CI = 1.48-1.79) and 1.51 among women (95% CI = 1.38-1.64). For patients with no comorbidity (having diabetes mellitus as their only hospital discharge diagnosis), the SMR was 1.29 (95% CI = 1.08-1.53). The excess mortality persisted 10 or more years after enrollment in the cohort (SMR = 1.33; 95% CI = 1.12-1.58).

For rectal cancer, the increased incidence was more evident among men (SIR = 1.36; 95% CI = 1.21-1.52) than among women (SIR = 1.10; 95% CI = 0.95-1.26) (Table 1). Six cases occurred among patients enrolled in the cohort before age 40 years (SIR = 1.27; 95% CI = 0.46-2.77). The overall SMR was 1.61 among men (95% CI = 1.41-1.82) and 1.36 (95% CI = 1.17-1.57) among women. For patients with no comorbidity, the SMR was 0.98 (95% CI = 0.73-1.29). The SMRs were significantly increased up to 10 years of follow-up but not afterwards (SMR = 1.17; 95% CI = 0.89-1.51).

For both colon and rectal cancers, there was no significant trend with the duration of follow-up in either sex. Thus, selection bias is an unlikely explanation for our findings. We found no appreciable differences in SIRs whether or not the patient was ever hospitalized for complications of diabetes (i.e., neuropathy, nephropathy, or retinopathy). There was also no difference in risk between patients born before 1900 (probably NIDDM) or afterwards (data not shown).

Our results support the hypothesis of a positive association between diabetes mellitus and colorectal cancer, but further studies are needed to assess whether this association is because of diabetes or shared risk factors, such as obesity, body fat distribution, diet, or physical inactivity.

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Notes

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Re: Reversal of Relation Between Body Mass and Endogenous Estrogen Concentrations With Menopausal Status

The brief communication by Potischman et al. (1) in a recent issue of the Journal refuted the argument based on anovular cycles to explain the reduced risk of breast cancer in obese premenopausal women. The brief communication also provides the data supporting the hypothesis that I formulated (2,3)—that lean premenopausal women showed higher serum estrogen concentrations than their overweight counterparts. Potischman et al. (1) suggested, however, that obesity is the cause of low serum estrogen levels in premenopausal women as a result of estradiol uptake by adipocytes and the higher metabolic clearance rate in such women, whereas my hypothesis was that high estrogen levels are the cause of leanness in premenopausal women. This assumption is based on the inverse relationship we demonstrated (4) between body mass index (BMI) and high-density lipoprotein (HDL)–cholesterol serum concentrations. HDL–cholesterol serum concentrations parallel serum estrogen levels over a woman’s life, with a progressive increase between menarche and menopausal decrease (5). The stimulation of hepatic lipoprotein lipase by estrogen (6) results in high HDL–cholesterol and low serum triglycerides, hence low BMI. This metabolic link suggests that leanness in premenopausal women is due to high estrogen levels, a risk factor for breast cancer. This mechanism does not preclude the origin of hyperestrogenemia, although elevated insulin–like growth factor (IGF)-1 levels appear to be an essential factor. Increased levels of IGF-1 result from an elevated secretion of growth hormone, possibly associated with an energy-rich diet during prepuberty and puberty. IGF-1, a growth factor in itself, is also capable of inhibiting hepatic synthesis of sex hormone-binding globulin (SHBG), leading to higher levels of estrogens unbound to SHBG and of up-regulating steroid hormone synthesis. The latter effect might result in a chronic hormone dysregulation (7), known as “functional ovarian hyperandrogenism,” further aggravating the primary effect of IGF-1.

Obesity in postmenopausal women is generally considered to be the cause of extragonadal estrogen synthesis. However, not only is the estrogen hepatic metabolism different, but also the serum concentrations are much lower than in premenopausal women, reducing the possibility of secondary activation of hepatic lipoprotein lipase. These low estrogen levels raise the likelihood that it
is the estrogens themselves that mediate the risk. Moreover, visceral/abdominal obesity, the specific type of obesity described as a risk factor for breast cancer, is associated with insulin resistance and high levels of IGF-1 and testosterone. This global hormonal dysregulation may be the major effector of increased risk.

To discriminate between the mechanism proposed by Potschman et al. (1) and the mechanism that I proposed, larger studies designed to evaluate the influence of BMI and especially the type of fat distribution, as indicated by Potschman et al. (1), should include the measurement of insulin, serum lipids, and lipoproteins and of estradiol in adipocytes. Phenotyping of apolipoprotein E may be of interest, since an interaction between visceral obesity and estrogen replacement therapy has been observed only in women with apolipoprotein E4 (Garry PJ: personal communication).

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References


Note

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Re: Breast Cancer Risk in Rats Fed a Diet High in n-6 Polyunsaturated Fatty Acids During Pregnancy

Hilikiv-Clarke et al. (1) reported that consumption of a diet high in corn oil (50% linoleic acid) during pregnancy increases the risk in rats of developing carcinogen-induced mammary tumors, possibly by increasing pregnancy levels of circulating estrogens. Because of the relevance to human breast cancer, the conclusions of this study are of considerable interest to those involved in the study of nutritional carcinogenesis. However, two aspects of this article concern the reader. First, the diet itself, although isocaloric, differs significantly, not only with regard to total fat but also to total fiber. In fact, there is a fourfold difference in fiber intake between animals fed the high-fat versus low-fat diets. This is not a minor difference, particularly in light of our recent article on the role of fiber in carcinogen-induced rat mammary cancer (2). Since fiber, even a simple fiber such as purified cellulose, can alter the enterohepatic circulation of estrogens, it may play a key role in the effects noted. Second, tumor incidence is extremely low, not to mention the total tumor number, suggesting a methodologic problem with either 7,12-dimethylbenz[a]anthracene administration or purity.

In light of the above considerations, the authors might well have more accurately described their diets as “low-fat/high-fiber” and “high-fat/low-fiber” and their tumor data as preliminary at best.

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References


Note

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Response

We thank Dr. Cohen for his interest in our work and for raising the issue of fiber versus fat in affecting mammary tumorigenesis. Two aspects of our paper concerned Dr. Cohen: 1) the use of fiber to adjust the caloric content of the high- and low-fat diets, and 2) the low 7,12-dimethylbenz[a]anthracene (DMBA)-induced mammary tumor incidence. Rodents efficiently regulate their daily caloric intake. If they are fed a diet high in fat and calories compared with a diet low in fat and calories, their feed intake is significantly reduced. This is particularly true during pregnancy. We found that pregnant rats consume 21 g/day of a diet containing 24.6 g corn oil/100 g feed (caloric density, 4.8 kcal/g) and 32 g/day of a diet containing 5 g corn oil/100 g feed (caloric density, 3.8 kcal/g) (34% difference in daily food intake). The daily caloric intake is significantly higher (21%) in the low-fat group (122 kcal/day) than in the high-fat group (101 kcal/day) (P<.001) (17% difference in daily caloric intake). Similar findings have been reported by others (1). Reflecting the difference in daily caloric intake, the serum estradiol (E2) levels do not differ in pregnant rats kept on nonscaloric high- and low-fat diets. These findings may explain the failure to observe a difference in circulating estrogens in adult animals kept on the nonscaloric high- and low-fat diets. To ensure the same daily caloric intake, we fed pregnant rats isocaloric diets. The high caloric density of the high-fat diet is compensated for by adding noncaloric fiber to the diet. Thus, the high-fat diet is a high-fat/high-fiber diet, not a high-fat/low-fiber diet. Examples of how fiber affects caloric density are given in Table 1. Because fiber increases fecal excretion of estrogens (2), we expected the serum E2 levels to be only moderately different between the pregnant rats kept on the isocaloric high-fat/high-fiber and low-fat/low-fiber diets. We found that the high-fat-fed animals, either pregnant or not, have a 30%-100% higher circulating E2 content than the low-fat-fed animals (3,4). Thus, despite the high fiber content of the high-fat diet (which would reduce serum E2) and the low fi-

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