

Age and Cancer Risk

A Potentially Modifiable Relationship

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Abstract: This article challenges the idea that cancer cannot be prevented among older adults by examining different aspects of the relationship between age and cancer. Although the sequential patterns of aging cannot be changed, several age-related factors that contribute to disease risk can be. For most adults, age is coincidentally associated with preventable chronic conditions, avoidable exposures, and modifiable risk behaviors that are causally associated with cancer. Midlife is a period of life when the prevalence of multiple cancer risk factors is high and incidence rates begin to increase for many types of cancer. However, current evidence suggests that for most adults, cancer does not have to be an inevitable consequence of growing older. Interventions that support healthy environments, help people manage chronic conditions, and promote healthy behaviors may help people make a healthier transition from midlife to older age and reduce the likelihood of developing cancer. Because the number of adults reaching older ages is increasing rapidly, the number of new cancer cases will also increase if current incidence rates remain unchanged. Thus, the need to translate the available research into practice to promote cancer prevention, especially for adults at midlife, has never been greater.

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Grow old along with me! The best is yet to be, the last
of life, for which the first was made.

~Robert Browning

Introduction

Age, defined by completed units of time,¹ is used in virtually all studies of cancer epidemiology and is one of the most studied risk factors for cancer. Cancer can be considered an age-related disease because the incidence of most cancers increases with age,² rising more rapidly beginning in midlife. Age also can be considered a surrogate measure for the complex biological processes associated with aging. However, aging, the process of getting older, can be distinguished from age-associated diseases.³ Paradoxically, adults with the longest longevity are less likely to develop cancer.^{4–6} Thus, aging can be viewed as a natural process, not pathology, and old age does not necessarily lead to cancer.

Some of the same biologic mechanisms that regulate aging also may be involved in the pathogenesis of age-related diseases such as cancer.^{3,7} If the environmental factors that influence these biologic mechanisms⁸ can be modified, the rate of aging may be slowed and the onset of cancer delayed or even prevented. The preventability of many cancers over a person's life span is supported by a substantial body of scientific research.⁹ This article reviews the literature on different aspects of the association between age and cancer as well as potential opportunities during midlife to reduce the likelihood of developing cancer at older ages. It focuses on people aged 45–64 years, while recognizing that this age range is an arbitrary and imprecise measure of midlife. As described by Ory and colleagues elsewhere in this supplement, midlife represents a “watershed” period for cancer prevention.¹⁰

Cancer Occurrence at Older Ages

Life expectancy and the percentage of the U.S. population that is surviving at older ages has increased dramatically over the last century.¹¹ In 1900, the average life expectancy from birth was 47 years; in 2011, life expectancy from birth was about 76 years for men and 81 years for women.¹² Just since 1960, life expectancy at age 65 years has increased by 5 years.¹³ Life expectancy also shifts

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Table 1. Life expectancy at selected ages, by gender, U.S., 2011

Age (years)	Life expectancy (years)	
	Male	Female
0	76.3	81.1
45	34.0	37.8
50	29.6	33.2
55	25.5	28.8
60	21.5	24.5
65	17.8	20.4
70	14.3	16.5
75	11.0	12.9
80	8.2	9.7
85	5.9	6.9
90	4.1	4.8
95	2.9	3.3
100	2.1	2.3

Note: The life expectancy at a given age for 2011 represents the average number of years of life remaining if people at that age were to experience the death rates for 2011 over the course of their remaining life.

upward as people survive to older ages (Table 1).¹² For example, in 2011, men aged 65 years were expected to live another 18 years (total life expectancy of 83 years), whereas women aged 65 years were expected to live another 20 years (total life expectancy of 85 years). More than half of the adults aged 85 years in 2011 can expect to live at least another 6 years. During 2010–2050, the number of adults aged 85 years and older in the U.S. is projected to grow from 5.5 million to 19 million.¹³

The risk of receiving a diagnosis of different types of cancer varies throughout a person’s life span. The cumulative risk for all cancers combined increases with age, up to age 70 years then decreases slightly (Table 2).¹⁴ For the total U.S. population, the lifetime risk of ever being diagnosed with cancer is approximately 41%.¹⁴ However, a substantial proportion of older adults will reach the end of their life span without clinically detected cancer (excluding indolent tumors). After age 90 years, cancer is uncommon as a cause of disease or death.⁶

Still, slightly more than half of all cancers in 2009 occurred in adults aged ≥65 years (Figure 1).² Over time, the shape of this curve is expected to shift toward a greater number of cancer cases at older ages as the Baby Boom generation born after World War II ages. In addition, the total number of cancers is projected to increase by 45% from 2010 to 2030,¹⁵ driven largely by

the growing number of older adults. By 2030, an estimated 70% of all cancers will occur among adults aged ≥65 years. The challenges posed to the U.S. healthcare system by the expected increase in cancer incidence are considerable^{10,11,16,17} and point to the growing need to focus on opportunities for primary prevention rather than relying on treatment alone.

Midlife as a Critical Period in the Life Course for Cancer Risk and Prevention

Cancer development is a complex process that occurs over a span of many years.¹⁸ A life course approach^{10,19,20} is particularly well suited to understanding the contributions of various cancer risk factors over a person’s life span. As Rando observed, the biologic processes of aging are mysterious and highly variable.⁸ Aging is influenced by genetically determined processes but also can be modified by environmental influences.^{8,15,21} For example, cigarette smoke is thought to accelerate the aging process.²²

When applied to cancer research, the life course approach has been used to examine the influence of prenatal and early life events on cancer development in adulthood.^{23,24} A recent federal, interagency report on breast cancer research, for example, highlighted evidence that exposures that cause molecular and cellular changes in mammary tissue during puberty or earlier can

Table 2. Lifetime risk (%) of receiving a diagnosis or dying of cancer, by age, U.S.

Current age (years)	Risk of receiving a cancer diagnosis				Risk of dying of cancer
	≥10 years	≥20 years	≥30 years	Ever	
0	0.17	0.35	0.79	41.24	21.00
10	0.18	0.63	1.67	41.62	21.25
20	0.45	1.5	4.13	41.65	21.31
30	1.06	3.73	9.85	41.74	21.45
40	2.72	8.98	20.14	41.55	21.57
50	6.57	18.29	31.00	40.77	21.55
60	13.09	27.28	35.94	38.20	20.86
70	17.85	28.74	—	31.59	18.56
80	16.83	—	—	21.23	14.15

Note: Risk of receiving a cancer diagnosis in 10, 20, or 30 years and lifetime risk if cancer-free at current age; invasive cancer only; for both genders and all U.S. racial and ethnic groups combined. Data source is 18 SEER (Surveillance, Epidemiology, and End Results) Areas, 2007–2009.

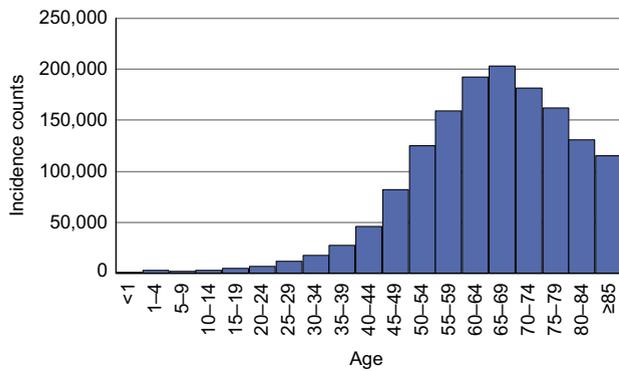


Figure 1. Invasive cancer incidence, by age, U.S., 2009

influence breast cancer development many years later.²⁵ The finding that breast cancer incidence rates fell after the decline in the use of hormone replacement therapy at menopause suggests that critical periods for breast cancer development also exist later in life.²⁶ In addition, opportunities may exist to intervene at midlife to alter or reverse disease processes that were initiated at earlier life stages.²⁷

As a marker of time, age captures the duration of exposures and the accumulation of cancer risk.²⁸ Nine hallmarks of aging have been proposed,²⁹ including genomic instability and epigenetic alteration, which are also the hallmarks of cancer.¹⁸ Whether the relationship between age and cancer risk is due primarily to the time-dependent accumulation of genetic and epigenetic mutations or to an increased susceptibility of older adults to oncogenic mutations is not fully understood.^{30,31} The multifactorial process of transformation from normal cells to cancer includes the accumulation of DNA damage and mutations over time coupled with disruptions of the DNA repair and cell growth regulation system.^{18,32}

The role of epigenetic alterations such as DNA methylation in the complex aging process is an emerging area of research.³³ Although the potential for reversing gene expression suggests a role for dietary or other modifications, the biological or clinical significance of these epigenetic changes have yet to be fully elucidated.³⁴ Risk factors such as environmental or occupational exposures to chemical and physical agents, tobacco smoke, and viral infections might affect different points along this multistep process of transformation and accelerate damage; removing these risk factors may reverse damage.³⁵ Current research also suggests that the transformation to malignancy requires age-associated changes in the cellular microenvironment or tissue, such as increased inflammation or decreased immune function that selects for mutations that support proliferation and dissemination of transformed cells.^{36,37} Precursor

lesions, such as the adenomatous polyp in colorectal cancer, may be prevented from progressing to cancer through risk factor modification and intervention.³⁸ It has also been proposed that calorie restriction or drugs that possess anti-aging activity may be able to delay or prevent cancer.³⁹ Thus, midlife and older age can be seen as a time of increased vulnerability to cancer and an appropriate focus for expanded research and prevention efforts.

Radiation exposure in particular has been associated with increasing cancer risks for people at midlife. For most adults, their greatest exposure to ionizing radiation is from medical imaging.⁴⁰ Use of medical imaging procedures such as CT scans and PET scans has increased dramatically over the past 20 years, particularly among those in midlife who have chronic conditions.^{41,42} Evidence from epidemiologic studies and models of radiation-induced cancer show that exposures to radiation during midlife may increase risk more than exposures at other ages.⁴³ This evidence is consistent with research showing that the processes that promote cancer may also increase at older ages.⁴³ Vulnerability to cancer has also been demonstrated for exposure to ultraviolet radiation during midlife. A recent meta-analysis of sunburns and melanoma concluded that sunburn at any age increases the risk of cutaneous melanoma,⁴⁴ suggesting the importance of preventing excessive sun exposure not only among the young but across the life span.

Increased Prevalence of Selected Chronic Conditions and Infections with Age

Health at midlife establishes the foundation for health and longevity later in life. Midlife is also the time when some well-recognized risk factors for cancer and other diseases (e.g., tobacco use, lack of physical activity, poor nutrition, excessive alcohol consumption, certain chronic infections) begin to demonstrate an impact.^{45,46} The prevalence of several preventable chronic conditions and diseases, such as obesity and diabetes, tends to increase during midlife, and some of these conditions have been associated with increased cancer risk and reduced cancer survival. Although members of the current generation of adults aged 45–64 years are expected to live longer than members of earlier generations, they are also experiencing higher rates of chronic conditions such as obesity and diabetes, and they tend to rate their health lower than previous generations at the same age.^{27,47} Thus, the prevention or management of chronic conditions and the promotion of general health during midlife are promising strategies to prevent or delay cancer incidence at older ages.

Diabetes

Type 2 diabetes is associated with an increased risk of developing cancer of the colon; breast (post-menopausal); and pancreas.^{48–50} Approximately 11.7% of U.S. adults aged 45–64 years have received a diagnosis of diabetes, and prevalence is even higher (18.9%) among those aged ≥ 65 years.⁵¹ According to blood glucose data from the National Health and Nutrition Examination Survey, many more U.S. adults may have undiagnosed diabetes.⁵² Diabetes accelerates biologic aging and is recognized as a rapidly growing problem among older adults.⁵³ Thus, efforts to prevent and better manage diabetes during midlife could reduce the risk for certain cancers later in life.

Weight and Metabolic Syndrome

Excess body weight has also been linked to an increased risk of many types of cancer, including cancer of the esophagus; pancreas; thyroid; gallbladder; colon and rectum; breast (post-menopausal); endometrium; and kidney.^{50,54–56} Visceral adipose tissue produces cytokines that create chronic inflammation and promote tumor growth through multiple biologic mechanisms.^{57,58} According to data collected in 2009–2010, the prevalence of obesity was 35.7% among U.S. adults aged ≥ 20 years and 36.6% among adults aged 40–59 years.⁵⁹

Excess body weight contributes to metabolic syndrome,⁵⁸ which has also been linked to increased cancer risk.^{53,60,61} The National Cholesterol Education Program's Adult Treatment Panel III report defines metabolic syndrome as the presence of three or more of the following characteristics: abdominal obesity (waist circumference > 102 cm for men and > 88 cm for women); triglycerides ≥ 150 mg/dL; low high-density lipoprotein (HDL) cholesterol (< 40 mg/dL for men and < 50 mg/dL for women); blood pressure of $\geq 135/\geq 85$ mm Hg; and a fasting glucose ≥ 100 mg/dL.⁶² During 2003–2006, the percentage of adults meeting the criteria for metabolic syndrome was more than twice as high among those aged 40–59 years (41% of men and 37% of women) than among those aged 20–39 years (20% of men and 16% of women).⁶³ Facilitating healthy dietary choices and physical activity among adults may potentially help to not only reduce the prevalence of metabolic syndrome but also reduce risk for certain related cancers.

Infections

Chronic infection with hepatitis C virus (HCV) is associated with an increased risk of hepatocellular carcinoma and other HCV-related liver disease.⁶⁴ The prevalence of HCV infection in the U.S. is highest among adults who were born during 1945–1965 (3.25%) because

of the substantial number of incident infections during the 1970s and 1980s and the persistence of chronic HCV infection.⁶⁴ New antiviral treatments are available that can halt HCV-related disease progression and provide a cure for HCV infection in most people.^{64,65} The CDC recommends one-time testing for HCV among adults born during 1945–1965 as a strategy for reducing HCV-related morbidity and mortality.⁶⁴ The U.S. Preventive Services Task Force (USPSTF) recently updated its review of the evidence on HCV screening and now also recommends offering one-time screening to adults born between 1945 and 1965.^{66,67} If a person is found to be infected with HCV, preventive care can be offered to limit the progression from HCV infection to liver cancer.

A substantial proportion of older adults are sexually active,⁶⁸ and thus at risk of sexually transmitted infections. Infections of special concern are HIV and human papillomavirus (HPV). HIV infection is associated with an increased risk of several non-AIDS cancers (e.g., anal cancer, Hodgkin's disease, liver cancer), perhaps because of HIV-associated immune dysfunction.³ Oncogenic HPV is associated with cervical, vulvar, vaginal, penile, anal, and oropharyngeal cancers, and incidence rates for these cancers increase after age 50 years.⁶⁹ Older adults are at special risk because they are less likely to use a condom, and their health professionals may fail to ask about unsafe sexual behaviors.⁷⁰ Even at midlife, safe sexual practices can reduce the risk of cancers associated with HPV or HIV infection.

The Social Dimension of Age

Causal paradigms for cancer typically categorize age along with gender, race, and ethnicity as individual characteristics that are not amenable to intervention.⁷¹ Just as research has shown a lack of precision in various racial and ethnic categories,⁷² a great deal of heterogeneity can exist within any age category.⁷³ In addition, the experience of age is subject to social and cultural influences. Although the challenges of examining differences by race and ethnicity without contributing to societal racism has been noted previously,^{72,74,75} the influence of stereotypes and prejudice based on age has received far less attention.^{76,77}

Age prejudice has been characterized as “one of the most socially-condoned and institutionalized forms of prejudice.”⁷⁸ Pervasive myths of aging and stereotypes about age⁷⁶ need to be recognized and addressed by both older adults and healthcare providers when addressing cancer prevention at midlife. When a person believes that aging leads to poor health, this belief can operate as a self-fulfilling prophecy and contribute to poor health.^{79,80} A meta-analysis of research on age stereotypes demonstrated

that negative age stereotypes had a much stronger influence on adult behavior than did positive age stereotypes, and that the harmful effect of pervasive negative stereotypes about age is not easily offset by less-frequent, positive stereotypes.⁷⁹ The perception among some healthcare providers that illnesses such as cancer are an inevitable part of the aging process may lead to a focus on disease management instead of prevention.⁷⁸ If the detrimental effects of negative age stereotypes can be avoided, then opportunities for cancer prevention among older adults are more likely to be recognized and pursued.

Approaches to Cancer Prevention at Midlife

A large body of evidence supports the use of selected cancer screening technology as one approach to cancer control in midlife. Currently, the USPSTF has identified sufficient evidence to support population screening for only a few cancers—colorectal, cervical, and female breast cancer—as a way to reduce cancer deaths.⁸¹ In December 2013, the USPSTF issued a recommendation on annual lung screening with low-dose CT scans, but only for people at high risk for lung cancer.⁸² Some types of screening tests, such as the Pap test for cervical cancer, involve the identification and subsequent removal of precancerous lesions before they develop into cancer. Other types of screening tests, such as mammography for breast cancer, are limited to the early detection of cancer.

Less attention has focused on approaches for the primary prevention of cancer at midlife, a point in the life course when incidence rates for most cancers begin to increase significantly. Given the growing understanding of the variety of factors that are associated with cancer risk, more opportunities to make changes to prevent cancer are becoming evident. Although the sequential patterns of aging cannot be changed,⁸³ the factors that contribute to the development of chronic diseases, including cancer, can be changed to promote a healthier transition from midlife to older age. Evidence supports, to varying degrees, an association between increased risk for cancer and prevalent behaviors among U.S. adults, such as smoking, excessive alcohol consumption, poor sleep hygiene, a diet lacking in fruits and vegetables and high in red meat, and insufficient physical activity.^{84–86}

Smoking

Smoking cessation is an important example of how the adoption of a healthy behavior in midlife can help prevent cancer. Smoking reduces life expectancy by about 10 years but smokers who quit can benefit from reduced risk.⁸⁷ One study from the United Kingdom found that smoking cessation even up to age 60 years significantly reduced the risk of developing lung cancer.⁸⁷

Similar findings from two studies in the U.S. showed that life expectancy was extended and risk of death associated with continued smoking was significantly reduced for those who quit smoking in midlife.^{88,89} At any age, smokers should be encouraged to quit and offered assistance to achieve success in quitting.

Alcohol

The mechanisms by which excessive alcohol consumption causes cancer, including DNA damage, formation of DNA adducts, production of reactive oxygen species, chronic inflammation, folate and other nutritional deficiencies, and increased estrogen concentration, are not well studied and differ by target organ.^{90,91} However, adequate evidence exists to support a linear dose-response relationship between alcohol intake and increased cancer risk, with no safe level of consumption.^{54,90} Thus, limiting or avoiding alcohol consumption may reduce the risk of cancer.⁹²

Other Health-Related Behaviors

Emerging evidence points to the association of sleep disturbance and cancer risk,⁹³ suggesting that good sleep hygiene may help prevent cancer in adults. In addition, increasing physical activity and reducing time spent engaging in sedentary behaviors (e.g., sitting) may be a particularly important strategy for cancer prevention at midlife.¹⁰

Behavioral Interventions

Sabia and colleagues⁹⁴ studied middle-aged adults in the context of successful aging, finding that those in midlife who ate a healthy diet, refrained from smoking and excessive alcohol use, and engaged in moderate levels of physical activity were less likely than study participants who did not engage in healthy behaviors to suffer from cancer 16 years after the study began. In a subsequent report based on the same study cohort, diet at midlife was found to be associated with overall health at older ages.⁹⁵ In particular, adults who consumed a diet high in fried foods, sweets, processed food, red meat, refined grains, and high-fat dairy products were less likely to meet the criteria for ideal aging at follow-up. Other research has demonstrated that behavior change in midlife—such as eating more fruits and vegetables daily, exercising regularly, maintaining a healthy weight, and not smoking—was associated with a reduced risk of cardiovascular disease and death.⁹⁶ However, physical activity and fruit and vegetable intake decreased among adults during 1988–2006.⁹⁷ Thus, more research is needed on effective interventions and policy and environmental strategies to increase and sustain healthy behaviors in midlife and older ages.

Environmental Carcinogens

Another way to prevent cancer is to reduce people's exposures to environmental carcinogens,⁹⁸ and many known human carcinogens (e.g., asbestos, benzene, formaldehyde, radon, and ultraviolet radiation) are highly prevalent in the general environment, consumer products, or the workplace.⁹⁹ In 2012, 75.2% of U.S. adults aged 45–54 years and 60.6% of those aged 55–64 years were employed,¹⁰⁰ making exposure to occupational carcinogens especially relevant at this stage of life. The National Institute for Occupational Safety and Health has identified more than 130 substances as potential occupational carcinogens.¹⁰¹ Many thousands of chemicals and other substances are in use but have never been evaluated for possible carcinogenicity.⁹⁸ Workplace hazards, working conditions, and personal risk factors may interact to contribute to chronic diseases such as cancer among working adults.¹⁰² Primary prevention policies that reduce exposure to known carcinogens have been found to reduce cancer risk (e.g., eliminating exposure to asbestos to reduce lung cancer).¹⁰³ In addition, for potentially large numbers of workers, the workplace could be an effective place to use comprehensive strategies that protect and promote health for adults at midlife and at older ages.^{104,105}

Conclusion

More than 30 years ago, James Fries proposed a model for national health that would delay the onset of disease with age so that more adults could reach the end of life disease-free.¹⁰⁶ As life expectancy has increased and the number of older Americans has grown, so have efforts to promote healthy aging.¹⁰⁷ However, the occurrence of cancer at older ages poses unique challenges to achieving a high quality of life.¹⁰⁸ Patients and providers both need to recognize that for most adults, age is coincidentally associated with preventable chronic conditions, avoidable exposures, and modifiable health habits that are causally associated with cancer. In addition to changing individual behaviors to reduce cancer risk, multilevel system and environmental interventions that address multiple diseases and risk factors could prevent or delay the occurrence of cancer and other age-related diseases.^{109,110} Clinical preventive services that address multiple chronic conditions and health behaviors at midlife also are important for cancer prevention later in life. To increase their effectiveness, these clinical services could be supported and reinforced by community-based prevention policies and programs.¹¹¹ The workshop summary in this supplement highlights potentially promising approaches and strategies for cancer prevention at midlife.¹¹²

Current research suggests that for most adults, cancer does not have to be an inevitable consequence of growing older. On the contrary, the prevention or at least delay of cancer occurrence can be viewed as an effective strategy for achieving a healthy, long life. By applying the available scientific evidence to promote cancer prevention at midlife, it should be possible to substantially modify the relationship between age and cancer risk.

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