

Mathematically, it can be shown (3) that for this model the posterior probability (after observing the Scandinavian data) that the relative risk is less than any value x is

$$\Phi \left\{ \left[\log x - \frac{\log r}{1 + \sigma^2/\tau^2} \right] \sqrt{1/\sigma^2 + 1/\tau^2} \right\},$$

where Φ denotes the cumulative normal distribution function. For the Scandinavian data, there is a 23% chance that the relative risk attributable to tamoxifen is less than 1.5, a 64% chance that it is less than 2, and a 97% chance that it is less than 3. We might interpret this finding as indicating that the hypothesis that tamoxifen is associated with a substantial risk of colorectal cancer is more credible than before the report of the Scandinavian data, but the risk should not be viewed as established on the basis of these data. We would interpret this finding as indicating that the tamoxifen-associated risk of colorectal cancer, if it exists at all, is likely to be relatively small (relative risk, <3). If we were less conservative in interpreting our prior information, we might have used $\tau = 0.30$, corresponding to a 1% (rather than a 5%) chance that the relative risk exceeds 2 (rather than 5). In this case, we would have obtained a posterior probability of .95 that the relative risk of colorectal cancer is less than 2. This finding can be interpreted as indicating that, even in light of the Scandinavian data, the chance of a strong association between tamoxifen therapy and an increase in risk of colorectal cancer is slight.

This Bayesian analysis provides one post-hoc approach to interpreting a finding resulting from multiple comparisons. Because it is subjective, however, it does not negate the importance of testing this prospectively stated hypothesis on independent data. Although the data in Table 2 derived from NSABP protocol B-14 do not approach statistical significance

for the association between tamoxifen use and colorectal cancer, 95% confidence intervals for the relative risk do appear to include the estimate of 1.9 reported from the Scandinavian data. Hence, although the article by Rutqvist et al. (1) does not clearly establish an association between tamoxifen use and risk of colorectal cancer, it is consistent with a modest increase in such risk. Although an association between tamoxifen use and colorectal cancer does not appear to have a strong biological basis, it would be appropriate to examine whether such an association exists in other randomized clinical trials. Further follow-up of the Scandinavian patients and the NSABP patients may also provide additional information.

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Are Dietary Fat and Vasectomy Risk Factors for Prostate Cancer?

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Prostate cancer, the most commonly diagnosed malignancy among U.S. males, varies markedly in worldwide occurrence from about 2 ($\times 10^{-5}$ per year, age-adjusted) in Shanghai, China, and 10 in Miyagi Province, Japan, to about 20 and 33, respectively, among Chinese and Japanese in Los Angeles, to about 62 and 82, respectively, for U.S. whites and blacks. Mortality due to prostate cancer is twofold higher among U.S. blacks than among U.S. whites. At present, prostate cancer costs more than \$1 billion annually, requires a quarter of a million hospitalizations, and results in more than 40 400 deaths (1-3).

A familial component is important in determining prostate cancer risk (4,5) but does not appear to explain the variation in rates between U.S. blacks and whites (6). Dietary fat, the con-

sumption of which varies on a national basis in parallel with prostate cancer rates (7), may be a major risk factor for this disease (8,9). In a search for other risk factors, Rosenberg et al. (10), in 1990, noted an increased risk for prostate cancer among men who have had a vasectomy. Since more than 50 million couples worldwide use this method of birth control (11), the study raised concern about the causal nature of this association (12).

In this issue of the Journal, two articles from a population-based case-control study describe 1) the association of prostate

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cancer with patterns of diet and the related factors of physical activity and body size (13) and 2) the association of this cancer with a history of vasectomy (14). This study, which included more than 1500 cases and controls and was carried out among blacks, whites, Chinese-Americans, and Japanese-Americans in five cities in the U.S. and Canada, allowed for assessment over a wide risk-factor spectrum—particularly important for the evaluation of diet, which tends to be relatively homogeneous within ethnic groups.

On the basis of detailed dietary interviews, Whittemore et al. (13) show that prostate cancer risk increases with higher intake of saturated fat. Risk was significantly elevated for Asian-Americans; for blacks and whites, the pattern was less pronounced but consistent with an overall excess. Risk was unrelated to intake of other macronutrients, intake of vitamin A/carotenoids, intake of fruits and vegetables, body mass, or physical activity weighing against some earlier reports [reviewed in (15,16)] that had raised concern about retinol and its precursors. Whittemore et al. (13) found among Asian-Americans that long-term residents of the United States were at greatest risk of prostate cancer, consistent with the observations from migrant studies (17). This result was not dependent on dietary fat intake, which suggests that other factors associated with long-term residence may also be involved.

This study (13) contributes to the growing evidence of a link between prostate cancer and intake of dietary fat, associations that have been observed in case-control (18-25) and cohort (26-29) studies, although some reports are negative (30-34). Animal sources and saturated fats have received the most attention. The finding by Whittemore et al. of a specific association with saturated fat supports this link and is encouraging because saturated fat intake has been falling since the late 1950s, whereas polyunsaturated fat intake has increased (35,36). Some investigators, however, have suggested a role for unsaturated fats (7,24,28,29) and total energy intake (34) in the development of prostate cancer. The finding (12) of increased risk with high fat intake among Asians could also be due in part to associated decreases in intake of cancer protective compounds common to the Asian diet (51). Clearly, clarification of this point is essential for the design of cancer-control programs.

Whittemore et al. (13) and other investigators (24,26,27) provide evidence that fat is most strongly associated with advanced tumors. In pathology studies of latent prostatic cancer, earlier investigators had suggested a link between environmental factors, such as diet, and tumor progression because only the infiltrating lesions paralleled the geographic and ethnic frequency of clinical cancer rates, while noninfiltrating lesions were equally prevalent in all groups (2). Dietary interventions in clinic- and population-based settings could directly test this hypothesis. The development of early markers of prostatic disease (37) will facilitate the efforts to study the impact of dietary change.

Whittemore et al. (13) found increased risk associated with saturated fat intake among both younger and older men, in contrast to investigators who suggested age-specific effects (18,22,24). Statistical variability associated with smaller numbers of subjects in the earlier studies may account for their findings.

The Rosenberg et al. (10) finding of an increased risk for prostate cancer following vasectomy is supported by several other investigations (38-44), with most studies suggesting excesses in men who had a vasectomy at a young age or many years before prostatic cancer diagnosis (38,39,41-44). An analysis, in 1994, of more recent data by Rosenberg et al. (45), however, showed only a weak temporal link, and other studies have shown no association (20,46-48). In this issue of the Journal, John et al. (14) report that vasectomy is not related to the development of prostate cancer. Their statistical estimates excluded increases in risk of about 30% or more, and they did not find consistent increases by age at vasectomy or number of years since vasectomy. Exclusion of control subjects with elevated prostate-specific antigen (PSA) and restriction to advanced prostatic cancer patients did not alter this result.

In vasectomized control subjects, John et al. (14) found consistent decreases in sex hormone-binding globulin and increases in the ratio of dihydrotestosterone to testosterone. Although hormones are believed to play a key role in prostate carcinogenesis, the significance of these specific alterations is unclear (49). Endocrine, immunologic, and other effects of vasectomy have been examined (50), but there is scant information about the long-term consequences of this procedure in humans. Population-based epidemiologic studies like this one provide an excellent opportunity to learn about long-term sequelae of vasectomy.

With the new information from this large population-based investigation (14), vasectomy appears either not to cause prostate cancer or to have only a relatively weak relationship to the disease, but the reasons for differences with the previous positive studies are not evident. The epidemiologic evaluation of relatively weak associations between medical interventions and chronic disease is challenging because biases may confound the association of the medical intervention (i.e., vasectomy) with the disease. As examples, biased selection and participation of case patients and control subjects and errors of vasectomy reporting may occur, and men who have had a vasectomy may have different health-care patterns (they may be more likely to undergo a diagnostic workup for prostate cancer). Continued surveillance of this procedure as a risk factor for prostate cancer is warranted; however, these evaluations will need to further consider the many issues affecting validity.

The public health impact of prostate cancer continues to increase in the aging U.S. male population; however, until recently, this cancer has been understudied (2). The epidemiologic studies presented in this issue of the Journal (13,14) represent significant advances in our understanding of the etiology of this disease, indicating that dietary fat causes prostate cancer and that vasectomy is likely not a major risk factor for this disease.

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