chemotherapeutic activities [3]. The chemopreventive activity of ET and derivatives, such as ellagic acid has been primarily associated with their antioxidant capacity, that varies with the degree of hydroxylation [5,57] and depends from both a direct radical scavenging and iron chelation activity.

The well-known anti-inflammatory capacity represents another important feature of ET chemopreventive and antitumor activity [55], that being persisting inflammation involved both as a causative and a facilitating factor in carcinogenesis and cancer development [58]. For example, pomegranate ET inhibit pro-inflammatory pathways including, but not limited to, the NF-κB pathway, whose activation leads to immune reactions, inflammation, and the transcription of genes involved in cell survival, such as Bclx and inhibitors of apoptosis. Constitutive activation of NF-κB has been observed in prostate cancers, where it sustains chronic inflammation and promotes the development of high-grade prostate cancer. With respect to inflammation, it is worth noting that, similarly to many polyphenols, the antioxidant activity of ET participates to an "anti-inflammatory loop" with other mechanisms, since it lowers the levels of radicals which otherwise would act as pro-inflammatory stimuli.

The direct antiproliferative effects of ET have been attributed to multiple mechanisms (see the next subchapters) including the cell cycle arrest capacity and the properties enabling cancer cells to follow apoptosis through the mitochondrial route and self-destruction after replication [59–62]. In addition to directly targeting tumor cell survival, the cytotoxic/cytostatic activities of ET might also concur with the chemopreventive potential, since they prevent tumor cells from converting into more malignant phenotypes and from replicating.

A study on 1,3-di-*O*-galloyl-4,6-(s)-HHDP-β-D-glucopyranose (an ET from *Balanophora japonica* MAKINO) points to the complexity and multiplicity of the mechanisms contributing to the anticancer activity of ET, *i.e.*, the same complexity and multiplicity characterizing also other classes of phytochemicals. Indeed, the antiproliferative activity of 1,3-di-*O*-galloyl-4,6-(s)-HHDP-β-D-glucopyranose in human Hep-G2 liver cancer cells was also associated to an altered regulation of 25 miRNAs including the let-7 family members miR-370, miR-373, and miR-526b, identified as likely targets with roles in cell proliferation and differentiation [63]. The fact that in cell culture systems combinations of ET or of ET and other phytochemicals present in plant or fruit extracts are more cytotoxic than any single ET [64], is suggestive of the multifactorial effects, chemical synergy, and multiplicity of the mechanisms behind their antitumor activity. To this regard, the capacity of some ET to inhibit angiogenesis, a fundamental event accompanying tumor growth, both in *in vitro* and *in vivo* prostate cancer models [65], and to reduce endothelial cell growth through binding to vascular endothelial growth factor receptors [66] represents a further and significant antitumor mechanism.

In analogy to other polyphenols, ET could also be utilized to increase the sensitivity of tumor cells to standard chemotherapeutic drugs [67], with the aim of obtaining an increase of their antitumor efficacy along with a reduction of their doses and, consequently, of their severe adverse effects which often represent a limiting factor for the prosecution of the therapeutic regimens.

As a premise to the literature data discussed in the next paragraphs, it is important noting that, since ET are not absorbed systemically after oral administration as such [48], the studies where ET

extracts were given to cultured cancer cells are unlikely to be predictive of the effects which could be attained after oral ingestion *in vivo*. Rather these data could be representative of intravenously administered ET, but the toxicology of this administration route is not known.

The next sections of the review will discuss more in depth the ET anticancer mechanisms and properties emerging from *in vivo* and *in vitro* studies on a panel of tumors or tumor cells which appear as potentially sensitive targets for these phytochemicals.

5.1. Prostate Cancer

Prostate cancer is the second leading cancer-associated death risk factor among U.S. males [68]. Phytochemicals originating from various food sources slow down the progression of prostate cancer, whereas a majority of other nutrients are reported to be non-effective in either preventing or curing prostate cancer [69]. Evidence-based findings support the consolidated role of fruits, vegetables, and various culinary herbs of different cultures in averting various forms of cancers, but relatively weak and inconsistent relationships have been presented so far for prostate cancer [70,71]. Somehow more promising seem to be the edible fruits containing high amounts of ET, which have been extensively tested *in vivo* for their prostate cancer inhibitory properties. As it has been shown in animal models, higher concentrations of ET are recorded in prostate and colon tissues as compared to the others [72]. Pomegranate holds one of the highest concentration of ET [55]. Antitumor activities of pomegranate fruit juice, peel extracts, and seed oil have been reported against prostate cancer cells [73]. Dose-dependent anti-proliferative and pro-apoptotic effects of pomegranate fruit extracts (10–100 μg/mL) have been documented against aggressive human prostate cancer cells (PC3) [74]: induction of pro-apoptotic mediators (Bax and Bak), downregulation of Bcl-2 and Bcl-XL, and reduced expression of cyclin-dependent kinases 2, 4, 6, and cyclins D1, D2, and E have been identified as the mechanisms responsible for these effects.

Pomegranate extract inhibited proliferation of endothelial (HUVEC) and prostate (LNCaP) cancer cells; the extract also reduced LNCaP prostate cancer xenograft size, tumor vessel density, VEGF peptide levels and HIF-α expression after four weeks of treatment in severe combined immunodeficient mice [65].

Oenothein B, a macrocyclic ET, and quercetin-3-*O*-glucuronide from *Epilobium* sp. herbs—used in traditional medicine to treat benign prostatic hyperplasia and prostatic adenoma—have been proven to strongly inhibit the proliferation of human prostate cancer cells [75]. *Hibiscus sabdariffa* leaf extracts, which contain high amounts of ellagic acid, have been reported to inhibit the growth [76] and the expressions of metastasis-related molecular proteins [75] of LNCaP cells via activation of the mitochondrial pathway and suppression of the Akt/NF-kB signaling pathway, respectively. *Terminalia chebula*—a common ayurvedic ethnic drug of the Indian subcontinent—has been recognized for its potential biological and pharmacological properties [77]. Chebulinic acid is the predominant and more characteristic ET among the various constituents of chebula fruit (*T. chebula*). Methanolic extract (70%) of *T. chebula* fruits was shown to inhibit proliferation and induce cell death in PC3 prostate cancer cells as well as in PNT1A non-tumorigenic human prostate cells in a dose-dependent manner [78]. At low concentrations, the extract promoted initiation of apoptotic cell death, while at higher doses necrosis was the predominant type of cell demise; chebulinic acid, tannic acid, and ellagic acid were the most cytotoxic phenolics, and are likely responsible for the antitumor activity of *T. chebula* fruit extracts [78].

5.2. Colon Cancer

Cancer statistics, as reported from Centers for Disease Control and Prevention, rate colon cancer as the fourth highest death factor in USA [68]. It is widely accepted that herbal sources may provide therapeutically relevant compounds for the management of colorectal cancers. In this regard, it is worth noting that World Health Organization estimates over 80% of the entire world population rely on biomolecules with broad ethnopharmacological properties as a primary health care solution [79].

The strict correlation between chronic inflammation, malignant transformation and development of colorectal cancer is widely recognized [80]. Indeed, non-steroidal anti-inflammatory drugs have proven to be effective in preventing the formation of colorectal tumors and their malignant transformation in both preclinical and clinical studies [81]. However, unwanted, sometimes severe or even fatal, side effects (ulceration, renal toxicity, gastric bleeding) represent a major limitation for the use of these synthetic drugs: in search of alternative therapeutic options, exploration and utilization of natural biomolecules as anti-inflammatory formulations are in progress [82]. Various phytochemicals modulate inflammatory cell signaling in colon cancer: among them, pomegranate ET (*i.e.*, punicalagin and ellagic acid) have been shown to suppress cyclooxygenase-2 (COX-2) protein expression in human colon cancer (HT-29) cells [83]. Exposing HT-29 cells to 50 mg/L of powdered pomegranate juice, total pomegranate ET, or punicalagin reduces the expression of COX-2 protein by 79%, 55%, and 48%, respectively, and inhibits production of pro-inflammatory prostaglandins [83]. Another study conducted by Kasimsetty *et al.*, [84] reported that pomegranate ET and their metabolites, *i.e.*, urolithins A and C, inhibit HT-29 cells proliferation via G0/G1 and G2/M arrest, followed by induction of apoptosis. Interestingly, urolithins display advantageous pharmacokinetics over other agents, in that they tend to persist in the colon through enterohepatic circulation. Scarce information is available on the mechanistic role of ET and their metabolites, mainly urolithins, in colon cancer chemoprevention. Sharma *et al.*, [85] showed that fruit ET and their metabolites inhibit canonical Wnt signaling pathway, which is involved in the development of the majority (~90%) of colon cancers. In this light, ET and their colon-derived metabolites may be most relevant in relation to cancer prevention rather than treatment. To this regard, it is important noting that the concentrations of ET and their metabolites such as ellagic acid or urolithin A resulting in a 50% inhibition of Wnt signaling in 293T human colon cancer cells are comparable with those nutritionally attainable after regular consumption of ET-rich fruits or beverages [85].

5.3. Breast Cancer

Breast cancer is the most prevalent, spontaneous hormone-associated malignancy in women and is the most common gender-related cause of death around the globe [86,87]. Estrogen is the major stimulating factor of breast cancer cells' proliferation and tumor cells' growth. Upregulation of growth hormone receptors in breast malignant cells, as compared to the normal breast tissue, points to the key role of the pituitary, as well as the growth hormones, in the development of breast cancer in humans [88].

Complementary and alternative medicines in the form of bioactive fractions and raw decoctions of herbs, edible and inedible segments of various fruits and vegetables, are under assessment for their potential in treating breast cancer [89]. Pomegranate, its juice, and other fractions of the fruit are the richest source of high-molecular-weight ET, in particular punicalagin, as compared to any other known and commonly-consumed fruit [55]. Estrogen-induced expression of peptides growth factors is the major concern in the development and growth of estrogen-responsive mammary cancer: inhibition of this circuitry is the rationale for the use of antiestrogens and aromatase inhibitors to treat these types of breast cancer [90,91]. Pomegranate ET-derived compounds have been shown to block endogenous estrogen synthesis by inhibiting aromatase activity. Polyphenol-rich fractions derived from fermented juice, aqueous pericarp extract and cold-pressed or supercritical CO_2-extracted seed oil of pomegranate (Wonderful cultivar) have been reported to inhibit aromatase and 17-beta-hydroxysteroid dehydrogenase type 1 (a key determinant of the increase in estradiol/estrone ratio) activities [92]. The same authors found that the polyphenol-rich fractions from fermented juice and pericarp inhibited the viability of MCF-7 estrogen-dependent tumor cells to a higher extent as compared to estrogen-independent MB-MDA-231 cells; interestingly, normal human breast epithelial cells (MCF-10A) were far less sensitive to the inhibitory effect of polyphenol-rich fractions. Among some other fruits, the ripened fruit and seeds of *Syzygium cumini* (commonly known as *jamun* in Indian subcontinent culture) and *Eugenia jambolana* have also been reported as good reservoir of ellagic

acid/ET which, in addition to anthocyanins, can exhibit anti-proliferative properties against various cancer cells [93]. Accordingly, and in strict analogy with the study by Kim *et al.*, [92], *Jamun* fruit extracts have been shown to inhibit over-expressing aromatase and estrogen-dependent MCF-7aro cell proliferation (IC50 27 μg/mL) more effectively as compared to estrogen receptor-negative MDA-MB-231 (IC50 40 μg/mL) breast cancer cells [94]. Pro-apoptotic effects were observed (200 μg/mL) against both MCF-7aro and MDA-MB-231 breast cancer cells, but not toward the normal MCF-10A breast cells.

Upregulation of the phosphoinositide-3 kinase (PI3K)/Akt signaling pathway is a common feature in most human cancers, including breast cancer. Targeting the PI3K pathway with small molecule inhibitors has been studied for therapeutic purposes, and inhibitors such as GDC-0941 or GDC-0980 have entered preclinical trials [95].

Cistaceae family—rock rose family—has been traditionally used in Mediterranean cultures since ancient times. Aqueous extracts recovered from the leaves of *C. populifolius*, which contain high amounts of punicalagin and other ET, have been shown to be cytotoxic against HER 2-dependent (MCF 7/HER2) and -independent (JIMT-1) human breast cancer cells [96]. Since JIMT-1 cells are representative of trastuzumab-resistant cells, *C. populifolius* extracts may be important in the treatment of breast tumors insensitive to this targeted drug.

Finally, oenothein B has proven to exert *in vitro* inhibitory properties against mammary ascites tumors (MM2) cells and Meth-2 solid tumors by releasing interlukin-1 and interlukin-1β-like cytokines [97].

5.4. Oral, Esophageal, and Gastric Cancers

Enzinger and Mayer [98] in their report published in the New England Journal of Medicine indicated esophageal cancer as the deadliest and least-studied type of cancer, with relatively small advancements in diagnosis and treatment over a three decades period. Among other etiological factors of esophageal cancer, inhalation of cigarette smoke is the most obnoxious one in exposing esophageal mucosa to potential carcinogens (*i.e.*, nitrosamines) [99]. Fruits, particularly berries, are a good source of antioxidant including vitamins, anthocyanins, ET, and a wide range of phenolic acids [100]. Consumption of fruits and vegetables has been linked with lower risks of gastrointestinal tract cancer development. This is one of the reasons that prompted researchers to exploit the nutraceutical potential of berries and their biomolecules as chemopreventive food and dietary supplements [101].

As demonstrated by Yoshida *et al.*, [23], high molecular weight oligomeric ET (eucarpanins and elaeagnatins) and macrocyclic dimers including camelliin B, oentothein B, and woodfordin C have cytotoxic properties and induce apoptosis through a pro-oxidant mechanism in tumor cells of oral squamous cell carcinoma (HSC-2, HSG) to a higher extent as compared to normal fibroblasts. These ET are contained in high amounts in flowering plants of *Myrtaceae* and *Elaeagnaceae* family. Black raspberries possess conspicuous quantities of anthocyanins and ET that make them rational candidates for a preventive and therapeutic approach against certain GI tract cancers [102]. Previous studies by Mandal and Stoner [103] and Daniel and Stoner [104] demonstrated that ellagic acid (4 g/kg b.w.) significantly decreased (~60%) the number of *N*-nitrosomethylbenzylamine (NBMA)-induced esophageal tumors in rats. Latter work by Stoner and Morse [105] confirmed the potent anti-tumorigenic property of ellagic acid in rats exposed to NMBA and tobacco nitrosamines through the inhibition of cytochrome P450, which is responsible for the metabolic activation of these carcinogens. Another study by Stoner *et al.*, [100] showed that a lyophilized mix of berries (black raspberries, blackberries, and strawberries) inhibits tumor initiation and progression via downregulation of COX-2 and inducible nitric oxide synthase, events leading to reduced prostaglandin production and nitrate/nitrite levels in the esophagus, respectively.

In a more recent study [106], NBMA-treated rats fed 5%–10% freeze-dried black raspberries showed fewer hyperplastic and dysplastic esophageal lesions, reduced tumor incidence (~54%), multiplicity (~62%), and proliferation as compared to NBMA control rats; more interestingly, it was

shown that black raspberries modulate the expression of a panel of genes and proteins involved in the late stages of NMBA-induced rat esophageal tumorigenesis, such as genes involved in carbohydrate and lipid metabolism, cell proliferation and death, inflammation, and proteins involved in cell-cell adhesion, cell proliferation, apoptosis, inflammation, angiogenesis, and both COX and lipoxygenase pathways of arachidonic acid metabolism.

However, the question of which is the relative contribution of ET and anthocyanins to the above chemopreventive activity of berries in esophageal cancer is still open. Indeed, a study by Wang *et al.*, [107] reported that different berries suppress NMBA-induced tumorigenesis irrespective of their ET and anthocyanin content. This finding suggests that also other components of the active preparations of berries, such as lignans and fibers, contribute to the whole chemopreventive capacity, which does not necessarily coincide with the simple sum of the intrinsic activity of each active constituent, but rather depends on positive (or negative) interactions occurring at specific proportions.

Gemin A and B, two ET from *Geum japonicum* Thunb., were found to exert mild cytotoxic effects on human BGC-823 gastric cancer cells [108].

As to oral cancer, Zhang *et al.*, reported that strawberry crude extracts or their isolated components including ellagic acid were toxic toward human oral CAL-27 and KB tumor cells [109]; ellagic acid alone (50–200 μM) exhibited selective cytotoxicity against HSC-2 oral carcinoma cells [110].

Lyophilized strawberries (LS), which carry 42.9% ET and their derivatives and 48.8% anthocyanins, have been referred as an effective option to prevent oral carcinogenesis: indeed a diet containing 5% LS reduced the number of 7,12-dimethylbenz[a]anthracene (DMBA)-induced cheek pouch tumors in hamsters inhibiting Ras/Raf/ERK-dependent cell proliferation, VEGF-dependent angiogenesis, 5-LOX/LTB4 pathway, and prevented oxidative damage [111]; LS was also found to modulate the genetic signature related to DMBA-induced tumor development, such as $p13^{Arf}$, p16, p53, and Bcl-2 [112].

In the same experimental model of hamster buccal pouch carcinoma, it was demonstrated that dietary supplementation of ellagic acid (up to 0.4%) modulated the expression profiles of 37 genes involved in DMBA-induced oral carcinogenesis [113], blocked the development of carcinomas by suppression of Wnt/β-catenin signaling associated with the inactivation of NF-κB and modulation of key components of the mitochondrial apoptotic network [114], and prevented angiogenesis by abrogating hypoxia-driven PI3K/Akt/mTOR, MAPK, and VEGF/VEGFR2 signaling pathways. These effects were mediated by the suppression of histone deacetylase 6 and HIF-1α responses [115].

By virtue of these properties, LS and its major component ellagic acid are considered among the most important and attractive nutraceutical tools for the prevention of oral cancer [116].

5.5. Liver Cancer

Primary liver cancer is, globally, the sixth most frequent cancer, and the second leading cause of cancer death, with a 17% five year survival rate; the leading cause of liver cancer is cirrhosis due to either hepatitis B, hepatitis C, or alcohol [117].

PGG, a major component of *Paeonia suffruticosa* ANDREWS and from *Rhus chinensis* Mill, was found to exhibit *in vitro* antiproliferative activity on human SK-HEP-1 hepatocellular carcinoma cells [118]. The growth-inhibitory effect was related to the ability to cause a G0/G1-phase arrest and to suppress the activation of NF-κB, likely via an IκB-mediated mechanism. PGG was also shown to induce atypical senescence-like S-phase arrest in HepG2 and Huh-7 human hepatocarcinoma cells at sub-lethal doses, increased senescence-associated β-galactosidase activity, and loss of proliferative capacity, through a mechanism involving intracellular generation of oxygen free radicals [119]. No evidence of necrosis or apoptosis was noticed in this study. Interestingly, a more recent report from the same group showed that autophagy was involved in the PGG-induced senescence-like growth arrest, and that activation of MAPK8/9/10 (mitogen-activated protein kinase 8/9/10/c-Jun *N*-terminal kinases) was an essential upstream signal for autophagy to occur [120]; interestingly, these *in vitro* results were also validated *in vivo* in a xenograft mouse model of human HepG2 liver cancer.

Intraperitoneal administration of corilagin from *Phyllanthus urinaria* was found to significantly reduce the *in vivo* growth of xenografted Hep3B hepatocellular carcinoma cells in athymic nude mice with no adverse effects on liver [121]. Corilagin inhibited the growth of normal or tumor hepatic cells with remarkably different IC50s: indeed the values for normal Chang-liver cells *vs.* the hepatocarcinoma cell lines Bel7402 and SMMC7721 were 131.4 *vs.* 24.5 and 23.4 μM, respectively [122]. The antiproliferative effect in SMMC7721 cells was causally associated with arrest at the G2/M phase by the activation of phospho-p53-p21$^{(Cip1)}$-cdc2/cyclin. Furthermore, a 47.3% growth inhibition was recorded in hepatocarcinoma MHCC97-H cells xenografted in Balb/c mice intraperitoneally treated with 30 mg/kg b.w. corilagin for five weeks.

In a parallel, but different direction, corilagin was found to enhance the cytotoxicity of the reference antitumor drugs cisplatin and doxorubicin on Hep3B hepatoma cells at nutritionally-attainable concentrations [67]. The association of corilagin with low dosages of standard anticancer drugs such as cisplatin or doxorubicin could increment their anticancer effect, enhance their cytotoxic activity toward multi-drug resistant cells, and reduce their toxicity.

Thonningianin A from *Thonningia sanguinea* inhibited the proliferation of HepG-2 human hepatocellular carcinoma cells [123]. Thonningianin A induced caspase-dependent apoptotic cell death, accompanied by an increase in the sub-G1 cell population and DNA fragmentation. Several mechanisms contributing to the antitumor effects were identified: thonningianin A disrupted the mitochondrial membrane potential promoting an increased generation of reactive oxygen species, downregulated the Bcl-xL mRNA expression, induced cell-cycle arrest by changing the cyclin D1 and CDK4 mRNA expression levels. Furthermore, thonningianin A significantly downregulated the NF-κB cell survival pathway concomitantly with the upregulation of the expression level of phosphorylated P38 and downregulation of the expression level of phosphorylated ERK.

5.6. Cervical Cancer

Cervical cancer has long remained a leading cause of malignancies-related death in women from United States of America. However, the number of cervical cancer patients and associated death toll has significantly decreased since last few decades, probably due to the regular Human Papilloma Virus (HPV) screening [124]. Apart from other risk factors, strong association exists between cervical cancers and HPV infection, and HPVs are indicated as central etiological factor in incidents of cervical cancer, globally [125]. Ramasamy *et al.*, [126] found that *Phyllanthus watsonii* extract induced apoptosis in HPV-transformed CaSki epidermoid cervical carcinoma cells, and attributed to the high ellagic content its cytotoxic effect. Raspberry extracts naturally enriched with ET inhibit proliferation of cervical cancer cells (HeLa) in a dose-dependent manner [127]. The study further reported the bound ET-enriched fraction of raspberry extracts as more effective (IC50 = 13 μg/mL) than the unbound anthocyanin-enriched fraction (IC50 = 67 μg/mL).

Hydrolysable tannins improve dysfunctional gap junctions communication, which are involved in carcinogenesis. Tellimagrandin I and chebulinic acid restore dysfunctional gap junctions in HeLa cells. *In vitro* exposure of HeLa cells to tellimagrandin I inhibits their proliferation as well as their substrate-independent growth [128].

Camelliin B, the hydrolysable tannin isolated from a non-edible plant (*i.e.*, *Gordonia axillaris* or fried eggplant), is another example of phytochemical useful for cervical cancer treatment. Camelliin B isolated from *G. axillaris* inhibited the growth of HeLa cells with an IC50 of 46.3 μg/mL as compared to the IC50 of 108.0 μg/mL observed in normal cervical fibroblasts [129]. The study showed that camelliin B induces chromatin condensation, a hallmark of apoptosis. Furthermore, camelliin B also exhibited DNA fragmentation properties and inhibited the DNA repair-associated enzyme poly (ADP-ribose) polymerase in HeLa cells. Walnut extracts rich in tellimagrandin I and II induce cytotoxic effects in human HeLa cancer cells by reducing mitochondrial respiration and promoting apoptosis [130]. Ellagic acid was shown to induce G1 arrest via induction of p21 and apoptosis in CaSki human cervix carcinoma cells [59].

The elevated risk of cervical cancer in cigarette smokers is thought to depend on the increased mutations in cervical cells caused by the persistence of smoke habit-associated DNA damage in the presence of HPV infection. Importantly, ellagic acid significantly attenuates cigarette smoke-induced DNA damage in HPV16-transformed human ECT1/E6 E7 ectocervical cells [131], an effect which is likely to derive from ellagic acid antioxidant and free-radical scavenging activity and that further support its chemopreventive potential.

5.7. Lung Cancer

Lung cancer is the most prevalent cancer worldwide [68]. The prognosis of lung cancer patients is still poor, and while it is not the most frequently diagnosed cancer in the United States, it is by far the leading cause of cancer-related deaths in the US and also worldwide. Therefore, advances in the treatment of lung cancer are urgently needed.

Although the relative importance of its major constituents, ET and anthocyanins, was not addressed, pomegranate extracts have been found to exert antiproliferative and chemopreventive activities against lung cancer *in vitro* and in animal models [132,133]. Other reports suggest a specific and important role for ET in the pomegranate extract activity against this type of malignancy, in both *in vitro* and animal experimental settings. In a study focusing on purified ellagic acid and punicalagin, Zahin *et al.*, [134] demonstrated that these two compounds were antimutagenic, prevented the formation of benzo[a]pyrene-induced DNA adducts, and were antiproliferative in non-small cell lung cancer A549 and H1299 lung cancer cells. It is worth noting that punicalagin, using the same toxicity tetrazolium assay, had been shown to be far less antiproliferative toward the same A549 cell line [135] as compared to the data reported by Zahin *et al*, [134]. This apparent discrepancy, which points to the importance of standardizing the experimental settings in this kind of studies, is likely to depend on the post-treatment incubation times before determining cell viability: in the first study, cell viability was determined at 24 h [121], while in the second one at 48 h [122], a time which allows a more accurate estimate of the growth inhibitory activity. Kuo *et al.*, [136] found that the ET casuarinin from the bark of *Terminalia arjuna* induced apoptosis in human breast adenocarcinoma MCF-7 cells and in A549 cells by blocking cell-cycle progression in the G0/G1 phase.

Similarly, *jamun* (*Syzygium cumini* L.) seeds and pulp hydrolyzed extracts have been reported to exert antiproliferative activity in A549 cells, which has been associated with the presence of ellagic acid [93].

5.8. Skin Cancer

Prolonged exposure of skin to UV radiation is causally linked to several pathological conditions, including photo-aging and photocarcinogenesis. UV damage is partly attributable to increased skin reactive oxygen species generation. Pomegranate fruit extract, which contains very high amounts of ET, has been shown to exert a significant protective effect against UV rays insult and pathological consequences. Orally-administered pomegranate extract containing 90% ellagic acid, by virtue of its antioxidant activity, has been shown to inhibit skin pigmentation induced by exposure to UV radiation in brown guinea pigs [137]; under the same conditions, the extract decreased melanocyte proliferation and melanin synthesis via inhibition of tyrosinase activity to a degree comparable to that of arbutin, an established tyrosinase inhibitor.

Several studies have confirmed the ability of standardized pomegranate extract and pomegranate ET (500–10,000 mg/L) to inhibit free radical generation in UVA- and UVB-irradiated human skin, thus protecting it from DNA fragmentation, skin burns, and pigmentation, and finally decreasing the risk of malignant transformation [4]. Various mechanisms involved include reduction of DNA damage, prevention of UVB-caused matrix metalloproteinases induction, inhibition of matrix metalloproteinases 2 and 9 activity, and decrease in UVB-induced c-Fos protein expression and c-Jun phosphorylation [138].

Animal studies further confirmed the chemopreventive and anticancer activity of ET-rich pomegranate extract: in a UVB initiation-promotion protocol, SKH-1 hairless mice receiving oral pomegranate extract supplementation showed reduced tumor incidence, prolonged latency periods of tumor appearance, and lower tumor body burden compared to that of unsupplemented UVB-irradiated control animals [139].

6. Risks and Safe Consumption Levels

In contrast with the widely accepted notion that ET, similarly to other phytochemicals, are health-promoting, chemopreventive, and therapeutically-valuable compounds, data emerged from some studies raised the question of the safety of their consumption [140]. In general, tannins may be toxic to cells and tissues because of their protein precipitation, enzymes inhibition, and mineral binding properties [140,141]. Furthermore, it was reported that pomegranate hydroalcoholic extract exerts mutagenic, genotoxic and clastogenic effects in a panel of *in vitro* and *in vivo* assays [142]. In Chinese hamster B14 cells, ellagic acid and gallic acid caused the production of DNA single-strand breaks with no relation to the concentration used, cytotoxic effects and increased lipid bilayer fluidity, an event which the authors suggested as contributing to DNA single-strand breakage [143]. However, these results are controversial and contradicted by studies demonstrating the lack of mutagenicity of ellagic acid in similar experimental settings [144] and by the hundreds of reports on the DNA protective activity of polyphenols, including ET, against established genotoxic agents.

A study conducted by Filippich *et al.*, [145] linked the generation of lesions on mice liver, early and severe liver necrosis, to punicalagin. However, an update on punicalagin risk assessment revealed neither hepatotoxic nor nephrotoxic effects following sub-chronic oral exposure (6% daily) to Sprague–Dawley rats [146].

ET have been reported to act as α-glucosidase inhibitors and, thus, proposed as adjunctive agents in type-2 diabetes management [147]: a caveat has been associated with this property since the dietary intake of any α-glucosidase inhibitor in normal circumstances might generate risks of carbohydrate malabsorption, gastrointestinal discomfort, flatulence, and diarrhea, such as for acarbose [148,149]. However, to the best of our knowledge, there is no report of such side effects causally linked to ingestion of ET-rich food and fruits.

ET, alongside the condensed tannins, could be considered as antinutritional in animal diets due to their ability of interacting with protein and inhibiting certain enzymes. Antinutritional effects have been reported in animal models, where diet carrying tannins at dosages higher than 10 g/kg b.w. affected animal growth and digestive capacity [150]. However, levels $\geqslant$10 g/kg b.w. are unlikely to be attained using standard nutritional regimens; furthermore, a study conducted for risk assessment of chestnut hydrolysable tannins included in lamb diet revealed the lack of any toxic response in terms of weight gain, protein conversion efficiency, and histopathological features [151].

To date, incomplete information is available on toxicity and risk assessment of individual ET. However, the no observed effect levels (NOEL) and no observed adverse effect levels (NOAEL) as determined in some reports are unlikely to portray dietary consumption-associated toxicity. For example, a 90-day sub-chronic toxicity study performed in F344 rats showed that ellagic acid NOEL was 3011 mg/kg b.w./day for males and the NOAEL and NOEL in females were 3254 mg/kg b.w./day and $\leqslant$778 mg/kg b.w./day, respectively, and there were no obvious histopathological changes in any of the groups [152]. A 90-day sub-chronic study showed that the LD50 of a standardized pomegranate fruit extract containing 30% punicalagin in Wistar rats was >5 g/kg b.w., with no visible sign of toxicity in terms of feed consumption, weight gain, ophthalmic, and pathological evaluation [153].

Dietary intake of ET varies among cultures, communities and region as has been evidently documented in studies from different countries [6,154]. A global report on the dietary consumption of phytonutrients reveals that peoples from Western Europe have maximum ellagic acid consumption trends in both genders (7.6 mg/day in males and 7.9 mg/day in females). Berries account approximately for 90% of the daily ellagic acid intake [154]. A few reports on the nutritional habits of

German and Finnish communities indicate that consumption of berries provides up to 5 mg and 12 mg ET per day, respectively [6,155,156]. Correlating ET consumption trends from various dietary sources with the so far identified NOEL or NOAEL for these biomolecules undoubtedly indicate that ET pose negligible threats to the safety and health security of the consumers, consolidating the notion that ET, either in individual or composite form, can potentially be exploited as health-promoting and potential chemopreventive phytonutrients.

As a final consideration, it could be speculated that an increasing use of ET as anticancer agents could pave the way to the adoption of administration routes different from oral one, such as the intravenous administration: such a route, however, would need to be characterized from the toxicological point of view since this kind of data is still lacking.

7. Concluding Remarks

The increasing awareness and knowledge of the capacity of plant-derived compounds to modify cell transformation and cancer cell growth suggest that they could serve as new tools for either preventive and therapeutic interventions. Today, ET are recognized as a class of phytochemicals characterized by a strong potential for development as chemopreventive, and possibly as therapeutic, agents against various human cancers. This could have a direct clinical and translational relevance to cancer patients if consumption of ET-rich fruits and vegetables will unequivocally prove to contrast the process of carcinogenesis and tumor growth, with positive outcomes in terms of survival and quality of life of the patient. To this end, future research should be addressed to define the actual clinical potential of ET through specific studies such as the determination of the systemic bioavailability from either food sources or concentrated formulations, the optimal period of administration and dosing, the toxicity and side effects (if any), the anticancer activity. The effects of single ET and of rational combinations of different ET should also be addressed. A multidisciplinary and coordinated approach will be needed and will involve basic research investigations, epidemiological and preclinical studies including the effect of combining ET with conventional antineoplastic drugs.

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Original Article

Annual Report to the Nation on the Status of Cancer, Part I: National Cancer Statistics

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BACKGROUND: The American Cancer Society (ACS), the Centers for Disease Control and Prevention (CDC), the National Cancer Institute (NCI), and the North American Association of Central Cancer Registries (NAACCR) collaborate to provide annual updates on cancer occurrence and trends in the United States. **METHODS:** Incidence data were obtained from the CDC-funded and NCI-funded population-based cancer registry programs and compiled by NAACCR. Data on cancer deaths were obtained from the National Center for Health Statistics National Vital Statistics System. Trends in age-standardized incidence and death rates for all cancers combined and for the leading cancer types by sex, race, and ethnicity were estimated by joinpoint analysis and expressed as the annual percent change. Stage distribution and 5-year survival by stage at diagnosis were calculated for breast cancer, colon and rectum (colorectal) cancer, lung and bronchus cancer, and melanoma of the skin. **RESULTS:** Overall cancer incidence rates from 2008 to 2014 decreased by 2.2% per year among men but were stable among women. Overall cancer death rates from 1999 to 2015 decreased by 1.8% per year among men and by 1.4% per year among women. Among men, incidence rates during the most recent 5-year period (2010-2014) decreased for 7 of the 17 most common cancer types, and death rates (2011-2015) decreased for 11 of the 18 most common types. Among women, incidence rates declined for 7 of the 18 most common cancers, and death rates declined for 14 of the 20 most common cancers. Death rates decreased for cancer sites, including lung and bronchus (men and women), colorectal (men and women), female breast, and prostate. Death rates increased for cancers of the liver (men and women); pancreas (men and women); brain and other nervous system (men and women); oral cavity and pharynx (men only); soft tissue, including heart (men only); nonmelanoma skin (men only); and uterus. Incidence and death rates were higher among men than among women for all racial and ethnic groups. For all cancer sites combined, black men and white women had the highest incidence rates compared with other racial groups, and black men and black women had the highest death rates compared with other racial groups. Non-Hispanic men and women had higher incidence and mortality rates than those of Hispanic ethnicity. Five-year survival for cases diagnosed from 2007 through 2013 ranged from 100% (stage I) to 26.5% (stage IV) for female breast cancer, from 88.1% (stage I) to 12.6% (stage IV) for colorectal cancer, from 55.1% (stage I) to 4.2% (stage IV) for lung and bronchus cancer, and from 99.5% (stage I) to 16% (stage IV) for melanoma of the skin. Among children, overall cancer incidence rates increased by 0.8% per year from 2010 to 2014, and overall cancer death rates decreased by 1.5% per year from 2011 to 2015. **CONCLUSIONS:** For all cancer sites combined, cancer incidence rates decreased among men but were stable among women. Overall, there continue to be significant declines in cancer death rates among both men and women. Differences in rates and trends by race and ethnic group remain. Progress in reducing cancer mortality has not occurred for all sites. Examining stage distribution and 5-year survival by stage highlights the potential benefits associated with early detection and treatment. ***Cancer* 2018;124:2785-800**. © *2018* The Authors. *Cancer* published by Wiley Periodicals, Inc. on behalf of American Cancer Society. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

KEYWORDS: Annual Report to the Nation, cancer, incidence, mortality, National Program of Cancer Registries (NPCR), National Vital Statistics System (NVSS), North American Association of Central Cancer Registries (NAACCR), Surveillance, Epidemiology, and End Results (SEER), survival, trends.

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See companion article on pages 2801-14, this issue.

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INTRODUCTION

The American Cancer Society (ACS), Centers for Disease Control and Prevention (CDC), National Cancer Institute (NCI), and North American Association of Central Cancer Registries (NAACCR) have collaborated annually since 1998 to provide updates on cancer incidence and mortality patterns in the United States.[1-19] This report uses a single database to estimate delay-adjusted incidence to monitor population-based cancer trends. In addition to reporting on incidence and mortality trends overall and for common cancer sites, this year's report highlights 4 cancer sites (female breast, colon and rectum [colorectal], lung and bronchus, and melanoma of the skin) by presenting the percentage of cases by stage at diagnosis and 5-year survival estimates by stage at diagnosis.

MATERIALS AND METHODS

Data Sources

Cancer incidence data

Population-based cancer incidence data by age, sex, and race/ethnicity were obtained from 42 state registries that participate in the CDC's National Program of Cancer Registries (NPCR) and/or the NCI's Surveillance, Epidemiology, and End Results (SEER) Program. The data satisfied the NAACCR's data quality criteria and represented cases diagnosed from 1999 through 2014,[20] covering 89% of the US population. Information on incident cases came primarily from the abstracts of inpatient and outpatient medical records but also from a variety of other sources, including pathology reports and death certificates. This database of 42 registries was used to derive all incidence statistics presented in this report.

Anatomic site and histology were coded according to the International Classification of Diseases for Oncology (ICD-O) edition in use at the time of diagnosis and were converted to the third edition (ICD-O-3) coding[21] and categorized according to SEER site groups.[22] Only cases defined as malignant under ICD-O-2 and ICD-O-3 were included in this report, with the exception of bladder cancer. In situ and malignant cancers were combined when reporting bladder cancer incidence rates. All case counts and rates were adjusted for delay in reporting.[23] After adjusting for reporting delay, the 5-year fixed interval incidence rates are based on 3.6 million male cases and 3.5 million female cases diagnosed between 2010 and 2014.

Cancer mortality data

Although cancer incidence data were available through 2014, an additional year of data was available for analysis of mortality. Cause of death by age, sex, and race/ethnicity (1999-2015) came from the National Vital Statistics System and was based on death certificate information reported to state vital statistics offices and compiled into a national file covering all states in the United States by the National Center for Health Statistics (NCHS).[24] Categorization methods for cause of death have been described in previous reports.[19]

Race/ethnicity data

In this report, information on race and ethnicity was based on medical records for incidence or death certificates from the NCHS for mortality. Race was categorized as white, black, Asian/Pacific Islander (API), and American Indian/Alaska Native (AI/AN). Race information for AI/AN, however, was considered reliable only for geographic areas covered by the Indian Health Service Contract Health Service Delivery Areas (CHSDA)[10,25,26]; therefore, incidence and mortality data for AI/AN were based only on these areas. Overall, 83% of the AI/AN population lived in CHSDA areas between the years 2010 and 2014. This percentage varied by geographic area, with 100% or close to 100% of the AI/AN population living in CHSDA areas in Alaska, the Pacific Coast, the Southern Plains, and the East; 67% living in the Northern Plains; and 60% living in the Southwest. Hispanic ethnicity included individuals from all races identified as Hispanic. Although the accuracy of race and ethnicity reporting has improved over time, recent studies have demonstrated that reporting of race in medical records remains less accurate for API, Hispanic, and AIs/ANs than for whites and blacks.[27,28] We present incidence and mortality data separately by race and by Hispanic ethnicity. The number of cases included in the 5-year incidence rate calculation ranged from 12,000 male and 13,500 female AIs/ANs residing in CHSDA areas to almost 3 million white men and women.

Population data

The population estimates used as the denominators to calculate incidence and death rates were a modification of the intercensal and Vintage 2015 annual times series of July 1, county population estimates by age, sex, race, and Hispanic origin produced by the US Census Bureau's Population Estimates Program in collaboration with the NCHS and with support from the NCI.[29] The estimates incorporate intercensal (for July 1, 2000-2009) and Vintage 2015 (for July 1, 2010-2015) bridged, single-race estimates that are derived from the original multiple-race categories in the 2000 and 2010 Censuses, as specified in

the 1997 Office of Management and Budget standards for the collection of data on race and ethnicity.[30,31] Some additional adjustments were made to refine the July 1 population estimates, as with previous reports.[19]

Survival data

Estimates for 5-year relative survival were calculated for cases diagnosed from 2007 through 2013. We used 34 central cancer registries (33 states and 1 metropolitan area, referenced hereafter as states) compiled by the NAACCR (covering 70% of the US population) to examine survival differences by sex and cancer stage at diagnosis for cancers of the lung and bronchus, breast, colon and rectum, and melanoma of the skin.[32] These 34 states were considered to have sufficient vital status follow-up to conduct survival analyses, because they either conducted recent National Death Index linkages or they routinely conduct active vital status follow-up of all cases.[33] Cancers that were identified by death certificate or autopsy only were excluded from the survival analysis, as were patients who died so soon after diagnosis that their survival time was not measurable. The first site-specific cancer of the analysis period (2007-2013) was used in the analysis. Patients were followed for vital status through December 31, 2013, because not all registries had complete information on vital status through December 31, 2014.

Statistical Methods

Cancer incidence and death rates and trends

Cross-sectional incidence (2010-2014) and death (2011-2015) rates for all ages combined were calculated for all cancer sites combined and for the most common cancer sites by sex, race, and ethnicity. These rates were calculated with their 95% confidence intervals using SEER*-Stat software, version 8.3.4.[34,35] Incidence rates were adjusted for delay in reporting.[36] Similarly, we calculated overall cancer incidence and death rates for children (ages 0-14 years). All rates were age-standardized to the 2000 US standard population and were expressed per 100,000 persons.[34] Rates based on fewer than 16 cases were deemed to be statistically unstable and were suppressed.

Temporal trends in age-standardized, delay-adjusted cancer incidence (1999-2014) and death (1999-2015) rates were estimated using joinpoint regression,[37,38] with a maximum of 2 joinpoints (3 line segments) allowed in each model for incidence and 3 joinpoints (4 line segments) allowed in each model for mortality. The maximum number of joinpoints is based on the number of data points in the series.[39] The resultant trends were described by the annual percent change (APC). The 5-year average APCs (AAPCs) for 2010 through 2014 (incidence) and for 2011 through 2015 (mortality) were calculated using a weighted average of the slope coefficients of the underlying joinpoint regression line, with the weights equal to the length of each segment over the interval. The AAPC was equal to the APC when the AAPC was entirely within the last joinpoint segment.[40] Two-sided statistical significance ($P < .05$) for the APC and the AAPC was determined using a t test for the APC and for the AAPC when it lay entirely within the last joinpoint segment; and a Z test was used when the AAPC extended beyond the last joinpoint segment.[39]

In describing trends, the terms *increase* and *decrease* are used when the slope of the trend (APC or AAPC) was statistically significant; otherwise, the term *stable* is used. Trends based on fewer than 10 cases in any of the data years (1999-2014 for incidence and 1999-2015 for mortality) were considered statistically unstable and were suppressed.

RESULTS

Cancer Incidence Rates for All Sites Combined and for the Most Common Cancers

Figure 1 illustrates trends from 1999 to 2014 in age-standardized, delay-adjusted incidence rates for all cancer sites combined among men and among women. Incidence rates among men decreased throughout the study period, with the decrease accelerating from 0.6% (on average) per year during 1999 to 2008 to 2.2% (on average) per year during 2008 to 2014. In contrast, over the same 15-year period, incidence rates among women were stable.

Figure 2 presents average annual incidence rates and 5-year AAPCs (2010-2014) for the 17 most common cancers among men and the 18 most common cancers among women. Among men, incidence rates decreased for 7 of the 17 most common cancers: prostate (5-year AAPC, −7.6%), lung and bronchus (−2.4%), colon and rectum (colorectal) (−1.9%), urinary bladder (bladder) (−0.8%), esophagus (−1.6%), brain and other nervous system (−0.2%), and larynx (−2.3%) (Table 1 and Fig. 2). In contrast, incidence rates among men increased for 8 cancers: melanoma of the skin (5-year AAPC, 2.3%), kidney and renal pelvis (kidney) (1.1%), leukemia (1.6%), oral cavity and pharynx (1.3%), pancreas (1.0%), liver and intrahepatic bile duct (liver) (2.8%), myeloma (2.5%), and thyroid (2.4%). Incidence rates were stable for non-Hodgkin lymphoma (NHL) and stomach cancer.

Among women, incidence rates decreased for 7 of the 18 most common cancers: lung and bronchus (5-year

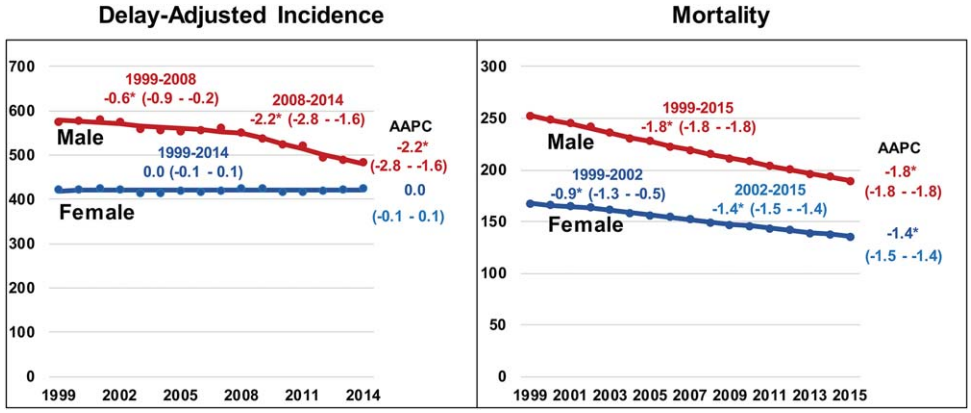

Figure 1. Trends in age-standardized incidence (1999-2014) and mortality rates (1999-2015) are illustrated for all cancer sites combined, all races/ethnicities combined, and by sex. An asterisk indicates that the annual percent change (APC) or the average APC (AAPC) is statistically significantly different from zero (2-sided *t* test; $P<.05$). UNK indicates unknown. Rates were age-standardized to the 2000 US standard population (19 age groups; Bureau of the Census. Current Population Reports, Publication 25-1130. Washington, DC: US Government Printing Office; 2000 [Census 25-1130]). Scattered points indicate observed rates, and lines are fitted rates according to joinpoint regression. Incidence rates were delay-adjusted and covered 89% of the US population, and mortality covered the entire United States. The following registries were included for incidence: Alabama, Alaska, Arizona, Arkansas, California, Colorado, Connecticut, Delaware, Florida, Georgia, Hawaii, Idaho, Illinois, Indiana, Iowa, Kentucky, Louisiana, Maine, Maryland, Massachusetts, Michigan, Missouri, Montana, Nebraska, New Hampshire, New Jersey, New York, North Carolina, North Dakota, Ohio, Oklahoma, Oregon, Pennsylvania, Rhode Island, South Carolina, Texas, Utah, Vermont, Washington, West Virginia, Wisconsin, and Wyoming. The AAPC is a weighted average of the APCs over the fixed interval (2010-2014 for incidence; 2011-2015 for mortality) using the underlying Joinpoint model for the period from 1999 to 2014 for incidence and the period from 1999 to 2015 for mortality. Joinpoint models with up to 2 joinpoints for incidence and up to 3 joinpoints for mortality are based on rates per 100,000 persons age standardized to the 2000 US standard population (19 age groups; Census P25-1130). For joinpoint analysis, the Joinpoint Regression Program was used (version 4.5.01; Bethesda, MD: Statistical Research and Applications Branch, National Cancer Institute; June 2017).

AAPC, −1.2%), colorectal (−1.7%), NHL (−0.4%), ovary (−1.6%), bladder (−0.8%), cervix uteri (cervix) (−1.0%), and brain and other nervous system (−0.7%). However, incidence rates increased for 10 cancers: breast (0.4%), corpus and uterus not otherwise specified (uterus) (1.2%), thyroid (1.9%), melanoma of the skin (1.2%), leukemia (1.4%), kidney (0.4%), pancreas (1.1%), oral cavity and pharynx (0.8%), myeloma (1.6%), and liver (3.8%). Incidence rates remained unchanged for stomach cancer (Table 1 and Fig. 2). Liver cancer replaced thyroid cancer as the most rapidly increasing incident cancer among women. For most cancer sites, the increasing or decreasing trends from 2010 to 2014 among men and among women were continuations of past trends (Supporting Table 1).

At the end of this Results section, incidence and mortality trends for female breast cancer, colorectal cancer, lung and bronchus cancer, and melanoma of the skin are discussed in greater detail—along with stage at diagnosis and survival by stage. Prostate cancer incidence and mortality are examined in detail in Part II of this report.

Cancer Death Rates for All Sites Combined and for the Most Common Cancers

Figure 1 illustrates trends in death rates from 1999 to 2015 for all cancer sites combined, by sex. Death rates decreased during this period by 1.8% on average per year among men and by 1.4% on average per year among women.

Figure 3 presents average annual death rates and 5-year AAPCs (2011-2015) for the 18 most common cancers among men and the 20 most common cancers among women. Among men, death rates during this period decreased for 11 of the 18 cancers: lung and bronchus (5-year AAPC, −3.8%), prostate (−2.2%), colorectal (−2.5%), leukemia (−2.2%), NHL (−2.0%), esophagus (−1.1%), kidney (−0.5%), stomach (−1.6%), myeloma (−0.9%), melanoma of the skin (−3.0%), and larynx (−2.5%). In contrast, death rates among men increased for cancers of the pancreas (0.2%), liver (1.6%), brain and other nervous system (0.5%), oral cavity and pharynx (1.0%), nonmelanoma skin (2.8%), and soft tissue (including heart) (0.8%). The death rate among men was stable for bladder cancer (Fig. 3 and Table 2).

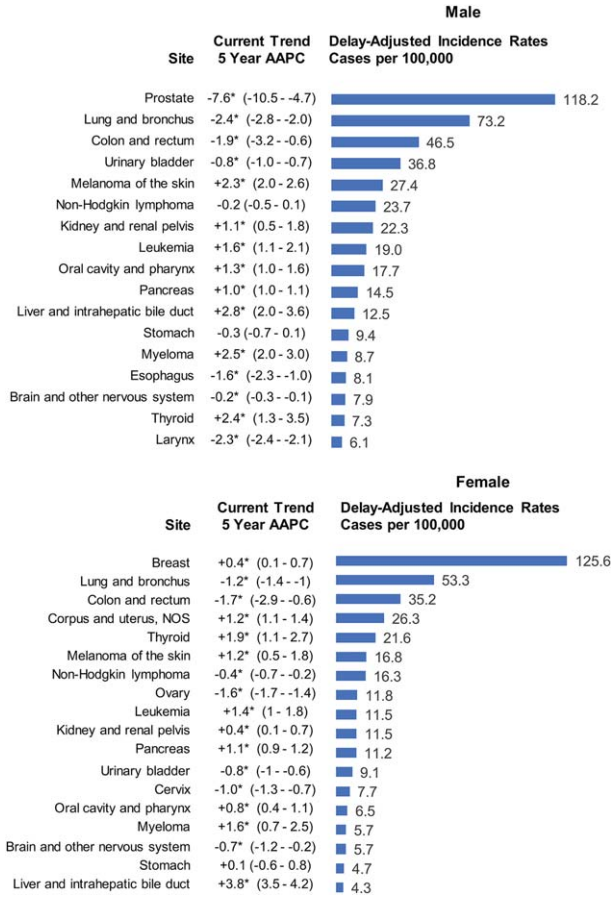

Figure 2. Age-standardized, delay-adjusted incidence rates and recent trends (2010-2014) are illustrated for the 17 most common cancers in men and the 18 most common cancers in women for all races/ethnicities combined and by sex. The 5-year average annual percent change (AAPC) is based on the joinpoint trend from 1999 to 2014. An asterisk indicates that the AAPC is statistically significantly different from zero (2-sided *t* test or *Z* test; $P < .05$). Rates were age-standardized to the 2000 US standard population (19 age groups; Census P25-1130), were delay-adjusted, and covered 89% of the US population. The following registries were included in the analyses: Alabama, Alaska, Arizona, Arkansas, California, Colorado, Connecticut, Delaware, Florida, Georgia, Hawaii, Idaho, Illinois, Indiana, Iowa, Kentucky, Louisiana, Maine, Maryland, Massachusetts, Michigan, Missouri, Montana, Nebraska, New Hampshire, New Jersey, New York, North Carolina, North Dakota, Ohio, Oklahoma, Oregon, Pennsylvania, Rhode Island, South Carolina, Texas, Utah, Vermont, Washington, West Virginia, Wisconsin, and Wyoming. The AAPC is a weighted average of the annual percent changes (APCs) over the fixed interval (2010-2014) using the underlying joinpoint model for the period from 1999 to 2014. Joinpoint models with up to 2 joinpoints are based on rates per 100,000 persons age standardized to the 2000 US standard population (19 age groups; Census P25-1130). For joinpoint analysis, the Joinpoint Regression Program was used (version 4.5.0.1; Bethesda, MD: Statistical Research and Applications Branch, National Cancer Institute; June 2017).

Among women, during the same time period, death rates decreased for 14 of the 20 most common cancer types: lung and bronchus (5-year AAPC, −2.4%), breast (−1.6%), colorectal (−2.7%), ovary (−2.3%), leukemia (−2.3%), NHL (−2.7%), kidney (−1.4%), stomach (−1.8%), cervix (−0.7%), bladder (−0.5%), melanoma of the skin (−2.6%), esophagus (−1.6%), oral cavity and pharynx (−1.3%), and gallbladder (−1.3%) (Fig. 3 and Table 2). In contrast, death rates among women increased for cancers of the pancreas (0.2%), uterus (1.9%), liver (2.7%), and brain and other nervous system (0.5%). Death rates among women were stable for myeloma and soft tissue (including heart). Like the incidence trends, increases or decreases in death rates for most cancers among men and women were continuations of past trends (Supporting Table 2).

Current Cancer Incidence Rates and Trends by Sex, Race, and Ethnicity

Table 1 lists average annual age-standardized, delay-adjusted incidence rates and trends for the most recent 5-year period (2010-2014) by cancer site, sex, race, and ethnicity. For all cancer sites combined, rates were higher among men than among women overall (all races/ethnicities combined; 502.0 vs 420.6 per 100,000 persons) and among persons in every racial/ethnic group. Black men and white women had higher overall cancer incidence rates than other racial groups. Non-Hispanic men and women had higher incidence rates than those of Hispanic ethnicity. API men and API women had the lowest rates relative to other racial and ethnic groups. In every racial and ethnic group, prostate cancer among men and breast cancer among women were the most frequent incident cancers, followed by lung and bronchus cancer, and colorectal cancer, except among Hispanics. Among Hispanic men and Hispanic women, colorectal cancer was more frequent than lung and bronchus cancer. Rankings for several other cancers varied substantially by race and ethnicity among both men and women. Among men, for example, melanoma of the skin ranked fifth in whites and 19th in blacks; and liver cancer ranked 11th in whites, sixth in blacks, and fourth in APIs.

Among men in each racial/ethnic group, incidence trends during 2010 to 2014 for all cancer sites combined and for each of the 17 most common cancers were generally similar in direction (decrease or increase) to those for all races/ethnicities combined (Table 1). Incidence rates among men in each racial and ethnic group decreased for all cancers combined and for each of the 3 most common cancers (prostate, lung and bronchus, colorectal), except that the rate was stable for lung and bronchus cancer among AIs/ANs. Rates also decreased among men in each racial/ethnic group for cancers of the bladder, stomach,

TABLE 1. Age-Standardized, Delay-Adjusted Incidence Rates and Fixed-Interval Trends (2010-2014) for the Most Common Cancers by Sex, Race, and Ethnicity for Areas in the United States With High-Quality Incidence Data[a,b]

	All Races[c]				White[c]				Black[c]				API[c]				AI/AN (CHSDA)[c]				Hispanic[c]				Non-Hispanic[c]			
Sex/Cancer Site or Type[d]	2010-2014 Rank	Rate[e]	AAPC[f]	*P*	2010-2014 Rank	Rate[e]	AAPC[f]	*P*	2010-2014 Rank	Rate[e]	AAPC[f]	*P*	2010-2014 Rank	Rate[e]	AAPC[f]	*P*	2010-2014 Rank	Rate[e]	AAPC[f]	*P*	2010-2014 Rank	Rate[e]	AAPC[f]	*P*	2010-2014 Rank	Rate[e]	AAPC[f]	*P*
All sites[g]																												
Both sexes		453.8	−1.0[h]	.001		457.3	−1.0[h]	.001		467.5	−1.4[h]	<.001		299.1	−0.4[h]	<.001		423.4	0.1	.43		356.2	−1.2[h]	<.001		465.7	−0.9[h]	.002
Males		502.0	−2.2[h]	<.001		500.1	−2.1[h]	<.001		558.2	−3.0[h]	<.001		309.0	−2.6[h]	<.001		446.8	−0.5[h]	.04		392.6	−2.8[h]	<.001		514.7	−2.1[h]	<.001
Females		420.6	0.0	.96		428.7	0.0	.59		406.8	0.3[h]	<.001		295.8	0.7[h]	<.001		409.9	0.6[h]	<.001		335.3	0.6	.14		431.5	0.1	.07
Males																												
Prostate	1	118.2	−7.6[h]	<.001	1	110.1	−7.0[h]	<.001	1	193.5	−6.0[h]	<.001	1	62.5	−9.5[h]	<.001	1	86.6	−9.0[h]	<.001	1	101.6	−7.8[h]	<.001	1	120.2	−7.6[h]	<.001
Lung and bronchus	2	73.2	−2.4[h]	<.001	2	73.1	−2.3[h]	<.001	2	85.8	−3.0[h]	<.001	2	46.4	−1.5[h]	<.001	2	74.4	−0.5	.16	3	41.4	−2.6[h]	<.001	2	76.3	−2.2[h]	<.001
Colon and rectum	3	46.5	−1.9[h]	.004	3	45.5	−1.9[h]	.005	3	56.1	−2.8[h]	<.001	3	38.2	−2.2[h]	<.001	3	53.2	−1.8[h]	.01	2	43.0	−2.7[h]	<.001	3	47.0	−1.8[h]	.003
Urinary bladder	4	36.8	−0.8[h]	<.001	4	39.3	−0.7[h]	<.001	5	20.3	0.7[h]	<.001	6	15.6	−0.4[h]	.03	5	21.5	0.4	.38	7	20.2	−1.9[h]	<.001	4	38.3	−0.6[h]	<.001
Melanoma of the skin	5	27.4	2.3[h]	<.001	5	31.1	2.5[h]	<.001	19	1.2	−0.3	.52	18	1.6	0.2	.72	12	10.1	11.7	.12	15	5.1	3.1	.10	5	30.0	2.6[h]	<.001
Non-Hodgkin lymphoma	6	23.7	−0.2	.11	6	24.4	−0.4[h]	.02	7	17.6	0.2	.12	5	16.4	0.4	.14	7	18.1	0.1	.94	5	20.6	−0.2	.32	6	24.1	−0.2	.85
Kidney and renal pelvis	7	22.3	1.1[h]	.001	7	22.5	0.7[h]	.001	4	24.7	1.0[h]	.03	9	11.4	2.3[h]	<.001	4	31.9	2.1[h]	.002	4	21.5	1.0	.21	7	22.5	1.2[h]	.001
Leukemia	8	19.0	1.6[h]	<.001	8	19.8	1.6[h]	<.001	11	14.7	1.0[h]	<.001	10	10.4	0.8[h]	.03	9	14.0	0.5	.55	8	14.1	0.5[h]	.03	8	19.3	1.7[h]	<.001
Oral cavity and pharynx	9	17.7	1.3[h]	<.001	9	18.3	1.6[h]	<.001	10	14.8	−1.9[h]	<.001	8	11.7	0.5	.13	8	17.1	1.3	.07	11	10.9	−0.9[h]	.003	9	18.6	1.6[h]	<.001
Pancreas	10	14.5	1.0[h]	<.001	10	14.4	1.1[h]	<.001	8	17.0	0.6[h]	.003	11	10.3	0.5[h]	.04	10	12.6	1.3	.19	10	12.3	0.5[h]	.03	10	14.7	1.1[h]	<.001
Liver and intrahepatic bile duct	11	12.5	2.8[h]	<.001	11	11.3	3.3[h]	<.001	6	17.7	2.6[h]	.002	4	20.6	−1.7[h]	.003	6	20.7	4.6[h]	<.001	6	20.4	1.1	.18	11	11.7	2.9[h]	<.001
Stomach	12	9.4	−0.3	.13	12	8.6	0.0	.95	12	14.3	−1.8[h]	<.001	7	14.3	−2.8[h]	<.001	11	11.9	−2.2[h]	.01	9	13.1	−2.1[h]	<.001	12	9.0	−0.1	.70
Myeloma	13	8.7	2.5[h]	<.001	15	8.0	2.3[h]	<.001	9	16.9	2.2[h]	<.001	13	5.2	2.6[h]	<.001	13	8.7	1.8	.11	12	8.5	1.5[h]	<.001	13	8.7	2.5[h]	<.001
Esophagus	14	8.1	−1.6[h]	<.001	14	8.4	−1.3[h]	.002	14	7.0	−4.7[h]	<.001	15	3.8	−1.0	.10	14	8.1	−0.8	.50	17	4.9	−3.6[h]	<.001	14	8.4	−0.9	.21
Brain and other nervous system	15	7.9	−0.2[h]	.003	13	8.5	−0.1	.08	15	5.0	0.3	.24	14	4.4	0.3	.32	15	6.1	1.0	.34	13	6.1	−0.5[h]	.003	15	8.3	0.0	.95
Thyroid	16	7.3	2.4[h]	<.001	16	7.8	2.3[h]	.001	16	3.9	4.9[h]	<.001	12	7.1	5.6[h]	<.001	18	4.8	4.2[h]	.01	14	5.5	4.5[h]	<.001	16	7.7	2.3[h]	<.001
Larynx	17	6.1	−2.3[h]	<.001	18	6.0	−2.1[h]	<.001	13	8.5	−3.2[h]	<.001	16	2.2	−2.9[h]	.001	17	5.1	−1.9[h]	.04	16	5.0	−3.0[h]	<.001	17	6.2	−2.2[h]	<.001
Females																												
Breast	1	125.6	0.4[h]	.008	1	126.9	0.4[h]	.03	1	125.6	0.7[h]	.03	1	94.9	1.7[h]	<.001	1	108.8	1.9[h]	.001	1	95.3	0.4[h]	.03	1	129.5	0.5[h]	.002
Lung and bronchus	2	53.3	−1.2[h]	<.001	2	55.1	−1.1[h]	<.001	2	49.8	−0.9[h]	.001	2	28.6	0.2	.07	2	58.1	−2.0[h]	.02	3	25.6	−0.8[h]	<.001	2	56.2	−1.0[h]	<.001
Colon and rectum	3	35.2	−1.7[h]	.004	3	34.5	−1.7[h]	.02	3	41.5	−2.0[h]	.01	3	27.8	−3.5[h]	<.001	3	44.1	−0.8[h]	.04	2	30.0	−1.1	.11	3	35.9	−1.7[h]	.01
Corpus and uterus, NOS	4	26.3	1.2[h]	<.001	4	26.8	1.1[h]	<.001	4	25.9	2.4[h]	<.001	5	18.9	2.2[h]	<.001	4	23.5	1.5[h]	.005	4	22.7	2.7[h]	<.001	4	26.7	1.2[h]	<.001
Thyroid	5	21.6	1.9[h]	<.001	5	22.7	1.6[h]	<.001	6	14.1	2.7[h]	.05	4	21.8	1.5	.22	6	16.2	5.9[h]	<.001	5	20.5	2.5[h]	.002	5	21.9	1.8[h]	.001
Melanoma of the skin	6	16.8	1.2[h]	.002	6	19.6	1.4[h]	<.001	21	1.0	0.4	.38	18	1.3	−0.3	.66	16	6.5	1.7[h]	.04	17	4.4	0.2	.51	6	18.7	1.4[h]	.001
Non-Hodgkin lymphoma	7	16.3	−0.4[h]	.002	7	16.9	−0.5[h]	.001	8	12.5	0.7[h]	<.001	6	11.1	0.2	.44	7	14.7	0.2	.80	6	15.7	0.1	.42	7	16.4	−0.4[h]	.002
Ovary	8	11.8	−1.6[h]	<.001	8	12.2	−1.6[h]	<.001	10	9.5	−0.6[h]	.002	7	9.6	−0.2	.30	8	11.5	−0.5	.58	8	10.6	−1.3[h]	<.001	8	11.9	−1.6[h]	<.001
Leukemia	9	11.5	1.4[h]	<.001	9	12.0	1.1[h]	<.001	11	9.4	2.1[h]	<.001	11	6.7	1.1[h]	.002	10	9.8	0.6	.53	11	9.7	0.5[h]	.02	9	11.6	1.4[h]	<.001
Kidney and renal pelvis	10	11.5	0.4[h]	.03	10	11.7	0.4[h]	.03	7	12.7	−0.1	.89	14	5.1	−0.2	.79	5	18.9	1.7[h]	.01	7	12.4	2.0[h]	<.001	10	11.4	0.3	.09
Pancreas	11	11.2	1.1[h]	<.001	11	10.9	1.1[h]	<.001	5	14.6	0.8[h]	<.001	8	9.0	0.8[h]	.003	9	11.1	0.8	.32	9	10.6	0.6[h]	<.001	11	11.3	1.1[h]	<.001
Urinary bladder	12	9.1	−0.8[h]	<.001	12	9.6	−0.7[h]	<.001	14	6.8	−0.3	.19	15	4.0	−0.4	.42	15	6.6	1.8[h]	.05	15	5.2	−1.3[h]	.001	12	9.5	−0.6[h]	<.001
Cervix uteri	13	7.7	−1.0[h]	<.001	13	7.5	−0.7[h]	.004	12	9.4	−3.7[h]	.001	12	6.2	−2.8[h]	<.001	11	9.4	−6.3[h]	.03	10	9.9	−1.6	.10	13	7.4	−0.8[h]	.001
Oral cavity and pharynx	14	6.5	0.8[h]	<.001	14	6.7	1.0[h]	<.001	15	5.2	−0.8[h]	.001	13	5.3	−0.7	.09	14	6.6	0.7	.53	18	4.3	−0.2	.60	14	6.8	0.9[h]	<.001

TABLE 1. *Continued*

Sex/Cancer Site or Type[d]	All Races[c]				White[c]				Black[c]				API[c]				AI/AN (CHSDA)[c]				Hispanic[c]				Non-Hispanic[c]			
	2010-2014				2010-2014				2010-2014				2010-2014				2010-2014				2010-2014				2010-2014			
	Rank	Rate[e]	AAPC[f]	*P*	Rank	Rate[e]	AAPC[f]	*P*	Rank	Rate[e]	AAPC[f]	*P*	Rank	Rate[e]	AAPC[f]	*P*	Rank	Rate[e]	AAPC[f]	*P*	Rank	Rate[e]	AAPC[f]	*P*	Rank	Rate[e]	AAPC[f]	*P*
Myeloma	15	5.7	1.6[h]	.003	16	5.0	2.3[h]	<.001	9	12.5	2.0[h]	<.001	16	3.4	1.0	.06	17	5.8	−1.0	.35	14	5.7	2.0[h]	.003	16	5.7	1.6[h]	.004
Brain and other nervous system	16	5.7	−0.7[h]	.008	15	6.1	−0.7[h]	.01	17	3.6	0.1	.71	17	3.4	3.7[h]	.001	18	3.9	0.1	.95	16	4.6	−1.1[h]	<.001	15	5.9	−0.6[h]	.03
Stomach	17	4.7	0.1[h]	.77	17	4.1	0.5	.32	13	8.0	−1.3[h]	<.001	9	8.3	−2.5[h]	<.001	13	6.7	−1.5	.09	12	7.9	−1.5[h]	<.001	17	4.4	−0.8[h]	<.001
Liver and intrahepatic bile duct	18	4.3	3.8[h]	<.001	18	4.0	4.5[h]	<.001	16	5.2	3.6[h]	<.001	10	7.8	−0.5	.05	12	9.2	3.9[h]	.002	13	7.8	2.3[h]	<.001	18	4.0	4.1[h]	<.001

Abbreviations: AAPC, average annual percent change; AI/AN, American Indian/Alaska Native; APC, annual percent change; API, Asian/Pacific Islander; CHSDA, Indian Health Service Contract Health Services Delivery Area; NOS, not otherwise specified.

[a] Source: National Program of Cancer Registries and Surveillance, Epidemiology, and End Results areas reported by the North American Association of Central Cancer Registries as meeting high-quality incidence data standards for the specified time periods.

[b] The following registries were included in the incidence rates (2010-2014) and Joinpoint models (1999-2014) for all races/ethnicities, white, black, AI/AN, API, Hispanic, and non-Hispanic (42 states): Alabama, Alaska, Arizona, Arkansas, California, Colorado, Connecticut, Delaware, Florida, Georgia, Hawaii, Idaho, Illinois, Indiana, Iowa, Kentucky, Louisiana, Maine, Maryland, Massachusetts, Michigan, Missouri, Montana, Nebraska, New Hampshire, New Jersey, New York, North Carolina, North Dakota, Ohio, Oklahoma, Oregon, Pennsylvania, Rhode Island, South Carolina, Texas, Utah, Vermont, Washington, West Virginia, Wisconsin, and Wyoming.

[c] White, black, API, and AI/AN (CHSDA 2012 counties) include Hispanic and non-Hispanic; the race and ethnicity categories are not mutually exclusive. AI/AN (CHSDA 2012) statistics exclude data from Kansas.

[d] Cancers are sorted in descending order according to sex-specific rates for all races/ethnicities. More than 15 cancers may appear under males and females to include the top 15 cancers in every race/ethnicity group.

[e] Rates are per 100,000 persons and were age standardized to the 2000 US standard population (19 age groups; US Bureau of the Census, Current Population Reports, Publication 25-1130. Washington, DC: US Government Printing Office; 2000 [Census P25-1130]).

[f] The AAPC is the average APC and is a weighted average of the APCs over the fixed interval from 2010 to 2014 using the underlying Joinpoint model for the period from 1999 to 2014. Joinpoint models with up to 2 joinpoints are based on rates per 100,000 persons and age standardized to the 2000 US standard population (19 age groups; Census P25-1130). For joinpoint analysis, the Joinpoint Regression Program was used (version 4.5.0.1; Bethesda, MD: Statistical Research and Applications Branch, National Cancer Institute; June 2017).

[g] For all sites, myelodysplastic syndromes are included for the rate calculations but not for the APC calculations; they are excluded from cancer-specific analysis. Ovary excludes borderline tumors.

[h] The AAPC is statistically significantly different from zero (two-sided $P < .05$).

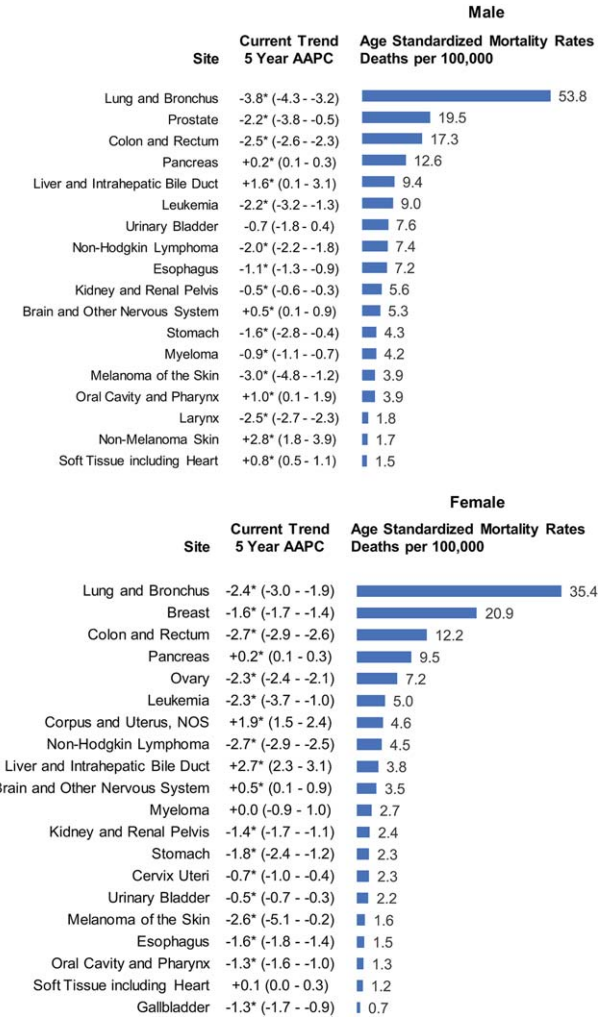

Figure 3. Age-standardized death rates and recent fixed-interval trends (2011-2015) are illustrated for the 18 most common cancers in men and the 20 most common cancers in women, for all races/ethnicities combined, and by sex. The 5-year average annual percent change (AAPC) is based on the joinpoint trend from 1999 to 2015. An asterisk indicates that the AAPC is statistically significantly different from zero (2-sided *t* test or *Z* test; $P<.05$). Rates were age-standardized to the 2000 US standard population (19 age groups; Bureau of the Census. Current Population Reports, Publication 25-1130. Washington, DC: US Government Printing Office; 2000 [Census P25-1130]). The AAPC is a weighted average of the annual percent changes over the fixed interval (2011-2015) using the underlying joinpoint model for the period from 1999 to 2015. Joinpoint models with up to 3 joinpoints are based on rates per 100,000 persons age standardized to the 2000 US standard population (19 age groups; Census P25-1130). For joinpoint analysis, the Joinpoint Regression Program was used (version 4.5.0.1; Bethesda, MD: Statistical Research and Applications Branch, National Cancer Institute; June 2017).

TABLE 2. US Cancer Death Rates and Fixed-Interval Trends (2011-2015) for the Most Common Cancers by Sex, Race, and Ethnicity[a]

Sex/Cancer Site or Type[c]	All Races[b]				White[b]				Black[b]				API[b]				AI/AN (CHSDA)[b]				Hispanic[b]				Non-Hispanic[b]			
	2010-2015				2011-2015				2011-2015				2011-2015				2011-2015				2011-2015				2011-2015			
	Rank Rate[d]	AAPC[e]	*P*		Rank Rate[d]	AAPC[e]	*P*		Rank Rate[d]	AAPC[e]	*P*		Rank Rate[d]	AAPC[e]	*P*		Rank Rate[d]	AAPC[e]	*P*		Rank Rate[d]	AAPC[e]	*P*		Rank Rate[d]	AAPC[e]	*P*	
All sites[f]																												
Both sexes	163.5	−1.5[f]	<.001		163.8	−1.4[f]	<.001		189.8	−2.1[f]	<.001		101.3	−1.3[f]	<.001		150.4	−0.7[f]	.001		114.6	−1.3[f]	<.001		167.7	−1.5[f]	<.001	
Males	196.7	−1.8[f]	<.001		196.4	−1.6[f]	<.001		239.9	−2.7[f]	<.001		120.4	−1.6[f]	<.001		181.4	−0.6[f]	.009		140.0	−1.6[f]	<.001		201.4	−1.7[f]	<.001	
Females	139.5	−1.4[f]	<.001		140.0	−1.3[f]	<.001		159.0	−1.6[f]	<.001		87.7	−1.0[f]	<.001		127.6	−1.4[f]	<.001		96.7	−1.0[f]	<.001		143.4	−1.4[f]	<.001	
Males																												
Lung and bronchus	1 53.8	−3.8[f]	<.001	1	53.9	−3.7[f]	<.001	1	65.1	−4.4[f]	<.001	1	31.0	−2.9[f]	<.001	1	45.0	−1.1[f]	.009	1	26.4	−3.0[f]	<.001	1	56.2	−3.7[f]	<.001	
Prostate	2 19.5	−2.2[f]	.01	2	18.2	−1.9[f]	.02	2	39.9	−4.1[f]	<.001	4	8.7	−2.8[f]	<.001	3	19.7	−1.2	.06	2	16.1	−2.8[f]	<.001	2	19.7	−2.1[f]	.01	
Colon and rectum	3 17.3	−2.5[f]	<.001	3	16.8	−2.0[f]	<.001	3	24.4	−2.6[f]	<.001	3	12.0	−2.0[f]	<.001	2	20.2	−0.4	.48	3	14.6	−1.6[f]	<.001	3	17.5	−2.5[f]	<.001	
Pancreas	4 12.6	0.2[f]	<.001	4	12.6	0.4[f]	<.001	4	14.8	−0.5[f]	.001	5	8.3	0.1	.64	5	9.6	−1.2	.31	5	9.5	0.1	.66	4	12.8	0.3[f]	<.001	
Liver and intrahepatic bile duct	5 9.4	1.6[f]	.03	6	8.7	1.8[f]	.03	5	13.2	0.8[f]	.41	2	14.0	−1.9[f]	.05	4	14.8	3.0[f]	<.001	4	13.0	−0.7	.45	6	9.1	1.8[f]	.02	
Leukemia	6 9.0	−2.2[f]	<.001	5	9.3	−2.1[f]	<.001	8	7.4	−1.5[f]	<.001	8	4.9	−0.6	.12	10	5.5	0.0	.96	8	6.0	−0.8[f]	.004	5	9.1	−2.2[f]	<.001	
Urinary bladder	7 7.6	−0.7	.21	7	8.0	0.1	.28	12	5.3	−0.4	.16	10	2.9	−0.2	.74	12	3.6	—[g]		10	3.9	−0.7[f]	.05	7	7.9	0.1	.23	
Non-Hodgkin lymphoma	8 7.4	−2.0[f]	<.001	8	7.7	−2.0[f]	<.001	11	5.4	−2.0[f]	<.001	7	5.0	−1.7[f]	<.001	9	5.6	−0.7	.43	7	6.1	−1.4[f]	<.001	8	7.5	−2.0[f]	<.001	
Esophagus	9 7.2	−1.1[f]	<.001	9	7.6	−0.6[f]	<.001	9	5.8	−4.8[f]	<.001	11	2.8	−1.3[f]	.03	8	5.9	−0.7	.44	11	3.9	−1.2[f]	.003	9	7.5	−1.0[f]	<.001	
Kidney and renal pelvis	10 5.6	−0.5[f]	<.001	10	5.8	−0.3[f]	.01	10	5.5	−0.9[f]	<.001	12	2.6	0.4	.52	6	8.4	−1.0	.17	9	5.0	−0.7[f]	.03	10	5.7	−0.4[f]	.002	
Brain and other nervous system	11 5.3	0.5[f]	.01	11	5.8	0.6[f]	.003	15	3.2	−0.1	.83	13	2.5	0.1	.82	14	3.0	2.0	.07	12	3.4	0.2	.56	11	5.6	0.6[f]	.003	
Stomach	12 4.3	−1.6[f]	.01	15	3.7	−2.0[f]	<.001	6	8.3	−3.3[f]	<.001	6	6.8	−4.0[f]	<.001	7	7.3	−3.0[f]	.008	6	6.7	−2.8[f]	<.001	14	4.0	−1.8[f]	.003	

and larynx, except that rates were stable for bladder cancer among AIs/ANs, were stable for stomach cancer among whites and non-Hispanics, and increased for bladder

TABLE 2. *Continued*

Sex/Cancer Site or Type[c]	All Races[b]				White[b]				Black[b]				API[b]				AI/AN (CHSDA)[b]				Hispanic[b]				Non-Hispanic[b]			
	2010-2015				2011-2015				2011-2015				2011-2015				2011-2015				2011-2015				2011-2015			
	Rank	Rate[d]	AAPC[e]	*P*	Rank	Rate[d]	AAPC[e]	*P*	Rank	Rate[d]	AAPC[e]	*P*	Rank	Rate[d]	AAPC[e]	*P*	Rank	Rate[d]	AAPC[e]	*P*	Rank	Rate[d]	AAPC[e]	*P*	Rank	Rate[d]	AAPC[e]	*P*
Myeloma	13	4.2	−0.9[f]	<.001	13	4.0	−0.8[f]	<.001	7	7.5	−1.2[f]	<.001	14	2.0	0.2	.78	13	3.4	−2.1[f]	.04	13	3.4	−0.9[f]	.03	12	4.3	−0.8[f]	<.001
Melanoma of the skin	14	3.9	−3.0[f]	.001	12	4.5	−2.8[f]	.003	25	0.5	−0.5	.45	21	0.4	—[g]		19	1.1	—[g]		17	1.0	−0.2	.71	13	4.2	−2.9[f]	.002
Oral cavity and pharynx	15	3.9	1.0[f]	.04	14	3.8	1.4[f]	.01	13	4.8	−3.2[f]	<.001	9	3.0	4.3	.20	11	3.7	−0.8	.41	14	2.4	2.5	.24	15	4.0	1.1[f]	.03
Larynx	16	1.8	−2.5[f]	<.001	17	1.7	−2.2[f]	<.001	14	3.3	−3.6[f]	<.001	17	0.7	−1.9[f]	.05	16	1.4	—[g]		15	1.5	−2.6[f]	<.001	16	1.8	−2.4[f]	<.001
Nonmelanoma skin	17	1.7	2.8[f]	<.001	16	1.8	3.3[f]	<.001	19	0.7	−2.4[f]	<.001	23	0.3	—[g]		18	1.1	—[g]		18	0.8	0.8	.23	17	1.8	3.7[f]	<.001
Soft tissue including heart	18	1.5	0.8[f]	<.001	18	1.6	0.9[f]	<.001	16	1.5	0.0	.93	16	1.0	1.0	.28	15	1.5	—[g]		16	1.2	0.9	.08	18	1.6	0.8[f]	<.001
Females																												
Lung and bronchus	1	35.4	−2.4[f]	<.001	1	36.6	−2.1[f]	<.001	1	33.5	−3.3[f]	<.001	1	17.7	−0.6[f]	.001	1	30.6	−1.6[f]	.002	2	13.3	−1.3[f]	<.001	1	37.4	−2.4[f]	<.001
Breast	2	20.9	−1.6[f]	<.001	2	20.3	−1.5[f]	<.001	2	28.6	−1.5[f]	<.001	2	11.3	1.1	.57	2	14.3	−1.1	.44	1	14.2	−1.2[f]	<.001	2	21.5	−1.6[f]	<.001
Colon and rectum	3	12.2	−2.7[f]	<.001	3	11.9	−1.5[f]	.01	3	16.0	−3.2[f]	<.001	3	8.6	−1.7[f]	<.001	3	13.6	−0.6	.39	3	9.0	−2.1[f]	<.001	3	12.5	−1.7[f]	.006
Pancreas	4	9.5	0.2[f]	<.001	4	9.4	0.3[f]	<.001	4	12.2	−0.2[f]	.01	4	7.3	0.3	.13	4	8.0	0.0	.96	4	7.7	0.1	.43	4	9.7	0.3[f]	<.001
Ovary	5	7.2	−2.3[f]	<.001	5	7.5	−2.5[f]	<.001	6	6.3	−1.4[f]	<.001	6	4.3	−1.1[f]	<.001	6	6.3	−0.8	.41	6	5.3	−1.2[f]	<.001	5	7.3	−2.4[f]	<.001
Leukemia	6	5.0	−2.3[f]	.001	6	5.2	−1.2[f]	<.001	9	4.5	−1.5[f]	<.001	10	2.9	−7.1[f]	.004	11	3.3	—[g]		9	3.9	−3.1[f]	.05	6	5.0	−1.3[f]	<.001
Corpus and uterus, NOS	7	4.6	1.9[f]	<.001	8	4.3	1.8[f]	<.001	5	8.3	2.5[f]	<.001	9	2.9	2.1[f]	<.001	8	3.6	—[g]		10	3.8	1.6[f]	<.001	7	4.7	1.9[f]	<.001
Non-Hodgkin lymphoma	8	4.5	−2.7[f]	<.001	7	4.6	−2.7[f]	<.001	12	3.4	−2.1[f]	<.001	8	3.2	−1.8[f]	<.001	10	3.4	−3.0[f]	.007	8	3.9	−2.3[f]	<.001	8	4.5	−2.7[f]	<.001
Liver and intrahepatic bile duct	9	3.8	2.7[f]	<.001	10	3.6	2.9[f]	<.001	8	4.6	1.5[f]	<.001	5	6.0	−1.1[f]	.007	5	7.0	0.8	.43	5	5.9	1.3[f]	<.001	10	3.7	2.7[f]	<.001
Brain and other nervous system	10	3.5	0.5[f]	.03	9	3.9	0.5[f]	.04	15	2.1	−0.1	.82	11	1.8	1.9[f]	.003	14	2.0	—[g]		12	2.5	0.0	.98	9	3.7	0.6[f]	.007
Myeloma	11	2.7	0.0	.92	12	2.4	−1.1	.26	7	5.5	1.0	.27	13	1.3	−1.7[f]	.03	12	2.7	−2.1	.14	13	2.3	−1.6[f]	<.001	11	2.7	−0.8	.46
Kidney and renal pelvis	12	2.4	−1.4[f]	<.001	11	2.5	−1.1[f]	<.001	14	2.4	−1.3[f]	<.001	15	1.1	−0.7	.24	7	4.1	−0.6	.52	14	2.3	−0.3	.36	12	2.4	−1.4[f]	<.001
Stomach	13	2.3	−1.8[f]	<.001	15	2.0	−1.6[f]	.001	10	3.9	−3.6[f]	<.001	7	4.2	−3.7[f]	<.001	9	3.5	−3.6[f]	.001	7	4.0	−2.2[f]	<.001	15	2.1	−2.3[f]	<.001
Cervix uteri	14	2.3	−0.7[f]	.001	14	2.2	0.6	.28	11	3.7	−2.6[f]	<.001	12	1.8	−2.8[f]	<.001	13	2.6	−2.2	.07	11	2.6	−2.4[f]	<.001	13	2.3	−0.6[f]	.003
Urinary bladder	15	2.2	−0.5[f]	<.001	13	2.2	−0.3[f]	.008	13	2.4	−1.5[f]	<.001	16	0.9	−0.9	.17	17	1.4	—[g]		15	1.3	−1.3[f]	.03	14	2.2	−0.4[f]	.001
Melanoma of the skin	16	1.6	−2.6[f]	.04	16	1.9	−0.5[f]	.005	24	0.3	−1.8[f]	.03	22	0.3	—[g]		20	0.5	—[g]		21	0.6	−0.8	.23	16	1.7	−0.5[f]	.005
Esophagus	17	1.5	−1.6[f]	<.001	17	1.5	−1.0[f]	<.001	16	1.8	−4.4[f]	<.001	19	0.7	−2.1[f]	.02	16	1.6	—[g]		19	0.8	−2.2[f]	<.001	17	1.5	−1.4[f]	<.001
Oral cavity and pharynx	18	1.3	−1.3[f]	<.001	18	1.3	−1.1[f]	<.001	18	1.3	−2.5[f]	<.001	14	1.1	−1.5[f]	.03	18	1.0	—[g]		18	0.8	−0.6	.24	18	1.4	−1.2[f]	<.001
Soft tissue, including heart	19	1.2	0.1	.11	19	1.1	−0.1	.17	17	1.5	0.4	.15	17	0.8	1.1	.15	19	0.9	—[g]		17	0.9	−0.2	.69	19	1.2	0.3[f]	.02
Gallbladder	20	0.7	−1.3[f]	<.001	20	0.7	−1.6[f]	<.001	19	1.0	0.1	.74	18	0.8	−1.0	.12	15	1.7	−3.8[f]	.001	16	1.2	−0.6	.41	20	0.7	−1.4[f]	<.001

Abbreviations: AAPC, average annual percent change; AI/AN, American Indian/Alaska Native; APC, annual percent change; API, Asian/Pacific Islander; CHSDA, Indian Health Service Contract Health Services Delivery Area; NOS, not otherwise specified.

[a] Source: National Center for Health Statistics public-use data file for the total United States, 1975 to 2015.

[b] White, black, API, and AI/AN (CHSDA 2012 counties) include Hispanic and non-Hispanic; the race and ethnicity categories are not mutually exclusive.

[c] Cancers are sorted in descending order according to sex-specific rates for all races/ethnicities. More than 15 cancers may appear under males and females to include the top 15 cancers in every race/ethnicity group.

[d] Rates are per 100,000 persons and are age standardized to the 2000 US standard population (19 age groups: ages < 1 year, 1-4 years, 5-9 years, . . ., 80-84 years, ≥ 85 years; US Bureau of the Census. Current Population Reports, Publication 25-1130. Washington, DC: US Government Printing Office; 2000 [Census P25-1130]).

[e] The AAPC is the average APC and is a weighted average of the APCs over the fixed interval from 2011 to 2015 using the underlying Joinpoint model for the period from 1999 to 2015. Joinpoint models with up to 3 joinpoints are based on rates per 100,000 persons and are age standardized to the 2000 US standard population (19 age groups; Census P25-1130). For joinpoint analyses, the Joinpoint Regression Program was used (version 4.5.0.1; Bethesda, MD; Statistical Research and Applications Branch, National Cancer Institute; June 2017).

[f] The APC is statistically significantly different from zero (1-sided $P < .05$).

[g] The statistic could not be calculated. The APC change is based on <10 cases for at least 1 year within the time interval.

cancer among blacks. Incidence rates among men increased in each racial and ethnic group for leukemia, myeloma, and cancers of the kidney, thyroid, pancreas, and liver, except that rates were stable for kidney and liver cancers among Hispanics and for leukemia, myeloma, and pancreas cancer among AIs/ANs.

Among women, overall cancer incidence rates increased during 2010 to 2014 among blacks, APIs, and AIs/ANs but remained stable in whites, Hispanics, and non-Hispanics. Incidence rates increased for female breast cancer in each racial and ethnic group (Table 1). Incidence rates among women also increased for cancers of the thyroid, liver, and uterus in each racial and ethnic group, except that rates remained stable for thyroid cancer and liver cancer among APIs. Incidence rates among women decreased for lung and bronchus cancer and colorectal cancer in each racial and ethnic group, except that rates were stable for lung and bronchus cancer among APIs and for colorectal cancer among Hispanics. As with men, for most cancer sites incidence trends for women in each racial and ethnic group were similar in direction to those for all women combined.

Current Cancer Death Rates and Trends by Sex, Race, and Ethnicity

Average annual death rates and trends from 2011 to 2015 are presented by cancer site, sex, race, and ethnicity in Table 2. For all cancer sites combined, similar to incidence rates, death rates (per 100,000 persons) were higher among men than among women overall (196.7 vs 139.5 for all races/ethnicities combined) and in every racial and ethnic group. Black men and black women had the highest cancer death rates of any racial group for all cancer sites combined, for 8 of the most common cancers in men, and for 9 of the most common cancers in women. Non-Hispanic men and women had higher overall cancer death rates than those of Hispanic ethnicity. Among men, lung and bronchus cancer was the leading cause of cancer death in every racial and ethnic group, followed by prostate and colorectal cancer in black, white, and Hispanic men; liver and colorectal cancer in API men; and colorectal and prostate cancer in AI/AN men. Among women, lung and bronchus, breast, and colorectal cancers were the leading causes of cancer death in every racial and ethnic group except Hispanics, in whom breast cancer replaced lung and bronchus cancer as the leading cause.

During 2011 to 2015, death rates declined overall and for the most common cancers (lung and bronchus, prostate, colorectal, breast) among men and women in all racial and ethnic groups, except that breast cancer death rates were stable among API and AI/AN women, colorectal cancer death rates were stable among AI/AN men and women, and prostate cancer death rates were stable among AI/AN men (Table 2). Death rates for most of the other cancer sites declined or were stable among men and women in each racial and ethnic group. However, death rates increased for some cancers in some racial and ethnic groups: liver cancer in white men and women, black women, AI/AN men, Hispanic women, and non-Hispanic men and women; pancreas cancer in white men and women and non-Hispanic men and women; uterus cancer in white, black, API, Hispanic, and non-Hispanic women; brain cancer in white men and women, non-Hispanic men and women, and API women; oral cavity and pharynx cancer in white men and non-Hispanic men; nonmelanoma skin cancer in white men and non-Hispanic men; and soft tissue (including heart) cancer in white men and non-Hispanic men and women.

Incidence and Mortality Trends, Survival by Stage, and Stage at Diagnosis for Female Breast Cancer, Colorectal Cancer, Lung and Bronchus Cancer, and Melanoma of the Skin

Figure 4 illustrates delay-adjusted incidence (1999-2014) and mortality (1999-2015) trends, 5-year survival estimates by stage (2007-2013), and the stage distribution at diagnosis for female breast cancer, colorectal cancer, lung and bronchus cancer, and melanoma of the skin. We focus on these 4 cancer sites because they are among the 5 sites that have the highest number of expected cases in 2017.[41] In addition to these 4 cancer sites, prostate cancer is among the top 5 sites based on the number of expected cases, but we do not include prostate cancer here because it is examined in detail in Part II of this report.

Female breast cancer incidence had been declining before 2004 but has increased since then at an average rate of 0.4% per year (Supporting Table 1). Female breast cancer mortality decreased during 1999 to 2015 (Supporting Table 2). Seventy-eight percent of cases were diagnosed at stage I or II, for which 5-year survival was high (100% and 92%, respectively) (Fig. 4). Approximately 6% of cases were diagnosed at stage IV, for which 5-year survival was 26.5%.

Colorectal cancer incidence rates decreased during 1999 to 2012 among men and women, although rates have been stable since 2012 (Supporting Table 1). Colorectal cancer mortality decreased during 1999 to 2015 among men and women (Supporting Table 2). Five-year survival for colorectal cancer (men and women combined) varied from 88.1% for cases diagnosed at stage I (23% of

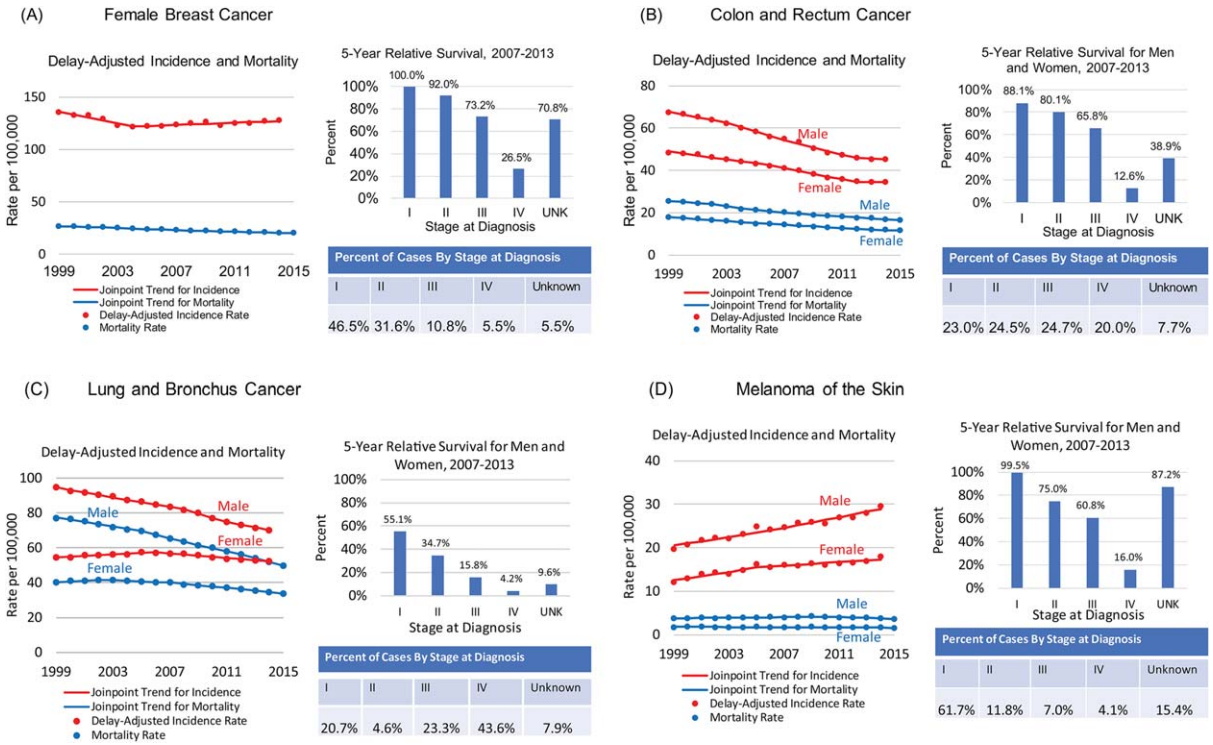

Figure 4. Delay-adjusted incidence (1999-2014) and mortality (1999-2015) trends, 5-year survival estimates by stage (2007-2013), and stage distribution at diagnosis are illustrated for (A) female breast cancer, (B) colon and rectum cancer, (C) lung and bronchus cancer, and (D) melanoma of the skin. Rates were age-standardized to the 2000 US standard population (19 age groups; Bureau of the Census. Current Population Reports, Publication 25-1130. Washington, DC: US Government Printing Office; 2000 [Census P25-1130]). Scattered points indicate observed rates, and lines are fitted rates according to joinpoint regression. Incidence rates were delay-adjusted and covered 89% of the US population, and mortality covered the entire United States. The following registries were included for incidence: Alabama, Alaska, Arizona, Arkansas, California, Colorado, Connecticut, Delaware, Florida, Georgia, Hawaii, Idaho, Illinois, Indiana, Iowa, Kentucky, Louisiana, Maine, Maryland, Massachusetts, Michigan, Missouri, Montana, Nebraska, New Hampshire, New Jersey, New York, North Carolina, North Dakota, Ohio, Oklahoma, Oregon, Pennsylvania, Rhode Island, South Carolina, Texas, Utah, Vermont, Washington, West Virginia, Wisconsin, and Wyoming. Joinpoint models with up to 2 joinpoints for incidence and up to 3 joinpoints for mortality are based on rates per 100,000 persons age standardized to the 2000 US standard population (19 age groups; Census P25-1130). For joinpoint analysis, the Joinpoint Regression Program was used (version 4.5.0.1; Bethesda, MD: Statistical Research and Applications Branch, National Cancer Institute; June 2017). Five-year relative survival rates covered 69.5% of the US population. The following registries were included for survival: Alabama, Alaska, Arizona, California, Colorado, Connecticut, Delaware, Florida, Georgia, Hawaii, Idaho, Illinois, Indiana, Iowa, Kentucky, Louisiana, Maine, Maryland, Michigan, Montana, Nebraska, New Hampshire, New Jersey, New York, North Carolina, Pennsylvania, Rhode Island, South Carolina, Utah, Vermont, Seattle, West Virginia, Wisconsin, and Wyoming.

cases) to 12.6% for cases diagnosed at stage IV (20% of cases) (Fig. 4).

Lung and bronchus cancer incidence and mortality rates remain higher among men than among women, but men have experienced a longer and more pronounced decrease in both rates over time (Fig. 4, Supporting Tables 1 and 2). Among women, lung and bronchus cancer incidence decreased during 2006 to 2014, and lung and bronchus cancer mortality decreased during 2002 to 2015 (Supporting Tables 1 and 2). Lung and bronchus cancer survival (men and women combined) was low, ranging from 55.1% for stage I (21% of cases) to 4.2% for cases diagnosed at stage IV (44% of cases) (Fig. 4).

The incidence of melanoma of the skin increased substantially since 1999 among men and among women, although the rates of increase among women began slowing in 2005 (Fig. 4 and Supporting Table 1). Melanoma mortality was stable during 1999 to 2015 in women; in men, it was stable during 2009 to 2013 and decreased during 2013 to 2015 (Supporting Table 2). Sixty-two percent of cases were diagnosed with stage I disease and 12% were diagnosed with stage II disease, for which the 5-year survival rates were 99.5% and 75%, respectively. Four percent were diagnosed at stage IV, for which the 5-year survival rate was 16% (Fig. 4).

TABLE 3. Delay-Adjusted Childhood Cancer Incidence Rates for Areas With High-Quality Data and US Childhood Cancer Death Rates by Race/Ethnicity, Both Sexes Combined, and Their Fixed-Interval Trends[a,b]

	Children: Ages 0-14 Years[c]							
	Incidence (2010-2014)				Mortality (2011-2015)			
Race/Ethnicity[d]	Rate[e]	AAPC[f]	95% CI	*P*	Rate[e]	AAPC[f]	95% CI	*P*
All races	16.6	0.8[g]	0.6, 1.0	<.001	2.1	−1.5[g]	−1.8, −1.2	<.001
White	17.3	0.7[g]	0.5, 0.9	<.001	2.2	−1.4[g]	−1.7, −1.0	<.001
Black	12.9	−1.1	−3.7, 1.3	.30	2.0	−1.6[g]	−2.1, −1.0	<.001
API	13.7	1.1[g]	0.4, 1.7	.004	1.7	−2.4[g]	−3.9, −1.0	.003
AI/AN CHSDA	12.6	−0.1	−1.4, 1.2	.84	1.9	—[h]		
Hispanic	16.1	0.4[g]	0.1, 0.6	.02	2.1	−2.0[g]	−2.5, −1.5	<.001
Non-Hispanic	16.8	1.0[g]	0.8, 1.1	<.001	2.1	−1.4[g]	−1.7, −1.0	<.001

Abbreviations: AAPC, average annual percent change; AI/AN, American Indian/Alaska Native; API, Asian/Pacific Islander; CHSDA, Indian Health Service Contract Health Services Delivery Area; CI, confidence interval.

[a] Source: National Program of Cancer Registries and Surveillance, Epidemiology, and End Results areas reported by the North American Association of Central Cancer Registries as meeting high-quality incidence data standards for the specified time periods.

[b] The following registries were included in the incidence rates (2010-2014) and Joinpoint models (1999-2014) for all race/ethnicities, white, black, AI/AN, API, Hispanic, and non-Hispanic (42 states): Alabama, Alaska, Arizona, Arkansas, California, Colorado, Connecticut, Delaware, Florida, Georgia, Hawaii, Idaho, Illinois, Indiana, Iowa, Kentucky, Louisiana, Maine, Maryland, Massachusetts, Michigan, Missouri, Montana, Nebraska, New Hampshire, New Jersey, New York, North Carolina, North Dakota, Ohio, Oklahoma, Oregon, Pennsylvania, Rhode Island, South Carolina, Texas, Utah, Vermont, Washington, West Virginia, Wisconsin, and Wyoming.

[c] For incidence, AI/AN (CHSDA 2012) statistics exclude data from Kansas.

[d] White, black, API, and AI/AN (CHSDA 2012 counties) include Hispanic and non-Hispanic; the race and ethnicity categories are not mutually exclusive.

[e] Rates are per 100,000 persons and were age standardized to the 2000 US standard population (19 age groups US Bureau of the Census. Current Population Reports, Publication 25-1130. Washington, DC: US Government Printing Office; 2000 [Census P25-1130]).

[f] The AAPC is the average APC and is a weighted average of the APCs over the fixed interval (2009-2013 for incidence; 2010-2014 for mortality) using the underlying Joinpoint model for the period from 1999 to 2014 for incidence and the period from 1999 to 2015 for mortality. Joinpoint models with up to 2 joinpoints for incidence and up to 3 joinpoints for mortality were based on rates per 100,000 persons that were age standardized to the 2000 US standard population (19 age groups; Census P25-1130). For joinpoint analysis, the Joinpoint Regression Program was used (version 4.5.0.1; Bethesda, MD: Statistical Research and Applications Branch, National Cancer Institute; June 2017).

[g] The AAPC is statistically significantly different from zero (2-sided $P < .05$).

[h] The statistic could not be calculated. The average APC is based on <10 cases for at least 1 year within the time interval.

Cancer Incidence and Mortality Among Children

The most common cancer sites for children vary by age. Overall, the most common sites are leukemia, brain and other nervous system, soft tissue, NHL, and kidney and renal pelvis. Bone and joint cancer and Hodgkin lymphoma are more common in older children. Among children ages birth to 14 years, the average annual, age-standardized, delay-adjusted incidence rates (all cancer types combined; per 100,000 persons) during 2010 to 2014 ranged from 12.6 among AIs/ANs to 17.3 among whites (both sexes combined) (Table 3). The average, annual age-standardized death rates during 2011 to 2015 ranged from 1.7 among APIs to 2.2 among whites. Incidence rates increased during 2010 to 2014 for all racial/ethnic groups combined (0.8% per year) and among children in 4 racial/ethnic groups (APIs, 1.1% per year; non-Hispanics, 1.0% per year; whites, 0.7% per year; and Hispanics, 0.4% per year). Among AI/AN and black children, incidence rates were stable. In contrast, death rates among children during 2011 to 2015 decreased overall (−1.5% per year; all races/ethnicities combined) and among children in every racial and ethnic group, except that the AAPC for AIs/ANs could not be calculated because of sparse data (Table 3). The greatest decrease in cancer mortality was observed among API children (−2.4%), and the smallest decreases were among white children and non-Hispanic children (−1.4% in each group).

DISCUSSION

Cancer incidence rates for all races/ethnicities combined continued to decline among men and were stable among women. Incidence rates from 2010 to 2014 decreased for 7 of the 17 most common cancers among men and for 7 of the 18 most common cancers among women, and rates increased for 8 cancer sites among men and 10 sites among women.

The largest increases in incidence rates were observed for liver cancer, myeloma, melanoma of the skin, thyroid cancer, and leukemia. Additional cancers with rising incidence trends during the most recent years include kidney and female breast. The increase in thyroid cancer incidence rates is largely thought to be caused by increased detection of small and indolent tumors through imaging[42,43]; however, the rates increased for both small and large tumors, suggesting a role for unidentified risk factors

in the rising trend.[44,45] It is believed that the increase in kidney cancer incidence rates in part reflects increased detection resulting from wider application of imaging techniques[46] as well as the obesity epidemic.[14] For all cancer sites combined, men had higher incidence rates than women within every racial and ethnic group. Overall, black men and white women had higher rates than other racial groups, and non-Hispanic men and women had higher rates than Hispanic individuals. These racial and ethnic differences were driven largely by the incidence of prostate cancer, female breast cancer, and lung cancer.

The increase in the breast cancer incidence rate continues the 0.4% increase observed in last year's report.[19] After decreasing in the early 2000s after cessation of hormone-replacement therapy,[47,48] the increase from 2004 to 2014 may in part reflect the obesity epidemic.[17] Increased detection through mammography is unlikely to have contributed to the recent trend, because mammography rates remained unchanged during the corresponding period.[49] The continued increase in melanoma incidence rates is thought to reflect increased harmful recreational sun exposure and tanning bed use, as well as increased detection.[50] The survival rates for early stage breast cancer and melanoma of the skin are extremely high (100% and 99.5% for stage I breast cancer and melanoma, respectively), suggesting the influence of screening on survival. These high survival rates may result from a combination of better prognosis because of early detection, some level of overdiagnosis associated with screening, and individuals with screen-detected disease being healthier than the general population.[51]

Overall cancer death rates have continued to decrease among both men and women for all major racial and ethnic groups, with the greatest decrease among black men and the smallest among AI/AN men. From 2011 to 2015, death rates for all races/ethnicities combined decreased for 11 of the 18 most common cancers among men and for 14 of the 20 most common cancers among women, including lung and bronchus (men and women), colorectal (men and women), female breast, and prostate. In contrast, cancer death rates increased for liver, pancreas, and brain and other nervous system among men and women; for oral cavity and pharynx, nonmelanoma skin, and soft tissue (including heart) among men; and for uterus among women. Black men and black women had the highest cancer death rates of any racial group during the most recent 5-year period. Except for female lung cancer, black men and black women had the highest death rates for cancer sites with the highest mortality in the overall population: lung, prostate, female breast, colorectal, and pancreas. Non-Hispanic men and women had higher overall cancer death rates than men and women of Hispanic ethnicity.

Factors that have contributed to the continued decreases in cancer death rates for the 4 most common cancers have been discussed in previous reports.[14-19] Briefly, the sustained decrease in lung and bronchus cancer death rates since the early 1990s among men and since the early 2000s among women has been attributed to the reduction in cigarette smoking over the past 5 decades.[11] Between 1964 and 2012, cigarette smoking decreased by about 50% because of public health policies against tobacco use (eg, increased excise taxes on cigarette smoking, smoke-free air laws) and increased awareness about the health hazards of smoking.[52] However, cigarette smoking still accounts for over one-quarter of cancer deaths in the United States.[53-55]

The continued decreases in death rates for female breast cancer, prostate cancer, and colorectal cancer largely reflect improved early detection and more effective treatments.[14-19] Because mammography use has been stable since the early 2000s,[48] the recent decrease in breast cancer death rates may largely reflect improvement in treatments, such as targeted therapies.[56] The use of prostate-specific antigen testing has substantially decreased following the US Preventive Services Task Force recommendations against routine testing for men aged 75 and older in 2008 and for all ages in 2012,[57,58] which may have contributed to the less rapid decline in prostate cancer death rates during the most recent years compared with the previous period. See Part II of this report for details on prostate cancer rates and prostate-specific antigen testing patterns. In contrast, it is believed that the rapid decrease in colorectal cancer death rates over the past decades is because of increased colonoscopy use[59,60] after reimbursement of the procedure was granted by Medicare for high-risk individuals in 1998 and for all eligible persons in 2001.[61] Unlike increases in breast cancer screening, which resulted in a large percentage of cases being diagnosed with stage I disease, increased colorectal cancer screening—because it detects precancerous polyps so they can be removed before becoming cancer—has instead resulted in decreases in incidence.

In addition to the decreases for the 4 most common cancers, death rates decreased for many other cancers. These include larynx (men), bladder (women), and esophagus (men and women)—mainly because of reductions in cigarette smoking and other tobacco use—and leukemia (men and women) and NHL (men and women) because of improved treatments.[19]

We have observed that death rates continued to increase for several cancers, including liver (both sexes), pancreas (both sexes), uterus, and oral cavity and pharynx cancer (men only). The increase in liver cancer death rates has been associated with the high prevalence of hepatitis C virus infection among Baby Boomers caused by sharing of contaminated needles for intravenous drug use from the 1960s through the 1980s, as well as the obesity epidemic.[18] It is also believed that the obesity epidemic has contributed to the increase in endometrial (uterus lining) and pancreas cancer death rates.[14] It is estimated that obesity accounts for 25% and 68% of pancreas and uterus cancer deaths, respectively, in the United States.[62] The recent increase in oral cavity and pharynx cancer death rates among men, confined to whites, is thought to be associated with an increase in human papillomavirus infection.[63] A recent study estimated that approximately 11 million men and 3.2 million women have oral human papillomavirus infection in the United States.[64]

The incidence of childhood cancers continues to increase, whereas mortality is decreasing. The cancers occurring in children represent a heterogeneous group of cancer sites that vary by age. To better understand the factors influencing the rates, a careful examination of specific cancer sites within this age group would be necessary.

Limitations

A limitation of this report is misclassification of race/ethnicity information in medical records (incidence), death certificates, and the Census. Since 2000, the Census has given respondents the option to self-select multiple race/ethnicity categories; this has created incompatibility with race/ethnicity information in medical records and death certificates, which often have single race/ethnicity categories. To address this problem, the US Census Bureau, in collaboration with the CDC's NCHS and the NCI, have developed methods to generate single-race population estimates—but with some uncertainties about the population estimates and resultant rates.[65] Furthermore, race/ethnicity information on death certificates is underascertained for AI/AN, API, and Hispanic populations,[27,28] leading to an underestimation of cancer rates. In addition, cancer rates for broad racial and ethnic groups (eg, Hispanics and APIs) may mask important variations in cancer burden by country of origin.

Conclusions

For all cancer sites combined, cancer incidence rates decreased among men but were stable among women. Overall, there continue to be significant declines in cancer death rates among both men and women. Differences in rates and trends by race and ethnic group remain. Progress in reducing cancer mortality has not occurred for all sites, the most notable exceptions being liver cancer and uterus cancer. Examining stage distribution and 5-year survival by stage highlights the potential benefits associated with early detection and treatment. The continued monitoring of national statistics identifies areas for potential intervention and control to reduce the burden of cancer in the US population.

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CONFLICT OF INTEREST DISCLOSURES

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AUTHOR CONTRIBUTIONS

Kathleen A. Cronin: Conceptualization, supervision, visualization, writing–original draft, and writing–review and editing. **Andrew J. Lake**: Software, validation, formal analysis, data curation, writing–original draft, writing–review and editing, and visualization. **Susan Scott**: Writing–original draft and project administration. **Recinda L. Sherman**: Conceptualization, methodology, writing–original draft, writing–review and editing, and visualization. **Anne-Michelle Noone**: Conceptualization, methodology, writing–original draft, and writing–review and editing. **Nadia Howlader**: Conceptualization, methodology, writing–original draft, and writing–review and editing. **S. Jane Henley**: Writing–review and editing. **Robert N. Anderson**: Writing–review and editing. **Albert U. Firth**: Software, validation, formal analysis, data curation, writing–original draft, writing–review and editing, and visualization. **Jiemin Ma**: Writing–review and editing. **Betsy A. Kohler**: Conceptualization, data curation, resources, and writing–review and editing. **Ahmedin Jemal**: Conceptualization, writing–original draft, and writing–review and editing.

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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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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).

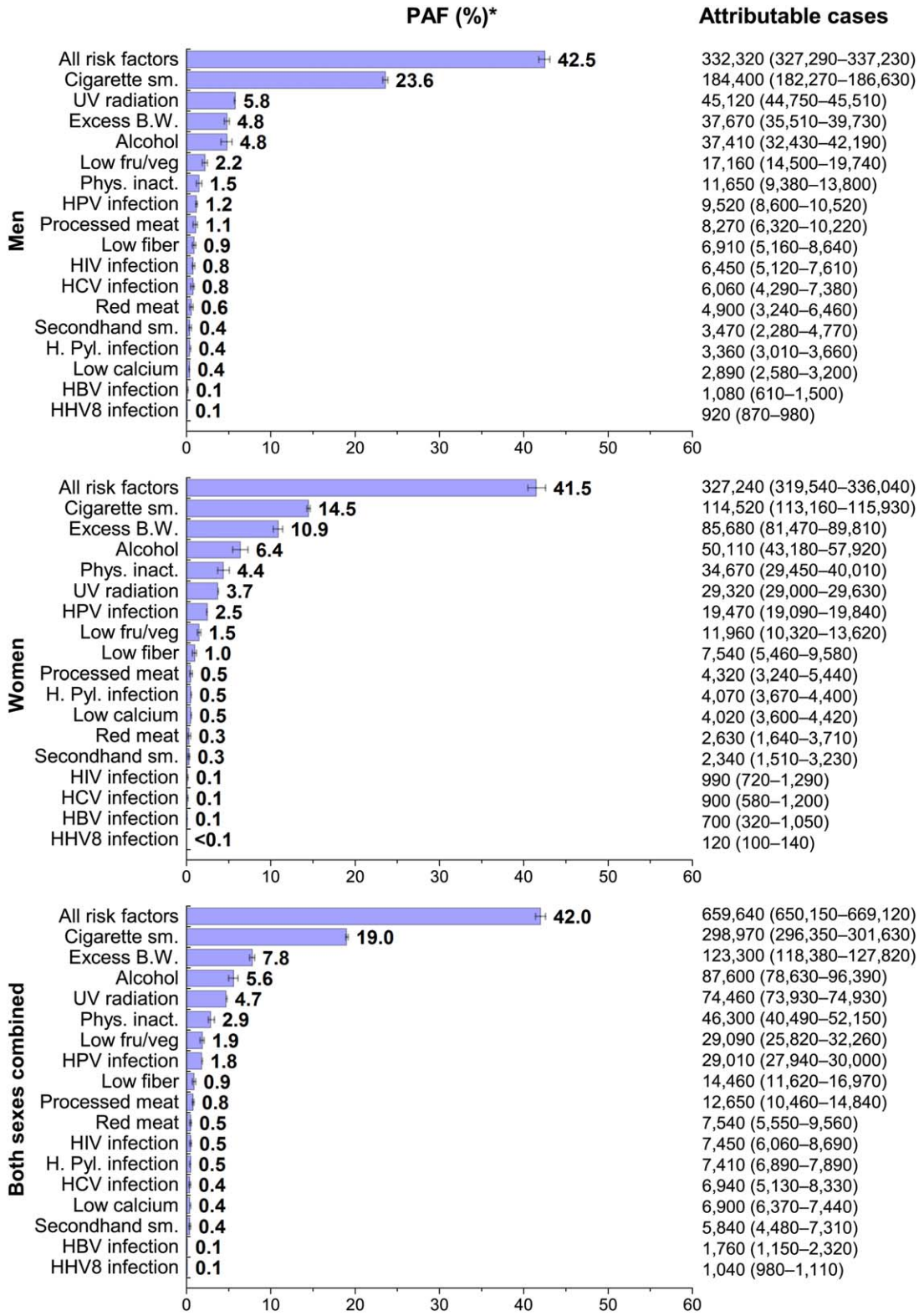

FIGURE 1. Estimated Proportion and Number of Incident Cancer Cases Attributable to Evaluated Risk Factors in Adults Aged 30 Years and Older in the United States in 2014, by Sex.

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.

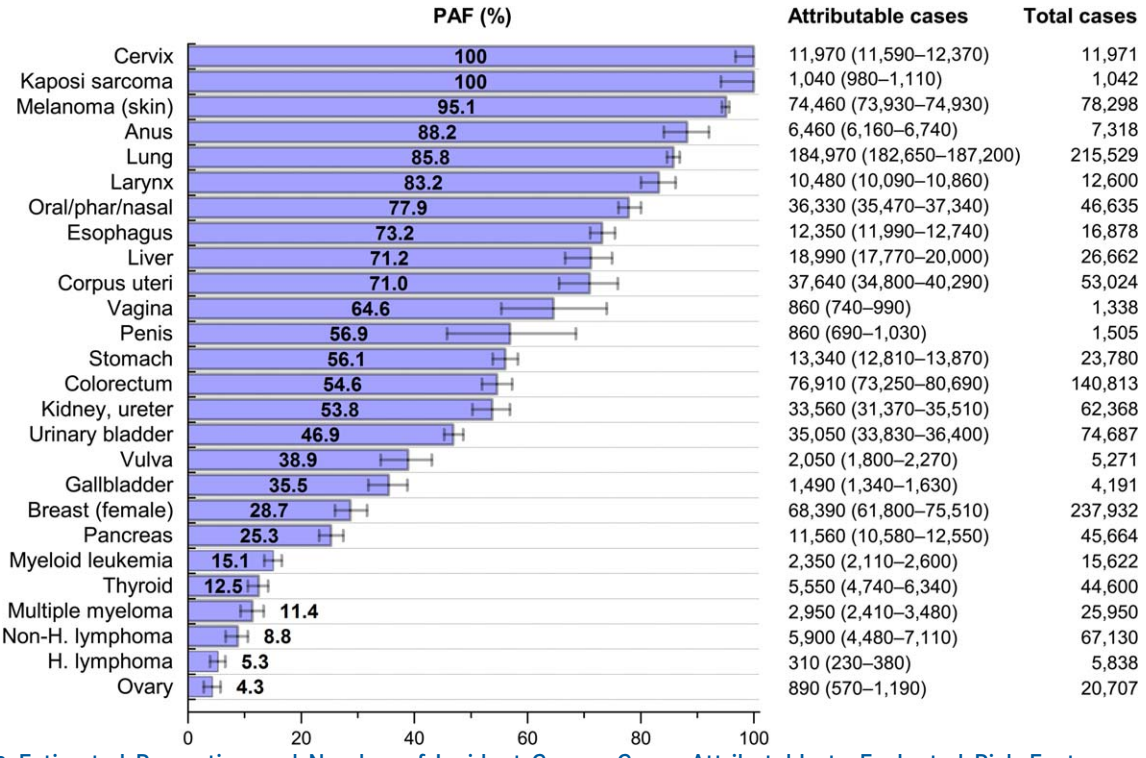

FIGURE 2. Estimated Proportion and Number of Incident Cancer Cases Attributable to Evaluated Risk Factors and Number of Total Cases in Adults Aged 30 Years and Older in the United States in 2014, by Cancer Type.

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

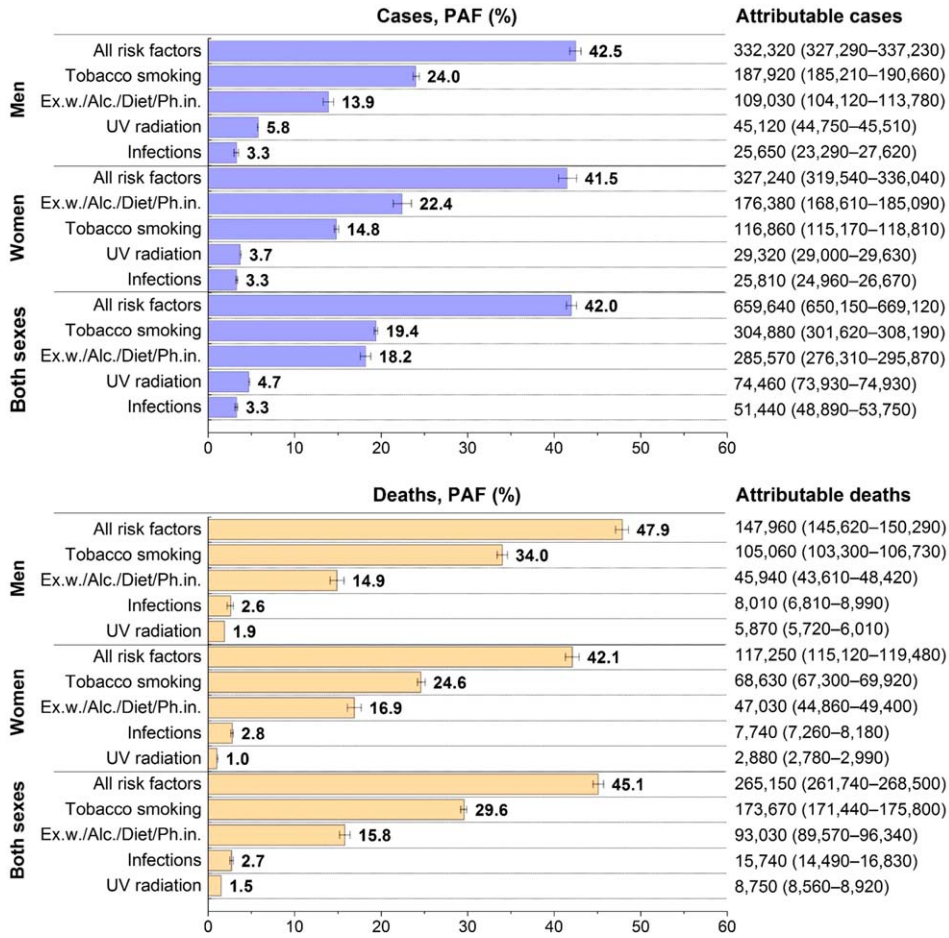

FIGURE 3. Estimated Proportion and Number of Incident Cancer Cases and Cancer Deaths Attributable to Risk Factor Groups in Adults Aged 30 Years and Older in the United States in 2014, by Sex.

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%).

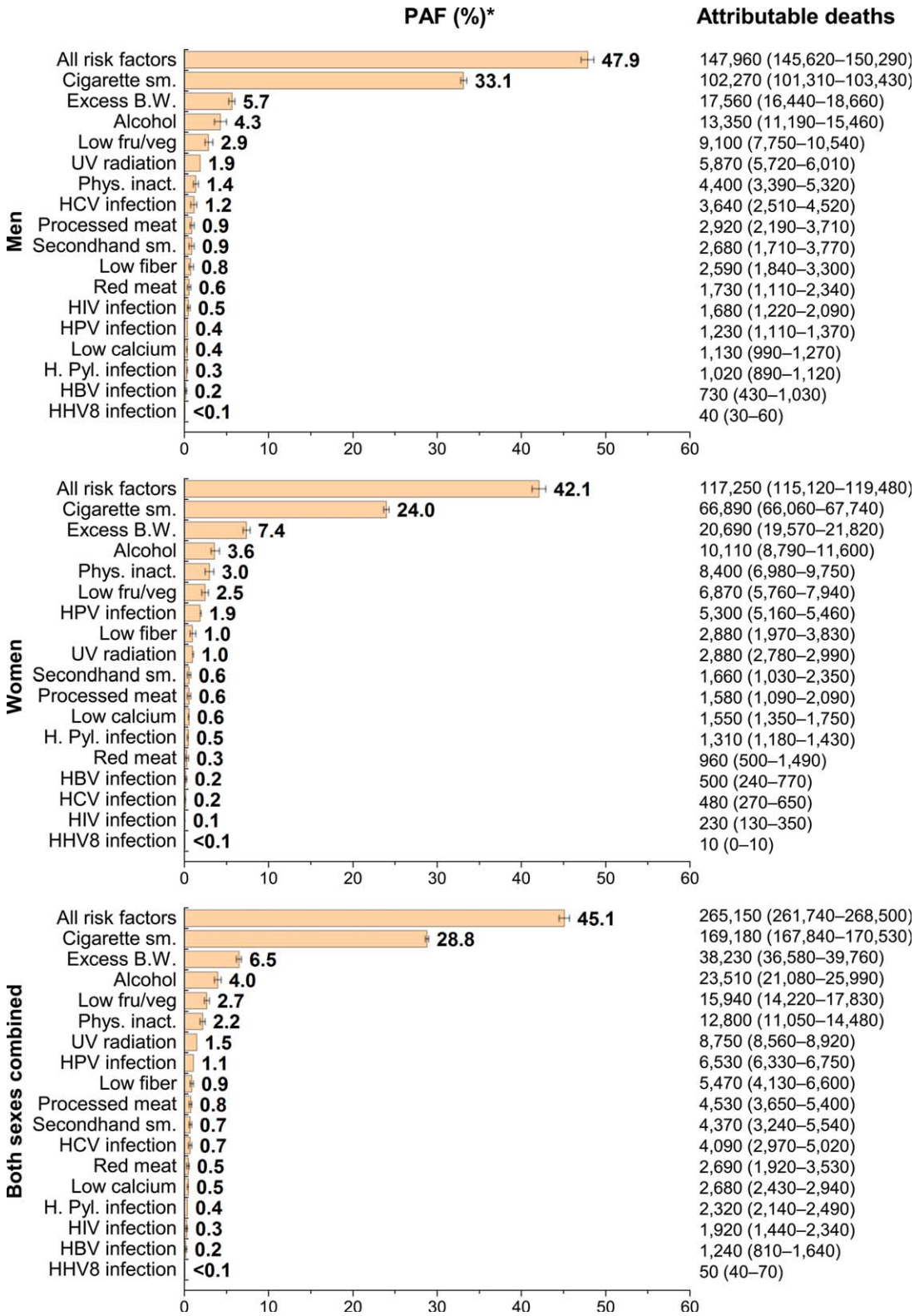

FIGURE 4. Estimated Proportion and Number of Cancer Deaths Attributable to Evaluated Risk Factors in Adults Aged 30 Years and Older in the United States in 2014, by Sex.

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.

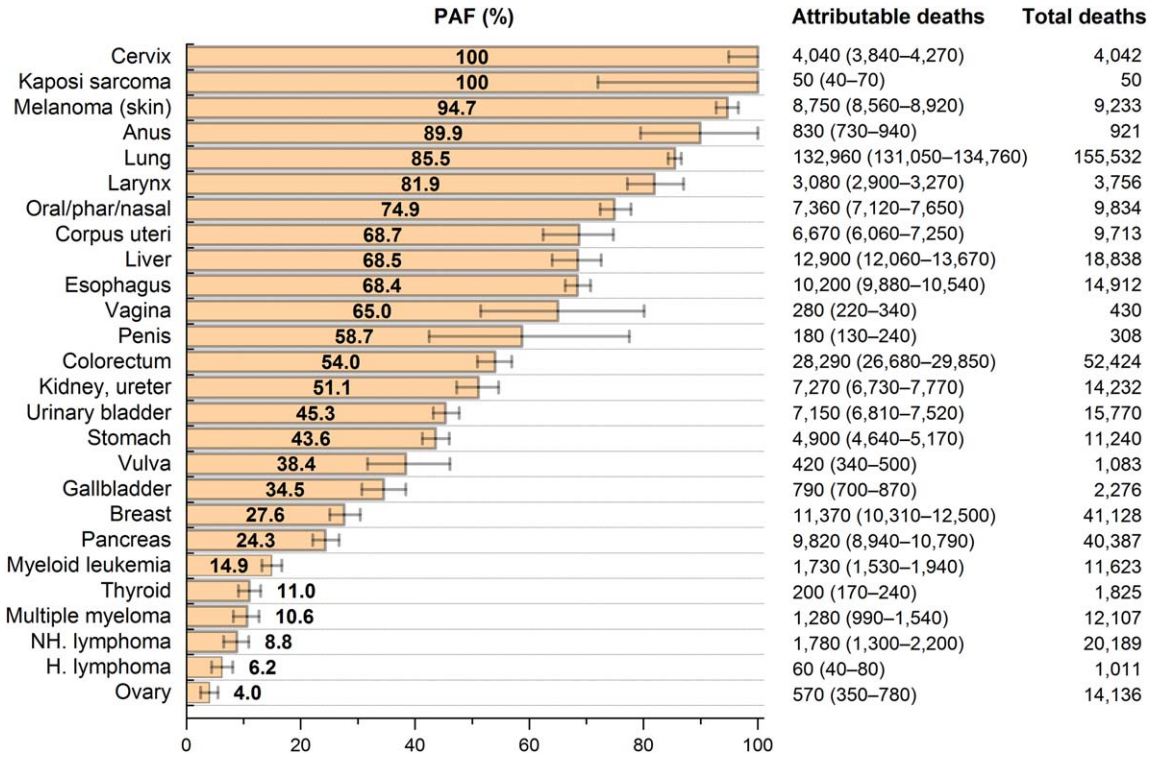

FIGURE 5. Estimated Proportion and Number of Cancer Deaths Attributable to Evaluated Risk Factors and Number of Total Cancer Deaths in Adults Aged 30 Years and Older in the United States in 2014, by Cancer Type.

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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