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DIETARY FACTORS AND BREAST CANCER RISK

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As part of a case-control study in northern Alberta, Canada, 577 women aged 30-80 with breast cancer diagnosed during 1976-77 and a population-based age-stratified random sample of 826 disease-free female controls were questioned about certain aspects of their diet. Computing relative risks (RRs) by tertiles, significant increasing trends were found with more frequent consumption of beef (RRs of 1.0, 2.3, 1.5; test for trend, $p < 0.001$) , pork (RRs of 1.0, 1.6, 2.2; test for trend, $p < 0.001$), and sweet desserts (RRs of 1.0, 1.3, 1.5; test for trend, $p = 0.01$). Elevated risks were also noted for use of butter at the table and for frying with butter or margarine, as opposed to vegetable oils. The association of total beef and pork consumption with breast cancer was not materially affected by controlling for age at first birth, family history of breast cancer, previous benign breast biopsy or socioeconomic status. Nor was the association reduced by controlling for ages of menarche and menopause, even though within the control series the intake of beef and pork reported in adult life was higher among those with a lower age at menarche or a older age at natural menopause.

The substantial international variation in breast cancer incidence suggests the role of environmental determinants, notably nutritional factors, since there is a strong correlation with *per capita* availability of meat and fat in different countries (Armstrong and Doll, 1955; Drasar and Irving, 1973; Gray *et al.*, 1979; Hems, 1978; Lea, 1966). Animal experiments indicate that dietary fats may influence mammary cancer risk (Carrol, 1975; Hankin and Rawlings, 1978; Kelsey, 1979), but case-control studies evaluating this issue have been limited in number and their results weakly positive (Phillips, 1975; Miller *et al.*, 1978). Taking advantage of a population-based case-control study which was undertaken to investigate the high incidence of breast cancer in northern Alberta, Canada (Lubin *et al.*, 1981), we examined several food frequency questions for their relationship to breast cancer risk.

MATERIAL AND METHODS

The methods of ascertainment of cases and controls and interview procedures have been previously reported in detail (Lubin *et al.*, 1981). In brief, interviews were completed for 577 women aged 30 to 80 diagnosed with breast cancer in northern Alberta, Canada, during the years 1976-77. Interviews were also completed for 826 disease-free women selected from the general population of northern Alberta. While the case group comprised 95% of the cases reported from the northern region to the population-based Alberta Cancer Registry, the controls consisted of the 72% of an age-stratified random sample who were successfully interviewed. Reasons for the relatively high (28%) non-response among the controls are noted in Lubin *et al.* (1981). Subsequent analyses based on an intensive follow-up of non-responders and on a comparison between interviewed controls and Canadian census statistics, however, indicated that differences between the control sample and the general population were slight.

The questionnaire primarily concerned demographic, reproductive and medical histories, but it also covered the frequency with which eight food items (beef and other red meat, pork, chicken and other fowl, fish, eggs, cheese, creams and sweet desserts) were usually consumed. For each question the respondent was asked to categorize frequency of consumption into one of the following levels: never, not more than once per month, more than once per month but less than once per week, 1-3 days per week, 4-6 days per week, and daily. Questions were also asked about the amount and type of milk consumed and the use of butter. Thus the major sources of animal fat and animal protein were represented. One question concerning the consumption of tea or coffee (but not each separately) was also asked.

In the analyses, data were stratified into four age groups (30-44, 45-54, 55-64, and 65-80 years) with summary relative risks (RRs) across age and other strata estimated by the method of Gart (1970). Tests for linear trends in risk with increasing food consumption were carried out using the Mantel extension procedure (Mantel, 1963) by assigning consecutive integers to the exposure categories. A multivariate logistic model for disease incidence was applied in order to simultaneously control for the influence of several variables on dietary patterns (Prentice and Pyke, 1979). A factor analysis was also employed to assess the interrelations among the eight food items and to combine them into a smaller number of variables, which describe patterns of food consumption (Nie *et al.*, 1975).

RESULTS

Table I shows that the age-adjusted RR of breast cancer significantly increased with greater consumption of beef, pork and sweet desserts. These patterns of increasing risks were noted for all ages. The risk of breast cancer with a beef consumption of 4-6 days/week relative to less than 4 days/week was over 2-fold, but slackened to 1.5 for daily consumption. The RR of breast cancer rose smoothly from 1.0 to 1.8 to 2.2 as pork consumption rose from the lowest to highest levels of consumption.

The correlation coefficients between individual food items ranged from a high of 0.22 for creams and desserts and 0.20 for fish and fowl to a low of –0.16

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TABLE I

AGE-ADJUSTED RELATIVE RISK OF BREAST CANCER FOR VARIOUS FOOD ITEMS CATEGORIZED BY TERTILES

	Level[1]	Cases	Controls	RR	95% CI
Beef	6	87	127	1.53[2]	(1.1, 2.1)
	5	274	301	2.25	(1.8, 2.9)
	1–4	197	397	1.00	
Pork	4–6	320	398	2.16[2]	(1.6, 2.9)
	3	120	181	1.76	(1.3, 2.5)
	1–2	112	246	1.00	
Fowl	4–6	368	621	0.87	(0.6, 1.4)
	3	151	151	1.54	(0.9, 2.5)
	1–2	39	53	1.00	
Fish	4–6	288	438	1.02	(0.8, 1.3)
	3	141	185	1.26	(0.9, 1.7)
	1–2	129	201	1.00	
Eggs	6–5	160	254	0.84	(0.6, 1.2)
	4	293	449	0.88	(0.6, 1.2)
	1–3	105	121	1.00	
Cheese	6	199	310	1.11	(0.9, 1.4)
	5	126	159	1.37	(1.0, 1.9)
	1–4	232	354	1.00	
Creams – full, sour, ice, whipped	5–6	79	120	0.92	(0.7, 1.2)
	4	184	307	0.90	(0.7, 1.2)
	1–3	290	301	1.00	
Sweet desserts	5–6	183	224	1.45[3]	(1.1, 1.9)
	4	189	286	1.26	(1.0, 1.6)
	1–3	176	316	1.00	

[1]Food frequency levels are defined as: 6 – daily, 5 – 4-6 days/week, 4 – 1-3 days/week, 3 – >1 day/month and <1 day/week, 2 – ≤1 day/month, 1 – never. – [2]Test for linear trend, $p < 0.001$. – [3]Test for linear trend, $p = 0.01$.

for fish and beef, with all other correlations having an absolute value less than 0.11. Examination of all pairwise correlations via factor analysis showed that certain items tended to be consumed together, as indicated by the weightings for four factors shown in Table II. Creams and sweet desserts predominate (have relatively larger weights) in Factor 1, fowl and fish in Factor 2, beef opposed to fowl and fish in Factor 3, and cheese, eggs and creams in Factor 4. The mean scores for Factors 1 and 3 were significantly higher for cases than for controls ($p < 0.01$), while significantly lower for Factor 2 ($p < 0.001$). These case/control differences did not vary significantly with age, although in the older age strata both cases and controls tended to consume less beef, eggs, cheese and creams, and more fish and fowl. Table III shows that relative risks, after categorizing the factor scores, were higher in the upper quartiles for scores from Factors 1 and 3, and were lower for scores from Factor 2.

TABLE II

FACTOR SCORE COEFFICIENTS OBTAINED FROM A FACTOR ANALYSIS OF EIGHT FOOD ITEMS

Item	Factor			
	1	2	3	4
Beef	0.05	–0.11	0.36	0.12
Pork	0.10	0.11	0.07	–0.03
Fowl	–0.01	0.43	–0.15	–0.10
Fish	–0.05	0.28	–0.26	0.05
Eggs	–0.08	0.15	0.10	0.20
Cheese	–0.04	–0.06	0.11	0.36
Creams – full, sour, ice, whipped	0.33	–0.05	–0.01	0.17
Sweet desserts	0.43	–0.01	0.07	–0.05

Table III also shows RRs for the food items classified into traditional food groups. As anticipated from Table I, risks increased steadily to more than 2-fold between high and low consumption of beef/pork, while the trend with total meat/fish consumption was less convincing. Risks increased with creams/desserts consumption and decreased with fowl/fish consumption. Levels of consumption of beef/pork, fowl/fish and creams/desserts were each categorized into two equal-sized groups. Adjusting for age and the remaining two food groups, the RR and 95% CI for high relative to low consumption was 2.1 (1.6, 2.7) for beef/pork, 0.9 (0.7, 1.1) for fowl/fish and 1.1 (0.9, 1.4) for creams/desserts. Thus, while the risk with beef/pork consumption remained elevated, the trends with fowl/fish and creams/desserts consumption could be attributed, at least in part, to the correlations among the food groups.

Indices of mean daily intake of animal fat, animal protein and cholesterol were developed by estimating a usual serving size for each food item, calculating the nutrient content per serving with USDA food composition data (Adams, 1975), and summing nutrient intake across all eight food items. Although these nutrient indices are the most reasonable ones that can be derived from food frequency data, and

TABLE III

AGE-ADJUSTED RELATIVE RISKS OF BREAST CANCER FOR FACTOR SCORES, FOOD GROUPS AND NUTRIENT INDICES, CATEGORIZED FROM LOWEST (I) TO HIGHEST (IV) QUARTILE

	Level				*p*-value for linear trend
	I	II	III	IV	
Factor 1[1]	1.00	1.27	1.27	1.69	0.003
Factor 2	1.00	0.75	0.57	0.67	0.004
Factor 3	1.00	1.28	2.17	2.06	<0.001
Factor 4	1.00	1.00	1.21	1.16	NS
Meat/fish/eggs/cheese	1.00	1.06	1.29	1.44	0.01
Meat/fish	1.00	1.77	1.78	1.67	0.001
Beef/pork	1.00	1.65	2.25	2.66	<0.001
Fowl/fish	1.00	0.82	0.72	0.56	0.007
Eggs/cheese	1.00	1.00	0.91	1.00	NS
Creams/desserts	1.00	1.30	1.31	1.46	0.06
Animal fat	1.00	1.62	1.49	1.80	0.002
Animal protein	1.00	1.48	1.46	1.85	<0.001
Cholesterol	1.00	1.13	1.19	1.22	NS

[1]For factor scores, larger values signify higher consumption of positively and lower consumption of negatively weighted food items.

the eight food items include most of the sources of the these nutrients in the diet, they are only rough approximations because of the lack of information on actual portion size and cooking methods. Table III shows that the RRs increased significantly with the indices of animal fat and animal protein intake, although the trends were not uniform, but not with cholesterol intake. As also shown in Table III, the association between breast cancer and beef/pork consumption was stronger and showed a more convincing gradient than the associations between breast cancer and the nutrient indices, the other food groups, and the factor scores.

The use of butter or margarine in frying, as opposed to vegetable oil, and the consumption of butter at the table were linked to an increased RR (Table IV). There was also a non-significant increased risk associated with drinking more than five cups per day of coffee or tea compared to drinking less. These associations were reduced, but remained positive, when adjusting for beef/pork consumption.

Additional analyses were carried out probing the relationships between the several dietary variables with significantly elevated RRs and other risk factors

TABLE IV

AGE-ADJUSTED RISKS OF BREAST CANCER FOR SEVERAL FOOD ITEMS

		Cases	Controls	RR	95% CI
Milk (glasses/d)					
Whole +2%	≧3	24	53	0.77	(0.5, 1.3)
	1–2	277	383	1.20	(0.9, 1.5)
Skim	≧1	44	67	1.04	(0.7, 1.6)
None	0	180	292	1.00	
Tea/coffee (cups/d)					
	>5	210	313	1.16	(0.9, 1.5)
	≦5	339	513	1.00	
Type of fat for frying					
	Butter	34	27	2.33	(1.4, 4.0)
	Margarine	175	137	2.40	(1.8, 3.2)
	Veg. oil	256	508	1.00	
	Other	68	137	1.06	(0.8, 1.5)
Use of butter at the table					
	Yes	196	228	1.47	(1.2, 1.9)
	No	354	589	1.00	

TABLE V

RELATIVE RISK OF BREAST CANCER ASSOCIATED WITH CONSUMING MORE THAN THE MEDIAN AMOUNT OF BEEF/PORK (>5 TIMES PER WEEK) COMPARED TO CONSUMING LESS. ALL RRs ARE ADJUSTED FOR AGE

	RR[1]	95% CI
Age at menarche		
>15	2.70	(1.6, 4.6)
14	2.05	(1.2, 3.5)
≦13	1.82	(1.3, 2.5)
Weight (kg) / height (m)^2		
>69	1.59	(1.1, 2.4)
61–69	2.78	(1.6, 4.8)
≦60	2.06	(1.4, 3.0)
Age at natural menopause		
>49	2.11	(1.3, 3.6)
45–49	1.78	(0.9, 3.4)
≦44	5.91	(2.2, 16.0)
Age at first term birth		
Nulliparous	1.83	(0.9, 3.7)
>25	1.75	(1.1, 2.8)
20–24	1.95	(1.3, 2.8)
≦19	1.73	(0.8, 3.6)
Previous breast biopsy		
Yes	2.56	(1.2, 5.3)
No	1.91	(1.5, 2.4)
Menopausal status		
Natural	2.21	(1.6, 3.1)
Surgical	2.81	(0.9, 8.4)
Pre-	1.82	(1.2, 2.2)
Breast cancer in mother or sister		
Yes	1.67	(1.0, 2.8)
No	2.21	(1.7, 2.9)

[1]Age-adjusted RR and 95% CI for consuming more than the median amount of beef/pork is 2.00 (1.6, 2.5).

TABLE VI

PERCENTAGE OF CONTROL WOMEN WITH LATE AGE AT MENARCHE AND PERCENTAGE WITH EARLY AGE AT NATURAL MENOPAUSE ACCORDING TO BEEF/PORK CONSUMPTION AND AGE

Indicator	Beef/pork consumption (days/week)	Age in 1978			
		30–44	45–54	55–64	65–80
Menarche after age 14	>5	18%	14	18	32
	≤5	21	27	34	32
Menopause before age 45	>5	—	16	13	17
	≤5	—	16	26	30

found within this study population (Lubin *et al.*, 1981). Table V shows that adjusting for age at menarche, age at natural menopause and Quetelet's index [weight(kg)/height(m)^2], all of which may reflect dietary patterns, had no significant effect on the 2-fold excess in risk among those consuming more than the median amount of beef/pork. Similarly, the risk with beef/pork consumption was not affected by age at first full-term birth, previous benign breast biopsy, menopausal status, or breast cancer in the mother or any sister. To control for confounding from socioeconomic factors, we stratified on education level and found no material change in the RRs. Similarly, the RRs for the type of fat used for frying and use of butter at the table were not greatly affected when stratifying by the variables in Table V.

In a single multivariate logistic analysis to simultaneously control for the socioeconomic variables and the risk factors of Table V, RRs rose with increased scores for Factors 1 and 3 and did not vary by age strata, while significant relationships were not seen for Factors 2 and 4. In another logistic model, which included the fat, protein and cholesterol indices by age stratum, and the same stratifying and risk variables, the RRs rose at all ages with increased animal fat and animal protein intake ($p<0.001$), but not with cholesterol intake. A logistic analysis with the last four food groups in Table III paralleled those results, exhibiting a significant positive association only with beef/pork intake. The estimated RRs, obtained from the various logistic models, were similar to those of Table III.

DISCUSSION

Despite the inherent limitations of case-control surveys of dietary patterns associated with chronic diseases, the results suggest an association between breast cancer and the consumption of beef and pork. These findings are consistent with the higher breast cancer rates in areas of the world with higher *per capita* beef and fat availability (Armstrong and Doll, 1975; Drasar and Irving, 1973; Gray *et al.*, 1979; Hems, 1978; Lea, 1966), the gradually increasing rates among Japanese after migration to the US (Buell, 1973), and the higher risk associated with increased body size (Brinton *et al.*, 1979; de Waard, 1979; Wynder *et al.*, 1978). A case-control study of Japanese men whose wives had breast cancer showed a positive association with the degree of "Westernized" diet (Nomura *et al.*, 1978), while a cohort study in Japan related breast cancer risk to a high intake of fat-containing foods (Hirayama, 1979). A standardized mortality ratio (SMR) of 85 for breast cancer was observed among British nuns who abstain from eating meat when compared to single women throughout Great Britain (Kinlen, 1980). A non-significant SMR of 85, based on much larger numbers of deaths, was also observed among Seventh Day Adventists, approximately half of whom conform to a vegetarian diet (Phillips *et al.*, 1980). In North America, two case-control studies evaluated diet in relation to breast cancer (Miller *et al.*, 1978; Phillips, 1975), and both suggested a slightly increased risk with high fat intake. Thus we were surprised to find such large diet-related risks in our study. The greater excess in risk may be due to differences in the dietary questions asked, the methods of analysis, the larger number of cases than reported by one study (Phillips, 1975), and the use of population-based samples rather than neighborhood controls (Miller *et al.*, 1978), whose potentially similar dietary patterns could tend to reduce RRs. Still other factors, including limitations of our study design as described below, may have contributed.

Although our results may be influenced by case recall bias, it is unlikely that women with breast cancer would selectively remember certain dietary items (beef and pork) and not others (fish and fowl) as compared to controls. It is also unlikely that the development of breast cancer or a precursor state produced these specific associations, and efforts were made to assess usual dietary habits prior to diagnosis. It is noteworthy, however, that interviews for cases were conducted at a referral clinic by nurses during 1976-77, while professional interviewers questioned the controls in their homes during the spring of 1978. We were able to evaluate the possibility of inteviewer or temporal biases by comparing responses to the eight food items between 45 cases, who did not attend the clinic and were interviewed in their homes by the professional interviewers, and the 526 cases interviewed by the nurses. There were no major differences except for a slightly higher frequency of pork consumption for the nurse-interviewed cases. Although this suggests an overestimate of the risks associated with high pork intake, the possibility of bias seems not to apply to beef, which was reported no more often by the cases interviewed in the clinic. The possibility that the beef/pork association may be confounded by other risk factors for breast cancer, or by socioeconomic status, as measured by education, appears slight, since no change in the RR was seen after adjustment for these variables.

Certain aspects of the data collected determined the analyses that could be conducted. For example, we could not distinguish coffee from tea consumption since separate questions were not asked. The nutrient indices were computed without milk consumption, because of the non-comparability in the questions. Milk consumption has been correlated with increasing breast cancer mortality in a statewide survey in the USA (Gaskill *et al.*, 1979), but we found no direct link in this study. In addition, although vegetable oils constitute an increasing pro-