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A monthly update of developments in female reproductive medicine

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A Prospective Study of Folate Intake and the Risk of Breast Cancer

ABSTRACT & COMMENTARY

This study used the nurses' health study cohort to test the hypothesis that "higher folate intake might reduce the risk of breast cancer, particularly among women with greater alcohol consumption, which itself moderately increases breast cancer risk." The rationale for this hypothesis is that alcohol is a known folate antagonist and folate is required for DNA repair mechanisms. Therefore, chronic alcohol use might induce a relative folate deficiency and predispose that individual to faulty DNA repair and cancer. Zhang and colleagues were not able to look at these relationships in women known to be at risk for faulty DNA repair mechanisms, (i.e., BRCA1 and BRCA2 carriers.) The study methodology is described in exacting detail and is adequate to address the query as posed. The diet information was collected by questionnaire initially in 1980 and then at subsequent timepoints. Higher folate intakes (> 400 g/d) in general did not reduce the risk of invasive breast cancer. Higher folate intakes typically were achieved via daily multivitamin ingestion. In women who consumed more than 15 g/d of alcohol from any source (12 ounces of beer contains 12.8 g; 4 ounces of wine 11.0 g, and 1.5 ounces of spirits 14.0 g), the increased relative risk of breast cancer (RR = 1.24, CI 1.11 - 1.39) was reduced if folate intake was 600 g/d. This relationship held in both premenopausal and postmenopausal women. (Zhang S, et al. *JAMA* 1999;281:1632-1637.)

■ COMMENT BY SARAH L. BERGA, MD

No longer is folate the obstetrician's vitamin. Folate is forever! Adequate folate intake is implicated in the chemoprevention of neural tube defects, colorectal cancer, cardiovascular disease, and now breast cancer associated with higher alcohol intakes. Folate takes its name from foliage, as in green leafy vegetables. But the predominant source in most American diets is fortified breakfast cereal and multivitamins. Fortunately, these sources provide a highly bioavailable form of folate, so the strategy of food fortification and multivit-

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amin use in this context appears to be a wise one.¹ Folate from food sources such as orange juice and vegetables is labile (destroyed by food processing and exposure to heat and air). Also, absorption from food can be hindered by other components of the food matrix. Based on this and other similar studies, it makes sense to hedge bets and recommend adequate folate intake, not only to pregnant women and those contemplating conception, but to all women, especially those who drink alcohol regularly.

I wonder how many physicians regularly ask their patients about habits of daily living, such as smoking, alcohol intake, diet in general, vitamin and supplement use in particular, and exercise. There is so much to cover when in the office and so little time. To a great extent, we are dependent on patients to raise issues of importance to them. For example, when a patient asks me about hormones and breast cancer, not only do I tell her that it is unlikely that postmenopausal hormone use is a major promoter of breast cancer, I also use this opportunity to ask about alcohol intake. I explain that small amounts of alcohol are also unlikely to promote breast

cancer, but that larger amounts may. However, not all women see a physician on a regular basis. Thus, it also would be a good idea to conduct a campaign to raise the nutrition IQ of doctors and patients alike with the goal of getting us to obtain most of our nutrients from food. Since this strategy is expensive, variably effective, and time-consuming, shortcuts have been advocated and effected. These shortcuts are multivitamin use and food fortification. For certain nutrients, such as folate, vitamin E, and vitamin D, these shortcuts make sense. However, just as it may be unrealistic to expect everyone to get everything they need nutritionally from food, I like to remind patients that it is also unrealistic to expect to get all the nutrients they need from food supplements and multivitamins. There is no substitute for a good diet if for no other reason than the fact that we do not know everything there is in food that we need. Until we get much smarter and can readily individualize nutritional advice, I suggest that the best strategy is to take an inexpensive multivitamin (i.e., one that contains types and amounts of vitamins within the recommended ranges) and eat according to the newest food group pyramid. ❖

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Reference

1. Jacques PF, et al. *N Engl J Med* 1999;340:1449-1454.

Identifying Women With Cervical Neoplasia

ABSTRACT & COMMENTARY

Synopsis: *Among women with ASCUS Pap smear reports, HPV testing is as accurate as repeat Pap smear for identifying women for referral for colposcopy.*

Source: Manos MM, et al. *JAMA* 1999;281:1605-1610.

Following the introduction of the Bethesda System (TBS) terminology for Pap smear reporting, the ASCUS group became and remains a category that confuses both clinicians and patients. Although most women with ASCUS reports do not have significant disease (HGSIL or invasive cancer), some women with such reports do harbor a neoplastic lesion that must be treated. Many clinicians repeat an ASCUS Pap smear within 4-6 months and refer for colposcopy those women who once again have an abnormal report. Other clinicians perform colposcopy on all women with ASCUS cytology.

This study was developed in an effort to determine whether HPV DNA testing could identify those women with HGSIL or greater lesions among women who had an initial ASCUS cytology report.

The study population included 46,000 who received their health care from the Kaiser Permanente program in northern California. Initially 995 women with ASCUS reports were identified, though slightly fewer women were used for various aspects of the study based on appropriate exclusions. During the study, all women had conventional cytology performed using a cervical broom. The broom was then rinsed in the cytologic preservation fluid that is used for ThinPrep cytology slides. A brush device was then used to collect another sample that was placed in a transport medium for HPV testing.

Of the 46,000 women who had Pap smears, 3.5% were reported as showing ASCUS changes. An attempt was made to contact all women who had ASCUS reports based on the conventional smear. These women were asked to report for colposcopy. At the time of the colposcopic evaluation, cytology and HPV specimens were again collected prior to the application of acetic acid. Colposcopy was performed with biopsy and ECC as indicated.

Appropriate blinding of the colposcopist and the histopathologist was performed. HPV testing was performed both on the ThinPrep preservative and on the HPV transport medium. Hybrid Capture II was used to detect "high risk" HPV. Sixty-one percent of women with ASCUS reports participated in the study. The median age of the study's participants was 37 years. Approximately one-half of the ASCUS reports favored reactive changes, a quarter of the ASCUS reports favored neoplasia, and approximately one-quarter were unclassified.

Among women who had an ASCUS smear followed by colposcopy and biopsy, normal histology was found in 79%. Sixty-four cases of HGSIL and one invasive cancer were identified. Approximately half of the HGSIL and cancer cases originally had an ASCUS report that favored neoplasia. In the study, 39.5% of women with ASCUS reports had a high-risk HPV detected in the original sample, and 39.9% of the repeat Pap smears were abnormal. When a matched-pairs comparison between HPV testing and repeat Pap smear collection was performed, the results demonstrated that both techniques were equally effective in detecting HGSIL or cancer lesions.

Based on the results of this study, a similar number of women would be referred for colposcopy, regardless of whether HPV testing or a repeat abnormal smear were

the indicator for colposcopic referral. Manos and colleagues suggest that, because HPV testing can be performed on the preservative used for ThinPrep cytology specimens, it is possible that HPV testing might be more efficient than a collection of repeat-cytology specimens.

■ COMMENT BY KENNETH NOLLER, MD

HPV DNA testing has been available for clinical use for a number of years. However, there has never been a clear-cut indication for its use, and the test is costly.

The results of this study suggest there might be a roll for HPV DNA testing that might be cost effective, though cost-effectiveness was not addressed in this particular study. Because the triage suggested by Manos et al requires that both ThinPrep cytology (increased cost) be used as well as HPV DNA testing (increased cost), a cost-effectiveness study is certainly indicated.

My interpretation of the article is that HPV DNA testing could be used in the following stepwise manner:

1. Cytology would be collected using the ThinPrep technique.
2. The laboratory would prepare and read all cytology slides and would retain the preservative solution for all cases.
3. For all ASCUS reports, the preservative solution would be submitted for HPV DNA testing.
4. All women who had a high risk HPV identified would be referred for colposcopy.

Using the above triage system would result in a similar rate of HGSIL identification as repeat cytology. Repeat cytology requires the patient to make another physician appointment, travel to the office, and miss work. The additional visit and cytology specimen generate a charge (cost). Although the HPV triage system requires use of a more expensive initial cytology method (costs associated with storage and handling of all preservative solutions and the cost of HPV testing), the overall cost of this type of triage might be less than repeat cytology. However, at this time, it is not clear to me which of the above methods of handling ASCUS smears is more appropriate since they both result in a similar number of women identified who have HGSIL. If the two methods are equally cost effective, the HPV DNA testing triage would seem to be superior since it does not require a second visit to the clinician. If the clinician uses both HPV testing and repeats the cytology in a few months, the triage costs skyrocket. One system or the other should be adopted, not both. ❖

Oral Contraceptive Use and Risk of Gestational Trophoblastic Tumors

ABSTRACT & COMMENTARY

Synopsis: Long duration of oral contraceptive use before conception increases the risk of gestational trophoblastic tumors. However, changes in use of oral contraceptives are not warranted, because the incidence attributable to oral contraceptive use is low.

Source: Palmer JR, et al. *J Natl Cancer Inst* 1999;91:635-640.

Palmer and associates undertook a multicenter case-control study of gestational trophoblastic tumors to test the hypothesis that long-term use of oral contraceptives before conception may increase the risk of gestational trophoblastic tumors. Telephone interviews were conducted with 235 case patients, including 50 with gestational choriocarcinoma, and 413 control subjects matched on recentness of pregnancy, age at pregnancy, and area of residence. The relative risk estimate for ever having used oral contraceptives before the index pregnancy was 1.9 (95% confidence interval [CI] = 1.2-3.0), and the risk increased with duration of use (P for trend = 0.05). The estimate was highest for women who used oral contraceptives during the cycle in which they became pregnant (relative risk = 4.0; 95% CI = 1.6-10), but there was no consistent pattern, according to the time interval, since last use. Relative risk estimates were similar for choriocarcinoma and persistent mole—2.2 and 1.8, respectively. Control for the number of sexual partners, which was independently associated with risk (P for trend = 0.05), did not materially change the results. Palmer et al concluded that this study, the largest to date, indicates that long duration of oral contraceptive use before conception increases the risk of gestational trophoblastic tumors. They noted, however, that changes in use of oral contraceptives are not warranted because the incidence attributable to oral contraceptive use is low.

■ COMMENT BY DAVID M. GERSHENSON, MD

The major findings of this study are that oral contraceptive use increases the risk of gestational trophoblastic disease, and that duration of use was associated with the degree of increased risk. In addition, having had 10 or more sexual partners before the index pregnancy inde-

pendently doubled the risk. Although this is the largest study to date, several other studies have reported this phenomenon. The pathogenesis of gestational trophoblastic tumors is poorly understood. In their discussion of this article, Palmer et al point out that, in addition to the influence of oral contraceptive use, younger women and perimenopausal women are at higher risk for developing gestational trophoblastic disease. Common in all these situations is either physiologic or exogenous interference with ovulation. The fact that the number of sexual partners also influenced the development of gestational trophoblastic tumors is unexplained. Again, as Palmer et al note, it raises the possibility of a sexually transmitted disease acting as an etiologic agent. Despite the findings of this study, the risk of oral contraceptive use is not great, and no change in our practice appears indicated other than appropriate counseling. ❖

Screening Mammography Under Age 50

ABSTRACT & COMMENTARY

Synopsis: An update of recent data supports screening mammography under age 50.

Source: Antman K, Shea S. *JAMA* 1999;281:1470-1472.

Antman and Shea from Columbia University in New York review the controversy surrounding mammography screening under age 50, and assess the results from more recent clinical trials. The promotion of mammography screening began around 1989 after the completion of the first six randomized mammography trials. In 1992, the National Cancer Institute (NCI) sponsored a conference to consider all available clinical trial data. The conference concluded that a 15-17% reduction in breast cancer mortality in women aged 40-49 years was not statistically significant. However, when the results of a controversial 1992 Canadian trial were excluded, the benefit for women aged 40-49 years was significant.

In 1997, new Swedish data indicating a significant decrease in mortality for women aged 40-49 years prompted another NCI conference. This conference was described as an "NCI brawl" in an editorial in *Science*.¹ The controversy was fueled by the recognition that breast cancer is less frequent in younger women and a greater number of mammograms (accompanied by false

positive results) are required to have an impact on breast cancer mortality.

Antman and Shea conclude that the recent data (a 24% reduction in breast cancer mortality in the Swedish trials) support mammography screening for women in their forties. However, they recommend that women without risk factors “might” begin screening between ages 45 and 50 years. They point out that there are no clinical trials providing information regarding screening for young women who have multiple first-degree relatives developing breast cancer at a young age, or in women known to carry BRCA1 or BRCA2 mutations.

■ COMMENT BY LEON SPEROFF, MD

It appears to me that the real issue in this controversy is cost effectiveness. The expense of mammography screening younger than age 50 is increased because of the lower frequency of breast cancer at this age and the greater difficulty of accurate mammography because of more dense breast tissue (hence, more false positive results requiring more interventions). However, this argument is derived from data based upon less advanced equipment and a time when mammograms were more expensive. Indeed, new machines using digitized computer technology will soon eliminate the problems associated with dense breasts.

Antman and Shea argue that mammography screening should begin at age 40 for women who have substantial risk factors and for women who are eager for screening. With appropriate education and support, every woman should be eager for mammography screening. Advanced equipment, lower costs, and eager women make a powerful combined argument in favor of mammography screening beginning at age 40.

False-positive mammograms leading to a large number of biopsies represent a serious obstacle, not only because of cost to the health care system, but for the individual as well in terms of stress and anxiety. All of the reviews of the mammography controversy have failed to take into account a new approach for breast cancer diagnosis. The number of unnecessary surgical procedures can be minimized by the “triple approach—,” the combination of examination, mammography, and needle aspiration. The failure to detect a malignancy with at least one of the three diagnostic tests is unlikely.²

About 19% more breast cancers occur in women 40-49 than in women aged 50-59, accounting for approximately 20% of all deaths due to breast cancer.³ Furthermore, tumors in younger women grow faster; and mammography screening at a rate of less than annually will detect these tumors at a later stage of the disease. Once detected by mammography, survival expectations are the same

comparing women aged 40-49 with women older than age 50 when tumors are adjusted for stage of disease.

Mammography is the most potent weapon we possess in the battle against breast cancer. Younger women should not be deprived of annual screening; indeed, the more rapid tumor growth at a younger age, combined with better technology and the triple approach, make a strong argument in favor of annual mammography screening under age 50. Until data become available, women with a first-degree relative with premenopausal breast cancer should begin annual mammography five years before the age of the relative’s initial diagnoses. ❖

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A Randomized Trial of Pelvic Radiation Therapy vs. No Further Therapy in Selected Patients With Stage IB Carcinoma of the Cervix

ABSTRACT & COMMENTARY

Synopsis: *Adjuvant pelvic radiotherapy following radical surgery reduces the number of recurrences in women with stage IB cervical cancer at the cost of 6% grade 3/4 adverse events vs. 2.1% in the observation group.*

Source: Sedlis A, et al. *Gynecol Oncol* 1999;73:177-183.

Sedlis and colleagues evaluated the benefits and risks of adjuvant pelvic radiotherapy aimed at reducing recurrence in women with stage IB cervical cancer treated by radical hysterectomy and pelvic lymphadenectomy. Two hundred seventy-seven eligible patients were entered with at least two of the following risk factors: more than 1/3 stromal invasion, capillary lymphatic space involvement, and large clinical tumor diameter. Of 277 patients, 137 were randomized to pelvic radiotherapy (RT) and 140 to no further treatment (NFT). Twenty-one patients (15%) in the RT group and 39 (28%) in the NFT group had a cancer recurrence, 18 of whom were vaginal/pelvic in the RT and 27 in the NFT group. In the RT group, of 18 (13%) who died, 15 died of

cancer. In the NFT group, of the 30 (21%) who died, 25 died of cancer. A life table analysis indicated a statistically significant (47%) reduction in risk of recurrence (relative risk = 0.53; P = 0.008) among the RT group, with recurrence-free rates at two years of 88% vs. 79% for the RT and NFT groups, respectively. Severe or life-threatening urologic adverse effects occurred in four (3.1%) in the RT group and two (1.4%) in the NFT group; three (2.3%) and one (0.7%) hematologic; four (3.1%) and zero gastrointestinal; and one (0.8%) and zero neurologic, respectively. One patient's death was attributable to grade 4 GI adverse effects. Sedlis et al concluded that adjuvant pelvic radiotherapy following radical surgery reduces the number of recurrences in women with stage IB cervical cancer at the cost of 6% grade 3/4 adverse events vs. 2.1% in the NFT group.

■ **COMMENT BY DAVID M. GERSHENSON, MD**

This study demonstrates that adjuvant pelvic radiotherapy is superior to observation for patients with stage IB cervical cancer who undergo radical hysterectomy and pelvic lymphadenectomy and are found to have unfavorable factors in the primary tumor: deep stromal invasion, capillary lymphatic space involvement, and large tumor diameter. Importantly, all patients in this study had negative pelvic lymph nodes. In an accompanying editorial, Dr. Anthony Russell raises a much broader question with regard to this group of patients and the selection of primary treatment. He notes that at least 74 patients entered on this study had primary cancers larger than 4 cm and asks, "Since GOG 92 confirms that adjuvant pelvic radiation favorably impacts relapse-free survival, is it still appropriate to treat 4 cm and larger cancers of the cervix with attempted radical surgery?" In other words, many patients end up having both radical surgery and pelvic radiotherapy, thereby increasing the risk of complications as noted in this study. Russell is eloquent in his argument but, by no means, the first to raise this issue. This controversy is all the more important in view of a presentation of a more recent GOG study at this year's annual meeting of the Society of Gynecologic Oncologists, in which Dr. William Peters presented data indicating that a combination of chemotherapy and radiation is superior to radiation alone following radical surgery for early-stage cervical cancer with positive pelvic lymph nodes.¹ Size of the primary cervical cancer can be determined pretreatment, and the degree of lymphatic invasion and depth of invasion could be determined to varying degrees from generous cervical biopsies or conization. In 1999, we have to ask if we are doing our best for women with early cervical cancer. ❖

Reference

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Special Feature

Work During Pregnancy: Potential Risks and Benefits

By Steven G. Gabbe, MD

Today, most women work during pregnancy. This article examines the issues commonly raised by women concerned about the potential risks associated with working while pregnant: Does work during pregnancy increase adverse perinatal outcomes? Are there identifiable risk factors associated with particular jobs that increase the likelihood of poor perinatal outcome? Are there particularly hazardous behaviors or exposures that the pregnant worker should avoid? What guidance should the obstetrician-gynecologist give the pregnant woman who works?

Today, most pregnant women work. Recent data indicate that nearly two-thirds of women worked for pay for at least six months during their pregnancies, and most worked full time.¹ In fact, more than half of working women continue their employment during the month before birth. Women are most commonly employed in technical, sales, and administrative occupations (44%), followed by managerial and professional positions (26%), service (18%), and employment in manufacturing and as laborers (9%).¹ Working women might be expected to have better pregnancy outcomes than those who are not employed. Working women usually have a higher income and have health insurance, are better educated, have a more stable home situation, and are less likely to drink and smoke. It could be argued that women who continue to work are able to do so because they are infertile or have had pregnancy losses. In these workers, adverse pregnancy outcome might be increased.

Most studies examining the impact of work during pregnancy have been retrospective questionnaire surveys, usually completed after delivery. The size of the populations studied has been small and many confounding variables, such as the patient's past obstetrical history, smoking, and substance and alcohol abuse have not been examined. Clearly, there is great need for better data on pregnancy outcomes for working women. A classic retrospective study conducted by Mamelle and

colleagues examined the impact of a variety of behaviors at work on the likelihood of preterm birth in French women.² Mamelle et al considered the effects of standing for three or more hours a day, working on an industrial machine, repeated heavy lifting, jobs requiring little attention, and adverse environmental factors, such as cold and damp conditions, on pregnancy outcome. Mamelle et al developed a point system for each of these risks and created a “fatigue score.” they found that working more than nine hours a day, more than 40 hours per week, or more than six days per week significantly increased the risk of preterm birth. In Mamelle’s study and others that followed, prolonged standing emerged as an important risk factor. Luke studied preterm birth in women who were members of the Association of Women’s Health, Obstetric and Neonatal Nurses.³ Working more than 36 hours a week, more than 10 hours a shift, or standing for more than 4-6 hours increased the rate of preterm birth. Of course, pregnant women work not only at their place of employment, but at home as well. Luke has expanded her studies to combine both a “work score” with a “home score,” which includes a variety of housekeeping activities.⁴ She concluded that fatigue from paid employment and work at home contributed significantly to hospitalizations as well as visits to the Emergency Room and Labor and Delivery.

Is residency training associated with poor pregnancy outcome? Klebanoff and colleagues performed a large questionnaire study of women residents and, as a control group, the wives of male residents.⁵ House officers in obstetrics and gynecology composed approximately 10% of the study population. Klebanoff et al reported that female residents experienced no increase in spontaneous abortion, ectopic pregnancy, stillbirths, preterm births, or intrauterine growth restriction (IUGR). Preterm labor was likely to be diagnosed more often in women residents, as was preeclampsia, but there was no increase in adverse outcomes associated with these problems. The rate of preterm birth was increased in

female residents who worked 100 or more hours per week.

Healthcare workers, including residents, are at greater risk for a variety of potentially dangerous exposures.⁶ Anesthetic gases, if not properly scavenged, increase the risk of spontaneous abortion and infertility. An association between exposure to antineoplastic drugs with pregnancy loss and fetal malformations has been observed. A recent prospective study demonstrated an association between exposure to organic solvents and an increased risk for fetal malformations, particularly in symptomatic women, that is, women who described irritation of the eyes or respiratory system, breathing difficulties, or headache.⁷ Of course, healthcare workers experience a greater likelihood of exposure to a variety of infectious agents, including hepatitis B, hepatitis C, and HIV.⁶ Exposure to ionizing radiation must also be carefully monitored. The National Council on Radiation Protection recommends that exposure during pregnancy be limited to a total of 0.5 rads or 0.05 rads per month. For nonpregnant workers, the Occupational Safety and Health Administration recommends that radiation exposure be limited to 1.25 rads per quarter or 5 rads per year. Many pregnant women, including healthcare professionals, commonly use video display terminals (VDTs). While early reports associated VDT use with spontaneous abortion and malformation, these adverse outcomes have not been supported by prospective studies.

In summary, most pregnant women are working outside the home in a wide variety of occupations. Overall, working while pregnant has not been associated with an increased risk of adverse perinatal outcomes such as preterm delivery and IUGR. While most women can continue working during the third trimester, attention should be paid to those occupations that require prolonged periods of standing and long working hours, as these risk factors have been associated with an increased likelihood of preterm birth and IUGR. Consideration

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should be given to modifying the workplace to allow women to take rest breaks, especially if they are at increased risk for adverse pregnancy outcomes. Residency training itself has not been associated with a greater likelihood of poor pregnancy outcome. Women should be counseled about the potential reproductive hazards of work before pregnancy. Patients should be asked about their employment and risk factors identified. The obstetrician may want to speak with a physician or nurse at the place of employment who has expertise in occupational safety. If specific hazardous exposures are of concern, a Material Safety Data Sheet can be obtained from OSHA. Questions should also be asked if the patient is working at home. ❖

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CME Questions

1. Which of the following statements is false?
 - a. With sufficient attention to detail, it is possible to select a constellation of food supplements and vitamin pills that ensure adequate nutritional intake in all categories.
 - b. Folate is essential for DNA repair processes.
 - c. Alcohol intakes of greater than 15 g daily have been found to be a risk factor for breast cancer.
 - d. It makes sense to take an inexpensive multivitamin as long as the formulation does not contain excess amounts of vitamins.
 - e. For certain nutrients like folate and vitamin D, food fortification makes sense.
2. Manos et al studied HPV DNA testing among women with ASCUS Pap smear reports. They found that:
 - a. HPV DNA testing was superior to repeat Pap smear testing.
 - b. HPV DNA testing was as good as repeat cytology testing.
 - c. Repeat cytology testing was superior to HPV testing.
 - d. All women with ASCUS smears should be referred for colposcopy.

3. Ever having used oral contraceptives increases a woman's risk of developing gestational trophoblastic tumors by:
 - a. twofold.
 - b. fivefold.
 - c. tenfold.
 - d. twentyfold.
 - e. fortyfold.
4. The following statements are true regarding breast cancer and mammography except:
 - a. A statistically significant decrease in breast cancer mortality has been demonstrated in the most recent clinical trials of mammography screening in women younger than age 50.
 - b. The "triple approach" adds ultrasonography to physical examination and mammography.
 - c. Breast cancers in women younger than age 50 grow faster compared with tumors in women older than age 50.
 - d. Breast cancers of the same stage have the same prognosis comparing women younger than age 50 with women older than age 50.
5. Based on recent information, all are acceptable contemporary treatments for various stages of cervical cancer except:
 - a. Radical surgery
 - b. Radiotherapy alone
 - c. Chemotherapy followed by radiation
 - d. Concomitant chemotherapy and radiation
 - e. Radiation followed by extrafascial hysterectomy
6. Which of the following exposures at work has been associated with an increased risk for preterm birth?
 - a. Prolonged standing
 - b. Anesthetic gases
 - c. Organic solvents
 - d. Antineoplastic drugs
 - e. Video display terminals

Readers Are Invited...

Readers are invited to submit questions or comments on material seen in or relevant to: Holland Johnson—Reader Questions, *OB/GYN Clinical Alert*, c/o American Health Consultants, P.O. Box 740059, Atlanta, GA 30374. Or, you can reach the editors and customer service personnel for *OB/GYN Clinical Alert* via the Internet by sending e-mail to holland.johnson@medec.com. You can visit our home page at <http://www.ahcpub.com>. We look forward to hearing from you. ❖

In Future Issues:

Assessment of Automated Primary Screening on PAPNET of Cervical Smears in the PRISMATIC Trial