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LETTERS TO THE EDITOR

RE: "POLYCYSTIC OVARIES AND THE RISK OF BREAST CANCER"

Gammon and Thompson (1) recently reported in the *Journal* the results of an analysis of data from the Center for Disease Control's Cancer and Steroid Hormones Study to examine the association between a history of physician-diagnosed polycystic ovaries and the risk of breast cancer. Despite the small number of exposed cases (n = 23) and controls (n = 44), their data strongly support the conclusion that a history of polycystic ovaries protects against premenopausal and early postmenopausal breast cancer. These results are in apparent conflict with those reported in a previous cohort study by Coulam et al. (2), who found a threefold increase in postmenopausal breast cancer in women with polycystic ovaries. Such discrepancy may reflect real, albeit unexplained differences between premenopausal and postmenopausal women in the influence of endogenous hormones on breast cancer.

These results are unexpected—the study was designed to test a positive association between polycystic ovaries and breast cancer. The authors have difficulties interpreting their results on biologic grounds, and their arguments are not convincing. Indeed, it is hard to reconcile a serious chronic endocrine imbalance, characterized by hypersecretion of ovarian androgens, with protection against any epithelial cancer. The only argument that the authors venture to propose is that polycystic ovaries induce anovulation, which, in turn, protects against breast cancer by reducing the breast's cyclical exposure to progesterone. This hypothesis had been proposed by others (e.g., by Henderson et al. (3)), but has not yet been tested convincingly. In the case of polycystic ovaries, explaining the strong observed protective effect solely in terms of reduced exposure to progesterone may be an oversimplification of a complex phenomenon.

There is one aspect that Gammon and Thompson have not addressed. This is the question of the medical and/or surgical treatment that, by definition, all exposed cases and controls have received for their polycystic ovaries. In the period of time that is relevant to the Cancer and Steroid Hormones Study (i.e., 1950–1980), bilateral wedge resection of the ovaries was frequently used to normalize the excessive androgenic secretion. Wedge resection was quite effective, resulting in ovulatory cycles in nearly 85 percent of Stein-Leventhal patients (4, 5), probably because of the removal of a critical amount of androgen-producing hyperplastic ovarian interstitial tissue. In more recent years, less aggressive pharmacologic treatments were introduced which are based on very effective ovarian or adrenal suppression (6). Furthermore, polycystic ovaries or, more often, wedge resection, may cause complications, such as heavy bleeding or internal adhesions, leading to bilateral oophorectomy, a well-known protective factor for breast cancer (7).

Our point is that the results of Gammon and Thompson's analyses may have more to do with the effects of *treatment* for polycystic ovary syndrome rather than with the biologic consequences of a history of the condition. Furthermore, one should consider that probably the vast majority of women affected by polycystic ovaries, which is regarded as the most common endocrine condition of women in their reproductive years (8), remain undetected. Thus, an unknown, but large fraction of cases and controls must have been unrecognized clinical and subclinical carriers of the underlying ovarian abnormalities. Only women presenting with evident symptoms of obesity, hirsutism, dysmenorrhea, and anovulation had a chance of being diagnosed and effectively treated. In the absence of detailed information on specific treatments, the question of partial or total oophorectomy and of its timing in relation to both exposure and disease should be addressed.

In conclusion, women who are treated for polycystic ovary syndrome, or who are oophorectomized because of the condition, may be less likely to develop breast cancer than untreated women with the disease. The protective effect may be due to the success of surgical and medical treatment and/or to the removal of the ovaries rather than to a biologic effect of the condition per se. These are observations of great potential public health and research relevance, because they seem to suggest that early detection of, and treatment for, undetected polycystic ovaries could make quite an impact on the primary prevention of breast cancer.

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THE AUTHORS REPLY

Toniolo and Whittemore (1) express concern that the reduced risk of breast cancer noted among women with a history of polycystic ovaries in our analysis of data from the Cancer and Steroid Hormone Study (2) may be due to the medical and/or surgical treatment that these women received for their condition. Among the treatments that have been used within the 30 years prior to collection of the data (1950–1980), or among the possible medical sequelae of this condition (3), only bilateral oophorectomy at an early age is known to reduce the risk of breast cancer (4–7).

In our analysis, we made adjustments for the possible confounding effects of some medical treatments and sequelae of polycystic ovaries, including oral contraceptive use, other hormone use, and menopausal status; with adjustments for these covariates, the odds ratio for breast cancer in relation to polycystic ovaries was only minimally affected (2). As shown in table 2 of our paper (2), we found that the association between breast cancer and polycystic ovaries did not vary with menopausal status. The age-adjusted odds ratio for breast cancer among women with surgical menopause (defined as menopause induced by hysterectomy, hysterectomy in combination with partial or total oophorectomy, or bilateral oophorectomy without hysterectomy) was 0.62 (95% confidence interval 0.29–1.33). We acknowledge that categorizing women with a surgical menopause into a single group incompletely controls for the effects of a bilateral oophorectomy. However, this method of classification should not affect the other groups of women who had not had surgical menopause including a bilateral oophorectomy. As shown in table 2 of our original article, women with polycystic ovaries who were pre-, peri-, or naturally postmenopausal also had a reduced risk of breast cancer (0.56, 0.52, and 0.38, respectively).

Toniolo and Whittemore (1) also suggest that there may be a large number of women who have clinically unrecognized or subclinical polycystic ovaries that have never come to medical attention. Because there is no reason to suspect that such misclassification of "exposure" varies by case or control status, the effect would be to attenuate our estimates of effect toward the null hypothesis (8).

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