Published in final edited form as:
Biochim Biophys Acta. 2009 October ; 1790(10): 1133–1138. doi:10.1016/j.bbagen.2009.02.002.

Modulating Human Aging and Age-Associated Diseases

Luigi Fontana, M.D., Ph.D.
Division of Geriatrics and Nutritional Science and Center for Human Nutrition, Washington University School of Medicine, St. Louis, Missouri, USA and the Division of Nutrition and Aging, Istituto Superiore di Sanità, Rome, Italy

Abstract

Population aging is progressing rapidly in many industrialized countries. The United States population aged 65 and over is expected to double in size within the next 25 years. In sedentary people eating Western diets aging is associated with the development of serious chronic diseases, including type 2 diabetes mellitus, cancer and cardiovascular diseases. About 80 percent of adults over 65 years of age have at least one chronic disease, and 50 percent have at least two chronic diseases. These chronic diseases are the most important cause of illness and mortality burden, and they have become the leading driver of healthcare costs, constituting an important burden for our society. Data from epidemiological studies and clinical trials indicate that many age-associated chronic diseases can be prevented, and even reversed, with the implementation of healthy lifestyle interventions. Several recent studies suggest that more drastic interventions (i.e. calorie restriction without malnutrition and moderate protein restriction with adequate nutrition) may have additional beneficial effects on several metabolic and hormonal factors that are implicated in the biology of aging itself. Additional studies are needed to understand the complex interactions of factors that regulate aging and age-associated chronic disease.

Keywords

aging; chronic disease; calorie restriction; physical exercise; prevention

Introduction

At the beginning of the 20th century, the average life expectancy at birth was about 47 years (1). Infectious diseases were the leading cause of death (2). Over-crowded housing, malnutrition, poor hygiene, inadequate sewage disposal, and contaminated food and water supplies were major contributors to the spread of infectious diseases and deaths from infections. Approximately 30 percent of infants in the US and Europe died during their first year of life. Maternal mortality rate was also high because of poor obstetrical practices and birth-related infections (3).

In the first few decades of the 20th century, implementation of preventive care and public health procedures, such as improvements in sanitation and working conditions, better nutrition and

Send correspondence to: Luigi Fontana, M.D., Ph.D, Washington University School of Medicine, 4566 Scott Avenue, Campus Box 8113, St. Louis, Missouri 63110, Phone: 314-747-1485, Fax: 314-362-7657, lfontana@dom.wustl.edu.

Financial Disclosures: The author had no conflicts of interest.

housing, organized sewage disposal, improved animal and pest control, water chlorination, national vaccination programs, development of antibiotics and better medical practice, caused a steep decline in deaths from infectious diseases, maternal mortality, and infant mortality (2, 3).

By the beginning of the 21st century, the average life expectancy at birth was about 77.8 years, a gain of approximately 30 years compared to 1900 (1). Today the likelihood of dying prematurely from an infectious disease in a developed country is extremely low. In contrast, the likelihood of dying of a noncommunicable chronic disease is very high in spite of major advances in the diagnosis and treatment of these diseases. Heart disease, cancer, stroke, and chronic lower respiratory diseases are now the leading cause of death in industrialized countries and in many developing countries (4). Cardiovascular disease (CVD), cancer, stroke and diabetes account for nearly 70% of the deaths in the United States and Europe (4,5). About 80 percent of adults over 65 years of age have at least one chronic disease, and 50 percent have two or more of these chronic diseases that accelerate the aging process (4).

Many things have changed in men's and women's health during the 20th century, but the major causes of disease and death continue to be largely preventable. According to a recent World Health Organization report, over 40% of cancer and at least 80% of all heart disease, stroke and type 2 diabetes would be prevented, if the modifiable risk factors for these age-associated chronic diseases (e.g. unhealthy diets, physical inactivity, and tobacco consumption) were eliminated (6). By preventing these diseases significant extension of healthspan and lifespan could be achieved, and suffering, disability, and health care costs could be reduced (5,6). Recent data suggest that more drastic interventions (i.e. calorie restriction without malnutrition and moderate protein restriction with adequate nutrition) might have additional beneficial effects on the aging process itself (7).

The purpose of this article is to succinctly review the current knowledge on risk factors for age-associated diseases and accelerated aging in humans, and on the effects of nutrition, exercise and other lifestyles on disease risk and life expectancy, which have important clinical implications for clinicians and health care providers.

Aging and chronic diseases

Aging is associated with the development of serious chronic diseases, including type 2 diabetes mellitus, cancer, heart, kidney and neurological diseases in mammals. However, association is not equal to causation. Indeeed, experimental data indicate that aging and age-associated chronic diseases are not inextricably linked processes. During their lifetime the vast majority (>90%) of laboratory rodents fed an ad-libitum chow diet, that contains all the essential macro- and micro-nutrients, develop at least one serious and eventually fatal disease (8-11). In contrast, data from post-mortem pathological studies have demonstrated that ~ 30% of the calorie restricted (CR) rodents and 25% to 50% of the long-lived mutant rodents (e.g. Ames and Snell dwarf mice, Growth hormone receptor knockout mice) die without evidence of lethal pathological lesions when they are very old (8-11). Delayed incidence and/or progression of both neoplastic and non-neoplastic lesions, and reduced disease burden are also common pathological findings in CR rodents and long-lived mutant rodents (7,8-11,12,13).

However, these data must be used with caution because major species differences between humans and rodents exist in metabolism, lifespan and susceptibility to diseases. For example, in humans cardiovascular diseases (e.g. ischemic heart disease and stroke) are the main cause of death, accounting for nearly 40% of the deaths (4). Rodents, however, are resistant to ischemic heart disease, even when fed high-fat atherogenic diets (14). Cancer is the second leading cause of death in humans, accounting for nearly 23% of the deaths in many developed

countries (4). Cancers of the epithelial cells (e.g. breast, colon, prostate and lung carcinomas) are responsible for almost 85% of all cancers, whereas leukaemias/lymphomas and sarcomas (e.g. bone sarcomas and soft tissue sarcomas) account for only 7% and 1% of all cancers, respectively (15). In rodents, instead, cancer is the leading cause of death, accounting for 70-80% of the deaths (8-11). In rats, pituitary tumors, subcutaneous tumors in males, and mammary gland tumors in females are the most common cancers. In mice, hemolymphoreticular tumors, lung and liver tumors are the most common cancers (16,17). Chronic progressive nephropathy and glomerulonephropathy are the second leading causes of death in rodents, whereas in humans these are not common cause of death (8-11). Nutritional requirements are also different between humans and rodents. For example, rats have a methionine requirement that is ~50% higher than that of humans (18). In addition, the common practice to extrapolate data obtained from interventions in genetically homogeneous animal models to genetically heterogeneous human populations must be tempered, because complete reliance on the results from these animal experiments can be dangerously misleading, potentially resulting in damage to human health.

Cardiovascular disease: the number 1 killer of men and women

Despite a ~50% decline in mortality from heart disease in the United States in the last 3 decades, CVD remains the leading cause of morbidity and mortality, claiming more lives each year than cancer, chronic lower respiratory diseases, and accidents combined (4). Unfortunately, it has been postulated that this downward trend in CVD mortality will soon end or may even reverse because of the recent increase in the prevalence of abdominal obesity, type 2 diabetes, and its associated medical complications (19). Well-established risk factors for CVD include hypertension, dyslipidemia, diabetes mellitus, cigarette smoking, inflammation and abdominal obesity. The absence of all these risk factors at age 50 is associated with very low lifetime risk for CVD and markedly longer survival (20). In the Framingham Heart Study participants with optimal cardiovascular risk factor levels had substantially lower lifetime risks compared with participants with ≥ 2 major risk factors (5.2% versus 68.9% in men, 8.2% versus 50.2% in women) and had markedly longer median survivals (20). In this study the definition of optimal risk factors was: total cholesterol <180 mg/dl, blood pressure <120/80 mm Hg, fasting glycemia < 125 mg/dl and no smoking. However, accumulating evidence suggests that there is no threshold for many CVD risk factors below which cardiovascular risk does not decrease. Physiologically optimal LDL-cholesterol levels should be approximately 50 to 70 mg/dl, optimal blood pressure values should be below 115/75 mmHg, optimal fasting glucose concentration should be below 86 mg/dl, optimal serum C-reactive protein concentration should be lower than 0.7 mg/L, and optimal waist circumference should be ≤ 94 cm for men and ≤ 88 cm for women) (21-23). Unfortunately, due to the chronic consumption of unhealthy diets and to physical inactivity, present average values for many cardiometabolic risk factors in Western populations are far from being optimal. According to the 1999-2002 National Health and Nutrition Examination Survey (NHANES) the age-adjusted mean LDL cholesterol level of adults age 20 and over is 123 mg/dl; 43.1% of the US men and 35.8% of the US women have a LDL-cholesterol higher than 130 mg/dl (25). According to the 1999-2000 NHANES, 8% of people aged 18 to 39 years, and 65% of people aged 60 yrs or older, have hypertension, defined as blood pressure higher than 140/90 mmHg (26). The prevalence of prehypertension (blood pressure higher than 120/80 mmHg) and hypertension, instead, is 40% among individuals aged 18 to 39 years, and 88% among those 60 years and older (26). In US men and women, according to NHANES III data, median CRP is ~ 2mg/L; 16.4% of US men and women have a CRP higher than 5 mg/L (27). Finally, according to NHANES 1999-2000 data, the age-adjusted prevalence of high-risk waist circumference is ~37% in men (≥ 102 cm) and 55.1% in women (≥ 88 cm) (28). We must also bear in mind that these classical risk factors for atherosclerosis and CVD do not explain the full risk of CVD. Indeed, 10-20% of patients with CVD lack any of the conventional risk factors, implying that other factors play a role in

the development of CHD. Some of these emerging risk factors are high levels of triglycerides, lipoprotein (a), apolipoprotein (apo) A-I, apolipoprotein B-100, fibrinogen, plasminogen activator inhibitor-1, microalbuminuria, insulin resistance, endothelial dysfunction, physical inactivity and hypovitaminosis D (30).

Cancer: the silent killer

Cancer is the second leading cause of death in many developed countries, accounting for approximately one fourth of all deaths (4). Among women aged 40 to 79 and among men aged 60 to 79 cancer is the leading cause of death in the U.S. (15). The lifetime probability of developing cancer is ~46% for men and ~38% for women. Among men, cancers of the prostate, lung, and colon-rectum account for ~56% of all newly diagnosed cancers and for ~51% of all cause of cancer death in the U.S. Among women, cancers of the breast, lung, colon, and uterine corpus account for ~61% of all new cancer cases and for ~55% of all cause of cancer death in the U.S (15).

Although genetic inheritance influences the risk of cancer, most of the variation in cancer risk across populations and among individuals is due to environmental and lifestyle factors. Evidence that lifestyle factors (e.g. unhealthy diets, excessive adiposity, and smoking) play a key role in promoting cancer comes from several sources. First, studies show that the chances of identical twins developing cancer at the same site are generally less than 10% (34). Second, studies of migrants moving from a low- to a high-risk area have shown that they acquire the cancer pattern of the host country within a single generation (35). Finally, data from epidemiological studies strongly suggest that excessive calorie intake and adiposity, low intake of vegetables, fruits, beans and whole grains are key players in the pathogenesis of the most common types of cancer (5). Data from several large epidemiological studies indicate that excessive adiposity, especially abdominal adiposity, is a major contributor to the increased incidence and/or death from adenocarcinoma of the oesophagus, colon cancer, post-menopausal breast cancer, endometrial, kidney, liver, gallbladder and pancreas cancers (36). Excessive adiposity due to excessive energy intake and minimal physical activity is associated with insulin resistance, low-grade inflammation, and changes in hormone and growth factor levels that likely play a central role in the pathogenesis of many cancers (37). Chronic positive energy balance promotes adipose tissue hypertrophy, adipokine-mediated insulin resistance, compensatory hyperinsulinemia, and increased sex hormone availability (37). Insulin, estrogens and androgens are strong mitogens for cells and stimulate the development and growth of several tumors (38,39). Interestingly, the development of two of the most common cancers affecting men and women in the Western world (i.e. prostate and premenopausal breast cancer) are not directly associated with adiposity or chronic hyperinsulinemia (36), suggesting that other metabolic factors play a role in their pathogenesis. Several epidemiological studies have found a strong association between plasma levels of IGF-1 and the risk of developing prostate cancer, premenopausal breast cancer and colon cancer (40-43). Nutrient intake is a major regulator of circulating IGF-1, which promotes tumor development by stimulating cell proliferation and inhibiting cell death (44,45). Recent data from observational studies indicate that long-term protein intake, but not calorie intake, regulates serum IGF-1 concentration in humans, suggesting that long-term protein intake is an important cancer risk factor (46-48).

Several other factors have been hypothesized to increase risk of cancer, including (1) lack of adequate consumption of vegetables, fruits, beans and whole grains that are rich in antioxidant vitamins and protective phytochemicals, (2) consumption of animal foods rich in fat and genotoxic heterocyclic amines and polycyclic aromatic hydrocarbons, (3) hypovitaminosis D, (4) exposure to tobacco smoke, pollutants and pesticides (49-54).

Chronic lower respiratory diseases

Chronic lower respiratory diseases (CLRD) refer to chronic diseases that affect the lower respiratory tract, such as chronic obstructive pulmonary disease, emphysema and chronic bronchitis. Approximately 1 in 8 people in the US have a CLRD. CLRD are the fourth leading cause of death in many developed countries accounting for ~5% of all deaths (4). Cigarette smoking is the most important risk factor for CLRD accounting for the majority of cases. Cigarette smokers are 10 times more likely to die from these diseases than nonsmokers (55). The remaining 20% of cases are due to exposure to indoor and urban pollution, or biomass fuels. Smoking cessation early in the natural history of CLRD stops the decline in pulmonary function and reduces mortality (56).

Modulation of age-associated disease

Many age-associated chronic diseases, such as ischemic heart disease, cancer, stroke, and diabetes, share several metabolic and hormonal risk factors that can be largely prevented, especially if they are diagnosed early. For example, insulin resistance, hyperinsulinemia and inflammation play an important role in the pathogenesis of both cancer and CVD (5,23,36, 37,38,57,58). Excessive calorie intake and a sedentary lifestyle cause abdominal obesity. Greater abdominal adiposity, and in particular accumulation of fat in the visceral adipose tissue depots, is strongly associated with insulin resistance, hyperinsulinemia, systemic inflammation, hypertension, dyslipidemia, low circulating levels of adiponectin and other metabolic and hormonal alterations which play essential roles in the pathogenesis of type 2 diabetes, stroke, ischemic heart disease and some types of cancer (36,37). Intentional weight loss has important therapeutic effects in individuals with excessive abdominal adiposity because it simultaneously improves multiple metabolic risk factors for type 2 diabetes, CVD and cancer, and reduces morbidity and mortality (59-62). Many of these beneficial effects are already apparent after only modest weight losses of 5% to 10% of initial body weight in overweight and obese patients (63). Energy deficits induced by CR and EX in overweight and obese subjects are accompanied by similar improvements in glucose tolerance and insulin action, and similar reductions in several major CHD risk factors, including plasma LDL-cholesterol concentration, TChol:HDL-cholesterol ratio, and tryglicerides (64-67). Moreover, data from observational studies have shown that CR improves metabolic profiles in normal weight subjects also. Data from a series of studies conducted in members of the CR Society, which is a group that practices self-imposed CR with adequate nutrition (approximately 30% reduction in daily calories), show that long-term CR results in profound and sustained beneficial effects on the major atherosclerosis risk factors, such as serum total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, blood pressure, and carotid artery intima-media thickness, that usually increase with advancing age (68). They further show that CR provides a powerful protective effect against obesity and insulin resistance, and provide evidence for a decrease in inflammation, as reflected in extremely low CRP, and tumor necrosis factor-α levels (68,69). Finally, compared with control volunteers consuming a Western diet, the CR society members have reduced circulating levels of insulin, PDGF, TGF-β and proinflammatory cytokines (68-69). However, caloric intake and adiposity are not the only determinants of health risk and longevity. There are several other important factors that play a crucial role in promoting or preventing age-associated diseases, independently of adiposity and energy intake. For example, it is well-known that the over-consumption of animal foods rich in saturated fatty acids and of processed foods packed with trans-fatty acids are responsible for the high levels of total cholesterol and LDL-cholesterol, which are major cardiovascular risk factors, even in lean and physically active individuals (70-72). Excessive consumption of salt and salt-preserved foods has been linked to hypertension, hemorrhagic stroke and gastric cancer independently of adiposity (73). Excessive protein intake, which results in a chronic positive nitrogen balance, is an emerging important risk factor for cancer, because it modulates

serum IGF-1 concentration (46-48). Furthermore, cooking meat, starches and oils at high temperatures (i.e. frying, broiling, and grilling) produces heterocyclic amines, polycyclic aromatic hydrocarbons, acrylamide and 4-hydroxy-trans-2-nonenal, which are potent genotoxic carcinogens in rodents and humans (50).

Diets rich in nutrient-dense foods, such as vegetables, beans, whole grains, fruits, nuts, seeds and fish, may have additional health benefits in the prevention of a variety of age-associated chronic diseases. Plant foods, for example, contain a wide range of phytochemicals (i.e. polyphenols, terpenes, sterols, indoles, and isothiocyanates) and vitamins that have shown beneficial effects against inflammation, oxidative stress, cancer and CVD in experimental studies (74,75). Important dietary sources of phytochemicals are onions and garlic (organosulfur compounds and flavonols); tea, apples, and red wine (flavonols, catechins and stilbenes); citrus fruit (flavanones and cyclic monoterpenes); berries and cherries (anthocyanidins and falvonols); soy (isoflavones), cabbage family (isothiocyanates and indoles), carrots and celery (polyacetylenes and flavones), extra-virgin olive oil (tyrosol, oleocanthal), whole grains and beans (ferulic acid and lignans) and cocoa (proanthocyanidins) (76-86). Data from epidemiological and randomized clinical trials indicate that the consumption of omega-3 fatty acids from fish reduces the risk of cardiovascular events and mortality. The mechanisms responsible for the observed effects of omega-3 fatty acids on cardiovascular health, include hypotriglyceridemic and antiarrhythmic effect, decreased platelet aggregation and improved endothelial function (87).

Finally, cigarette smoking, second-hand smoke, and urban pollution are risk factors for coronary heart disease, cancer (especially lung cancer), and chronic obstructive pulmonary disease (88,89). The risk of death from coronary heart disease, cancer and chronic obstructive pulmonary disease drops substantially in people that quit smoking (90).

Modulation of Intrinsic Aging

Aging was not believed to be a regulated process; however, this view has changed. Several studies have now pointed out that intrinsic aging can be affected by changes in food intake or mutations in simple genes (7-13,90-91). Data from studies conducted in laboratory rodents have found that CR without malnutrition and reduced function mutations in the insulin/IGF-I signaling pathway promote longevity in part by preventing or delaying the occurrence of several age-associated chronic diseases, and in part by slowing the rate of intrinsic aging (7-13,90-91). Intrinsic aging is the progressive deterioration in physical structure and biological function that occurs with advancing age independent of diseases. For example, aging is associated with graying of hair, loss of skin elasticity, and some degree of vision, hearing, muscle and bone loss (94,95). Moreover, a number of cardiovascular, pulmonary, renal and immune physiological functions/anatomical properties decrease more or less linearly with age between the ages of 30yr and 70yr, with an accelerated decline after age 70 yr (96-99). These anatomical and physiological changes, that occur with normal aging and reduce physiological reserves of most body systems, are not synonymous with disease, but with an increased vulnerability to challenges, that may decrease the ability of the organism to survive stressful conditions.

The most studied intervention that has consistently been shown to slow intrinsic aging in small mammals is CR without malnutrition (7-13). The reader is referred to the review by Masoro in this issue of BBA concerning the anti-aging mechanisms of CR in rats and mice (100). CR not only increases maximal lifespan in rodents, but also preserves function at more youthful-like states. For example, normal aging causes a decline in cardiac performance, manifesting as an age-related impairment in left ventricular diastolic function, with little or no change in systolic function in mice, rats, and healthy humans (101,10298). Several studies have shown

that CR improves diastolic function in mice, rats and humans (69,103,104). In particular, in one study transmitral Doppler flow diastolic function indexes in individuals practicing long-term CR were similar to those of individuals that were ~16 yr younger, and measures reflecting ventricular elasticity and efficiency were significantly higher than in controls (69). More studies are needed to determine whether humans develop the full range of metabolic and functional adaptive responses to CR that occur in rodents, and whether vascular, pulmonary, kidney, brain and immune aging are slowed by CR in humans.

Reduced IGF-I signaling is also known to extend maximal life-span in several genetic animal models of longevity, such as growth hormone (GH)-deficient, GH receptor-deficient, IGF-1 receptor-deficient mice, and klotho transgenic mice (90-91). CR also decreases serum IGF-1 concentration by 30-40% in rodents, and this reduction has been hypothesized to be important in mediating its anti-cancer, and possibly, its anti-aging effects (7-13). However, unlike in rodents, chronic severe CR does not reduce serum IGF-1 concentrations in humans (48). Instead, recent data from epidemiological and observational studies indicate that long-term moderate protein restriction significantly reduces serum total and free IGF-1 concentrations (48,105,106). This is important because at least half of the US males and females are eating 40% or more protein (≥ 1.34 g kg–1 per day) than the recommended daily intake (0.83 g kg–1 per day), which implies a state of chronic positive nitrogen balance and anabolic stimulation (107,108).

More studies are necessary to understand the biological and clinical implications of a chronic high protein intake and positive nitrogen balance on longevity.

Conclusions

1Aging and age-associated chronic disease are key issues in the challenge to improve health, delay the onset of frailty and dependency, and promote healthy aging. Data from epidemiological studies and clinical trials indicate that many age-associated chronic diseases can be prevented, and even reversed, with the implementation of healthy lifestyle interventions. Several recent studies suggest that more drastic interventions (i.e. calorie restriction without malnutrition and moderate protein restriction with adequate nutrition) may have additional beneficial effects on several metabolic and hormonal factors that are implicated in the biology of aging itself. Additional studies are needed to understand the complex interactions of factors that regulate aging and age-associated chronic disease. Both our health and quality of life in the coming 50 years, as well as the sustainability of our healthcare system, depend on our ability to meet these challenges.

Acknowledgments

Funding/Support: Supported by NIH General Clinical Research Center Grant RR00036, Istituto Superiore di Sanità/National Institutes of Health Collaboration Program Grant, a grant from the Longer Life Foundation (an RGA/Washington University Partnership) and a donation from the Scott and Annie Appleby Charitable Trust.

Role of the Sponsor: The funding agency had no role in the analysis or interpretation of the data or in the decision to submit the report for publication.

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