THE MED
REVIEW

Hannah Arem, PhD, and Erikka Loftfield, PhD

Cancer Epidemiology: A Survey
of Modifiable Risk Factors for
Prevention and Survivorship

Abstract: *Approximately 40% of men and women in the United States will be diagnosed with cancer at some point in their lives. There have been dramatic developments in our understanding of cancer development and progression in recent decades, leading to improvements in screening and treatment, and in turn greater numbers of survivors living longer after diagnosis. Epidemiologic evidence of lifestyle-related factors and cancer risk and survival has been explored extensively in the published literature, with recommendations for cancer prevention and control and strategies for implementation evolving over time. This review summarizes the burden of cancer, general measurement issues in cancer epidemiology, and the current state of the science in specific lifestyle-related risk factors and cancer. It is estimated that one third to one half of cancers could be prevented by healthier lifestyle choices.*

Keywords: cancer epidemiology; lifestyle; survivorship

Cancer Burden and
MeasurementBurden of Cancer in the
United States and Abroad

There were an estimated 1 685 210 new cancer cases diagnosed in the

United States in 2016.¹ The 5 most common cancer types among women include cancers of the breast, lung and bronchus, colon and rectum, uterine, and thyroid. Among men, the most common cancer sites include prostate, lung and bronchus, colon and rectum, urinary bladder, and melanoma of the skin.

Despite improvements in treatment and prognosis over the past decades, at present cancer is the second most common cause of death in the United

States, with an estimated 1630 cancer deaths each day.¹ One quarter of all annual cancer deaths are attributed to cancers of the lung and bronchus, making it the most common cause of cancer death for both men and women.²

The burden of cancer has increased worldwide. Alarming, the World Health Organization (WHO) predicts that the number of new cancer cases is expected to rise by approximately 70% over the next 20 years.³ While there is

Despite improvements in treatment and prognosis over the past decades, at present cancer is the second most common cause of death in the United States.

considerable overlap in common types of cancers worldwide, developing countries tend to have higher incidence and death rates for viral infection-related cancers such as hepatitis-related liver cancer and human papillomavirus (HPV)-related cervical cancer.

An estimated one third to one half of cancers could be prevented by healthy lifestyle choices: eliminating tobacco use,

maintaining a healthy body mass index (BMI), moderating alcohol consumption, and maintaining an active lifestyle.^{4,5}

Other major areas of epidemiologic research on modifiable risk factors and cancer risk or survival included in this review include exposure to infectious agents and hormones. While radiation, environmental, occupational, and genetic risk factors also play definitive roles in

DOI: 10.1177/1559827617700600. Manuscript received October 27, 2016; revised February 3, 2017; accepted March 01, 2017. From the Department of Epidemiology and Biostatistics, Milken Institute School of Public Health, George Washington University, Washington, DC (HA) and Division of Cancer Epidemiology and Genetics, Metabolic Epidemiology Branch, National Cancer Institute, Rockville, Maryland (EL). Address correspondence to: Hannah Arem, PhD, Department of Epidemiology and Biostatistics, Milken Institute School of Public Health, George Washington University, 950 New Hampshire Avenue NW, Office 514, Washington, DC 20052; e-mail: hannaharem@gwu.edu.

For reprints and permissions queries, please visit SAGE's Web site at <http://www.sagepub.com/journalsPermissions.nav>.

Copyright © 2017 The Author(s)

risk of cancer, these exposures are beyond the scope of this review.

Early detection and advancements in treatment have improved survival rates. In 2016, there were an estimated 15.5 million cancer survivors in the United States, and the survivor population is projected to grow to over 20 million in the United States by the end of 2025.⁶ In 2016, the 5 largest site-specific survivor groups, not including non-melanoma skin cancer, were female breast (~3.56 million), prostate (~3.3 million), colon and rectum (~1.45 million), endometrial (757 190), and melanoma (614 460).⁶ Cancer survivorship is an increasingly important public health concern, as this rapidly growing population faces risk of recurrence and long-term adverse treatment-related effects as well as elevated risks of physical and psychosocial-related comorbidities. However, cancer diagnosis is widely viewed as a “teachable moment” since survivors may be more motivated to change health behaviors that had previously not been of concern.⁷ This population may thus be more ready to consider changing some of the lifestyle-related factors described below if they are shown to improve cancer outcomes.

Measurement

Randomized controlled trials (RCTs) are generally considered the gold standard in efficacy trials, providing the strongest evidence of a causal relation between a specific intervention and outcome. While RCTs have high internal validity, the results may not be generalizable to diverse populations. The application of RCTs to certain questions related to lifestyle and cancer is limited as it is unethical to study interventions hypothesized to cause harm (eg, tobacco smoking or increasing sedentary time)⁸ and often not feasible to study exposures and cancer endpoints with long latency. Many RCTs investigating lifestyle and cancer risk, therefore, focus on intermediary outcomes; for example, a dietary study on a low-fat, high fiber, high fruit and vegetable intake study identified polyps as the primary outcome, which is a precursor for

colorectal cancer.⁹ RCTs continue to play an important role in establishing efficacy in lifestyle-related intervention studies for intermediary outcomes, but widespread application to the study of rare exposures or longer term cancer or survival outcomes remains inexpedient.

Prospective cohort studies have been widely used in evaluating lifestyle factors and cancer risk because the prospective nature of data collection eliminates recall bias and long follow-up periods allow for analysis of outcomes that develop over longer time periods. Thus, many recommendations on diet and physical activity in relation to cancer risk are based on large, prospective cohort studies that enrolled populations who were cancer-free at baseline and followed over many years, either actively (eg, direct contact with participant) or passively (eg, link to registry data), to assess cancer incidence as well as total and cause-specific mortality. While cohort studies offer unique opportunities to look at various exposures and cancer sites, they can be limited in power for rare events. Increasingly, even these large studies of tens to hundreds of thousands of individuals are being pooled to increase statistical power to detect small effect sizes or risk factors for rare cancers. Thus, the US National Cancer Institute formed a Cohort Consortium, bringing together over 50 high-quality cohorts with over 7 million participants to accelerate opportunities in cancer research.¹⁰

Case-control studies are most commonly used for rare cancers such as pancreatic or ovarian but have been widely criticized for evaluating self-reported lifestyle behaviors that may be subject to recall bias (eg, diet, physical activity). These studies by nature are retrospective, and individuals with disease may be more likely to report risk factors from the past than those without disease at the time of data collection. Still, case-control studies have made important contributions to the epidemiologic literature, and will continue to serve targeted studies.

Studies of cancer survivorship require unique data sets, to which attention has

grown in recent years. Large, prospective cohorts with individuals who are cancer-free at baseline can be leveraged for looking at pre- and postdiagnosis exposures and survival,¹¹ while RCTs may be more appropriate for studying the effect of short-term exposure to physical activity or diet modification and biomarker changes. Randomized trials to address causation rather than association may be limited by duration constraints and costs, and may have limited external validity. The first RCTs of physical activity, weight loss, and cancer recurrence (ie, disease-free survival), rather than intermediary biomarkers, are underway for colon and breast cancers.^{12,13} Cohorts of cancer survivors (enrolled after cancer diagnosis) can also collect more detailed information on exposures of interest, and are an additional option to examine higher risks of recurrence, side-effects, or mortality among cancer survivors. A 2011 workshop hosted by the National Cancer Institute led to an effort to gather existing resources and set new priorities for cancer survivorship research; output from this workshop summarizing survivorship cohort resources is available at <http://epi.grants.cancer.gov/survivor-cohort-resources/>.

Lifestyle-Related Cancer Risk Factors

Tobacco

Tobacco use increased dramatically over the course of the 20th century, peaking in the 1960s, at which time the 1964 landmark Surgeon General's Report, *Smoking and Health*, outlined the health risks associated with smoking and marked a major step toward reducing smoking rates in the United States. A 2014 Surgeon General's report documenting 50 years of evidence after the initial report found that numerous cancers, including acute myeloid leukemia and cancers of the head and neck, bronchus and lung, stomach, liver, pancreas, kidney and ureter, cervix, bladder, colon, and rectum, are causally linked to smoking.¹⁴ Cancer of the lung or bronchus is the second most common

cancer in both men and women and the leading cause of cancer death.¹ While many known lifestyle factors are incrementally associated with disease risk or mortality, *smokers have an estimated 25-fold risk* of developing lung cancer as compared with never smokers.¹⁴ Secondhand smoke and smokeless tobacco are also known risk factors for cancer.^{15,16}

Despite knowledge of the harms of smoking and the public policies aimed at lowering smoking rates, smoking remains the leading cause of premature disease and death in the United States.¹⁴ The Centers for Disease Control and Prevention report that approximately 40 million US adults are current cigarette smokers, with higher smoking rates in the Midwest and South.¹⁷ Still, the American Lung Association reports that over 70% of smokers want to quit, and that 44% of these smokers tried to quit in the last year, with limited success.¹⁸ The Surgeon General's Report estimated that 10 years after smoking cessation, the lung cancer death rate of a former smoker is half of that of a current smoker.¹⁴ This desire to quit, and the subsequent change in risk of lung cancer death, highlight a continued opportunity for studies aimed at multilevel interventions (eg, individual, community, workplace, policy) to reduce tobacco utilization.

The multitude of tested approaches to tobacco control are demonstrated through a PubMed search with the term "tobacco cessation" that yields nearly 28 000 publications. Additionally, states, countries, and multinational organizations such as the WHO have created and advanced tobacco control programs via mass media, taxes, and legislative measures restricting sale and use of tobacco products. Notably, the WHO's Framework Convention on Tobacco Control, adopted in 2003, is a legally binding agreement among 168 Signatories that is aimed to reduce both the demand for and supply of tobacco products, marking one of the largest public health efforts to date on lifestyle-related risk factors. Future research may be able to draw on national and

international trends to assess the impact of this historic tobacco control effort.

Electronic cigarettes have been suggested as a favorable alternative to reduce consumption of traditional cigarettes or to aid smoking cessation efforts. However, the health consequences, including the risk of cancer, associated with e-cigarettes remain unknown.¹⁹ Studies are currently underway to determine the health effects of e-cigarettes, and ongoing research will be needed to understand long-term effects on health.

Individuals who continue smoking after cancer diagnosis may be at increased risk of treatment complications, recurrence, and second primary cancers.^{14,20} A survey of adult cancer survivors showed that 88% to 92% of cancer survivors reported not smoking, as compared with 80% of healthy US adults.²¹ While research suggests that lung cancer screening may be a "teachable moment" to promote smoking cessation,²² more research is needed to understand optimal interventions to reduce smoking rates among cancer survivors.

Energy Balance

Obesity. Nationally representative surveys in the United States suggest that over one third of US adults are obese, with a BMI ≥ 30 kg/m².²³ The high prevalence of obesity translates to a substantial public health impact; a 2002 handbook on cancer prevention published by the International Agency for Research on Cancer (IARC) presents estimates suggesting that obesity explains 11% of colon cancer cases, 9% of postmenopausal breast cancer cases, 39% of endometrial cancer cases, 25% of kidney cancer cases, and 37% of esophageal cancer cases.²⁴ Five-year trends suggest a concerning increase in obesity among women over age 60, from 31.5% in 2003 to 38.1% in 2012.²³ This trend toward weight gain in older women is particularly alarming in relation to cancer risk, as cancer is a disease of aging and risk could be amplified by weight gain.

IARC convened a working group in April 2016 to update a previous study on

the preventative effects of weight control in relation to cancer. This working group produced a review of over 1000 epidemiologic studies from around the world, which confirmed previously reported findings that overweight or obese individuals are at higher risk for developing adenocarcinoma of the esophagus, and cancers of the colon, breast (postmenopausal), endometrium, and kidney.²⁴ Combining study results suggested relative risks ranging from 1.03 (95% confidence interval [CI] = 1.02-1.04) for colorectal cancer to 1.56 (95% CI = 1.45-1.66) for endometrial for a 1-unit change in BMI (kg/m²).²⁵ In addition to confirming previously observed dose-response associations, the 2016 update also reported associations between higher BMI and risk of 8 additional cancers: gastric cardia, liver, gallbladder, pancreas, ovary, thyroid, multiple melanoma, and meningioma.²⁶ Risk estimates showed a dose-response effect, with associations growing stronger as BMI increased.

Obesity has been associated not only with cancer risk but also with cancer mortality. A landmark study published in the *New England Journal of Medicine* in 2003 investigated the associations between BMI and cancer mortality in a cohort study of over 1 million US men and women who were cancer-free at baseline.²⁷ This study reported that compared to normal weight men (BMI 18.5-24.9 kg/m²), those who were overweight (BMI 25.0-29.9) had no increased cancer mortality risk, but those who were class I obese (BMI 30.0-34.9) had a 9% increased cancer mortality risk, those who were class II obese (BMI 35.0-39.9) had a 20% increased cancer mortality risk, and those who were class III obese (BMI ≥ 40) had a 52% higher cancer mortality risk. Among women, the authors observed a statistically significant increased all cancer mortality risk for all overweight or obese groups, showing a dose-response relationship from 8% increased risk (BMI 25.0-29.9) to 62% increased risk (BMI ≥ 40 kg/m²) compared with women with a normal BMI.²⁷ This association was strongest for endometrial cancer-specific mortality,

with a mortality relative risk of 6.25 (95% CI = 3.75-10.42) comparing women with a BMI ≥ 40 kg/m² to women with a normal BMI.

The “obesity paradox,” which has been observed in some studies, suggests that those who are normal weight have worse survival than those who are overweight. One recent study in cancer patients found that the obesity paradox using BMI as a predictor of mortality disappeared when sarcopenia (low muscle mass) was accounted for. Sarcopenia was an independent predictor of mortality after adjusting for BMI and other characteristics.²⁸ Timing of weight loss in relation to diagnosis, treatment, and survival is another active and important area of research, as patient needs may differ by where they are in the cancer experience.²⁹ For instance, cachexia, a multifactorial syndrome that includes loss of skeletal muscle mass and reduced food intake, is a concern during treatment, and may predict worse outcomes.^{30,31} However, for those who have completed chemotherapy, weight gain may worsen prognosis, particularly among postmenopausal women with breast cancer.^{32,33} Consequently, the American Cancer Society (ACS) recommends that cancer survivors maintain a “healthy” weight, and suggest that those who are overweight or obese increase physical activity and decrease consumption of high calorie foods and beverages.³⁴

A 2012 study using data from the National Health Interview Survey estimated that 30.6% of cancer survivors are obese, with a BMI ≥ 30 kg/m².³⁵ Studies of cancer survivors suggest poorer outcomes among obese patients, with the most evidence for breast cancer.^{27,36} Still, mechanisms underlying the observed associations between obesity and survival, for instance among women with breast cancer, are poorly understood, and more research is needed to understand how weight loss after diagnosis affects survival by specific cancer site.³⁷ Other concerns about obesity among cancer survivors may be treatment related. For instance, for endometrial cancer, which is strongly

associated with obesity, chemotherapy dosing regimens are not always standardized by weight, which may influence cancer outcomes.^{38,39} In 2012, the American Society of Clinical Oncology convened an Expert Panel to review evidence on appropriate cytotoxic chemotherapy dosing for obese adults with cancer and recommended that dose of chemotherapy should be weight-based rather than fixed.³⁹ Still, evidence in this area is limited, and additional studies are needed to determine long-term effects of toxicity.

Physical (In)Activity. Physical inactivity is another prevalent lifestyle-related risk factor for cancer. The *2008 Physical Activity Guidelines for Americans* recommend 2 components of activity: (1) a minimum of 150 minutes of moderate-intensity or 75 minutes of vigorous-intensity aerobic activity and (2) 2 or more muscle-strengthening activities involving all major muscle groups per week for health benefits.⁴⁰ The Centers for Disease Control and Prevention estimates that half of US adults meet this minimum for aerobic activity but that only 20% of adults fulfill both components of the recommendation.⁴¹ Among adults 65 years and older, adherence to the aerobic activity component of the guidelines ranges from 27.3% to 44.3% depending on the data surveillance source, indicating that older adults, who are also at higher risk of cancer, are less likely to meet the recommended aerobic minimum.⁴²

Physical inactivity has been recognized as a global pandemic that causes an estimated 10% of breast and colon cancers, and 9% of premature mortality overall.⁴³ Consequently, the health burden from physical inactivity has been compared to that from smoking or obesity.⁴³ Epidemiologic studies frequently use leisure-time, moderate- to vigorous-intensity physical activity (MVPA) as the exposure of interest. This category includes activities such as a brisk walk, cycling, jogging, swimming, as described in the widely referenced compendium of physical activity that assigns intensity levels to specific

activities.⁴⁴ Other physical activity studies may include occupational activity, household chores, or light-intensity activities. However, some experts argue that non-leisure time or light activities may be harder to recall and may be more subject to measurement bias. More research is needed to understand associations between non leisure-time MVPA and cancer risk.

A 2016 publication combining data from 1.44 million participants reported protective associations between higher levels of leisure time MVPA and risk of 13 different types of cancers, including (in order of magnitude of effect) esophageal carcinoma, liver, lung, kidney, gastric cardia, endometrial, myeloid leukemia, myeloma, colon, head and neck, rectal, bladder, and breast.⁴⁵ The hazard ratios ranged from 0.58 to 0.90, comparing high to low leisure time physical activity; notably, risk reductions were 20% or greater for 7 of the cancers. This study was the most comprehensive analysis of physical activity and cancer risk to date, adding convincing evidence of associations for more cancer sites than previously described in the literature.

Pre- and postdiagnosis physical activity has also been associated with lower breast and colon cancer-specific mortality in observational studies.⁴⁶ Published RCTs have focused on physical activity and biomarkers of cancer intermediaries, such as hormone levels and inflammation, as these intermediaries have been linked to higher cancer risk.⁴⁶ Additional studies have debunked the idea that women with breast cancer-related lymphedema should avoid strength training and have demonstrated that weight lifting is not only safe, but also beneficial for reducing symptoms of lymphedema and increasing strength.⁴⁷ Ongoing RCTs are now studying the effects of physical activity on disease-free survival among colon cancer survivors⁴⁸ and the effect of weight loss on recurrence among breast cancer survivors¹³; such evidence is needed to better assess causality.

Still, additional research is needed to refine when, where, and how cancer survivors should integrate physical

activity into health promotion activities based on individual considerations about baseline fitness, cancer or treatment-specific needs, or readiness for change.⁴⁹ Furthermore, although there is emerging research in “precision oncology” and differences in exercise response by tumor characteristics,⁵⁰ mechanisms by which physical activity may affect cancer recurrence or mortality are not well understood.

Sedentary Time. Sedentary time is also increasingly supported in the literature as an independent cancer risk factor; currently there are no federally published guidelines on recommended sitting time. It is important to recognize the distinction between sedentary time and inactivity as two different categories of behavior. Sedentary time is defined as activities requiring ≤ 1.5 metabolic equivalents, done in a sitting or reclining position, while physical inactivity (in the context of the *US Physical Activity Guidelines for Americans*) refers specifically to a lack of MVPA. A 2015 meta-analysis of 14 studies reported that sedentary time was positively associated with a cancer risk (relative risk [RR] = 1.13 for all cancers, 95% confidence interval 1.05-1.21), after adjusting potential confounders.⁵¹ The estimate was similar for total cancer mortality. In addition, increasing sedentary time was associated with the following site-specific cancers: female breast, colon, rectal, endometrial, and epithelial ovarian cancer. A 2016 paper published as part of the *Lancet* series on physical activity examined whether the detrimental effects of more sitting time were eliminated by more activity. Surprisingly, the detrimental effects were observed at all but the highest level of physical activity, which was defined as 60 to 75 minutes of moderate-intensity activity daily, or almost 5 times the minimum recommended by the *US Physical Activity Guidelines for Americans*.⁵² More research is needed to determine how breaks in sedentary time mitigate the detrimental effects of sitting. Additionally, 2 studies using data from large, prospective cohorts have found a positive association between sitting/

television viewing time and mortality among colorectal cancer survivors^{53,54}; replication of this association in diverse populations and among other groups of cancer survivors is warranted. Finally, it is unknown how intervening to reduce sedentary time among cancer survivors affects cancer-related outcomes such as quality of life, recurrence, or survival.

Diet

Studies of diet and cancer risk have often reported inconsistent and even conflicting results, leading to a great deal of confusion in public perceptions of dietary risk factors for cancer. In 1981, Doll and Peto published a landmark report at the request of the US Congress Office of Technology Assessment in which they estimated that 35% of cancer could be attributed to poor diet; this estimate was, however, accompanied by a wide confidence interval (ie, 10% to 70%), highlighting the limited nature of the evidence and their own uncertainty.⁵⁵ Nearly 35 years later, a commentary on Doll and Peto's report was published, reiterating their uncertainty but approximating that 20% of cancers could be attributed to diet and related factors, including obesity.⁵⁶

In 2007, the World Cancer Research Fund (WCRF) and American Institute for Cancer Research (AICR) published a comprehensive report on *Food, Nutrition and Physical Activity and the Prevention of Cancer* and have since been producing continuous updates with additional site-specific evidence.²⁵ The report provides detailed reviews of foods in relation to specific cancers, classifying associations as *convincing*, *probable*, *limited-suggestive*, or *unlikely* depending on the level of evidence. In summary, several diet-cancer associations have been classified as *convincing or probable increased risk*; these include red meat with colorectal cancer, processed meat with colorectal and stomach (non-cardia only) cancers, Cantonese-style salted fish with nasopharyngeal cancer, salt-preserved foods with stomach cancer, and alcoholic drinks with oral, pharyngeal, laryngeal, esophageal (squamous cell

carcinoma only), liver, colorectal, and breast cancers.⁵⁷ In contrast, a number of diet-cancer associations have been classified as *convincing or probable decreased risk*; these include dietary fiber-containing foods with colorectal cancer, nonstarchy vegetables with oral, pharyngeal, and laryngeal cancers, fruits with oral, pharyngeal, laryngeal, and lung cancers, garlic and diets high in calcium with colorectal cancer, coffee with liver and endometrial cancers, and alcoholic drinks with kidney cancer.²⁵ While dietary supplements are not recommended for cancer prevention, and there is *convincing* evidence of increased risk of lung cancer among smokers taking beta-carotene, there is *probable* evidence linking supplemental calcium to reduced risk of colorectal cancer and *limited evidence* linking supplemental selenium, in selenium-deficient men, to reduced risk of prostate cancer.²⁵

Dietary components are consumed in combination and can be highly correlated with one another. Thus, rather than focusing on single nutrients, food items, or even food groups, for which the evidence is often mixed, a primary aim of recent nutritional epidemiologic research has been to examine dietary patterns in relation to cancer risk. Dietary pattern indices can either be based on recommended diets (eg, Healthy Eating Index [HEI]-2010, based on the 2010 Dietary Guidelines for Americans) or on data-driven patterns of consumption in a specific population using factor analysis.⁵⁸ For example, one study considered 4 different a priori indices, including the HEI-2010, in relation to cancer mortality and observed an 18% to 24% lower risk of cancer mortality among those with higher (ie, healthier) index scores as compared with those with lower scores.⁵⁹

Nonprofit and professional organizations also publish dietary guidelines for the public based on available evidence. These guidelines often emphasize pattern-based findings over findings for single dietary components. For example, the ACS cautions that studies based on single foods or nutrients cannot generally be

translated into actionable public health recommendations. Additionally, the ACS highlights the complex nature of diet, whereby exposure is cumulative, occurring multiple times per day over many years, making controlled dietary trials over extended periods of time unfeasible. Consequently, the 2012 ACS dietary recommendations for cancer prevention are general, promoting diets that are plant-based, recommending consumption of at least 2.5 cups of fruit and vegetables daily, recommending whole grains over refined grain products, and cautioning that consumption of alcohol, high-calorie foods and beverages, and processed and red meat should be limited.³⁴ Further establishing the carcinogenic potential of red and processed meat, IARC classified processed meat as *carcinogenic to humans*, based on sufficient evidence from epidemiologic studies for colorectal cancer, and red meat as *probably carcinogenic to humans*, based on limited evidence from epidemiologic studies for colorectal cancer.⁶⁰ Following the consideration of more than 800 epidemiologic studies, the IARC Working Group estimated, on the basis of 10 cohort studies, a 17% increased risk (95% CI 1.05-1.31) of colorectal cancer per 100 g per day of red meat and an 18% increased risk (95% CI 1.10-1.28) of colorectal cancer per 50 g per day of processed meat.⁶⁰

The ACS recommends that after treatment cancer survivors consume a diet that is high in vegetables, fruits, and whole grains.⁶¹ The Continuous Update Project from the AICR/WCRF report on breast cancer survivorship reported *probable* protective effects of diets high in fiber and soy and *probable* harmful effects of total and saturated fat on all-cause mortality.⁶² However, RCTs exploring the impact of consuming a healthy diet after breast cancer diagnosis have produced conflicting results. For instance, the Women's Health Eating and Living (WHEL) reported no association between dietary improvement and prognosis, while the Women's Intervention Nutrition Study (WINS) found improved prognosis for women in

the intervention group in terms of ipsilateral localized recurrences.⁶³ Studies on other cancer sites and with other outcomes are needed to better understand how diet affects health outcomes among cancer survivors.

Combined Effects of Obesity, Physical Activity, Sedentary Time, and Diet

Studies of obesity, physical inactivity, sedentary time, and diet as risk factors for cancer incidence or survival are faced with complicated questions about synergism and independence. Studies attempting to demonstrate independence of one of these risk factors generally present both unadjusted and adjusted estimates. Investigators will often consider the other factors confounders, or mediators of the association of interest. How an investigator operationalizes these interrelated factors in statistical analyses should be carefully considered and well described in publications, as experts have differing options on how to best model these factors together. In terms of applied public health, the US Department of Health and Human Services, the WHO, and cancer-specific independent research bodies generally recommend similar goals for both pre- and postdiagnosis behaviors related to diet, physical activity, and weight. At present there are no federal guidelines related to sedentary time for either the general public or for cancer survivors.

Alcohol

In 2007 and again in 2012, an IARC Working Group classified alcoholic beverages as *carcinogenic to humans* and concluded that oral, pharyngeal, laryngeal, esophageal, liver, colorectal, and female breast cancer are causally related to alcohol consumption, but that the evidence for pancreatic cancer is *limited*.⁶⁴ In addition, the WHO estimated that harmful use of alcohol resulted in approximately 3.3 million deaths in 2012 and that 4% to 25% of the global cancer burden could be attributed to alcohol consumption.⁶⁵ A concurrent meta-analysis, including more than 500

studies from across the globe and nearly half a million cancer cases, tested associations between alcohol consumption and 23 cancer sites.⁶⁶ Dose-response relationships, with the highest risk among heavy drinkers (>50 g/day) as compared with nondrinkers and occasional drinkers, were observed for the following cancer sites: 5.13 (95% CI 4.31-6.10) for oral and pharyngeal cancer, 2.65 (95% CI 2.19-3.19) for laryngeal cancer, 4.95 (95% CI 3.86-6.34) for esophageal squamous cell carcinoma, 1.44 (95% CI 1.25-1.65) for colorectal cancer, and 1.61 (95% CI 1.33-1.94) for female breast cancer. Furthermore, heavy alcohol drinkers, as compared with nondrinkers and occasional drinkers, were at higher risk of stomach cancer (RR = 1.21, 95% CI 1.07-1.36), liver cancer (RR = 2.07, 95% CI 1.66-2.58), gallbladder cancer (RR = 2.64, 95% CI 1.62-4.30), pancreatic cancer (RR = 1.19, 95% CI 1.11-1.28), and lung cancer (RR = 1.15, 95% CI 1.02-1.30), but evidence of a dose-response relationship was lacking. Alcohol has also shown synergistic effects with smoking for risk of multiple cancers.⁶⁷ General WCRF/AICR guidelines suggest that adults moderate intake of alcohol to 1 drink per day for women and 2 drinks per day for men.²⁵

The evidence on alcohol consumption after diagnosis and prognosis is limited. However, in general, the recommendations for cancer survival are the same as those for cancer prevention. A review of 7 studies concluded that alcohol consumption after breast cancer diagnosis was not associated with prognosis.⁶⁸ Further studies have suggested that low to moderate alcohol intake is not associated with breast cancer recurrence or mortality, and in fact, that low consumption was associated with better survival outcomes.^{69,70} This observed protective effect of alcohol intake after breast cancer diagnosis on mortality may, however, be due to confounding by factors related to socioeconomic status. The ACS notes that the decision to drink alcohol for women who have had breast cancer is difficult because of the mixed evidence comparing an increased risk of

recurrent or second primary breast cancer to the lower risk for cardiovascular disease.⁶¹

Viruses and Infections

Chronic disease and infectious disease epidemiology are often regarded as distinct disciplines, with different methodological approaches, disease distributions, risk factors, and endpoints. However, the distinction between these disciplines has evolved in recent years as researchers discover more links between infectious and chronic disease. Current estimates connect infectious agents to 12% of incident cancers worldwide.⁷¹ At least 7 viruses have been causally associated with cancer risk, including Epstein-Barr virus, hepatitis B virus (HBV), HPV, human T-cell lymphotropic virus, hepatitis C virus (HCV), Kaposi's sarcoma herpes virus, and Merkel cell polyomavirus.⁷¹

Arguably one of the most important recent advances in understanding cancer development was the identification of HPV as a causal factor for cervical cancer as well as for cancers of the vagina, vulva, penis, and oropharynx.⁷² There are an estimated 40 known sexually transmitted HPV types, with 15 classified as oncogenic.⁷³ HPV types 16 and 18 specifically have been estimated to cause 60% to 70% of cervical cancer cases worldwide, with other HPV types causing most of the other cases.⁷³ Over the past decade vaccines against various HPV types have become widely available and have been shown to be efficacious in preventing HPV infection in both males and females.⁷⁴ The Advisory Committee on Immunization Practices in 2015 recommended 3 possible vaccines for routine vaccination at age 11 or 12 years, or among females aged 13 to 26 years and males aged 13 to 21 years who were not previously vaccinated.⁷⁵ Despite this advance in prevention with vaccine development, at present cervical cancer is more common than both breast and liver cancer in regions low on the Human Development Index.⁷⁶

Other infections associated with cancer development are HBV and HCV. Worldwide, approximately 3 out of every

4 cases of hepatocellular carcinoma (HCC), the predominant type of primary liver cancer, can be attributed to HBV (~50%) or HCV (~25%) infection, with attributable fractions varying considerably by region.⁷⁷ HCC is the sixth most common cancer worldwide and the second most common cause of cancer death; however, there is substantial geographic variation in the distribution of HBV and HCV infection, with the highest burden falling in Asia and Africa.⁷⁸ In 1994, on the basis of *sufficient evidence in humans*, IARC classified both chronic infection with HBV and chronic infection with HCV as *carcinogenic to humans*.⁷⁹

An estimated two thirds of the world's population is infected with *Helicobacter pylori*, although many individuals show no symptoms. Still, *H pylori* infection has been causally linked to gastric cancer. Gastric cancer is more common in developing countries, with nearly 1 million annual cases and nearly 700 000 annual deaths worldwide.⁸⁰ *H pylori* bacteria are found in contaminated food and water, and washing hands with soap and water after use of the restroom or before eating may help prevent infection. Treating *H pylori* infection with antibiotics may reduce gastric cancer risk.⁸¹

Reproductive Factors and Exogenous Hormones

Hormones, particularly estrogens, are known to play important roles in cancer development, progression, and survival. Not surprisingly, cancers affecting reproductive organs, such as breast, endometrial, and ovarian cancers, have been studied extensively in this regard, but cancers affecting other organ sites such as the lung have also been studied in relation to hormone levels. For women, lifestyle factors that affect hormone levels and potentially alter cancer risk include lactation, oral contraceptive use, and menopausal hormone therapy. For men, the evidence linking sex hormones to cancer risk is less consistent.

In 2010, the WCRF and AICR published a report on breast cancer as a part of

their collaborative Continuous Update Project.⁸² This report, which was reflective of earlier expert reviews, found consistent evidence of a modest association between total duration of lactation and lower risk of breast cancer that did not vary by menopausal status.⁸² A pooled study of 47 case-control and cohort studies, conducted in 30 countries, showed that the relative risk of breast cancer decreased by 4.3% and 7.0% for every 12 months of breastfeeding and for each birth, respectively.⁸³ Additional pregnancy-related factors that have been associated with lower risk of certain breast cancer subtypes include younger age at first full-term pregnancy, parity, and history of preeclampsia.^{84,85} While evidence from case-control studies has shown a positive association between abortion (induced or spontaneous) and breast cancer, this finding has been consistently refuted by prospective studies showing no association.⁸⁶

Oral contraceptive use has been associated with lower risk of endometrial⁸⁷ and ovarian⁸⁸ cancers, but higher risk of breast cancer,⁸⁹ cervical cancer, and benign liver tumors.⁹⁰ In 2007, an IARC Working Group evaluated the carcinogenic risk of combined estrogen-progestogen contraceptives and menopausal therapy in women. Overall, combined oral estrogen-progestogen contraceptives were classified as *carcinogenic to humans* on the basis of *sufficient evidence* of increased risk for breast cancer among current and recent users as well as increased risk for cervical and liver cancer among populations at low risk for HBV infection.⁹¹ However, the IARC Working Group also highlighted convincing evidence of protective associations for oral contraceptive use with endometrial and ovarian cancers.⁹¹ In contrast, an earlier IARC Monograph classified progestogen-only contraceptives as *possibly carcinogenic to humans* owing to *inadequate evidence* of carcinogenicity in human studies.⁹²

Menopausal hormone therapy (MHT), including combined estrogen-progestogen⁹³ and estrogen-alone

hormone use,⁹² was also classified by IARC as *carcinogenic to human* on the basis of *sufficient evidence* for increased breast and endometrial cancer risk, respectively. The Women's Health Initiative was a large RCT enrolling ~64 500 postmenopausal women designed to evaluate multiple outcomes including the benefits of taking menopausal hormone therapy on coronary heart disease and other cardiovascular diseases, and risk of hip and other fractures, in addition to the possible harmful increase in breast cancer.⁹⁴ This study found that breast cancer risk was higher among women using combined hormone therapy, mammography was less effective among women using combined or estrogen-alone therapy, and lung cancer mortality but not incidence was higher among women using combined therapy.⁹⁵⁻⁹⁷ These findings led to early termination of the estrogen plus progestin arm of the clinical trial.⁹⁸ However, risk of breast cancer was not increased among postmenopausal women with prior hysterectomy who received estrogen alone.⁹⁹

The publication of the Women's Health Initiative findings led to drastic reductions in the number of US women taking menopausal hormone therapy, with office-based physicians reporting 16.3 million MHT visits in 2001 as compared with 6.1 million MHT visits in 2009.¹⁰⁰ Still, there are recent studies suggesting that timing of hormone therapy use may explain the previously observed risks, and that starting hormone therapy shortly after menopause rather than many years after menopause is associated with improved cardiovascular outcomes and no increased risk of cancer.¹⁰¹ More research is needed to understand the importance of timing of hormone therapy in relation to cancer risk.

For breast cancer survivors, hormones blocking ovarian function, estrogen production, or estrogen's effects are commonly used as adjuvant therapy for hormone receptor-positive breast cancer.¹⁰² A detailed discussion of hormone-related cancer therapies is, however, beyond the scope of this review.

Summary

In summary, these potentially modifiable risk factors may explain up to one half of incident cancers. Additional research is needed to better understand timing and dose of many of the described exposures as risk factors for cancer or prognosis. Apart from the important ongoing work on other areas of cancer epidemiology such as genetics or environmental and occupational risks, the risk factors described above present an enormous opportunity for public health programming to encourage and support healthier behaviors. The field of implementation research is taking up that challenge, working to test implementation of efficacious findings in real-world settings. Still, additional research is needed to better understand how to change cancer-related behaviors and how changing such behaviors might affect cancer incidence and survival. Given the challenges of behavioral modification, policymakers and public health practitioners should consider multilevel initiatives that target not only individual level but also community- and systemic-level practices.

Declaration of Conflicting Interests

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

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: Funding was provided by the George Washington University, Milken Institute School of Public Health, and the Intramural Research Program of the National Cancer Institute.

AJLM

References

1. American Cancer Society. Cancer facts and figures 2016. <http://www.cancer.org/acs/groups/content/@research/documents/document/acspc-047079.pdf>. Accessed March 17, 2017.
2. US Cancer Statistics Working Group. 1999-2013 Incidence and mortality web-based report. www.cdc.gov/uscs. Accessed March 17, 2017.
3. World Health Organization. Cancer fact sheet. <http://www.who.int/mediacentre/factsheets/fs297/en/>. Accessed March 17, 2017.
4. Katzke VA, Kaaks R, Kühn T. Lifestyle and cancer risk. *Cancer J*. 2015;21:104-110.
5. Song M, Giovannucci E. Preventable incidence and mortality of carcinoma associated with lifestyle factors among white adults in the United States. *JAMA Oncol*. 2016;2:1154-1161.
6. Miller KD, Siegel RL, Lin CC, et al. Cancer treatment and survivorship statistics, 2016. *CA Cancer J Clin*. 2016;66:271-289.
7. Demark-Wahnefried W, Aziz NM, Rowland JH, Pinto BM. Riding the crest of the teachable moment: promoting long-term health after the diagnosis of cancer. *J Clin Oncol*. 2005;23:5814-5830.
8. Smith GC, Pell JP. Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials. *BMJ*. 2003;327:1459-1461.
9. Lanza E, Yu B, Murphy G, et al. The Polyp Prevention Trial-Continued Follow-up Study: no effect of a low-fat, high-fiber, high-fruit, and -vegetable diet on adenoma recurrence eight years after randomization. *Cancer Epidemiol Biomarkers Prev*. 2007;16:1745-1752.
10. National Cancer Institute. NCI Cohort Consortium. <http://epi.grants.cancer.gov/Consortia/cohort.html>. Accessed March 17, 2017.
11. Elena JW, Travis LB, Simonds NI, et al. Leveraging epidemiology and clinical studies of cancer outcomes: recommendations and opportunities for translational research. *J Natl Cancer Inst*. 2013;105:85-94.
12. Courneya KS, Vardy JL, O'Callaghan CJ, et al. Effects of a structured exercise program on physical activity and fitness in colon cancer survivors: one year feasibility results from the CHALLENGE trial. *Cancer Epidemiol Biomarkers Prev*. 2016;25:969-977.
13. Dana-Farber Cancer Institute. Dana-Farber and Fitbit partner to test if weight loss can prevent breast cancer recurrence. <http://www.dana-farber.org/Newsroom/News-Releases/dana-farber-cancer-institute-and-fitbit-partner-to-test-if-weight-loss-prevent-breast-cancer-recurrence.aspx>. Published April 27, 2016. Accessed March 17, 2017.
14. Centers for Disease Control and Prevention. *The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General*. Atlanta,

- GA: Centers for Disease Control and Prevention; 2014.
15. World Health Organization. *Tobacco Smoke and Involuntary Smoking: IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*. Geneva, Switzerland: World Health Organization; 2004.
 16. Boffetta P, Hecht S, Gray N, Gupta P, Straif K. Smokeless tobacco and cancer. *Lancet Oncol*. 2008;9:667-675.
 17. Centers for Disease Control and Prevention. Current cigarette smoking among adults in the United States. http://www.cdc.gov/tobacco/data_statistics/fact_sheets/adult_data/cig_smoking/. Accessed March 17, 2017.
 18. American Lung Association. Tobacco policy trend report: helping smokers quit. <http://www.lung.org/assets/documents/tobacco/helping-smokers-quit2008.pdf>. Accessed March 17, 2017.
 19. Brown J, Beard E, Kotz D, Michie S, West R. Real-world effectiveness of e-cigarettes when used to aid smoking cessation: a cross-sectional population study. *Addiction*. 2014;109:1531-1540.
 20. McBride CM, Ostroff JS. Teachable moments for promoting smoking cessation: the context of cancer care and survivorship. *Cancer Control*. 2003;10:325-333.
 21. Blanchard CM, Courneya KS, Stein K. Cancer survivors' adherence to lifestyle behavior recommendations and associations with health-related quality of life: results from the American Cancer Society's SCS-II. *J Clin Oncol*. 2008;26:2198-2204.
 22. Taylor KL, Cox LS, Zincke N, Mehta L, McGuire C, Gelmann E. Lung cancer screening as a teachable moment for smoking cessation. *Lung Cancer*. 2007;56:125-134.
 23. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of childhood and adult obesity in the United States, 2011-2012. *JAMA*. 2014;311:806-814.
 24. World Health Organization. *Weight Control and Physical Activity*. Geneva, Switzerland: World Health Organization; 2002.
 25. World Cancer Research Fund & American Institute for Cancer Research. *Food, Nutrition, Physical Activity, and the Prevention of Cancer: A Global Perspective*. Washington, DC: American Institute for Cancer Research; 2007.
 26. Lauby-Secretan B, Scoccianti C, Loomis D, Grosse Y, Bianchini F, Straif K. Body fatness and cancer: viewpoint of the IARC Working Group. *N Engl J Med*. 2016;375:794-798.
 27. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of US adults. *N Engl J Med*. 2003;348:1625-1638.
 28. Gonzalez MC, Pastore CA, Orlandi SP, Heymsfield SB. Obesity paradox in cancer: new insights provided by body composition. *Am J Clin Nutr*. 2014;99:999-1005.
 29. Courneya KS, Friedenreich CM. Framework PEACE: an organizational model for examining physical exercise across the cancer experience. *Ann Behav Med*. 2001;23:263-272.
 30. Fearon K, Strasser F, Anker SD, et al. Definition and classification of cancer cachexia: an international consensus. *Lancet Oncol*. 2011;12:489-495.
 31. Tisdale MJ. Cachexia in cancer patients. *Nat Rev Cancer*. 2002;2:862-871.
 32. Kroenke CH, Chen WY, Rosner B, Holmes MD. Weight, weight gain, and survival after breast cancer diagnosis. *J Clin Oncol*. 2005;23:1370-1378.
 33. Nichols HB, Trentham-Dietz A, Egan KM, et al. Body mass index before and after breast cancer diagnosis: associations with all-cause, breast cancer, and cardiovascular disease mortality. *Cancer Epidemiol Prev Biomarkers*. 2009;18:1403-1409.
 34. Kushi LH, Doyle C, McCullough M, et al. American Cancer Society guidelines on nutrition and physical activity for cancer prevention. *CA Cancer J Clin*. 2012;62:30-67.
 35. National Cancer Institute. Cancer survivors and obesity. <http://progressreport.cancer.gov/after/obesity>. Accessed March 17, 2017.
 36. Chan DS, Vieira AR, Aune D, et al. Body mass index and survival in women with breast cancer-systematic literature review and meta-analysis of 82 follow-up studies. *Ann Oncol*. 2014;25:1901-1914.
 37. Protani M, Coory M, Martin JH. Effect of obesity on survival of women with breast cancer: systematic review and meta-analysis. *Breast Cancer Res Treat*. 2010;123:627-635.
 38. Modesitt SC, van Nagell JRJ. The impact of obesity on the incidence and treatment of gynecologic cancers: a review. *Obstet Gynecol Surv*. 2005;60:683-692.
 39. Griggs JJ, Mangu PB, Anderson H, et al. Appropriate chemotherapy dosing for obese adult patients with cancer: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol*. 2012;30:1553-1561.
 40. US Department of Health and Human Services. *Physical Activity Guidelines for Americans*. Washington, DC: US Department of Health and Human Services; 2008.
 41. Centers for Disease Control and Prevention. Exercise or physical activity. <http://www.cdc.gov/nchs/fastats/exercise.htm>. Accessed March 17, 2017.
 42. Keadle SK, McKinnon R, Graubard BI, Troiano RP. Prevalence and trends in physical activity among older adults in the United States: a comparison across three national surveys. *Prev Med*. 2016;89:37-43.
 43. Lee IM, Shiroma EJ, Lobelo F, Puska P, Blair SN, Katzmarzyk PT. Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. *Lancet*. 2012;380:219-229.
 44. Ainsworth BE, Haskell WL, Whitt MC, et al. Compendium of physical activities: an update of activity codes and MET intensities. *Med Sci Sports Exerc*. 2000;32(9 suppl 1):S498-S504.
 45. Moore SC, Lee IM, Weiderpass E, et al. Association of leisure-time physical activity with risk of 26 types of cancer in 1.44 million adults. *JAMA Intern Med*. 2016;176:816-825.
 46. Ballard-Barbash R, Friedenreich CM, Courneya KS, Siddiqi SM, McTiernan A, Alfano CM. Physical activity, biomarkers, and disease outcomes in cancer survivors: a systematic review. *J Natl Cancer Inst*. 2012;104:815-840.
 47. Schmitz KH, Ahmed RL, Troxel A, et al. Weight lifting in women with breast-cancer-related lymphedema. *N Engl J Med*. 2009;361:664-673.
 48. Courneya KS, Booth C, Gill S, et al. The colon health and life-long exercise change (CHALLENGE) trial (CO. 21). *Curr Oncol*. 2008;15(6):8-16.
 49. Buffart LM, Galvão DA, Brug J, Chinapaw MJM, Newton RU. Evidence-based physical activity guidelines for cancer survivors: current guidelines, knowledge gaps and future research directions. *Cancer Treat Rev*. 2014;40:327-340.
 50. Jones LW. Precision oncology framework for investigation of exercise as treatment for cancer. *J Clin Oncol*. 2015;33:4134-4137.
 51. Biswas A, Oh PI, Faulkner GE, et al. Sedentary time and its association with risk for disease incidence, mortality, and hospitalization in adults: a systematic review and meta-analysis. *Ann Intern Med*. 2015;162:123-132.

52. Ekelund U, Steene-Johannessen J, Brown WJ, et al. Does physical activity attenuate, or even eliminate, the detrimental association of sitting time with mortality? A harmonised meta-analysis of data from more than 1 million men and women. *Lancet*. 2016;388:1302-1310.
53. Arem H, Pfeiffer RM, Engels EA, et al. Pre- and postdiagnosis physical activity, television viewing, and mortality among patients with colorectal cancer in the National Institutes of Health-AARP Diet and Health Study. *J Clin Oncol*. 2015;33:180-188.
54. Campbell PT, Patel AV, Newton CC, Jacobs EJ, Gapstur SM. Associations of recreational physical activity and leisure time spent sitting with colorectal cancer survival. *J Clin Oncol*. 2013;31:876-885.
55. Doll R, Peto R. The causes of cancer: quantitative estimates of avoidable risks of cancer in the United States today. *J Natl Cancer Inst*. 1981;66:1192-1308.
56. Blot WJ, Tarone RE. Doll and Peto's quantitative estimates of cancer risks: holding generally true for 35 years. *J Natl Cancer Inst*. 2015;107(4). doi:10.1093/jnci/djv044.
57. World Cancer Research Fund International. Summary of strong evidence on diet, nutrition, physical activity and prevention of cancer. <http://wcrf.org/sites/default/files/WCRFI-Matrix-for-all-cancers.pdf>. Accessed October 17, 2016.
58. Reedy J, Wirfält E, Flood A, et al. Comparing 3 dietary pattern methods—Cluster analysis, factor analysis, and index analysis. *Am J Epidemiol*. 2010;171:479-487.
59. Reedy J, Krebs-Smith SM, Miller PE, et al. Higher diet quality is associated with decreased risk of all-cause, cardiovascular disease, and cancer mortality among older adults. *J Nutr*. 2014;144:881-889.
60. Bouvard V, Loomis D, Guyton KZ, et al. Carcinogenicity of consumption of red and processed meat. *Lancet Oncol*. 2015;16:1599-1600.
61. Rock CL, Doyle C, Demark-Wahnefried W, et al. Nutrition and physical activity guidelines for cancer survivors. *CA Cancer J Clin*. 2012;62:242-274.
62. World Cancer Research Fund & American Institute for Cancer Research. *Diet, Nutrition, Physical Activity and Breast Cancer Survivors*. Washington, DC: American Institute for Cancer Research; 2014.
63. Pierce JP. Diet and breast cancer prognosis: making sense of the WHEL and WINS trials. *Curr Opin Obstet Gynecol*. 2009;21:86-91.
64. Baan R, Straif K, Grosse Y, et al. Carcinogenicity of alcoholic beverages. *Lancet Oncol*. 2007;8:292-293.
65. World Health Organization. *Global Status Report on Alcohol and Health*. Geneva, Switzerland: World Health Organization; 2014.
66. Bagnardi V, Rota M, Botteri E, et al. Alcohol consumption and site-specific cancer risk: a comprehensive dose-response meta-analysis. *Br J Cancer*. 2015;112:580-593.
67. Boffetta P, Hashibe M. Alcohol and cancer. *Lancet Oncol*. 2006;7:149-156.
68. Patterson RE, Cadmus LA, Emond JA, Pierce JP. Physical activity, diet, adiposity and female breast cancer prognosis: a review of the epidemiologic literature. *Maturitas*. 2010;66:5-15.
69. Flatt SW, Thomson CA, Gold EB, et al. Low to moderate alcohol intake is not associated with increased mortality after breast cancer. *Cancer Epidemiol Biomarkers Prev*. 2010;19:681-688.
70. Barnett GC, Shah M, Redman K, Easton DF, Ponder BA, Pharoah PD. Risk factors for the incidence of breast cancer: do they affect survival from the disease? *J Clin Oncol*. 2008;26:3310-3316.
71. White MK, Pagano JS, Khalili K. Viruses and human cancers: a long road of discovery of molecular paradigms. *Clin Microbiol Rev*. 2014;27:463-481.
72. Munoz N, Castellsagué X, de González AB, Gissmann L. HPV in the etiology of human cancer. *Vaccine*. 2006;24:S1-S10.
73. Khan MJ, Castle PE, Lorincz AT, et al. The elevated 10-year risk of cervical precancer and cancer in women with human papillomavirus (HPV) type 16 or 18 and the possible utility of type-specific HPV testing in clinical practice. *J Natl Cancer Inst*. 2005;97:1072-1079.
74. Giuliano AR, Palefsky JM, Goldstone S, et al. Efficacy of quadrivalent HPV vaccine against HPV infection and disease in males. *N Engl J Med*. 2011;364:401-411.
75. Petrosky E, Bocchini JA Jr, Hariri S, et al. Use of 9-valent human papillomavirus (HPV) vaccine: updated HPV vaccination recommendations of the advisory committee on immunization practices. *MMWR Morb Mortal Wkly Rep*. 2015;64(11):300-304.
76. Bray F, Jemal A, Grey N, Ferlay J, Forman D. Global cancer transitions according to the Human Development Index (2008-2030): a population-based study. *Lancet Oncol*. 2012;13:790-801.
77. Perz JF, Armstrong GL, Farrington LA, Hutin YJF, Bell BP. The contributions of hepatitis B virus and hepatitis C virus infections to cirrhosis and primary liver cancer worldwide. *J Hepatol*. 2006;45:529-538.
78. McGlynn KA, Petrick JL, London WT. Global epidemiology of hepatocellular carcinoma: an emphasis on demographic and regional variability. *Clin Liver Dis*. 2015;19:223-238.
79. *Hepatitis Viruses*. (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol 59). Lyon, France: International Agency for Research on Cancer; 1994. Available at <http://monographs.iarc.fr/ENG/Monographs/vol59/index.php>
80. Wroblewski LE, Peek RM, Wilson KT. *Helicobacter pylori* and gastric cancer: factors that modulate disease risk. *Clin Microbiol Rev*. 2010;23:713-739.
81. Fuccio L, Zagari R, Eusebi L, et al. Meta-analysis: can *Helicobacter pylori* eradication treatment reduce the risk for gastric cancer? *Ann Intern Med*. 2009;151:121-128.
82. World Cancer Research Fund International & American Institute for Cancer Research. *Breast Cancer 2010 Report. Food, Nutrition, Physical Activity and the Prevention of Breast Cancer*. Washington, DC: American Institute for Cancer Research; 2010.
83. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and breastfeeding: collaborative reanalysis of individual data from 47 epidemiological studies in 30 countries, including 50302 women with breast cancer and 96973 women without the disease. *Lancet*. 2002;360:187-195.
84. Bernstein L. Epidemiology of endocrine-related risk factors for breast cancer. *J Mammary Gland Biol Neoplasia*. 2002;7:3-15.
85. Nechuta S, Paneth N, Velie EM. Pregnancy characteristics and maternal breast cancer risk: a review of the epidemiologic literature. *Cancer Causes Control*. 2010;21:967-989.
86. Committee on Gynecologic Practice. ACOG Committee Opinion No. 434: induced abortion and breast cancer risk. *Obstet Gynecol*. 2009;113:1417-1418.
87. Emons G, Fleckenstein G, Hinney B, Huschmand A, Heyl W. Hormonal interactions in endometrial cancer. *Endocr Relat Cancer*. 2000;7:227-242.
88. Hankinton SE, Colditz GA, Hunter DJ, Spencer TL, Rosner B, Stampfer MJ. A quantitative assessment of oral

- contraceptive use and risk of ovarian cancer. *Obstet Gynecol.* 1992;80:708-714.
89. Hunter DJ, Colditz GA, Hankinson SE, et al. Oral contraceptive use and breast cancer: a prospective study of young women. *Cancer Epidemiol Biomarkers Prev.* 2010;19:2496-2502.
 90. La Vecchia C, Tavani A. Female hormones and benign liver tumours. *Dig Liver Dis.* 2006;38:535-536.
 91. IARC Working Group on the Evaluation of Carcinogenic Risk to Humans. *Combined Estrogen-Progestogen Contraceptives and Combined Estrogen-Progestogen Menopausal Therapy.* Lyon, France: International Agency for Research on Cancer; 2007.
 92. International Agency for Research on Cancer. *Hormonal Contraception and Post-Menopausal Hormonal Therapy* (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans). Lyon, France: International Agency for Research on Cancer; 1999.
 93. International Agency for Research on Cancer. *Combined Estrogen-Progestogen Contraceptives and Combined Estrogen-Progestogen Menopausal Therapy* (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans). Lyon, France: International Agency for Research on Cancer; 2007.
 94. Design of the Women's Health Initiative clinical trial and observational study. The Women's Health Initiative Study Group. *Control Clin Trials.* 1998;19:61-109.
 95. Chlebowski RT, Anderson GL, Manson JE, et al. Lung cancer among postmenopausal women treated with estrogen alone in the women's health initiative randomized trial. *J Natl Cancer Inst.* 2010;102:1413-1421.
 96. Chlebowski RT, Anderson GL, Gass M, et al. Estrogen plus progestin and breast cancer incidence and mortality in postmenopausal women. *JAMA.* 2010;304:1684-1692.
 97. Chlebowski RT, Kuller LH, Prentice RL, et al. Breast cancer after use of estrogen plus progestin in postmenopausal women. *N Engl J Med.* 2009;360:573-587.
 98. Rossouw JE, Anderson GL, Prentice RL, et al; Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the women's health initiative randomized controlled trial. *JAMA.* 2002;288:321-333.
 99. Stefanick ML, Anderson GL, Margolis KL, et al. Effects of conjugated equine estrogens on breast cancer and mammography screening in postmenopausal women with hysterectomy. *JAMA.* 2006;295:1647-1657.
 100. Tsai SA, Stefanick ML, Stafford RS. Trends in menopausal hormone therapy use of U.S. office-based physicians, 2000-2009. *Menopause (New York, NY).* 2011;18:385-392.
 101. Schierbeck LL, Rejnmark L, Tofteng CL, et al. Effect of hormone replacement therapy on cardiovascular events in recently postmenopausal women: randomised trial. *BMJ.* 2012;345:e6409.
 102. Dowsett M, Forbes JF, Bradley R, et al. Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. *Lancet.* 2015;386:1341-1352.