



Report 4 of the Council on Scientific Affairs

Women's Health: Sex- and Gender-based Differences in Health and Disease

Tables and appendix (PDF, 34KB)

Note: This report, presented as CSA Report 4 at the 2000 Interim AMA Meeting, represents the medical/scientific literature on this subject as of December 2000

Full text

In recent years, women's health has become an increasingly visible and important policy issue. The realization that research findings on men cannot be extrapolated to women, combined with the relative lack of evidence-based information on which to guide treatment decisions in women, has fostered changes in the federal institutions that fund research and foster health services delivery, the Food and Drug Administration (FDA), the pharmaceutical industry, and in medical school curricula.¹ A chronological list of important historical developments appears in the Appendix (PDF, 34KB).

The overarching purpose of these research changes was to increase women's participation in clinical trials to obtain better information about women's health, while assuring the representation of relevant populations and the assessment of possible differences in treatment effects. Sex- and gender-based differences in cardiovascular disease have been the focus of much attention in this area, although the degree to which these efforts have been successful is currently a matter of debate. Although women comprised a majority of subjects included in trials sponsored by the National Institutes of Health (NIH) from 1993-1998, only a fraction of the final reports of these studies provided sex-based analysis of the data.^{2,3} Furthermore, although women were adequately represented in studies of coronary artery disease and hypertension, they were underrepresented in studies of heart failure.⁴

Relevant policies of the American Medical Association (AMA) are based on two previous reports, one issued by the Council on Ethical and Judicial Affairs and a joint report offered by the Council on Medical Education and the Council on Scientific Affairs (CSA).^{5,6} The AMA supports the inclusion of sufficient numbers of women in all research on human subjects, except where the inclusion would be scientifically irrational (Policies H-525.988 and H-525.988, AMA Policy Database). The AMA also encourages the development of women's health/gender-based biology curricula in medical schools; the definition of appropriate residency-based training objectives in women's health; and continuing medical education for physicians in this area (Policy H-295.890). The AMA also advocates that physicians examine their practices and attitudes for possible gender biases and ensure that gender is not used inappropriately as a consideration in clinical decision-making (Policy H-525.990).

Previously, the Society for Women's Health Research approached the CSA with the idea for a report on sex- and gender-based differences in women's health. This report expands on an earlier draft developed by the Society in conjunction with the CSA.

Methods. Literature searches were conducted in the MEDLINE database and Lexis/Nexis GenMed library for articles published between 1985 and September 2000 using the terms: *sex characteristics* and health, disease, or *epidemiology*. Secondary searches were conducted for articles published between 1995 and September 2000 using the search term *sex factors*, combined with *alcohol, anxiety disorders, arrhythmia, asthma, autoimmune diseases, cardiovascular diseases, congestive heart failure, diabetes, eating disorders, gastrointestinal diseases, hepatic diseases, hypertension, human immunodeficiency virus, lung diseases, menopause, mood disorders, myocardial infarction, osteoporosis, thyroid diseases, schizophrenia, smoking cessation, substance-related disorders, and urologic disorders*. References containing information relevant to sex- or gender-based differences in health and disease were examined further. Additional references were culled from the bibliographies of these pertinent references.

The Web sites of several institutes, centers, and offices within the , the FDA, the Society for Women's Health Research, the National Women's Health Resource Center, the National Women's Health Network, and several national medical specialty societies were also searched for information relating to sex- and gender-based differences in health and disease.

Women's health issues. Issues in women's health concern the prevention, diagnosis, and management of conditions or diseases that may be unique to women; that are more prevalent in women than in men, or that manifest differently in women than men. This review focuses on the latter two categories, particularly where differences have been identified that carry important treatment or public policy issues. As such, this report does not specifically discuss diseases and issues related to reproductive physiology per se or other urogynecologic disorders and cancers that are unique to women. Menopause deserves special consideration, however, because it represents a transition into higher risk for certain diseases, and issues related to hormone-replacement therapy remain unsettled. While this report focuses on non-reproductive women's health issues, the CSA recognizes that pregnancy is a unique event in women's health. Birth outcomes for both mother and child are heavily influenced by women's health status entering the pregnancy. Although maternal mortality has decreased dramatically, women with serious underlying illness (eg, uncontrolled diabetes, lupus with severe kidney involvement, rheumatic heart disease) remain at risk. Therefore, it is essential that physicians caring for women with serious illnesses counsel their patients about the impact of potential pregnancy on their health.

While these traditional areas of women's health continue to receive appropriate research emphasis, there is now widespread recognition that women's health must be approached in a more broad-based fashion, examining how differences in sex factors, gender, culture, ethnicity, and socioeconomic background influence the causes, diagnoses, progression, and treatment of diseases unique to women, as well as those that are not sex-specific. Many diseases and the subsequent health status of women have their roots in adolescence. Nutritional habits and life style choices including exercise level; use of tobacco, alcohol and other drugs; and sexual responsibility are formed or initiated during this period. Continued attention needs to be paid to ways in which preventive practices can be augmented during this critical period of development. Progress in the human genome project and the emerging dominance of genetic models of disease causation promise to introduce another element to this analysis.

Violence against women. While also not the focus of this report, the critical issue of violence against

women must be acknowledged as a woman's health issue. Two reports have recently examined violence against women, particularly intimate partner abuse and coerced sex.^{7,8} Women are more likely than men to be victimized by a family member or intimate partner. In the United States, nearly one in four women report having been raped or physically assaulted by a current or former spouse, cohabiting partner, or date. Such violence is often accompanied by emotionally abusive and controlling behavior, progressive social isolation or deprivation, and economic control.

Women with a history of physical or sexual abuse are at increased risk for unintended pregnancy, high-risk sexual behavior, sexually transmitted diseases, and other gynecological problems. Sexual coercion exists along a continuum, from forcible rape to other forms of pressure that coerce women to engage in sex against their will.

In addition to potentially devastating effects on women's reproductive health, violence is a risk factor for injury and disability; mental health disorders (mood, anxiety, and eating disorders); chronic pain syndromes and somatic complaints; and other negative health behaviors (smoking, alcohol and drug abuse, physical inactivity, overeating). Abused women are at increased risk for emergency room visits and hospitalizations, another measure of the significant impact of violence on women's health.⁹

General considerations

Sex versus gender. Specifically, "sex" denotes biologically based differences and "gender" indicates culturally and socially shaped variations between men and women. Unfortunately, in the published medical literature, many authors have replaced "sex" with "gender," using the term "gender differences" to describe any observed differences between men and women, including relative rates of mortality and morbidity, as well as purely biological differences in sex organs and sex-specific diseases.¹⁰ Common use of the term "gender differences" now often implies an uncertain understanding of the relative contribution of "biology" and "culture" even though studies may not have been designed to examine differences from a "gender" perspective.

Used in this way, "gender-based differences" may emanate from a biomedical (genetic, hormonal, anatomic, physiological); psychosocial (personality, coping, symptom reporting); epidemiologic (population-based risk factors); or even a more global perspective. The latter analyzes large-scale cultural, social, economic, and political processes that ultimately produce differential health risks for women and men.¹¹ Effective integration of these approaches is required to fully examine issues related to women's health.

Women's unequal status in society jeopardizes their health and well being. Women experience higher mortality and morbidity in states where they have lower levels of political participation, economic autonomy, and higher levels of poverty.¹¹ The context of women's lives has a major impact on health and the ability to get care. Women are more often single parents who are uninsured or underinsured and have more limited access to health care resources than men. These factors are exacerbated in the elderly and disabled, two "populations" that contain more women. Use of the categories of "men" and "women" tends to ignore the complex interaction of race, sex, and social class within our health care system and may obscure the fact that differences among women are larger than differences between, for example, white men and white women.

Symptom reporting. When considering sex differences in disease prevalence, it must be recognized that women consistently report symptoms more frequently than men and there is a higher likelihood that their symptoms will be considered medically unexplained. Various physiological, sociocultural, and psychological explanations have been advanced for this phenomenon. This difference in reporting persists in individuals seeking health care, even when controlling for psychiatric comorbidities.¹²

Sex and gender-based differences in pain have been noted, but the etiology of an apparent greater female sensitivity to pain is not established.¹³ Attempts to assess hormonal influences, generalize from experimental pain models to clinical symptoms, or to implicate family history in pain tolerance have been inconsistent.¹⁴⁻¹⁶ There may be sex and gender differences in the analgesic response to kappa opioid agonists and in behavioral mediators of pain.¹⁷ There are also several, seemingly diverse chronic syndromes that predominately affect women in which pain is a cardinal feature such as fibromyalgia, temporomandibular joint disorder, recurrent migraine headache, genital and pelvic pain disorders, and irritable bowel syndrome.

Life expectancy. The backdrop of sex- and gender-based differences in health and disease is the differential in life expectancy, which has been a central feature of mortality trends in the 20th century. Women have lower mortality than men in every age group and for most causes of death (Table 1, PDF, 34 KB). Based on mortality statistics from 1998, women in the United States are expected to outlive men by an average of 5.7 years, although this differential continues to shrink, largely because of decreasing mortality from cardiovascular disease and cancer in men.¹⁸ White females continue to have the highest life expectancy (80 years), followed by black females (74.8 years), white males (74.5 years), and black males (67.6 years). The leading cause of death for women continues to be heart disease, followed by malignancy, and stroke, although differences emerge for the various age clusters (Table 2, PDF, 34KB). Of note, more than twice as many women die annually from cerebrovascular disease as from breast cancer. Lung cancer is the number one killer among malignancies.

Sixty percent of individuals over 65 years of age are women; 70 percent over the age of 85 are women. Because women live longer than men, they have a greater lifetime risk of functional disability and chronic illnesses, including cancer, cardiovascular disease, and dementia, as well as a greater need for long-term care. The economic burden of disease for conditions commonly affecting postmenopausal women is substantial.¹⁹ For example, osteoarthritis affects almost 21 million adults in United States, 75 percent of whom are women, and ranks second to heart disease as a cause for disability payments.

General trends and risk factors for disease. Premenopausal women are at much lower risk for cardiovascular disease than men, an advantage that diminishes after menopause. Women are at much higher risk for autoimmune disease, and more than twice as many women as men suffer from depression and anxiety disorders. Women appear to be more susceptible to the damaging effects of cigarette smoke (including those attributable to passive exposure) and alcohol.

Thirty-five percent of women over 20 years of age are obese; rates of obesity in African-American and Hispanic women approach 50 percent.²⁰ At any given threshold of body mass index, women have greater fat mass than men. One in four women reports no regular physical activity, more than half of women >45 years of age have elevated blood pressure, and approximately 40 percent of women older than 55 years have elevated cholesterol.

The pharmacokinetics and pharmacodynamics of many prescription drugs differ between women and men.^{21,22} A failure to account for these differences may render women more susceptible to adverse drug events, an outcome that has received attention recently as a major cause of morbidity and mortality in the health care system.

Diseases that are more prevalent or manifest differently in women

Autoimmune diseases

Autoimmune disease affects nearly 10 million people in the United States; of these a disproportionate number (about 6.8 million) are women (Table 3). At least 24 diseases have been characterized as having direct or strong circumstantial evidence of autoimmune pathogenesis.²³ Distinct immune environments in men and women underlie some of the sex differences in autoimmunity; women generate a more robust proinflammatory environment after challenge with an infectious agent or antigen. Women also tend to demonstrate greater antibody production and increased cell-mediated immunity after immunization.²⁴ Sex hormones modulate the immune response as do other sexually dimorphic hormones including prolactin, growth hormone, and insulin-like growth factor-1. Because many autoimmune diseases lack distinct ICD-9 codes, their contribution to mortality is underrepresented. A recent analysis concluded that autoimmune disease deaths exceeded the 10th leading cause of death in every age category for women < 65 years of age, and exceeded the 8th leading cause of death in the 15 to 24, 25 to 44, and 45 to 64-year age brackets.²⁵

Pregnancy exacerbates the course of some autoimmune diseases, while it improves the course of others. Additionally, corticosteroids are commonly used in many of these disorders, which increases the risk of osteoporosis. Autoimmune disease explains much of the burden suffered by women in rheumatologic disorders and thyroid disease.

Thyroid disease. Thyroid disorders are much more common in women. The peak incidence of Hashimoto's thyroiditis and Graves disease occurs in the 2 decades that precede menopause. Autoimmune hypothyroidism frequently is associated with infertility. Hyperthyroidism during pregnancy presents special concerns because radioactive iodine is contraindicated and the standard antithyroid drugs are teratogenic.²⁶ Thyroid nodules are also more common in women than in men, although the proportion of nodules that are malignant in males is double that in females. Women also may be at increased risk of interferon-alpha induced thyroid dysfunction.²⁷

Rheumatologic disorders. Rheumatoid arthritis is the most common cause of chronic inflammatory arthritis, affecting one to two percent of the general population. Three out of four patients are women. Most patients exhibit a chronic fluctuating course of disease that, if left untreated, results in progressive joint destruction, deformity, disability, and premature death. The disease tends to behave more aggressively in women, leading to a worse long-term prognosis. Approximately 20 percent of patients with rheumatoid arthritis have secondary Sjogren's syndrome and are at high risk of developing lymphoma.

Systemic lupus erythematosus is much more common in women (9:1). African-American and Asian women are at higher risk than white or Hispanic women. Drug-induced lupus affects both sexes equally.

Cardiovascular disease

Heart disease is the leading cause of mortality and morbidity in the United States for both women and men. At any given age, the prevalence of coronary heart disease (CHD) is greater in men than in women, but more women die from heart disease than men because of their extended life expectancy. Below the age of 55 years, the incidence of CHD in women is one third that of men; however, this ratio approaches unity at age 75 years. On average, the disease appears 10 years later in women, with the incidence of myocardial infarction in women lagging somewhat more than in men. Recent declines in the mortality rate from heart disease for women have been less than for men and death rates are higher in African-American women.²⁸

Thus, there has been a shift in the burden of heart disease to elderly women in the population. In addition to age differences in onset, sex-based differences have been identified in the relative importance of coronary risk factors; the typical presentation of symptoms; use of diagnostic interventions and treatments; and mortality.²⁹ Nevertheless, most women do not perceive that heart disease is a substantial health concern and report that they are not well informed about their risk. Programs directed at young women that address the effects of lifestyle behaviors on long-term health are needed. Better communication between physicians and patients is also warranted.³⁰

Risk factors. The major risk factors for CHD in women are similar to those noted in men (cigarette smoking, hypertension, dyslipidemia, diabetes, obesity, sedentary lifestyle, poor nutrition) but some relative differences are apparent, particularly with regard to diabetes and dyslipidemia. Risk factors that diminish female protection from CHD are age, onset of menopause, total/HDL-cholesterol ratios >7.5, high triglyceride levels, diabetes, and the development of left ventricular hypertrophy.^{31,32}

Menopause accelerates coronary risk threefold and greatly erodes the early advantage of women over men. Diabetes also removes the normal sex differences in the prevalence of CHD.^{33,34} When adjusted for other risk factors, the risk of coronary events in women with diabetes is at least double that of women without diabetes. Low levels of HDL-cholesterol are predictive of CHD in women and appear to be a stronger risk factor for women over age 65 years than for men over age 65, as are high triglycerides. Insulin sensitivity is independently associated with a low risk for CHD. Women are more sensitive to insulin than equally fit men.³⁵ However, even in nondiabetic women, a rise in insulin concentration occurs with age (5th-8th decade) in contrast to declines seen in men. Variations in insulin levels may be a common pathway for sex/age trends in fasting glucose, apolipoprotein B, total cholesterol, HDL- and LDL-cholesterol, triglycerides, and blood pressure.³⁶

The American College of Cardiology has published a guide to risk reduction for heart disease for women.³⁷ The guide suggests that more aggressive targets should be considered for triglycerides and HDL-cholesterol in nondiabetic women, and for LDL-cholesterol in patients with diabetes. The guide also recommends the use of HMG CoA-reductase inhibitors for primary lipid reduction in postmenopausal women, rather than estrogen replacement therapy.

Symptom presentation. Heart disease in women often goes undetected and untreated until the disease has become severe. Among individuals presenting to the hospital with apparent ischemic cardiac pain, men are more likely to have Q-wave infarction and women are more likely to have clinically insignificant coronary artery stenosis, despite angina symptoms.³⁸⁻⁴¹

Women with CHD may experience symptoms that are "less classic" than men's symptoms. Despite the notion that chest pain is of more limited prognostic value, it remains the most common initial

manifestation of CHD in women.⁴² However, women with CHD are more likely than men to present with midback pain, nausea and/or vomiting, dyspnea, palpitations, and indigestion.⁴³ Although there are some gender differences in non-chest pain symptoms, there are more similarities than differences in symptoms in women and men presenting to the hospital with suspected cardiac ischemia.

Standard exercise testing is less accurate in women due in part to an increased rate of false- positive results. A significantly lower specificity of ST-segment depression is associated with treadmill tests in women compared with men.⁴⁴ Stress-imaging studies can improve the diagnostic yield, although thallium stress-testing may be less reliable in revealing heart damage in some women than in men because breast tissue impairs the signal emanating from normal radiocontrast agents. The use of technetium-99m sestamibi perfusion scans using gated SPECT in women improves specificity.

Mortality and morbidity. Many reports have concluded that women with CHD have a worse prognosis than men with this disease. Based on data generated by the Framingham study, 44 percent of women die within one year of suffering a myocardial infarction (MI) compared with 27 percent of men.⁴⁵ Crude event rates including death and nonfatal infarction are higher in women than in men hospitalized for CHD. Although women suffering MI are less likely to be smokers and less likely to have had a prior infarction, they are generally older and more likely to have hypertension, elevated cholesterol, diabetes, and congestive heart failure. They also are more likely to suffer complications during hospitalizations, including pulmonary edema, atrial arrhythmia, and hemodynamic instability.

After adjustment for such differences, some studies have concluded that sex is not an independent predictor of mortality after acute MI,⁴⁶⁻⁵⁴ while others maintain that the higher risk of death among women is independent of base-line variables.⁵⁵⁻⁵⁸ Although one study concluded that much of the increased morbidity and mortality in women with MI can be accounted for by the effects of advanced age and age-related coexisting illness,^{38a} a recent study confirmed an increased risk for women until age 75; younger women with MI had higher risks of death relative to men.⁵⁹

Randomized treatment trials of beta blockers, ACE inhibitors, and thrombolytics in patients with MI also were characterized by increased (50 percent to 60 percent) crude, short-term mortality rates in women,^{52,54,60-63} with some analyses suggesting that a substantial portion of the differences between men and women is explained by the increased age and/or co-existing illness.^{60,61,64} Sex differences in mortality are greatest in younger patients, who are less likely to receive thrombolysis.⁶⁵

Some of these disparate findings may be related to the mix of coronary syndromes examined. Women and men with acute coronary syndromes likely have different clinical profiles, presentation, and outcomes. In one study, the increase in female mortality occurred only in patients with Q-wave infarction. Outcomes in women and men with unstable angina or non Q-wave infarction were similar.³⁸

Interventions. While reported differences in mortality rates may reflect differences in baseline characteristics and case-mix, other factors also may contribute to the difference between men and women in survival after MI in the post-thrombolytic era. These include (1) a lower frequency of acute diagnostic and therapeutic interventions; (2) differences in utilization and responsiveness to revascularization procedures; and (3) less aggressive post-infarct risk reduction.

Several studies have found that women are less likely to be referred for cardiac catheterization and revascularization procedures than men.^{38,46,66-74} In studies that controlled for the severity of disease,

comorbidity, or the extent of disease found at angiography, differences in the rates of revascularization between men and women tended to disappear.^{38,39,46,75-77} However, in community hospitals, women with CHD were only half as likely as men to be referred for acute catheterization, angioplasty, thrombolysis, or coronary bypass surgery and had twice the risk of hospital mortality.^{42,74} Women with unstable angina with positive criteria were also somewhat less likely to undergo bypass surgery.⁷⁸ Among patients who have cardiac catheterization early after MI, women and men are equally likely to have angioplasty, but women are less likely than men to have coronary artery bypass graft surgery (CABG).³⁹

Thrombolysis. Clinical trials examining the efficacy of various thrombolytic regimens indicate that women are at greater risk for bleeding and stroke, although the overall benefit is similar to that for men.^{51,56,57,64,79-80} Women do not differ significantly from men with regard to early infarct-related artery patency rates, reocclusion after thrombolytic therapy, or ventricular functional response to injury/reperfusion, but crude early mortality rates remain higher.^{60,61} Female sex is an independent determinant of 30-day mortality after thrombolysis for acute MI.⁸¹ A substantial portion of the differences between men and women is explained by the increased age of women, a delay (relative to men) in receiving prompt therapy, and other variables predictive of 30-day mortality. During 1-year follow-up, the late mortality of women is no greater than that of age-matched men.⁶⁰

Revascularization procedures. Numerous studies evaluating the outcome of coronary revascularization performed with percutaneous transluminal coronary angioplasty (PTCA) or CABG have reported higher rates of mortality and major complications in women compared with men.⁸²⁻⁸⁶ Successful PTCA carries a similar long-term prognosis in women and men, but procedural morbidity and mortality for PTCA is three-fold higher in women. The factors responsible for this sex difference in outcome are uncertain, but advanced age, comorbid disease, hypertensive heart disease, and small vessel size may play a role. CABG is also characterized by a higher procedural mortality in women. Older age; worse functional class; smaller, more technically challenging coronary arteries; higher likelihood of emergent surgery in women; and comorbidities that increase operative risks contribute to this disparity. Women appear to have comparable immediate and late survival rates. Recurrent angina, perioperative MI, congestive heart failure, incomplete revascularization, and early and late graft reocclusion following surgery also may be more prevalent in women, although a recent study found that women have similar graft patencies at one year.^{87,88}

Indeed, many of the earlier studies reporting sex differences in outcomes of CABG and PTCA were performed before major advances in technology and improvements in revascularization technique. In a recent randomized clinical trial, survival at five years between men and women was similar.⁸⁹

An alternate view is that women are less likely than men to be referred for CABG when there is a low risk of cardiac death (when surgery may offer little or no survival benefit over medical treatment), but women are at least as likely as men to be referred for bypass surgery among more symptomatic and more severely diseased patients, in whom surgery offers the greatest survival benefits. Based on surgical survival benefits, these referral patterns may represent more appropriate treatment referral for women than men.⁷⁶

Are outcomes improving? The most recent analysis from the National Registry of Myocardial Infarction-I confirmed that women experiencing acute MI continue to be much older than men, with 56 percent of women experiencing their first heart attack after age 70.⁶⁸ Unfortunately, data from this registry also indicate that:

- women have a higher mortality rate even when controlled for age
- treatment with aspirin, heparin, or beta-blockers is less frequent in women
- when thrombolytic therapy is used, women are treated an average of almost 14 minutes later and experience a greater incidence of bleeding
- cardiac catheterization, PTCA, and CABG are used less often in women

The most recent analysis of Medicare beneficiaries suffering acute MI in 1994-95 found that, compared with men, women received somewhat less aggressive treatment during early management. However these differences were small, and there was no apparent effect on early mortality.⁹⁰

Secondary prevention. These results underscore the need for more effective primary and secondary preventive measures in women. The lack of women in many early postinfarction intervention trials was based on an upper age restriction of 65 years, which marks the point where prevalence of CHD in women begins to climb toward that of men. Nevertheless, current recommendations are to treat women like men with the use of aspirin, beta blockers, ACE inhibitors, etc. However, women are less likely to be advised to take aspirin (75 to 325 mg) for secondary prevention, a trend that is likely enhanced by the lack of adequate studies and evidence for the use of aspirin in women.⁹¹

Treatment of hyperlipidemia reduces the risk of coronary artery events in both women and men. Reduction in LDL-cholesterol with "statins" decreases the risk of CHD and all-cause mortality. Risk reductions are similar for men and women and for elderly and middle-aged persons.⁹² Women appear to benefit from decreases in LDL-cholesterol as much as men, regardless of baseline lipid concentrations or age; however, only about 47percent of women with known CHD receive treatment for their hypercholesterolemia.⁹³⁻⁹⁵ Data from the PEPI trial also showed that adding progesterone to estrogen (necessary for women with a uterus) is more effective than placebo for hypercholesterolemia.⁹⁶

Stroke. Strokes occur more often in men than women. Generally, the same risk factors apply to both sexes, although the risk of stroke associated with atrial fibrillation may be higher in women, and women are more likely than men to have a stroke within 6 years of a heart attack. Although the lifetime risk of stroke is higher in men, women are more likely to die, probably because of their older age at occurrence. Recommendations for acute interventions in women and men with stroke are the same.

Congestive heart failure. Improved survival of patients with other chronic cardiovascular conditions has increased the public health burden of congestive heart failure (CHF), reflecting the aging of the population. Heart failure causes significant morbidity and mortality in women, especially elderly women. Risk factors for the development of heart failure in women differ from those in men, with hypertension and diabetes playing a greater role in women and ischemic heart disease a greater role in men.⁹⁷⁻⁹⁹ This may reflect sex differences in the cardiac response to afterload.¹⁰⁰ Additionally, the risk of developing clinical heart failure after symptomatic MI is higher in women than in men.¹⁰¹

Although survival rates remain poor, results of previous observational, natural history, and randomized studies in broad populations of heart failure patients have found that women appear to live longer after the diagnosis of heart failure than men, particularly patients with a nonischemic etiology of ventricular dysfunction.¹⁰²⁻¹⁰⁵ However, in homogenous studies of patients with left ventricular dysfunction, women had more hospital admissions and higher mortality over a one-year period.¹⁰⁶

Recent data on elderly female and male patients hospitalized for heart failure suggest that women and men have similar hospital courses, treatment patterns and readmission rates, but that women live longer than men. When baseline differences are accounted for, the mortality risk of women and men is similar.⁵⁹

In recent clinical trials of medical therapy for heart failure, only 13 percent to 20 percent of patients enrolled were women. Although the incidence of heart failure is higher in men than in women, the prevalence is equal. When men and women with heart failure and a low left ventricular ejection fraction are compared, women are more symptomatic and have a similar poor outcome. However, because mortality is higher in men than in women in large populations of patients with heart failure, there must be important pathophysiologic differences. Substantial data suggest that women have diastolic dysfunction more often than men,¹⁰⁷ which may explain differences in mortality and contribute to the difficulty in enrolling women in studies of medical therapy for heart failure with underlying systolic dysfunction. There is a need for more trials in typical patients, as well as studies that include older subjects, and a shift in emphasis to prevention, early detection, and intervention.¹⁰⁸

Exercise-based rehabilitation improves skeletal muscle capacity, exercise tolerance, and health-related quality of life in women as well as men with moderate, chronic heart failure.¹⁰⁹ Results of large trials evaluating the efficacy of beta blockers have not reported sex-specific mortality. Meta-analysis of ACE inhibitor trials suggests that the survival benefit with active therapy is similar in both sexes.¹¹⁰ However, ACE inhibitors appear less effective in women with left ventricular systolic dysfunction and heart failure caused by MI.¹¹¹ Further investigation is necessary to better define sex-related differences and possible sex-specific therapies for those diseases resulting in heart failure.

Hypertension. Sex differences in the physiology, genetics, and treatment benefit of hypertension have been noted in several studies that have included women, but until recently women were underrepresented in clinical trials. These findings raised concerns about the generalizability to women of the results of previous investigations, although it is generally believed that women also benefit significantly when they receive therapy to normalize blood pressure. Current therapy recommendations are not sex-based.

Some data indicate that the prevalence of hypertension is higher in men than in women until age 60, and then reverses.¹¹² Such a crossover effect was not detected in the Framingham study, in which the incidence of hypertension in elderly women approached, but never exceeded that of men.¹¹³ Hypertension is more prevalent in African-American and Hispanic women older than 60 years, and in white women older than 70.

Women are more likely to be salt-sensitive in the presence of a positive family history.¹¹⁴ Oral contraceptive use increases the risk of hypertension, although the use of hormone replacement therapy in normotensive, postmenopausal women appears to be acceptable.¹¹⁵ Hypertension causes stroke more often, and is a stronger risk factor for the development of CHF in women.^{96,116} The presence of left ventricular hypertrophy in women is associated with significantly more risk than in men with similar degrees of hypertrophy.¹¹⁷

Of the 10 large hypertension treatment trials published between 1979 and 1993, 3 did not include women, 3 studied only elderly women, and the others were not designed or did not have the power to detect sex differences in outcomes adequately.¹¹⁸ Results, however, strongly support pharmacological therapy for elderly women with isolated systolic hypertension.¹¹⁹ Meta-analysis of more than 40,000 patients in

hypertension treatment trials showed reduction in risk for stroke and "major cardiovascular events" in women.¹²⁰ These benefits were not as substantial as those observed in men, but broader treatment effects may have been more difficult to detect in women because of their lower baseline risk.

Although some evidence shows that gender differences in hypertension exist, definitive studies are lacking from which to draw firm conclusions regarding the extent and importance of these differences. However, the prevalence of hypertension in women, the attributable risks of complications, and results of recent investigations suggest that treatment of women should be similar to that of men.

Arrhythmias. It is well established that women have a longer QT interval and also show a greater predisposition to the adverse effects of QT-prolonging drugs such as sotalol.¹²¹ The mechanism for the longer corrected QT interval in women is not completely known, but does not appear to be related to acute effects of estrogen or progesterone or to differences in autonomic innervation.

Women appear to have a lower incidence of atrial fibrillation, a difference in the age distribution of supraventricular tachycardia, and a lower incidence of arrhythmia-induced sudden death than men. The paradox of a longer corrected QT interval and higher incidence of torsades de pointes, but lower population-based incidence of sudden death in women has not been resolved. Further studies will be required to better understand the basic mechanisms involved in gender differences in electrophysiology and arrhythmias and to determine the extent to which these differences have implications for the clinical management of cardiac arrhythmias.¹²²

Substance use and addiction

Unfortunately, women are becoming more like men in the extent to which they use alcohol, tobacco, and illegal drugs, particularly among adolescents. Women suffering from drug addiction may trade sex for drugs increasing their risk for sexually transmissible diseases. As a consequence, a larger percentage of women (59 percent) than men (31 percent) now acquire human immunodeficiency virus (HIV) from intravenous drug use, or by having sex with an injection drug user. The origins, patterns and consequences of substance use are different for women and men. More women than men take prescription drugs for nonmedical purposes and one in five women smoke, drink or use drugs during pregnancy, threatening the health of their babies.

Women typically begin using substances later, have different reasons for continuing use, and may proceed more rapidly to drug addiction than men; however, they enter treatment earlier in the course of their illness. Differences exist in psychiatric comorbidities (more anxiety and depression) that predate addiction, and women suffer additionally from victimization and violence. Consequently, different treatment approaches and strategies may be necessary, but relatively little gender-specific information is available on which to guide treatment.¹²³ One of the major barriers to adequate drug treatment for young women is parenting responsibilities, which may totally preclude residential treatment programs

Alcohol use disorders affect women differently than men. Women reach higher peak blood alcohol concentrations more rapidly than men when ingesting the same dose, which may be related to sex-differences in gastric dehydrogenase activity. Women who drink generally consume less alcohol and have fewer alcohol-related problems and dependence symptoms than men. However, women are more vulnerable than men to alcohol-related liver disease, cardiomyopathy, and brain damage.¹²⁴⁻¹²⁷ Among the heaviest drinkers, women equal or surpass men in the number of problems that result from their drinking,

and female alcoholics have death rates 50 percent to 100 percent higher than male alcoholics. Furthermore, there is a dose-response relationship between alcohol consumption and the risk of fracture in both men and women. Compounding this problem is the fact that physicians have a low level of suspicion for alcohol and other substance addiction in women over age 60 years. Despite these differences, information on gender-specific assessment tools, outcome measures, and treatment approaches is lacking

Of concern, the declines in adult tobacco use have slowed, and tobacco use in youth is increasing again. Tobacco use patterns in women are particularly troublesome. Throughout the 1990s, teenage and college student smoking rates increased, more so in women than in men. Young women under the age of 23 are the fastest growing sector of smokers in the United States.

Tobacco use adversely affects women in unique ways throughout their lifespan, as follows:

- decreased lung growth in female adolescents compared with males
- decreased fertility; increased spontaneous abortion
- increased risk of stroke, venous thromboembolism, and myocardial infarction in women who use oral contraceptives
- premature menopause, accelerated osteoporosis, and possible diminution of benefits attributable to hormone-replacement therapy.

Whether there are significant sex- and gender-related differences in smoking cessation is controversial. Large-scale smoking-cessation trials show that women are less likely to initiate quitting, may be more likely to relapse if they do quit, and are less likely than men to maintain long-term smoking abstinence following an unaided quit attempt or when using the nicotine patch.¹²⁸⁻¹³⁰ However, women did not differ from men in smoking cessation rates in response to brief interventions.¹³¹ It is important for women entering smoking cessation programs to be aware that standard treatment regimens may have to be adjusted to compensate for sex differences in nicotine sensitivity.

Women face particular challenges when attempting to stop smoking. Cultural issues influence women's concerns about body weight and physical appearance, and women appear more likely than men to gain weight upon quitting. Fear of weight gain inhibits some women from initiating or persisting with cessation attempts. Also, concurrent depression can impede successful quit attempts, and women are more susceptible than men to depression.

Gastrointestinal diseases

Gastrointestinal diseases are among the most common disorders for which women seek medical attention. Functional gastrointestinal disorders are characterized by somatic symptoms and are associated with psychological factors.

Peptic ulcer disease. Increasing prevalence of ulcers in elderly women has been attributed to extensive use of nonsteroidal anti-inflammatory drugs. The mortality rate from gastric ulcers has risen significantly in patients older than 75 years, thus affecting women disproportionately. Colonization with *Helicobacter pylori* increases with age but there is no independent gender effect.

Irritable bowel syndrome (IBS). This functional gastrointestinal disorder is believed to affect at least twice as many women as men. The gender difference remains unexplained but may be related to the higher sensitivity and specificity of diagnostic criteria in women, sex differences in gastrointestinal transit times, and the reluctance of men to act on somatic symptoms with health-seeking behavior.¹³² The disorder typically is diagnosed between the ages of 20 and 40. IBS represents one condition where a sex-specific treatment has been developed. Women with IBS respond differently to 5-HT₃ receptor antagonists, which led to the development of alosetron, which is indicated for the treatment of women with diarrhea-predominant IBS.¹³³

Inflammatory bowel disease. Epidemiologic study of inflammatory bowel disease has been hampered by a lack of universal diagnostic criteria, misdiagnosis, and overselection of patients from tertiary care centers. Most studies reveal similar male and female incidence in ulcerative colitis, and a female preponderance in Crohn's disease.¹³⁴ Use of corticosteroids in patients with Crohn's predisposes women to bone loss.¹³⁵

Colorectal cancer. Many women mistakenly believe they are not at risk for colorectal cancer. Colorectal cancer strikes women nearly as often as men; 67,000 women each year are diagnosed with the disease and 40 percent of them will die from it. After age 70, colon cancer is more of a risk to women than breast cancer. Colorectal cancer has the third highest incidence of any cancer site for US men; ranks second to breast cancer for Hispanic, American Indian/Alaska Native, and Asian/Pacific Islander women; and ranks third for white and African-American women.

The prevalence of colorectal cancer screening by fecal occult blood testing (FOBT), sigmoidoscopy, or proctoscopy has been estimated based on data collected through the National Health Interview Survey (NHIS) and the Behavioral Risk Factor Surveillance System (BRFSS). Based on BRFSS results, the use of FOBT by people aged 50 years and older was 21 percent in women and 18.4 percent in men; 35.2 percent of men had either a sigmoidoscopy or proctoscopy whereas only 26.8 percent of women had either procedure. Although screening rates were low, data from the NHIS showed gradual and modest increases in the use of screening procedures for colorectal cancer from 1987 to 1998. The percentage of people who reported FOBT two years before the interview increased from 30 percent in 1992 to 33 percent in 1998, with rates varying by income and education. Women, as well as men, should be targeted to undergo screening tests for colorectal cancer.

HIV infection

HIV infection is now the leading cause of death in African-American women aged 25 to 44 years; however, most treatment data for HIV infection have been derived from studies of homosexual men. There is some evidence that the virus pool may be more heterogeneous with heterosexual (male to female) transmission than with male to male homosexual transmission.¹³⁶ Controversy exists about HIV-1 quantification in men and women and its association with disease progression.¹³⁷ Women (intravenous drug users) have been reported to have lower viral loads with equal progression or higher progression with equal viral loads, but other studies have found more rapid disease progression in older subjects compared with younger subjects and in older men who have sex with men compared with heterosexuals, intravenous drug users and transfusion recipients.¹³⁸⁻¹⁴¹ Currently, the *Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents* does not recommend different criteria for therapy in women versus men, with the exception of pregnant women.

Liver and hepatobiliary diseases

Women's significantly higher relative risk of developing alcohol-related liver disease than men for any given level of alcohol intake has been mentioned. Most diseases of the hepatic and biliary system affect both women and men, but gallstones, primary biliary cirrhosis (9:1), and autoimmune-mediated hepatitis (4:1) occur more often in women. Gallstones occur in 10 percent of the adult population but are twice as frequent in women. Women have smaller total bile acid pools with increased biliary cholesterol content that may lead to supersaturation. Incidence is increased by oral contraceptive (OC) use and during pregnancy.

Chronic liver disease from any cause can affect fertility. OC use can lead to cholestasis and increases the risk for hepatic adenomas. Women with chronic liver disease are at risk of developing osteoporosis; factors are a low body mass and use of corticosteroids.¹⁴² Women less than 40 years of age are uniquely responsive to interferon-alpha treatment, suggesting that hormonal activity, in particular the level of estrogen, may be associated with sustained elimination of the hepatitis C virus.¹⁴³

Lung diseases

Lung cancer. An estimated 164,100 new cases of lung cancer will be detected in 2000, accounting for 14 percent of cancer diagnoses. The incidence has declined significantly in men, from a high of 86.5 per 100,000 in 1984 to 69.1 in 1997. The incidence in women has increased significantly since 1973 but has leveled off since 1991 (43.1 in 1997).

Lung cancer will cause an estimated 156,900 deaths in 2000, accounting for 28 percent of all cancer deaths. During 1992-1996, mortality from lung cancer declined significantly among men (-1.7 percent per year) while rates for women were still significantly increasing (1.3 percent per year). Since 1987, more women have died each year of lung cancer than breast cancer, which, for over 40 years was the major cause of cancer death in women. Decreasing lung cancer incidence and mortality rates reflect the decline in smoking rates over the previous 30 years. However, as previously noted, decreasing smoking patterns among women lag behind those of men.

While women experience the same ill effects of smoking as men, women appear to be more susceptible than men to tobacco carcinogenesis. Females are also more susceptible to the harmful effects of tobacco smoking in developing chronic obstructive pulmonary disease.¹⁴⁴ Given the same level of lifetime exposure to smoke, the odds ratio for developing cancer is 1.2 to 1.7 times (20percent to 70percent) higher in women than in men.¹⁴⁵ Enzymatic, gene expression, and estrogen receptor-related variations have been noted that may contribute to increased susceptibility.¹⁴⁶⁻¹⁴⁸

The distribution of histological subtypes of lung cancer in women is different from that in men. Women are less likely to have squamous cell carcinoma and more likely to have adenocarcinoma or small cell lung cancer. Molecular biologic substaging of patients with Stage I non-small cell lung cancer (NSCLC) demonstrates cancer-specific survival according to marker expression, gender, and histologic subtype.¹⁴⁹ NSCLC in women is more likely than in men to harbor K-ras mutations, suggesting a role for estrogen exposure, but women retain a modest survival advantage.^{150,151}

Asthma. Throughout childhood, the prevalence of airway hyperresponsiveness is less in girls than in boys.¹⁵² Airways of women show cyclical changes throughout their reproductive years during which they

exhibit higher prevalence rates of airway hyperresponsiveness than men, with tobacco exposure being implicated in women and atopy more often in men.¹⁵³ In terms of public health implications, this hyperresponsiveness is believed to extend to other environmental exposures as well. Late-onset asthma is largely confined to women, usually starting around the period of menopause, with the risk increased by hormone replacement therapy.^{154,155}

Mental health

Epidemiologic studies have found that major depression, seasonal affective disorder, suicide attempts, eating disorders, phobias, generalized anxiety and panic disorder, and somatization are more prevalent in women, while substance use disorders, antisocial personality disorder, learning disabilities, and conduct disorder are more common in men.¹⁵⁶ An interaction of biological and psychosocial factors is believed to explain the differing rates of mental disorders between men and women across the lifespan.

Mood disorders. With the exception of bipolar disorder, women exhibit greater prevalence of all mood disorders compared with men. Depression is about twice as common in women as in men.^{157,158} This gender difference emerges around the time of puberty and persists through the childbearing years. After midlife, the gender gap decreases and is not evident in the elderly. Reproductive events and hormonal factors, psychosocial factors, abusive relationships, poverty, single parenthood, and a lack of control over one's fate are important risks faced disproportionately by women.¹⁵⁹ Despite differential prevalence rates of major depression for men and women, findings do not support a different process in outcome of illness for men and women.¹⁶⁰

Women often present with atypical depressive symptoms and comorbid disorders that can complicate both diagnosis and treatment. Women are more likely to present with reversed vegetative signs (increased appetite, weight gain, more anxiety and somatic symptoms).¹⁶¹ Anxiety disorders and eating disorders are most frequently comorbid with depression in women, whereas alcohol and substance abuse and dependence are more common in depressed men. Women may respond more poorly than men to tricyclic antidepressants, and more favorably to selective serotonin reuptake inhibitors and monoamine oxidase inhibitors.¹⁶¹ It is not established whether men and women respond differently to different types of psychotherapy, or to different combinations of somatic and psychosocial treatments, or to the gender of the psychotherapist.

While bipolar illness affects roughly equal numbers of women and men, its manifestations differ in women. Women suffer more often from rapid cycling (threefold), and possibly more often from mixed mania and more depressive episodes.¹⁶²

Anxiety disorders. Anxiety disorders including panic disorder, obsessive-compulsive disorder, post-traumatic stress disorder (PTSD), social phobia, and generalized anxiety disorder affect more than 19 million American adults aged 18 to 54 in a given year. Women outnumber men in each illness category except for obsessive-compulsive disorder, in which both sexes have an equal likelihood of being affected. Not only are women more likely to have panic with concurrent agoraphobia, but they are more likely than men to suffer a recurrence of panic symptoms after remission of panic.¹⁶³ Women are 2 to 3 times more likely to develop PTSD after trauma than males and to have persistent symptoms.¹⁶⁴

Eating disorders. The vast majority of people with eating disorders in the United States are adolescent and young adult women. In addition to causing various physical health problems, eating disorders are

associated with illnesses such as depression, substance abuse, and anxiety—especially obsessive-compulsive disorder. Eating disorders, including anorexia and bulimia, are about 10 times as common in women as in men. Among adolescent and young adult US women, it is estimated that between 0.5 percent and 1 percent suffer from anorexia nervosa, 1 percent to 3 percent have bulimia nervosa, and 0.7 percent to 4 percent experience binge-eating disorder.

Psychotic disorders. Schizophrenia is the most chronic and disabling of the mental disorders, with psychotic symptoms first appearing in the late teens or early twenties. Although men and women alike are affected, there are differences in the age of onset, pattern of symptoms, and treatment responses; brain structural differences also have been noted. Women experience their disease later and have significantly higher (premorbid) psychosocial function.^{165,166} Women experience more depressive symptoms, paranoia, and auditory hallucinations than men and tend to respond better to typical antipsychotic medications. During initial episodes, treatment response occurs earlier in women, characterized by a higher remission rate with smaller doses of a neuroleptic. Thus, women may benefit from a lower dose of neuroleptic over a shorter time period and from more aggressive psychosocial treatment.¹⁶⁷

Alzheimer's disease. The main risk factor for developing Alzheimer's disease (AD) is increased age. Epidemiological studies show that while the number of new cases of AD is similar in older adult women and men, the total number of existing cases in a given time period is somewhat higher among women than men. Caregivers of a person with AD are usually family members—either spouses or children—and are preponderantly wives and daughters. The chronic stress associated with the caregiving role contributes to mental health problems. Also, women with AD are older and less likely than men with AD to have a spouse who can serve as caregiver.

Menopause

Menopause is considered to have occurred after 12 months of amenorrhea resulting from the permanent cessation of ovarian function. The mean age at menopause is 51 years. The perimenopause, a time of changing ovarian function, precedes the final menses by several years. The loss of estrogens can lead to vasomotor symptoms, sleep disturbances, mood alteration, depression, urinary tract and vaginal atrophy, and increased health risks for several chronic disorders, including osteoporosis and cardiovascular disease.

Osteoporosis. Approximately one in 10 people in the United States is affected by this systemic skeletal disorder, which is characterized by low bone mass and structural deterioration of bone with resultant increases in bone fragility and fracture risk; 75 percent to 80 percent of affected individuals are women. Major predictors independent of bone density are personal or family history of fracture as an adult, cigarette smoking, and low body weight; white and Asian women are at greater risk than blacks. Adequate calcium intake and regular weight-bearing exercise are important preventive measures across the lifespan. The lifetime risk of osteoporotic fractures is approximately three-times higher in women than in men, but fractures attributable to osteoporosis also occur in the latter. Because the disease is asymptomatic until fracture occurs, efforts should be directed toward prevention of bone loss and early detection of low bone mineral density.

Perhaps the most serious consequence of osteoporosis is hip fracture, which leads to a 10 percent to 20 percent excess mortality within one year; 25 percent of individuals with hip fracture will require

long-term nursing care. Vertebral fractures also cause significant complications including back pain, height loss, and kyphosis. Pharmacological options to prevent and treat osteoporosis in women are estrogen (ERT) or estrogen plus progestin (HRT) replacement therapy; selective estrogen receptor modifiers (SERM) such as raloxifene; bisphosphonates such as alendronate; and calcitonin. In men at risk for fragility fractures, alendronate and calcitonin appear to produce responses similar to those in women.

ERT/HRT. Data from many observational studies and some clinical trials show that estrogen reduces the risk of hip fractures by about 30 percent and of spine fractures by about 50 percent with five years of use, and reduces all fractures by 50 percent to 75 percent with 10 or more years of use.¹⁶⁸ Even so, nearly 20 percent of women who take estrogen continuously after menopause experience a nontraumatic, nonvertebral fracture. Estrogen begun after age 60 years may offer nearly equal benefits.¹⁶⁹ If estrogen therapy is discontinued, within five to 10 years bone density and fracture risk are similar to those of women who never used ERT.

The use of ERT and HRT has been associated with improved cardiovascular risk factors and surrogate end points (eg, decreased total- and LDL-cholesterol; increased HDL-cholesterol; decreased lipoprotein A and fibrinogen) in postmenopausal women.¹⁷⁰ Epidemiological studies in women free of CHD suggest that HRT exerts cardioprotective effects and reduces overall mortality of postmenopausal women.¹⁷¹ Selection bias may overestimate estrogen's cardioprotective effect in these studies, although dose-response data support a real effect.^{170,172,173} However, data from the only large-scale randomized double-blind, placebo-controlled trial in women with existing CHD do not support a conclusion that HRT prevents the progression or recurrence of cardiovascular disease.¹⁷⁴

Estrogen therapy clearly increases risk for endometrial hyperplasia and cancer (10-fold if unprotected with concomitant progestin therapy), and doubles the risk of deep venous and pulmonary thromboembolism and gallbladder disease necessitating cholecystectomy.¹⁷⁵⁻¹⁷⁷ Long-term use also increases the risk of breast cancer. In women with over 5 years of use (median 11 years) the relative risk is approximately 1.35.^{178,179} Although the increased relative risk is significant, the excess number affected is relatively small in women 50 to 70 years of age who begin estrogen use. Absolute risk calculations show small increments in deaths attributable to breast cancer balanced by reductions in cardiovascular events.¹⁸⁰

Nevertheless, HRT is not widely used and once initiated suffers from poor compliance. Contributing to the reluctance to begin HRT is the availability of other drugs for primary and secondary prevention of CHD, especially lipid-lowering drugs. HMG-CoA reductase inhibitors ("statins") may offer the additional benefit of increased bone density. Only randomized clinical trials can confirm the direct benefit of ERT/HRT for protecting women from CHD. Ongoing trials that will help clarify the issue are the Women's Health Initiative (WHI) and the Women's International Study of Long Duration Estrogen After Menopause (WISDOM).

Other treatments. Alendronate and risendronate increase bone density by 5 percent to 10 percent and reduce the incidence of fracture at the spine, hip, and wrist by 50 percent in patients with osteoporosis. Alendronate is also approved to treat glucocorticoid-induced osteoporosis in men and women. No other treatments have been investigated nor labeled for the treatment of osteoporosis in men. Alendronate also prevents bone loss in early postmenopausal women.¹⁸¹

Raloxifene, which is a "selective estrogen receptor modifier" has antiestrogenic effects on breast and endometrial tissue and estrogenic effects on bone, lipid metabolism, and blood clotting. It reduces risk of vertebral fractures by 40percent to 50percent, but increases the risk of venous thromboembolism and does not relieve common menopausal symptoms.^{182,183} Raloxifene decreases LDL-cholesterol, but exerts little or no effect on HDL cholesterol and may not decrease lipoprotein A. In contrast to ERT, raloxifene does not increase the risk of endometrial cancer among postmenopausal women with osteoporosis, and the risk of invasive breast cancer is decreased. Tamoxifen has estrogen-like effects on the skeleton (about 70percent that of HRT) and lipid concentrations and exerts antiestrogen effects on the breast. However, tamoxifen users have an increased risk of endometrial cancer and thromboembolism, and the drug does not relieve menopausal symptoms in a majority of women. Calcitonin, administered as a nasal spray is somewhat less effective than alendronate and HRT in reducing vertebral fractures, and may not significantly reduce the incidence of hip fractures.

Urologic and kidney diseases

Diseases of the kidney and urinary system significantly impact women's health. Although women comprise a smaller proportion of the dialysis population and generally experience a less rapid deterioration than men, end-stage renal failure affects more than 120,000 US women.^{184,185}

Urinary tract infections (UTI). Asymptomatic bacteriuria occurs in 3 percent to 8 percent of premenopausal women, more commonly if the patient is diabetic. In adults, women are 30 times more likely than men to develop UTI. Women who are sexually active and use a diaphragm and spermicide for contraception are at increased risk. Urinary tract infections affect approximately 25 percent of women between the ages of 20 and 40. Twenty percent of these women will suffer at least three recurrences within a year as a result of reinfection from the colonized perineum or introitus. Pregnancy and the postmenopausal period are also associated with an increased risk of UTIs. Bacteriuria in men is rare until the fourth or fifth decade when prostatic diseases increase the risk of infection and the incidence of UTI in men approaches that in women.

Interstitial cystitis. This chronic syndrome has an unknown etiology and is characterized by regional or localized bladder/pelvic pain and irritative voiding symptoms without evidence of infection; symptoms can significantly affect quality of life in many patients.¹⁸⁶ More than 90 percent of affected individuals are women. Prevalence estimates range from 37 to 67 per 100,000 individuals.¹⁸⁷ Lack of objective diagnostic criteria and variability in symptoms, objective findings, and treatment outcomes have impeded characterization.¹⁸⁸ Importantly, there is often a significant delay in establishing the diagnosis and multiple physicians may be consulted in the process. Many symptomatic treatments have been used, but based on the chronicity of the disease they do not significantly relieve symptoms over time in many patients.¹⁸⁸

Urinary incontinence (UI). Incontinence affects approximately 13 million Americans, with the highest prevalence in the elderly in both community and institutional settings. Although UI is usually regarded as a condition affecting older women, it also occurs in 10 percent of young, nulliparous women, particularly during physical activity.¹⁸⁹ For noninstitutionalized persons older than 60 years of age, the prevalence of UI ranges from 15 percent to 35 percent, with women having twice the prevalence of men. The prevalence may be even higher in institutionalized individuals.

Bladder contractility, capacity, and the ability to postpone voiding declines with age in both sexes, and maximal urethral closure pressure and length probably decline with age in women.¹⁹⁰ In men, overflow incontinence and detrusor instability predominate, and stress incontinence usually occurs only in association with prostate surgery.¹⁹¹ Appropriate management can reduce the morbidity and cost of UI, particularly in institutionalized populations. Although the incidence of incontinence increases significantly with age, negative effects on the quality of life can be substantial across all age groups.

Summary and comment

Sex- and gender-based differences exist in the epidemiology, diagnosis, and treatment of many diseases. The health care needs of women cannot be explained solely in relation to reproductive function or other conditions that are unique to women. A variety of other diseases that are more prevalent in women or that manifest differently in women than in men also need attention. Health status, preferences for care, variations in health care utilization and financing, and the evidence-base that supports clinical decision-making need to be considered in addressing women's health issues.

Increased attention should be devoted to reduction in preventable risk factors for chronic disease such as tobacco, alcohol, and other drug use, which in women are increasing rather than decreasing. Increased attention on the part of both physicians and patients to modifiable risk factors for cardiovascular disease remains important given its predominant contribution to morbidity and mortality in older women. The treatment of menopause with respect to the risks and benefits of HRT, including prevention of cardiovascular disease and osteoporosis, requires clarification. Ongoing trials are expected to supply the evidence base to inform clinical decisions. Until these trials are completed, the use of HRT should be individualized on the basis of quality of life considerations and a personal risk assessment with consideration of risk factors for cardiovascular disease, osteoporosis, and cancer. Sex differences in pharmacologic responses and information on the genetic risks for disease also promise to become increasingly important.

Recommendations (adopted AMA policy and directives)

The following statements, recommended by the Council on Scientific Affairs, were adopted by the AMA House of Delegates as AMA policy at the 2000 AMA Interim Meeting:

1. The AMA supports the recent trend of increased research on women's health and participation of women in clinical trials, the results of which will permit development of evidence-based prevention and treatment strategies for all women from diverse cultural and ethnic groups, geographic locations, and socioeconomic status.
2. The AMA recommends that all medical/scientific journal editors require, where appropriate, a sex-based analysis of data, even if such comparisons are negative.

The following statements, recommended by the Council on Scientific Affairs, were adopted as directives at the 2000 AMA Interim Meeting:

1. The AMA commends the various federal agencies and medical association and women's health organizations that are providing valuable and credible physician/patient education on sex- and gender-based differences in health and disease.

2. The AMA encourages the Women Physicians Congress in its efforts to serve as a clearinghouse for organization resources and related information on sex- and gender-based differences in health and disease, including the use of various forums, such as the AMA Web site and Medem, to provide comprehensive and timely physician education resources on sex- and gender-based differences in health and disease.
3. The AMA will widely distribute this report to the Federation of Medicine, Association of American Medical Colleges, women's health organizations, and other relevant groups.

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