Pregnancy Termination and Risk of Breast Cancer

To the Editor.—In their article on the association between breast cancer and abortion, Dr Newcomb and colleagues[1] indicated awareness of the existence of underreporting of induced abortion in retrospective studies and of the possibility that women who have breast cancer might be more accurate in reporting their abortion histories than women who do not have cancer. However, the underreporting of induced abortion in their study may have been greater than they realized.

Using data collected by the Alan Guttmacher Institute[2] and the Centers for Disease Control and Prevention,[3] we estimate that 25% of females aged 15 through 44 years in 1989 had 1 or more induced abortions at sometime in their life. Although this percentage varies with age, it is a reasonable estimate for women younger than 45 years in the study by Newcomb et al. For women aged 45 years and older, most of whose abortions would have been illegal, we have data from two 1981 public opinion polls that asked women whether they had ever had an abortion.[4] Among women aged 40 years and older in 1981, between 2% and 6%, depending on the age group, responded affirmatively. These percentages, however, are undoubtedly low because of underreporting. For women aged 25 through 44 years in the survey, 9.8% reported having had an abortion compared with 16.9% estimated from national statistics on legal abortion.[4] On the assumption that women are at least as likely to underreport illegal abortions as they are legal ones, we adjusted the percentages for older women (age >45) upward by 72% (the ratio of 16.9% to 9.8%). Using these age-specific percentages, we estimate that in 1989, 11.2% of a national sample of women with the same age distribution as those in the study by Newcomb et al would have had an induced abortion. After adjusting for the lower average abortion rate of the 4 states in which the study by Newcomb et al was conducted, we estimate that 9% of the subjects in that study have had an induced abortion sometime in their lives.

However, Newcomb et al found that 2.7% of the controls and 2.9% of the cases reported having had induced abortions. Such low reporting of abortions suggests a high likelihood of recall bias, reporting bias, or both. The fact that only 4.7% of the cases refused to cooperate compared with 13.4% of the controls indicates that the 2 groups perceived the survey differently, despite efforts of the researchers to treat them identically. The researchers sought and achieved a high response rate to minimize sources of bias, but there is no reason to expect high response rates to reduce recall or reporting bias.

Given the high likelihood of bias in the measurement of induced abortion history, the study offers reassurance that induced abortions add little if any risk of breast cancer. It is unfortunate that the abstract of the article states that the risk associated with induced abortion "was somewhat greater than the risk associated with spontaneous terminations." This statement ignores the bias problem and is contradicted by the results, which show no statistically significant difference in risk according to abortion type.

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To the Editor.—Dr Newcomb and colleagues[1] observed a weakly positive association between abortion and risk of breast cancer. The increase in risk of breast cancer was not significantly different if the abortion was induced or spontaneous.

An allele of the estrogen receptor gene, called the *B′* allele, contains a silent mutation in codon 87, part of the receptor's B domain.[2] Because of the association reported of the *B′* allele, spontaneous abortion, and estrogen receptor–positive breast cancer,[3] a preliminary case-control study was performed to estimate the risk of breast cancer in women with the *B′* allele.[4] Among *BB′* heterozygote women with estrogen receptor–positive breast cancers (23 cases, 27 controls), the risk of breast cancer was associated with a history of spontaneous abortion; the age-adjusted odds ratios were 4.1 (95% confidence interval [CI], 0.95-18) after 1 spontaneous abortion and 9.7 (95% CI, 1.6-61) after 2 or more spontaneous abortions. No such association was seen for the risk of estrogen receptor negative breast cancer in *BB′* heterozygotes (n=18). Moreover, among *BB* homozygotes (137 cancer patients, 235 controls), spontaneous abortion was not related to an increased risk of breast cancer for either estrogen receptor–positive or estrogen receptor–negative cancers. In *BB′* patients with estrogen receptor–positive tumors, receptor concentrations were significantly ($P=.02$)[4] lower in patients who had a history of spontaneous abortion than in those without previous spontaneous abortions. These findings suggest involvement of a functional mutation associated with the *B′* allele, which is either elsewhere in the estrogen receptor gene region or in a closely linked gene.

A woman carrying the *B′* allele can be identified from assay of peripheral blood lymphocyte DNA. Since the *B′* allele is associated with an increase in breast cancer risk in women with a history of abortion, presence or absence of this estrogen receptor variant might be used to provide an estimate of the association of abortion and breast cancer risk.

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In Reply.—Dr Henshaw provides additional population-based information on abortion services in the United States and concludes, as we do in the abstract of our article, that the association between induced abortion and breast cancer risk may be due to reporting bias and was not significantly different than the slight risk for spontaneous abortion. Henshaw's estimates of the underascertainiment of induced abortion underscores the degree to which studies such as ours are susceptible to bias and the need for prospective investigations.

Dr Lehrer suggests that an inherited variant of the estrogen receptor gene may identify women at increased risk of breast cancer because of a history of spontaneous abortion.[1] The importance of these observations is unclear because the original relation between this polymorphism and spontaneous abortion has not been confirmed,[2] and Lehrer's subsequent findings[3] were based on small numbers of patients in selected subsets. While it remains a theoretical possibility that a polymorphism at this site might be associated with the magnitude of the relationship, if any, between spontaneous pregnancy loss and breast cancer risk, it seems unlikely that

induced abortion would in any way be modified by the presence of this variant in the estrogen receptor gene.

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Rabies Prevention: Cost to an Indian Laborer

To the Editor.—Rabies is a major health hazard in India[1] and other developing countries.[2] Approximately 500 000 persons receive postexposure treatment and more than 25 000 die annually from rabies in India.[2] These figures understate the actual incidence because nonreporting of rabies deaths is common. Currently available tissue-culture vaccines are highly immunogenic and safe, although postexposure treatment failures are occasionally reported.[3] The costs of the vaccine and other treatments, however, may limit their usefulness in developing countries.

Report of a Case.—A boy aged 12 years was bitten by a dog in an interior rural area in India when he tried to remove an iron chain from the dog's neck. He received multiple bite wounds on both legs and thighs. The wounds were cleaned and the patient was immunized against tetanus. When the dog died, 5 days after the bite, the patient was given his first dose of purified chick embryo cell rabies vaccine. He subsequently received 3 more doses of vaccine. Rabies immunoglobulin was not administered systemically nor were the wounds infiltrated. About 10 days after the fourth dose, he developed flaccid paralysis of all 4 limbs with urinary retention. There was no hydrophobia, aerophobia, or photophobia. He died 17 days after the last dose of vaccine. Delay in starting treatment and omission of passive immunization apparently contributed to the patient's death.

Comment.—Economic implications have an important bearing on treatment of animal exposures in developing countries. The father of this patient, a poor daily-wage laborer, sold 40 decimals (0.4 acre) of his valuable agricultural land to meet the cost of his son's treatment. Financial constraints apparently contributed to initial delay in purchase and administration of rabies vaccine.

Cost of Rabies Vaccines in India and the Approximate Number of Days a Laborer Has to Work to Meet the Cost*

Vaccine Dosage	Current Cost in India		No. of Days' Wages Required to Meet the Cost
	Rupees	Dollars	
HDCV 1 mL IM × 5 doses	3280	106	109
PCEC 1 mL IM × 5 doses	1075	35	36
PVRV 0.5 mL IM × 5 doses	1155	37	39
HRIG 20 IU/kg of body weight	4322	140	144

*HDCV indicates human diploid cell vaccine; IM, intramuscular; PCEC, purified chick embryo cell vaccine; PVRV, purified vero cell rabies vaccine; and HRIG, human rabies immunoglobulin.

A 60-kg patient with severe exposure to rabies needs 1200 IU of human rabies immunoglobulin, which costs about 4322 rupees (US $140) in addition to the cost of a 5-dose course of any tissue-culture vaccine available. An Indian laborer typically earns about 30 rupees per day. Therefore, a laborer would have to work 144 days to earn enough money to pay for the cost of postexposure rabies prophylaxis for 1 severely exposed patient (Table). Wound care, antibiotics, analgesics, tetanus immunization, and loss of wages during the period of treatment are additional costs.

Government subsidy of the cost of rabies immunoglobulin and tissue-culture vaccines is direly needed. Introduction of the intradermal method of vaccination, which is not currently approved in the United States, could reduce the cost of postexposure rabies prophylaxis.[4] One regimen involves administering intradermally 0.1 mL of tissue-culture vaccine at 2 sites on days 0, 3, and 7 and 0.1 mL at 1 site on days 30 and 90.[5] Alternative cost-saving regimens have also been proposed.[6]

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