To the Editor.—Regarding the article by Dr Hankinson and colleagues[1] on tubal ligation, hysterectomy, and risk of ovarian cancer, one possible mechanism not mentioned by the authors is that some infectious agent, probably a virus, is being prevented from reaching the ovaries by surgical closure of the route from the vagina to the ovaries. Also noted in their study was a somewhat lessened risk if the partner used condoms, again an argument for an infectious cause. Ascending bacterial infections commonly cause endometritis and salpingitis; surely viruses go where bacteria do not fear to tread. The association of Burkitt's lymphoma with the Epstein-Barr virus, cervical cancer with the human papillomavirus, and Kaposi's sarcoma with the human immunodeficiency virus lend at least some credence to the oncogenic virus theory. A virus inserting itself by mistake in the wrong sequence of DNA or RNA could plausibly cause the production of a tumor cell.

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1. Hankinson SE, Hunter DJ, Colditz GA, et al. Tubal ligation, hysterectomy, and risk of ovarian cancer: a prospective study. *JAMA.* 1993;270:2813-2818.

To the Editor.—Dr Hankinson and colleagues[1] report an inverse relationship between tubal ligation and ovarian cancer and propose mechanisms for a possible causal association that involve altered ovulatory cycles and gonadotropin, estrogen, and progesterone levels. They conclude that it "may be appropriate to consider the reduced risk of ovarian cancer when choosing among alternative methods of contraception." Their findings, which corroborate several studies, are interesting and important. However, it is imperative to question how tubal ligation may alter normal physiology of premenopausal women and what long-term effects it may have on accelerating two conditions which eventually occur in virtually all women, osteoporosis and atherosclerosis. In this context, the effects of ovulation and estrogen and progesterone levels on bone density and lipid levels should be considered.

Concerning bone density, it has been shown that even asymptomatic ovulatory disturbances may be associated with decreased spinal density.[2] With regard to lipids, estrogens are known to have a beneficial effect on lipid profiles through elevation of HDL and reduction of LDL cholesterol.[3] Significantly, these changes are associated with a decreased risk of cardiovascular death in postmenopausal women.[4] The effect of long-term alteration of endogenous estrogen levels on lipid profiles in normal premenopausal women who are not receiving oral contraceptives needs further elucidation. Current information about exogenous estrogen therapy suggests that the beneficial effect of estrogen on lipids is slightly greater in postmenopausal women given 1.25 mg of conjugated estrogen,[5] and another study has shown an upward trend in this beneficial effect in women given high as opposed to low-estrogen-content oral contraceptives.[6]

Before accepting the use of tubal ligation to reduce the risk of ovarian cancer, these and other possible theoretical consequences should be considered.

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1. Hankinson SE, Hunter DJ, Colditz GA, et al. Tubal ligation, hysterectomy, and risk of ovarian cancer: a prospective study. *JAMA.* 1993;270:2813-2818.
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3. Psaty BM, Heckbert SR, Atkins D, et al. A review of the association of estrogens and progestins with cardiovascular disease in postmenopausal women. *Arch Intern Med.* 1993;153:1421-1427.
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To the Editor.—Dr Hankinson and colleagues[1] have reported that tubal ligation, and perhaps hysterectomy, may substantially reduce risk of ovarian cancer. How this risk reduction might be mediated is unknown, and various mechanisms have been proposed.

There have been inconclusive reports on a "posttubal sterilization syndrome," affecting blood supply, ovulation, steroid production by the ovaries, and menstrual regularity. Moreover, tubal sterilization might prevent contact of the ovary with fluid from the uterine cavity carrying carcinogens, such as talcum powder. In addition, the retrograde menstruation associated with intact fallopian tubes has been linked with salpingitis, endometriosis, and possibly systemic lupus erythematosus; thus, menstrual debris might be a carcinogen.[2] Another possible mechanism to consider is the antitumor action of general anesthetic agents. For example, one study of these agents demonstrated increased production of tumor necrosis factor during their administration, which was four to five times greater than in controls.[3] In another study, halothane potentiated the antitumor activity of interferon gamma.[4] Tubal ligations performed on patients who have just delivered are usually performed under epidural anesthesia, but tubal ligations not associated with pregnancy are performed under general anesthesia; the procedure may last for 30 minutes or more. The duration of general anesthesia during hysterectomy is even longer.

Therefore, it would be worthwhile to see if reduced risk of ovarian cancer might be associated with other surgical procedures performed under general anesthesia, such as tonsillectomy or appendectomy. Such a study might further define the biologic mechanism of the observed ovarian cancer risk reduction.

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1. Hankinson SE, Hunter DJ, Colditz GA, et al. Tubal ligation, hysterectomy, and risk of ovarian cancer: a prospective study. *JAMA.* 1993;270:2813-2818.
2. Grimes DA. Primary prevention of ovarian cancer. *JAMA.* 1993;270:2855-2856.
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4. Rudnick S, Stevenson GW, Hall SC, Espinoza-Delgado I, Stevenson HC, Longo DL. Halothane potentiates the antitumor activity of γ-interferon and mimics calmodulin-blocking agents. *Anesthesiology.* 1991;74:115-119.

In Reply.—In response to Dr Myers, we unfortunately do not have data on the type of hysterectomy procedure performed (vaginal or abdominal). In response to Dr Silver, we asked women about their use of contraceptive foam or jelly on the first three study questionnaires. Only 6040 women reported use in 1976; reported use decreased on each subsequent questionnaire. In a multivariate analysis controlling for other ovarian cancer risk factors, the relative risk associated with use of foam or jelly was 0.60 with wide 95% confidence limits (0.24, 1.46); thus, further follow-up will be needed. As described in our article, we agree that a possible mechanism is the prevention of ovarian exposure by contaminants other than talc. We do not concur with Dr Wahlberg's observation that our data indicate a protective effect of condom use; the relative risk, although less than 1.0, was not near statistical significance. Dr Whitmore makes an important point. The influence, if any, of tubal ligation on other outcomes should be assessed; these data may lend insight into possible biologic mechanisms and are crucial in making overall risk-benefit decisions. In our article, we do not suggest that tubal ligation be used specifically to reduce risk of ovarian cancers; rather,