

METHYLXANTHINES AND BREAST CANCER

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We investigated the relationship between methylxanthine consumption and breast cancer using data from a case-control study which included 1,510 cases and 1,882 controls identified through a nation-wide breast cancer screening program. There was no evidence of a positive association between methylxanthine consumption and risk of breast cancer. In fact, there was some suggestion of a negative association, particularly in women diagnosed after age 50. In addition, there was no evidence of increased risk with past or recent methylxanthine consumption, or with the consumption of caffeine or specific beverages, most notably brewed or instant caffeinated coffee and tea.

The relationship between methylxanthines (caffeine, theophylline and theobromine) and breast cancer has been of concern since reports (Minton *et al.*, 1979a,b) were published linking methylxanthine consumption to fibrocystic disease, a well-known risk factor for breast cancer. Although the results of studies examining the relationship between methylxanthines and benign breast disease have been inconsistent, with some showing a positive association (Brooks *et al.*, 1981; Boyle *et al.*, 1984; La Vecchia *et al.*, 1985); and others showing no association (Lawson *et al.*, 1981; Marshall *et al.*, 1982; Ernster *et al.*, 1982; Heyden and Muhlbaier, 1984; Lubin *et al.*, 1985b; Schairer *et al.*, 1986), most epidemiologic studies (Lawson *et al.*, 1981; Lubin *et al.*, 1981; Phillips and Snowdon, 1983; Snowdon and Phillips, 1984; Rosenberg *et al.*, 1985; Lubin *et al.*, 1985a; Le, 1985) and several animal studies (Takayama and Kuwabara, 1982; Petrek *et al.*, 1985) have found no positive association between methylxanthine consumption and risk of breast cancer. Several other animal studies have found, however, that caffeine either alone (Welsch *et al.*, 1983) or in combination with other substances (Minton *et al.*, 1983), acts as a promoter in the development of breast cancer. Caffeine has also been shown to both inhibit and enhance malignant development of other cell types in animal models (Pozniak, 1985).

In order to examine further the relationship between methylxanthine consumption and breast cancer, we examined data from a large case-control study of breast cancer which obtained detailed information on the consumption of beverages containing methylxanthines.

METHODS

Study subjects were drawn from participants in the Breast Cancer Detection Demonstration Project (BCDDP), a 5-year screening program begun in 1973. Sponsored jointly by the National Cancer Institute and the American Cancer Society, this program enrolled over 280,000 women in 29 centers throughout the United States in a 5-year program of annual breast examinations consisting of a clinical examination, mammography and thermography.

Results of a case-control study based on breast cancer cases diagnosed during the first few years of screening (from July 1973 through May 1977) have been published (Brinton *et al.*, 1983). In a continuation of this study, the questionnaire was expanded to obtain information on methylxanthine consumption. This latter study focused on cases diagnosed with breast cancer during the later years of the screening program, through November 1980. Control subjects were selected from women who had not been recommended for, and had not undergone,

surgical evaluation during screening participation. Controls were selected for similarity to breast cancer cases with regard to screening center, age (same 5-year age group), ethnic origin (White, Black, Oriental, other), time of entry into the screening program (within same 6-month period) and length of participation in the program.

Home interviews lasting approximately 1 hr were obtained for 1,799 cases (73% of eligible subjects) and 2,208 controls (90%). The major reasons for non-response of study subjects were death (17% of cases vs. 2% of controls) and refusal (5% of cases vs. 6% of controls). The remaining subjects could not be located, had moved too far away for interviews to be conducted or were not interviewed for various other reasons.

Women with breast malignancies detected before entry into the screening program (73 breast cancer cases and 28 controls) were eliminated from all analyses. We also restricted analyses to White subjects, who comprised 87% of the entire study population.

The information on methylxanthine consumption included both seasonal and year-round consumption of the following beverages which contain methylxanthines: brewed coffee with caffeine (approximately 128 mg caffeine per 5-oz cup), instant coffee with caffeine (66 mg caffeine per 5-oz cup), decaffeinated coffee (3 mg caffeine per 5-oz cup), hot non-herbal tea (38 mg caffeine, 3 mg theobromine per 5-oz cup), hot cocoa (4 mg caffeine, 65 mg theobromine per 5-oz cup), iced tea (47 mg caffeine per 8-oz glass), chocolate milk (5 mg caffeine, 58 mg theobromine per 8-oz glass), cola soft drinks (24 mg caffeine per 8-oz glass) and diet cola drinks (24 mg caffeine per 8-oz glass) (Bunker and McWilliams, 1979; Zoumas *et al.*, 1980). Subjects were asked whether, as adults, they had consumed these beverages and, if so, the number of servings per week over 3 periods of time up until entry into the screening program: less than 30 years of age, 30-49 years and 50 years or older. To obtain age-specific estimates of methylxanthine consumption, we multiplied the number of servings of each beverage by the milligram content and summed over all beverages consumed in the age period. Similar calculations were made to obtain age-specific estimates of caffeine intake. From the age-specific estimates we calculated weighted averages of both methylxanthine and caffeine consumption taking into account the number of years spent in each age period. Because results for consumption of caffeine alone were very similar to those for total methylxanthine consumption, we present results primarily for total methylxanthine consumption, both averaged over the 3 age periods and specific to each age period. In order to examine the effects of each beverage, we also calculated the number of daily servings of each beverage averaged over the 3 age periods. We excluded from all analyses 37 breast cancer cases and 48 controls who had unknown reported frequency for at least one beverage, leaving 1,510 cancer cases and 1,882 controls available for analysis.

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TABLE I - ODDS RATIOS ASSOCIATED WITH METHYLXANTHINE CONSUMPTION AMONG BREAST CANCER CASES AND CONTROLS

Methylxanthines mg/day	Controls	Cases	OR	95% CI
< = 125	299	284	1.0	—
126-250	469	376	0.8	0.7-1.0
251-500	690	534	0.8	0.7-1.0
501-750	282	198	0.7	0.6-1.0
751-1000	70	72	1.1	0.7-1.6
> 1000	72	46	0.7	0.4-1.0
Mantel-Haenszel Chi			-1.9	$p=0.03$

Odds ratios (OR) and 95% confidence intervals (CI) were calculated to evaluate the effect of methylxanthine consumption on risk of disease (Woolf, 1955). An extension of the Mantel-Haenszel procedure using one-tailed p -values was used to test for the statistical significance of trends (Mantel, 1963). Logistic regression analyses were done to evaluate effects of potential confounding variables and to assess the statistical significance of interactions (Prentice, 1976). Matched analyses were also done (Lubin, 1981), but because results were similar to those from the unmatched analyses, only unmatched estimates are presented.

RESULTS

Cases consumed on average slightly fewer milligrams of methylxanthines per day than did controls (342 mg vs. 355 mg). Approximately 91% of study subjects reported ever drinking brewed or instant coffee with caffeine, 47% decaffeinated coffee, 88% hot or iced tea, 70% cola soft drinks or diet cola drinks and 54% cocoa or chocolate milk. Brewed coffee with caffeine, however, provided the bulk of the intake of methylxanthines, with both cases and controls averaging over 280 mg per day. Only 3 cases and 9 controls reported no consumption of beverages containing methylxanthines. Consumers of less than 126 mg per day (the equivalent of approximately one cup of brewed coffee with caffeine) were therefore used as the reference group when calculating odds ratios.

As shown in Table I, methylxanthine consumption was not associated with an elevated risk of breast cancer in this study population. In fact, there was evidence of a negative association, with consumers of more than 125 mg per day (the equiv-

TABLE II - ODDS RATIOS ASSOCIATED WITH CONSUMPTION OF BREWED AND INSTANT COFFEE WITH CAFFEINE AMONG BREAST CANCER CASES AND CONTROLS

Cups of brewed coffee with caffeine/day	Controls	Cases	OR	95% CI
0	208	171	1.0	
< = 1	595	502	1.0	0.8-1.3
2	396	311	1.0	0.7-1.2
3	282	205	0.9	0.7-1.2
4	166	127	0.9	0.7-1.3
> = 5	235	194	1.0	0.8-1.3
Mantel-Haenszel Chi			-0.6	$p=0.27$

Cups of instant coffee with caffeine/day	Controls	Cases	OR	95% CI
0	905	766	1.0	
< = 1	714	555	0.9	0.8-1.1
2	144	106	0.9	0.7-1.2
3	66	48	0.9	0.6-1.3
4	25	19	0.9	0.5-1.7
> = 5	28	16	0.7	0.3-1.3
Mantel-Haenszel Chi			-1.7	$p=0.04$

TABLE III - ODDS RATIOS ASSOCIATED WITH DECAFFEINATED COFFEE AND TEA CONSUMPTION AMONG BREAST CANCER CASES AND CONTROLS

Cups of decaffeinated coffee/day	Controls	Cases	OR	95% CI
0	987	798	1.0	
< = 1	674	545	1.0	0.9-1.2
2	107	90	1.0	0.8-1.4
3	64	36	0.7	0.4-1.1
4	29	22	0.9	0.5-1.7
> = 5	21	19	1.1	0.6-2.2
Mantel-Haenszel Chi			-0.6	$p=0.29$

Cups of hot non-herbal tea/day	Controls	Cases	OR	95% CI
0	626	534	1.0	
< = 1	1093	851	0.9	0.8-1.1
2	104	70	0.8	0.6-1.1
3	33	36	1.3	0.8-2.1
4	15	13	1.0	0.5-2.3
> = 5	11	6	0.6	0.2-1.9
Mantel-Haenszel Chi			-0.9	$p=0.19$

alent of one or more cups of brewed caffeinated coffee) generally being at reduced risk compared to light consumers. There was no consistent dose-response effect, however, even though the test for trend was statistically significant ($p=0.03$). Adjustment for age at diagnosis, Quetelet index, weight, age at menarche, family history of breast cancer, history of breast biopsies, age at first livebirth, number of livebirths, type of menopause, age at menopause, menopausal estrogen use, oral contraceptive use or smoking did not materially alter these estimates. Results were nearly identical when exposure was limited to milligrams of caffeine.

Odds ratios associated with daily servings of brewed and instant coffee with caffeine are shown in Table II. Neither drink was associated with increased risk of breast cancer. On the contrary, consumers of 5 or more cups daily of instant coffee with caffeine had an odds ratio of 0.7 compared to non-drinkers, suggesting a negative association (p -value for trend = 0.04). Consumption of decaffeinated coffee or hot non-herbal tea was not associated with increased risk of breast cancer (Table III), with odds ratios for the heaviest consumption reaching 1.1 and 0.6 for the 2 beverages, respectively. Similarly, no association was evident between consumption of iced tea, cocoa, chocolate milk, soft drinks or diet cola drinks and risk of breast cancer. Adjusting each beverage for consumption of the other beverages or for established breast cancer risk factors did not appreciably change these estimates.

In order to evaluate the effects of past and recent methylxanthine consumption (*i.e.*, consumption prior to and at time of entry into the screening program), we examined age-specific estimates separately for women who entered the screening program before or at age 50 or later (Table IV). For women who entered the screening program at or after age 50, there was no evidence of a positive association between risk of breast cancer and methylxanthine consumption either before age 30, between ages 30 and 49 or at or after age 50. The absence of a positive effect was also evident under various assumptions about induction time, which we examined by looking at the age-specific estimates according to age at diagnosis. Similarly, for women who entered the screening program before age 50, neither past nor recent methylxanthine consumption was associated with risk of breast cancer.

We further examined risk associated with methylxanthine consumption according to a number of breast cancer risk factors (Table V). Analysis by age showed that, for women

TABLE IV - ODDS RATIOS OF BREAST CANCER IN WOMEN ENTERING THE SCREENING PROGRAM PRIOR TO AND AT OR AFTER AGE 50, BY AGE AT METHYLXANTHINE CONSUMPTION

Consumption age (yrs)	Methylxanthines consumed per day (mg)				
	< = 125	126-250	251-500	501-750	> 750
Women entering prior to age 50					
< 30	1.0	0.9 (0.7-1.4) ¹	1.0 (0.7-1.4)	0.9 (0.6-1.4)	1.0 (0.6-1.5)
30-49	1.0	0.9 (0.6-1.4)	0.9 (0.6-1.2)	1.0 (0.7-1.6)	0.9 (0.6-1.4)
Women entering at or after age 50					
< 30	1.0	1.0 (0.8-1.2)	0.8 (0.6-1.0)	0.8 (0.6-1.1)	0.9 (0.6-1.4)
30-49	1.0	0.9 (0.7-1.3)	0.9 (0.7-1.2)	0.8 (0.6-1.2)	0.8 (0.6-1.2)
> = 50	1.0	0.7 (0.6-1.0)	0.8 (0.6-1.0)	0.8 (0.6-1.1)	0.8 (0.5-1.1)

¹95% confidence intervals shown in parentheses.

under 50, there was no consistent pattern of risk associated with methylxanthine consumption, whereas for women aged 50 years or more there was evidence of a negative association. The *p*-value for the interaction term in a logistic model was 0.02. When further examined according to menopausal status, the reduced risk among the older women appeared to be an age effect and not a menopausal effect. Risk also varied somewhat according to whether or not a woman had had a previous breast biopsy (*p*-value for interaction term in a logistic model = 0.06). Among women with one or more previous biopsies, heaviest consumers were at elevated risk compared to light consumers (OR = 2.3), whereas no elevation in risk was evident for heavy consumers among women who reported no previous biopsy. Odds ratios did not vary significantly according to Quetelet index, weight, age at menarche, family history of breast cancer, age at first livebirth, number of livebirths, type of menopause, age at menopause, menopausal estrogen use, oral contraceptive use or smoking status.

DISCUSSION

Overall, methylxanthine consumption was not associated with increased risk of breast cancer in this study population. In fact, there was some suggestion of a negative association, particularly in women 50 years of age and older. Results were similar when exposure was limited to milligrams of caffeine. In addition, neither past nor recent consumption was associated with increased risk, nor did risk vary significantly accord-

ing to levels of most established breast cancer risk factors. Although there was some evidence of elevated risk among heavy consumers of methylxanthines who reported having had one or more breast biopsies before entry into the screening program, this finding is based on small numbers and is inconsistent with several other reports (Rosenberg *et al.*, 1985; Le, 1985). Given our finding of no association between methylxanthines and benign breast disease in this population (Schaerer *et al.*, 1986), it is also unlikely that this result reflects an association between methylxanthines and benign breast disease underlying breast cancer. In view of the number of comparisons made, it may be due to chance. Finally, the fact that positive associations were not found with consumption of specific beverages, including brewed and instant caffeinated coffee, decaffeinated coffee, hot non-herbal tea and chocolate and cola drinks, suggests that substances in these drinks other than methylxanthines do not increase risk of breast cancer.

Several other epidemiologic studies which have examined the relationship between methylxanthine consumption and breast cancer have also found some evidence of a negative association (Lubin *et al.*, 1985a; Le, 1985). It is notable that the study by Lubin *et al.* (1985a) also found this association to be particularly evident in the group of older women. Although a number of other epidemiologic studies have found no evidence of a negative association, they have concluded that consumption of beverages containing methylxanthines does not significantly increase risk of breast cancer (Lawson *et al.*, 1981; Lubin *et al.*, 1981; Phillips and Snowdon, 1983; Snow-

TABLE V - CONSUMPTION OF METHYLXANTHINES BY SELECTED FACTORS AMONG BREAST CANCER CASES AND CONTROLS

	Methylxanthines consumed per day (mg)					
	< = 125	126-250	251-500	501-750	751-1,000	> 1,000
Age (in years)						
< 50	1.0	1.0 (0.6-1.5) ¹	1.1 (0.7-1.6)	0.9 (0.5-1.5)	2.0 (1.0-4.1)	1.0 (0.5-1.9)
> = 50	1.0	0.8 (0.6-1.0)	0.8 (0.6-0.9)	0.7 (0.5-0.9)	0.8 (0.5-1.3)	0.6 (0.3-1.0)
Number of previous biopsies						
0	1.0	0.9 (0.7-1.1)	0.8 (0.6-1.0)	0.7 (0.6-1.0)	1.0 (0.6-1.5)	0.6 (0.4-1.0)
> = 1	1.0	0.7 (0.4-1.1)	0.9 (0.5-1.4)	0.7 (0.4-1.3)	1.5 (0.6-3.7)	2.3 (0.6-11.4)

¹95% confidence intervals shown in parentheses.

don and Phillips, 1984; Rosenberg *et al.*, 1985). In addition, results from several animal studies indicate that administration of caffeine does not increase incidence of malignant breast tumors (Takayama and Kuwabara, 1982; Petrek *et al.*, 1985) and may, in fact, lead to some inhibition of tumor development in rats previously treated with DES (Petrek *et al.*, 1985).

Results from other animal studies indicate, however, that caffeine alone (Welsch *et al.*, 1983) or in combination with other substances (Minton *et al.*, 1983) may promote the development of mammary tumors. Welsch *et al.* (1983) found that caffeine consumption significantly enhanced the promoting phase but had no effect on the initiating phase in DMBA-induced rat mammary gland carcinogenesis. Minton *et al.* (1983), who evaluated the tumor promotional effects of caffeine alone, caffeine and unsaturated fat in combination, unsaturated fat alone and a standard rat chow diet, concluded that the caffeine and fat diet enhanced the development of mammary tumors in the DMBA-treated rats while caffeine alone delayed the induction of these tumors. However, these results were based only on rats developing at least one tumor. When rats which never developed tumors were included in the analysis, the average length of time to tumor development in the caffeine-fat group did not differ significantly from the water-standard chow group, while the caffeine-standard chow diet significantly delayed induction of tumors compared to the water-standard chow diet.

Because our study did not collect dietary information, we were unable to evaluate the association between caffeine and fat reported by Minton *et al.* (1983) or to evaluate the possible confounding effects of diet on the association between methylxanthines and breast cancer. In addition, our study did not obtain information on caffeine-containing pills, such as analgesics, common cold remedies, allergy and weight control medications, diuretics and stimulants. Questionnaires were administered in 1982 and 1983, well after articles hypothesizing the relationship between methylxanthines and fibrocystic disease were first published in 1979 (Minton *et al.*, 1979a,b).

Given the well-known relationship between fibrocystic disease and breast cancer, it is possible that the publicity surrounding methylxanthines and fibrocystic breast disease resulted in some misclassification of methylxanthine consumption even though questionnaires elicited information on methylxanthine consumption only up until the subjects' ages at entry into the screening program (corresponding to the years 1973-1975). Although systematic bias could have masked a substantial association, it is unlikely that random misclassification, which has a smaller impact if exposure is measured at multiple levels than if it is treated as a dichotomous variable, could have done so (Marshall *et al.*, 1981).

In summary, we find no evidence from this study to indicate that methylxanthine consumption increases the risk of breast cancer, a result consistent with the bulk of epidemiologic studies which have examined this issue. Although several animal studies have reported a promotional effect of caffeine, there has been no evidence that methylxanthines have an effect on the initiating phase of tumor development. In fact, there is both epidemiologic and animal evidence to suggest that methylxanthines might delay induction of malignant breast tumors.

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