Original Research

Influence of estrogen receptor status on dietary risk factors for breast cancer

T. Gregory Hislop, MD Lisa Kan, BSc Andrew J. Coldman, PhD Pierre R. Band, MD Gerhard Brauer, MA

It has been suggested that the relation between diet and breast cancer may depend on estrogen receptor (ER) status. We examined the responses to a self-administered questionnaire on frequency of consumption of various foods by 493 women with breast cancer (160 with ER-negative tumours and 333 with ER-positive tumours) and 527 controls whose menopausal status was known. Analysis of the reported consumption of foods selected for their fat or carotene content showed no clear distinction in dietary factors between the ER-negative and ER-positive groups. Frequent consumption of meat fats generally increased the risk of both ER-negative and ER-positive tumours; there were no clear trends in risk associated with vegetable consumption for either ER group. Fish was the only item affecting the risk for ER-negative and ER-positive tumours differently, frequent consumption reducing the risk for the former (p =0.02). The results do not support the hypothesis that ER status influences the relation between dietary fat consumption and risk of breast cancer.

On a cru que le rapport qui existe entre le régime alimentaire et la survenue d'un cancer du sein dépend de la présence ou de l'absence dans celui-ci de récepteurs d'estrogènes (RE).

From the Division of Epidemiology, Biometry and Occupational Oncology, Cancer Control Agency of British Columbia, Vancouver, and the Division of Planning Policy and Legislation, British Columbia Ministry of Health, Victoria

Reprint requests to: Dr. T. Gregory Hislop, Division of Epidemiology, Biometry and Occupational Oncology, Cancer Control Agency of British Columbia, 600 W 10th Ave., Vancouver, BC V5Z 4E6

Nous avons concu un questionnaire dans leguel ont consigné des informations sur leurs habitudes alimentaires 493 femmes porteuses de tels cancers (160 avec tumeurs RE négatifs et 333 avec tumeurs RE positifs) et 527 femmes témoins dont l'état menstruel est connu. L'estimation, à partir des réponses, des apports en graisse et en carotène ne montre pas une distinction de ceuxci entre les groupes RE. L'ingestion frequente de graisses animales paraît augmenter indifféremment le risque de tumeurs RE positif et négatif; les légumes n'ont aucun effet sur la survenue de cancers. Seul le poisson abaisse le risque de tumeur RE négatif (p = 0,02). Nos résultats n'appuient pas l'hypothèse voulant que la présence ou l'absence de RE modifie le rapport entre les graisses alimentaires et le risque de cancer du sein.

ifferences in the age-specific incidence patterns for estrogen-receptor (ER)-negative and ER-positive breast tumours^{1,2} suggest that risk factors for these two types of tumour may differ. Hildreth and colleagues³ reported an association between ER-positive breast cancer in postmenopausal women and nulliparity, late age at birth of first child and history of benign breast disease, several investigators have reported a direct association between obesity and ER-positive tumours,4-6 and we have previously reported an inverse association between obesity and ER-negative tumours.7 However, most studies have shown no differential association between ER status and risk factors for breast cancer other than age.1,8,9 Differences in risk factors may have clinical relevance, given that ER-negative tumours have a poorer prognosis.

Dietary factors have been associated with

breast cancer,¹⁰ and our earlier analysis suggested that this association may be influenced by menopausal status.¹¹ To examine the hypothesis that ER status influences the relation between dietary fat consumption and risk of breast cancer, we analysed the responses of patients with breast cancer and their controls to a questionnaire on frequency of consumption of selected food items, considering premenopausal and postmenopausal women separately.

Methods

The study group was drawn from a larger, provincial study of breast cancer in which 74% of iwomen with breast cancer and 79% of controls returned completed self-administered question-naires.¹¹ The subjects consisted of women with pathologically confirmed primary breast cancer diagnosed between June 1980 and May 1982 at the Cancer Control Agency of British Columbia. The patients were less than 70 years of age, and their menopausal status and ER status were known. The subjects were asked to provide the names and addresses of four neighbours or acquaintances who were of similar age. From these names one control within 5 years of the subject's age was randomly

selected to create a pool of age-frequency-matched controls. Any control who reported a personal history of breast cancer or whose menopausal status was unknown was excluded. The controls were selected and sent questionnaires shortly after the completed questionnaires were received from the subjects.

Data for 186 premenopausal subjects (60 with ER-negative tumours and 126 with ER-positive tumours), 203 premenopausal controls, 307 postmenopausal subjects (100 with ER-negative tumours and 207 with ER-positive tumours) and 324 postmenopausal controls were available for analysis. The 493 subjects represented 36% of all incident breast cancer cases registered with the provincial cancer registry over the study period. The distribution of demographic factors was similar for the subjects in the present study and those in the larger study¹¹ as well as for the controls in the present study and those in the larger study (Table I). The age distribution of the study subjects was similar to that for all women with breast cancer registered with the provincial cancer registry.

A woman was considered premenopausal if she was still menstruating and postmenopausal if she had had a natural menopause, had undergone bilateral oophorectomy, or had undergone hyster-

Table I — Distribution of demographic variables among women with breast cancer and the	neir controls in the present
study and in a larger, population-based study ¹¹ *	

	% of women					
	Sul	ojects	Controls			
Variable	Present study $(n = 493)$	Population-based study ($n = 846$)	Present study $(n = 527)$	Population-based study (n = 862)		
Age at diagnosis, yr†		netto ber. (1	wo tinte per wee	stonally (one or :		
< 45	20	21	25	25		
45–54	29	27	28	25		
≥ 55	52	52	47	50		
Family history of breast cancer						
No	88	88	93 7	93		
Yes	12	13	7	7		
Parity						
0	18	18	14	14		
1-2	37	36	41	40		
> 3	45	45	44	46		
Age at birth of first child, yr						
< 25	42	41	47	48		
25–29	26	25	27	25		
> 30	14	15	12	13		
Nulliparous	18	18	14	14		
Age at menarche, yr						
<13	35	33	34	33		
13	32	31	34	32		
>14	33	35	32	35		
Prior breast biopsy						
No	81	81	87	86		
Yes	19	19	13	14		

*Women with incident cases of breast cancer and matched controls whose menopausal status was known and who completed a questionnaire on diet.

[†]Age distribution at diagnosis for all women registered with the provincial cancer registry for 1980-81 was as follows: less than 45 years, 19%; 45 to 54 years, 26%; and 55 to 69 years, 55%.

ectomy and was 55 years of age or older. A subject was considered to have an ER-negative tumour if the binding index was less than 20% and the specific binding of estradiol was less than 3 fmol/mg of cytosol protein; if either value was above these limits the subject was considered to have an ER-positive tumour. These cutoff points are arbitrary, as linear trends in response rates are seen with increasing ER concentrations and there are no empirically determined cutoff points.¹² All the ER assays were done in one laboratory, with a method previously described and validated.¹

Data were obtained from two sources: the self-administered questionnaires (information on risk factors and diet) and medical records (ER status). Information on diet consisted of the frequency of consumption (daily, three to six times per week, one or two times per week, one to three times per month, less often or never) of 31 specific food items, 21 selected for their content of fat from animal, vegetable and dairy sources, and the remainder being vegetables, either cruciferous or selected for their carotene content. Food items were selected to represent diverse common sources of fat and carotene. The specific items are listed elsewhere.¹¹ The questions referred to usual eating habits in the past year (i.e., for subjects, before the diagnosis of breast cancer). Women were also asked how frequently they usually ate beef, pork, chicken (including other poultry) and fish (including shellfish).

The frequency categories were regrouped to better distribute the number of women within each category; these groupings were the same as those used in our earlier study.11 In general, the new categories were very rarely (less than once per month), rarely (one to three times per month), occasionally (one or two times per week) and often (three or more times per week). For dairy fats, vegetable oils, yellow vegetables and green vegetables the ratings for frequency of consumption of specific food items were added together and the summed scores divided into guintiles on the basis of overall frequency. This was done using information for all the women with known menopausal status; hence, there was some difference in the number of women within each category.

Statistical analysis was done separately for three groups: all women, premenopausal women and postmenopausal women. Multivariate analysis was done with binary and polychotomous logistic regression for each of the three groups. Two binary logistic regressions were done for each group, one in which the subjects were women with ER-negative tumours and one in which the subjects were those with ER-positive tumours. The controls included all women without breast cancer in each group. The analysis was also repeated with polychotomous logistic regression in which the dependent variable was considered to have three levels, ER-negative tumour, ER-positive tumour and control. In some cases polychotomous regression could not be accomplished with SPSS:LOGLINEAR¹³ because of the large number of data combinations. We report only the results of the binary logistic regression that did not give results that differed appreciably from those of the polychotomous regression when both had been done.

In each analysis the following known risk factors were forced into the regression: age (less than 40 years, 40 to 49 years, 50 to 59 years, or 60 years or more), family history of breast cancer in a first-degree relative (Yes or No), age at birth of first child (nulliparous, less than 25 years, 25 to 29 years, or 30 years or more), age at menarche (less than 13 years, 13 years, or 14 years or more) and history of biopsy for benign breast disease (Yes or No). Frequency-of-consumption variables were then introduced in a stepwise manner in the order of their statistical significance, as determined from differences in the log likelihood. Dietary variables in the model were also considered for stepwise deletion as further variables were added, but in no case was any variable deleted from the model once it had been included.

Odds ratios and their standard error were calculated in the usual way. In each case the odds ratios reported are those obtained after the five known risk factors and dietary factors found to be statistically significant were controlled for. Statistical testing for differences in risk factors was done with binary logistic regression in which women who had ER-negative tumours were compared with those who had ER-positive tumours. In this analysis the five known risk factors were included, and the dietary factors were examined individually.

Results

Dietary factors were examined separately for ER-negative and ER-positive tumours. The ageadjusted risk estimates for the subjects and controls are shown in Table II. Frequent consumption of meat fats was associated with both types of tumour: frequent consumption of gravy and drippings was significantly associated with ER-negative tumours (p = 0.01), and frequent consumption of beef (p = 0.01) and pork (p = 0.03) was significantly associated with ER-positive tumours. Fish was the only item affecting the risk for ER-negative and ER-positive tumours differently, frequent consumption reducing the risk for the former (p = 0.02). Although consumption of carrots and green vegetables was significantly associated with the risk of ER-positive (p = 0.01) and ER-negative (p = 0.02) tumours respectively, there were no clear trends across categories of consumption.

Dietary factors were also examined separately by menopausal status and ER status (Tables IIIA and IIIB). The trends for meat fats generally persisted for both premenopausal and postmenopausal women, although not reaching statistical significance. The associations between carrot

		ER-negative		E	R-positive	
frequency of contro	No. of controls (n = 527)	No. of subjects (n = 160)	Risk ratio (and 95% confidence limits [CL])	No. of subjects (n = 333)	Risk ratio (and 95% CL)	p value (test for difference between ER groups)
Visible fat on meat	indles, hav	10, 1903	ang Aling and Aling	heddreu	(200.0 + q).	0.81
Very rarely	380	111	1.00	234	1.00	
Rarely	71	23	1.18 (0.68, 2.05)	46	1.17 (0.76, 1.81)	
Occasionally	61	15	0.78 (0.41, 1.48)	37	1.03 (0.65, 1.64)	
Often	15	11	2.28 (0.93, 5.61)	16	2.17 (1.01, 4.67)	
Gravy and drippings			ensvin onu			0.40
Very rarely	129	32	1.00‡	65	1.00	
Rarely	134	25	0.74 (0.40, 1.36)	72	1.10 (0.71, 1.70)	
Occasionally	205	75	1.45 (0.88, 2.40)	144	1.30 (0.87, 1.94)	
Often .	59	28	1.88 (1.00, 3.54)	52	1.81 (1.09, 3.02)	
Beef					The month of T	0.68
Less than daily	456	131	1.00	268	1.00‡	
Daily	71	29	1.23 (0.73, 2.05)	65	1.62 (1.10, 2.41)	NO CLONED SUCO
Pork	म्हण्या रागि	7111132 97 89	againad au in jainis	erss 1910	1 10101 1000 105	0.90
Less than weekly	195	48	1.00	103	1.00‡	
Weekly	332	112	1.30 (0.85, 1.97)	230	1.40 (1.03, 1.92)	
Chicken						0.96
Less than weekly	88	27	1.00	55	1.00	
Weekly	439	133	1.25 (0.74, 2.12)	278	1.04 (0.70, 1.54)	and the second
Fish	Ha VIL ROMA		na ang not super leoot i	and a set a constant	(Testimination 2013 is	0.01
Less than weekly	231	89	1.00‡	142	1.00	
Weekly	296	71	0.63 (0.43, 0.92)	191	1.12 (0.83, 1.52)	
Dairy fats				No. si	No of	0.18
1 conceptible not	179	46	1.00	110	1.00	
2	120	38	1.19 (0.71, 2.02)	70	0.99 (0.66, 1.48)	
3	124	34	0.98 (0.57, 1.69)	80	1.06 (0.72, 1.57)	
4	52	18	1.22 (0.61, 2.41)	45	1.38 (0.84, 2.26)	
5	52	24	1.61 (0.85, 3.05)	28	0.90 (0.51, 1.57)	Viensa vielV
Whole milk	(0.59, 2.17)	11036	6910.23.2.011	0 01	62	0.83
Very rarely	283	77	1.00	166	1.00	
Occasionally	97	27	1.08 (0.64, 1.83)	58	1.07 (0.72, 1.60)	
Often	34	13	1.31 (0.63, 2.70)	29	1.37 (0.78, 2.39)	
Daily	113	43	1.21 (0.76, 1.93)	80	1.17 (0.81, 1.69)	
Vegetable oils		1.92	.35.(0.53/3.40)		1.00	0.60
1 00.0	82	28	1.00	54	1.00	
2	84	28	1.04 (0.53, 2.04)	64	1.21 (0.73, 2.01)	
3	110	32	0.85 (0.45, 1.63)	59	0.81 (0.49, 1.34)	
4 01,0	110	28	0.82 (0.42, 1.60)	77	1.07 (0.66, 1.75)	
5	141	44	0.96 (0.51, 1.81)	79	0.96 (0.59, 1.54)	0.10
Yellow vegetables	100	50	1.00	100	1.00	0.13
1 800.07	129	52	1.00	102	1.00	
2	158	38			0.64 (0.42, 0.98)	
3	87	18		61	0.80 (0.47, 1.35)	
4	66	22	1.17 (0.58, 2.36)	30	0.64 (0.33, 1.26)	
5	87	30	0.87 (0.43, 1.77)	54	0.86 (0.45, 1.66)	0.23
Carrots	EO	16	1.00	22	1.00‡	0.23
Rarely	50	16	1.00	32		
Occasionally	264	78	0.88 (0.45, 1.69)	176	1.02 (0.61, 1.69) 1.04 (0.61, 1.77)	
Often	166	54 12	1.05 (0.52, 2.16)	113 12	0.35 (0.16, 0.80)	
Daily Crean wagetables	47	12	0.83 (0.32, 2.13)	12	0.35 (0.10, 0.80)	0.15
Green vegetables	00	20	1.00‡	70	1.00	0.15
1	99 147	30 60	1.44 (0.84, 2.47)	103	1.05 (0.69, 1.61)	
2 3	147	26	0.76 (0.40, 1.41)	75	0.89 (0.56, 1.41)	
3	125		0.76 (0.40, 1.41) 0.66 (0.30, 1.43)	37	0.74 (0.43, 1.27)	
5	76 80	13 31	1.54 (0.81, 2.93)	48	0.96 (0.56, 1.64)	

*Adjusted for age, family history of breast cancer, parity, age at birth of first child, age at menarche, history of benign breast disease and consumption of significant food items.

 $\dagger 1 =$ least frequently; 5 =most frequently.

‡p < 0.05.

consumption and ER-positive tumours (p = 0.05) and between green vegetable consumption and ER-negative tumours (p = 0.006) were strongest for postmenopausal women. Inverse relations between fish consumption and ER-negative tumours were present for both premenopausal and postmenopausal women, being significant for premenopausal women (p = 0.009). Frequent consumption of dairy fat significantly increased the risk of ER-negative tumours in premenopausal women (p = 0.04).

Discussion

There was no clear distinction in dietary factors that were associated with ER-negative and ER-positive tumours. The frequent consumption of various sources of meat fat (visible fat on meat, gravy and drippings, beef and pork) generally increased the risks for both ER groups. Consumption of certain vegetables was associated with the risk of ER-negative and ER-positive tumours, especially in postmenopausal women; however, in general there were no trends in risk, and the results of most comparisons were not significant. Interestingly, the frequent consumption of fish and dairy fats significantly reduced and increased respectively the risk only of ER-negative tumours in premenopausal women.

A number of studies have examined the relation between dietary fat consumption and breast cancer.¹³ The previously observed relation between fish consumption and breast cancer in premenopausal women¹¹ may be partly explained by the inverse association between fish consumption and ER-negative tumours. The incidence of ERnegative tumours does not increase in the postmenopausal years, whereas the incidence of ERpositive tumours does,^{1,2} and this results in a preponderance of ER-positive tumours in the postmenopausal years. In fact, we found a reduced risk of ER-negative tumours in postmenopausal women who frequently consumed fish.

We did not find the expected increase in the incidence of ER-positive tumours in the post-

Food item; frequency of consumption†	No. of controls (n = 203)	E	R-negative	E	R-positive	p value (test for difference between ER groups)
		No. of subjects (n = 60)	Risk ratio (and 95% CL)	No. of subjects (n = 126)	Risk ratio (and 95% CL)	
Gravy and drippings						0.35
Very rarely	41	10	1.00	23	1.00	
Rarely	62	10	0.69 (0.23, 2.01)	31	1.05 (0.50, 2.17)	
Occasionally	77	31	2.06 (0.82, 5.19)	52	1.36 (0.69, 2.70)	
Often	23	9	1.70 (0.51, 5.70)	20	2.14 (0.90, 5.10)	
Beef						0.91
Less than daily	176	49	1.00	101	1.00	
Daily	27	11	1.35 (0.53, 3.40)	25	1.92 (0.99, 3.73)	
Pork						0.93
Less than weekly	67	15	1.00	34	1.00	0100
Weekly	136	45	1.69 (0.80, 3.57)	92	1.54 (0.90, 2.64)	
Fish						0.10
Less than weekly	102	41	1.00‡	67	1.00	0110
Weekly	101	19	0.43 (0.22, 0.84)	59	0.80 (0.49, 1.31)	
Dairy fats						0.003
1	60	16	1.00†	40	1.00	
2	48	17	1.21 (0.51, 2.88)	35	0.99 (0.52, 1.89)	
3	60	9	0.64 (0.24, 1.69)	31	0.76 (0.40, 1.44)	
4	16	5	1.08 (0.30, 3.86)	15	1.30 (0.54, 3.11)	
5	19	13	3.21 (1.18, 8.76)	5	0.38 (0.12, 1.19)	
Carrots			0.2.1 (0) 0.1 0)	101	0.00 (0.12, 1110)	0.52
Rarely	24	9	1.00	12	1.00	0.02
Occasionally	101	29	0.88 (0.33, 2.33)	65	1.39 (0.61, 3.17)	
Often	64	19	0.80 (0.28, 2.27)	45	1.49 (0.63, 3.50)	
Daily	14	3	1.12 (0.21, 5.85)	4	0.69 (0.17, 2.86)	
Green vegetables		1.0	- , ,,	No. 1		0.67
1	26	10	1.00	20	1.00	0.07
2	69	19	0.76 (0.28, 2.11)	43	0.71 (0.33, 1.51)	
3	48	13	0.77 (0.25, 2.31)	30	0.70 (0.32, 1.57)	
4	27	3	0.29 (0.06, 1.37)	11	0.45 (0.17, 1.20)	
5	33	15	1.19 (0.39, 3.62)	22	0.77 (0.32, 1.83)	

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menopausal years. The reason for this is not clear. We know that ER status is more closely related to age than to menopausal status, the proportion of ER-positive tumours increasing with advancing age.¹ Although in our study there was no lower age limit, there was an upper limit of 69 years, above which the proportion of ER-positive tumours continues to increase. Most of our subjects (75%) were 40 to 65 years of age; hence, there should be less change in the proportion of ERpositive tumours by menopausal status. We would not expect that ER status would affect the likelihood of referral to the Cancer Control Agency of British Columbia, the source of our subjects.

The significance of vegetable consumption in reducing the risk of ER-negative and ER-positive breast cancer would be of particular interest for preventive measures. In-vitro studies have shown that vitamin A and retinoids prevent mammary gland transformation by chemical carcinogens.^{14,15} Similarly, in-vivo studies have shown that dietary administration of retinoids after an initiating dose of chemical carcinogens suppressed the development of mammary adenocarcinoma and benign tumours in experimental animals.^{16,17} Further, evidence suggestive of a protective role of dietary vitamin A in breast cancer has been reported for postmenopausal women.¹⁸ However, vegetables are a source of carotene, not preformed retinoids; hence, any protective effects of vegetables may not be related to the provitamin A activity of carotene. Although we also found significant associations between the consumption of certain vegetables and the risk of breast cancer, especially in postmenopausal women, there were no clear trends in risk with increasing consumption, and the results of most comparisons were not significant.

Our study may have had several biases. Our controls may have been too closely matched, which would minimize the likelihood of detecting differences between subjects and controls. However, we detected dietary differences in our earlier analysis by menopausal status.¹¹ Selection biases are possible, as the study group was not population-based. We included only women referred to the Cancer Control Agency of British Columbia

Food item; frequency of consumption [†]	No. of controls (n = 324)	E	R-negative	E	R-positive	p value (test for difference between ER groups)
		No. of subjects (n = 100)	Risk ratio (and 95% CL)	No. of subjects (n = 207)	Risk ratio (and 95% CL)	
Gravy and drippings		Section of the				0.76
Very rarely	88	22	1.00	42	1.00	
Rarely	72	15	0.86 (0.40, 1.85)	41	1.29 (0.74, 2.25)	
Occasionally	128	44	1.31 (0.70, 2.43)	92	1.59 (0.98, 2.56)	
Often	36	19	2.11 (0.97, 4.60)	32	2.12 (1.13, 4.00)	
Beef						0.77
Less than daily	280	82	1.00	167	1.00	
Daily	44	18	1.39 (0.73, 2.66)	40	1.48 (0.91, 2.43)	
Pork						0.98
Less than weekly	128	33	1.00	69	1.00	
Weekly	196	67	1.30 (0.79, 2.15)	138	1.33 (0.91, 1.95)	
Fish						0.05
Less than weekly	129	48	1.00	75	1.00	-
Weekly	195	52	0.69 (0.42, 1.12)	132	1.18 (0.81, 1.71)	
Dairy fats	100	02	0.00 (0.12, 1.12)	102		0.91
1	119	30	1.00	70	1.00	0.01
2	72	21	1.22 (0.62, 2.40)	35	0.88 (0.52, 1.48)	
3	64	25	1.64 (0.84, 3.19)	49	1.34 (0.81, 2.20)	
4	36	13	1.54 (0.68, 3.52)	30	1.47 (0.81, 2.66)	
5	33	11	1.11 (0.47, 2.63)	23	1.24 (0.66, 2.36)	
Carrots	55		1.11 (0.47, 2.00)	20	1.24 (0.00, 2.00)	0.18
Rarely	26	7	1.00	20	1.00	0.10
Occasionally	163	49	1.03 (0.40, 2.65)	111	0.88 (0.45, 1.70)	
Often	103	35	1.36 (0.50, 3.69)	68	0.84 (0.42, 1.68)	
Daily	33	9	1.03 (0.31, 3.49)	8	0.31 (0.11, 0.85)	
Green vegetables	33	9	1.03 (0.31, 3.49)	0	0.31 (0.11, 0.85)	0.09
1	73	20	1.00±	50	1.00±	0.00
2	78	41	2.11 (1.10, 4.05)	60	1.18 (0.70, 1.98)	
3	78	13	0.63 (0.28, 1.41)	45	0.91 (0.53, 1.56)	
4	49	10	0.83 (0.28, 1.41)	26	0.84 (0.45, 1.58)	
5	49	16	1.31 (0.60, 2.90)	26	0.79 (0.42, 1.49)	
5	47	10	1.31 (0.00, 2.90)	20	0.75 (0.42, 1.45)	

whose ER status and menopausal status were known and who had completed the questionnaire on diet. However, when we compared the study group with the larger, incident group, no differences were apparent in the distribution of known risk factors for breast cancer. Less than 5% of subjects and 2% of controls were excluded because of missing dietary data.

Other biases are also possible. Imprecision and errors in measurement with a self-administered questionnaire on diet are likely to lead to estimates that are too low rather than too high.¹⁹ Differential misclassification by subjects and controls is not likely; however, we are investigating this possibility by readministering the questionnaire 5 years later to the study group. We do not expect that ER status would introduce a systematic bias for dietary recall.

It has been suggested that the relation between diet and breast cancer may depend on ER status.² Several studies have shown that obesity is associated with ER-positive tumours.⁴⁻⁶ Our results do not support the hypothesis that ER status influences the relation between dietary fat consumption and risk of breast cancer.

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