

Diazepam Use and Progression of Breast Cancer

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ABSTRACT

The relationship between diazepam and breast cancer was evaluated using data from a case-control study of breast cancer, in which 1075 cases and 1146 controls who were participants in a breast cancer screening program were interviewed. Diazepam use was negatively associated with extent of disease and lymph node involvement, and this effect seemed greatest for long-term users of diazepam. It is not certain to what extent these data reflect an ascertainment bias, an association with the reasons for which the drug was prescribed, or chance. Whatever the explanation, the findings do not support a previous contention that diazepam promotes or accelerates breast cancer growth.

INTRODUCTION

The acceleration of breast tumor growth by diazepam has been suggested by an animal experiment (5), along with a clinical report (9) that breast cancer patients using tranquilizers before diagnosis had a greater probability of recurrence or metastases. Epidemiological studies (2, 3, 6, 10) have found no association between diazepam and breast cancer risk. However, these studies generally did not relate recency or total years of drug use to breast cancer stage and lymph node involvement. Such data would address the issue of growth enhancement more directly. Previously, we reported no increased risk of breast cancer from diazepam use among screening program participants (7). In this report, we have evaluated this study population for the growth-promoting potential of diazepam by relating various measures of exposure to extent of disease.

MATERIALS AND METHODS

Case and control subjects were selected from participants in a national breast cancer screening program, the Breast Cancer Detection Demonstration Project. Over 280,000 asymptomatic women, 35 years of age or older, were recruited for 5 years of annual breast cancer screening at 29 centers. Participants with breast cancer detected between July 1973 and May 1977 at 28 centers were eligible for case selection. Women who did not have a breast biopsy or did not receive a recommendation for surgical evaluation while in the program were eligible controls. They were chosen to be comparable to the cases with respect to center, race (white, black, Oriental, other), age at entry to the Project (within 5 years), date of entry (within 6 months), and length of continuation as screening participants.

Home interviews were conducted by trained nurse interviewers for 86% of eligible breast cancer cases and for 74% of eligible controls. During the interview, cases and controls were asked about family history of breast cancer, reproductive and menstrual history, income and education, and use of particular medications including prescription drugs for

nervousness, depression, or anxiety. Interviewers recorded the name of the most recently used medication, 2 others taken for the longest period of time for any of these reasons, and dates of use.

For the present analysis, women were included if they were white and had no history of biopsy for malignant disease. If diazepam use was reported, use must have begun at least 6 months prior to the date of breast cancer diagnosis, or the equivalent date for controls. Pathology data were unavailable for 165 cases, and these patients were excluded from the analysis. Data on 1075 cases and 1146 controls are included in this analysis.

Based on information provided by each participating center using a standardized form, breast cancer cases were divided initially into 2 classes: *in situ* ($n = 180$); and invasive ($n = 895$). Among the invasive cases, data on tumor length, width, and depth were reviewed. Invasive lesions with each dimension ≤ 1 cm were classified as small invasive breast cancer ($n = 188$), and all others were classified as large invasive cancer ($n = 707$). Of this latter group, information was missing on size for 241 cases. Since exclusion of these subjects did not change the results, these cases were retained in all analyses.

Among the larger invasive cases, lymph node status was assessed for 630 patients (89%) who had lymph nodes examined histologically. Involvement was classified as none ($n = 461$), 1 to 3 ($n = 100$), or 4 or more positive lymph nodes ($n = 69$).

To determine the strength of association between diazepam use and breast cancer, we calculated odds ratios as estimates of the RR.² Maximum likelihood estimates of the RR and corresponding 95% CIs were derived after adjustment for age and other potentially confounding variables, when appropriate (4). For multiple exposure levels, we used the Mantel extension test (8) and calculated one-sided p values.

RESULTS

Table 1 shows no positive association between diazepam use and risk of larger invasive cancer (RR = 0.74), small invasive cancer (RR = 0.92), or *in situ* cancer (RR = 1.10). Adjustment for use of other tranquilizers did not change any of these risk estimates. A decreasing risk with increasing years of use was seen for larger invasive cases only; in this group, decreased risk appeared to be limited to women using diazepam for more than 1 year. Recent users (any use within 1 year of diagnosis provided use did not begin within 6 months of diagnosis) appeared to be at lower risk than were former users for all 3 stages. Since long-term users tended to be recent users, adjustment of recency effects by those of duration diminished the difference between the recent and former users.

Among the cases with invasive breast cancer, lymph node involvement was negatively associated with diazepam use. As shown in Table 2, the relative risk of breast cancer associated with diazepam use was less for patients with lymph node involvement (RR = 0.51; 95% CI = 0.3 to 0.8) than for those without metastases (RR = 0.81, 95% CI = 0.6 to 1.1). Risk decreased with increasing years of use, especially among women with nodal involvement (χ for trend, -3.44 ; $p < 0.001$). Recent and former users had similar risks, and risk was least for those with lymph

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² The abbreviations used are: RR, relative risk; 95% CI, 95% confidence interval.

Table 1
RR (age adjusted) of breast cancer by diazepam use

	Total yr of use						Recent use ^b			Former use ^b						
	<1		1-4		5+		No. of subjects	RR ^c	MH χ^d	p ₁	No. of subjects	RR ^c	95% CI	No. of subjects	RR ^c	95% CI
	No. of subjects	RR ^c	No. of subjects	RR ^c	No. of subjects	RR ^c										
Controls	865	1.00	111	0.63	75	0.56	133	1.00		46	1.00					
Invasive cases (>1 cm) (n = 707)	533	0.74	43	0.63	26	0.56	52	0.63	-3.12	0.001	15	0.53	0.3-0.9			
Invasive cases (≤1 cm) (n = 188)	138	0.92	19	1.07	9	0.75	19	0.89	-0.506	0.288	9	1.23	0.6-2.6			
In situ cases (n = 180)	126	1.10	20	1.24	10	0.92	22	1.13	-0.364	0.359	8	1.19	0.6-2.6			

^a Does not include subjects whose use of diazepam is unknown.
^b Limited to at least 1 year of use and adjusted for total years of use.
^c Values calculated relative to non-users.
^d MH χ , Mantel-Haenszel χ for linear trend; p₁, one-sided p value.

node involvement (RR = 0.38 for recent users; RR = 0.27 for former users).

We adjusted these risk estimates for income and education, since socioeconomic class might be independently related to drug use and to extent of breast cancer at diagnosis. The estimates were not affected by these adjustments or by adjustment for use of other tranquilizers or breast cancer risk factors such as parity, age at first birth, menarche, menopause type, age at menopause, previous breast biopsies, and family history of breast cancer.

Further attention focused on the relationship of diazepam use to prevalent cancers, which were detected at initial screening, as compared to incident cancers, diagnosed at later screenings. To account for effect of lesion size, we limited this analysis to large invasive cases only. Of 691 prevalent cancers, 422 (61%) were large invasive cases as were 242 (63%) of 384 incident cancers. Table 3 shows that no association with diazepam was observed for prevalent or incident breast cancer cases (RR =

Table 2
RRs (age adjusted) of large invasive breast cancer and lymph node involvement by diazepam use

Diazepam use ^a	Lymph node involvement					
			No		Yes	
	Controls	Cases	RR	Cases	RR	
Never	865	341	1.00	138	1.00	
Ever	281	90	0.81 (0.6-1.1) ^b	23	0.51 (0.3-0.8)	
Total yr						
<1	88	38	1.10	12	0.86	
1-4	111	31	0.70	8	0.45	
5+	75	19	0.64	2	0.17	
MH χ^c			-2.06		-3.44	
p ₁			0.02		0.0003	
Recent ^d	133	36	0.69 (0.5-1.0)	8	0.38 (0.2-0.7)	
Former ^d	46	12	0.66 (0.3-1.2)	2	0.27 (0.1-1.0)	

^a Does not include subjects whose use of diazepam is unknown.
^b Numbers in parentheses, 95% CI.
^c Mantel-Haenszel χ for linear trend; p₁, one-sided p value.
^d Limited to at least 1 year of use and adjusted for total years of use.

Table 3
RRs (age adjusted) of prevalent and incident large invasive breast cancers by diazepam use

Diazepam use ^a	Prevalent ^b			Incident ^c		
	Cases	Controls	RR	Cases	Controls	RR
Never	348	549	1.00	185	316	1.00
Ever	74	155	0.75 (0.6-1.0) ^d	57	126	0.77 (0.5-1.1)
Total yr						
<1	33	50	1.04	26	38	1.71
1-4	24	60	0.63	19	51	0.64
5+	15	42	0.56	11	33	0.57
MH χ^e			-2.39			-1.59
p ₁			0.01			0.06
Recent ^f	27	70	0.61 (0.4-1.0)	25	63	0.68 (0.4-1.1)
Former ^f	10	28	0.56 (0.3-1.2)	5	18	0.47 (0.2-1.3)

^a Does not include subjects whose use of diazepam is unknown.
^b Detected at initial screening.
^c Detected at later screening.
^d Numbers in parentheses, 95% CI.
^e MH χ , Mantel-Haenszel χ for linear trend; p₁, one-sided p value.
^f Limited to at least 1 year of use and adjusted for total years of use.

0.75 and 0.77, respectively). Risks were similar for prevalent and incident cases for duration and recency of use. There was also a negative trend of decreasing risk with increasing years of diazepam use.

DISCUSSION

In this case-control study of breast cancer, we found no evidence of a positive association between previous diazepam use and tumor size or lymph node involvement. In fact, diazepam was negatively associated with more progressive disease as manifested by larger invasive tumors and lymph node involvement. In addition, for both of these parameters of disease, our data showed a negative dose-response relationship with increasing years of diazepam use, independent of time since last use.

If diazepam promotes the development of tumor cells that are already initiated, women who are currently using diazepam should be at higher risk of breast cancer than are former users. In fact, we found evidence against the hypothesis that diazepam acted as a promoter. Recent diazepam users were not at higher risk than were former users, partially reflecting the fact that the recent group tended to be long-term users of the drug. If diazepam enhances the growth of tumors that are already formed, we would also expect breast cancer patients who had used diazepam to be diagnosed with more advanced disease, *i.e.*, larger invasive lesions with more extensive spread. This pattern was not seen in our study, and the effect of diazepam actually appeared to be "protective" among women with lymph node involvement, especially if they were long-term users of diazepam. If diazepam has growth-promoting potential, we would also expect the drug to be more strongly associated with incident cases than with prevalent cases of breast cancer. Prevalent cancers identified in screening programs are more often slow-growing tumors as compared with incident cancers (1). We found similar risks of prevalent and incident breast cancer associated with diazepam use for both recency of and duration of use.

Although our data indicated that diazepam may be associated with a decreased risk of breast cancer, this does not imply causality, since protection was limited to large invasive cases (RR = 0.74) and cases with lymph node involvement (RR = 0.51) only. For cases with *in situ* disease, the RR associated with diazepam use was 1.10, indicating no difference in use among cases and controls. Thus, the reduced risk observed among the women with more advanced disease may merely reflect an ascertainment bias related to the medical care use patterns among these women; *i.e.*, women presenting themselves for screening and diagnosed with advanced disease may have had less regular medical care and hence less opportunity to have been prescribed drugs, including diazepam. This could explain why there were more controls who used diazepam compared to cases with advanced disease, producing a spurious, negative association.

We were unable to evaluate fully the extent to which ascer-

tainment bias explained our findings. Since the negative associations were similar for the incident and prevalent series, other factors may be involved. For example, the reasons for which diazepam was prescribed may influence risk or tumor progression, although the negative effect observed is contrary to a hypothesis linking stress to breast cancer (9). Alternatively, the negative relationships could be due to chance, and it will take further study to explain the "protection" that we observed.

The lack of a positive association of breast cancer and diazepam use is consistent with other epidemiological studies using both cross-sectional (2, 3) and case-control (6, 10) approaches. In a study which assessed the influence of diazepam on metastatic disease (6), there was no significant difference in the frequency of regular diazepam use between cases with and without metastases (RR = 0.8 and 1.0, respectively). Although our study could not distinguish between sustained and occasional use of diazepam, we detected a RR of 0.87 for ever use, which resembles the RRs of 0.9 and 0.95 reported in the other case-control studies (6, 10). We found no support for claims based on laboratory and clinical observations that diazepam use is related to enhancement of breast cancer (5, 9). The animal study (5) showed a growth-enhancing effect at lower rather than high doses, and the clinical study (9) did not separate diazepam from other tranquilizers.

In summary, our findings suggest that diazepam does not accelerate or promote the growth of breast cancer. In fact, just the opposite occurred. A negative relationship with advanced disease was seen among recent and former diazepam users of at least 1 year's duration, and this effect increased with additional years of use. The case-control study is being expanded to increase the number of incident cases to evaluate the extent to which these findings reflect an ascertainment bias and to address any remaining concerns about dose and frequency of use.

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