

Estrogen-Progestin Replacement and Risk of Breast Cancer

To the Editor: Dr Schairer and colleagues¹ conclude that the estrogen-progestin regimen is associated with higher risks of breast cancer than estrogen alone. However, several aspects of the study deserve careful consideration.

First, the study was not conducted in a representative sample of women but in a select population for whom the risk of breast cancer may be high. Only a sample of women who had neither surgery nor the recommendation for it at baseline were included in the analysis. Furthermore, type of hormone used was not assessed in the first phase of follow-up. Some hormone use was measured retrospectively, possibly introducing recall bias.² Moreover, the authors report no results for women who had mammography regularly.

An analysis excluding cases of breast cancer that occurred in the first phase of the study would address the possibility of surveillance bias. An analysis of events by follow-up phase would add to a possible causal interpretation by providing a biologically appropriate lag time for cancer development. Presenting analyses stratified by frequency of mammography would strengthen the conclusion that these results were not caused by surveillance bias. It is well documented that women who receive hormone replacement therapy (HRT) also may be more likely to receive regular mammograms.^{3,4} In addition, an analysis comparing estrogen-progestin with estrogen alone may be in order given the authors' stated conclusions. Finally, a discussion of breast cancer mortality, total mortality, and risk vs benefit of HRT with respect to cardiovascular disease would help place these results in a public health context.

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- Schairer C, Lubin J, Troisi R, Sturgeon S, Brinton L, Hoover R. Menopausal estrogen and estrogen-progestin replacement therapy and breast cancer risk. *JAMA*. 2000;283:485-491.
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To the Editor: The relative risks (RRs) reported in the retrospective study by Dr Schairer and colleagues¹ are too small to claim a causal relationship. The clinical significance of the minimally elevated RRs cannot be interpreted as excess or attributable risk without incidence data. Assuming a yearly RR of 0.12 and an annual breast cancer incidence of 1 case per 1000, only 12 additional cancers would be diagnosed each year for every 100000 women treated with estrogen and progesterone. No additional

breast cancer deaths would occur (Schairer et al¹ previously confirmed improved breast cancer survival with HRT) while many cases of osteoporosis would be prevented each year.

The brief duration of hormone use (on average, 3.6 years for lean HRT users) seems more suggestive of diagnostic bias than a causal relationship. Diagnostic bias associated with initiation of HRT yields more events early on. Therefore, the requirement of the Poisson regression model that events be independent of time may not be met. The results are also inconsistent with other reports on weight and breast cancer in which stronger positive relationships were seen among postmenopausal women who never used HRT while lean women using estrogen were at lower risk for breast cancer than obese estrogen users,^{3,4} and obese women who had never used HRT were at higher risk for breast cancer than women who had used estrogen.⁵ There are many other studies on body mass index, HRT, and breast cancer that report different conclusions.

This lack of consistency argues against causality. In addition, changing the a priori planned analysis of body mass index quintiles may decrease the variance of the groups, thus increasing the chance of a type I error. The many small RRs with confidence intervals including 1 and the multiple comparisons (approximately 80 are described in the tables) also may increase the possibility that a significant result was found by chance.

Accurate and balanced presentation of the risks and benefits of HRT is an important public health issue. Patients should be counseled that the majority of studies suggest that HRT users are less likely to die from breast cancer, less likely to die from all cancers, and less likely to die from all causes than are nonusers.

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- Schairer C, Lubin J, Troisi R, Sturgeon S, Brinton L, Hoover R. Menopausal estrogen and estrogen-progestin replacement therapy and breast cancer risk. *JAMA*. 2000;283:485-491.
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Letters Section Editors: Stephen J. Lurie, MD, PhD, Contributing Editor; Phil B. Fontanarosa, MD, Executive Deputy Editor.

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5. Huang Z, Willett WC, Colditz GA, et al. Waist circumference, waist:hip ratio, and risk of breast cancer in the Nurses' Health Study. *Am J Epidemiol*. 1999;150:1316-1324.

To the Editor: Dr Schairer and colleagues¹ reported an RR for breast cancer of 1.4 for women who had used estrogen-progestin replacement therapy for 4 years compared with women who had never used estrogen or progestin therapy. This equates to a 40% increase in the risk of breast cancer, a figure that was seized on and widely reported by the media.

However, the data of Schairer et al suggest an absolute risk increase of estrogen-replacement therapy of 2.65% over 10 years. This statistic would allow a patient to be informed that fewer than 4 cases of breast cancer are likely to occur among 100 untreated women during a 10-year period, while 6 or 7 cases are likely to occur with 10 years of estrogen-progestin therapy. This data presentation is more meaningful, less sensationalistic, and more likely to facilitate sober and informed decision making by individual patients, the public as a whole, and the media. Measures of absolute risk also permit clinicians to determine number needed to treat or number needed to harm and to infer the likely consequences in their daily practice. In this instance, the 10-year number needed to harm for 1 additional case of breast cancer is 37.7.

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1. Schairer C, Lubin J, Troisi R, Sturgeon S, Brinton L, Hoover R. Menopausal estrogen and estrogen-progestin replacement therapy and breast cancer risk. *JAMA*. 2000;283:485-491.

To the Editor: Dr Schairer and colleagues¹ reported an increase in RR of breast cancer with the use of estrogen-progestin therapy compared with estrogen use alone. This increase in RR associated with progestin use may be reflected in the mammographic density changes seen with HRT.

Breast density increases in many women undergoing HRT. Among women undergoing continuous estrogen-progestin therapy, 27% had an increase in breast density, compared with 10% of those using cyclic combined therapy, and only 5% of women using estradiol alone.² Likewise, in premenopausal women, the breasts are more radiographically dense during the luteal phase than the follicular phase of the menstrual cycle³ when progesterone levels are highest. Conversely, use of tamoxifen citrate, which decreases breast cancer risk, is associated with a decrease in mammographic density.⁴

Studies using quantitative methods of assessing mammographic breast density have shown an increased risk of breast cancer for women with a higher percentage of the breast occupied by dense tissue.⁵ High-risk histology, such as atypical hyperplasia and lobular carcinoma in situ, is more commonly seen in women with high-density mammograms,⁵ thus

supporting the hypothesis that increased breast density is associated with an increase in breast cancer risk. Likewise, benign breast biopsy results from women using estrogen plus progestin have significantly higher proliferation indices compared with those from women using estrogen alone or those not receiving HRT.⁶ In addition, the proliferation noted in women using estrogen with progestin in this study was localized to the terminal duct-lobular unit, which is the site of development of most breast cancers.⁶

Since mammographically dense breasts are associated with an increase in breast cancer risk, women who have an increase in mammographic density in response to HRT may be at higher risk for developing breast cancer than those women who do not experience a change in density. Unlike most breast cancer risk factors, breast density can be influenced. Decreasing breast density also may decrease breast cancer risk, and further studies of this possible association may be helpful.

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To the Editor: Dr Schairer and colleagues¹ address concerns over bias introduced by estimating age at menopause² by repeating their analyses excluding women with unknown age at menopause, ostensibly leaving only women with natural menopause and bilateral oophorectomy in their sample.

They fail to consider, however, another possible source of bias. Women with bilateral oophorectomy, who also tend to have undergone hysterectomy, were likely overrepresented among the estrogen-only HRT-exposed group. Controlling for differences in age of menopause may leave residual confounding if oophorectomy reduces breast cancer risk through pathways other than its strong association with earlier age at menopause (eg, nonestrogen-mediated biologic effects, selection effects related to factors leading to reproductive surgery, or both). If this residual confounding is strong enough, the difference observed in the RRs for estrogen-only HRT and estrogen-progestin HRT could conceivably be artifactual.

In addition to supplementing their adjustment for age at menopause with additional adjustment for type of menopause, we urge Schairer et al to use their data to clarify the pos-

sible confounding role of surgical status on associations between HRT and breast cancer risk.

We feel that this potential for residual confounding adds an additional degree of uncertainty to the findings of Schairer et al. Until investigated further, this uncertainty should be considered in clinical decision making and communicated to patients.

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1. Schairer C, Lubin J, Troisi R, Sturgeon S, Brinton L, Hoover R. Menopausal estrogen and estrogen-progestin replacement therapy and breast cancer risk. *JAMA*. 2000;283:485-491.
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To the Editor: While the conclusions of Dr Schairer and colleagues¹ are supported by earlier studies,² several clarifications would help the reader better interpret the data that are presented. First, the authors describe the patient groups in the follow-up study as (1) those who underwent breast surgery for benign disease, (2) those who had a surgical consultation but did not have a biopsy or aspiration, and (3) those without either surgery or recommendation for consultation. As the patients from these groups were at different risks for developing breast cancer, were the 3 groups equally represented across the different HRT categories? Additionally, do the authors have data about the type of benign breast disease found in the 25 114 women who underwent biopsy? This could be of potential importance, since the risk of subsequent development of cancer may be influenced by the type of benign breast disease.^{3,4}

Second, it seems unusual that 38% of the person-years comprised unopposed estrogen and only 4% were combined estrogen-progestin use. This is not typical of current prescribing patterns⁵ and raises questions about whether the sample (although impressively large) is representative of the population of women receiving HRT.

Third, it appears that the increased risk of breast cancer is seen in the recent users only and increases with duration of exposure. If the duration of use was comparable in recent and nonrecent users, how do the authors explain the observation that discontinuation of estrogen (with or without progesterone) appeared to reverse the increased risk that would otherwise reasonably be attributed to the length of exposure?

Finally, how do the authors interpret the increase in the RR of breast cancers within 1 to 2 years of discontinuing estrogen (greater than that of current estrogen users and equal to that of current estrogen-progestin users)?

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1. Schairer C, Lubin J, Troisi R, Sturgeon S, Brinton L, Hoover R. Menopausal estrogen and estrogen-progestin replacement therapy and breast cancer risk. *JAMA*. 2000;283:485-491.
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3. Jacobs TW, Byrne C, Colditz G, Connolly JL, Schnitt SJ. Radial scars in benign breast-biopsy specimens and the risk of breast cancer. *N Engl J Med*. 1999;340:430-436.
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In Reply: We appreciate this opportunity to clarify and expand our results. In response to concerns that the patterns of hormone use in our patient population were atypical, we note that among hormone users in our study the percentage of person-years associated with estrogen-progestin use increased from 7% to 37% from 1979-1983 to 1992-1995. The figure for the later period compares with results from a nationally representative cohort in which 31% of women interviewed in 1992 who had used HRT received progestin.¹

The large proportion of women in our study with a history of benign breast disease raises questions about the generalizability of our results. However, we found no statistically significant differences in the association with ever use of hormones according to a prior history of benign breast disease ($P = .47$). Moreover, adjustment for a history of benign breast disease did not change our findings.

Confounding by type of menopause among women with a natural menopause or bilateral oophorectomy also did not account for the higher risk associated with the estrogen-progestin regimen than with estrogens alone; among these women, the increases in the RR associated with each year of estrogen and estrogen-progestin use were 0.01 (95% CI, -0.005 to 0.03) and 0.08 (95% CI, 0.01 to 0.17), respectively, after additional adjustment for type of menopause.

We discussed issues relating to recall and surveillance biases at length in our article. We add that among women screened annually, the observed RRs associated with less than 2 years, 2 to 4 years, and more than 4 years of estrogen-progestin use among recent users compared with nonhormone users were 0.8 (95% CI, 0.4-1.4), 1.3 (95% CI, 0.7-2.2), and 1.5 (95% CI, 1.0-2.4), respectively, suggesting that differential breast cancer surveillance did not account for our results.

We excluded women who had received estrogens alone in addition to the estrogen-progestin combination from our main analyses to ensure that associations with the estrogen-progestin regimen did not reflect risk associated with use of estrogens alone. Our findings of higher HRT-associated risks among women who were not overweight are similar to those from a recent collaborative reanalysis of the world's data on HRT and breast cancer risk.² Our results are also consistent with studies suggesting a stronger association with obesity and waist-hip ratio³ in women who had never used HRT than among users.

To provide clinical context for our results, we calculated that the excess cases per year of estrogen use and per year of estrogen-progestin use among recent users averaged over the follow-up period were 6.0 per 100 000 person-years (95% CI, 1-10) and 24 per 100 000 person-years (95% CI, 2-48), respectively.

Thus, our results were not changed as a result of addressing these concerns. Moreover, findings from a study published subsequent to ours are similar.⁴ Results similar to ours have also been reported for progestins of the norsteroid series.⁵ However, several important issues remain unresolved, including whether risk of breast cancer differs for the combined-cyclic vs combined-continuous regimen of HRT.

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4. Ross RK, Paganini-Hill A, Wan PC, Pike MC. Effect of hormone replacement therapy on breast cancer risk: estrogen versus estrogen plus progestin. *J Natl Cancer Inst*. 2000;92:328-332.
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Methadone Maintenance for Opioid Dependence

To the Editor: In the study by Dr Sees and colleagues¹ on methadone "treatment" for opioid dependence it is inappropriate to compare patients receiving a stable dose of methadone to those either undergoing detoxification or recently detoxified. The authors point out that 50% of the participants used illicit opioids and that there was no difference in cocaine use between the groups. They reported that neither group showed changes in 5 problem areas: employment, family, psychiatric, legal, and alcohol use. On the other hand, the 12-step recovery mode has been proven for 65 years. Once sober and totally drug free, the life of the recovering addict changes dramatically in all areas.

The tragedy of addiction has been overlooked time and again by well-meaning medical researchers who fail to grasp the underlying disease process and treatment of addiction. Sobriety or recovery is not a matter of switching to the correct pharmacological agent. Treatment for addiction must mean sobriety from all illicit or abusable substances. Someone taking metha-

done has no motivation and no conceptual framework to refuse cocaine, heroin, marijuana, or alcohol. Those with the disease of addiction do not care that methadone or benzodiazepines are prescribed by physicians. Hence, there is no recovery ethos to support further sobriety.

The primary treatment for addiction is support groups promoting "a desire to stop drinking" or using drugs.² Until the medical establishment recognizes and accepts this fact, we will be squandering money on research, replacement therapies, and jails and sadly neglecting the fundamental pathology of the disorder: the powerlessness of individuals to cease abuse on their own.

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1. Sees KL, Delucchi KL, Masson C, et al. Methadone maintenance vs 180-day psychosocially enriched detoxification for treatment of opioid dependence: a randomized controlled trial. *JAMA*. 2000;283:1303-1310.
2. *Alcoholics Anonymous: The Twelve Traditions*. 3rd ed. New York, NY: AA World Services Inc; 1976:564.

To the Editor: In their study of methadone maintenance, Dr Sees and colleagues¹ used suboptimal methadone doses. According to the National Institute of Drug Abuse (NIDA), Substance Abuse and Mental Health Services Administration (SAMSHA), and the Center for Substance Abuse Treatment (CSAT),^{2,3} the initial therapeutic dosage for methadone maintenance treatment is 80 to 120 mg/d, while the study by Sees et al restricted the dosage to 100 mg/d. In fact, many patients were receiving far lower dosages. It does nothing to remove the stigma from methadone maintenance treatment to subject patients to suboptimal doses and then publish the "failure" of methadone maintenance treatment by stating "that 50% of participants used an illicit opioid at least once a month is not encouraging" and then postulating that "failure may rest in the realm of psychosocial treatment," when neither program provided extensive legal, employment, family, or psychiatric services. I believe that the "failure" rests in the suboptimal dosing of the patients.

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1. Sees KL, Delucchi KL, Masson C, et al. Methadone maintenance vs 180-day psychosocially enriched detoxification for treatment of opioid dependence: a randomized controlled trial. *JAMA*. 2000;283:1303-1310.
2. Center for Substance Abuse Treatment. *State Methadone Treatment Guidelines: Treatment Improvement Protocol*. Rockville, Md: Dept of Health and Human Services; 1993:47-48.

In Reply: The comments of Dr Annitto and Ms Kelly aptly illustrate the diversity of views about methadone treatment within the clinical community. Some may find this diversity surprising, given the evidence indicating the clinical efficacy of methadone maintenance for the treatment of opioid dependence.¹ Annitto appears to have misconstrued the findings of our study to indicate that there were no differences between treatment