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GERIATRIC GYNECOLOGY

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Geriatric gynecology is a rapidly expanding field. In the United States, the percentage of women aged 65 years and older is projected to increase significantly in coming decades. [1] The number of older women seeking both routine and acute gynecologic care, as well as surgical interventions, can be expected to rise dramatically. We must learn how the gynecologic needs of younger and older women differ and then re-evaluate the gynecologic care we have routinely offered in the past to determine outcomes and benefits in this older population of women. With rapidly changing technology and advances in gynecologic care, we must determine which interventions are appropriate and beneficial, identify unmet needs, and allocate resources accordingly. This chapter assesses the progress made in geriatric gynecology research since the publication of *New Frontiers in Geriatrics Research* [2] and proposes areas requiring future investigation.

The three Key Questions in gynecology identified in *New Frontiers* are quoted below. Progress made in answering these questions is outlined in this review. However, important areas of geriatric gynecology remain open for investigation; two new topics with new items for the research agenda are proposed (see the section New Horizons in Geriatric Gynecology, at the end of this chapter).

> ***Gyn KQ1***: **How can the immediate and long-term functional impact of gynecologic surgery on older women be improved?**
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> ***Gyn KQ2***: **How can normal urogenital function be maintained in aging and age-related conditions?**
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> ***Gyn KQ3***: **Which older women should be encouraged to initiate or continue estrogen replacement or other hormonal therapy?**

METHODS

The MEDLINE database was searched via PubMed of the National Library of Medicine. All publications from 1 January 2001 to 31 December 2005 were included. The search was limited by the following specifications: English language, human female subjects, and subject age 65 years or greater. 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, electrolyte imbalance, falls, deconditioning, urinary incontinence, functional loss*), comorbidity, outcome, quality of life, prognosis, recovery, length of stay, and discharge planning. All articles identified by the search specifications were reviewed,

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and those containing information pertinent to the research questions were selected for inclusion in this review.

PROGRESS IN GERIATRIC GYNECOLOGY RESEARCH

PERIOPERATIVE MANAGEMENT FOR GYNECOLOGIC SURGERY

See *New Frontiers,* pp. 225–227.

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.**

New Research Addressing This Question: No prospective observational studies designed to investigate common geriatric perioperative complications specifically after gynecologic surgeries were identified. One retrospective study of 62 women aged 80 years and older undergoing gynecologic surgery found that 14% experienced perioperative complications. Three percent had mental status changes consistent with delirium. There were no perioperative deaths. Mean hospital stay was 3.6 days, and 3% of the patients were discharged to a skilled nursing facility. [3] Two prospective studies from the Second International Study of Postoperative Cognitive Dysfunction included elderly (60 years and older) women undergoing gynecologic surgeries. [4,5] The incidence of long-term postoperative cognitive dysfunction was not higher after major noncardiac surgery in patients randomized to general anesthesia than in those randomized to regional anesthesia. However, the results did suggest a possible increase in early postoperative cognitive dysfunction in those receiving general anesthesia. [4] For patients undergoing minor surgery under general anesthesia, age 70 years and older plus inpatient surgery were risk factors for postoperative cognitive dysfunction. [5] In another study, men and women (mean age 73) undergoing cystoscopy or hysteroscopy were found to have a higher rate of cognitive dysfunction 24 hours after surgery than age-matched control persons not undergoing surgery. [6] Among all inpatient falls reported over 13 weeks at an academic hospital, half were found to be elimination-related. [7]

Modification of This Question in Light of New Research: This question remains inadequately addressed and should remain on the research agenda. Prospective observational studies designed to investigate common geriatric complications specifically after gynecologic surgery are still needed.

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.**

New Research Addressing This Question: No observational studies designed to identify risk factors for geriatric perioperative complications specifically after gynecologic surgery

were identified. In a prospective study that included women (mean age 67) undergoing gynecologic surgery, age above 70, previous delirium, and pre-existing cognitive impairment were found to be predictive of postoperative delirium. [8]

Modification of This Question in Light of New Research: This question remains inadequately addressed, and studies are still needed to identify risk factors for geriatric perioperative complications after gynecologic surgery. The question should remain on the research agenda.

***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.**

New Research Addressing This Question: Most recent gynecologic surgery studies have included description of the comorbidities of their subjects. However, estrogen status is less often included (unless a focus of the study), and studies describing functional and cognitive status were not identified.

Modification of This Question in Light of New Research: Future gynecologic surgery studies that evaluate or describe outcomes, morbidity, or mortality should describe functional status, cognitive status, and estrogen status of elderly women subjects. Description of estrogen status should include both menopausal status and use of hormone replacement therapies.

***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.**

New Research Addressing This Question: Few large observational or randomized gynecologic surgery studies have been published. Because of the difficulties of surgical randomization and objective evaluation, most published studies are descriptive and rarely large enough to permit meaningful stratification. The VALUE study evaluating more than 37,000 women undergoing hysterectomy did stratify results according to age group, with the oldest stratum aged 60 years and older. [9]

Modification of This Question in Light of New Research: Results from gynecologic surgery studies should be stratified by age. Stratification should be standardized, using defined age groups to facilitate comparisons between studies. A standard scheme of 5-year strata is recommended, ie, age 65 to 69, 70 to 74, 75 to 79, etc. For smaller studies or as an additional analysis in larger studies, comparison of age groups 65 to 79 and age 80 and older will help identify differences that may exist in the very elderly population.

***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.**

New Research Addressing This Question: Only one study designed to compare quality-of-life outcomes between surgical and nonsurgical management of a gynecologic condition was identified. In a prospective study of women (aged 30 to 75 years) undergoing either prophylactic salpingo-oophorectomy or gynecologic screening for high risk for

hereditary ovarian cancer, no significant difference in general quality of life was found between the groups. Women undergoing prophylactic surgery had fewer condition-specific worries and a more favorable cancer risk perception, but also had significantly more endocrine symptoms and worse sexual function. [10]

Modification of This Question in Light of New Research: This question remains inadequately addressed, and studies comparing outcomes of surgical and nonsurgical management of gynecologic conditions are still needed. To improve study validity and facilitate comparisons, studies should employ standardized validated instruments for evaluation of quality-of-life and functional outcomes.

> ***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.**

New Research Addressing This Question: No studies were identified.

Modification of This Question in Light of New Research: No modification of this question is recommended.

> ***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.**

New Research Addressing This Question: No studies were identified.

Modification of This Question in Light of New Research: No modification of this question is recommended.

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

New Research Addressing This Question: No randomized controlled trials were identified. In one case-control study of women undergoing joint arthroplasty, no association was found between perioperative hormone replacement therapy and the incidence of postoperative venous thromboembolism. [11]

Modification of This Question in Light of New Research: This question has been inadequately addressed, and studies evaluating discontinuation of estrogen replacement therapy in the perioperative period are still needed. Because of the low incidence of postoperative vascular complications in elderly women undergoing gynecologic surgery and the decreasing prevalence of the use of hormone replacement therapy, multicenter studies may be required to answer this question.

> ***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.**

New Research Addressing This Question: No studies comparing different surgical techniques and using quality-of-life measurements as the primary outcome were identified. However, many studies now include quality of life as a secondary outcome. Six studies comparing various incontinence surgeries included quality-of-life data: suprapubic arch sling versus tension-free vaginal tape (TVT), [12] TVT versus pubovaginal sling, [13,14] periurethral versus transurethral collagen injections, [15] Burch versus laparoscopic colposuspension methods, [16] and Burch urethropexy versus TVT. [17] Quality-of-life outcomes were similar in all the comparisons in these studies except for two: improved subjective cure rates were better for open and laparoscopic colposuspensions utilizing suture placement than for laparoscopic mesh colposuspension, [16] and better for TVT than for Burch colposuspension. [17] One study on pelvic organ prolapse surgery included quality-of-life data in the comparison of abdominal sacral colpopexy and vaginal sacrospinous ligament suspension and found that both procedures improved postoperative quality of life. [18]

Modification of This Question in Light of New Research: The majority of gynecologic surgery studies are designed to evaluate a single procedure as treatment of a gynecologic condition and are commonly retrospective or descriptive. Studies are still needed comparing different procedures as treatment for the same gynecologic condition, especially for new surgical procedures. All studies evaluating outcomes of different surgical techniques should include quality-of-life data. To improve study validity and facilitate comparisons, studies should employ standardized validated instruments for evaluating quality-of-life outcomes.

> ***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.**

New Research Addressing This Question: No studies were identified.

Modification of This Question in Light of New Research: No modification of this question is recommended.

> ***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.**

New Research Addressing This Question: No guidelines have been presented or validated.

Modification of This Question in Light of New Research: Before guidelines for the selection of patients can be established, observational studies must be performed describing both objective and quality-of-life outcomes of gynecologic surgery in older institutionalized women.

> ***Gyn 12 (Level D)***: **As medical care changes and improves, descriptive and 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.**

New Research Addressing This Question: No studies were identified.

Modification of This Question in Light of New Research: Though many studies do describe comorbidities present in the study population (see Gyn 3), this is often provided solely to describe the study population. Few studies are adequately powered to provide meaningful data regarding the effect of these comorbidities on outcomes. The question should remain unmodified on the research agenda.

UROGENITAL HEALTH

Pelvic Organ Prolapse

See *New Frontiers*, pp. 228–230. For new agenda items under this topic, see the section New Horizons in Geriatric Gynecology at the end of the chapter.

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

New Research Addressing This Question: No studies were identified.

Modification of This Question in Light of New Research: No modification of this question is recommended.

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

New Research Addressing This Question: Observational studies evaluating surgical outcomes now more commonly include quality-of-life measures as a secondary outcome and more commonly use validated quality-of-life measures. Three studies included only postoperative quality-of-life data but described favorable quality-of-life results after vaginal paravaginal defect repair [19] and abdominal sacrocolpopexy. [20,21] Three years after high uterosacral ligament suspension, women were found to have had improvement in each component of a quality-of-life survey. [22] Quality of life was improved 24 months after cadaveric prolapse repair for treatment of cystocele and stress urinary incontinence. [23] Posterior colporrhaphy with graft augmentation was found to be associated with improved quality of life at 1 year postoperatively. [24] Two studies focused specifically on quality of life after prolapse repair in elderly women. After anterior vaginal wall surgery, women (mean age 70, range 6 to-88) reported improvement over preoperative values in all quality-of-life components. [25] Age-stratified results confirmed improvement in women aged 65 to 70 years, 71 to 79, and 80 or older. Cystocele repair in women (mean age 83, range 80 to 93) resulted in improved quality-of-life scores at 21 months. [26]

Modification of This Question in Light of New Research: All studies describing outcomes of surgical treatment of pelvic organ prolapse should include both preoperative and postoperative assessment of quality of life by the use of standardized, validated instruments. Long-term (5 years or longer) data on quality-of-life outcomes are still needed.

> ***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.**

New Research Addressing This Question: Two studies were identified evaluating factors associated with long-term pessary use. Of women (mean age 65 years, range 29 to 90) treated with a pessary for pelvic organ prolapse or urinary incontinence, 60% were found to have continued to use the pessary over the long term (median 147 days). [27] Another study found continued use to be significantly more likely in women being treated for prolapse and in those who were sexually active. After successful fitting and initial satisfaction at 2 months, 73% of women (mean age 71, range 40 to 92) continued to use a pessary at 1 year. Continued pessary use was found to be associated with older age and poor surgical risk, and decision to proceed with surgical repair to be associated with sexual activity, stress incontinence, stage III to IV posterior wall prolapse, and desire for surgery at first visit. Age 65 years or older was the best age cut-off to predict continued pessary use. [28]

Several studies have evaluated short-term outcomes of pessary use as treatment of pelvic organ prolapse and provide data important to an understanding of which women are more likely to use a pessary successfully. In women with pelvic organ prolapse (mean age 70, range 24 to 92), a ring or Gellhorn pessary was successfully fitted in 73%. Unsuccessful fitting was associated with vaginal length 6 cm or less and introitus 4 fingerbreadths or larger. In a 2-month follow-up of the women successfully fitted with a pessary, 92% of the women were satisfied with use of the pessary. [28] Vaginal bulge, pressure, discharge, and splinting were all significantly decreased with pessary use. In women with urinary symptoms prior to pessary placement, urinary symptoms were improved, but in those without baseline urinary symptoms, de novo stress incontinence occurred in 21%. [29] Continued pessary use at 3 weeks after successful fitting was not associated with prolapse stage or compartment and was lower in women with history of hysterectomy or prolapse surgery. [30]

Modification of This Question in Light of New Research: Studies have adequately described factors associated with successful pessary fitting and both short- and medium-term use. Observational studies are needed to determine the impact of pessary type on treatment of different degrees of prolapse, prolapse in different vaginal compartments, or for different combinations of prolapse. Observational studies are needed to describe factors associated with long-term (more than 1 year) and very long-term (more than 5 years) use of pessaries.

> ***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.**

New Research Addressing This Question: No studies were identified.

Modification of This Question in Light of New Research: No modification of this question is recommended.

> ***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.**

New Research Addressing This Question: Multiple studies in this area have been published or are under way. They are discussed here in three groups: those focused on pelvic

tissue alterations, those focused on anatomic changes, and those focused on genetics.

Six studies addressed smooth muscle alterations. Three studies found the fractional area of smooth muscle in vaginal cuff specimens and round ligament tissue to be smaller from women with pelvic organ prolapse than from those without prolapse. [31–33] Caldesmon, a protein involved in regulation of smooth muscle contractility, was found to be increased in vaginal muscularis from women with prolapse. [34] No difference was found in smooth muscle content of the arcus tendineus fasciae pelvis of premenopausal or postmenopausal women with anterior vaginal prolapse. [35] Comparison of myofibroblasts from vaginal tissue of women with and without prolapse found those from women with prolapse to be significantly less contractile. [36]

Three studies assessed elastin or elastolytic activity and prolapse: In periurethral vaginal tissue biopsies from women with urinary incontinence or prolapse or both, alpha-1 antitrypsin mRNA and protein levels were found to be significantly decreased. Elastolytic and proteolytic enzyme activity were not different between the groups. [37] The elastin content of the arcus tendineus fasciae pelvic in women with anterior wall prolapse was not found to be different premenopausal and postmenopausal women. [35] Biomechanical assessment of anterior vaginal wall specimens from premenopausal and postmenopausal women with symptomatic prolapse demonstrated a higher elastic modulus in and increased stiffness of the tissue in the postmenopausal women. [38]

Several studies focused on the role of collagen in pelvic organ prolapse. Collagen type I was decreased in arcus tendineus fasciae pelvic of unestrogenized menopausal women with anterior vaginal wall prolapse. [35] Another found the cervical collagen content of 14 women with pelvic organ prolapse (with or without stress urinary incontinence) to be significantly lower than in 17 control subjects. [39] The collagen type III content of paravaginal and uterosacral tissue was not found to differ in women with and without prolapse. [40] Other researchers found women with stress incontinence and pelvic organ prolapse to have increased collagen breakdown in comparison with women in the control group. [41] One study comparing women with and without uterine prolapse found that those with prolapse had decreased collagen content of the parametrial tissue; however, no differences in collagen content at the vaginal apex were found. [42] In parametrial tissue samples of women with and without prolapse, collagen type I content was found to be the same in both groups, but the collagen type I fiber of women with prolapse was shorter and thinner. [43]

One study of other tissue components found total glycosaminoglycans, chondroitin sulfate, dermatan sulphate, and heparin sulfate to be decreased in vaginal tissue of postmenopausal women with stage 2 or 3 prolapse. [44]

A number of studies examined hormone levels and receptors in prolapse. One such study found levels of androstene-3 beta, 16 beta, 17 beta-triol (5-AT), 11 beta-hydroxy, and 17 beta-estradiol to be increased in postmenopausal women with prolapse, but tetrahydrocortisone to be increased in women without prolapse. [45] The percentage of cells expressing estrogen receptor-α, estrogen receptor-β, androgen receptor, and progesterone receptor was found to be higher in cardinal ligament samples from women with prolapse. [46] In a study comparing premenopausal women with and without prolapse, serum estradiol levels and ligament estrogen receptor levels were found to be significantly lower in cardinal and uterosacral ligament and blood samples from those with prolapse. There was no difference in serum or tissue levels between postmenopausal women with

and without prolapse. [47] Analysis of uterosacral ligaments from 45 women revealed decreased numbers of estrogen and progesterone receptors in the ligaments of postmenopausal women; however, this change did not correlate with changes in ligament resilience. [48]

The role of anatomic alterations in pelvic organ prolapse was the focus of four studies. One such study, using color thickness mapping with magnetic resonance imaging, found women without prolapse to have bilaterally thicker and bulkier puborectalis muscles. [49] In a second magnetic resonance imaging study of women with varying stages of prolapse, changes in levator ani morphology were found to be independent of prolapse stage and were not identified in all women with prolapse. The levator hiatus was wider with increasing prolapse stage, suggesting changes in puborectalis function. [50] In another study, magnetic resonance imaging measurements indicated that women with prolapse at least 2 cm beyond the introitus had larger vaginal perimeter and cross-sectional area than women in the control group. These researchers saw no difference in vaginal thickness. [51] In a case-control study of women with and without pelvic floor disorders who underwent magnetic resonance imaging of the pelvis, wider transverse pelvic inlet and shorter obstetrical conjugate were found to be associated with pelvic floor dysfunction. [52]

Three studies have addressed the role of genetics in pelvic organ prolapse. In a study of nulliparous white twins and their sisters (ages 18 to 24), the majority (59%) of the variance in bladder neck descent as seen on ultrasound was found to be due to genetic factors. [53] In the same population, the association of pelvic organ and elbow mobility was also found to be mediated by common genes. [54] Analysis of gene expression in pubococcygeus muscle specimens from women with and without prolapse identified 280 genes that were underexpressed and 500 genes that were overexpressed in women with prolapse. Differential gene expression was seen in genes related to actin, myosin, and extracellular matrix proteins. [55]

Modification of This Question in Light of New Research: Many studies in the basic science of pelvic organ prolapse are ongoing, research attention which promises results that could impact clinical management. When and if genetic pathways are clearly delineated that predispose a woman to the development of pelvic organ prolapse, studies will be needed to identify and quantify the contribution of environmental factors on the expression of these genetic susceptibilities.

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

New Research Addressing This Question: No studies were identified.

Modification of This Question in Light of New Research: No modification of this question is recommended.

***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.**

New Research Addressing This Question: No long-term studies evaluating the relative contributions of delivery route on development of pelvic organ prolapse were identified.

Studies evaluating pelvic organ prolapse in the immediate postpartum period are available. Pelvic organ prolapse quantification (POP-Q) measurements were significantly different in women after vaginal delivery and nulliparous women who constituted the control group. Differences were seen in Aa, Ba, TVL, and GH after spontaneous delivery and in Aa, Ab, Ap, Bp, D, TVL, and GH after vacuum-assisted delivery. [56] In another study, nulliparous pregnant women who underwent POP-Q staging before and after delivery were found to have POP-Q stage that was higher in the third trimester and postpartum than during the first trimester. Postpartum POP-Q stage was higher after vaginal delivery than after cesarean delivery. [57] In a study of nulliparous pregnant women who underwent prolapse evaluation at 36 weeks gestation and 6 weeks postpartum, 32% who underwent spontaneous vaginal delivery and 35% who underwent cesarean section during active labor were found to have developed prolapse beyond that seen at 36 weeks. [58]

Modification of This Question in Light of New Research: Pelvic organ prolapse may develop during pregnancy and delivery. However, no data are available from studies evaluating regression or progression of pregnancy and delivery-related prolapse and its relationship to the development of symptomatic prolapse later in life. This question therefore should remain unmodified on the research agenda.

***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.**

New Research Addressing This Question: No studies were identified.

Modification of This Question in Light of New Research: No modification of this question is recommended.

***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.**

New Research Addressing This Question: One randomized, double-blind, placebo-controlled study of the effect of systemic estrogen on the progression of pelvic organ prolapse was identified. Women with similar stages of prolapse were randomized to 0.625 mg of conjugated equine estrogen, 20 mg of tamoxifen, 60 mg of raloxifene, or placebo for 20 weeks. After treatment, 75% of women receiving raloxifene, 60% receiving tamoxifen, 22% receiving estrogen, and 18% receiving placebo were found to have increases in prolapse on repeat examination. The changes in the raloxifene and tamoxifen groups were significant. However, only one subject had a large enough change in POP-Q measurements to increase the prolapse stage. [59] An analysis of three randomized, controlled, long-term trials of raloxifene found no evidence of increased rates of surgery for prolapse in women receiving the medication. [60]

Modification of This Question in Light of New Research: Even though short-term use of selective estrogen receptor modulators may be associated with greater progression of prolapse than the use of estrogen or placebo, these changes do not appear to be clinically significant. Long-term studies and studies evaluating the effect of local estrogen are still needed. This question should remain unmodified on the research agenda.

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.**

New Research Addressing This Question: No studies were identified.

Modification of This Question in Light of New Research: No modification of this question is recommended.

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.**

New Research Addressing This Question: As discussed in Gyn 21, women randomized to a 20-week course of raloxifene or tamoxifen had significantly greater progression of prolapse than women receiving estrogen or placebo. [59] However, changes appeared to be subclinical, and in an analysis of three randomized, controlled, long-term trials of raloxifene, there was no evidence of increased rates of surgery for prolapse in women receiving the medication. [61] In a randomized controlled trial of women aged 65 years or older that was stopped after 10 months because of adverse events, women randomized to levormeloxifene for the treatment of osteoporosis were found to have significantly increased pelvic organ prolapse in comparison with women on placebo (7% versus 2%). However, the method of prolapse quantification was not identified, and data on degree of prolapse or development of symptomatic prolapse were not presented. [60]

Modification of This Question in Light of New Research: The question has been inadequately addressed and should remain unmodified on the research agenda.

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

New Research Addressing This Question: No randomized controlled trials evaluating whether pessary use retards progression of pelvic organ prolapse were identified, but one observational study has been published. Women (mean age 75 years, range 62 to 83) who used a pessary for at least 1 year were evaluated for progression of prolapse. After 1 year, there was a significantly significant improvement in prolapse stage: 4 women were improved and no women were worse. However, prolapse evaluation after 1 year may have been compromised, as one third of the women did not remove their pessary at least 48 hours prior to examination. [62]

Modification of This Question in Light of New Research: The question has been inadequately addressed and should remain unmodified on the research agenda.

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.**

New Research Addressing This Question: One observational study was identified evaluating pelvic floor exercise in women age 60 or older to prevent progression of pelvic organ prolapse. After 24 months, 27.3% of women who were trained in pelvic floor

muscle exercise and followed a daily regimen showed progression of prolapse, in comparison with 72.2% of women in the control group. The difference in prolapse progression rate was significant only in women with severe prolapse.[63] No randomized controlled trials have evaluated pelvic floor muscle exercises as a treatment to retard progression of pelvic organ prolapse.

Modification of This Question in Light of New Research: The question has been inadequately addressed and should remain unmodified on the research agenda.

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

New Research Addressing This Question: Two studies on the natural history of pelvic organ prolapse were identified, one in pregnant women and one in postmenopausal women. In nulliparous pregnant women (mean age 21.7 years, range 18 to 38) who underwent POP-Q evaluation during their pregnancy, the majority had stage 1 prolapse and none had prolapse beyond stage 2. Comparisons of POP-Q measurements were not significantly different between the first and second or the second and third trimesters. However, significant differences were seen between the first and third trimesters, with an increase in POP-Q stage observed. The most important changes occurred at point Aa. No data were presented on further changes or resolution after delivery.[64] In the second study, 31.8% of women (mean age 64.9 years, range 50 to 79) enrolled in the Women's Health Initiative were found to have some degree of pelvic organ prolapse at baseline. The annual incidence rate was 9.3 per 100 women-years for cystocele, 5.7 for rectocele, and 1.5 for uterine prolapse. Annual progression rate for grade 1 prolapse to grade 2 or 3 (per 100 women-years) was 9.5 for cystocele, 13.5 for rectocele, and 1.9 for uterine prolapse. Progression rates for grade 0 to grade 2 or 3 were 1.2 for cystocele, 1.4 for rectocele, and .06 for uterine prolapse. No subjects progressed to grade 4 prolapse in any compartment. Annual regression rates for grade 2 or 3 prolapse to grade 0 were 9.3 for cystocele, 3.3 for rectocele, and 0 for uterine prolapse.[65]

Modification of This Question in Light of New Research: The Women's Health Initiative provides data on both progression and regression of prolapse in postmenopausal women over the course of 2 to 8 years. However, an unvalidated descriptive method of prolapse evaluation was used, and no data on development or regression of prolapse-related symptoms were provided. Without data regarding prolapse-related symptoms and correlation with stage of prolapse, the clinical relevance of the findings is unclear. Future studies describing the progression and regression of pelvic organ prolapse should describe prolapse by using a validated reproducible system such as the POP-Q and collect data regarding associated symptoms by using standardized questionnaires.

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

New Research Addressing This Question: No studies were identified.

Modification of This Question in Light of New Research: No modification of this question is recommended.

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

New Research Addressing This Question: In a cross-sectional analysis of women enrolled in the Women's Health Initiative, potentially modifiable risk factors (excluding childbirth) identified for prolapse were waist circumference greater than 88 cm, overweight (body mass index or BMI 25 to 30), obesity (BMI greater than 30), and constipation. [66] A case-control study of women with stage III or IV prolapse identified age, weight of largest vaginal delivery, hysterectomy, and previous prolapse surgery as risk factors for severe prolapse. [67] Of these, only history of hysterectomy may be potentially modifiable, as alternative treatments for conditions traditionally treated with hysterectomy are developed. In this study, BMI was not found to be a significant risk factor. In the Pelvic Organ Support Study, potentially modifiable risk factors for prolapse were overweight and obesity. [68] A second analysis of this study found straining at stool to be significantly associated with anterior vaginal wall prolapse and perineal descent. [69] A case-control study of women with prolapse (84% with stage III or IV) found the risk for constipation to be higher in women with prolapse, although this may be at least partially explained by lower fiber intake in that group. [70]

Modification of This Question in Light of New Research: This question has been adequately addressed and can be dropped from the research agenda.

Vulvovaginal Conditions

See *New Frontiers,* pp. 232–233.

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

New Research Addressing This Question: The Female Sexual Function Index was used in assessing 42 women with vulvodynia and was found to be a valid measure of sexual function in this population of women. [71] The Functional Assessment of Cancer Therapy—Vulvar was used in assessing 20 women undergoing treatment of vulvar cancer and was found to be a reliable and valid measure of quality of life of women with vulvar cancer. [72] Studies regarding the development of instruments evaluating other aspects of quality of life in women with vulvovaginal conditions were not identified.

Modification of This Question in Light of New Research: Only two validated questionnaires have been developed, and their use is limited to very specific populations. The question has been inadequately addressed and should remain unmodified on the research agenda.

> ***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.**

New Research Addressing This Question: No studies were identified.

Modification of This Question in Light of New Research: No modification of this question is recommended.

> ***Gyn 31 (Level 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.**

New Research Addressing This Question: Of women (mean age 42.1 years, range 18 to 84) evaluated at a vulvar specialty clinic, 66% reported an overall improvement in symptoms. In comparison with female norms in the United States, quality-of-life measures were found to be significantly lower in all three categories: general health, role physical, and role emotional; however, scores in all three categories were higher for women who were subjectively improved. Quality-of-life measures were not stratified by age. [73]

Modification of This Question in Light of New Research: The question has been inadequately addressed and should remain unmodified on the research agenda.

***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.**

New Research Addressing This Question: Randomized trials of local estrogen for treatment of urogenital symptoms were identified, with study periods from 3 months to 1 year. In postmenopausal women randomized to 25 μg estradiol tablet or 1 g of conjugated estrogen cream for 12 weeks, estrogen cream was found to be superior in relieving vaginal dryness and dyspareunia, but both medications produced improvement in urogenital symptoms. [74] Postmenopausal women (mean age 53.4, range 40 to 64) treated with transdermal hormone therapy (17-β-estradiol plus medroxyprogesterone acetate) for 4 months plus either vaginal estriol or placebo had similar improvements in urinary symptoms after 4 months. However, women in the vaginal estriol group reached significant improvement in urinary complaints more quickly than women randomized to placebo. [75] Another study found that treatment of postmenopausal women with intravaginal estriol ovules for 6 months produced greater improvement of urogenital symptoms than placebo. [76] A study comparing 25 μg of micronized 17-β-estradiol for 12 months and placebo found symptomatic improvement of vaginal atrophy to be significantly higher in the treatment group. Women in the treatment group had significant improvements in vaginal dryness, itching or burning, recurrent vaginitis, dyspareunia, and atrophy. [77]

Modification of This Question in Light of New Research: Treatment of urogenital symptoms with estrogen appears to be superior to placebo. This question has been adequately addressed, and the question can be dropped from the research agenda.

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

New Research Addressing This Question: No studies were identified.

Modification of This Question in Light of New Research: No modification of this question is recommended.

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

New Research Addressing This Question: In a family with four of five siblings diagnosed with lichen sclerosus, the HLA-B08 and HLA-B18 alleles were identified in each of the affected children and were absent in the unaffected sibling, suggesting a possible genetic link. [78] Analysis of tissue samples from patients with lichen sclerosus have also

suggested possible roles of oxidative stress, autoantibodies to extracellular matrix protein 1, antigen-mediated vasculitis, and alterations in cell-mediated immunity.[79–84] In one study, alterations in inter-α-trypsin inhibitor were found to cause accumulation of hyaluronic acid in the superficial dermis of persons with lichen sclerosus.[85] Differential distribution of transforming growth factor subtypes and collagens type I and III, elastin, and fibrillin have been identified in lichen sclerosus specimens.[86,87]

Modification of This Question in Light of New Research: Although a few studies have addressed this question, results are preliminary. The question has been inadequately addressed and should remain unmodified on the research agenda.

> ***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.**

New Research Addressing This Question: No studies were identified.

Modification of This Question in Light of New Research: No modification of this question is recommended.

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

New Research Addressing This Question: No studies were identified.

Modification of This Question in Light of New Research: No modification of this question is recommended.

> ***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.**

New Research Addressing This Question: No randomized trials were identified. Small observational studies have documented clinical improvement in vulvar intraepithelial neoplasia treated with topical imiquimod, although treatment may be limited by local side effects.[88–91] No studies evaluated its effect on progression to invasive disease.

Modification of This Question in Light of New Research: The question has been inadequately addressed and should remain unmodified on the research agenda.

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

New Research Addressing This Question: No studies were identified.

Modification of This Question in Light of New Research: No modification of this question is recommended.

Urinary Incontinence

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

Sexuality

See *New Frontiers*, pp. 234–235. For new agenda items under this topic, see the section New Horizons in Geriatric Gynecology at the end of the chapter.

***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.**

New Research Addressing This Question: No information was identified concerning the extension of ongoing studies to include older women.

Modification of This Question in Light of New Research: No modification of the question is recommended.

***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.**

New Research Addressing This Question: In one study, in postmenopausal women (aged 51 to 55 years) with hypertension, treatment with valsartan was found to significantly improve sexual desire, changes in behavior, and sexual fantasies, while treatment with atenolol resulted in worsened sexual desire and fantasies. [92]

Modification of This Question in Light of New Research: The question has been inadequately addressed and should remain unmodified on the research agenda.

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

New Research Addressing This Question: Searches of the literature addressing specific medical conditions were performed—hypertension, heart disease, diabetes mellitus, end-stage renal failure, stroke, breast cancer, and ovarian cancer—with the following results.

No studies evaluating the effects of hypertension on sexual function in older women were identified.

One study concerning heart disease was located. The medical outcomes study of the Heart and Estrogen/Progestin Replacement Study evaluated sexual function in 2763 women with a mean age of 67 years and known coronary disease. Of the women studied, 39% were sexually active and 65% reported at least one type of sexual dysfunction. No specific problems related to coronary artery disease were reported except that lack of chest discomfort was associated with being sexually active. [93]

No studies were identified evaluating sexual dysfunction in older women with diabetes mellitus.

Sexual dysfunction was found to be common in women undergoing routine hemodialysis for end-stage renal failure. Sexual dysfunction was associated with older age and depression, and women with lower sexual function scores also had poorer quality-of-life scores. [94]

Two small studies that included older women evaluated the effect of stroke on sexual function. Depressive symptoms, impaired activities of daily living or disability, age, and

psychological aspects or relationship with partner were found to be associated with worse sexual function. [95,96]

Breast cancer and sexuality were the focus of two studies. In a cross-sectional analysis of data from a randomized controlled trial of nonhormonal treatments of menopause symptoms, relationship factors and body self-image were identified as major contributors to sexual functioning in women with a history of breast cancer. However, conditions more amenable to physician intervention included vaginal discomfort and urinary incontinence. [97] No studies addressing sexual function in women currently undergoing breast cancer treatment were identified, but one study found that women's satisfaction with their sexual life is significantly decreased after surgical treatment of breast cancer. Most women in this study reported their partner to be supportive and to have the same attitude toward them after surgery. Women who underwent modified mastectomy with adjuvant therapy had greater changes in body image than those who underwent lumpectomy with radiation. [98]

One study addressed sexual function in ovarian cancer patients. Of women up to age 75 currently undergoing treatment for epithelial ovarian cancer, 50% engaged in sexual activity within the preceding month. The women who were sexually active reported decreased sexual desire, vaginal dryness, and dyspareunia. Reasons for sexual inactivity were lack of interest, physical limitations making sex difficult, and fatigue. Women were more likely to be sexually active if they were younger, had positive body self-image, were farther out from diagnosis, and were not receiving active treatment. [99]

Modification of This Question in Light of New Research: The question has been inadequately addressed, especially for hypertension and diabetes, which are commonly present in older women. The question should remain unmodified on the research agenda.

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.

New Research Addressing This Question: Two studies have evaluated the pharmacokinetics of oral testosterone undecanoate in postmenopausal women. In the first, women received two doses of 20, 40, or 80 mg at 12-hour intervals, and serum testosterone levels were found to be dose proportional after oral administration of two doses. [100] The second study found the administration of testosterone with food to increase bioavailability. [101]

Treatment of postmenopausal women (mean age 55.3 years, range 45 to 70) with 10, 20, or 30 mg of testosterone as a 1% testosterone percutaneous gel daily for 2 weeks resulted in adequate serum levels at the 10 mg dose. [102] A second dose-effect trial evaluated the transdermal testosterone patch in women (mean age 50, range 24 to 70) at doses of 150 µg/day, 300 µg/day, or 450 µg/day twice a week for 24 weeks. Women receiving the 300 µg/day patch experienced higher increases in sexual desire and in frequency of sexual activity than women receiving placebo. There was no apparent treatment effect in the 150 µg/day group, and there was no difference between the 450 µg/day group and the 300 µg/day or placebo groups. There were no differences in adverse effects between any of the groups. [103]

Modification of This Question in Light of New Research: This question has been adequately addressed, and it can be dropped from the research agenda.

***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).**

New Research Addressing This Question: Four studies investigating the effect of androgen replacement on sexual function were identified that enrolled women age 65 or older. Surgically postmenopausal women on estrogen replacement who also used the 300 µg/day testosterone patch for 24 weeks experienced significantly higher increases in sexual desire and in frequency of satisfying sexual activity than the women on placebo. [103] Women receiving esterified estrogen plus methyltestosterone (1.25mg/2.5mg) reported more frequent sexual activity and increased pleasure or orgasm than women receiving estrogen alone. [104] Postmenopausal women on estrogen plus progesterone replacement receiving oral testosterone supplements were found to have a significant improvement in sexual desire and satisfaction in comparison with those on unsupplemented hormone replacement. [105] Surgically menopausal women on estrogen replacement therapy with hypoactive sexual desire disorder treated with testosterone patch twice weekly were found to have increased sexual desire and satisfying sexual activity in comparison with women receiving placebo. [106] The addition of testosterone undecanoate to estrogen replacement therapy in postmenopausal women (aged 45 to 60) was found to improve enjoyment of sex, satisfaction with frequency of sexual activity, and interest in sex in comparison with estrogen alone. [107] Other outcomes associated with testosterone replacement therapy in older woman are reduction in total cholesterol, high-density lipoprotein, and triglyceride levels, reduction in plasma viscosity, increased total lean body mass, and decreased body fat percentage. [104,105,108] According to one study, the use of dehydroepiandrosterone in postmenopausal women does not increase muscle cross-sectional area, muscle strength, or muscle function. [109]

Modification of This Question in Light of New Research: The addition of androgen replacement to hormone replacement therapy in menopausal women appears to improve sexual function and may have other health benefits. This question has been adequately addressed and can be dropped from the research agenda.

***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.**

New Research Addressing This Question: One study of the effects of oral and transdermal estrogen replacement therapy on sex hormone–binding globulin (SHBG) and free testosterone levels was identified; however, the mean age of participants was 45 years. SHBG levels were significantly higher than baseline in the group on oral estrogen replacement after 1 year, although levels were not different at 2 years from those at 1 year. There was no increase in SHBG levels in the transdermal group at either 1 or 2 years. Free testosterone levels were significantly higher in the transdermal group than in the oral group after 2 years of therapy. There were no outcomes regarding sexual function. [110] In a randomized, double-blind, placebo-controlled, cross-over study of 40 women, use of the transdermal estrogen patch for estrogen replacement was found to be associated with high

variability in estrogen levels between women. Although there was an increase in levels of SHBG, there were no significant differences in androgen levels. [111]

Modification of This Question in Light of New Research: The question has been inadequately addressed and should remain unmodified on the research agenda.

> ***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.**

New Research Addressing This Question: In a study of 19 women, including 8 postmenopausal women, subjects underwent magnetic resonance imaging of the pelvis while watching erotic video. Changes observed in both pre- and postmenopausal women included increased width of vestibular bulb and labia minora and increased enhancement of the bulb, labia minora, and clitoris. Unlike premenopausal women, postmenopausal women did not show any enhancement of the vagina. There were no structural or enhancing changes in the labia majora, urethra, cervix, or rectum in either group. Blood flow changes were seen and were mainly the same in both pre-and postmenopausal women. [112]

Modification of This Question in Light of New Research: The question has been inadequately addressed and should remain unmodified on the research agenda.

> ***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.**

New Research Addressing This Question: No studies were identified.

Modification of This Question in Light of New Research: No modification of this question is recommended.

> ***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.**

New Research Addressing This Question: In one study, polycarbophil-based vaginal moisturizer treatment in postmenopausal women was found to have a positive effect on the vaginal maturation, as evidenced by increased mean cellular area; however, there were no differences in maturation value or index. [113] The only study identified on nonhormonal treatment of vaginal atrophy evaluated the effect of a soy-rich diet on the vaginal epithelium. In asymptomatic postmenopausal women under 60 years of age, both the hormone replacement and soy diet were found to increase vaginal maturation in comparison with the control group. Maturation indices were higher in the hormone replacement therapy group than in the diet group. [114]

Modification of This Question in Light of New Research: Though nonhormonal treatments may improve vaginal maturation index, no data are available indicating whether higher vaginal maturity index resulted in decreased dyspareunia. The question has been inadequately addressed and should remain unmodified on the research agenda.

PROGRESS IN ROUTINE CARE OF THE WELL ELDERLY WOMAN

CERVICAL CANCER SCREENING

See *New Frontiers*, pp. 236–239.

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.**

New Research Addressing This Question: Results from the Health and Retirement Study and the Asset and Health Dynamics Among the Oldest Old were combined to evaluate the cost of routine screening for cervical cancer in older women. The authors estimate that, in 2000, 3.7 million screening Pap smears were performed in women older than 70 years at a cost of $47 million. [115] No studies provided a measure of comprehensive costs to primary care providers for obtaining Pap smears in elderly women for comparison with reimbursement.

Modification of This Question in Light of New Research: The question has been inadequately addressed and should remain unmodified on the research agenda.

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.**

New Research Addressing This Question: In women aged 65 to 69 years, the incidence of cervical invasive neoplasia grade 3 was 1.39 per 1000 person-years. [116] Data from nine population-based cancer registries in the U.S. Surveillance, Epidemiology, and End Results Program described trends in incidence rates of cervical cancer between 1976 and 2000. In situ squamous carcinoma of cervix (SCC) has steadily increased in women aged 55 years or older. In situ adenocarcinoma increased in white American women aged 55 to 74, but decreased after age 75. This same increase was not seen in black American women. Invasive SCC decreased in both white and black American women over this time interval. Invasive adenocarcinoma of the cervix increased with age in black American women but plateaued with age in white American women. [117] No studies have specifically focused on the incidence of cervical neoplasia and associated risk factors in elderly women.

Modification of This Question in Light of New Research: No modification of the question is recommended.

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

New Research Addressing This Question: Of women treated for invasive cervical carcinoma, those 70 years or older were significantly more likely to present with more advanced stage tumors and to have nonsquamous neoplasms. There were differences in treatment offered to older women, with older women more likely to receive primary radiotherapy, less likely to undergo surgical treatment, and nine times more likely to

receive no treatment. The risk of death from cervical carcinoma was higher in women aged 70 or older. [118] Another study found that in women with invasive cervical cancer, 5-year survival rates for those aged 65 to 74 and 75 years or older (69% and 42%) were significantly lower than the 75% survival rate seen in women under age 65. Women aged 65 or older were more likely to present with advanced disease, including higher clinical stage, vaginal bleeding, and vaginal and parametrial involvement. Prognostic factors related to age were cervical gross appearance, clinical vaginal involvement, histologic grade, and microscopic cervical and parametrial involvement. [119] Other researchers found that women older than 60 years who were diagnosed with cervical cancer at an older age were more likely to die of their disease within 3 years than were younger women; however, this result was found no longer to be significant when controlled for stage at diagnosis. [120] Another study found that when cancer was diagnosed within 3 years of a normal Pap smear, women aged 60 or older were more likely to die within 3 years than women under 60. Significantly better survival in women aged 35 years or younger with adenocarcinoma of the cervix compared with women aged 65 or older was due to differing therapy; 90% of younger women but only 41% of older women underwent radical surgery. Twenty percent of older women had primary radiotherapy, and 6% had only palliative treatment. [121] Other researchers found that more than 16% of women aged 65 or older with stage IIB/IV received no treatment while 6% of those aged 50 or younger went untreated; 10.7% of women aged 65 or older were never staged. [122] Lower 5-year survival in women aged 65 or older was due to the presence of more advanced disease at diagnosis. [123] Women aged 70 or older were found to be more likely to have higher stage at diagnosis, less likely to undergo surgery, and more likely to receive primary radiotherapy or no treatment. [124]

Modification of This Question in Light of New Research: Observational studies indicate that higher cervical cancer mortality in elderly women may be attributable to more advanced disease at diagnosis, increased likelihood of having a nonsquamous lesion, and differences in treatment offered or accepted. This question has been adequately addressed and can be dropped from the research agenda.

***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.**

New Research Addressing This Question: Only one study was identified describing the impact of a cervical cancer screening program on the incidence of cervical cancer. The Norwegian coordinated cervical cancer screening program was started in 1995; letters were sent to women without a screen in the previous 3 years rather than the usual practice of inviting all women to screening regardless of past screening. In the last 2 years of the program, cervical cancer incidence was 22% lower than in the period prior to the screening program. The proportion of women receiving Pap smears increased while overall number of Pap smears decreased, as the screening interval was increased to 3 years. [125] No studies were identified describing screening programs and their impact on cervical cancer incidence specifically targeted to low-income or minority women.

Modification of This Question in Light of New Research: The question has been inadequately addressed and should remain unmodified on the research agenda.

***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.**

New Research Addressing This Question: No studies were identified.

Modification of This Question in Light of New Research: No modification of the question is recommended.

***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.**

New Research Addressing This Question: One study found that women with primary gynecologic cancers did not have quality-of-life scores different from the expected age-specific mean values of a healthy population. Cervical carcinoma patients (up to age 83, but not stratified by age) had increase in quality-of-life scores for physical functioning, bodily pain, vitality, social functioning, and mental health associated with increasing age, while lower scores were associated with increasing age in women with ovarian and endometrial cancers. Women with progressive or recurrent cervical cancer had the lowest scores in all quality-of-life scales. [126]

Modification of This Question in Light of New Research: The question has been inadequately addressed and should remain unmodified on the research agenda.

BREAST CANCER SCREENING

See *New Frontiers*, pp. 239–241.

***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.**

New Research Addressing This Question: The data from five Swedish mammography trials have been stratified by age for analysis of long-term outcomes. [127]

Modification of This Question in Light of New Research: Large mammography studies have presented data stratified by age. Stratification should be standardized, using defined age groups to facilitate comparisons between studies. A standard scheme of 5-year strata is recommended, ie, age 65 to 69, 70 to 74, 75 to 79, etc. For smaller studies or as an additional analysis in larger studies, comparison of age groups 65 to 79 and age 80 and older will help identify differences that may exist in the very elderly population.

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

New Research Addressing This Question: No observational studies were identified. Two large cross-sectional studies including women between 50 and 90 years of age have confirmed that overall rates of mammography decline with age; however, elderly women in subjectively poor health do not discontinue screening more often than healthy women. [115,128] In a third large cross-sectional study of women with a mean age of 79

years, the presence of medical comorbidities was not found to be associated with a decrease in screening, and both hypertension and the presence of multiple comorbidities were found to be associated with increased rates of screening.[129] Among community-living nursing home–eligible women (mean age 81), 17% experienced burden from screening mammography while only 0.9% may have received benefit from screening.[130]

Modification of This Question in Light of New Research: The question has been inadequately addressed and should remain unmodified on the research agenda.

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

New Research Addressing This Question: No guidelines were identified.

Modification of This Question in Light of New Research: Before guidelines can be developed, studies are needed identifying which, if any, functional impairments and comorbid conditions are associated with lack of mammography benefit.

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.**

New Research Addressing This Question: No studies were identified.

Modification of This Question in Light of New Research: No modification of this question is recommended.

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.**

New Research Addressing This Question: No clinical trials were identified. Several studies have been published describing successful strategies for increasing mammography screening rates among low-income and minority women, but none were designed to link these strategies to improved outcomes.[131–136]

Modification of This Question in Light of New Research: The question has been inadequately addressed and should remain unmodified on the research agenda.

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.**

New Research Addressing This Question: No studies were identified. The positive association between mammographic density and breast cancer has been confirmed in several studies that enrolled a substantial number of elderly women; however, none of the studies exclusively enrolled women over the age of 65 or included data on subsequent morbidity and mortality.[137–141] One study found that in older women (mean age 60 years), increased

breast density was associated with worse prognostic factors (tumors of higher grade, larger size, and estrogen receptor [ER] negative status) than in women with fatty breast tissue. Subjects were not stratified by use of hormone replacement therapy. [142] Mammographic density has been found to be associated with both ER-positive and ER-negative tumors, suggesting that factors other than estrogen are involved. [143] Current hormone replacement therapy users are more likely to have false-negative screening mammograms than non-users, but the effect cannot be entirely attributed to the increase in breast tissue density seen with hormone replacement therapy use. [144]

Modification of This Question in Light of New Research: The question has been inadequately addressed and should remain unmodified on the research agenda.

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

New Research Addressing This Question: Only one study was identified that investigated the interpretation of mammograms in women aged 50 to 69 years. The study found that rates of breast cancer detection were not related to the radiologist's mammography volume, but rates did increase when the facilities' overall mammography volume increased. False-positive rates were lower with increased volume. [145] No studies were identified that investigated concurrence and variability of mammogram interpretations by different radiologists. In one study of a general population of patients, accuracy in screening mammogram interpretation was found to be associated with interpretation by a recently trained radiologist, number of diagnostic breast imaging examinations at the facility, designation as a comprehensive breast diagnostic screening center or freestanding mammography center, and use of double reading. [146] Other researchers found no association between accuracy and years of experience or mammography volume. [147] However, higher accuracy was found in a separate study to be associated with more experience and higher focus on screening mammography rather than diagnostic mammography. Higher specificity was associated with greater experience, increased reading volume, and focus on screening rather than diagnostic mammography. [148]

Modification of This Question in Light of New Research: The question has been inadequately addressed and should remain unmodified on the research agenda.

PROGRESS IN ESTROGEN REPLACEMENT THERAPY

ESTROGEN REPLACEMENT AND CARDIOVASCULAR DISEASE

See *New Frontiers,* pp. 242–244.

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 (eg, C-reactive protein levels, homocysteine levels, activated protein C deficiency, intestinal calcium absorption).**

New Research Addressing This Question: Several studies have described the effects of hormone replacement therapy on cardiovascular biomarkers, including increases in C-reactive protein (CRP), interleukin-6 (IL-6), and reductions in lipoprotein a and homocysteine. [149–155] However, the relationship between these types of markers and outcomes is less clear. In a subset of women enrolled in the Women's Health Initiative, CRP and IL-6 levels were found to predict incident cardiovascular events independently of use or non-use of hormone replacement therapy. [149] In the Women's Health Initiative Observational Study, postmenopausal hormone therapy was found to be associated with higher CRP, high-density lipoprotein, and triglyceride levels. Homocysteine levels were lower in hormone users, and no differences were seen in IL-6 or total cholesterol levels between users and non-users. [156] The Estrogen Replacement on Progression of Coronary Artery Atherosclerosis trial evaluated effects of hormone replacement therapy on CRP and IL-6 in women with coronary artery disease and demonstrated a significant increase in CRP but no change in IL-6 in women on either estrogen or estrogen plus progesterone therapy. The changes in CRP were not associated with progression of atherosclerosis. [157] Hormone replacement with conjugated equine estrogens plus medroxyprogesterone (0.625 mg/5 mg per day) was found not to be associated with elevated homocysteine levels. [158]

Modification of This Question in Light of New Research: The question has been inadequately addressed and should remain unmodified on the research agenda.

> *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, lowering the dose, or discontinuation confers more cardiovascular benefit for older women.**

New Research Addressing This Question: No studies have been published evaluating the effects of continuation, dose adjustment, or discontinuation after 5 years of therapy on cardiovascular disease.

Modification of This Question in Light of New Research: No modification of the question is recommended.

> *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.**

New Research Addressing This Question: In the Multiple Outcomes of Raloxifene Evaluation trial, 7705 postmenopausal women (mean age 67) were randomly assigned to raloxifene (60 mg/day or 120 mg/day) or placebo for 4 years. Overall, there was no significant difference in the number of coronary and cerebrovascular events between the groups. [159] In the subset of women with increased baseline cardiovascular risk, women taking raloxifene were found to have significantly fewer cardiovascular events than those taking placebo (relative risk [RR] 0.60, confidence interval [CI] 0.38 to 0.95). Raloxifene was associated with an overall increased risk of venous thromboembolism (RR 2.1, CI 1.2 to 3.8). The risk was higher in the raloxifene group for the first 2 years of treatment, but then decreased to the same rate as the placebo group. [160]

In a randomized controlled trial of 4175 postmenopausal women taking adjuvant tamoxifen for prevention of breast cancer recurrence, women who took tamoxifen for 5 years were found to have significantly reduced mortality from coronary heart disease than women taking the drug for only 2 years (RR 0.67, CI 0.47 to 0.94). [161] In a breast cancer prevention trial, 13,338 women were randomized to tamoxifen or placebo. No difference in cardiovascular mortality was found between the groups after 2 years of follow-up. [162]

Between 1998 and 2000, the Raloxifene Use for the Heart trial recruited 10,101 postmenopausal women (mean age 68 years) for randomization to raloxifene (60 mg/day) or placebo. Approximately half of the women had documented coronary heart disease, and the rest had multiple cardiovascular risk factors. The study was completed in December 2005. [163]

Modification of This Question in Light of New Research: Overall, the available data suggest potential cardiovascular benefit from the use of selective estrogen receptor modulators. However, there is increased risk of venous thromboembolism. Results of the Raloxifene Use for the Heart trial are pending. The question should remain unmodified on the research agenda.

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).**

New Research Addressing This Question: No studies were identified that directly addressed this question. In an autopsy study of coronary arteries from 46 postmenopausal and 10 premenopausal women, estrogen-treated postmenopausal women were found to have lower mean coronary calcium content and plaque area than untreated postmenopausal women. The effect of estrogen status on calcium content and plaque size was independent of age. [164] Current hormone replacement therapy has been found to be associated with significant reduction in coronary artery calcium content. [165]

Modification of This Question in Light of New Research: The question has been inadequately addressed and should remain unmodified on the research agenda.

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.**

New Research Addressing This Question: Of the major randomized clinical trials investigating hormone replacement therapy and cardiovascular disease, only studies from the Women's Health Initiative included data stratified by age. [166,167]

Modification of This Question in Light of New Research: All hormone replacement studies should include data stratified by age. Stratification should be standardized, using defined age groups to facilitate comparisons between studies. A standard scheme of 5-year strata is recommended, ie, age 65 to 69, 70 to 74, 75 to 79, etc. For smaller studies or as an additional analysis in larger studies, comparison of age groups 65 to 79 and age 80 and older will help identify differences that may exist in the very elderly population.

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

New Research Addressing This Question: The Heart and Estrogen/Progestin Replacement Study of estrogen plus progestin for secondary prevention of coronary heart disease found no significant difference in coronary heart disease events among women taking aspirin. [168]

Modification of This Question in Light of New Research: The question has been inadequately addressed and should remain unmodified on the research agenda.

ESTROGEN REPLACEMENT THERAPY AND ALZHEIMER'S DISEASE

See *New Frontiers,* pp. 245–247.

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.**

New Research Addressing This Question: In rats, the administration of 17β-estradiol and progesterone, alone or in combination, potentiated the glutamate-mediated rise in intracellular calcium in rat hippocampal neurons. However, the administration of medroxyprogesterone acetate alone or with 17β-estradiol produced no effect or blocked the effect of 17β-estradiol, respectively. [169] In a water maze study of ovariectomized rats, both chronic estrogen and chronic estrogen plus progesterone replacement were found to prevent forgetting between tasks. The study results also suggested that future cognition studies should be conducted specifically on aged female animals. [170]

In a study of cynomolgus monkeys, treatment with conjugated equine estrogens plus medroxyprogesterone acetate for 2 years was found to be associated with reduced acetylcholine esterase activity in the basal forebrain in comparison with estrogen alone. [171]

Modification of This Question in Light of New Research: Estrogen and progesterone may have different effects on cognition, and effects may also depend on the type of progesterone administered. To increase the validity of results, future animal studies should be conducted specifically on aged female animals. The question has been inadequately addressed and should remain otherwise unmodified on the research agenda.

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.**

New Research Addressing This Question: No studies were identified.

Modification of This Question in Light of New Research: No modification of this question is recommended.

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.**

New Research Addressing This Question: No studies specifically designed to answer this question were identified. However, as discussed in Gyn 67, the choice of progestin may be important, and results of studies using different progestins may not be comparable.

Modification of This Question in Light of New Research: No modification of the question is recommended.

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

New Research Addressing This Question: No studies were identified.

Modification of This Question in Light of New Research: No modification of this question is recommended.

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.**

New Research Addressing This Question: Two substudies from the Women's Health Initiative evaluating the effect of estrogen plus progestin on global cognitive function and the incidence of dementia and mild cognitive impairment provided data for three age groups: 65 to 69, 70 to 74, and 75 years and older. [172,173] Results for the Multiple Outcomes of Raloxifene Evaluation trial reported results of 3 years of raloxifene treatment in 7705 women with osteoporosis. The effects of treatment on cognitive function were reported for women 70 years or younger and women older than 70 years. [174]

Modification of This Question in Light of New Research: All study results should be stratified by age. Stratification should be standardized, using defined age groups to facilitate comparisons between studies. A standard scheme of 5-year strata is recommended, ie, age 65 to 69, 70 to 74, 75 to 79, etc. For smaller studies or as an additional analysis in larger studies, comparison of age groups 65 to 79 and age 80 and older will help identify differences that may exist in the very elderly population.

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.**

New Research Addressing This Question: No studies specifically addressing continuation versus discontinuation in elderly women were identified; however, the results concerning cognition in two major long-term hormone replacement studies have been published.

In the Women's Health Initiative, 4532 women (aged 65 or older) were also enrolled in the estrogen plus progestin arm of the Women's Health Initiative Memory Study. All women were free of dementia at baseline and provided at least one follow-up cognitive function score before the study was ended. Mean follow-up was 4.2 years. There was a significant decline in Modified Mini-Mental Status Examination score in the treatment group in comparison with the placebo group (6.7% versus 4.8%, $P = .008$). [172] The hazard ratio for probable dementia in women in the estrogen plus progestin group was 2.05 (CI 1.21 to 3.48). However, there was no difference in development of mild cognitive impair-

ment between the groups. [173] The authors of both reports concluded that estrogen plus progestin should not be used for prevention of cognitive impairment or dementia. [172,173]

In the Heart and Estrogen/Progestin Replacement Study, 1063 postmenopausal women (mean age 71 years) enrolled in the cognitive function substudy. After 4 years, women in the treatment group had significantly worse scores on the verbal fluency test than those in the placebo group (P = .02), but no other differences were seen between the two groups. [175]

ESTROGEN REPLACEMENT THERAPY, MODIFIED ESTROGENS, AND CANCER

See *New Frontiers*, pp. 247–249.

***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.**

New Research Addressing This Question: Women diagnosed with breast cancer while on hormone replacement therapy are more likely to present with smaller tumor size, [176–179] lower stage, [177–180] and lower grade. [179–181] In addition, women on hormone replacement are more likely to be diagnosed with lobular cancers. [176,180] There are no differences between users and non-users in tumor expression of c-erb B-2, p53, her 2-neu, or Ki67. [178,182] Some studies have reported no difference in hormone-receptor status between users and non-users, [176,180] while others have found more estrogen receptor–positive tumors in women on long-term hormone replacement [178] and more estrogen receptor– and progesterone receptor–positive tumors only in women on continuous combined hormone replacement. [177]

Three prospective cohort studies were identified describing prognostic factors in women on hormone replacement at the time of diagnosis. In the Malmo preventive cohort, women diagnosed with breast cancer while on hormone replacement were more likely to present with stage 1 tumors, lobular carcinomas, and tubular tumors. Hormone-receptor status was not different between user and non-users. [182] The Danish Nurses' study found women on hormone replacement more likely to be diagnosed with hormone receptor–positive cancer, invasive ductal carcinoma, and cancer of a low histologic grade than women who had never used hormone replacement. [183] In the Nurses' Health Study, women on hormone replacement were found to be more likely to develop hormone receptor–positive cancer than women who were non-users, and this effect increased with duration of hormone use. The association between hormone receptor–positive cancer and hormone replacement therapy was stronger in women on combined therapy than in women on estrogen alone. [184]

Data regarding differential prognostic factors in women diagnosed with breast cancer while on hormone replacement in the Women's Health Initiative are different from data seen in observational studies. Women in the estrogen plus progestin treatment arm diagnosed with breast cancer had larger tumor size, more frequent node invasion, and more advanced stage than those diagnosed while on placebo. There were no differences between groups in histology, grade, or hormone-receptor status. [185]

Modification of This Question in Light of New Research: Data on the characteristics of breast cancer diagnosed in women on hormone replacement therapy from observational trials and the Women's Health Initiative are quite different. This may be attributable to the different study populations. Further studies are needed to adequately answer this question. The question should remain unmodified on the research agenda.

> ***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.**

New Research Addressing This Question: No studies were identified.

Modification of This Question in Light of New Research: No modification of this question is recommended.

> ***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.**

New Research Addressing This Question: Results from the Women's Health Initiative study regarding the risk of colorectal cancer with estrogen or estrogen plus progestin versus placebo are provided with age stratification (ages 50 to 59, 60 to 69, 70 to 79). [167,186] Results from the Polyp Prevention Trial prospectively evaluating the association between hormone replacement therapy and adenoma recurrence were provided with age stratification (ages younger than 55, 55 to 62, 63 to 69, 70 and older). [187] Women's Health Initiative results regarding breast cancer and mammography in women randomized to estrogen plus progestin or placebo are presented with age-stratified data (ages 50 to 59, 60 to 69, 70 to 79). [185,188]

Modification of This Question in Light of New Research: All study results should be stratified by age. Stratification should be standardized, using defined age groups to facilitate comparisons between studies. A standard scheme of 5-year strata is recommended, ie, age 65 to 69, 70 to 74, 75 to 79, etc. For smaller studies or as an additional analysis in larger studies, comparison of age groups 65 to 79 and age 80 and older will help identify differences that may exist in the very elderly population.

> ***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.**

New Research Addressing This Question: No studies were identified that enrolled only women continuously on hormone replacement therapy since menopause.

Modification of This Question in Light of New Research: The Kronos Early Estrogen Prevention trial study will be evaluating outcomes associated with hormone replacement therapy in postmenopausal women beginning within 3 years of menopause. [189] The study is expected to be completed in December 2010. The question should remain unmodified on the research agenda.

***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.**

New Research Addressing This Question: In the Breast Cancer Prevention Trial of the National Surgical Adjuvant Breast and Bowel Project P-1 Study, the risk of invasive breast cancer was found to be decreased in women on tamoxifen (RR 0.57, CI 0.46 to 0.70), as was the risk of noninvasive breast cancer (RR 0.63, CI 0.45 to 0.89). Of 288 women who developed breast cancer during this trial, 19% were found to have BRCA mutations. [190] Within this subset of women, tamoxifen reduced breast cancer in those with BRCA2 but not BRCA1 mutations. [191] In the Continuing Outcomes Relevant to Evista trial, raloxifene was found to significantly decrease the incidence of invasive breast cancer and estrogen receptor–positive invasive breast cancer in comparison with placebo. Hazard ratios were 0.34 (CI 0.22 to 0.50) and 0.24 (CI 0.15 to 0.40), respectively. [192] Results from the Multiple Outcomes of Raloxifene Evaluation trial found no difference in the incidence of colorectal cancer between treatment and placebo groups. [193]

Modification of This Question in Light of New Research: Use of selective estrogen receptor modulators appears to decrease the incidence of breast cancer, but data regarding the effect on breast cancer mortality are not available. The only randomized trial evaluating the effect on risk of colon cancer suggests no benefit. The question has been inadequately addressed and should remain unmodified on the research agenda.

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

New Research Addressing This Question: Estrogen receptor-beta (ERβ) is the predominant estrogen receptor expressed in human colon, and decreased levels of ERβ mRNA are associated with colon cancer in women. [194] Loss of ERβ expression is associated with advanced Dukes stage. [195] Differential expression of isoforms of ERβ may also be associated with differential effect on colorectal tumorigenesis. ERβ1 may be associated with microsatellite unstable colorectal cancer, a type characterized by mutations leading to failure of the mismatch repair system. [196] Microsatellite unstable colorectal cancer is associated with lack of estrogen and is more common in older women. [197] Polymorphisms of the ERβ gene may be associated with development of colorectal cancer. [198] Women who have two long alleles and are estrogen negative are at higher risk of colorectal cancer than women with short alleles and estrogen. The use of hormone replacement therapy reduces the risk of colon cancer in women with the R allele of the ERβ gene. Postmenopausal women with the R allele who did not take hormone replacement therapy were found to be at higher risk for developing colorectal cancer. Colon cancer risk was also increased in postmenopausal women not in hormone replacement therapy with $>$ 25 cytosine-adenine repeats of the ERβ gene. [199] Other investigations have implicated estrogen receptor–related receptor α, [198] acquired p53 mutations, [200] and insulin-like growth factor polymorphisms [201] in colorectal cancer in women.

Modification of This Question in Light of New Research: Data are available suggesting that genetic susceptibility to colon cancer may be modified by estrogen. Further studies

are needed to confirm genetic sources of susceptibility and the impact of menopause and estrogen therapy. The question should remain unmodified on the research agenda.

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

New Research Addressing This Question: Two randomized trials were identified. The Hormonal Replacement Therapy After Breast Cancer—Is It Safe? (HABITS) trial openly randomized women with a history of breast cancer to hormone replacement therapy or best treatment without hormones. After median follow-up of 2.1 years, the study was stopped when 26 women in the hormone therapy arm and 8 in the non-hormone group had breast cancer recurrences. The women who were enrolled will be followed for the originally intended 5 years after randomization.[202] In the Stockholm trial, postmenopausal women with a history of breast cancer were openly randomized to hormone therapy or no hormone therapy. After a median follow-up of 4.1 years, this trial was also stopped after analysis of the combined data from the Stockholm and HABITS trials revealed a significantly increased risk of cancer recurrence in women on hormone therapy. However, there was no significant increase in breast cancer recurrence specifically among hormone users enrolled in the Stockholm trial.[203] The difference in results may be due to the much higher percentage of women using tamoxifen in the Stockholm trial than in the HABITS trial (52% versus 21%).

Modification of This Question in Light of New Research: Data suggest that the use of hormone replacement therapy by women with a history of breast cancer may increase the risk of recurrence. However, this risk may be modified by the concurrent use of a selective estrogen receptor modulator. This question has been adequately addressed in its current form and can be dropped from the research agenda.

PROGRESS IN OSTEOPOROSIS

HORMONAL THERAPIES

See *New Frontiers,* pp. 250–251.

***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.**

New Research Addressing This Question: In a randomized study comparing neridronate and no treatment for osteoporosis in women (aged 65 to 80), 12 months of treatment was found to improve quality of life (pain, general health perception, vitality, emotional functioning, and physical functioning).[204] No studies evaluating quality-of-life outcomes of long-term therapy with estrogen, estrogen-progestin, or selective estrogen receptor modulator therapy were identified.

Modification of This Question in Light of New Research: The question has been inadequately addressed and should remain unmodified on the research agenda.

***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.

New Research Addressing This Question: In postmenopausal women (aged 40 to 65 years) randomized to weight-bearing and resistance exercise for 1 year, the combination of exercise and hormone replacement therapy was found to produce greater increases in bone mineral density than either alone. [205]

In elderly women (aged 75 to 87) on hormone replacement therapy, the addition of a supervised exercise program produced greater increases in lumbar spine bone mineral density than unsupervised exercise at home (3.5% versus 1.5%, $P = .048$). [206] There were no significant decreases in hip or total body bone mineral density. Postmenopausal women randomized to a supervised aerobic and weight-bearing exercise regimen three times a week had 1% increase in trochanteric bone mineral density; women who also used hormone replacement therapy had 1% to 2% increase in bone mineral density at the femoral neck, trochanter, and lumbar spine. [207]

Modification of This Question in Light of New Research: Combining hormone replacement therapy with a supervised exercise regimen increases bone mineral density more than hormone therapy alone or hormone therapy with unsupervised exercise. No studies investigating synergistic effects of selective estrogen receptor modulators with exercise or other interventions were identified. The question has been inadequately addressed and should remain unmodified on the research agenda.

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.**

New Research Addressing This Question: Two randomized, double-blind, placebo-controlled trials of low-dose estrogen on bone mineral density were identified. Postmenopausal women randomized to 0.25 mg/day of micronized 17β-estradiol or placebo for 3 years were found to have increased bone density at the hip, spine, and total body as well as reduced bone turnover. [208] Postmenopausal women randomized to 0.014 mg/day of transdermal estradiol for 2 years were found to have increased bone mineral density and decreased bone turnover. [209]

Modification of This Question in Light of New Research: Low-dose estrogen therapy increases bone mineral density and decreases bone turnover, but no data are available regarding the reduction of fracture risk. Studies of the initiation of low-dose estrogen therapy specifically at menopause were not identified. The question has been inadequately addressed and should remain unmodified on the research agenda.

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.**

New Research Addressing This Question: Results of the Women's Health Initiative trial pertaining to fracture and bone mineral density are presented with age stratification. [210] Results of the Million Women Study are also presented in an age-stratified manner. [211]

Modification of This Question in Light of New Research: All studies should include age stratification of data. Stratification should be standardized, using defined age groups to facilitate comparisons between studies. A standard scheme of 5-year strata is recommended, ie, age 65 to 69, 70 to 74, 75 to 79, etc. For smaller studies or as an additional analysis in larger studies, comparison of age groups 65 to 79 and age 80 and older will help identify differences that may exist in the very elderly population.

> *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.**

New Research Addressing This Question: No studies were identified.

Modification of This Question in Light of New Research: No modification of this question is recommended.

> *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.**

New Research Addressing This Question: No studies were identified.

Modification of This Question in Light of New Research: No modification of this question is recommended.

> *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.**

New Research Addressing This Question: No studies were identified.

Modification of This Question in Light of New Research: No modification of this question is recommended.

NONHORMONAL THERAPIES: CALCIUM AND VITAMIN D

See *New Frontiers,* pp. 252–253.

> *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.**

New Research Addressing This Question: In a study that assigned adolescent girls to calcium supplements or increased intake of dairy foods, both interventions were found to increase peak bone mass. Calcium increases volumetric bone density and dairy foods may also increase bone growth and periosteal bone expansion. [212] In adolescent girls, implementation of an exercise program has been found to be associated with increases in bone mineral density. [213–217] Daily intake of at least three servings of fruits and vegetables was found to be associated with increased bone area in early adolescent girls. [218]

Modification of This Question in Light of New Research: Early studies suggest that calcium supplementation, increased intake of dairy foods, diet including fruits and vegetables, and exercise may help in attaining maximum peak bone mass. No studies evaluated the effect of carbonated beverages. The question has been inadequately addressed and should remain unmodified on the research agenda.

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

New Research Addressing This Question: Calcium supplementation has been associated with mild transient hypotensive effects in postmenopausal women (mean age 74), [219] increases in high-density lipoprotein cholesterol levels in postmenopausal women, [220] and no increased risk of calcium oxalate nephrolithiasis. [221,222] In the Randomised Evaluation of Calcium or Vitamin D trial of 5292 people (including 4481 women) aged 70 or older, compliance with calcium supplementation was significantly lower partly because of gastrointestinal symptoms. Serious adverse effects were rare and were not different between groups. [223] In a randomized cross-over study in postmenopausal women, three readily available calcium sources (calcium carbonate, encapsulated calcium carbonate, calcium citrate) were all shown to be readily absorbed and equally bioavailable. Cost-benefit analysis determined that the less expensive calcium carbonate products were cost-effective for universal supplementation while the calcium citrate product was not. [224]

Modification of This Question in Light of New Research: Adverse effects of calcium supplementation are rare. Compliance may be limited by gastrointestinal symptoms. Calcium carbonate supplementation is cost-effective. This question has been adequately addressed and can be dropped from the research agenda.

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

New Research Addressing This Question: Postmenarchal girls (mean age 14) with a diet low in calcium randomized to placebo or 1000 mg calcium daily supplementation were found to have greater increase in total body bone mineral density and spine bone mineral density on calcium. The effect was enhanced in girls who had onset of menarche more than 2 years before intervention. [225] Early adolescent girls receiving 1000 mg calcium supplementation daily were found to have significantly greater distal and proximal radius bone mineral density, total body bone mineral density, and metacarpal cortical indices at 4 years than those on placebo. [212] At 7 years, significant effects remained at the proximal radius and metacarpals. [226] Women aged 45 or older taking 500 mg calcium plus 200 IU vitamin D daily for 30 months were found to have significantly different changes in bone mineral density than those on placebo; placebo use resulted in loss of bone mineral density. [227]

Modification of This Question in Light of New Research: Calcium supplementation appears to be beneficial in both adolescent girls and women over the age of 45 years. The question has been inadequately addressed and should remain unmodified on the research agenda.

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

New Research Addressing This Question: In a four-period, three-way, randomized cross-over trial of calcium carbonate, calcium citrate, or placebo in postmenopausal women, all calcium sources were found to have been equally absorbed and bioavailable. Cost analysis favored the least expensive calcium supplement—calcium carbonate. [224] In a four-way cross-over study of placebo versus calcium as calcium carbonate, calcium citrate, or calcium formate in adult women, calcium formate was found to produce significantly higher levels of serum calcium. [228] Calcium-fortified orange juice, calcium carbonate supplements, and milk were found to have similar bioavailabilities in subjects older than 50 years. [229]

Modification of This Question in Light of New Research: Calcium carbonate is consistently identified as readily absorbed and bioavailable as well as the most cost-effective method of supplementation. Although these studies did not specifically address side effects, serious adverse effects from calcium supplementation are rare (see Gyn 88). This question has been adequately addressed and can be dropped from the research agenda.

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

New Research Addressing This Question: No studies were identified.

Modification of This Question in Light of New Research: No modification of this question is recommended.

NONHORMONAL THERAPIES: BISPHOSPHONATES

See *New Frontiers,* pp. 253–254.

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.**

New Research Addressing This Question: There are no studies evaluating the very long-term use of bisphosphonates for postmenopausal osteoporosis. The majority of studies provide data for 3 to 5 years of use. In postmenopausal women with osteoporosis treated with risedronate for 3 years, one study found a significant decrease in bone formation rate reflecting decreased turnover in comparison with placebo, while bone mineralization remained normal. Treated women had formation of normal lamellar bone and normal osteoid thickness. Bone resorption was decreased with 58% and 47% reductions in mineralizing surface and activation frequency. [230] In another study, after 5 years of risedronate therapy or placebo, no significant histomorphometric differences were found between groups in structural or resorption parameters. Bone turnover was continuous in both groups, and lumbar spine bone mineral density was significantly increased in the risedronate group in comparison with the placebo group. [231]

After initial 5-year treatment with alendronate, a further 3 years of treatment was found to increase bone mineral density at the spine and to maintain it at the hip. In women taking placebo after 5 years of alendronate, bone mineral density and reduction in bone turnover was greater than at baseline. [232] Bisphosphonate suppression of bone formation is partially

reversible with intermittent parathyroid hormone.[233] In a study of women who took alendronate for 10 years, the fracture rate observed between 6 and 10 years was similar to the rate in years 1 to 3. Prolonged treatment was not found to be associated with any loss of benefit, and the drug was well tolerated.[234]

A potential risk of suppression of bone turnover and accumulation of microdamage with long-term use of bisphosphonates has been described. In a case series of 8 postmenopausal women and 1 man (aged 49 to 76) with atraumatic nonvertebral fractures on alendronate therapy for 3 to 8 years, 6 of the patients had delayed healing for 3 months to 2 years after diagnosis. All 9 patients had decreased bone volume and suppression of bone formation, and 4 patients continued to have delayed healing after discontinuation of alendronate.[235] In women (aged 55 to 80) receiving ibandronate (orally or IV) for 3 years, no differences in yearly rate of progression or in the 3-year change in aortic calcification were found between intervention groups. Three-year changes in bone mineral density and simultaneous changes in aortic calcification were not correlated.[236]

Modification of This Question in Light of New Research: The maximum length of bisphosphonate therapy investigated was 10 years. The question should remain unmodified on the research agenda.

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

New Research Addressing This Question: Isosorbide mononitrate is a precursor of nitric oxide, which is thought to mediate bone loss by decreasing osteoclast activity. In one study, postmenopausal women were randomly assigned to treatment with isosorbide mononitrate for 12 weeks or to placebo; significant increases in urine N-telopeptide and decreases in serum bone-specific alkaline phosphatase consistent with decreased bone resorption and increased bone formation were found in the treatment group. Women in the treatment group reported significantly more headaches, and 16 of them discontinued treatment because of headache but only 2 women in the placebo group did so.[237]

Modification of This Question in Light of New Research: Only one new medication was identified. The question has been inadequately addressed and should remain unmodified on the research agenda.

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

New Research Addressing This Question: Strontium ranelate is a compound of ranelic acid and two atoms of strontium that has been associated with stimulation of bone formation. In the Treatment of Peripheral Osteoporosis study, postmenopausal women were randomly assigned to either 2g/day strontium ranelate or placebo for 3 years. Treatment with strontium ranelate was shown to produce significant increase in bone mineral density at the femoral neck and hip and reduce the risk of nonvertebral fracture by 16%. There was no difference in adverse reactions between treatment and placebo groups.[238] The Strontium Ranelate for Treatment of Osteoporosis trial (Phase II) randomized postmenopausal women with osteoporosis and at least one previous vertebral fracture to 0.5g/day or 2g/day of strontium ranelate or placebo for 2 years. In the treatment groups, vertebral bone mineral density was significantly increased. Of the two doses studied, 2g/day of strontium ranelate produced the greatest increase in bone mineral density and

was associated with a significant decrease in incidence of vertebral fractures. The higher dose of strontium ranelate produced a significant increase in serum bone-specific alkaline phosphatase and significantly decreased urinary excretion of N-telopeptide. [239] In a phase III trial, postmenopausal women with osteoporosis and at least one vertebral fracture were randomized to 2g/day of strontium ranelate or placebo for 3 years. In the treatment group, relative risk of vertebral fracture was 0.59 (CI 0.48 to 0.73). Lumbar bone mineral density was increased by 14.4% and 8.3% at the femoral neck. No differences in adverse effects between treatment and placebo were found. [240]

Modification of This Question in Light of New Research: Only one new medication was identified. In initial studies, strontium ranelate does appear to increase bone mineral density and decrease the risk of fracture. The question has been inadequately addressed and should remain unmodified on the research agenda.

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

New Research Addressing This Question: One study found that healthy, early postmenopausal women taking 10 mg/day of alendronate for 6 years had significantly increased spine and hip bone mineral density and decreased incidence of fracture in comparison with those on placebo. Adverse effects were similar in treatment and placebo. [241] In the Fracture Intervention Trial subgroup analysis of postmenopausal women with osteopenia (but not osteoporosis) randomized to treatment with alendronate (5mg/day for 2 years, then 10 mg/day thereafter) found 60% and 43% decreases in risk of clinical and radiographic fracture, respectively, in comparison with placebo. [242]

Modification of This Question in Light of New Research: Alendronate therapy increases bone mineral density and decreases the risk of fracture in healthy women and women with osteopenia. This question has been adequately addressed and can be dropped from the research agenda.

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

New Research Addressing This Question: In postmenopausal women randomized in a 2 × 2 factorial design to hormone replacement therapy (conjugated equine estrogen 0.625 mg/day, with or without medroxyprogesterone 2.5 mg/day) and alendronate 10 mg/day, both agents, or neither for 3 years, those receiving combination therapy were found to have significantly higher femoral and vertebral bone mineral density than those receiving monotherapy. [243] In elderly women with normal bone density for their age, combination treatment with hormone replacement therapy and calcitriol was found to increase bone mineral density significantly more at the total hip and trochanter than did hormone replacement alone. [244] One study found that in postmenopausal women with osteoporosis, treatment with both teriparatide and raloxifene increased bone formation to the same degree as teriparatide alone, but that combination therapy produced greater decreases in bone resorption and increases in bone mineral density at the total hip than teriparatide alone. [245] In women with postmenopausal osteoporosis, therapy with parathyroid hormone and alendronate was not found to produce greater increases in bone mineral density at the

spine than parathyroid hormone alone. The anabolic effects of parathyroid hormone were reduced with the co-administration of alendronate. [233]

Modification of This Question in Light of New Research: Hormone replacement therapy may act synergistically with bisphosphonates or calcitriol. Combining parathyroid hormone with a selective estrogen receptor modulator may have additive effects, and combination with a bisphosphonate may reduce the anabolic effects of parathyroid hormone alone. Further studies are needed to identify potentially adverse interactions of combination therapy as well as additive effects. The question should remain unmodified on the research agenda.

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.**

New Research Addressing This Question: No studies were identified.

Modification of This Question in Light of New Research: No modification of this question is recommended.

NEW HORIZONS IN GERIATRIC GYNECOLOGY

PELVIC ORGAN PROLAPSE

The true prevalence of pelvic organ prolapse is unknown, and our ability to determine this prevalence is limited by lack of a standard and clinically relevant definition of the condition. The International Continence Society currently defines pelvic organ prolapse as descent of stage I or greater, although the authors themselves noted the definition to be inadequate. [246] By this definition, baseline data from the Women's Health Initiative suggests that 60% of women over the age of 50 have pelvic organ prolapse. [66] Age-group prevalences included 28% of women aged 50 to 69, 47% aged 60 to 69, and 24% aged 70 to 79. Similarly, the Pelvic Organ Support Study found pelvic organ prolapse of some degree in 75% of women undergoing annual gynecologic examination. However, with use of a clinical definition of prolapse as leading edge at -0.5 cm or greater from the hymen, only 22% of subjects were classified as having prolapse. [68] Several studies have advocated the use of a clinically relevant definition of prolapse, with the disease state defined as leading edge of prolapse at the hymen or beyond. [247–250]

Gyn 98 (Level B): **A clinically relevant definition of pelvic organ prolapse should be established and used to determine the prevalence of pelvic organ prolapse in elderly women. Subsequent surgical outcome studies should use this definition to describe outcomes.**

Gyn 99 (Level B): **Gynecologic surgery studies describing the outcomes of surgical treatment of pelvic organ prolapse should include both preoperative and postoperative description of prolapse using the pelvic organ prolapse quantification (POP-Q) system to facilitate comparison of results.**

***Gyn 100 (Level B)*: Observational studies are needed to determine the risk factors for recurrence of pelvic organ prolapse after surgical treatment in elderly women.**

Several studies have been published describing the use of local anesthesia with sedation for pelvic organ prolapse surgery as an alternative to general or regional anesthesia. [251–255] Minimizing anesthesia in elderly women undergoing gynecologic surgeries may reduce perioperative morbidity such as nausea, vomiting, and cognitive changes. However, no studies directly comparing anesthesia type in this population were identified.

***Gyn 101 (Level A)*: Randomized controlled trials of general, regional, and local anesthesia for pelvic organ prolapse surgery in elderly women are needed to determine whether their rates of perioperative morbidity differ.**

SEXUALITY

The prevalence of sexual dysfunction among older women is unknown. Indeed, the definition of normal sexual function in older women remains elusive. Lack of knowledge concerning what is "normal" complicates investigations of prevalence and treatment interventions. In a prospective longitudinal study, sexual responsivity was found to be significantly decreased with time in both women transitioning through the perimenopausal period and in postmenopausal women. From the early to late perimenopausal periods, overall sexual functioning significantly decreases. From late perimenopause to menopause, there are decreases in overall sexual function, libido, and frequency of sexual activity, as well as increased vaginal dyspareunia. [256] However, sexual inactivity in older women is not always related to their own sexual dysfunction. In a study of community-dwelling women with pelvic floor disorders, the most commonly cited reason for sexual inactivity was a partner's physical ailment making sexual activity embarrassing or uncomfortable. [257]

***Gyn 102 (Level B)*: Observational studies are needed to describe normal sexual function and activity of elderly women and to provide a basis for developing a definition of sexual dysfunction that is appropriate for women in this age group.**

***Gyn 103 (Level B)*: Observational studies are needed to establish the prevalence of sexual dysfunction in elderly women.**

***Gyn 104 (Level B)*: Observational studies are needed to establish the effect of sexual dysfunction on the quality of life of elderly women.**

***Gyn 105 (Level B)*: Observational studies are needed to establish the effect of partners' sexual dysfunction on the quality of life of elderly women.**

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