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GERIATRIC GYNECOLOGY

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Gynecologists play three roles in the health care of women aged 65 and over: surgeon, consultant and therapist for gynecologic disorders, and provider of primary and preventive health care. The research reviewed here addresses topics related to one or more of these roles. Our review indicates that, as the population ages, our astounding lack of knowledge about caring for elderly women in these three contexts must be addressed.

METHODS

The MEDLINE database was searched via PubMed. The period covered was from 1990 to March 21, 2001. The search was limited to English language and human subjects. The search strategy combined the MeSH terms for gynecologic surgical procedures, hormone replacement therapy, cervical cancer and cervical cancer screening, breast cancer and breast cancer screening, ovarian cancers and ovarian cancer screening, pelvic organ prolapse, and postmenopausal osteoporosis with terms for age factors, risk factors, perioperative care, perioperative complications (including the specific terms *delirium, decubitus ulcer, pneumonia,* and *cerebrovascular accident*), comorbidity, outcome, quality of life, prognosis, recovery, length of stay, functional status, resuscitation status, and discharge planning. In all, 9522 items were retrieved.

The search was then narrowed to 1638 by requiring that the term *age factors* or variants of the word *age* be included in the title. During the time from March 2001 until this monograph was completed, striking studies from the Women's Health Initiative with unexpected results were published about hormone replacement therapy. Therefore, sections about hormone replacement were updated to include the more recent information.

PERIOPERATIVE MANAGEMENT FOR GYNECOLOGIC SURGERY

Topics and research questions regarding general perioperative management of elderly patients are addressed in the chapter on cross-cutting issues (see Chapter 13). For this chapter, studies focused on gynecologic surgery were sought to determine the current state of knowledge and to identify gaps that suggest the best direction of future research.

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QUALITY OF DATA

Few studies have been published about gynecologic surgery in elderly women. In the published studies, many common geriatric complications were not recognized or sought by the investigators. For instance, none of the case series, retrospective reviews, or case-control studies noted delirium, falls, or electrolyte imbalance. These occur commonly in hospitalized elderly patients, and it is unlikely that they were completely absent in the populations described. Furthermore, all studies on the topic of gynecologic surgery generally were retrospective chart reviews, and undoubtedly geriatric complications were not well documented and therefore were not obtainable. Finally, no studies that evaluated functional or quality-of-life outcomes in older women were found.

Studies were found regarding the incidence and prevalence in older populations of hysterectomy, [1–3] the prevalence in older women of surgery for pelvic organ prolapse (POP), [4] complications in elderly women of gynecologic surgery (including benign and malignant diseases), [5–11] and preoperative evaluation of risk factors for cardiac complications in older women. [12] No studies involved institutionalized elderly persons.

RESULTS

Epidemiology

Annually from 1988 to 1990, 4 per 1000 women aged 65 to 74 and 2 per 1000 aged 75 and over underwent hysterectomy in the United States; [2] similar rates were reported in Finland. [9] In one state, the cumulative probability of a woman's having undergone a hysterectomy was 33% by age 55 and 43% by age 85. [1] Most hysterectomies in older women were found to have been done for POP, followed by malignant disease; roughly one third of all hysterectomies fell in each category. [1,2] Bilateral salpingo-oophorectomy was performed in 87% of abdominal and 7% of vaginal hysterectomies. [2] A woman has a 10% to 11% cumulative risk to age 80 of undergoing surgery for urinary incontinence or POP. [4,13]

Morbidity and Mortality

In Finland, age was associated with mortality in 300,000 hysterectomies, not controlling for comorbidities. [9] Six-week mortality ranged from 3 per 10,000 in the age group 40 to 50 years to 209 per 10,000 in those aged 80 and over. Sixty-three percent of deaths were due primarily to cancer, and 27% to cardiovascular events. In 66,478 Medicare patients undergoing continence procedures, the 30-day mortality was 0.33%. [5] Mortality increased linearly with age, from 0.2% at age 65 to 74 to 1.6% in those aged 85 and over. Age-specific mortality rates were not adjusted for comorbid conditions. Groups of patients who died had higher rates of diabetes mellitus and heart failure. Age was not found to be associated with morbidity and mortality in other studies of gynecologic surgery, [11] POP surgery, [7] and gynecologic oncologic surgery. [10] The only prospective morbidity study included all major noncardiac surgical procedures in women aged 50 or over. [8] This study found age to be significantly associated with a greater incidence of cardiogenic pulmonary edema, myocardial infarction, ventricular arrhythmia, bacterial pneumonia, respiratory failure, and in-hospital mortality. Older patients were not found to be more likely than younger ones to experience neuropathy after dorsal lithotomy positioning. [6] A retrospec-

tive review of postoperative fever evaluations found that older age increases the likelihood that the chest x-ray would "be positive" (definition not given). [14]

In a retrospective analysis of 406 women undergoing elective vaginal surgery, cardiac morbidity was found to have occurred only among postmenopausal women. [12] The four congestive heart failures, one unstable angina, one unstable arrhythmia, and two deaths (apparently secondary to myocardial infarction) were not predicted by either the Goldman Cardiac Risk Index or the New York Heart Association functional classification of heart disease. Only hypertension and ischemic heart disease were found to be risk factors.

SUMMARY

Few studies have examined outcomes of gynecologic surgery in elderly women, and these have not evaluated typical geriatric complications. No studies have evaluated functional outcomes, and few have evaluated intermediate- or long-term quality-of-life changes. Mortality risks with gynecologic surgery are low and most commonly are due to cardiac or cancer complications.

Gyn 1 (Level B): **Prospective observational studies should be undertaken to discover the magnitude and severity of common geriatric perioperative complications of gynecologic surgery, eg, delirium, electrolyte imbalance, falls, deconditioning, urinary incontinence, functional loss, and discharge to rehabilitation or long-term-care facilities.**

Gyn 2 (Level B): **Observational studies are needed to establish the risk factors for geriatric perioperative complications of gynecologic surgery, eg, delirium, electrolyte imbalance, falls, deconditioning, urinary incontinence, functional loss, and discharge to rehabilitation or long-term-care facilities.**

Gyn 3 (Level B): **All gynecologic surgery studies that evaluate or describe outcomes, morbidity, or mortality should describe comorbidities, functional status, cognitive status, and estrogen status of elderly women participants.**

Gyn 4 (Level B): **The results from existing and future gynecologic surgery studies should be stratified by age, even when statistical power is low, to facilitate systematic reviews of gynecologic surgery outcomes.**

Gyn 5 (Level B): **Prospective observational studies are needed to compare the quality-of-life and functional outcomes of surgical and nonsurgical management of gynecologic conditions.**

Gyn 6 (Level A): **Randomized controlled trials are needed to determine which interventions in elderly women are effective in reducing geriatric surgical risks, eg, delirium, electrolyte imbalance, falls, deconditioning, urinary incontinence, functional loss, and discharge to rehabilitation or long-term-care facilities.**

Gyn 7 (Level A): **Randomized controlled trials are needed to determine whether pre- and postoperative local estrogen therapy improves surgical outcomes in a variety of gynecologic conditions.**

Gyn 8 (Level A): **Randomized controlled trials are needed to determine whether discontinuation of estrogen replacement therapy improves perioperative morbidity in elderly women.**

Gyn 9 (Level D): **Observational studies are needed to compare quality-of-life outcomes of different surgical techniques for gynecologic conditions, eg, urinary incontinence and pelvic organ prolapse.**

Gyn 10 (Level D): **Observational studies should be performed to determine patient and condition characteristics that are associated with improvement in quality of life after surgical treatment.**

Gyn 11 (Level D): **Guidelines for selecting candidates for gynecologic surgery from among older institutionalized populations on the basis of quality-of-life benefits should be prepared and validated.**

Gyn 12 (Level D): **As medical care changes and improves, descriptive observational studies should be performed to compare the risks of gynecologic surgery that are associated with age alone and those that are associated with comorbidities.**

UROGENITAL HEALTH

Gynecologists treat both anatomic and functional aspects of urogenital health and health maintenance. Certain well-known age-related changes are secondary to estrogen deficiency and are easily treated with estrogen replacement. However, age-related functional changes are heterogeneous, and many questions remain about their causes and therapy. We address the research in POP, vulvovaginal conditions, urinary incontinence, and sexual health.

PELVIC ORGAN PROLAPSE

The surgical and nonsurgical management of POP together constitute a substantial portion of gynecologic care for older women. The exact prevalence and natural history of POP are unknown. It is the most common reason for gynecologic surgery in women aged 65 and over. Surgical repair usually consists of full vaginal reconstruction. However, vaginal obliteration with the Le Fort colpocleisis is still a useful alternative to major surgery for some frail elderly women. There is also a resurgence in conservative therapy using pessaries, as the older population grows and the imperfection of long-term surgical results becomes more evident.

Quality of Data

Epidemiology. Data regarding the prevalence of POP requiring surgery are included in the section, above, on gynecologic surgery. Prevalence data for POP apart from surgical correction are few. One descriptive study using routine gynecologic care patients included 66

women aged 60 to 82. [15] One paper retrospectively reviewed admissions to a long-term-care facility. [16] Risk factors for POP that requires surgery were evaluated in a case-control study; [17] the risk factors for symptomatic pelvic floor dysfunction (including POP) were evaluated in a study using population-based cross-sectional interview data; [13] and risk factors for urinary incontinence or POP that requires surgery were assessed through a Kaiser Permanente database review. [4]

Complications. Hydronephrosis as a complication of POP has been reported in two retrospective case series. [18,19] No studies were found about other well-known complications, abrasions, or urinary retention due to a large cystocele.

Nonsurgical Management. We found no data on the natural history of POP. Articles about pessaries are based mostly on expert opinion, and some are case reports. One retrospective chart review reported indications, continuation, and complications. [20]

Surgical Management. A retrospective chart review evaluated age and voiding function following POP surgery. [21] One small prospective randomized study evaluated the effect of local estrogen prior to reconstructive vaginal surgery. [22] A case series compared the Le Fort procedure in medically compromised women to pelvic reconstruction in healthier women. [23] Some case series described major comorbidities, postoperative complications, and outcomes, [24,25] including one of POP repair under local anesthesia. [26] Several case series describing technique and results included younger and older women but rarely stratified them by age, and these studies are therefore not reviewed here.

Results

Epidemiology. In one study of older patients receiving routine gynecologic care, 50% to 60% were found to have stage II POP; stage III prolapse was present in 9% of the women aged 60 to 69 and 21% of the women aged 70 and over. [15] A review of long-term-care facility admissions found 25% of the women to have POP, 11% of which was beyond the introitus. [16] Age was found to be an independent risk factor for symptomatic pelvic floor dysfunction (including POP) in a large Australian household survey. [13] A Kaiser database study also found age to be an independent risk factor for pelvic floor surgery. [4] The effect of age was not evaluated in a case-control study of women aged 34 to 75. [17] Other risk factors that have been identified are parity, [4,13,17] body mass index, [4,13] and chronic lung disease or coughing. [4,13] Forceps delivery was found to be a risk factor in an epidemiologic survey, [13] but not a case-control study. [17] There was no difference in POP prevalence with a history of cesarean section or of nonoperative vaginal delivery, [13,17] once the number of vaginal deliveries was controlled for. [17] It must be noted that these studies evaluated the range of younger and older women. No studies evaluated the risk factors just for the older women.

Complications. In one study, 11% of 189 women undergoing POP surgery were found to have mild hydronephrosis and 4% had severe hydronephrosis. [18] Women with hydronephrosis were older (mean age 68 $\pm$ 10) than those without (mean age 61 $\pm$ 11). However, in multivariable logistic regression, only uterine (rather than anterior vaginal wall) prolapse was found to be statistically associated with hydronephrosis. Age was not associated. Among 323 POP surgical patients at the Cleveland Clinic who had preoperative imaging, 8% were found to have had hydronephrosis—4% mild, 3% moderate, and

1% severe. [19] Mean age was 75 in women with and 67 in women without hydronephrosis ($P < .001$). Uterine prolapse was more strongly associated than vaginal vault prolapse with hydronephrosis, even after adjusting for age and degree of prolapse. The two patients with renal insufficiency both had complete procidentia.

Nonsurgical Management. No studies compared types of pessaries. In a case series that preferentially placed Gellhorn pessaries, 96 of 101 women used a Gellhorn. [20] Of five women who could not retain a Gellhorn because of poor perineal support, four used a ring pessary and one a cube. Of 50 patients who continued pessary use 2 months to 5 years, 45 removed and reinserted the pessaries themselves. Forty percent discontinued pessary use because of inadequate symptom relief or inconvenience, but the authors did not further quantify this.

Surgical Management. A retrospective review of 23 women undergoing POP surgery did not find age to correlate with duration of catheterization (independently of estrogen status). [21] Among 43 women who underwent prolapse repair, preoperative vaginal estradiol, compared with placebo, was not found to influence the 3-year relapse rate, although bacteriuria was lower in the immediate postoperative period. [22] Twenty-one medically compromised women who underwent Le Fort procedures, mean age 82 years, and 42 women who had vaginal reconstruction, mean age 67, had a similar number of postoperative complications, including one cardiac arrhythmia and three urinary tract infections in each group. [23] Both groups had 90% to 95% long-term success. In a series of 33 women treated with colpocleises, mean age 78, postoperative complications included congestive heart failure (2) and pneumonia (1). [24] One woman required a second repair. Postoperative complications occurred in 29% of 38 women in another Le Fort procedure case series, including cardiac (11%), respiratory (5%), and urinary (13%) complications. [25] Local anesthesia was used successfully for vaginal POP repair in 20 women, mean age 80 years, including anterior and posterior colporrhaphy, enterocele repair, and Le Fort colpocleisis. [26] The only major complication was venous thrombosis. Pyometra followed a re-do Le Fort colpocleisis in a 92-year-old woman. [27]

Summary

Few data exist on the incidence of or risk factors for POP, with the exception of cases that undergo surgery. The benefit of estrogen prior to POP repair, if any, is unknown. Older age, parity, and operative vaginal delivery are risk factors for POP surgery. The risks of pregnancy alone, regardless of route of delivery, or of the number of vaginal deliveries are not clear. In women with POP, age may be a risk factor for the development of hydronephrosis, but uterine procidentia confers the most risk. Pessary management is virtually all by clinical experience, usually passed on by tradition or invented by individual physicians.

Gyn 13 (Level B): **Observational studies are needed to define long-term quality-of-life outcomes of nonoperative management of pelvic organ prolapse.**

Gyn 14 (Level B): **Observational studies are needed to define long-term quality-of-life outcomes of operative management of pelvic organ prolapse.**

Gyn 15 (Level B): **Observational studies are needed to determine the patient factors, device factors, and management factors that are associated with successful long-term pessary use.**

Gyn 16 (Level B): **Pessaries (or other devices) should be developed for use in conservative management of pelvic organ prolapse in women with poor introital support and in whom currently available pessaries are not retained.**

Gyn 17 (Level B): **Basic science and clinical studies should be performed to delineate the pathophysiology of pelvic organ prolapse, particularly the way that genetic tissue factors confer risk.**

Gyn 18 (Level B): **Therapies to retard the progression of pelvic organ prolapse by targeting the pathophysiologic tissue factors should be developed.**

Gyn 19 (Level B): **Long-term observational studies are needed to determine the relative contributions of routes of delivery (cesarean section, operative vaginal, spontaneous vaginal) to the development of pelvic organ prolapse.**

Gyn 20 (Level B): **Observational studies are needed to determine the condition-specific functional impact of surgery for incontinence and pelvic organ prolapse in elderly women, including sexual function.**

Gyn 21 (Level A): **Long-term randomized controlled trials are needed to determine whether estrogen use, local or systemic, confers benefit or risk for the progression of pelvic organ prolapse.**

Gyn 22 (Level A): **Randomized controlled trials are needed to determine whether pre- and postoperative local estrogen therapy improves outcomes of pelvic organ prolapse surgery.**

Gyn 23 (Level A): **Long-term randomized controlled trials are needed to determine whether selective estrogen receptor modulator use confers benefit or risk for the progression of pelvic organ prolapse.**

Gyn 24 (Level C): **Randomized controlled trials should be performed to determine whether pessary use in early stages of pelvic organ prolapse retards progression.**

Gyn 25 (Levels D, C): **Long-term observational trials are needed to obtain indications as to whether pelvic floor muscle exercises retard the progression of pelvic organ prolapse; subsequently, these hypotheses need to be tested through randomized controlled trials.**

Gyn 26 (Level D): **Longitudinal observational studies are needed to define the natural history of untreated pelvic organ prolapse.**

Gyn 27 (Level D): **Observational studies are needed to determine the incidence of hydronephrosis in pelvic organ prolapse.**

Gyn 28 (Level D): **Observational studies are needed to determine modifiable risk factors for pelvic organ prolapse other than childbirth.**

VULVOVAGINAL CONDITIONS

The nature of atrophic postmenopausal vulvovaginal changes is reasonably well established, but the contributions to these changes of aging, factors common in aging, and hypoestrinism are unclear. The pathophysiology of vaginal and, to a lesser extent, vulvar disorders is a unique combination of hormonal, dermatologic, microbiologic, structural supportive, environmental, neurologic, and psychologic factors. Vulvar pathophysiology is primarily dermatologic, with strong environmental influences and less well understood hormonal components.

The lower vagina, vulva, urethra, and bladder trigone have a common embryologic origin, the urogenital sinus, and are estrogen-responsive tissues. Dermatologic symptoms, vaginal discharge, dyspareunia, irritative voiding symptoms, and urinary tract infections may all be a consequence of prolonged hypoestrinism. Data regarding the prevalence of symptomatic vulvovaginal changes with aging are divergent and difficult to obtain without the inclusion of urologic symptoms such as dysuria, frequency, urgency, and urge incontinence.

Unclear factors associated with aging, hypoestrinism, or local environment increase vulvar susceptibility to dermatologic disorders, including lichen sclerosus, squamous hyperplasia, and neoplasia.

Quality of Studies

Relevant studies of urogenital symptoms include community-based observational surveys [28–32] and a case series of menopause clinic visits. [33] A meta-analysis summarized estrogen therapy trials, [34] an uncontrolled trial evaluated estrogen therapy, [35] and an observational study reported associations with sexual activity. [36] Vulvar cancer data are taken from a population-based study and case series. [37–39] Review articles and one randomized controlled trial are cited regarding vulvar dermatoses and neoplasia. [40–43]

Results

Two large surveys gathered data through personal interviews. [28,29] In one, urogenital symptoms were found to be prevalent in 30% of 3000 European women aged 55 to 75. [29] Eleven percent were found to have vaginal itch or burning, of whom 41% had a moderate problem and 17% a severe one. Of women aged 65 to 74, 9% reported having urinary frequency, 6% urinary incontinence, and 4% vaginal burning or itch. Of 2045 British women aged 55 to over 85 years interviewed in their homes, 49% reported having urogenital symptoms some time since menopause, and 31% within the past 2 years. [28] Vaginal itching occurred in 11%, vaginal dryness in 8%, dyspareunia in 2%, and irritative voiding symptoms in 16%. Only 27% were sexually active. Of 900 61-year-old Swedish questionnaire respondents, 38% reported vaginal dryness and dyspareunia, and 15% reported itch, discharge, and "smarting" pain. [32] Among 850 randomly selected postmenopausal Dutch women, 23% reported vaginal itching and 16% dyspareunia. [31] Clinically assessed vulvovaginal atrophy was evident in 34% of women evaluated in a menopause clinic. [33] Approximately 25% of the sexually active women had dyspareunia secondary to vulvovaginal pain.

A meta-analysis of 10 randomized controlled trials and 68 other relevant articles concerning older women, mean ages ranging from 54 to 72, showed that estrogen relieves

urogenital atrophy symptoms, including vaginal dryness, itching, burning, and discharge; dyspareunia; urinary frequency; nocturia; urgency; dysuria; and recurrent urinary tract infections. [34] All administration routes were found to be effective. Intramuscular estrogen has been found to improve irritative voiding symptoms, as well as urge incontinence, in 84% to 94% of 24 postmenopausal women, mean age 70. [35] A cross-sectional analysis of women with a mean age of 57 found fewer symptoms and less vaginal atrophy in those who continued regular sexual activity through menopause than in those who did not. [36]

The incidence of vulvar dermatoses is unknown. [41,44] Lichen sclerosus may affect all age groups, but it seems to occur most commonly at times of low sex hormone output, in both the pediatric and postmenopausal ages. [44] Incidence is highest in the fifth and sixth decades in women. The incidence among dermatology referrals ranges from 1 in 300 to 1 in 1000, but the condition is more commonly seen by gynecologists who care for postmenopausal women. Squamous cell cancer occurs in 4% to 5% of known cases, but the contribution of lichen sclerosus to neoplasia is unknown. [44] Topical testosterone and progesterone are time-honored therapies, but their effectiveness may be no better than that of the carrier used without the steroid. [42] Topical petrolatum alone has been found to relieve symptoms in 75% of patients aged 35 to 83. [45] High- and medium-potency topical corticosteroids are the treatments of choice. [44]

The incidence of vulvar cancer rises sharply at age 60 until at least the ninth decade, reaching 0.02 to 0.03 in the ninth decade, [37,38] although melanoma may peak in the seventh decade. [39]

Summary

Most urogenital symptoms are related to hypoestrinism and are reversed with estrogen therapy. Symptoms are multifactorial, relating also to urinary tract dysfunction, microbial influences, dermatoses, and local environment. Aging-specific symptoms apart from endocrine failure are unclear. The incidence of vulvar cancer and non-neoplastic dermatoses rises with age. Susceptibility factors are poorly understood. The contributions of endocrine failure to these disorders are unknown.

Gyn 29 (Level B): **Quality-of-life instruments targeting vulvovaginal symptoms need to be developed and validated.**

Gyn 30 (Level B): **Clinical studies, including studies of young castrates, are needed to determine the relative contributions of hypoestrinism, local environment, and aging to vulvovaginal symptoms.**

Gyn 31 (Levels B, A): **Observational studies (and eventually randomized controlled trials) should be performed to determine what degree of quality-of-life improvement in frail older women can be attained by detection and treatment of vulvovaginal disorders.**

Gyn 32 (Level A): **Randomized controlled trials are needed to determine the impact of long-term local estrogen replacement therapy on the incidence and prevalence of urogenital symptoms.**

Gyn 33 (Level A): **Randomized controlled trials are needed to determine the relative contributions of local estrogen and vehicle to improved urogenital symptoms.**

Gyn 34 (Level D): **Basic science and clinical investigations are needed to learn more about the causes of lichen sclerosus.**

Gyn 35 (Level D): **Basic science and clinical investigations are needed to learn more about the age-related factors that increase susceptibility to vulvar cancer.**

Gyn 36 (Level D): **Observational studies should be performed to determine the profiles of susceptibility to vulvar cancer.**

Gyn 37 (Level C): **Randomized trials are needed to determine whether topical immune modulators (eg, imiquimod) reduce the incidence of vulvar cancer in vulnerable individuals.**

Gyn 38 (Level D): **Observational studies are needed to determine the prevalence of untreated vulvovaginal symptoms in frail and institutionalized populations.**

URINARY INCONTINENCE

Urinary incontinence in elderly persons is covered in the chapter on geriatric urology (see Chapter 10).

SEXUALITY

Two areas are of interest in older women's sexuality: sexual function and sexual dysfunction. Continued sexual activity into advanced age has been well documented. The fact that no diagnostic codes exist for female sexual dysfunction except psychologic disorders and dyspareunia bespeaks our remarkable ignorance, but medical knowledge of the pathophysiology of female sexual dysfunction is slowly expanding. The study of sexual dysfunction in elderly women is probably even more complex than that in younger women because of numerous relevant health and medication interactions, because of longer and more complex relationship issues, and because insufficient information is available about norms of physical response, as well as about the effects of androgens and estrogens (other than for urogenital atrophy).

Quality of Studies

Several questionnaires of varying scope and quality have been reported about sexual function and dysfunction in aging and are summarized in recent articles. [29,46–50] Demographic data are limited by convenience samples and low survey response rates. Community-based surveys have also been done. [46,50] One questionnaire was obtained before and after a three-part instructional program. [51] Masters and Johnson's 1966 work remains the definitive study of physiologic age-related changes in the sexual response cycle. [52] Most sexual dysfunction studies concern only the treatment of atrophic vaginitis. [47,50]

Results

Sexuality remains an important part of many older women's lives. One survey found that 30% of women aged 80 to 102 were sexually active, [53] as have other population–based studies. [29] Nonintercourse intimate activities increase in importance for men and maintain

or increase in importance for women. [51] Many sexually "inactive" women continue to be interested in sexual relations and masturbation. [46,49,51] Advanced age is inversely associated with sexual activity in men but may not affect women when other factors, including partner status, are controlled for. [46] Heterosexual activity correlates with marital status [46,49] and is most often limited by lack of a partner or by male sexual dysfunction. [50,51] However, in one population survey, *satisfaction* with sexual activity or lack of activity was not found to correlate with marital status. [46] Age was associated with both activity and satisfaction in men but not in women. Specific medical conditions often but not invariably correlate with less activity or satisfaction, but overall health status is important uniformly. [46,47,49,50,54–56]

Age-related changes in the sexual response cycle, comparing pre- with postmenopausal women, include decreased skin flush, muscle tension, reaction time, secretions, vaginal lubrication and expansion, congestion, and number of contractions with orgasm. [52] Dyspareunia and decreased lubrication secondary to urogenital atrophy are the most common sexual dysfunction findings. [29,47,50,53,57] Urinary incontinence and POP also negatively impact sexual activity, [50] but not necessarily satisfaction. [58] However, little is known about specific disorders of desire, arousal, and orgasm in older women. Animal studies show that fibrosis of erectile tissue associated with cardiovascular disease may be linked with sexual arousal disorders in women, as has been found in men. [59,60] The sexual effects of a decline in androgens with age [61] or of hormone replacement therapy (HRT) [62] have not been evaluated in the geriatric age group.

Summary

Regular sexual activity of elderly women is often limited by lack of a partner. However, given the documented level of interest, it is likely that medicine could still make a positive impact on elderly women's sexual vitality and therefore on their sense of well-being. Research is sparse and needed in virtually every aspect of this field.

Gyn 39 (Level B): **Current investigations into the diverse causes of younger women's sexual dysfunction and its pathophysiology and management should be extended to include older women.**

Gyn 40 (Level B): **Observational studies are needed to determine the medication side effects that adversely affect specific aspects of sexual function in older women.**

Gyn 41 (Level B): **Observational studies are needed to define the adverse effects on older women's sexuality of specific medical conditions.**

Gyn 42 (Level B): **Dose-effect cohort studies of optimal dosage, frequency, and route of administration are needed to learn more about androgen replacement in elderly women.**

Gyn 43 (Level A): **Clinical trials are needed to determine the ability of androgen replacement in older women to enhance outcomes, including specific aspects of sexual function (eg, libido, orgasmic function).**

Gyn 44 (Level A): **Randomized controlled trials should be performed to determine whether oral estrogen replacement adversely affects**

sexual function in older women, presumably by decreasing free testosterone levels, and whether this is avoided by the use of transdermal estrogen.

Gyn 45 (Level D): **The emotional and physical components of the sexual response cycle in the older woman should be observed and defined in light of new and more sophisticated information about female sexuality.**

Gyn 46 (Level D): **Pilot studies should be performed to determine educational strategies for partners of cognitively impaired patients that enable them to deal with sexuality issues.**

Gyn 47 (Level C): **Clinical trials should be undertaken to improve the treatment of dyspareunia secondary to urogenital atrophy in women unable to use estrogen products.**

ROUTINE CARE OF THE WELL ELDERLY WOMAN

The benefits derived from routine gynecologic examination and subsequent care in both healthy and frail older women are unknown. Pelvic examination may prompt evaluation and treatment of several disorders, as well as provide an opportunity for cancer screening. However, little is known about the impact of gynecologic examination in specific populations, such as institutionalized, homebound, and frail older women. Does gynecologic evaluation lead to the detection and management of issues that impact quality of life that would otherwise be ignored or minimized by the community-dwelling patient? How can the additional costs to the primary care provider of routine gynecologic examination be adequately reimbursed? Essentially no studies answer these questions. This chapter summarizes the topics most reported in gynecologic care for the well older woman: cervical and breast cancer screening.

CERVICAL CANCER SCREENING

Cervical cancer screening with Papanicolaou (Pap) smears, initiated in 1943, has never been evaluated in a randomized controlled trial. However, the observational evidence is overwhelming that regular Pap smear screening reduces the incidence and mortality of invasive cervical cancer. The incidence of invasive cervical cancer is lower in women aged 65 and over, but mortality is higher, largely because stage at the time of diagnosis is more advanced. [63] Therefore, recommendations to discontinue screening in older age groups must be viewed with caution.

Quality of Studies

Epidemiology of Screening. Epidemiologic data regarding the prevalence of screening and of the incidence and prevalence of abnormalities in older women are obtained primarily from observational retrospective reviews of health databases, [64–71] cross-sectional and retrospective reviews, [70,72–79] and one prospective cohort study. [80] In addition, we found three screening intervention studies targeting or reporting on elderly women, [81–83] one

prospective cohort study within a randomized controlled trial to determine the positive predictive value (PPV) of Pap smears, [84] and one prospective cohort study to evaluate the effect of Pap smears on mortality. [85] Two studies evaluate the influence of HRT on Pap smear abnormalities, one of them a prospective cohort nested in a randomized clinical trial of HRT and cardiovascular disease, [84] and one, a retrospective case analysis. [69]

Screening Improvement. One survey and a quasi-experimental study evaluated interventions to increase screening in elderly women. [81,82] Screening improvement trials with low-income women aged 40 and over were also found: [83] Mexican American and black women aged 40 to 70 years, [86] Cambodian women aged 50 years and over, [87]and black American women aged 40 and over. [88]

Screening Cost-effectiveness. The cost-effectiveness of screening for cervical cancer was calculated in a decision analysis applied to hypothetical 65-year-old women [89] and by using a retrospective chart review in an urban municipal hospital. [90]

Consensus Recommendations. The recommendations of national organizations for cervical cancer screening in older women are based primarily on expert opinion. [91–94]

Results

Epidemiology of Screening. Age was found to be inversely associated with having had a Pap smear in a retrospective database analysis, [71] a cross-sectional survey, [79] and a prospective cohort study. [80] However, in another study, of economically disadvantaged women aged 50 and over, age was not found to be a correlate of having had cervical cancer screening. [95] In this group, income and access to a telephone were strong correlates of cervical cancer screening. Low rates of screening may also occur more often in some ethnic minorities, as well as among women with less education and a lower socioeconomic status. [67,70,71,75–77,79,80] In an analysis of data from the Iowa Behavioral Risk Factor Surveillance System (BRFSS) and Iowa's Surveillance, Epidemiology, and End Results (SEER) study, barriers to screening were found to include rurality and limitations in activities of daily living. [96]

In a retrospective review of 96 abnormal Pap smears and their outcomes in women aged 55 and older, the prevalence of atypical cells of undetermined significance (ASCUS) was found to be 2%, lower than the 4% to 6% found in younger women. [69] The likelihood of pathology was also found to be lower: about 15% low-grade squamous intraepithelial lesion in the older women but 25% to 33% in the younger women. However, about 5% of ASCUS smears resulted in a diagnosis of cancer, including cervical, endometrial, and ovarian. An observational study of 1542 women aged 65 and over found a 1.5% prevalence of abnormal Pap smears. [64] Seventy-five percent of the women had not had regular Pap smear screening, and 25% had never been screened. Age, race, prior screening, and gynecologic symptoms failed to predict Pap smear abnormality. Two studies have found an association between HRT and abnormal (ASCUS) Pap smears. [69,84] These studies do not clarify whether a more active squamocolumnar junction due to hormonal influences places a woman at greater risk for true abnormalities or artifactual abnormalities, or whether a more accessible transition zone allows improved screening.

In a prospective cohort study nested within the Heart and Estrogen/progestin Replacement Study (HERS) randomized controlled trial, the incidence of new cytologic abnormalities within 2 years of a normal Pap smear was 23 per 1000 woman-years, with a PPV

for dysplasia of 1%.[84] Centers for Disease Control and Prevention 1991–1998 data showed that the incidence of high-grade Pap smear abnormalities within 3 years of one normal Pap smear declined from 66 per 10,000 women aged 30 or younger to 10 per 10,000 women aged 65 or older.[97]

A review of cancer deaths in women in Australia aged 50 or over found that 70% could have been avoided by appropriate screening.[78] In the women aged 50 to 74, 67% had never been screened, and none of those aged 75 and over had had a Pap smear. A retrospective case analysis in 1989–1990 of 798 Scottish women with cervical intraepithelial neoplasia and cervical cancer found that the 26 aged 50 or over with microinvasive or invasive cancer had not been screened adequately.[72] Greater age was associated with a later stage at diagnosis of cancer [74,98] and a higher risk of death within 6 months of diagnosis [73] in cross-sectional epidemiologic studies using cancer registries. In women aged 21 to 96 years, each additional year of life conferred 3% increased odds of late-stage diagnosis.[74] Independent covariates were being unmarried and uninsured, but not race, education, income level, smoking status, medical comorbidity, or urban residence. In a Swedish population, the incidence of cervical cancer was only 3 per 100,000 among women aged 70 or over who had at least one normal Pap smear in the previous 10 years.[85]

Screening Improvement. Elderly black women improved their screening rates following a survey and when offered screening by a nurse practitioner.[81,82] Having lay health advisors interview low-income women was found to be effective "across age and insurance strata."[83] Other trials to improve screening rates included few elderly subjects.

Screening Cost-effectiveness. The cost per year of life saved in hypothetical 65-year-old women ranged from $2254 for triennial to $7345 for annual screening.[89] Triennial screening reduced cervical cancer mortality by 74%. It was calculated from a chart review that 100 Pap smears in low-income elderly women could save $5907 and 3.7 years of life.[90]

Consensus Recommendations. Consensus recommendations for frequency of Pap smears in older women vary from discontinuation after age 65[94] to continued screening until age 70[93,99] to no upper age limit.[91,92] The most commonly recommended screening interval is 3 years.

Posthysterectomy. Pap smears have little or no utility in women who have had a total hysterectomy (*corpus* and *cervix uteri*) for benign disease.[100,101] The American College of Obstetrics and Gynecology recommends "periodic" vaginal cuff Pap smears in women with any risk factors for cervical cancer or any endometrial, vaginal, or vulvar neoplasia.[91] Several factors speak for documenting at least one normal vaginal Pap smear in elderly women and possibly continuing "periodic" vaginal Pap smears:

- Most practitioners do not take a full past sexual history for older women.
- Data regarding the relevance of known risk factors (human papilloma virus, sexual practices) to vaginal intraepithelial neoplasia in older women are lacking.
- Data regarding the relevance of a remote operation for gynecologic cancer to vaginal Pap smears in elderly women are lacking.

- Elderly women may not know why, and occasionally if, a hysterectomy was performed, and whether the hysterectomy was total (*corpus et cervix uteri*) or subtotal (*corpus uteri*).

Summary

Screening rates are low among women aged 65 or over, particularly those who are older, unmarried, and with poor medical financial coverage. In these women, the death rate from cervical cancer is much higher than in screened women, owing in large part to diagnosis at a more advanced stage. Extending the screening interval beyond 3 years leads to a greater incidence of abnormal Pap smears. Studies of Pap smear benefits have examined primarily disease incidence and mortality, rather than quality-of-life and functional issues, and thus have not included important outcomes relevant to geriatric care. Interventions to promote cervical cancer screening in elderly women are effective.

Gyn 48 (Level B): **Cost analysis should be performed to measure the comprehensive costs to the primary care provider of obtaining a Pap smear in an elderly woman and to compare these with current Medicare reimbursement.**

Gyn 49 (Level B): **As the baby boomers age, observational studies are needed to determine the cervical cancer incidence in a changing elderly population with different sexual risk factors and to compare this with previous incidence rates.**

Gyn 50 (Level B): **Observational studies are needed to delineate all factors associated with the increased mortality rate of cervical cancer among elderly women.**

Gyn 51 (Level A): **Clinical trials should be performed to determine whether strategies to improve cervical cancer screening in impoverished and minority elderly women result in decreased cervical cancer mortality, and which strategies are most cost-effective.**

Gyn 52 (Level D): **Observational studies should be performed to determine the relationship of well-established risk factors (eg, multiple sex partners, history of human papilloma virus, cervical dysplasia, smoking, medical or viral immune suppression) to the incidence of cervical or vaginal cancer in elderly women.**

Gyn 53 (Level D): **Observational studies should be performed to determine whether early detection of cervical neoplasia confers quality-of-life benefits on frail elderly women.**

BREAST CANCER SCREENING

Almost half of all breast cancers occur in women aged 65 and over. The average life expectancy of elderly women is usually underestimated. These facts imply that there is a substantial benefit to screening mammography for older women. However, few data exist to support or refute this presumption. Far fewer elderly than young women have been

included in screening trials. Most studies use longevity as an outcome, rather than quality of life or burden of disease, which are of greater concern to older persons.

Quality of Studies

Only two randomized controlled trials of mammography, conducted in Sweden, included women to age 74 at entry. [102,103] Systematic reviews presented results from five Swedish trials, [104] seven randomized controlled trials and six case-control studies, [105] and thirteen randomized controlled trials with 7 to 9 years of follow-up. [106] Case-control studies from the Netherlands reported mammography benefit in women aged 65 and over. [107,108] Retrospective cohort and cross-sectional studies reported the impact of mammography on cancer incidence and stage at diagnosis in women aged 65 and over. [109–114] Studies have looked at the impact of age on the PPV, [108,110,111,115,116] recall rate, [110] cost-effectiveness, [117–119] and sensitivity among estrogen replacement therapy (ERT) users. [120] Retrospective database reviews have evaluated factors associated with screening prevalence. [96,121–125]

Results

Six of eight randomized controlled mammography trials demonstrated a 20% to 30% decline in mortality for women aged 50 to 70. [103] In 5 to 13 years, Swedish mammography trials demonstrated reduced mortality among women aged 50 to 69 (relative risk or RR 0.71), but no effect was seen in women aged 70 to 74. [104] The one trial including these older women was closed after only two screenings. A meta-analysis of seven randomized controlled trials including women to age 74 and six case-control studies including women to age 70 demonstrated that screening mammography reduces mortality (RR 0.70, 95% confidence interval or CI = 0.63 to 0.78 and RR 0.32, 95% CI = 0.28 to 0.38, respectively). [105] The true benefit may have been higher in the randomized controlled trials, which were confounded by low compliance rates in the treatment groups (50% to 80%) and prescreening in the control groups (20% to 30%). A meta-analysis of randomized controlled trials found lower mortality in screened women aged 50 to 74 years after 7 to 9 years of follow-up regardless of the number of mammographic views per screen, the screening interval, or the number of years of follow-up. [106] Case-control studies using one mammographic view every 2 years found lower mortality in women aged less than 65 years and 65 to 74 years (one with and one without statistical significance), but no demonstrable benefit in women aged 75 and over. [107,108] Retrospective cohort and cross-sectional studies have found among screened women aged 65 and over less metastatic disease and a lower stage at diagnosis. [109–114] One study in women aged 85 and over found that point estimates were similar but statistical significance was lost. [112]

The PPV of mammography increased with age in most, [110,111,115,116] but not all [108] studies. ERT has been found to have less negative impact on mammogram sensitivity in women aged 70 and older than in those who are younger. [120] Studies have found greatest cost-effectiveness in women with high bone mineral density (BMD) [117] and in women aged 50 to 79 [118] and 50 to 69. [119] Database reviews have shown costs (ie, Medicare copayment), functional activity limitations, advanced age, and rurality to be associated with less mammographic screening. [96,121–125]

Summary

Regular mammography benefits women to age 74 and probably to age 85, lowering breast cancer morbidity and mortality. Studies that have shown no statistical benefit in women aged 70 and over or 74 and over have evaluated only mortality. Studies looking at the burden of disease and stage at diagnosis have shown benefit to age 85 and perhaps beyond. Financial and functional barriers reduce screening.

Gyn 54 (Level B): **The results of existing and future mammography studies should be stratified by age, even when power is low, to facilitate systematic reviews of results in older women.**

Gyn 55 (Level B): **Observational studies are needed to determine what functional impairments and comorbid conditions are associated with a lack of mammography benefit.**

Gyn 56 (Level B): **Guidelines using functional impairment and comorbid condition measures for discontinuation of mammography should be developed and validated.**

Gyn 57 (Level A): **Randomized controlled trials are needed to determine the impact of mammography on the quality of life and burden of disease in older women.**

Gyn 58 (Level A): **Clinical trials are needed to determine whether strategies to improve mammography screening rates among impoverished and minority elderly women result in decreased breast cancer mortality or burden of disease, and which strategies are most cost-effective.**

Gyn 59 (Level D): **Observational studies should be performed to determine whether the increase in mammographic density that is related to hormone replacement therapy increases breast cancer mortality or burden of disease in older women.**

Gyn 60 (Level D): **The concurrence and variability of mammogram interpretations by different radiologists in elderly women should be observed and defined.**

ESTROGEN REPLACEMENT THERAPY

Estrogen is prescribed to elderly women as a preventive medication, not for menopausal symptoms. Because of the number of potential ERT candidates and the number of potentially affected organ systems, the decision to initiate or continue ERT is the greatest public health issue in geriatric gynecology. Although its prescription is within the purview of all primary care providers, as long as women have uteri that may bleed, gynecologists will play a substantial, and often the only, role in guiding and managing estrogen use. This summary addresses several of the topics most pertinent to elderly women. ERT and osteoporosis is addressed in the final section of this chapter.

ESTROGEN REPLACEMENT AND CARDIOVASCULAR DISEASE

Despite the huge body of literature published about the impact of ERT on cardiovascular disease, opinions about benefit and risks conflict in almost every therapeutic aspect. Even less is clear about the impact of ERT on cardiovascular disease in the elderly woman because data are sparse.

The research on estrogen, estrogen-progestin, and selective estrogen receptor modulator (SERM) therapy is reviewed. Except when estrogen alone is designated, the term *hormone replacement therapy* (HRT) will be used for both estrogen alone and estrogen plus progestin when studies either do not distinguish between the two or find little difference in main outcomes between them. SERMs have estrogenic effects in some organ systems (skeletal, cardiovascular) and antagonistic effects in other organs (breast, uterus). Currently available SERMs in the United States are tamoxifen, raloxifene, and toremifene. Toremifene is approved for the treatment of metastatic breast cancer. Data on potential preventive health benefits of this agent are inadequate and are not reviewed. Studies are cited that use cardiovascular disease, events, or mortality. Many additional studies can be found that report ERT, HRT, and SERM effects on cardiovascular risk factors.

Quality of Data

Estrogen. One systematic review of ERT and cardiovascular disease literature gave information specifically on older women. [126] Four randomized controlled trials, [127–130] ten prospective cohort studies, [126,131–139] three case-control studies, [140–142] and one cross–sectional study [143] were found. Four studies of carotid arterial disease that are relevant to elderly women were also found—one randomized clinical trial, [144] one cohort study, [145] one case–control study, [146] and one cross-sectional study. [147]

Estrogen Dosage. A recent Nurses' Health Study (NHS) report included 20,000 woman-years of conjugated equine estrogen (CEE) 0.3 mg per day, but ages were not reported. [131] One epidemiologic study of HRT and myocardial infarction stratified results by dose. [148]

Selective Estrogen Receptor Modulators. Four randomized controlled trials have evaluated tamoxifen use and cardiovascular endpoints. [149–152] No studies of raloxifene with cardiovascular outcomes have been published.

Results

Estrogen. In a 1991 systematic review of observational studies, [126] Stampfer and Colditz noted that two previous studies [139,153] found an apparent cardioprotective effect of estrogen across all ages, one found a stronger beneficial association in older women, [154] one found apparent benefit in women of all ages but more in younger women, [142] and one study with a mean age of 73 showed substantially less cardiovascular disease among HRT users. [138] Only an early observational publication from the Framingham trial found greater risk in older women taking HRT, [155] and these conclusions were later essentially retracted. [156] Four recent randomized controlled trials found no coronary heart disease benefit of HRT. Two were from the same 4-year trial, the HERS. [127,128] However, in the last 2 years of the trial, HRT was found to be associated with less coronary heart disease. The mean age of participants was 67, but no information specific to older women was given.

In a 3-year trial including 309 women, mean age 66 (range 42 to 80), HRT was not found to affect the progression of coronary atherosclerosis in women with established disease, even when stratified by age. [129] The Women's Health Initiative (WHI) enrolled women aged 50 to 79, mean age 63 at baseline, with over 8000 participants in each study arm. [130] The estrogen-progestin arm of the trial was stopped prematurely after an average of 5.2 years (range 3.5 to 8.5) because of an increase in a global risk index over that with placebo, which included small but statistically significant increases in nonfatal myocardial infarction, nonfatal stroke, pulmonary embolism, and deep-vein thrombosis. Age was not found to interact with HRT effects on any cardiovascular events (data not given). Results from the estrogen-only participants are still pending.

Most observational cohort studies have found lower coronary heart disease and improved survival in older (as well as younger) women taking HRT. The NHS has shown this in three trials, [131,133,134] which included women to age 75 at the 20-year follow-up, although most were under age 65. Current HRT users were found to have a coronary heart disease RR of 0.61 (95% CI = 0.52 to 0.71), but results were not stratified by age. An Iowa Women's Health Study 6-year follow-up (of women aged 55 to 69 years at entry) found current HRT users to have a 25% lower risk of death or coronary heart disease mortality, [135] with 50% risk reduction if use was longer than 5 years. [132] The Leisure World Cohort, mean initial age of 73 years, found a 20% lower all-cause mortality in ever-users than in never-users after 7.5 years of follow-up. [136] Current users had better health, but long duration of use was also found to be associated with benefit. However, in the NHS and the Iowa Women's Health Study, improved health was found to be associated only with current, not past, use. A Swedish cohort study found greater survival in older but not younger women who started HRT, probably because of preferential prescription only to healthy elderly women. [137] Another Swedish cohort study found a lower risk of myocardial infarction in women taking HRT. [157]

Two case-control studies and one cross-sectional analysis of older women found less coronary heart disease among HRT users. Kaiser Permanente patients on long-term HRT were found to have a 46% lower all-cause mortality, largely because there was less coronary heart disease. [140] A case-control study of women with a mean age of 65 found 65% less angiographically documented coronary arterial disease among HRT users. [142] The association was significant for women younger than 60 (P = .002) and aged 60 to 69 (P = .03), but not for those aged 70 and over (P= .5). A cross-sectional evaluation of women 65 to 100 years old, mean age 72, found a similar reduction in cardiovascular disease in HRT users both older and younger than 75 years. [143] In addition, an Italian case-control study found fewer nonfatal myocardial infarctions among women 60 years and older and younger than age 60 who had a late menopause. [141]

Three cross-sectional analyses and one randomized controlled trial evaluated ERT and carotid arterial disease. ERT use was found to be associated with a decrease in arterial wall thickness in older women. [145–147] In a randomized controlled trial of women aged 40 to 70 years, 4 months of ERT was found to be associated with increased carotid artery distensibility, but not significantly in the subgroup over the age of 59. [144]

Estrogen Dosage. The large cohort NHS observed that women using doses of ERT lower than CEE 0.625 mg per day obtain the same apparent cardioprotection as those using the standard strength, whereas those using higher estrogen dosages had less. [131,134] Furthermore, stroke risk tended to be less with lower dosages. However, results were not strati-

fied by age, and the number of women in each therapy group is unknown. One observational study found that the reduction of risk for myocardial infarction with CEE 0.625 mg per day was not seen with the 0.3 mg dose, but these results were based on a small number of ERT users. [148]

Selective Estrogen Receptor Modulators. Two U.S. randomized controlled trials found a nonsignificant [150] or no [149] reduction in cardiovascular mortality with tamoxifen use. In contrast, European trials found a lower risk of fatal myocardial infarction [151,152] and hospitalization for cardiac disease. [158] Potential cardioprotective effects of raloxifene are currently being evaluated in the Raloxifene Use for The Heart (RUTH) trial. [159]

Summary

Conflicting results between high-quality large observational trials (showing benefit) and high-quality large randomized controlled trials (showing detriment) leave us in a quandary about the cardiovascular effects of hormone replacement. The discrepancies seem attributable either to crucial differences between the populations being studied, to the drugs being studied, or to a "healthy user effect" confounding observational trial outcomes even more than previously imagined. The randomized trials enrolled primarily older, overweight women who had not taken hormones for at least 5 to 10 years since menopause, gave them continuous estrogen plus progestin, and studied them for a short time relative to the postmenopausal life span. The observational trials studied primarily women who took hormones since menopause, at least half of whom took estrogen only, and whose average cardiovascular-related health measures (eg, weight, blood pressure, exercise) were better among hormone users than nonusers; greatest "benefit" was found with the longest use, although this was sometimes attenuated in advanced age. Interestingly, the most obvious cause of increased cardiovascular risk in the randomized trials could be attributed to a procoagulant effect of HRT, but the estrogen-only arm of the WHI was not discontinued prematurely, as would have been expected on the basis of thrombosis alone. Further study is necessary to understand hormone actions upon the cardiovascular system and to determine the patient characteristics that are associated with benefit and detriment.

At the current time, it is relatively contraindicated to start older postmenopausal women on ERT or HRT. However, the risks and benefits to those who have taken hormones since menopause are unclear. Results from the WHI to be completed in 2006 will guide the direction of current clinical care and future research. Although SERMs may improve cardiovascular risk profiles in older women, their effect on coronary heart disease and longevity in elderly women is unknown.

> *Gyn 61 (Level B)*: **Basic science research, pilot studies, and observational trials are needed to determine which are the more sophisticated measures of potential cardiovascular benefits and risks associated with hormone replacement—C-reactive protein levels, homocysteine levels, activated protein C deficiency, intestinal calcium absorption.**
>
> *Gyn 62 (Level A)*: **Placebo-controlled randomized trials, starting with women who have been on hormone replacement therapy for more than 5 years, are needed to determine whether continuation, lower-**

ing the dose, or discontinuation confers more cardiovascular benefit for older women.

Gyn 63 (Level A): **Randomized controlled trials should be performed to determine the effect in elderly women of selective estrogen receptor modulators on primary cardiovascular endpoints, such as myocardial infarction, cardiac death, pulmonary embolism, and stroke.**

Gyn 64 (Level A): **Randomized controlled trials should be performed to determine whether age modifies hormone effects on the cardiovascular system and cardiovascular risk factors (eg, platelet function, arterial distensibility, angiotensinogen levels, calcium absorption).**

Gyn 65 (Level B): **The results from existing and future studies of hormone replacement should be stratified by age, even when power is low, to facilitate systematic reviews.**

Gyn 66 (Level C): **Randomized controlled trials are needed to determine whether aspirin eliminates the thrombogenic effect of estrogen in elderly women.**

ESTROGEN REPLACEMENT THERAPY AND ALZHEIMER'S DISEASE

The age-specific incidence of Alzheimer's disease (AD) is higher for women than for men. [160] The effect of estrogen loss at menopause and of hormone replacement on the development of AD remains in question. Plausible biological theories and laboratory studies support a protective effect, but clinical studies have widely discrepant findings. Few risk factors for AD are known, with education being the only well-established modifiable one. Given the devastating nature of the disease and lack of other preventive strategies, hormone use or avoidance becomes an important individual and public health concern.

Quality of Data

Prevention. The biology of AD and potential neuroprotective mechanisms of estrogen have been well summarized in several reviews of AD and hormone therapy. [160–163] One randomized controlled trial of HRT for AD prevention has been published. [164] Large cohorts from which both prospective cohort and nested case-control studies were published include the Leisure World retirement community, [165,166] a longitudinal study of aging in Manhattan, [167] the Cardiovascular Health Study, [168] the Baltimore Longitudinal Study on Aging, [169] the Rancho Bernardo cohort, [170,171] the Duke Established Populations for Epidemiologic Studies of the Elderly, [172] the Italian Longitudinal Study on Aging, [173] the United Kingdom General Practice Research Database, [174] and the Cache County Study. [175] Preventive effects of endogenous estrogens were explored within the Study of Osteoporotic Fractures. [176] One cross-sectional study evaluated cognitive function and endogenous estrogens and androgens. [171] One longitudinal study compared cognitive ability over 2 years in older women taking no hormones, estrogen only, and estrogen-progestin. [177]

Treatment. Several clinical trials, including four with placebo control and randomization, have evaluated the effects of ERT in women with mild or moderate AD. [160,178–180] Many studies were small or used brief cognitive rating instruments. [160] All randomized controlled trials used oral CEE.

Results

Prevention. The Women's Health Initiative Memory Study randomized controlled trial showed worsening dementia with estrogen-progestin use for an average of 5 years (3 to 8) among women over age 65, 80% of whom had not taken hormones before. [164] AD specifically was increased with HRT, but at a slightly lower rate than for all-cause dementia. Among past users of estrogen alone, the increased risk of dementia was found not to be statistically significant. Too few women had used estrogen-progestin replacement prior to the study for meaningful comparison with the observational trials of long-term HRT use.

Observational data conflict regarding the protective effect of ERT or HRT use on AD. Apparent benefit was observed in large prospectively followed cohorts. [167,169,175] In a well-designed and -executed study of 1890 women and 1360 men over age 65 in Utah, incident dementia over a period of 3 years was found to be greater after age 80 among women. Women who had used hormones for more than 10 years (72% unopposed estrogen, mostly past use) were found to have the same AD incidence as men, whereas nonusers were found to have more than twice the risk. Women who used hormones less than 10 years had a greater risk of AD (not statistically significant), which essentially concurs with the randomized trial. [164] There was some suggestion that risk reduction with ERT or HRT is greater in women with two $\epsilon 4$ alleles ($P = .19$). [175] In contrast, one study found less cognitive decline with estrogen use in women negative for the APOE-$\epsilon 4$ allele, but not in $\epsilon 4$-positive women. [168] In a 2-year prospective study, cognitive performance was found to improve more for current unopposed estrogen users and less for estrogen-progestin users than for nonusers. [177] Another study found ERT use to be associated with less cognitive decline but not less impairment, but multivariate analyses did not confirm statistical significance. [172] Unexpectedly, higher serum estrone levels have been associated with worse performance on two cognitive tests, [176] but free estradiol with less decline. [181] Past, current, or no ERT use ever was not found to be associated with cognitive function in a large cohort. [170]

Retrospective case-control studies, [182–185] nested case-control studies, [165,166] and a cross–sectional study [173] have found less ERT use among demented women or less AD among ERT users. However, a large nested case-control study found similar odds ratios for AD among none ever, past, or current ERT users. [174] A case-control study based on pharmacy records found no association of ERT and AD. [186]

Treatment. Most treatment studies have found no benefit of ERT for AD, [160,178,179] the largest having 120 subjects. [180] One intriguing prospective cohort study within a randomized controlled trial found that ERT may enhance response to tacrine. [187] Some AD symptoms, such as naming, seem more amenable to improvement with ERT. [188]

Summary

Estrogen-progestin replacement therapy initiated in women who are several years postmenopausal increases the risk of dementia, including AD, with relatively short-term use. This does not entirely exclude the possibility of a neutral effect or benefit with

long-term use, as found in some observational studies. It also does not exclude a potential benefit of estrogen alone, nor of HRT initiated at menopause. Discrepancies in study findings may relate to subgroups of women who respond favorably or adversely to hormones. These subgroups should be sought, to clarify the confusing clinical observations of postmenopausal hormone use. ERT has no proven benefit for women with established AD, but benefit in some individuals or synergism with cholinesterase inhibition is not excluded.

Gyn 67 (Level B): **Basic science research and animal studies are needed to determine the differential effects of estrogen and estrogen-progestin replacement on cognition.**

Gyn 68 (Level B): **Basic science research, animal studies, and observational studies are needed to determine which physiologic characteristics, if any, are associated with a benefit or detriment of long-term postmenopausal hormone use.**

Gyn 69 (Level B): **Basic science research is needed to reconcile and explain the discrepant findings of estrogen neuroprotection in the laboratory in comparison with cognitive detriment with estrogen-progestin in clinical experience.**

Gyn 70 (Level B): **Autopsy studies should be performed to determine the types of dementia most associated with postmenopausal hormone use.**

Gyn 71 (Level B): **Results from existing and future studies of hormone replacement and Alzheimer's disease should be stratified by age, even when power is low, to facilitate systematic reviews.**

Gyn 72 (Level A): **Randomized controlled trials of long-term postmenopausal hormone users are needed to determine whether discontinuation or continuation into the 70s, 80s, and 90s affects cognition.**

ESTROGEN REPLACEMENT THERAPY, MODIFIED ESTROGENS, AND CANCER

The incidence rates for both breast and colon cancer increase with advanced age, and they may be impacted by ERT or HRT. An abbreviated literature summary with issues pertinent to elderly women is summarized here. An increase in the incidence of endometrial cancer with the use of unopposed ERT is well understood and does not need comment.

Colon cancer is the leading cause of cancer mortality in women aged 85 and over. A protective influence of hormones was postulated by McMichael and Potter in 1980. [189] Given the vast number of observational studies that have looked at ERT and breast cancer, surprisingly little has been studied in elderly women.

Quality of Data

Colon Cancer. Approximately 40 studies have evaluated the association of ERT with colon cancer, including five meta-analyses, [190–193] and one randomized controlled trial with partial results. [130]

Breast Cancer. Despite the inclusion of many elderly women in breast cancer and ERT studies, few stratify results by age. The NHS provided data on a subset of women aged 60 to 64. [194] The Collaborative Group on Hormonal Factors in Breast Cancer summarized 51 studies from 21 countries and evaluated associations with age. [195] However, few older women were estrogen users. One large randomized controlled trial enrolled women to age 79. [130]

Selective Estrogen Receptor Modulators and Breast Cancer. The Multiple Outcomes of Raloxifene Evaluation (MORE) is a large randomized controlled trial that included women aged 31 to 80 and reported breast cancer results. [196] Eighty percent of the participants were aged 60 or over, mean age 67. The National Cancer Institute undertook a randomized controlled trial in 1990 to evaluate tamoxifen for the prevention of breast cancer in high-risk women. [149] Thirty percent of subjects were aged 60 and older, including 6% aged 70 and older.

Results

Colon Cancer. Of 35 observational studies reviewed, 23 suggested a protective effect of ERT on colon cancer, 11 were neutral, and 1 reported a negative impact. [190] Greater benefit is generally seen in studies published since 1990, [191] approximating an RR of 0.83 (95% CI = 0.66 to 1.04) in one meta-analysis. [189] The Leisure World cohort study of 7700 older women found 30% less colon cancer in current ERT users. [191] Risk reduction remained but lost statistical significance among past users. Other observational studies have also found current use but not longer duration to be beneficial. [192,193] A case-control study found a 65% ERT-related risk reduction, but the 23% reduction in those 70 and older was not statistically significant. [197] One third or more of subjects in the large randomized WHI were aged 65 or over. [130] Six fewer colon cancers per 10,000 women per year (statistically significant) occurred among estrogen-progestin users than with placebo after an average of 5 years (3.5 to 8.5). Age-specific risks were not evaluated.

Breast Cancer. In the NHS, breast cancer risk was found to be 70% higher in 60- to 64-year-old current ERT users who had been taking it at least 5 years. [194] A recent review of 51 epidemiologic studies, including 52,700 women with breast cancer, found a steady increase in risk among current ERT users of 1.023 for each year of hormone use. [195] RRs were 1.3 in women under age 60 and 1.40 in those aged 60 and over. However, the median age at breast cancer diagnosis was 60, and 92% of users stopped use prior to age 65, thus offering little information about the older woman. One third or more of subjects in the large randomized WHI were aged 65 or over. [130] Eight more breast cancers per 10,000 women per year (not statistically significant) occurred among estrogen-progestin users than among placebo users after an average of 5 years (3.5 to 8.5). No interactions with age were found.

Selective Estrogen Receptor Modulators and Breast Cancer. Raloxifene use for 3 years was associated with a 75% breast cancer risk reduction. [196] Estrogen-receptor-positive cancers were suppressed by 90%, but estrogen-receptor-negative cancers were not. Tamoxifen use for 4 years was found to reduce invasive breast cancer by 49% in 13,400

mostly younger women; this included a 55% reduction in those aged 60 and over. [149] No effect was seen on colon cancer.

Summary

Colon Cancer. Colon cancer is decreased among current HRT users, with concurrence of observational and randomized trial data. Although no study has shown statistical significance among women aged 65 and over, this is likely due to lack of data rather than a lack of effect. The effects of past use are unclear.

Breast Cancer. Long-term and current estrogen-progestin use slightly increases the risk of breast cancer, with concurrence of observational and randomized trial data. It is unclear whether age interacts with HRT. The effects of estrogen use alone are uncertain. Only observational data evaluate breast cancer mortality, which is not higher among HRT users. Still, relatively few data inform risks for the older woman. SERMs suppress, delay, or inhibit estrogen-receptor-positive breast cancers in young-elderly women, but study durations have been relatively short in relation to clinical breast cancer development (7 years).

Gyn 73 (Level B): **Cross-sectional or prospective cohort studies should be performed to determine the factors, whether breast cancer pathophysiology or other health factors, that are associated with the apparent lower mortality among women whose breast cancer is diagnosed during hormone replacement therapy use.**

Gyn 74 (Level B): **Observational studies are needed to determine what functional factors and comorbidities are associated with a lack of benefit of mammography or colon cancer screening, for the development of clinical guidelines.**

Gyn 75 (Level B): **The results from existing and future studies of estrogen, estrogen-progestin, and selective estrogen receptor modulator use should be stratified by age, even when power is low, to facilitate systematic reviews.**

Gyn 76 (Level A): **Randomized trials of continuous therapy since menopause are needed to determine the effects of estrogen and hormone replacement on breast and colon cancer incidence and mortality.**

Gyn 77 (Level A): **Randomized trials are needed to determine the effects of long-term use of selective estrogen receptor modulators on breast and colon cancer incidence and mortality.**

Gyn 78 (Level D): **Basic science and observational trials are needed to determine the mechanisms by which estrogen reduces colon cancer incidence.**

Gyn 79 (Level C): **Randomized trials are needed to determine whether estrogen or estrogen-progestin replacement after breast cancer treatment affects recurrence and mortality.**

OSTEOPOROSIS

HORMONAL THERAPIES

The lifetime risk of osteoporotic fractures in a 50-year-old white woman has been estimated to be 30% to 40% in the United States, including a 15% to 18% risk for hip fractures. [198] (See also Chapter 11, section on osteoporosis and falls.) In women aged 60 years and over, osteoporosis prevention or treatment has been the predominant reason for initiation of ERT. [199] A lack of randomized data led to the Food and Drug Administration's withdrawal of the indication of osteoporosis treatment for ERT, although it is still approved for prevention. Data from more recent research may reverse this. Some data are also available for SERMs (raloxifene, tamoxifen). Studies on phytoestrogen effects in elderly women have not been published.

Quality of Data

Estrogen. For a thorough discussion of studies pertinent to elderly women, the reader is referred to reviews of this subject. [198,200–203] Cohort, case-control, and randomized controlled trials evaluate the effects of ERT on BMD and bone turnover in older women. [200,202] Fracture data regarding elderly women are primarily from observational studies. [204–212] Most earlier studies suffered from several design flaws, such as including in the estrogen-user group women who had discontinued ERT use several years earlier. A meta-analysis of fracture data in older women included published and unpublished reports of all randomized clinical trials in the preceding decade. [203] The trials are well described and five include young-old women [128,129,213–215] and two include middle-old women. [180,216] A recent randomized controlled trial of HRT includes fracture data for women aged 50 and over. [130]

Selective Estrogen Receptor Modulators. A large, well-conducted randomized controlled trial (MORE trial) reported the effect of raloxifene on BMD and fracture risk. [217] A large, well-described cross-sectional case-control study of tamoxifen and fracture risk was conducted in nursing-home residents aged 65 years and older. [218]

Results

Estrogen. Virtually all studies show improved BMD or bone turnover in the elderly woman that was essentially equal to that in younger women. [200,202] However, fracture benefit in older women is less clear. Studies generally show a reduction in risk that does not achieve statistical significance. Pooled randomized controlled trial data of women aged 60 and over showed a 21% hip fracture risk reduction ($P = .26$), and a 12% wrist fracture risk reduction ($P = .63$). [203] These results do not prove a lack of ERT benefit, because most randomized controlled trials were not designed with fracture as the primary outcome, and the data regarding older women are heavily influenced by the large HERS trial, [128] in which women with osteoporosis were systematically excluded, thereby limiting the generalizability of the results. [219] Exclusion of the HERS trial (see above) led to a more impressive fracture risk reduction of 38% ($P = .06$). In four observational studies it is possible to distinguish between women who started HRT before and after age 60 years. [203,204,208,211,212] All show a large reduction in fractures among women starting before age 60 years, with three studies showing statistical significance. [208,211,212] However,

none found statistical significance among women who started after age 60. ERT was found to be most effective for hip fracture prevention among long-term and current ERT users aged 75 or over who started within 5 years of menopause. [211] One third or more of women in the randomized WHI were aged 65 or over. [130] Twenty-five percent to 35% fewer hip, vertebral, and other osteoporotic fractures occurred in the HRT group than in the placebo group. Age-specific rates were not given.

Low doses of ERT (0.3 mg esterified estrogen, 25 μg transdermal estrogen, 0.3 mg CEE) improved BMD in several studies, albeit less than standard doses. [202] One randomized controlled trial in 128 healthy white women aged 65 or over, mean age 73 ± 5 years, found an increase in BMD with low-dose ERT. [216] Fracture data are not available for low ERT doses.

Selective Estrogen Receptor Modulators. The MORE (raloxifene) trial included more than 7000 osteoporotic women aged 31 to 80 years, mean age 67. [217] Bone density was found to increase, but nonvertebral fractures were not significantly affected. Age was mentioned for only one outcome: the 50% reduction in vertebral fracture rate was the same "across all age groups." Tamoxifen was found to reduce fracture risk among nursing-home residents with 10 mg but not 20 mg daily. [218]

Summary

HRT reduces the risk of osteoporotic fractures, especially when started after menopause and used long term. The risk reduction when HRT is started in the 60s and 70s is not proven. Evidence points toward a modest (10% to 20%) effect. Low ERT doses help maintain BMD, but fracture benefit is unknown. SERMs are potentially an excellent alternative to ERT for osteoporosis. However, hip fracture data, particularly in middle-old and old-old women, are needed.

Gyn 80 (Level B): **Prospective cohort studies are needed to compare the quality-of-life outcomes of long-term estrogen, estrogen-progestin, selective estrogen receptor modulator, and bisphosphonate use.**

Gyn 81 (Level B): **Observational and pilot studies are needed to determine whether hormone replacement therapy and selective estrogen receptor modulators act synergistically with other fracture-prevention interventions, such as physical therapy for balance and strength.**

Gyn 82 (Levels B, A): **Observational and eventually randomized trials are needed to determine whether low-dose estrogen replacement therapy initiated at menopause reduces hip, vertebral, and other osteoporotic fractures in advanced age.**

Gyn 83 (Level B): **Results from existing and future studies of hormone replacement to prevent or treat osteoporosis need to be stratified by age, even when power is low, to facilitate systematic reviews.**

Gyn 84 (Level A): **Randomized trials are needed to determine the differences in overall quality of life with hormone replacement therapy, selective estrogen receptor modulators, and bisphosphonates.**

Gyn 85 (Level A): **A placebo-controlled randomized trial should be performed to determine whether bisphosphonates, hormone replacement therapy, or selective estrogen receptor modulators best reduce osteoporosis morbidity and mortality in frail and institutionalized elderly women, including data on overall cost, burden of care, and quality of life.**

Gyn 86 (Level A): **A randomized controlled trial should be performed to determine the fracture benefit of initiating selective estrogen receptor modulators after age 75 among both osteoporotic and osteopenic women.**

NONHORMONAL THERAPIES: CALCIUM AND VITAMIN D

The nonhormonal pharmacotherapeutics most relevant to osteoporosis in elderly women are nutritional supplementation (reviewed in this section) and bisphosphonates (reviewed in the next section). Other therapies (calcitonin, androgens, fluoride) have less demonstrated efficacy, are poorly studied in elderly women, or may even increase fracture risk.

The need for adequate calcium and vitamin D is well documented. Vitamin D promotes calcium absorption. Its benefit is largely lost within 2 years of discontinuation. [220]

Quality of Data

Randomized controlled trials of calcium and vitamin D and of combined therapy using fracture outcomes in older individuals have been reported. Large trials and moderate-sized trials have compared calcium plus vitamin D with placebo, [221–224] calcium with placebo, [225,226] vitamin D with calcium, [227] and vitamin D with placebo. [228] Several smaller trials have compared vitamin D with placebo, calcium, and other forms of vitamin D. [220] Dietary calcium and fracture associations were prospectively assessed in a large cohort. [229]

Results

Administration of vitamin D plus calcium was found to reduce hip, nonvertebral, and vertebral fractures in elderly women. [221–223] The Finnish study did not demonstrate fracture reduction, but power to do so and treatment duration were low. [224] Vitamin D alone was not found to reduce hip fractures in 2600 healthy and frail elderly women. [228] Calcium supplementation was found to lower the vertebral fracture rate in elderly women with baseline vertebral fractures, but not in those without. [225,226] Current calcium use was found to be associated with an increased hip-fracture risk in a large cohort, but this was presumed to be due to confounding by indication for supplements. [229]

Summary

Adequate intake of both vitamin D and calcium reduces fracture risk, and both are most important in those who are deficient or osteoporotic. Both together reduce vertebral and nonvertebral fractures in elderly women. Randomized data for the use of calcium alone are weak; data for vitamin D alone are slightly stronger, but still not certain.

Gyn 87 (Level D): **Observational trials and pilot studies are needed to determine the importance of factors in adolescence, such as milk**

and carbonated beverage consumption, on peak bone mass and bone matrix.

Gyn 88 (Level D): **Observational studies are needed to define the costs and side effects associated with calcium and vitamin D supplementation.**

Gyn 89 (Level C): **Randomized trials are needed to determine the optimal time in a woman's life span to benefit from calcium supplementation.**

Gyn 90 (Level C): **Randomized trials should be performed to determine the best method of calcium supplementation to maximize absorption and minimize side effects.**

Gyn 91 (Level C): **Randomized trials are needed to determine the best form of vitamin D supplementation.**

NONHORMONAL THERAPIES: BISPHOSPHONATES

Although the mechanism of action of bisphosphonates is incompletely understood, they have proven to be profoundly effective in the prevention and treatment of osteoporosis.

Quality of Studies

Bisphosphonates have undergone rigorous clinical efficacy trials, since their use for osteoporosis is a fairly new indication. Available data include randomized controlled trials in elderly women.

Alendronate. A meta-analysis including five randomized controlled trials published in 1994 and 1995 of alendronate use for at least 2 years reported data dichotomized at age 65. [230] Women aged 55 to 81 with and without existing vertebral fractures were studied in the Fracture Intervention Trial (FIT). [231–233]

Risedronate. The Vertebral Efficacy with Risedronate Therapy (VERT) trial reported approximately 1000 women, mean age 69, with low bone density and baseline vertebral fractures. [234]

Etidronate. Four etidronate randomized controlled trials with elderly women reported fracture data. [235–238]

Results

Alendronate. In the meta-analysis, the RRs for fracture ranged from 0.34 to 0.91, with the greatest risk reduction in those aged 65 and over. [230] In the FIT trial, women with a baseline vertebral fracture were found to have a reduced risk of subsequent vertebral or nonvertebral fracture. [231] Among women without a baseline vertebral fracture, only the risk for vertebral fracture was reduced. Results were consistent across age groups. [232] Among the women with baseline hip osteoporosis, the 36% reduction in clinical fractures was statistically significant, but no effect was demonstrable in women with higher baseline BMD.

Risedronate. Risedronate was found to reduce vertebral and nonvertebral fractures significantly in women with baseline osteoporosis, although in one report the nonvertebral fracture risk reduction was of borderline certainty ($P = .06$). [234,239] A trial of risedronate in 9000 severely osteoporotic women aged 70 or older (hip T score > 4.0) found a 30% decrease in hip fracture risk among those aged 70 to 79, but not significantly in women aged 80 and older ($P = .35$). [240]

Etidronate. In three of the four randomized controlled trials, mean ages 65 to 72 years, vertebral but not nonvertebral fractures were reduced. [235,236,238]

Summary

Bisphosphonates are well studied in elderly women and are effective. Alendronate decreases vertebral and nonvertebral fractures in osteoporotic women. A significant benefit in elderly women without osteoporosis is unlikely with therapy of short duration (> 4 years). Risedronate effectively lowers fracture rates in elderly osteoporotic women, although hip fracture benefit is less certain. Trials have included only osteoporotic women, so the preventive benefits of this agent are unknown. Etidronate is not first-line bisphosphonate therapy.

Gyn 92 (Level B): **Long-term observational studies are needed to obtain information about the efficacy, safety, and adverse effects of very long-term bisphosphonate use (30 to 40 years) for postmenopausal osteoporosis prevention and treatment.**

Gyn 93 (Level B): **Medications that selectively reduce bone resorption without limiting bone formation should be developed.**

Gyn 94 (Level B): **Medications that stimulate bone formation should be developed.**

Gyn 95 (Level A): **Randomized controlled trials are needed to determine the utility of bisphosphonates for osteoporosis benefit in healthy women.**

Gyn 96 (Level A): **Randomized controlled trials should be performed to determine the additive effects, if any, of hormonal and nonhormonal osteoporosis therapies.**

Gyn 97 (Level D): **Decision and cost-effectiveness analyses are needed to calculate whether health care dollars spent on medication, including evaluation and management of complications, would be better spent on physical and occupational therapy in frail elderly women.**

KEY RESEARCH QUESTIONS IN GERIATRIC GYNECOLOGY

Gyn KQ1: **How can the immediate and long-term functional impact of gynecologic surgery on older women be improved?**

Hypothesis-generating: Prospective or cross-sectional cohort studies are needed to give clues to the functional impact of gynecologic surgery on elderly women of differing functional status.

Hypothesis-testing studies are needed to define what preoperative, intraoperative, and postoperative interventions enhance functional recovery. Hypothesis-testing studies are needed to establish benefits and risks of estrogen replacement therapy preoperatively, both locally for incontinence and prolapse surgery, and systemically on the cardiovascular and hematologic systems (eg, thrombophilia).

***Gyn KQ2*: How can normal urogenital function be maintained in aging and age-related conditions?**

Hypothesis-generating: Observational studies are needed to understand the epidemiology of urogenital disorders other than urinary incontinence, including vulvovaginal conditions, pelvic organ prolapse, and sexual dysfunction. Observational studies are needed to suggest preventive and therapeutic interventions (other than estrogen therapy) to minimize urinary incontinence, voiding dysfunction, pelvic organ prolapse, and vulvovaginitis. Hypothesis-generating studies are needed to find potential therapeutic interventions for sexual dysfunction in older women.

Hypothesis-testing studies are needed to determine the impact of estrogen replacement therapy on urogenital health. Hypothesis-testing studies are needed to evaluate the functional and quality-of-life benefits of currently available interventions for urinary incontinence and pelvic organ prolapse, including behavioral programs and pelvic floor reparative procedures. Hypothesis-testing studies are needed for the treatment of urinary incontinence in demented elderly women.

***Gyn KQ3*: Which older women should be encouraged to initiate or continue estrogen replacement or other hormonal therapy?**

Hypothesis-generating: Observational studies are needed to sort out complex relationships among age, hormone replacement, and genetic and environmental predisposition to disease.

Hypothesis-testing studies are needed to establish the impact of selective estrogen receptor modulators and long-term ($>$ 10 years) estrogen and estrogen-progestin replacement therapy on conditions that affect a large number of elderly women—cardiovascular disease, stroke, dementia, colon cancer, breast cancer, age-related macular degeneration, cataracts, poor dentition, arthritis, and osteoporosis. Sexual function issues should be included among the outcomes studied. Studies are needed to address the several hormone replacement therapeutic options, such as dose, route of administration, types and schedules of progestins, and the use of selective estrogen receptor modulators instead of estrogens and progestins. In all studies, the questions of continuation in old age should be addressed.

REFERENCES

1. Merrill RM. Prevalence corrected hysterectomy rates and probabilities in Utah. Ann Epidemiol 2001;11:127-135.
2. Wilcox LS, Koonin LM, Pokras R, et al. Hysterectomy in the United States, 1988-1990. Obstet Gynecol 1994;83:549-555.

3. Schofield MJ, Hennrikus DJ, Redman S, Sanson-Fisher RW. Prevalence and characteristics of women who have had a hysterectomy in a community survey. Aust N Z J Obstet Gynaecol 1991;31:153-158.
4. Olsen AL, Smith VJ, Bergstrom JO, et al. Epidemiology of surgically managed pelvic organ prolapse and urinary incontinence. Obstet Gynecol 1997;89:501-506.
5. Sultana CJ, Campbell JW, Pisanelli WS, et al. Morbidity and mortality of incontinence surgery in elderly women: an analysis of Medicare data. Am J Obstet Gynecol 1997;176:344-348.
6. Warner MA, Warner DO, Harper CM, et al. Lower extremity neuropathies associated with lithotomy positions. Anesthesiology 2000;93:938-942.
7. Panayiotis G, Ellenbogen A, Grunstein S. Major gynecologic surgical procedures in the aged. J Am Geriatr Soc 1978;26:459-462.
8. Polanczyk CA, Marcantonio E, Goldman L, et al. Impact of age on perioperative complications and length of stay in patients undergoing noncardiac surgery. Ann Intern Med 2001;134:637-643.
9. Virtanen HS, Makinen JI. Mortality after gynaecologic operations in Finland, 1986-1991. Br J Obstet Gynaecol 1995;102:54-57.
10. Nahhas WA, Brown M. Gynecologic surgery in the aged. J Reprod Med 1990;35:550-554.
11. Lambrou NC, Buller JL, Thompson JR, et al. Prevalence of perioperative complications among women undergoing reconstructive pelvic surgery. Am J Obstet Gynecol 2000;183:1355-1358; discussion 1359-1360.
12. Shackelford DP, Hoffman MK, Kramer PR, Jr., et al. Evaluation of preoperative cardiac risk index values in patients undergoing vaginal surgery. Am J Obstet Gynecol 1995;173:80-84.
13. MacLennan AH, Taylor AW, Wilson DH, Wilson D. The prevalence of pelvic floor disorders and their relationship to gender, age, parity and mode of delivery. BJOG 2000;107:1460-1470.
14. Fanning J, Neuhoff RA, Brewer JE, et al. Frequency and yield of postoperative fever evaluation. Infect Dis Obstet Gynecol 1998;6:252-255.
15. Swift SE. The distribution of pelvic organ support in a population of female subjects seen for routine gynecologic health care. Am J Obstet Gynecol 2000;183:277-285.
16. Quinlivan LG. The gynecological findings in elderly women. Geriatrics 1964;Sept:654-657.
17. Chiaffarino F, Chatenoud L, Dindelli M, et al. Reproductive factors, family history, occupation and risk of urogenital prolapse. Eur J Obstet Gynecol Reprod Biol 1999;82:63-67.
18. Gemer O, Bergman M, Segal S. Prevalence of hydronephrosis in patients with genital prolapse. Eur J Obstet Gynecol Reprod Biol 1999;86:11-13.
19. Beverly CM, Walters MD, Weber AM, et al. Prevalence of hydronephrosis in patients undergoing surgery for pelvic organ prolapse. Obstet Gynecol 1997;90:37-41.
20. Sulak PJ, Kuehl TJ, Shull BL. Vaginal pessaries and their use in pelvic relaxation. J Reprod Med 1993;38:919-923.
21. Theofrastous JP, Addison WA, Timmons MC. Voiding function following prolapse surgery. Impact of estrogen replacement. J Reprod Med 1996;41:881-884.
22. Mikkelsen AL, Felding C, Clausen HV. Clinical effects of preoperative oestradiol treatment before vaginal repair operation. A double-blind, randomized trial. Gynecol Obstet Invest 1995;40:125-128.
23. Denehy TR, Choe JY, Gregori CA, Breen JL. Modified Le Fort partial colpocleisis with Kelly urethral plication and posterior colpoperineoplasty in the medically compromised elderly: a comparison with vaginal hysterectomy, anterior colporrhaphy, and posterior colpoperineoplasty. Am J Obstet Gynecol 1995;173:1697-1701; discussion 1701-1692.
24. DeLancey JO, Morley GW. Total colpocleisis for vaginal eversion. Am J Obstet Gynecol 1997;176:1228-1232; discussion 1232-1235.
25. Ahranjani M, Nora E, Rezai P, Bujewski S. Neugebauer-Le Fort operation for vaginal prolapse. A review of 38 cases. J Reprod Med 1992;37:959-964.

26. Miklos JR, Sze EH, Karram MM. Vaginal correction of pelvic organ relaxation using local anesthesia. Obstet Gynecol 1995;86:922-924.
27. Kohli N, Sze E, Karram M. Pyometra following Le Fort colpocleisis. Int Urogynecol J Pelvic Floor Dysfunct 1996;7:264-266.
28. Barlow DH, Cardozo LD, Francis RM, et al. Urogenital ageing and its effect on sexual health in older British women. Br J Obstet Gynaecol 1997;104:87-91.
29. Barlow DH, Samsioe G, van Geelen JM. A study of European womens' experience of the problems of urogenital ageing and its management. Maturitas 1997;27:239-247.
30. Stenberg A, Heimer G, Ulmsten U. The prevalence of urogenital symptoms in postmenopausal women. Maturitas 1995;22 Suppl:S17-S20.
31. Rekers H, Drogendijk AC, Valkenburg HA, Riphagen F. The menopause, urinary incontinence and other symptoms of the genito-urinary tract. Maturitas 1992;15:101-111.
32. Iosif CS, Bekassy Z. Prevalence of genito-urinary symptoms in the late menopause. Acta Obstet Gynecol Scand 1984;63:257-260.
33. Versi E, Harvey MA, Cardozo L, et al. Urogenital prolapse and atrophy at menopause: a prevalence study. Int Urogynecol J Pelvic Floor Dysfunct 2001;12:107-110.
34. Cardozo L, Bachmann G, McClish D, et al. Meta-analysis of estrogen therapy in the management of urogenital atrophy in postmenopausal women: second report of the Hormones and Urogenital Therapy Committee. Obstet Gynecol 1998;92:722-727.
35. Ishigooka M, Hashimoto T, Tomaru M, et al. Effect of hormonal replacement therapy in postmenopausal women with chronic irritative voiding symptoms. Int Urogynecol J Pelvic Floor Dysfunct 1994;5:208-211.
36. Leiblum S, Bachmann G, Kemmann E, et al. Vaginal atrophy in the postmenopausal woman. The importance of sexual activity and hormones. JAMA 1983;249:2195-2198.
37. van der Velden J, van Lindert AC, Gimbrere CH, et al. Epidemiologic data on vulvar cancer: comparison of hospital with population-based data. Gynecol Oncol 1996;62:379-383.
38. Edwards CL, Balat O. Characteristics of patients with vulvar cancer: an analysis of 94 patients. Eur J Gynaecol Oncol 1996;17:351-353.
39. Raber G, Mempel V, Jackisch C, et al. Malignant melanoma of the vulva. Report of 89 patients. Cancer 1996;78:2353-2358.
40. Benign disorders of the vulva. In Beers MH, Berkow R (eds): The Merck Manual of Geriatrics, 3rd ed. Whitehouse Station, NJ: Merck Research Laboratories, 2000:1200-1201.
41. Elchalal U, Gilead L, Vardy DA, et al. Treatment of vulvar lichen sclerosus in the elderly: an update. Obstet Gynecol Surv 1995;50:155-162.
42. Lynch PJ, Edwards L. White patches and plaques. In Genital Dermatology. New York: Churchill Livingstone, 1994:149-162.
43. Wingate MB. Vulvar dystrophies in geriatric patients. Compr Ther 1986;12:39-42.
44. Powell JJ, Wojnarowska F. Lichen sclerosus. Lancet 1999;353:1777-1783.
45. Sideri M, Origoni M, Spinaci L, Ferrari A. Topical testosterone in the treatment of vulvar lichen sclerosus. Int J Gynaecol Obstet 1994;46:53-56.
46. Matthias RE, Lubben JE, Atchison KA, Schweitzer SO. Sexual activity and satisfaction among very old adults: results from a community-dwelling Medicare population survey. Gerontologist 1997;37:6-14.
47. Gentili A, Mulligan T. Sexual dysfunction in older adults. Clin Geriatr Med 1998;14:383-393.
48. Young M, Denny G, Young T, Luquis R. Sexual satisfaction among married women age 50 and older. Psychol Rep 2000;86:1107-1122.
49. Johnson BK. A correlational framework for understanding sexuality in women age 50 and older. Health Care Women Int 1998;19:553-564.
50. Gelfand MM. Sexuality among older women. J Womens Health Gend Based Med 2000;9 Suppl 1:S15-S20.

51. Wiley D, Bortz WM, 2nd. Sexuality and aging–usual and successful. J Gerontol A Biol Sci Med Sci 1996;51:M142-M146.
52. Masters WH, Johnson VE. Human Sexual Response. Boston, MA: Little, Brown, 1966.
53. Bretschneider JG, McCoy NL. Sexual interest and behavior in healthy 80- to 102-year-olds. Arch Sex Behav 1988;17:109-129.
54. Bortz WM, 2nd, Wallace DH. Physical fitness, aging, and sexuality. West J Med 1999;170:167-169.
55. Drory Y, Kravetz S, Weingarten M. Comparison of sexual activity of women and men after a first acute myocardial infarction. Am J Cardiol 2000;85:1283-1287.
56. Wright JG, Rudicel S, Feinstein AR. Ask patients what they want. Evaluation of individual complaints before total hip replacement. J Bone Joint Surg Br 1994;76:229-234.
57. Tobin JM, Harindra V. Attendance by older patients at a genitourinary medicine clinic. Sex Transm Infect 2001;77:289-291.
58. Barber MD, Visco AG, Wyman JF, et al. Sexual function in women with urinary incontinence and pelvic organ prolapse. Obstet Gynecol 2002;99:281-289.
59. Tarcan T, Park K, Goldstein I, et al. Histomorphometric analysis of age-related structural changes in human clitoral cavernosal tissue. J Urol 1999;161:940-944.
60. Park K, Goldstein I, Andry C, et al. Vasculogenic female sexual dysfunction: the hemodynamic basis for vaginal engorgement insufficiency and clitoral erectile insufficiency. Int J Impot Res 1997;9:27-37.
61. Kraemer RR, Synovitz LB, Gimpel T, et al. Effect of estrogen on serum DHEA in younger and older women and the relationship of DHEA to adiposity and gender. Metabolism 2001;50:488-493.
62. Slater CC, Zhang C, Hodis HN, et al. Comparison of estrogen and androgen levels after oral estrogen replacement therapy. J Reprod Med 2001;46:1052-1056.
63. Wright TC, Ferenczy A, Kurman RJ. Carcinoma and other tumors of the cervix. In Kurman RJ (ed): Blaustein's Pathology of the Female Genital Tract, 4th ed. New York: Springer-Verlag, 1994:279-326.
64. Mandelblatt J, Gopaul I, Wistreich M. Gynecological care of elderly women. Another look at Papanicolaou smear testing. JAMA 1986;256:367-371.
65. Fink DJ. Change in American Cancer Society Checkup Guidelines for detection of cervical cancer. CA Cancer J Clin 1988;38:127-128.
66. Mandelblatt JS, Hammond DB. Primary care of elderly women: is Pap smear screening necessary? Mt Sinai J Med 1985;52:284-290.
67. American Cancer Society. Cancer facts and figures, 1997. Racial and ethnic patterns. 1997.
68. Incidence of Pap test abnormalities within 3 years of a normal Pap test–United States, 1991-1998. MMWR Morb Mortal Wkly Rep 2000;49:1001-1003.
69. Rader AE, Rose PG, Rodriguez M, et al. Atypical squamous cells of undetermined significance in women over 55. Comparison with the general population and implications for management. Acta Cytol 1999;43:357-362.
70. Coughlin SS, Uhler RJ, Blackman DK. Breast and cervical cancer screening practices among American Indian and Alaska Native women in the United States, 1992-1997. Prev Med 1999;29:287-295.
71. Ruchlin HS. Prevalence and correlates of breast and cervical cancer screening among older women. Obstet Gynecol 1997;90:16-21.
72. van Wijngaarden WJ, Duncan ID. Rationale for stopping cervical screening in women over 50. BMJ 1993;306:967-971. [Erratum in BMJ 1993;306:1373].
73. Gatta G, Capocaccia R, Hakulinen T, et al. Variations in survival for invasive cervical cancer among European women, 1978-89. EUROCARE Working Group. Cancer Causes Control 1999;10:575-581.

74. Ferrante JM, Gonzalez EC, Roetzheim RG, et al. Clinical and demographic predictors of late-stage cervical cancer. Arch Fam Med 2000;9:439-445.
75. Ackermann SP, Brackbill RM, Bewerse BA, et al. Cancer screening behaviors among U.S. women: breast cancer, 1987-1989, and cervical cancer, 1988-1989. Morb Mortal Wkly Rep CDC Surveill Summ 1992;41:17-25.
76. Womeodu RJ, Bailey JE. Barriers to cancer screening. Med Clin North Am 1996;80:115-133.
77. Calle EE, Flanders WD, Thun MJ, Martin LM. Demographic predictors of mammography and Pap smear screening in US women. Am J Public Health 1993;83:53-60.
78. Mitchell H, Medley G, Higgins V. An audit of the women who died during 1994 from cancer of the cervix in Victoria, Australia. Aust N Z J Obstet Gynaecol 1996;36:73-76.
79. Mandelblatt J, Traxler M, Lakin P, et al. Mammography and Papanicolaou smear use by elderly poor black women. The Harlem Study Team. J Am Geriatr Soc 1992;40:1001-1007.
80. Ives DG, Lave JR, Traven ND, et al. Mammography and pap smear use by older rural women. Public Health Rep 1996;111:244-250.
81. Mandelblatt J, Traxler M, Lakin P, et al. Targeting breast and cervical cancer screening to elderly poor black women: who will participate? The Harlem Study Team. Prev Med 1993;22:20-33.
82. Mandelblatt J, Traxler M, Lakin P, et al. A nurse practitioner intervention to increase breast and cervical cancer screening for poor, elderly black women. The Harlem Study Team. J Gen Intern Med 1993;8:173-178.
83. Margolis KL, Lurie N, McGovern PG, et al. Increasing breast and cervical cancer screening in low-income women. J Gen Intern Med 1998;13:515-521.
84. Sawaya GF, Grady D, Kerlikowske K, et al. The positive predictive value of cervical smears in previously screened postmenopausal women: the Heart and Estrogen/progestin Replacement Study (HERS). Ann Intern Med 2000;133:942-950.
85. Stenkvist B, Bergstrom R, Eklund G, Fox CH. Papanicolaou smear screening and cervical cancer. What can you expect? JAMA 1984;252:1423-1426.
86. Suarez L, Nichols DC, Brady CA. Use of peer role models to increase Pap smear and mammogram screening in Mexican-American and black women. Am J Prev Med 1993;9:290-296.
87. Kelly AW, Fores Chacori M, Wollan PC, et al. A program to increase breast and cervical cancer screening for Cambodian women in a midwestern community. Mayo Clin Proc 1996;71:437-444.
88. Paskett ED, Phillips KC, Miller ME. Improving compliance among women with abnormal Papanicolaou smears. Obstet Gynecol 1995;86:353-359.
89. Fahs MC, Mandelblatt J, Schechter C, Muller C. Cost effectiveness of cervical cancer screening for the elderly. Ann Intern Med 1992;117:520-527.
90. Mandelblatt JS, Fahs MC. The cost-effectiveness of cervical cancer screening for low-income elderly women. JAMA 1988;259:2409-2413.
91. Committee on Gynecologic Practice. American College of Obstetricians and Gynecologists. ACOG committee opinion. Recommendations on frequency of Pap test screening. Number 152–March 1995. Int J Gynaecol Obstet 1995;49:210-211.
92. NIH Consensus Development Panel. National Institutes of Health Consensus Development Conference statement on cervical cancer. April 1-3, 1996. Gynecol Oncol 1997;66:351-361.
93. Miller AB, Anderson G, Brisson J, et al. Report of a national workshop on screening for cancer of the cervix. CMAJ 1991;145:1301-1325.
94. U.S. Preventive Services Task Force. Screening for cervical cancer. In Guide to Clinical Preventive Services, 2nd ed. Baltimore, MD: Williams and Wilkins, 1996:105-117.
95. Weinrich S, Coker AL, Weinrich M, et al. Predictors of Pap smear screening in socioeconomically disadvantaged elderly women. J Am Geriatr Soc 1995;43:267-270.

96. Schootman M, Fuortes LJ. Breast and cervical carcinoma: the correlation of activity limitations and rurality with screening, disease incidence, and mortality. Cancer 1999;86:1087-1094.
97. From the Centers for Disease Control and Prevention. Incidence of Pap test abnormalities within 3 years of a normal Pap test–United States, 1991-1998. JAMA 2000;284:2714-2715.
98. Chen F, Trapido EJ, Davis K. Differences in stage at presentation of breast and gynecologic cancers among whites, blacks, and Hispanics. Cancer 1994;73:2838-2842.
99. American Geriatrics Society Clinical Practice Committee. Screening for cervical carcinoma in older women. J Am Geriatr Soc 2001;49:655-657.
100. Pearce KF, Haefner HK, Sarwar SF, Nolan TE. Cytopathological findings on vaginal Papanicolaou smears after hysterectomy for benign gynecologic disease. N Engl J Med 1996;335:1559-1562.
101. Fox J, Remington P, Layde P, Klein G. The effect of hysterectomy on the risk of an abnormal screening Papanicolaou test result. Am J Obstet Gynecol 1999;180:1104-1109.
102. Tabar L, Fagerberg CJ, Gad A, et al. Reduction in mortality from breast cancer after mass screening with mammography. Randomised trial from the Breast Cancer Screening Working Group of the Swedish National Board of Health and Welfare. Lancet 1985;1:829-832.
103. Balducci L. Breast cancer in the older woman: recent advances. Ann Long Term Care 2001;9:37-44.
104. Nystrom L, Rutqvist LE, Wall S, et al. Breast cancer screening with mammography: overview of Swedish randomised trials. Lancet 1993;341:973-978.
105. Demissie K, Mills OF, Rhoads GG. Empirical comparison of the results of randomized controlled trials and case-control studies in evaluating the effectiveness of screening mammography. J Clin Epidemiol 1998;51:81-91.
106. Kerlikowske K, Grady D, Rubin SM, et al. Efficacy of screening mammography. A meta-analysis. JAMA 1995;273:149-154.
107. van Dijck JA, Holland R, Verbeek AL, et al. Efficacy of mammographic screening of the elderly: a case-referent study in the Nijmegen program in The Netherlands. J Natl Cancer Inst 1994;86:934-938.
108. van Dijck J, Verbeek A, Hendriks J, et al. Mammographic screening after the age of 65 years: early outcomes in the Nijmegen programme. Br J Cancer 1996;74:1838-1842.
109. Smith-Bindman R, Kerlikowske K, Gebretsadik T, Newman J. Is screening mammography effective in elderly women? Am J Med 2000;108:112-119.
110. Hunt KA, Rosen EL, Sickles EA. Outcome analysis for women undergoing annual versus biennial screening mammography: a review of 24,211 examinations. AJR Am J Roentgenol 1999;173:285-289.
111. Olivotto IA, Kan L, d'Yachkova Y, et al. Ten years of breast screening in the Screening Mammography Program of British Columbia, 1988-97. J Med Screen 2000;7:152-159.
112. McCarthy EP, Burns RB, Freund KM, et al. Mammography use, breast cancer stage at diagnosis, and survival among older women. J Am Geriatr Soc 2000;48:1226-1233.
113. Field LR, Wilson TE, Strawderman M, et al. Mammographic screening in women more than 64 years old: a comparison of 1- and 2-year intervals. AJR Am J Roentgenol 1998;170: 961-965.
114. Gabriel H, Wilson TE, Helvie MA. Breast cancer in women 65-74 years old: earlier detection by mammographic screening. AJR Am J Roentgenol 1997;168:23-27.
115. Welch HG, Fisher ES. Diagnostic testing following screening mammography in the elderly. J Natl Cancer Inst 1998;90:1389-1392.
116. Kerlikowske K, Grady D, Barclay J, et al. Positive predictive value of screening mammography by age and family history of breast cancer. JAMA 1993;270:2444-2450.

117. Kerlikowske K, Salzmann P, Phillips KA, et al. Continuing screening mammography in women aged 70 to 79 years: impact on life expectancy and cost-effectiveness. JAMA 1999;282:2156-2163.
118. Lindfors KK, Rosenquist CJ. The cost-effectiveness of mammographic screening strategies. JAMA 1995;274:881-884.
119. Boer R, de Koning HJ, van Oortmarssen GJ, van der Maas PJ. In search of the best upper age limit for breast cancer screening. Eur J Cancer 1995;31A:2040-2043.
120. Kavanagh AM, Mitchell H, Giles GG. Hormone replacement therapy and accuracy of mammographic screening. Lancet 2000;355:270-274.
121. Kelaher M, Stellman JM. The impact of Medicare funding on the use of mammography among older women: implications for improving access to screening. Prev Med 2000;31:658-664.
122. Blustein J. Medicare coverage, supplemental insurance, and the use of mammography by older women. N Engl J Med 1995;332:1138-1143.
123. Carney PA, Goodrich ME, O'Mahony DM, et al. Mammography in New Hampshire: characteristics of the women and the exams they receive. J Community Health 2000;25:183-198.
124. Blustein J, Weiss LJ. The use of mammography by women aged 75 and older: factors related to health, functioning, and age. J Am Geriatr Soc 1998;46:941-946.
125. Rakowski W, Pearlman D, Rimer BK, Ehrich B. Correlates of mammography among women with low and high socioeconomic resources. Prev Med 1995;24:149-158.
126. Stampfer MJ, Colditz GA, Willett WC, et al. Postmenopausal estrogen therapy and cardiovascular disease. Ten-year follow-up from the nurses' health study. N Engl J Med 1991;325:756-762.
127. Shlipak MG, Simon JA, Vittinghoff E, et al. Estrogen and progestin, lipoprotein(a), and the risk of recurrent coronary heart disease events after menopause. JAMA 2000;283:1845-1852.
128. Hulley S, Grady D, Bush T, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. JAMA 1998;280:605-613.
129. Herrington DM, Reboussin DM, Brosnihan KB, et al. Effects of estrogen replacement on the progression of coronary-artery atherosclerosis. N Engl J Med 2000;343:522-529.
130. WHI Study Group. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA 2002;288:321-333.
131. Grodstein F, Manson JE, Colditz GA, et al. A prospective, observational study of postmenopausal hormone therapy and primary prevention of cardiovascular disease. Ann Intern Med 2000;133:933-941.
132. Sellers TA, Mink PJ, Cerhan JR, et al. The role of hormone replacement therapy in the risk for breast cancer and total mortality in women with a family history of breast cancer. Ann Intern Med 1997;127:973-980.
133. Grodstein F, Stampfer MJ, Colditz GA, et al. Postmenopausal hormone therapy and mortality. N Engl J Med 1997;336:1769-1775.
134. Grodstein F, Stampfer MJ, Manson JE, et al. Postmenopausal estrogen and progestin use and the risk of cardiovascular disease. N Engl J Med 1996;335:453-461.
135. Folsom AR, Mink PJ, Sellers TA, et al. Hormonal replacement therapy and morbidity and mortality in a prospective study of postmenopausal women. Am J Public Health 1995;85:1128-1132.
136. Henderson BE, Paganini-Hill A, Ross RK. Decreased mortality in users of estrogen replacement therapy. Arch Intern Med 1991;151:75-78.
137. Persson I, Adami HO, Bergstrom R, et al. Survival in women receiving hormone replacement therapy. A record-linkage study of a large population-based cohort. J Clin Epidemiol 1990;43:677-685.

138. Henderson BE, Paganini-Hill A, Ross RK. Estrogen replacement therapy and protection from acute myocardial infarction. Am J Obstet Gynecol 1988;159:312-317.
139. Bush TL, Barrett-Connor E, Cowan LD, et al. Cardiovascular mortality and noncontraceptive use of estrogen in women: results from the Lipid Research Clinics Program Follow-up Study. Circulation 1987;75:1102-1109.
140. Ettinger B, Friedman GD, Bush T, Quesenberry CP, Jr. Reduced mortality associated with long-term postmenopausal estrogen therapy. Obstet Gynecol 1996;87:6-12.
141. Fioretti F, Tavani A, Gallus S, et al. Menopause and risk of non-fatal acute myocardial infarction: an Italian case-control study and a review of the literature. Hum Reprod 2000;15:599-603.
142. Sullivan JM, Vander Zwaag R, Lemp GF, et al. Postmenopausal estrogen use and coronary atherosclerosis. Ann Intern Med 1988;108:358-363.
143. Manolio TA, Furberg CD, Shemanski L, et al. Associations of postmenopausal estrogen use with cardiovascular disease and its risk factors in older women. The CHS Collaborative Research Group. Circulation 1993;88:2163-2171.
144. Angerer P, Kothny W, Stork S, von Schacky C. Hormone replacement therapy and distensibility of carotid arteries in postmenopausal women: a randomized, controlled trial. J Am Coll Cardiol 2000;36:1789-1796.
145. Westendorp IC, Veld BA, Bots ML, et al. Hormone replacement therapy and intima-media thickness of the common carotid artery: the Rotterdam study. Stroke 1999;30:2562-2567.
146. Tremollieres FA, Cigagna F, Alquier C, et al. Effect of hormone replacement therapy on age-related increase in carotid artery intima-media thickness in postmenopausal women. Atherosclerosis 2000;153:81-88.
147. Jonas HA, Kronmal RA, Psaty BM, et al. Current estrogen-progestin and estrogen replacement therapy in elderly women: association with carotid atherosclerosis. CHS Collaborative Research Group. Cardiovascular Health Study. Ann Epidemiol 1996;6:314-323.
148. Hernandez Avila M, Walker AM, Jick H. Use of replacement estrogens and the risk of myocardial infarction. Epidemiology 1990;1:128-133.
149. Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. J Natl Cancer Inst 1998;90:1371-1388.
150. Costantino JP, Kuller LH, Ives DG, et al. Coronary heart disease mortality and adjuvant tamoxifen therapy. J Natl Cancer Inst 1997;89:776-782.
151. McDonald CC, Stewart HJ. Fatal myocardial infarction in the Scottish adjuvant tamoxifen trial. The Scottish Breast Cancer Committee. BMJ 1991;303:435-437.
152. McDonald CC, Alexander FE, Whyte BW, et al. Cardiac and vascular morbidity in women receiving adjuvant tamoxifen for breast cancer in a randomised trial. The Scottish Cancer Trials Breast Group. BMJ 1995;311:977-980.
153. Stampfer MJ, Willett WC, Colditz GA, et al. A prospective study of postmenopausal estrogen therapy and coronary heart disease. N Engl J Med 1985;313:1044-1049.
154. Gruchow HW, Anderson AJ, Barboriak JJ, Sobocinski KA. Postmenopausal use of estrogen and occlusion of coronary arteries. Am Heart J 1988;115:954-963.
155. Wilson PW, Garrison RJ, Castelli WP. Postmenopausal estrogen use, cigarette smoking, and cardiovascular morbidity in women over 50. The Framingham Study. N Engl J Med 1985;313:1038-1043.
156. Eaker ED, Castelli WP. Coronary heart disease and its risk factors among women in the Framingham Study. In Eaker E, Packard B, Wenger NK, et al (eds): Coronary Heart Disease in Women. New York: Haymarket Doyma, 1987:122-132.
157. Falkeborn M, Persson I, Adami HO, et al. The risk of acute myocardial infarction after oestrogen and oestrogen-progestogen replacement. Br J Obstet Gynaecol 1992;99:821-828.

158. Rutqvist LE, Mattsson A. Cardiac and thromboembolic morbidity among postmenopausal women with early-stage breast cancer in a randomized trial of adjuvant tamoxifen. The Stockholm Breast Cancer Study Group. J Natl Cancer Inst 1993;85:1398-1406.
159. Bush TL, Blumenthal R, Lobo R, Clarkson TB. SERMs and cardiovascular disease in women. How do these agents affect risk? Postgrad Med 2001;Spec No:17-24.
160. Birkhauser MH, Strnad J, Kampf C, Bahro M. Oestrogens and Alzheimer's disease. Int J Geriatr Psychiatry 2000;15:600-609.
161. Munoz DG, Feldman H. Causes of Alzheimer's disease. CMAJ 2000;162:65-72.
162. Monk D, Brodaty H. Use of estrogens for the prevention and treatment of Alzheimer's disease. Dement Geriatr Cogn Disord 2000;11:1-10.
163. Benson S. Hormone replacement therapy and Alzheimer's disease: an update on the issues. Health Care Women Int 1999;20:619-638.
164. Shumaker SA, Legault C, Thal L, et al. Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. JAMA 2003;289:2651-2662.
165. Paganini-Hill A, Henderson VW. Estrogen deficiency and risk of Alzheimer's disease in women. Am J Epidemiol 1994;140:256-261.
166. Paganini-Hill A, Henderson VW. Estrogen replacement therapy and risk of Alzheimer disease. Arch Intern Med 1996;156:2213-2217.
167. Tang MX, Jacobs D, Stern Y, et al. Effect of oestrogen during menopause on risk and age at onset of Alzheimer's disease. Lancet 1996;348:429-432.
168. Yaffe K, Haan M, Byers A, et al. Estrogen use, APOE, and cognitive decline: evidence of gene-environment interaction. Neurology 2000;54:1949-1954.
169. Kawas C, Resnick S, Morrison A, et al. A prospective study of estrogen replacement therapy and the risk of developing Alzheimer's disease: the Baltimore Longitudinal Study of Aging. Neurology 1997;48:1517-1521.
170. Barrett-Connor E, Kritz-Silverstein D. Estrogen replacement therapy and cognitive function in older women. JAMA 1993;269:2637-2641.
171. Barrett-Connor E, Goodman-Gruen D. Cognitive function and endogenous sex hormones in older women. J Am Geriatr Soc 1999;47:1289-1293.
172. Fillenbaum GG, Hanlon JT, Landerman LR, Schmader KE. Impact of estrogen use on decline in cognitive function in a representative sample of older community-resident women. Am J Epidemiol 2001;153:137-144.
173. Baldereschi M, Di Carlo A, Lepore V, et al. Estrogen-replacement therapy and Alzheimer's disease in the Italian Longitudinal Study on Aging. Neurology 1998;50:996-1002.
174. Seshadri S, Zornberg GL, Derby LE, et al. Postmenopausal estrogen replacement therapy and the risk of Alzheimer disease. Arch Neurol 2001;58:435-440.
175. Zandi PP, Carlson MC, Plassman BL, et al. Hormone replacement therapy and incidence of Alzheimer disease in older women: the Cache County Study. JAMA 2002;288:2123-2129.
176. Yaffe K, Grady D, Pressman A, Cummings S. Serum estrogen levels, cognitive performance, and risk of cognitive decline in older community women. J Am Geriatr Soc 1998;46:816-821.
177. Rice MM, Graves AB, McCurry SM, et al. Postmenopausal estrogen and estrogen-progestin use and 2-year rate of cognitive change in a cohort of older Japanese American women: The Kame Project. Arch Intern Med 2000;160:1641-1649.
178. Henderson VW, Paganini-Hill A, Miller BL, et al. Estrogen for Alzheimer's disease in women: randomized, double-blind, placebo-controlled trial. Neurology 2000;54:295-301.
179. Wang PN, Liao SQ, Liu RS, et al. Effects of estrogen on cognition, mood, and cerebral blood flow in AD: a controlled study. Neurology 2000;54:2061-2066.

180. Mulnard RA, Cotman CW, Kawas C, et al. Estrogen replacement therapy for treatment of mild to moderate Alzheimer disease: a randomized controlled trial. Alzheimer's Disease Cooperative Study. JAMA 2000;283:1007-1015.
181. Yaffe K, Lui LY, Grady D, et al. Cognitive decline in women in relation to non-protein-bound oestradiol concentrations. Lancet 2000;356:708-712.
182. Waring SC, Rocca WA, Petersen RC, et al. Postmenopausal estrogen replacement therapy and risk of AD: a population-based study. Neurology 1999;52:965-970.
183. Harwood DG, Barker WW, Loewenstein DA, et al. A cross-ethnic analysis of risk factors for AD in white Hispanics and white non-Hispanics. Neurology 1999;52:551-556.
184. Henderson VW, Paganini-Hill A, Emanuel CK, et al. Estrogen replacement therapy in older women. Comparisons between Alzheimer's disease cases and nondemented control subjects. Arch Neurol 1994;51:896-900.
185. Mortel KF, Meyer JS. Lack of postmenopausal estrogen replacement therapy and the risk of dementia. J Neuropsychiatry Clin Neurosci 1995;7:334-337.
186. Brenner DE, Kukull WA, Stergachis A, et al. Postmenopausal estrogen replacement therapy and the risk of Alzheimer's disease: a population-based case-control study. Am J Epidemiol 1994;140:262-267.
187. Schneider LS, Farlow MR, Henderson VW, Pogoda JM. Effects of estrogen replacement therapy on response to tacrine in patients with Alzheimer's disease. Neurology 1996;46:1580-1584.
188. Henderson VW, Watt L, Buckwalter JG. Cognitive skills associated with estrogen replacement in women with Alzheimer's disease. Psychoneuroendocrinology 1996;21:421-430.
189. Hebert-Croteau N. A meta-analysis of hormone replacement therapy and colon cancer in women. Cancer Epidemiol Biomarkers Prev 1998;7:653-659.
190. Crandall CJ. Estrogen replacement therapy and colon cancer: a clinical review. J Womens Health Gend Based Med 1999;8:1155-1166.
191. Paganini-Hill A. Estrogen replacement therapy and colorectal cancer risk in elderly women. Dis Colon Rectum 1999;42:1300-1305.
192. Grodstein F, Newcomb PA, Stampfer MJ. Postmenopausal hormone therapy and the risk of colorectal cancer: a review and meta-analysis. Am J Med 1999;106:574-582.
193. Nanda K, Bastian LA, Hasselblad V, Simel DL. Hormone replacement therapy and the risk of colorectal cancer: a meta-analysis. Obstet Gynecol 1999;93:880-888.
194. Colditz GA, Hankinson SE, Hunter DJ, et al. The use of estrogens and progestins and the risk of breast cancer in postmenopausal women. N Engl J Med 1995;332:1589-1593.
195. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. Lancet 1997;350:1047-1059.
196. Cummings SR, Eckert S, Krueger KA, et al. The effect of raloxifene on risk of breast cancer in postmenopausal women: results from the MORE randomized trial. Multiple Outcomes of Raloxifene Evaluation. JAMA 1999;281:2189-2197.
197. Newcomb PA, Storer BE. Postmenopausal hormone use and risk of large-bowel cancer. J Natl Cancer Inst 1995;87:1067-1071.
198. Kamel HK, Perry HM, 3rd, Morley JE. Hormone replacement therapy and fractures in older adults. J Am Geriatr Soc 2001;49:179-187.
199. Ettinger B, Pressman A, Silver P. Effect of age on reasons for initiation and discontinuation of hormone replacement therapy. Menopause 1999;6:282-289 [Erratum in Menopause 2000;7:135].
200. Miller KL. Hormone replacement therapy in the elderly. Clin Obstet Gynecol 1996;39:912-932.

201. Kenny AM, Prestwood KM. Osteoporosis: pathogenesis, diagnosis, and treatment in older adults. Rheum Dis Clin North Am 2000;26:569-591.
202. Doren M, Samsioe G. Prevention of postmenopausal osteoporosis with oestrogen replacement therapy and associated compounds: update on clinical trials since 1995. Hum Reprod Update 2000;6:419-426.
203. Torgerson DJ, Bell-Syer SE. Hormone replacement therapy and prevention of nonvertebral fractures: a meta-analysis of randomized trials. JAMA 2001;285:2891-2897.
204. Hutchinson TA, Polansky SM, Feinstein AR. Post-menopausal oestrogens protect against fractures of hip and distal radius. A case-control study. Lancet 1979;2:705-709.
205. Paganini-Hill A, Chao A, Ross RK, Henderson BE. Exercise and other factors in the prevention of hip fracture: the Leisure World study. Epidemiology 1991;2:16-25.
206. Ettinger B, Genant HK, Cann CE. Long-term estrogen replacement therapy prevents bone loss and fractures. Ann Intern Med 1985;102:319-324.
207. Kiel DP, Felson DT, Anderson JJ, et al. Hip fracture and the use of estrogens in postmenopausal women. The Framingham Study. N Engl J Med 1987;317:1169-1174.
208. Naessen T, Persson I, Adami HO, et al. Hormone replacement therapy and the risk for first hip fracture. A prospective, population-based cohort study. Ann Intern Med 1990;113:95-103.
209. Paganini-Hill A, Ross RK, Gerkins VR, et al. Menopausal estrogen therapy and hip fractures. Ann Intern Med 1981;95:28-31.
210. Kanis JA, Johnell O, Gullberg B, et al. Evidence for efficacy of drugs affecting bone metabolism in preventing hip fracture. BMJ 1992;305:1124-1128.
211. Cauley JA, Seeley DG, Ensrud K, et al. Estrogen replacement therapy and fractures in older women. Study of Osteoporotic Fractures Research Group. Ann Intern Med 1995;122:9-16.
212. Michaelsson K, Baron JA, Farahmand BY, et al. Hormone replacement therapy and risk of hip fracture: population based case-control study. The Swedish Hip Fracture Study Group. BMJ 1998;316:1858-1863.
213. Wimalawansa SJ. A four-year randomized controlled trial of hormone replacement and bisphosphonate, alone or in combination, in women with postmenopausal osteoporosis. Am J Med 1998;104:219-226.
214. Alexandersen P, Riis BJ, Christiansen C. Monofluorophosphate combined with hormone replacement therapy induces a synergistic effect on bone mass by dissociating bone formation and resorption in postmenopausal women: a randomized study. J Clin Endocrinol Metab 1999;84:3013-3020.
215. Orr-Walker BJ, Evans MC, Clearwater JM, et al. Effects of hormone replacement therapy on bone mineral density in postmenopausal women with primary hyperparathyroidism: four-year follow-up and comparison with healthy postmenopausal women. Arch Intern Med 2000;160:2161-2166.
216. Recker RR, Davies KM, Dowd RM, Heaney RP. The effect of low-dose continuous estrogen and progesterone therapy with calcium and vitamin D on bone in elderly women. A randomized, controlled trial. Ann Intern Med 1999;130:897-904.
217. Ettinger B, Black DM, Mitlak BH, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. JAMA 1999;282:637-645.
218. Breuer B, Wallenstein S, Anderson R. Effect of tamoxifen on bone fractures in older nursing home residents. J Am Geriatr Soc 1998;46:968-972.
219. Grady D, Cummings SR. Postmenopausal hormone therapy for prevention of fractures: how good is the evidence? JAMA 2001;285:2909-2910.

220. Gillespie WJ, Avenell A, Henry DA, et al. Vitamin D and vitamin D analogues for preventing fractures associated with involutional and post-menopausal osteoporosis. Cochrane Database Syst Rev 2001:CD000227.
221. Chapuy MC, Arlot ME, Duboeuf F, et al. Vitamin D3 and calcium to prevent hip fractures in the elderly women. N Engl J Med 1992;327:1637-1642.
222. Garay Lillo J, Parreno J, Gonzalez Y, Gonzalez JA. [Geminis: a prospective, multicentric, randomised study to evaluate the effect of tricalcium phosphate versus tricalcium phosphate plus 25(OH) vitamin D on the risk of fractures in older women]. Geriatrika 1997;13:24-28.
223. Dawson-Hughes B, Harris SS, Krall EA, Dallal GE. Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. N Engl J Med 1997;337:670-676.
224. Inkovaara J, Gothoni G, Halttula R, et al. Calcium, vitamin D and anabolic steroid in treatment of aged bones: double-blind placebo-controlled long-term clinical trial. Age Ageing 1983;12:124-130.
225. Chevalley T, Rizzoli R, Nydegger V, et al. Effects of calcium supplements on femoral bone mineral density and vertebral fracture rate in vitamin-D-replete elderly patients. Osteoporos Int 1994;4:245-252.
226. Recker RR, Hinders S, Davies KM, et al. Correcting calcium nutritional deficiency prevents spine fractures in elderly women. J Bone Miner Res 1996;11:1961-1966.
227. Tilyard MW, Spears GF, Thomson J, Dovey S. Treatment of postmenopausal osteoporosis with calcitriol or calcium. N Engl J Med 1992;326:357-362.
228. Lips P, Graafmans WC, Ooms ME, et al. Vitamin D supplementation and fracture incidence in elderly persons: a randomized, placebo-controlled clinical trial. Ann Intern Med 1996;124:400-406.
229. Cumming RG, Cummings SR, Nevitt MC, et al. Calcium intake and fracture risk: results from the study of osteoporotic fractures. Am J Epidemiol 1997;145:926-934.
230. Liberman UA, Weiss SR, Broll J, et al. Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. The Alendronate Phase III Osteoporosis Treatment Study Group. N Engl J Med 1995;333:1437-1443.
231. Black DM, Cummings SR, Karpf DB, et al. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group. Lancet 1996;348:1535-1541.
232. Ensrud KE, Black DM, Palermo L, et al. Treatment with alendronate prevents fractures in women at highest risk: results from the Fracture Intervention Trial. Arch Intern Med 1997;157:2617-2624.
233. Cummings SR, Black DM, Thompson DE, et al. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. JAMA 1998;280:2077-2082.
234. Harris ST, Watts NB, Genant HK, et al. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. Vertebral Efficacy With Risedronate Therapy (VERT) Study Group. JAMA 1999;282:1344-1352.
235. Harris ST, Watts NB, Jackson RD, et al. Four-year study of intermittent cyclic etidronate treatment of postmenopausal osteoporosis: three years of blinded therapy followed by one year of open therapy. Am J Med 1993;95:557-567.
236. Storm T, Kollerup G, Thamsborg G, et al. Five years of clinical experience with intermittent cyclical etidronate for postmenopausal osteoporosis. J Rheumatol 1996;23:1560-1564.
237. Montessori ML, Scheele WH, Netelenbos JC, et al. The use of etidronate and calcium versus calcium alone in the treatment of postmenopausal osteopenia: results of three years of treatment. Osteoporos Int 1997;7:52-58.

238. Lyritis GP, Tsakalakos N, Paspati I, et al. The effect of a modified etidronate cyclical regimen on postmenopausal osteoporosis: a four-year study. Clin Rheumatol 1997;16:354-360.
239. Reginster J, Minne HW, Sorensen OH, et al. Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. Vertebral Efficacy with Risedronate Therapy (VERT) Study Group. Osteoporos Int 2000;11:83-91.
240. McClung MR. Bisphosphonates in osteoporosis: recent clinical experience. Expert Opin Pharmacother 2000;1:225-238.