Letter to the Editor


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In the editorial “The National Surgical Adjuvant Breast Project (NSABP) Breast Cancer Prevention Trial Revisited” (1), Richard R. Love presents his reservations with the tamoxifen breast cancer prevention trial. In its discussion of possible toxic effects of tamoxifen, he acknowledges the increased risk of endometrial cancer, but claims without reference that “the liver cancer concern appears to have been overstated.” To the contrary, we believe that the potential for induction of liver and other cancers in women generally has been understated.

There are two ways in which the cancer hazards of pharmaceuticals to humans are assessed; one is through preclinical toxicology and the other is through the monitoring of treated patients. For tamoxifen, the preclinical toxicology clearly raises concerns of a human cancer hazard. Tamoxifen is a strong hepatocarcinogen in rats, leading to a low incidence of liver tumors within 6 months and a high incidence by 1 year at doses that yield the same blood levels in rats as the therapeutic dose (2, 3). Even at the lowest dose yet tested in a 2-year carcinogenicity bioassay (i.e., 5 mg/kg), it produced a low incidence of liver tumors (4). Moreover, tamoxifen forms DNA adducts in the livers of mice, rats and hamsters (3, 5–7).

Dr. Love did not refer to these findings but rather stated unequivocally that tamoxifen is an “hepatocellular cancer hormonal promoter,” apparently based on a referenced study by Dragan et al. (8). There are indeed three studies reporting an enhancing effect of tamoxifen on liver carcinogenesis in rats when given after other liver carcinogens (8–10). Although these observations may represent promoting activity, they could also be because of a syncarcinogenic effect of two carcinogens administered sequentially (11). In fact, the report of Ghia and Mereto (10) described initiating activity of tamoxifen, which is supported by our studies (2, 3), and could be the basis of syncarcinogenesis. Also, the assertion that the hepatocarcinogenicity of tamoxifen is “hormonal” is called into question by the observation that the closely related antiestrogen, toremifene, which exerts comparable estrogen agonist and antagonist activities in rat liver (12), is not hepatocarcinogenic in rats (3). Moreover, the studies cited above establish that tamoxifen is DNA-reactive, which is a characteristic of a carcinogen, not a promoter (11). Given the facts that tamoxifen is related structurally to a known human carcinogen, diethylstilbestrol, is DNA reactive, and is strongly hepatocarcinogenic in rats (3), it must be presumed to be a human cancer hazard, unless some mechanistic explanation can be adduced as to why humans would be refractory to these various adverse effects or it is proven that humans who are given tamoxifen do not develop cancer.

With respect to the latter, the monitoring of patients that have received tamoxifen is widely believed to have excluded hepatocarcinogenicity (13), as Dr. Love also suggests. The experience to date, as cited by Nayfield et al. (13), has not disclosed any liver cancer in most of the adjuvant therapy trials that are being conducted, with the exception of the Stockholm trial (14), in which two cases treated with 40 mg/kg/day of tamoxifen were recorded as having liver cancer after a median follow-up period of 4–5 years (15). However, scrutiny of the published methodology used in all of these trials reveals that application of diagnostic pathology during follow-up was intended in only the Stockholm trial in which endometrial and liver cancer were identified.

In none of the other trials cited by Nayfield et al. (13) was an increase in any cancer reported, although increased endometrial cancer has been found by several investigators (16–19). This raises the possibility of under-reporting of non-breast pathology in these trials. In any event, the reports of the trials other than the Stockholm trial do not comment on liver cancer and an absence of data cannot be taken as no effect.

Another important consideration is that little information is available on patients treated with tamoxifen for more than 10 years (20), which is significant in that increased risk of liver tumor with the use of oral contraceptives requires long-term use, up to 8 years (21). Furthermore, it must be remembered that the potential carcinogenic activity in humans of a genotoxic chemical will not necessarily be restricted to the principal target organ affected in the test rodent. Thus, tamoxifen recipients in prevention trials should be monitored systematically for primary liver and other cancer types, particularly those of endometrial origin.

References

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