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Host Factors and Breast Cancer Growth Characteristics

David M. Ingram, Anthony Roberts and Elizabeth M. Nottage

The rate of growth and spread of breast cancer varies considerably from patient to patient. An observational study was undertaken to identify possible associations between breast cancer growth characteristics and a wide variety of host factors, including demographic, anthropometric, hormonal and dietary variables in 91 patients with breast cancer. Increasing age was associated with favourable growth characteristics, while previous tonsillectomy was associated with adverse growth characteristics. There were no significant associations in anthropometric variables. For postmenopausal women, increasing bioavailability of oestradiol was associated with favourable growth characteristics, while increasing prolactin concentration was associated with adverse growth characteristics. Increasing consumption of sugar, fibre, fruit and vegetables and vitamins was associated with favourable growth characteristics. Consumption of fat (monounsaturated and saturated) was associated with adverse characteristics when adjustment was made for total energy intake. The host environment may play a role in the control of breast cancer growth. In particular, the associations with oestrogen and progesterone receptor status indicate that nutrients may be of value as biological response modifiers in patients having hormonal therapy. This requires further investigation to assess therapeutic potential.
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INTRODUCTION

THE RATE of growth and spread of breast cancer varies considerably from patient to patient. Some patients with apparently early disease at diagnosis die rapidly from widespread metastases, while other patients may report a breast lump which has barely changed over several years, yet biopsy confirms it to be malignant.

The growth of breast cancer is determined in part by the genetic make-up of the cell, and in part by a variety of host factors which may influence the local milieu around the breast cancer cells. The best-known of these host factors is the oestrogen environment, alteration of which by oophorectomy or by oestrogen receptor competitors may halt tumour growth or result in regression of the tumour [1].

To explore the possibility that some of the many host variables, as well as the oestrogen environment, may influence breast cancer growth, an observational study was undertaken to identify possible associations between breast cancer growth characteristics and a wide variety of host factors. If host factors which influence breast cancer growth can be identified, modification of these variables may open new avenues by which tumour growth can be influenced. Variables studied included demographic, anthropometric, hormonal and dietary variables in 91 patients with breast cancer.

Correspondence to D. M. Ingram.
D. M. Ingram and E. M. Nottage are at the University Department of Surgery, Queen Elizabeth II Medical Centre, Perth, Western Australia 6009; A. Roberts is at Ballarat Base Hospital, Victoria, Australia.
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METHODS

Patients

91 women were identified as having early breast cancer from the pathology records at the Queen Elizabeth II Medical Centre, Perth, Western Australia. Each of these women had undergone surgery for early breast cancer and had consented to take part in the study. At around 3 months after the operation for their primary lesion, the women were interviewed at home using a structured questionnaire, had a morning, mid-luteal blood sample taken, each completed a food frequency questionnaire in regard to their dietary habits up to and including the time of the diagnosis of early breast cancer, and each had measurements of height, weight and subscapular skinfold thickness taken.

Demographic data

Data were collected at the interview in regard to date of birth, obstetric history, previous illnesses and operations, current and recent past medications including vitamin supplements, alcohol, caffeine and tobacco consumption, hormonal use including use of the oral contraceptive pill, and physical activity. Alcohol consumption was estimated in grams per day; caffeine from coffee, tea, chocolate and cola drinks was estimated in milligrams per day; tobacco consumption as the number of cigarettes per day and an estimate of physical activity based on the number of hours per week spent in activities of at least a moderate nature. No women were using the oral contraceptive pill at time of their diagnosis of breast cancer, and none were taking oestrogen replacement therapy.

Anthropometric data

At the time of interview, measurements were made of height, weight and subcapsular skinfold thickness using the same measure, scales and callipers, respectively. Body mass index was calculated using the formula: weight divided by the square of height.

Nutritional consumption

After verbal instruction and demonstration of standard portion sizes, each woman completed a food frequency questionnaire in her own time and returned the completed questionnaire by post. Returned questionnaires were checked for completeness and any problems resolved per telephone. The food frequency questionnaire identified 179 different foods and was scored for portion size and frequency of consumption. Despite this, in 2 subjects the dietary data were incomplete and so these were excluded from the dietary analysis. Nutrient intakes were calculated by the program FREQUAN, developed by the Commonwealth Scientific and Industrial Research Organisation Division of Human Nutrition [2]. The program provides a breakdown of food consumption into nutrients and main food groups (Tables IV and V). In addition, nutrient consumption was recalculated after adjustment for total energy consumption [3].

Hormone assays

A single morning fasting mid-luteal (for premenopausal women) blood sample was collected, the serum promptly separated and glass phials each containing 1 ml of serum were frozen and stored at −70°C. The specimens were assayed in batches for total concentration of oestradiol, progesterone, prolactin and sex hormone binding globulin (SHBG) by radioimmunoassay using commercial kits. The non-protein-bound proportion was determined by rate dialysis [4] and the albumin-bound component by the same method after heat treatment of serum at 60°C for 1 h [5]. Women taking medications known to interfere with hormone levels, namely tamoxifen and chemotherapeutic agents, were excluded from the hormonal component of the data analysis (number excluded = 16). The hormonal variables were analysed separately for pre- and postmenopausal women in view of the considerable differences in hormone concentration between these groups. Where menopausal status was not apparent from history, this was determined on the basis of follicular stimulating hormone, oestrogen and progesterone concentrations. In all except 10 cases, it was not possible to clearly assign the women to pre- or postmenopausal categories.

Pathological variables

The histopathology slides of each case were reviewed by a single pathologist (A.R.) and scored for histological grade and for vessel invasion. The histological grade was based on a 9-point system, and tumours scoring 8 or 9 were regarded as poorly differentiated; 6 or 7 as moderately differentiated; and 5 or less, well differentiated. Vascular invasion was scored as positive if either lymphatic or blood vessel invasion was seen. In addition, data were extracted from the original pathology reports with regard to tumour diameter and the number of involved lymph nodes. 4 patients had only a simple mastectomy and so no data with regard to lymph node involvement were available, and in 11 reports the tumour diameter was not accurately recorded. Finally, oestrogen receptor assay data were available for 68 tumours and progesterone receptor assay data for 56 tumours, all assays having been performed at the same laboratory. Oestrogen and progesterone status was considered to be positive if the oestrogen receptor and progesterone receptor content was more than 10 fmol/l of protein, respectively.

Statistical analysis

The data were entered into a personal computer and analysed using the program EPILOG (Epicentre Software, Pasadena, California) and SAS (SAS Institute Inc., Cary, North Carolina). Associations between tumour growth characteristics and the independent variables were determined by unconditional logistic regression. Where significant associations were found for independent variables, a model was sought by stepwise logistic regression.

Means were determined for each of the variables and statistical associations determined by analysis of variance. The means are displayed in Tables 1–5.

Due to the high correlation between total energy intake and the specific nutrients, adjustment was made to the nutrients so that valid comparisons could be made. The approach of Willett and Stampfer was used [3]. A regression model was fitted with total energy as the independent variable and the specific nutrients as the dependent variables, and the data normalised by log transformation. The adjusted value for the nutrient is determined from the residuals.

RESULTS

Demographic variables (Table 1)

From our data it is apparent that older women had better-differentiated tumours which were more likely to be oestrogen receptor positive. Of the other demographic variables, there were no other significant associations, although patients who had a previous tonsillectomy were more likely to have more poorly differentiated, larger tumours with vascular invasion than patients not having a previous tonsillectomy (Fig. 1). Similarly, smoking tended to be associated with adverse characteristics, and physical activity with favourable characteristics; but these were not statistically significant.

Anthropometric variables (Table 2)

There were no significant associations for any of the anthropometric variables; however, the association between skinfold thickness and oestrogen receptor status almost reached significance, and in general a reduced skinfold thickness was associated with favourable characterics.

Hormonal variables (Table 3)

A high total oestradiol concentration was in general associated with favourable growth characteristics, both for pre- and postmenopausal groups. For postmenopausal women, significant associations were also found between the binding of oestradiol

Table 1. Demographic variables

	Differentiation				Vascular invasion			Tumour diameter (mm)				Lymph nodes				Oestrogen receptor status			Progesterone receptor status		
	Well	Mod.	Poor	*P* value	Absent	Present	*P* value	<1.5	1.5–2	>2	*P* value	0	1–3	>3	*P* value	Pos.	Neg.	*P* value	Pos.	Neg.	*P* value
*n**	14	21	56		44	46		27	24	30		51	22	15		32	36		23	33	
Age (years)	61.1	61.4	53.1	0.013	56.6	55.6	0.721	56.9	57.9	56.0	0.861	57.3	58.5	51.4	0.120	59.3	52.8	0.032	59.0	56.0	0.410
Smokers (%)	7	14	30	0.226	18	28	0.378	15	38	23	0.298	18	36	27	0.361	25	22.	0.987	17	33	0.308
Alcohol (g/day)	72	59	70	0.922	68	68	0.942	90	41	81	0.302	72.2	46.2	96.3	0.429	86	64	0.465	89	75	0.697
Caffeine (mg/day)	223	294	258	0.496	270	249	0.561	246	295	250	0.570	268	266	240	0.862	260	251	0.839	213	253	0.407
Activity (days/year)	108	65	70	0.641	86	65	0.486	103	87	51	0.410	81	74	66	0.939	115	65	0.200	56	91	0.393
Parity (no.)	3.1	3.1	2.9	0.900	2.9	3.1	0.599	2.7	3.5	3.2	0.404	3.0	3.0	3.5	0.682	2.6	3.3	0.150	2.9	3.1	0.794
Tonsillectomy (%)	29	33	50	0.370	36	48	0.375	26	47	60	0.068	45	45	40	0.991	50	36	0.363	48	42	0.899
Appendicectomy (%)	36	38	32	0.963	39	30	0.551	37	25	40	0.675	37	32	27	0.896	38	36	0.893	26	48	0.158
Hysterectomy (%)	21	38	27	0.728	32	26	0.714	41	21	23	0.370	27	27	40	0.820	25	33	0.627	26	33	0.776

* Total $n = 91$. The figures given are the mean value for each group, and the significance is determined by one-way analysis of variance.

Table 2. Anthropometric variables

	Differentiation				Vascular invasion			Tumour diameter (mm)				Lymph nodes				Oestrogen receptor status			Progesterone receptor status		
	Well	Mod.	Poor	*P* value	Absent	Present	*P* value	< 1.5	1.5–2	> 2	*P* value	0	1–3	> 3	*P* value	Pos.	Neg.	*P* value	Pos.	Neg.	*P* value
*n**	14	21	56		44	46		27	24	30		51	22	15		32	36		23	33	
Weight (kg)	65.1	67.6	65.4	0.740	65.5	65.0	0.841	66.6	69.3	63.2	0.156	66.3	64.5	68.4	0.607	64.6	66.0	0.648	64.4	64.0	0.909
Height (cm)	157	154	173	0.758	160	161	0.926	161	160	161	0.870	160	160	161	0.775	160	161	0.599	160	161	0.598
Skin fold (mm)	15.6	15.4	17.3	0.758	15.8	17.3	0.531	15.3	17.1	17.4	0.774	16.7	16.8	16.4	0.995	13.4	19.3	0.051	13.6	18.5	0.176
Body mass index (kg/m^2)	25.3	26.6	25.4	0.605	25.4	25.7	0.762	25.8	25.2	26.4	0.743	25.8	25.2	26.4	0.743	25.2	25.5	0.765	25.1	25.0	0.946

* Total $n = 91$. The figures given are the mean value for each group, and the significance is determined by one-way analysis of variance.

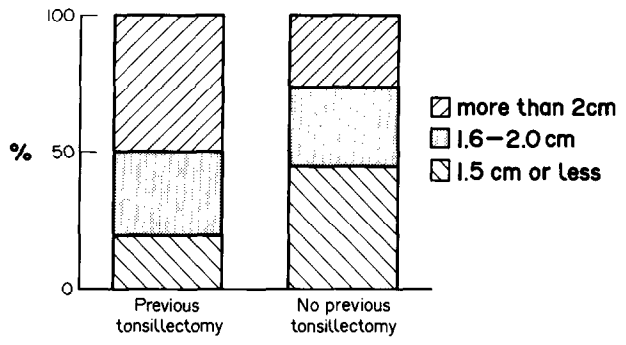

Fig. 1. The proportion of patients (%) with large (> 2 cm), medium (1.6–2.0 cm) and small (1.5 cm or less) tumours, comparing women who had had previous tonsillectomy with those who had not had previous tonsillectomy. Previous tonsillectomy is associated with an increased tumour diameter.

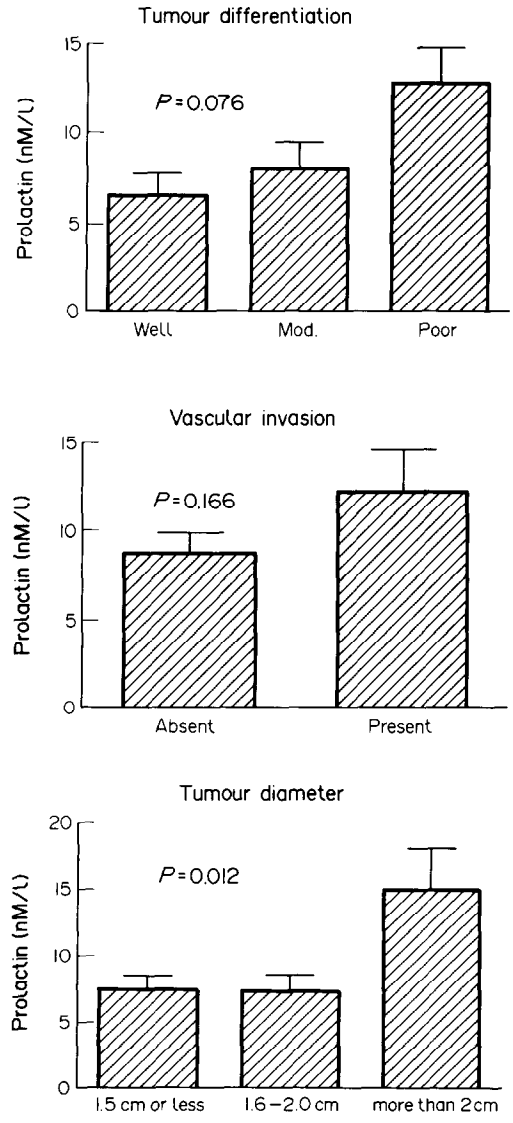

Fig. 2. Plot of mean (S.E.M.) prolactin concentration (nmol/l) for postmenopausal women by tumour differentiation, vascular invasion and tumour diameter. High prolactin levels are associated with adverse tumour growth characteristics.

(the proportion of non-protein-bound and albumin-bound oestradiol) and tumour differentiation, vascular invasion and progesterone receptor status, with higher proportions again being associated with favourable features. For prolactin, high concentrations were associated with poor growth characteristics, especially tumour grade and tumour diameter, again only in the postmenopausal group of women (Fig. 2).

Nutritional variables (Tables 4, 5)

Associations were demonstrated between a number of nutrients and food groups and tumour growth characteristics. Specifically, a high sugar consumption, both as actual consumption and after adjustment for total energy consumed, was associated with improved tumour differentiation, and almost reached significance for oestrogen receptor status. A high consumption of fibre was associated with improved tumour differentiation, reduced vascular invasion and particularly with oestrogen and progesterone receptor positivity. Increased beta-carotene consumption was associated with an improved tumour differentiation, less vascular invasion and a positive progesterone receptor status (Fig. 3); increased consumption of vitamin C was associated with an improved tumour grade and progesterone receptor positivity (Fig. 4); and vitamin B_6 consumption was associated with less vascular invasion and with oestrogen and progesterone receptor positivity.

Protein consumption, consumption of fats, consumption of unrefined carbohydrate, consumption of retinol and total energy intake were not associated with any of the tumour growth characteristics when estimated for actual consumption. However, after adjustment for total energy consumption, the association with sugar remained, but now there were significant associations with fat consumption (Fig. 5). An increasing consumption of fat was associated with adverse growth characteristics, in particular with differentiation, vascular invasion, tumour diameter and oestrogen receptor status. It was the saturated and monounsaturated components which contributed to this.

Of the food groups, only fruit and vegetable consumption had significant associations, with an increasing consumption being associated with better-differentiated tumours with less vascular invasion and oestrogen and progesterone receptor positivity.

Multivariable analysis

After multivariable analysis of variables found to be statistically significant, or of near statistical significance, on individual regression, the following variables were fitted to the model for each of the pathological variables: for tumour differentiation-beta-carotene consumption, proportion of energy from monounsaturated fat; for vascular invasion-previous tonsillectomy, sugar consumption; for tumour diameter-previous tonsillectomy, consumption of leafy and orange-red vegetables; for lymph node involvement-no associations; for oestrogen receptor status-fibre consumption, age; for progesterone receptor status, fibre consumption.

DISCUSSION

In recent years there have been considerable advances made in our knowledge of the mechanisms for control of tumour cell growth, particularly in regard to growth factors [1]. The eventual aim of such research is to develop strategies by which tumour cell growth may be modified to the benefit of the host. Despite these advances, there are still knowledge deficiences as to what extent host factors may influence tumour cell growth, and how

Table 3. Hormonal variables

	Differentiation				Vascular invasion			Tumour diameter (mm)				Lymph nodes				Oestrogen receptor status			Progesterone receptor status		
	Well	Mod.	Poor	*P* value	Absent	Present	*P* value	< 1.5	1.5–2	> 2	*P* value	0	1–3	> 3	*P* value	Pos.	Neg.	*P* value	Pos.	Neg.	*P* value
Premenopausal																					
*n**	6		20		9	17		7	6	11		19		7		8	12		7	8	
Total oestradiol (pmol/l)	359		458	0.329	551	362	0.042	497	398	392	0.630	461		299	0.154	513	371	0.161	610	289	0.005
Progesterone (nmol/l)	25		39	0.321	47	28	0.161	36	24	38	0.686	38		23	0.355	46	30	0.288	49	24	0.124
SHBG (nmol/l)	57		78	0.316	88	65	0.201	93	60	70	0.397	72		77	0.799	81	65	0.455	76	58	0.356
Free oestradiol (%)	1.17		1.29	0.195	1.18	1.32	0.062	1.17	1.34	1.29	0.217	1.26		1.29	0.733	1.19	1.27	0.234	1.27	1.25	0.745
Albumin-bound E_2 (%)	62		62	0.980	58	65	0.101	58	66	63	0.452	61		66	0.307	58	64	0.149	61	62	0.692
Prolactin (nmol/l)	13.8		16.8	0.348	18.3	16.0	0.538	16.6	13.3	18.4	0.538	17.0		16.2	0.837	19.4	14.6	0.297	16.3	14.0	0.638
Postmenopausal																					
n†	7	13	19		24	15		15	10	10		24	9	5		12	14		8	15	
Total oestradiol (pmol/l)	50	39	33	0.532	43	30	0.256	54	18	36	0.025	41	38	22	0.549	46	37	0.550	41	36	0.728
SHBG (nmol/l)	51	50	60	0.552	56	53	0.688	56	61	51	0.728	52	72	46	0.093	58	62	0.717	43	57	0.082
Free oestradiol (%)	1.41	1.46	1.28	0.052	1.41	1.30	0.101	1.37	1.27	1.35	0.452	1.34	1.29	1.49	0.258	1.36	1.30	0.437	1.46	1.29	0.035
Albumin-bound E_2 (%)	72	73	63	0.009	71	63	0.023	70	62	66	0.163	67	66	70	0.758	66	65	0.829	71	64	0.112
Prolactin (nmol/l)	6.5	8.1	12.8	0.076	8.8	12.2	0.66	7.4	7.3	15.0	0.012	10.1	9.3	8.9	0.916	9.2	11.1	0.567	8.7	11.5	0.470

* Total $n = 26$.

† Total $n = 39$.

The figures given are the mean value for each group, and the significance is determined by one-way analysis of variance.

The numbers in some groups of the premenopausal women are very small, and so have been combined (tumour differentiation, no. of lymph nodes involved).

Women taking medications which might influence hormone levels, such as tamoxifen, have been excluded from the analysis ($n = 16$), as were women whose menopausal status was unclear ($n = 10$).

Table 4. Nutrient variables

	Differentiation				Vascular invasion			Tumour diameter (mm)				Lymph nodes				Oestrogen receptor status			Progesterone receptor status		
	Well	Mod.	Poor	*P* value	Absent	Present	*P* value	< 1.5	1.5–2	> 2	*P* value	0	1–3	> 3	*P* value	Pos.	Neg.	*P* value	Pos.	Neg.	*P* value
*n**	14	21	54		43	45		26	24	30		51	22	14		32	35		23	32	
Actual consumption																					
Energy (kJ/day)	8355	8824	7950	0.448	8428	8072	0.540	8680	7707	8267	0.447	8498	7525	8666	0.314	8716	7691	0.140	8171	7790	0.593
Total carbohydrate (g/day)	242	251	205	0.051	227	218	0.577	234	216	212	0.544	228	205	233	0.482	240	206	0.096	224	208	0.477
															0.875					115	
Sugars (g/day)	139	141	108	0.020	124	119	0.638	125	128	111	0.469	124	117	119	0.146	136	111	0.064	129	92	0.399
Starches (g/da7)	101	109	96	0.481	103	99	0.636	109	88	101	0.172	104	87	113	0.269	103	95	0.395	95	80	0.777
Protein (g/day)	81	90	83	0.511	88	81	0.276	87	79	85	0.514	86	77	91	0.313	88	78	0.153	80	67	0.923
Fat (total (g/day)	66	72	72	0.794	71	71	0.922	73	65	76	0.379	73	64	78	0.545	72	69	0.663	70	30	0.716
Saturated (g/day)	28	31	31	0.799	30	32	0.513	31	29	33	0.617	32	28	33	0.299	31	30	0.801	29	25	0.810
Monounsaturated (g/day)	25	27	27	0.710	27	27	0.910	28	24	29	0.315	27	25	30	0.266	27	26	0.641	26	12	0.704
Polyunsaturated (g/day)	13	14	13	0.856	14	13	0.422	14	11	14	0.184	14	12	15	0.606	14	13	0.578	15	23	0.177
Fibre (g/day)	31	29	25	0.118	29	25	0.078	28	24	24	0.256	27	26	29	0.606	31	24	0.012	31	23	0.005
Vitamins																					
Retinol (units/day)	903	912	789	0.881	672	1006	0.152	769	1067	789	0.607	775	723	1326	0.205	993	702	0.268	847	756	0.771
Betacarotene (μg/day)	10235	8658	6929	0.019	8847	6860	0.028	8324	7482	6905	0.432	7948	7744	7798	0.980	8448	7025	0.165	9642	6658	0.011
B_1 (mg/day)	1.47	1.48	1.34	0.441	1.44	1.35	0.384	1.47	1.33	1.34	0.476	1.40	1.27	1.59	0.165	1.52	1.31	0.100	1.47	1.26	0.075
B_6 (mg/day)	2.03	1.91	1.71	0.145	1.96	1.68	0.028	1.91	1.64	1.75	0.250	1.83	1.63	2.04	0.146	1.96	1.62	0.019	1.89	1.62	0.081
C (mg/day)	248	175	149	0.0002	177	163	0.428	193	155	150	0.104	173	147	194	0.222	184	159	0.216	197	150	0.046
E (mg/day)	6.8	6.5	5.7	0.195	6.3	5.9	0.353	6.3	5.4	5.9	0.271	6.0	5.9	6.8	0.544	6.7	5.6	0.070	6.7	5.4	0.058
Energy adjusted consumption																					
Sugars	137	125	108	0.014	120	114	0.396	118	126	109	0.234	116	124	110	0.536	125	115	0.266	126	115	0.295
Starches	97	100	98	0.899	98	99	0.820	102	93	98	0.330	99	93	105	0.288	97	98	0.814	95	95	0.986
Protein	77	83	82	0.355	83	81	0.357	83	82	81	0.929	81	81	85	0.690	82	80	0.631	79	82	0.411
Fats																					
Saturated	27	27	37	0.020	28	31	0.015	27	31	31	0.045	29	31	29	0.747	28	31	0.046	29	31	0.226
Monounsaturated	23	24	28	0.001	25	27	0.205	25	26	28	0.050	26	26	27	0.483	25	27	0.109	26	26	0.907
Polyunsaturated	12	13	13	0.804	13	13	0.863	13	12	14	0.362	13	12	14	0.313	13	13	0.730	14	12	0.331

* Total $n = 89$.

The figures given are the mean value for each group, and the significance is determined by one-way analysis of variance.

Table 5. Food group variables

	Differentiation				Vascular invasion			Tumour diameter (mm)				Lymph nodes				Oestrogen receptor status			Progesterone receptor status		
	Well	Mod.	Poor	*P* value	Absent	Present	*P* value	< 1.5	1.5–2	> 2	*P* value	0	1–3	> 3	*P* value	Pos.	Neg.	*P* value	Pos.	Neg.	*P* value
*n**	14	21	54		43	45		26	24	30		51	22	14		32	35		23	32	
Cereal products (g/day)	67	81	70	0.467	67	76	0.366	75	67	71	0.753	72	65	86	0.241	74	34	0.940	73	69	0.660
Cakes and desserts (g/day)	54	56	38	0.221	43	47	0.645	50	50	42	0.767	53	36	30	0.159	53	37	0.167	46	47	0.932
Dairy (total) (g/day)	58	70	62	0.545	61	65	0.496	61	64	65	0.902	63	62	69	0.752	66	64	0.765	61	64	0.737
Eggs (g/day)	3.6	6.5	4.5	0.083	4.3	5.3	0.294	4.1	4.8	5.0	0.701	4.4	5.4	5.0	0.645	5.3	4.3	0.318	5.0	4.1	0.432
Marg. and butter (g/day)	12.2	13.7	12.7	0.860	12.6	13.2	0.713	14.0	11.2	13.7	0.375	12.4	12.5	16.4	0.247	11.7	14.1	0.223	11.9	12.2	0.886
Milk products (g/day)	42	49	45	0.771	44	47	0.629	43	47	46	0.852	46	44	48	0.911	49	45	0.618	44	48	0.678
Meat (total) (g/day)	50	59	59	0.511	61	55	0.296	59	52	61	0.485	60	51	59	0.368	59	51	0.245	52	55	0.603
Red meat (g/day)	32	44	43	0.340	44	40	0.429	44	35	45	0.331	44	36	42	0.454	42	36	0.360	36	39	0.739
Chicken and fish (g/day)	17.7	15.4	15.3	0.638	16.4	15.0	0.433	14.4	16.7	15.3	0.651	15.6	14.7	17.2	0.697	16.7	15.1	0.466	15.3	16.5	0.635
Savouries (total) (g/day)	50	48	47	0.966	52	43	0.168	51	40	48	0.433	49	41	57	0.288	49	45	0.641	46	42	0.594
Pizza, stew, etc. (g/day)	33	39	33	0.627	38	30	0.133	34	31	33	0.887	37	28	37	0.339	35	30	0.369	32	28	0.529
Chips, twisties (g/day)	16.4	9.3	14.5	0.434	14.1	13.1	0.786	16.6	9.2	15.6	0.328	12.2	13.2	20.4	0.332	13.4	15.4	0.688	14.0	13.5	0.937
Fruit (total) (g/day)	69	57	42	0.011	51	48	0.623	49	50	47	0.908	50	43	58	0.364	58	46	0.142	60	44	0.100
Yellow/orange (g/day)	28	21	16	0.082	17	20	0.540	19	20	16	0.809	18	17	22	0.666	22	18	0.412	27	18	0.191
Other (g/day)	41	37	26	0.032	34	28	0.195	30	31	30	0.997	32	26	36	0.374	36	28	0.134	35	26	0.189
Vegetables (g/day)	58	52	55	0.8490	62	49	0.042	63	48	51	0.170	54	56	58	0.936	59	47	0.093	61	43	0.012
Leafy/orange (g/day)	28	20	21	0.240	26	19	0.037	27	20	18	0.073	22	25	19	0.537	25	19	0.112	28	17	0.011
Starchy (g/day)	30	32	34	0.818	36	30	0.177	36	28	33	0.406	33	331	38	0.629	34	28	0.223	33	26	0.133
Fruit and veg. (total) (g/day)	127	110	97	0.077	114	97	0.086	111	98	98	0.379	105	99	116	0.535	117	93	0.031	121	88	0.008

* Total $n = 89$.

The figures given are the mean value for each group, and the significance is determined by one-way analysis of variance.

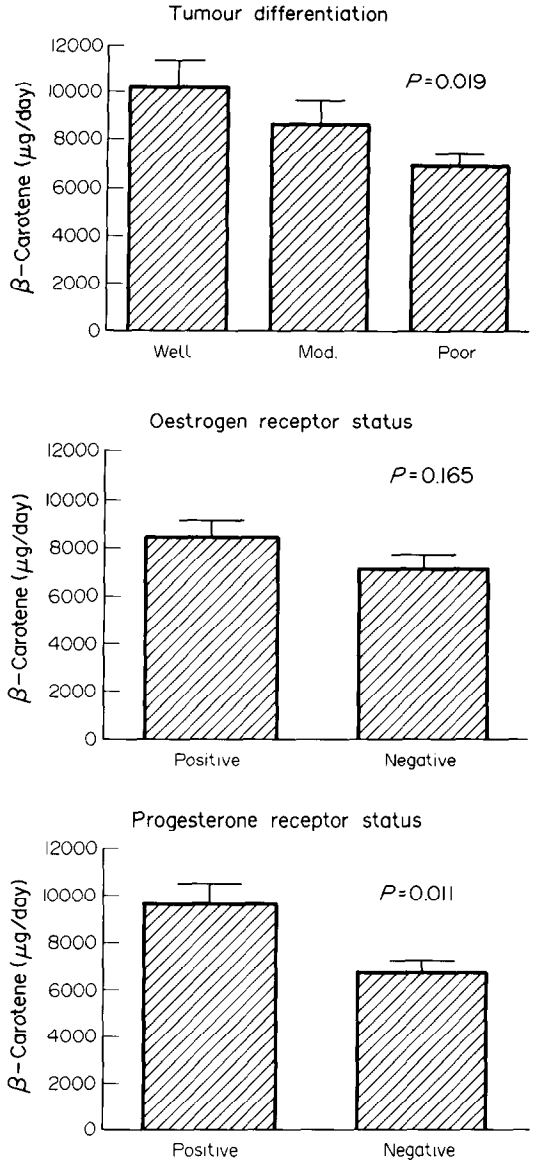

Fig. 3. Plot of mean (S.E.M.) beta-carotene consumption (μg/day) by tumour differentiation, and oestrogen and progesterone receptor status. A high consumption of beta-carotene was associated with favourable tumour growth characteristics.

much is inherent in the genetic make-up of the cell itself. Our study sought to add to this knowledge by investigating associations between a broad range of host factors and breast cancer growth characteristics.

Discussing each association in turn, the association with age has been previously described, with older patients having better-differentiated tumours [6]. The association between previous tonsillectomy and more aggressive breast cancer growth characteristics has not been previously reported; and there has been only one report that previous tonsillectomy is a risk factor for the development of breast cancer [7]. If such an association is real, then presumably there is an immunological link.

The lack of associations with weight and body mass index is surprising, although skinfold thickness did appear to be associated with adverse features. Several reports in the past have documented that obese women with breast cancer have a poorer prognosis [8–10], and we have previously reported that obese women are more likely to have large tumours [11]. This probably has a hormonal basis and relates to both the reducing binding of oestradiol to SHBG in obese women, and to the lipocyte as a site of conversion of precursors to oestrogen.

Oestradiol is transported in the serum either non-protein-bound (free), loosely bound to albumin or tightly bound to SHBG. It is believed that the free and albumin-bound proportions represent the available and thus biologically important components [12]. Significant, but inverse, associations were demonstrated between the binding of oestradiol and various growth characteristics in postmenopausal women, i.e. as the proportion of oestradiol which was non-protein-bound or albumin-bound increased, the tumours were better differentiated with less vascular invasion and a tendency to hormone receptor positivity. This rather unexpected finding is out of context with the concept that oestrogens promote breast cancer growth. Prior to the advent of tamoxifen, however, oestrogens were often

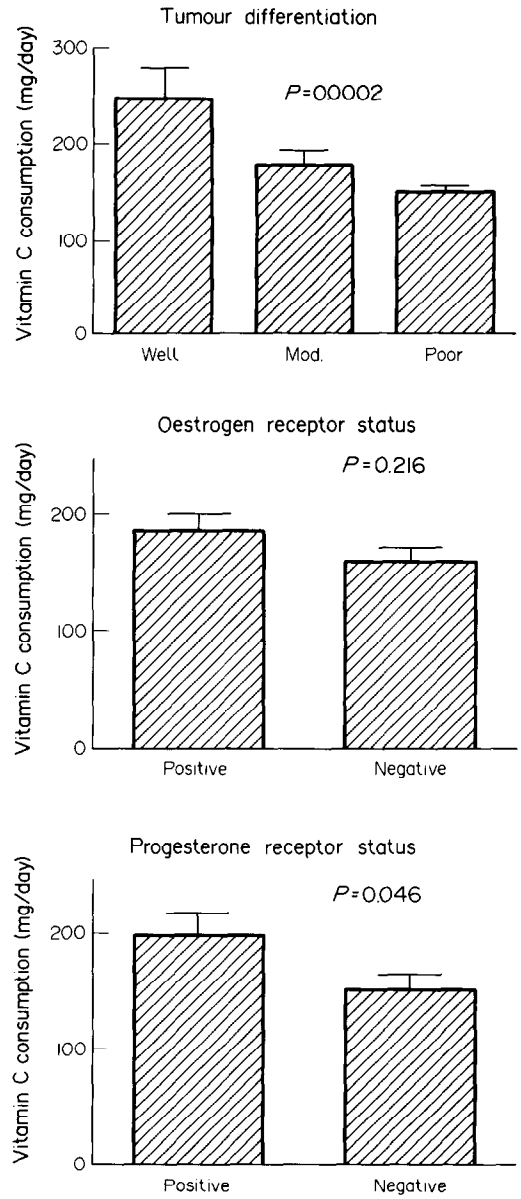

Fig. 4. Plot of mean (S.E.M.) vitamin C consumption (mg/day) by tumour differentiation, and oestrogen and progesterone receptor status. High levels of vitamin C consumption were associated with favourable growth characteristics.

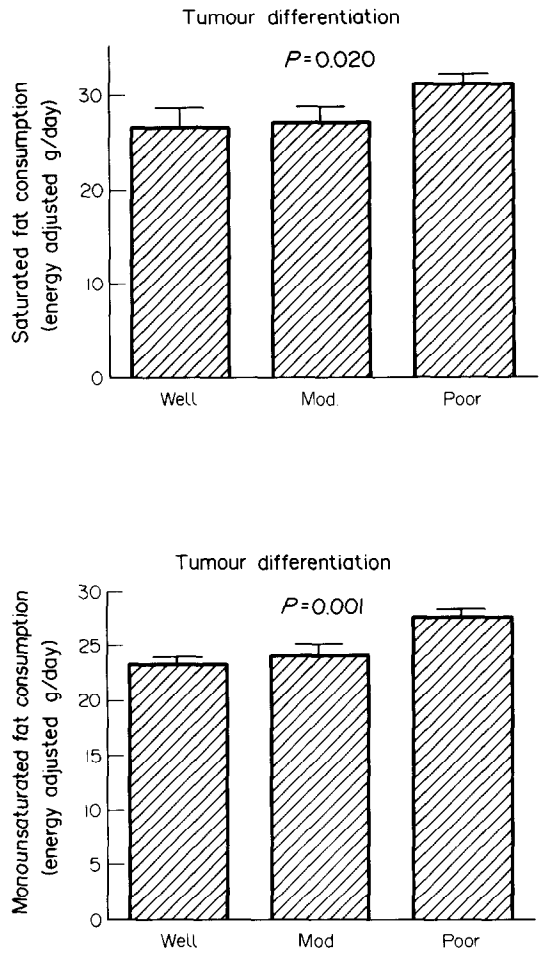

Fig. 5. Plot of the adjusted energy consumption of fat (saturated and monounsaturated) by tumour differentiation [mean (S.E.M.)]. An increased fat consumption was associated with more poorly differentiated tumours.

prescribed for patients with advanced breast cancer with good effect [13], suggesting they may also have a suppressor role. The finding of an association between prolactin concentration and tumour differentiation and tumour diameter for postmenopausal women, suggests that this hormone promotes tumour growth. Prolactin antagonists are not widely used in breast cancer management [14], although in the light of our findings perhaps these agents should be investigated further.

The finding of an association between consumption of fat and breast cancer prognostic indicators has been previously reported [15], as have associations with fibre and carbohydrate consumption [16]. Our study confirms these and provides additional data. In particular, the numerous associations between vitamins and tumour growth characteristics and the associations with fruit and with vegetable consumption have not previously been reported in humans, and may provide the beginning of a scientific basis for the use of nutrients as tumour growth modifiers in breast cancer patients. These findings may also explain the observation that breast cancer mortality in the United Kingdom fell dramatically at the start of World War II, coincident with a marked increase in the consumption of fruit and vegetables [17]. Perhaps this dietary change altered the rate of tumour growth, with consequent reduction in mortality? Similarly, breast tumours in Japanese women are better differentiated, with longer patient survival, an observation which may be explained by our findings in relation to associations between nutrient consumption and growth characteristics [18].

In conclusion, this study has made a number of observations which need to be followed further. In particular, the nutritional associations need to be investigated, as there is therapeutic potential as biological growth modifiers, especially when one considers the associations of nutrients with oestrogen and progesterone receptor status. Repeating the study with another set of breast cancer patients, testing the observations in an animal model, investigating the relationship of nutritional intake to tumour growth factors and eventually looking at nutrition in relation to survival are all avenues which should be explored.

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