

ens the reliability of the conclusions. In addition, other reports on the effect of HRT use on ovarian cancer risk are inconsistent. Of the 5 case-control studies cited by Rodriguez et al that measured ovarian cancer risk among women who used HRT for 5 or more years, 4 found no statistically significant difference.²⁻⁴ One study found a statistically significant increased risk of endometrioid ovarian adenocarcinoma among women who used unopposed estrogen (OR, 2.81; 95% CI, 1.15-6.89).⁵ For the more common serous carcinomas, the OR of 2.03 was barely statistically significant (95% CI, 1.04-3.97). A recent meta-analysis reported no association between HRT use and ovarian cancer.⁶

Approximately 11 million US women routinely use postmenopausal HRT. The positive effects of HRT on bone metabolism and the lower genital tract mucosa of women are well documented. In women who still have a uterus, the increased risk of endometrial cancer associated with unopposed estrogen use can be negated by the concomitant use of progestins. The impact, if any, of HRT on the risk of developing breast or ovarian cancer remains controversial.

The study by Rodriguez et al should motivate further investigation of whether an association exists between ovarian cancer and postmenopausal HRT use. However, the existing data are not strong enough to cause an immediate change in clinical practice.

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1. Rodriguez C, Patel AV, Calle EE, Jacob EJ, Thun MJ. Estrogen replacement therapy and ovarian cancer mortality in a large prospective study of US women. *JAMA*. 2001;285:1460-1465.
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In Reply: The findings of Dr Bosetti and colleagues support the association that we observed between ovarian cancer and HRT use. In both analyses, the increased risk diminished after cessation of use. The critical question for clinical practice continues to be whether estrogen and progestin in combination or only unopposed estrogen use affects ovarian cancer risk.

We agree with Dr Hernandez that the data relating ovarian cancer to ever users of HRT are inconsistent. Case-control studies assessing ovarian cancer risk with 5 or more years of HRT use, however, have consistently reported increased risk, as we mentioned in our article. Nevertheless, we agree with Hern-

andez that the current evidence is incomplete and does not warrant an immediate change in clinical practice. Hernandez does, however, raise a more general and relevant question. When is the evidence from observational data sufficient to change medical practice? In the case of postmenopausal HRT, appropriate guidelines for individual women ultimately should be based on a full understanding of the balance between risk and benefits. Hernandez states that the association between postmenopausal HRT and breast and ovarian cancer is controversial. While we agree with this statement as it relates to ovarian cancer, we believe that the positive association between breast cancer and HRT use has been clearly established.^{1,2} Results from the Women's Health Initiative Trial will help clarify the impact of HRT use on risk of cardiovascular disease, osteoporosis, and breast cancer. The effect of postmenopausal HRT use on relatively rare diseases, such as ovarian cancer, cannot be studied with randomized trials and will likely only be evaluated through epidemiologic studies.

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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.
2. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. *Lancet*. 1997;350:1047-1059.

Breast Cancer in Women With HIV/AIDS

To the Editor: Drs Frisch and colleagues¹ reported that breast cancer was the only malignancy, at least in women, to exhibit a statistically significant pattern of decreasing relative risk (RR) with increasing amounts of time following a diagnosis of acquired immunodeficiency syndrome (AIDS). A recent study also found a statistically significant decrease in the incidence of breast cancer, in both men and women, following the AIDS epidemic in Tanzania.² Furthermore, some studies³ have found that immunosuppressed transplant recipients have a diminished incidence of breast cancer relative to other malignancies. This is contrary to what one would expect, since human immunodeficiency virus (HIV) infection theoretically increases the susceptibility to malignancy because of an acquired deficiency in immunosurveillance of tumor cells and/or an increased susceptibility to oncogenic viruses.

In an attempt to accumulate cases to determine the clinicopathological correlation of breast cancer in HIV-positive persons at our hospital, we searched the *International Classification of Diseases, Ninth Revision (ICD-9)*⁴ billing codes of

approximately 1.8 million patients for HIV disease. Of these patients, 2460 had at least 1 diagnostic code for HIV. We then searched these patient records for breast cancer codes and were surprised to find that only 2 patients had both HIV and breast cancer, particularly since our medical center serves as a referral center for patients with breast disease and HIV-related illness.

It is unclear why so few HIV-positive patients are diagnosed with breast cancer. Is this phenomenon related to the fact that patients infected with HIV die before they manifest breast cancer, or are such infected individuals truly protected from developing breast cancer because of some direct or indirect effect on their breast epithelium and/or immune system?

Replication of HIV within human mammary epithelial cells has been shown in vitro to reduce the growth of epithelial cells and to down-regulate their growth-factor receptors.⁵ Exactly what role the host's immune response plays in facilitating breast cancer development, however, remains controversial.⁶ Unquestionably, the answers will not only advance understanding of the biology of breast cancer but also may provide us further insight into alternative treatment modalities, such as immunotherapy.

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3. Stewart T, Tsai SCJ, Grayson H, Henderson R, Opelz G. Incidence of de-novo breast cancer in women chronically immunosuppressed after organ transplantation. *Lancet*. 1995;346:796-798.
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5. Toniolo A, Serra C, Conaldi PG, Basolo F, Falcome V, Dolei A. Productive HIV-1 infection of normal human mammary epithelial cells. *AIDS*. 1995;9:859-866.
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In Reply: As we noted in our article, the negative trend was not accompanied by an overall deficit of breast cancer cases. The 143 breast cancers in our study occurring from 60 months before to 27 months after AIDS onset in the cohort of 302834 men and women with HIV infection and AIDS corresponded closely to the expected number ($n = 135.3$) based on incidence rates for the general population (RR, 1.1; 95% confidence interval [CI], 0.9-1.2).

It is difficult to judge whether 2 cases of breast cancer in a group of 2460 HIV-positive individuals treated at the Beth Israel Deaconess Medical Center is more or less than one should expect. This expected number depends strongly on the sex, age, and race composition of this group and on the

observation time these individuals were at risk of breast cancer. However, assuming that their patients were similar to our cohort in terms of sex (16.2% female), age, race, and duration of observation, the expected number of breast cancer cases would only be 1.1 ($[2460 \times 135.3] \div 302834$). Even if one third of the cohort that was followed up by Drs Pantanowitz and Dezube was female, the expected number of breast cancer cases (again assuming an age and race composition and a mean follow-up similar to that of ours) would be 2.3, and the corresponding RR would not be significantly reduced (RR, 0.9; 95% CI, 0.1-3.1).

Thus, finding 2 cases of breast cancer in this group does not provide evidence in favor of reduced breast cancer risk in HIV-infected individuals. Whether breast cancer risk is truly influenced by immune dysregulation will remain a difficult issue to settle in the HIV/AIDS setting. Reproductive factors, such as age at first pregnancy, are major epidemiological determinants of breast cancer risk. These factors are likely to differ considerably between HIV-positive and HIV-negative women.

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A Novel About Bioterrorism

To the Editor: The Association of Pakistani Physicians of North America (APPNA) strongly protests the publication of Dr Panwalker's review of *Germ of War* by Ketan Desai.¹ Panwalker quotes portions of the book that denigrate Pakistan and its people. The passages chosen present slavery as a norm in Pakistan and talk of a group of slaves among whom the protagonist, a future Pakistani physician, learns to inflict "unspeakable acts of cruelty." Subsequently, this capability catches the eye of "the sinister head of Pakistan's intelligence service" culminating in the protagonist's admission to a medical school in Lahore. Finally, Pakistan (a very poor country) is found to be funding US medical research at the Mayo Clinic! Slavery is obviously not practiced in Pakistan; admissions to medical college are not based on recommendations of the Pakistan's secret service, and research on biological weapons is not being carried on in any US university at the behest of Pakistani intelligence agencies.

The executive council of the APPNA believes that publication of material that targets particular nationalities does not constitute an exercise of the right to free speech. We also hope that in the future *JAMA* will demonstrate a better understanding of

the motives underlying such books of “fiction” as well as those of their reviewers.

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1. Panwalker AP. Suspense. *JAMA*. 2001;285:1221-1222. Review of: Desai K. *Germes of War*.

In Reply: The task of a book reviewer is to present to potential readers the content of that book and to express a personal opinion about how readable, entertaining, or educational the material is. It is essential for the reviewer to be fair and accurate because much labor has been expended in producing the book. I believe that my review of *Germes of War* is an accurate depiction of the contents of that book. My opinion that it is a compelling story and an entertaining thriller would not be changed if the references to Pakistan had been omitted by the author.

Dr Akbar’s statement that “slavery is obviously not practiced in Pakistan” is inaccurate. Sadly, slavery in various forms, including the sale of children, exists in India, Pakistan, and other nations. Although the supreme court of Pakistan abolished forced labor or traffic in 1988 and parliament passed the Bonded Labor (Abolition) Act in 1992 and made the “peshgi” (earnest money) system illegal, these practices continue. A report from the Human Rights Watch/Asia in July 1995 quotes the Human Rights Commission of Pakistan as stating that millions of people

are held in debt bondage and the trafficking of women and child servitude continued unchecked.¹

While Desai clearly states that the characters in the book are fictional, I can imagine how its contents might have an unsettling effect on some individuals or groups. Akbar’s assertion that he supports free speech, however, is contradicted by his suggestion that *JAMA* should somehow decipher the motives of book reviewers before publishing their reviews. The resulting specter of censorship might turn away many reviewers who would make honest efforts to evaluate books that they are asked to review.

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1. Contemporary forms of slavery in Pakistan: Human rights watch/Asia. Available at: <http://www.hrw.org/reports/1995/Pakistan.htm>. Accessibility verified June 15, 2001.

In Reply: *Germes of War* is not intended to and does not denigrate Pakistani physicians in any way. Every ethnic and religious group has individuals in it that can be manipulated by forces of evil, and this book pinpoints one such fictional scenario. Given recent events in Afghanistan and Pakistan, however, I believe that my book presents a possible scenario for biological armageddon.

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