

Susceptibility of the Aging Lung to Environmental Injury

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ABSTRACT

With an ever-increasing number of elderly individuals in the world, a better understanding of the issues associated with aging and the environment is needed. The respiratory system is one of the primary interfaces between the body and the external environment. An expanding number of studies suggest that the aging pulmonary system (>65 years) is at increased risk for adverse health effects from environmental insult, such as by air pollutants, infection, and climate change. However, the mechanism(s) for increased susceptibility in this subpopulation are not well understood. In this review, we provide a limited but comprehensive overview of how the lung ages, examples of environmental exposures associated with injury to the aging lung, and potential mechanisms underlying the increased vulnerability of the aging lung to injury from environmental factors.

KEYWORDS: Aging lung, susceptibility, environmental injury

In populations exposed similarly to air pollutants, pulmonary function and inflammatory responses are more severe in certain groups of individuals than in others, particularly for pregnant women, infants, children, and the elderly.¹ The rapid growth in the number of elderly individuals in developed countries has major implications for public health, including the need to better understand the risks posed to older adults by environmental factors, such as by air pollution, infection, and climate change.² The respiratory system is one of the primary interfaces between the body and the external environment and must, therefore, satisfy unique demands to handle and detoxify inhaled gases, particles, and infectious agents.³ It is generally agreed that lung function declines with age, and that oxidant stress related to smoking, chronic lung inflammation, or car-

diopulmonary diseases may increase the rate of decline.^{4,5} Furthermore, the decline in antioxidant capacity with age strongly correlates with increased risk of mortality from a wide range of entities.⁶ A growing number of studies suggest the aging pulmonary system (>65 years) is at increased risk for adverse health effects from environmental insults that include air pollutants, airborne pathogens, and various aeroallergens.^{4,7,8} However, the mechanisms underlying increased susceptibility in the aging population are not well understood. In this review, we provide a brief overview of the aging lung and give examples of environmental injuries and potential mechanisms by which the aging lung is believed to be more susceptible to these environmental insults. The goal of this review is to highlight those areas of investigation important to the field of pulmonary geriatrics.

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THE AGING LUNG

Changing Lung Function and Anatomy

The lung matures by 20 to 25 years of age. Thereafter, aging is associated with a progressive decline in lung function.^{8–10} The alveolar dead space increases with age, affecting arterial oxygen.⁹ The pulmonary transfer factor for carbon monoxide (TLCO), which is dependent on lung volume [total lung capacity (TLC)] and alveolar ventilation, declines with age.¹¹ Older adults have decreased sensation of dyspnea and diminished ventilatory response to hypoxia and hypercapnia^{12,13} accompanied by a decrease in CO₂ threshold.¹⁴

Even in the absence of disease, the respiratory system undergoes a variety of anatomical and physiological changes with age (Table 1).¹⁵ Structural changes include deformities of the chest wall and thoracic spine that impair respiratory system compliance and increase work of breathing.¹⁶ Diminished respiratory effort in response to upper airway occlusion and impaired perception of bronchoconstriction can occur with advanced age.¹⁷ Respiratory muscle strength decreases with age and can impair effective cough, which is important in airway clearance.¹⁸ Deposition, retention, and clearance of particulates in the airways also change with age. Adult aging per se does not appear to alter the regional deposition fraction of aerosols;¹⁹ however, changes in inspiratory peak flow may impair deposition of drugs in the elderly.⁹ The lung parenchyma loses supporting structure, leading to

dilation of air spaces or “senile emphysema.”²⁰ An age-related decrease in elastic fibers with an increase in type III collagen deposition within alveolar walls is indicative of an impaired repair mechanism, which could play a significant role in the pathogenesis of senile emphysema.^{21,22}

Age-related changes in airway receptors, critical in airway homeostasis, are not well understood. For instance, substance P receptor (neurokinin-1 receptor) decreases with age in normal sheep,²³ whereas β -adrenoreceptor density remains unchanged; however, receptor affinity is significantly reduced.²⁴ Changes in muscarinic receptor subtypes and receptor coupling to G proteins have been noted with senescence.²⁵ Cysteinyl-leukotriene (CysLT1) receptors undergo functional changes with age and are less likely to respond to drugs that have been found to be effective in younger individuals to treat the same disorders.^{26–28} These aging-related structural and functional changes in the normal lung may predispose the elderly population to ventilatory failure during high demand states, such as conditions of heart failure or pneumonia, with potentially poor outcomes.

Oxidative Stress and Lung Antioxidant Defenses

A commonly held theory of aging is based on the free-radical or oxidative-stress hypothesis: the accumulation of reactive oxygen species (ROS) in cells with increasing age results in various forms of reversible and irreversible oxidative modifications of proteins (carbonylation or nitro-modifications), lipids (hydroperoxide lipid derivatives), and DNA (adducts and breaks) that eventually lead to loss of molecular function. The human lung is continuously exposed to oxidative stress. Particulates, such as cigarette smoke,^{29,30} ambient airborne aerosols,³¹ coal dust or silica,³² all possess intrinsic free radical activity. Diesel emission particulates also contain compounds that catalyze the generation of ROS,³³ as well as other exogenous toxins that activate lung-resident cells to produce ROS.³⁴

The lung has a remarkable array of responses and defenses to oxidative stress.³⁵ Low-level stress may invoke adaptive responses, including growth arrest and preferential expression of genes responsible for repair of damage.³⁶ Oxidative stress results in the transcription of over 40 genes.³⁷ The lung normally defends itself against ROS damage through the use of specific ROS-reducing mechanisms that encompass enzymatic reactions involving superoxide dismutase (SOD), glutathione peroxidases, and catalases or nonenzymatic components such as vitamin A, C, and E; urate; ferritin; ceruloplasmin; surfactant; and ubiquinone.³⁸

As the lung ages, changes in antioxidant defenses will also occur. These changes include decreased ascorbic

Table 1 The Aging Lung and Associated Environmental Influences

| Age-Related Changes | Environmental Influences |
|---|-----------------------------|
| | Cell and tissue injury |
| | Oxidative damage |
| | Radiation |
| | Mutagens |
| Accumulated genetic injury | Carcinogens |
| Structural changes in chest wall and lung | Diet |
| Alveolar matrix proteins | Obesity |
| Senile emphysema | Hormonal changes |
| Increased chest wall stiffness | |
| Decreased respiratory muscle strength | |
| Impaired defense mechanisms | Inhaled irritants/particles |
| Antioxidants | Cigarette smoke |
| Immune cell function | Allergens |
| Neural reflexes | Pathogenic organisms |
| Mucociliary clearance | Gastric secretions |
| Impaired control of breathing | Cigarette smoke |
| Pulmonary vascular remodeling | Alcohol |
| | Cigarette smoke |

Adapted from Green, Pinkerton 2004.¹⁵

acid,^{39,40} reduction in glutathione levels,^{41,42} and decreased activity of SOD and glutathione peroxidase⁴³ in lung tissues. NF-E2-related factor 2 (NRF2) is a transcription factor that protects cells and tissues from oxidative stress by activating protective antioxidant and detoxifying enzymes.⁴⁴ NRF2 expression has been found to be decreased in the alveolar macrophages of older current smokers and patients with COPD, compared with younger subjects.⁴⁵ Heme oxygenase-1 (HO-1) is the rate-limiting enzyme that catalyzes heme and is known to be readily inducible to confer cytoprotection against oxidative stress.⁴⁶ A recent study in mice demonstrated age-related defects in HO-1 induction in whole lung as well as in alveolar macrophages in response to lipopolysaccharide.⁴⁷

Immune System Changes with Aging

Immune mechanisms underlie many chronic degenerative diseases of the lung. Both innate and acquired immunity are affected by aging.¹⁵ The impact of age on innate and adaptive immune responses is summarized in Table 2. The elements of innate immunity include the functions of antigen-presenting cells, phagocytic cells, inflammatory mediators released from leukocytes, natural killer lymphocytes, antimicrobial molecules (such as nitric oxide), surfactant-associated proteins, defensins, lactoferrin, and complement.^{15,48} Several reports have suggested that the total number and phagocytic activity of neutrophils and macrophages in the peripheral blood remain unchanged with age,^{49–51} however, the ability of neutrophils to self-proliferate as well as kill infectious agents is reduced in elderly subjects. In contrast, neutrophils in elderly subjects have increased ROS production and impaired apoptosis, which may result in the prolonged presence of neutrophils in either the systemic circulation or local tissue sites where they might induce local damage. Macrophages have been demonstrated to have impaired antigen presentation and reduced major histocompatibility complex (MHC) II molecule expression in aged mice.⁵¹ Although the number of natural killer cells in circulation increases with age, the ability to perform cytotoxic effector functions and to produce interferon-gamma (IFN- γ) and interleukin-8 (IL-8) in response to IL-2 declines *in vitro*.^{52,53} Dendritic cells (DCs), which play a key role in initiating an adaptive immune response, are reduced in number in the peripheral blood and lymphoid follicles in the elderly.⁵⁴ In addition, chemotaxis and phagocytosis of DCs are impaired, and therefore, stimulation of naïve CD41 T cells to generate an effective adaptive immune response to an antigen may fail.⁵⁵

Age-related changes to the adaptive immune system include a decrease in the number of T cells in the peripheral blood of older adults with significantly reduced T cell receptor repertoire.⁵⁶ With aging, an increase in

Table 2 Altered Immunity in the Elderly

| Cell-Mediated Immunity | Change with Age |
|---|-----------------|
| Involution of the thymus naïve T cell output | ↓ |
| Thymocyte differentiation | variable |
| Peripheral blood memory T-cells | ↑ |
| Hyporesponsive memory cells | ↓ |
| Proliferative responses to mitogens or antigens | ↓ |
| T cell receptor repertoire diversity | ↓ |
| Shift of Th1 to Th2 cytokine profile | ↓ |
| HLA-DR+ | ↑ |
| Fas-mediated apoptosis | ↓ |
| Humoral Immunity | |
| Helper T cell function | ↓ |
| B cell number | ↓ |
| Germinal center formation | ↓ |
| Altered B cell repertoire expression | variable |
| Antibody responses to specific antigens | ↓ |
| Altered generation of primary B cells | ↓ |
| Generation of memory B cells | ↓ |
| Ability to generate high-affinity protective antibody | ↓ |
| IgG and IgA | ↑ |
| Organ-specific autoantibodies | ↓ |
| Non-organ-specific autoantibodies | ↓ |
| Innate Immunity | |
| Neutrophils | |
| Apoptosis and killing | ↓ |
| Production of ROS | ↑ |
| Macrophages function | ↓ |
| Natural killer cells number | ↑ |
| Cytotoxic activity | ↓ |
| Dendritic cells | |
| Number of plasmacytoid dendritic cells | ↓ |
| B cell stimulation | ↓ |
| Capacity to capture antigen | ↓ |
| Capacity to phagocytose apoptotic cells | ↓ |

HLA-DR, human leukocyte antigen; IgA, immunoglobulin A; IgG, immunoglobulin G; ROS, reactive oxygen species; Th, T-helper. Adapted from Green, Pinkerton 2004¹⁵ and Sharma et al 2009.¹⁸⁸

CD81 CD28null Tregs (regulatory T) cells inhibits antigen-specific CD41 T cell responses, leading to a decline in the adaptive immune response and immunosenescence.⁵⁷ Hematopoietic stem cell (HSC) production is another important component of immune system maintenance that slows with aging in both animals and humans. Older individuals are more likely to suffer toxicity such as prolonged myelosuppression in response to traditional cytotoxic chemotherapy drugs, suggesting a reduced marrow regenerative capacity.^{58–60} Moreover, the volume of hematopoietic bone marrow tissue decreases with aging,⁶¹ resulting in reduced production of B cells, which have a reduced capacity to proliferate and

Table 3 Changes in Bronchoalveolar Lavage Fluid in Healthy Aged Individuals

| Parameter | Change |
|---------------------------|--------|
| Lymphocytes | ↑ |
| CD4+:CD8+T cell ratio | ↑ |
| HLA-DR + T-cells | ↑ |
| B-cells | ↓ |
| IgM, IgA, and IgG | ↑ |
| Total protein | ↑ |
| Neutrophils | ↑ |
| Interleukins (IL-6, IL-8) | ↑ |
| α1-antitrypsin | ↑ |

HLA-DR, human leukocyte antigen; IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M. Adapted from Meyer⁴⁸ and Green, Pinkerton 2004.¹⁵

impaired ability to be activated in older adults. The quantity and efficacy of antibodies produced in response to antigen exposure in older adults are also reduced.⁶²

Changes in the composition of bronchoalveolar lavage fluid have also been noted in association with aging (Table 3). Some of these parameters reflect innate as well as acquired immune responses. The reduction in the adaptive immune system is associated with an innate immune system stimulated and upregulated by external environmental insults or internal antigenic stimuli from oxidative stress, creating a chronic proinflammatory state with aging. Inflammation is central to the pathogenesis of obstructive lung diseases, including asthma, chronic bronchitis, and emphysema.¹⁵

The severity and prevalence of some diseases associated with hyperimmune states may increase or decrease with aging. The most important diseases that increase with age are autoimmune diseases that affect the lung such as systemic lupus erythematosus (SLE), scleroderma, and rheumatoid disease.⁶³ These diseases are associated with, and possibly triggered by, environmental exposures.⁶⁴ Dusts containing crystalline silica have been particularly implicated in their pathogenesis.⁶⁵ An important disease that has a greater prevalence in younger individuals is asthma.⁶⁶ However, asthma prevalence appears to be increasing in the elderly and may have unique characteristics,⁶⁷ which may reflect some of the important changes in T and B cell immune function in the elderly that relate to allergy (listed in Table 3).

Endocrine Changes with Aging

Hormonal changes are thought to play a role in the loss of lung tissue mass, impaired respiratory and peripheral muscle function, and reduced exercise capacity in the elderly. Changes in the hypothalamic-pituitary-adrenal axis occur with age, and attenuated diurnal variability may account for some hormonal changes.⁶⁸ Growth hormone (GH), insulin-like growth factor,⁶⁹ estrogen,⁷⁰ glucocorticoids,⁷¹ testosterone,⁷² and vitamin D⁷³ have

been demonstrated to change with aging. An age-related decline in GH parallels changes in body composition, such as a reduction in lean body mass and bone mineral density and an increase in visceral fat.⁶⁹ The loss in muscle protein mass, function, and quality also accompanies advancing age.⁷⁴

Hormonal changes are associated with a decline in lung function. A recent study suggests alveolar hypoventilation and attendant arterial hypercapnia in healthy postmenopausal women are due in part to a reduction in circulating sex steroid hormone concentrations.⁷⁵ Longitudinal analysis of the relationship between basal plasma cortisol concentration and forced expiratory volume in 1 second (FEV₁) over an average of 4.7 years revealed a significant ($p = 0.008$) relationship between the plasma cortisol concentration and the rate of decline of FEV₁ after adjustment for age, height, smoking status, and initial FEV₁.⁷¹ Moreover, the authors' multivariate model predicted that subjects with cortisol concentrations one standard deviation (23.3 ng/mL) below the mean would experience FEV₁ declines of 71.6mL/year greater than subjects with cortisol concentrations one standard deviation above the mean. The difference was comparable to an estimated 69.5mL/year difference between current smokers and never-smokers.⁷¹ These data indicate that physiological concentrations of cortisol may modulate the processes that are responsible for the deterioration of ventilatory function with aging. A separate study of 631 male participants in the normative aging study (age range 44 to 85 years) showed that 2-hour urinary excretion of serotonin, but not 5-hydroxy indole acetic acid (5-HIAA), decreased with age.⁷⁶ Animal studies suggest that the serotonin-dependent augmentation of respiratory motor output is reduced in old rats.⁷⁷ Current active smokers secrete significantly more serotonin than never-smokers, while former smokers did not differ significantly from never-smokers.⁷⁶

Body Mass

Body mass is positively associated with airway hyperresponsiveness⁷⁸ and with progressive reductions in forced vital capacity (FVC), FEV₁ and FEV₁:FVC ratio.⁷⁹ Cross-sectional^{80,81} and longitudinal⁸² studies have shown a relationship between asthma and obesity, particularly in women.⁸³ Static lung volumes significantly increase following weight loss in middle-aged and older, obese men. In contrast, aerobic exercise has no effect on pulmonary function but does increase maximal oxygen uptake (VO₂ max).⁸⁴ The contribution of body composition, physical activity, and smoking to lung function in older people has been investigated;⁸⁵ fat-free mass and physical activity both exerted significant independent effects on FEV₁. These results, in contrast to the former study,⁸⁴ indicate that heavy

intense physical activity may be more important in contributing to preservation of forced expiratory function than previously recognized.¹⁵

Cellular Senescence

Programmed senescence is a driving force behind aging of all organs in the body, including the lung.¹⁵ It is not clear what causes cells to undergo senescence, but studies have shown that senescence can be induced by a variety of stimuli (Fig. 1).⁸⁶ Dysfunctional telomeres trigger a classical DNA damage response (DDR).⁸⁷ The DDR enables cells to sense damaged DNA, particularly double-strand breaks (DSBs), and to respond by arresting cell-cycle progression and repairing the damage if possible (Fig. 2). It has been suggested that only one or a few such shortened, dysfunctional telomeres in cells are sufficient to trigger senescence.^{88,89} One study showed that both current and former smokers had shorter telomeres than did age-matched nonsmokers.⁹⁰

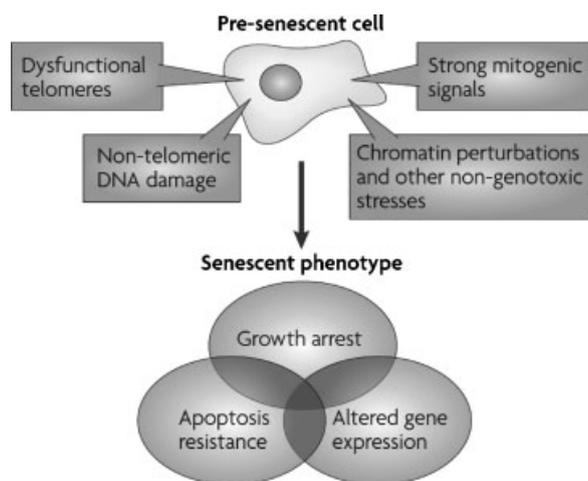


Figure 1 The senescent phenotype induced by multiple stimuli. Mitotically competent cells respond to various stressors by undergoing cellular senescence. These stressors include dysfunctional telomeres, nontelomeric DNA damage, excessive mitogenic signals such as those produced by oncogenes (which also cause DNA damage), nongenotoxic stress such as perturbations to chromatin organization, and, probably, stresses with an as-yet-unknown etiology. The senescence response causes striking changes in cellular phenotype. These changes include an essentially permanent arrest of cell proliferation, development of resistance to apoptosis (in some cells), and an altered pattern of gene expression. The expression or appearance of senescence-associated markers such as senescence-associated β -galactosidase, p16, senescence-associated DNA-damage foci (SDFs), and senescence-associated heterochromatin foci (SAHF) are neither universal nor exclusive to the senescent state and are not shown. (Reprinted by permission from Macmillan Publishers Ltd.: Campisi J et al, Cellular senescence: when bad things happen to good cells. *Nat Rev Mol Cell Biol* 2007;8:729–740.)

Nontelomeric DNA damage occurs anywhere in the genome, and damage that creates double-strand breaks causes many cell types to undergo senescence.^{91,92} Excessive mitogenic signals, including those produced by oncogenes, such as *RAS* and other members of the *RAS* signaling pathway (*RAF*, *MEK*, *MOS*, and *BRAF*), as well as pro-proliferative nuclear proteins (for example, E2F-1), cause senescence when overexpressed or expressed as oncogenic versions (which also cause DNA damage).^{93–96}

Mechanisms proposed by which senescent cells contribute to aging include upregulation of genes that encode extracellular-matrix-degrading enzymes, inflammatory cytokines, and growth factors, which can affect the behavior of neighboring cells or even distal cells within tissues.⁸⁶ The products of these genes can disrupt the normal tissue structure and function in cell-culture models,^{97,98} thereby stimulating growth and angiogenic activity of nearby premalignant cells both in culture and in vivo.^{99–102} Therefore, senescent cells, although unable to form tumors, may fuel the progression of nearby premalignant cells and facilitate the development of cancer in aging organ systems.

INCREASED SUSCEPTIBILITY OF THE AGING LUNG TO SPECIFIC ENVIRONMENTAL INJURIES

Ozone

Exposure to ozone has been documented to cause decrements in lung function in healthy subjects,¹⁰³ and numerous studies in both humans and animals have shown that susceptibility to ozone varies with age.¹⁰⁴ Age-related changes recorded in response to ozone exposure include changes in pulmonary eicosanoid metabolism in rabbits and rats,¹⁰⁵ altered ventilatory responses to CO₂ in rats,¹⁰⁶ altered hydroxylation of salicylate in lungs of Fischer 344 rats,¹⁰⁷ and altered lung mitochondrial respiration, reactive oxygen species (ROS) production, and lung pro/antioxidant status in rats.¹⁰⁸ Overall, the cellular and biochemical effects of ozone exposure appear greater in senescent Fisher 344 rats (24 months old) compared with juvenile or adult rats.^{40,109} Moreover, in aged rats, the increase in cytosolic SOD and GPx (glutathione peroxidases) activities during ozone exposure was not sufficient to prevent impairment of mitochondrial function or the accumulation in lung 8-oxodG.¹¹⁰ In humans, many studies and meta-analyses have found an association between acute ambient ozone exposure and increased risk of death.¹¹¹ In addition, ambient ozone has been associated with increased respiratory-related emergency department visits and hospital admission in the elderly.^{112,113} These findings suggest that the elderly are particularly susceptible to the effects of ozone. However, previous studies have found that

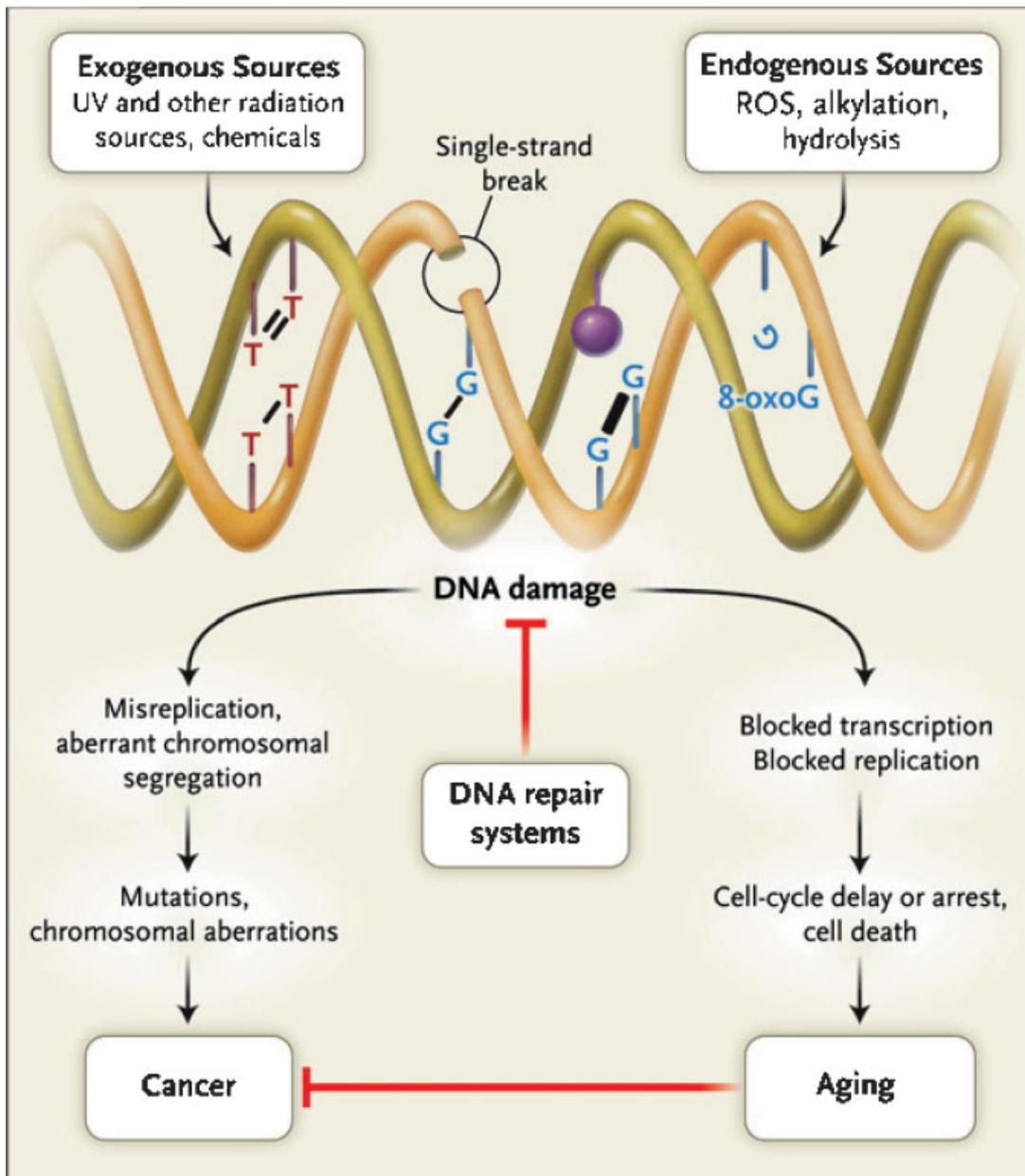


Figure 2 Sources and consequences of DNA damage. DNA damage can be induced by exogenous physical agents, by endogenous chemical genotoxic agents that are the products of metabolism such as reactive oxygen species (ROS), or by spontaneous chemical reactions such as hydrolysis. Examples of DNA damage are ultraviolet (UV)-induced photoproducts (left), interstrand and intrastrand crosslinks, bulky chemical adducts (solid sphere), abasic sites, and oxidative damage such as 8-oxoguanine (8-oxoG). The consequences of DNA damage are essentially twofold. After misrepair or replication of the damaged template, surviving cells may be subject to permanent changes in the genetic code in the form of mutations or chromosomal aberrations, both of which increase the risk of cancer. Alternatively, damage may interfere with the vital process of transcription or induce replication arrest, which may trigger cell death or cellular senescence, contributing to aging. Damage-induced cell death protects the body from cancer. G, guanine; T, thymidine. (Reprinted with permission from Hoeijmakers JHJ. DNA damage, aging, and cancer. *N Engl J Med* 2009;361:1475–1485. Copyright © 2009 Massachusetts Medical Society. All rights reserved.)

functional responsiveness to ozone has been no greater, and usually lower, among older adults than in young adults, but these studies typically include only healthy nonsmokers.^{114,115} More recent studies suggest that ozone has an acute effect on lung function in the elderly. Ozone-induced effects may also be modified

by the presence of specific polymorphisms in antioxidant genes¹¹⁶ or other preexisting health conditions, such as obesity and airways hyperresponsiveness (AHR).¹¹⁷ The long-term effects of ozone on the human lung are not well established but appear to enhance aging.¹¹⁸

Cigarette Smoke

Smoking is well accepted as an important cause of lung cancer, with the highest incidence of primary lung cancer occurring late in life between 60 and 70 years of age, at which time the lung may have lost its full competency for defense and immunity. Life-time cigarette smokers also have a higher prevalence of other common diseases, such as atherosclerosis and chronic obstructive pulmonary disease (COPD) with significant systemic impact.¹¹⁹ It has been estimated that cigarette smoking reduces life span by an average of 7 years, and tobacco consumption accounts for a shortening of disease-free life by 14 years.¹²⁰ The exact mechanisms by which smoking causes disease and death are generally not well understood, but evidence continues to mount that cigarette smoking exhausts cellular defense and repair functions, leading to an accumulation of damage (e.g., mutations and malfunctioning proteins).¹²⁰

There is increasing evidence that cigarette smoking is associated with premature aging. It has been proposed that cigarette smoke accelerates the aging of lung or worsens aging-related events in the lung by induction of senescence in alveolar epithelial cells and impaired reepithelialization.¹²¹ Smoking also causes defective resolution of inflammation and consequently induces accelerated progression of COPD.¹²² A recent study suggests that aging also increases susceptibility to cigarette smoke-induced inflammation in a mouse model through robust mRNA upregulation and nuclear translocation of nuclear factor (NF)-kappaB in bronchiolar epithelium.¹²³ The reaction of components of cigarette smoke with plasma and extracellular matrix proteins resulting in the formation of covalent adducts, such as advanced glycation end products (AGEs), also has been shown to play a role in the development of many of the pathological sequelae of aging and diabetes, such as cardiovascular diseases and cancer growth and metastasis.^{124,125}

Other smoking-related effects on the lung that enhance lung aging include accelerated maturation of the fetal lung, impairment of lung growth, shortening of the plateau phase of FEV₁, and acceleration of age-related declines in FVC and FEV₁.¹²⁶ These effects have also been shown for cigar and pipe smoking.¹²⁷ Chronic asthma, a disease triggered by exposure to airborne allergens, is also associated with accelerated declines in FEV₁ with age and has additive effects with cigarette smoking⁸ (Fig. 3). Smoking also increases the risk of bacterial pneumonias by impairing host immune response, which in turn contributes to the incremental declines in FEV₁ associated with COPD.¹²⁸ Some animal models also provide insights into the pathogenesis of these clinical observations. Mutant mice with accelerated senescence are more susceptible to smoke-induced emphysema than wild-type control

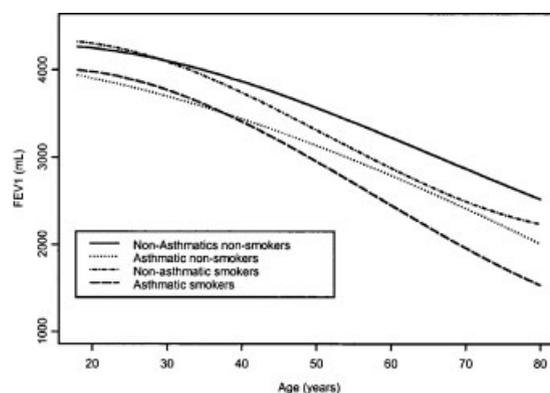


Figure 3 Age-related decline in forced expiratory volume in 1 second (FEV₁) by strata in females derived from linear mixed-effects models. Mean FEV₁ in milliliters (corrected for height, weight, and age at first survey) for ages 18 to 80 years for females: nonsmoking females without asthma (continuous line), nonsmoking with asthma (dotted line), smoking without asthma (dashed and dotted line), and smoking with asthma (dashed line). For clarity of presentation, error ranges are not included. The graph illustrates the cumulative effects of two environmental diseases (asthma and cigarette smoke-induced chronic obstructive pulmonary disease) on the decline in pulmonary function with age. (Reprinted with permission of the American Thoracic Society. Copyright © American Thoracic Society. From James et al.⁸)

mice.^{129,130} Older rats showed seriously impaired ability to resist oxidative damage by cigarette smoke, whereas the activation of polyaromatic hydrocarbons to their carcinogenic forms remains intact, which may predispose these rats to the development of cancer.¹³¹

Particulates

Particulate matter (PM) is an important air pollutant of concern due to its contribution to adverse health effects. Use of motor vehicles has resulted in a consequent rise in exhaust-generated PM emissions in urban areas worldwide.¹³² Airborne PM varies in size and composition (heavy metals, PAHs [polycyclic aromatic hydrocarbons], etc.). Aging is associated with accumulation of particles and metals in the mammalian lung,^{133–135} and exogenous carbonaceous particles appear to accumulate progressively with age, but accurate quantification has not been achieved.¹⁵ Numerous studies over the past decades have observed associations between inhaled PM (PM₁₀ and PM_{2.5}) and various health outcomes, including mortality, hospitalization for respiratory and cardiovascular diseases, increased predisposition to asthma attacks, and adverse lung function.¹³²

The elderly, typically considered to be individuals over 65 years of age, represent one of the subpopulations that are most sensitive to the adverse health effects of inhaled PM.¹³⁶ To what extent this increased susceptibility to PM exposure results from aging per se is not clear. It is likely that many factors play a role, including

aging-associated systemic changes discussed earlier. Progressive accumulation of particles in the lung throughout life and the increased incidences of serious respiratory, cardiac, and circulatory diseases in the elderly may also contribute to the increased sensitivity of older individuals to the adverse effects of inhaled pollutants.¹³⁶

The effects of PM on age-associated changes have been studied in rats and mice. Mauderly et al¹³⁶ exposed normal rats and rats with elastase-induced emphysema to whole diesel exhaust at a soot concentration of 3500 $\mu\text{g}/\text{m}^3$ for 2 years beginning at 18 weeks of age. The study showed that the presence of emphysema protected the rats from particle-associated effects (measured by functional and biochemical parameters) and that a reduction in retained lung dust was observed in the emphysematous animals.¹³⁷ In another study, young (4 months) and aged (20 months) male Fisher 344 rats were exposed to concentrated Boston ambient particulate matter at an average concentration of 100 $\mu\text{g}/\text{m}^3$ for 3 days.¹³⁸ Total cell numbers in bronchoalveolar lavage fluid (BALF) were greater in both control and particulate-exposed young rats than in older rats. Sunil et al¹³⁸ exposed young (2 months) and aged (18 months) mice to diesel exhaust (300 and 1000 $\mu\text{g}/\text{m}^3$) for 3 hours for 1 day or for 3 days. They found altered patchy thickening of the alveolar septa, increased IL-8, and decreased MnSOD (manganese superoxide dismutase) expression in aged mice. They also found a small but significant decrease in total cell numbers in BALF in old mice compared with young animals.¹³⁹

Studies of the short-term effect of PM on human health mostly focus on mortality and hospital admissions. Some of the most interesting findings are from studies that observed changes in daily death counts associated with short-term changes in PM air pollution. Most of the results suggest that a 10 $\mu\text{g}/\text{m}^3$ increase in PM₁₀ is associated with a 0.5% to 1.5% increase in daily mortality.^{140–143}

Evidence of long-term effects on lung health from exposure to relatively low levels of air pollution has increased substantially during the past decade.^{144–146} One study investigating the effect of PM on longitudinal change in lung function showed that a greater decline in FEV₁ in adults was associated with residence near major roads.¹⁴⁷ Another study demonstrated that reduced exposure to concentrations of PM less than 2.5 μm in aerodynamic diameter (PM_{2.5}) was associated with a reduction in mortality from all causes, including from cardiovascular events and lung cancer.¹⁴⁸ Downs et al¹⁴⁸ conducted a prospective study from 1991 to 2002 to examine the association between age-related decline in lung function and decline in exposure to PM₁₀ in Switzerland. The authors found that decreasing exposure to airborne particulates appears to attenuate the decline in lung function related to exposure to PM₁₀, and the effects

are greater in small airways.¹⁴⁹ These findings suggest that an accelerated decline in lung function in the elderly with higher exposure to PM, as compared with lower exposure, may represent a step toward increased mortality risk.

Infectious Agents

The elderly are more susceptible to a wide variety of respiratory infections, particularly to those caused by newly emerging and reemerging pathogens, which are often of greater severity. Suboptimal nutrition, deteriorating lung mechanics, and declined immunity with age all appear to play a role,¹⁵ among which the age-related senescence in the immune system, including changes in both innate and adaptive immunity, is likely to be the most important factor associated with the increased susceptibility to the various respiratory infections. Group housing also plays a role in the elderly, contributing to the spread of diseases associated with influenza A and *Legionella*.⁴⁸ In the case of influenza infections, even though the hospitalization rates for children less than 5 years and adults over 70 years of age are almost identical, individuals older than 70 years have a 35-fold increase in mortality.^{150,151} Paradoxically, death rates from the recent (2009–2010) H1N1 influenza pandemic have been lower in individuals over 60 years of age compared with younger individuals.¹⁵² This has been attributed to partial immunity resulting from exposure to a related influenza virus and its immediate descendants that were prevalent prior to 1976.¹⁵³ Vaccination can reduce the rates of hospitalization; however, protection induced by immunizations is diminished in the elderly compared with adults, as demonstrated by lower antibody titers and higher rates of respiratory illness.¹⁵⁴ In addition, cell-mediated immune responses to vaccinations are decreased in the elderly.^{155–158} The elderly have an increased morbidity and mortality due to influenza as a result of secondary bacterial and viral infections.¹⁵⁹ *Streptococcus pneumoniae* is most frequently associated with community-acquired pneumonia (CAP).¹⁶⁰ In developed countries, despite aggressive vaccination policies, *S. pneumoniae* remains a major medical problem in the elderly population, especially among those aged 65 or more. Pneumococcal pneumonia in the elderly is characterized by rapid onset, increased severity, and high case-fatality rate,¹⁶¹ which may be due to a priming effect of chronic inflammation and Toll-like receptor dysfunction with age.¹⁶² The generation of antigen-specific CD4+ T cell-mediated immunity is delayed or impaired in old people,¹⁶³ and poor CD4+ T cell-mediated immunity may contribute to the increased susceptibility of the elderly to develop tuberculosis.¹⁶⁴ The proportion of tuberculosis in the elderly has risen in recent decades, with approximately one fifth of all tuberculosis cases in

the United States occurring in the elderly.¹⁶⁵ This is frequently overlooked and is commonly diagnosed postmortem.¹⁶⁶ The prevalence of *Mycoplasma pneumoniae* has been reported to be low in the elderly;¹⁶⁷ however, recent reports suggest that *M. pneumoniae* accounts for 4 to 10% of cases of pneumonia in the elderly population.^{168,169}

Climate Change

Like other environmental stressors, climate change can have differential effects on different subpopulations, depending on a variety of susceptibility factors.¹⁷⁰ The impact of climate change on health is likely to be significant, particularly for more vulnerable subpopulations, such as the elderly, due to their susceptibility to respiratory and cardiovascular diseases with aging.^{171,172} Older people do not tolerate drastic climatic changes well because they are more sensitive to temperature extremes, particularly heat.^{173,174} Individuals 65 years of age and older comprised 72% of the heat-related deaths in the 1995 Chicago heat wave.¹⁷⁵ Over a 5-year period, from 1999 to 2003, a total of 3442 heat-related deaths were reported in the United States (an annual average of 688).¹⁷⁶ In August 2003, in excess of 2000 deaths of older adults in England and Wales and nearly 15,000 deaths of mainly elderly people in France were caused by temperatures rising to more than 40°C.¹⁷⁷

The elderly are more likely to have preexisting medical conditions, such as cardiovascular and respiratory illnesses, which may put them at greater risk of severe morbidity or mortality from climate-related events or conditions. A 2004 rapid needs assessment of older adults in Florida found that Hurricane Charley exacerbated preexisting, physician-diagnosed medical conditions in 24 to 32% of elderly households.¹⁷⁶ Storms and floods are also threats to the elderly because they have diminished response to stressors and are often less ambulatory. They are thus less able to evacuate quickly and are more prone to accidents.^{178,179}

Climate change also indirectly affects human health through its impact on air pollution. A positive association has been found between temperatures greater than 32°C (>90°F) and ground-level ozone production.¹⁸⁰ Increasing evidence suggests that ozone and high temperature affect mortality in a synergistic fashion. Similarly, heat wave mortality is greatest on days with high PM₁₀.¹⁸¹ As a result, the aging population will be more vulnerable to these environmental injuries and less able to adapt to dramatic climate change.

Lung Injury during Early Life

Data obtained from human genomic studies and genetic manipulation in rodents indicate that early abnormal lung development may be a significant susceptibility

factor in selected respiratory diseases that become clinically detectable in later life, such as COPD, cystic fibrosis, and asthma.¹⁸² Disturbances during lung development may result in transient or irreversible long-term effects in both lung function and immune response.¹⁸³ Exposure to environmental insults during fetal development and early postnatal life is associated with adverse birth outcomes, including low birth weight, very low birth weight, preterm birth, intrauterine growth restriction, congenital defects, and intrauterine and infant mortality. Environmental insults in early life may also decrease lung growth and increase rates of respiratory tract infections, childhood asthma, behavioral problems, as well as neurocognitive deficits.¹⁸³ Intrauterine growth retardation and low birth weight have been linked to alterations of respiratory function at all stages of postnatal life.¹⁸⁴ Intrauterine growth retardation may lead to increased susceptibility to adverse effects of air pollution exposure and other environmental factors,¹⁸⁵ and low birth weight is an independent risk factor for COPD, which is associated with poor lung growth and lung function during childhood and adulthood.¹⁸⁶ Frequent respiratory infections during childhood have been shown to play an important role in the occurrence of chronic airway diseases in adult life.¹⁸⁷ Acute lung injuries produced by common pathogenic bacteria, for example *Staphylococcus aureus*, are usually associated with complete recovery and subsequent normal lung function. Viral infections, however, may produce more long-lasting effects, notably infections due to respiratory syncytial virus (RSV), adenovirus, and chlamydia. Children who survive these infections are likely to have unhealthy lungs that might predispose them to COPD in later life.¹⁸⁸

CONCLUSIONS

The respiratory system represents a critical interface with the external environment and must meet unique demands to handle and detoxify inhaled gases, particles, and infectious agents. The lung must be ready to constantly mount a controlled and defensive response that preserves its primary function of gas exchange, yet the respiratory system must be protected from xenobiotic insults and potential injury. The health effects associated with exposure to environmental agents may range from subtle, subclinical biochemical and physiological changes to the exacerbation of preexisting respiratory and cardiovascular disease or the genesis of a completely new disease. The aging lung must continually contend with changes that affect its ability to maintain homeostasis. With a growing elderly population and a strong correlation of aging-associated changes in the lung with increased susceptibility to environmental injuries, it is imperative to extend future research to better determine the effects of age on the respiratory system. Understanding the mechanisms behind the adverse effects of environmental factors on the

aging lung will greatly assist in designing preventive strategies to enhance the quality of life while further decreasing mortality and morbidity in the elderly.

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