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DIET, BODY BUILD, AND BREAST CANCER

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INTRODUCTION

Breast cancer rates have been steadily increasing worldwide. This malignancy is presently the leading cause of death in middle-aged US women (34). Breast

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cancer incidence and mortality rates vary more than fivefold from country to country (50), and the rates among children of migrants who have moved from low- to high-incidence regions approach those of the adopted country (56, 76). These observations strongly suggest that lifestyle factors play an important role in the cause and prevention of breast cancer, and diet is one of the likely causes. We first address evidence that indicates that energy balance, reflected by body size, may be associated with breast cancer risk. Of the aspects of dietary composition that may be related to breast cancer, high fat intake has received the most attention as a possible risk factor. We therefore review evidence of this relationship before turning to data relating micronutrients, alcohol, caffeine, and anticarcinogenic phytochemicals to breast cancer incidence. A more detailed review of this topic can be found elsewhere (48).

TOTAL ENERGY INTAKE, BODY SIZE, AND RISK OF BREAST CANCER

Animal Studies

In studies conducted more than 50 years ago, Tannenbaum (110) showed that rodents fed diets high in fat developed a greater number of mammary tumors than those on low-fat diets. Although this finding has been confirmed repeatedly, the interpretation has been controversial (124). Because fat is the most energy-dense nutrient, high-fat diets tend to be higher in energy intake unless strict care is taken to hold energy intake constant. In a meta-analysis of diet and mammary cancer experiments in mice, Albanes (3) observed a strong positive correlation with total energy intake, whereas fat composition of the diet (adjusted for energy intake) was weakly inversely associated with mammary tumor incidence. In a carefully designed study to address the independent effects of total energy intake and dietary fat composition, Ip (52) found a powerful effect of energy restriction on mammary carcinogenesis. Conversely, the effect of dietary fat composition was relatively weak. Thus, animal data show the potential importance of total energy intake for human breast cancer risk and the necessity of controlling for energy intake in epidemiologic studies.

Height

The hypothesis that total energy intake is an important determinant of human breast cancer risk is difficult to test directly. First, the validity of reporting by subjects of preadult energy intake is uncertain and may be biased by the occurrence of breast cancer. Moreover, in studies of free-living humans, as opposed to laboratory animals in a constrained environment, variation in energy intake is largely determined by physical activity (126) which, if anything, may be protective for breast cancer. If energy balance is important, the rela-

tionship between energy intake and breast cancer risk could even be inverse, as it is for coronary heart disease. Thus, the hypothesis that childhood and adolescent energy balance influences human breast cancer risk can probably only be addressed indirectly, using measures of body size. Children who experience energy deprivation fail to reach their full potential height, and in countries where childhood energy intake varies sufficiently, attained height may be a proxy for childhood energy intake (38). In Japan, a substantial increase in average height occurred during this century, presumably as a result of improved nutrition (38). Because reduced growth and cell proliferation may mediate the biological effect of energy restriction, a deficiency of protein or of other essential nutrients sufficient to cause stunting may also have the same effect. The relationship between height and breast cancer has been extensively studied; in Table 1 we report case-control studies with more than 500 cases, and all published prospective studies.

Most case-control studies indicate a modest positive association between attained height and risk of breast cancer. Interestingly, this association is not confined to countries where energy restriction during growth is expected to be common; indeed, the two largest increases in risk occurred in studies conducted in the US (54, 125). In three studies conducted in Western Europe, however, no elevation in risk was noted (7, 18, 113). Only three studies provided separate data for pre- and postmenopausal women, and each observed a greater increase in risk for tall postmenopausal women than for tall premenopausal women (18, 39, 42).

Fewer cohort data are available, but all studies support a modest association between height and breast cancer risk (Table 1). In a follow-up of the National Health and Nutrition Examination Surveys (NHANES) I population in which women at risk for malnutrition were oversampled, a nearly twofold increase in risk was observed for the tallest compared with the shortest women. Vatten & Kvinnsland (119, 120) found that the positive relationship between height and risk of breast cancer was most linear in the birth cohort of women (1929–1932) who experienced their peripubertal period during World War II, when the average attained height was reduced due to food scarcity. This finding supports the role of growth restriction rather than height per se (which is also strongly influenced by genetic factors) as a determinant of breast cancer risk.

Body Mass Index (BMI)

Several studies have examined the hypothesis that the relationship between BMI (weight/height^2) and breast cancer risk differs on the basis of menopausal status. The relative risk for the highest category of BMI compared with the lowest was greater for postmenopausal women than for premenopausal women in 11 of 13 case-control studies summarized in Table 2. For postmenopausal women, this risk was >1.0 in 12 of the 13 studies; in only 6 studies was this

Table 1 Studies (case-control studies with at least 500 cases) of the association between height and breast cancer

Study (Reference)	Population	Number of cases	Menopausal status	All women		
				Comparison (cm)	RR	95% CI
Case control studies						
Staszewski et al, 1977 (105)	Poland	850	All	≥ 170 vs < 160	1.4[@]	NS[†]
Dubin et al, 1984 (17)	New York City	1283	All	> 165 vs 157–160	1.2	1.0–1.5[@]
				< 157 vs 157–160	0.8	0.7–1.0[@]
Kalish, 1984 (54)	US	852	All	> 168 vs < 155	2.1	1.7–2.6
Whitehead et al, 1985 (125)	US	696	All	> 170 vs < 152	1.7	1.1–2.5
Hislop et al, 1986 (39)	British Columbia	831	All	> 170 vs < 157	1.1	0.8–1.5
Toti et al, 1986 (113)	Italy	1556	All	≥ 165 vs ≤ 155	0.7	0.5–0.9[@]
Ewertz, 1988 (18)	Denmark	1130	Pre	≥ 175 vs < 160	0.7	0.4–1.4
			Post	≥ 170 vs < 160	0.9	0.5–1.4
Swanson et al, 1989 (108)	US	2560	All	170 vs 155*	1.3	1.1–1.5
Bouchardy et al, 1990 (7)	France	975	All	≥ 171 vs < 151	0.9	0.6–1.6
Hsieh et al, 1990 (42)	International	3993	All	10-cm increment	1.1	1.0–1.2
Prospective studies						
de Waard & Baanders, 1974 (15)	Holland	70	Post	≥ 170 vs < 155	2.4	—
Swanson et al, 1988 (109)	US	121	All	169 vs 153*	1.9	1.1–3.2
Tornberg et al, 1988 (112)	Sweden	1182	All	5-cm increment	1.1	1.05–1.16
London et al, 1989 (69)	US	1078	Pre	≥ 168 vs < 160	1.1	0.9–1.3
			Post	≥ 168 vs < 160	1.3	1.0–1.7
Tretli et al, 1989 (114)	Norway	8427	Post	15-cm increment	1.4[#]	
Vatten & Kvinnsland, 1990 (120)	Norway	236	All	≥ 167 vs < 159	2.0	1.4–3.0
Vatten & Kvinnsland, 1992 (119)	Norway	291	All	≥ 167 vs < 159	1.4	1.2–1.7

*Values given are the quartile means.
[@]Adjusted for body weight.
[#]Pooled relative risk calculated from age-specific data.
[†]NS = Not significant.

risk >1.0 for premenopausal women. However, available prospective studies provide less evidence of a positive relationship between BMI and breast cancer for postmenopausal women, although they do support an inverse association for premenopausal women. A similar inverse association between weight at age 18 and risk of breast cancer has been observed for pre- but not postmenopausal breast cancer among women in the Nurses' Health Study (69).

Why the relatively consistent positive association between BMI and breast cancer risk seen in case-control studies of postmenopausal women has not been reproduced in prospective studies remains unclear. In by far the largest prospective study to date, Tretli (114) observed a significant relative risk of 1.2 for each 10 $kg.m^{-2}$ increase in Quetelet's index among postmenopausal women. This finding suggests that if a positive association exists, it is weak. The relatively consistent inverse association between BMI and breast cancer risk among premenopausal women could be due to delayed detection of breast cancer among obese women, although analyses accounting for delay in detection suggest that this explanation is unlikely (69).

DIETARY FAT AND BREAST CANCER

Animal Studies

As noted above, in animal studies the effect of energy intake on mammary tumor risk tends to be stronger and more consistent than that of dietary fat composition. Nevertheless, a modest independent effect of fat composition is observed in some but not all models. The relevance of typical animal models that use large doses of carcinogens to the relationship between fat intake and human breast cancer is uncertain. Thus, the findings of an extremely large study in rats and mice fed substantially different amounts of dietary fat as corn oil without administration of an inducing carcinogen are of particular interest. In that study, cancers occurred at relatively low frequency, a finding which reflects the human experience more accurately than other studies, and no appreciable effects of dietary fat were observed (5).

Ecologic Studies

The dietary fat hypothesis is largely derived from the observation that per capita fat consumption around the world is strongly correlated with national breast cancer mortality (6). However, data on average fat consumption are highly questionable because they are based on "food-disappearance" calculations rather than on actual intake; the fat intake of persons in the US estimated by this method is at least 50% greater than measured intake (128). In an ecological study of 65 Chinese counties (73), both dietary intake and mortality rates were measured using standardized methods. Per capita fat intake varied

Table 2 Studies (case-control studies with at least 500 cases) of the association between body mass index ($kg.m^{-2}$) and breast cancer

Study (Reference)	Population	Number of cases	Comparison ($kg.m^{-2}$)	Premenopausal women (RR)	Postmenopausal women (RR)	All women (RR)
Case-control studies						
Mirra et al, 1971 (82)	Brazil	536	≥ 27 vs < 22	1.2[@]	1.6[@@]	..
Staszewski et al, 1977 (105)	Poland	911	≥ 30 vs < 24	—	—	1.4
Paffenbarger et al, 1980 (86)	San Francisco	1403	≥ 25 vs < 22	0.7	1.4	-
Helmrich et al, 1983 (35)	US, Canada, Israel	1158	≥ 28 vs < 21	0.5	1.3	.
Lubin et al, 1985 (72)	Israel	947	≥ 27 vs ≤ 19	--	—	2.4*
						2.5**
Hislop et al, 1986 (39)	British Columbia	823	≥ 27 vs ≤ 21	0.8	0.9	0.9
Toti et al, 1986 (113)	Italy	1553	≥ 27 vs < 22	1.2	1.5	1.3
La Vecchia et al, 1987 (65)	Italy	1102	≥ 30 vs < 20	1.9	1.4	1.6
Schatzkin et al, 1987 (100)	US	521	≥ 30 vs ≤ 24	1.2	2.5	—
Ewertz, 1988 (18)	Denmark	1128	≥ 32 vs < 20	1.3	1.3	
Swanson et al, 1989 (108)	US	2560	30 vs 20[†]	1.0	1.3	1.1
Bouchardy et al, 1990 (7)	France	974	≥ 27 vs < 21		—	0.6
Franceschi et al, 1990 (23)	Italy	2663	≥ 28	1.0	1.4	1.3
Hsieh et al, 1990 (42)	International	3993	4 $kg.m^{-2}$ increment	1.0	1.1	1.1
Rosenberg et al, 1990 (98)	Toronto	599	≥ 26 vs < 21	0.8	1.2	--
Chu et al, 1991 (10)	US	2600	≥ 32 vs < 20	1.3	2.7	—
Parazzini et al, 1992 (88)	Italy	3037	≥ 27 vs < 23	—		1.4

Prospective studies						
de Waard & Baandes, 1974 (15)	Holland	70	≥ 31 vs < 25	—	1.2	—
Tornberg et al, 1988 (112)	Sweden	1182	1 $kg.m^{-2}$ increment	1.0#	1.0##	1.0
London et al,	US	1078	≥ 29 vs < 21	0.6	1989 (69)	—
Tretli et al,	Norway	8427	10 $kg.m^{-2}$ increment	0.8#	1989 (114)	1.1###
Folsom et al., 1990 (20)	Iowa	221	> 28 vs < 24	—	1.1	—
Vatten & Kvinnsland, 1990 (121)	Norway	236	≥ 27 vs < 22	0.4@	0.7@@	0.5
Vatten & Kvinnsland, 1992 (119)	Norway	291	≥ 27 vs < 22	0.6@	—	0.8

@< 51 years of age.
@@≥ 51 years of age.
#< 50 years of age.
##≥ 50 years of age.
###Pooled RR calculated from age-specific data.
*Surgical controls.
**Neighborhood controls.
†Values are quartile means.

from 6–45% of energy, and only a weak positive association was observed between fat intake and breast cancer mortality.

A more serious problem with ecologic comparisons of diet and breast cancer is that the prevalence of known and other suspected risk factors varies with fat intake. National per capita fat consumption is closely associated with economic development, so much so that the relationship between per capita GNP and breast cancer incidence is actually slightly stronger than that between breast cancer incidence and fat consumption (6). Although Prentice et al (92) found that an ecologic relationship between fat disappearance and breast cancer incidence remains significant after controlling for per capita GNP and estimated age at menarche, other breast cancer risk factors such as late age at first birth, low parity, and low level of physical activity are all more common in affluent countries and thus would be expected to confound the apparent association with dietary fat. Furthermore, children raised in affluent countries are least likely to experience growth retardation due to nutritional factors or recurrent infections. Because height can also statistically explain much of the international variation in breast cancer rates (32) and because per capita energy intake is highly correlated with fat intake, international variations in energy intake may account for much of the apparent international correlation between dietary fat intake and breast cancer rates.

Temporal Trends

Breast cancer incidence rates have increased dramatically in the US during the past 60 years, as have the estimates of per capita fat consumption based on food-disappearance data. However, these data, which seem to support the dietary fat hypothesis (92), are seriously flawed. Increases in fat disappearance from 1961–1963 and 1975–1977 were accompanied by proportional and implausible increases in per capita energy disappearance, which suggests that increased food wastage accounts for much of the apparent increase (92, 93). In fact, surveys based on individual intake rather than on food disappearance indicate that consumption of energy from fat has actually declined in the past several decades (107), while breast cancer incidence has increased. The increase in breast cancer incidence in Japan (37) during this century has also been linked to higher dietary fat consumption; however, this increase has been relatively small and could possibly be due to an increased prevalence of reproductive risk factors as well as higher energy intake during growth (consistent with a large increase in average adult height). Increases in breast cancer mortality rates in Japan are consistent with a birth cohort effect; little increase has occurred among women born before around 1925 (4). This finding suggests that adult fat intake does not substantially influence breast cancer risk. Although one might argue that older women have not changed their lifestyle and

diet, dramatic increases at all ages in colon cancer mortality (4) suggest that this explanation is unlikely.

Special Populations

The interpretation of cancer rates among special populations with distinct dietary patterns must also be approached with caution because these populations often have unusual distributions of nonnutritional risk factors such as alcohol consumption and reproductive behavior. Nevertheless, these data are valuable because adherence to a particular diet over many years may represent a more stable long-term pattern than that of most free-living adults, whose diets may change substantially over time. For example, Seventh-Day Adventists, who consume relatively small amounts of meat and other animal products, have only slightly lower breast cancer rates but substantially lower rates of colon cancer compared with US whites of similar socioeconomic status (90). This discordance is consistent with other observations that animal fat intake is strongly associated with colon cancer risk but not with breast cancer (129). In a comparison of breast cancer rates among British nuns who ate very little or no meat with rates among single women in the general population, Kinlen did not observe any substantial difference in risk of breast cancer (58). These data are not compatible with a strong relationship between animal fat and breast cancer risk.

Case-Control Studies

A number of case-control studies in which reports of previous fat intake by patients with breast cancer are compared with those of women without cancer have been conducted to investigate this relationship. In the largest study to date (30), the fat intake of 2024 women with breast cancer was compared with that reported by 1463 women controls entering hospital with benign conditions; both animal fat and total fat intake were essentially identical in the two groups. Howe et al summarized 12 smaller case-control studies in a meta-analysis (41) that included 4312 cases and 5978 controls. Significant positive associations were observed in four studies, nonsignificant positive associations in six, and inverse associations in two. When the data were pooled, a significant positive association was noted for both total fat and saturated fat intake. The pooled relative risk (RR) was 1.35 for a 100 g increase in daily total fat intake; the risk was somewhat higher for postmenopausal women (RR = 1.48). Because total fat consumption is ~ 70 g/day for US women (107), a daily reduction in fat intake of 100 g would be impossible for most. The result of this pooled analysis implies that the decrease in risk for a more achievable change in total fat intake would be relatively small; the predicted reduction in risk for a 20 g/day decrease among postmenopausal women, for example, would be ~ 10%.

A major problem in case-control studies of diet and cancer is the possibility

that bias in recall by women with recently diagnosed breast cancer could influence the results. Giovannucci et al (27) evaluated this methodologic bias among members of the Nurses' Health Study cohort who prospectively completed food-frequency questionnaires in 1986. Women who were subsequently diagnosed with breast cancer and age-matched controls were asked to complete a second food-frequency questionnaire about their diet before the diagnosis of breast cancer. Using the prospective data, no appreciable association was observed between total fat intake and risk of breast cancer. However, using the retrospective questionnaires, completed after diagnosis in the cases, the investigators found a positive association similar to that calculated for the pooled analysis of case-control studies discussed above. This finding does not prove that the elevation in odds ratios reported from the pooled analysis of case-control studies is due to bias, but it suggests that recall and selection biases can produce associations of this magnitude.

Cohort Studies

A growing body of data from prospective cohort studies, which are not subject to recall bias, is available to assess the relationship between dietary fat intake and breast cancer in developed countries. Table 3 shows the findings from 10 prospective studies with at least 50 incident cases of breast cancer. Not one study found a significant association (comparing the highest category of total fat intake with the lowest), and the average relative risk for the nine studies providing confidence intervals (CIs) (weighted by the inverse of the variance in each study) was 1.03 (95% CI 0.91–1.18). The largest prospective study, the Nurses' Health Study, followed 89,494 women for 8 years, and 1439 cases of breast cancer were documented (127). The relative risk comparing the highest and lowest deciles of fat intake as a percent of energy intake at baseline was 0.86 (95% CI 0.67–1.08). The upper bound of this CI excludes all but the smallest increases in risk. In none of the prospective studies was there a suggestion of a stronger positive association among postmenopausal women.

It has been suggested that the consistent absence of any clear positive association between dietary fat intake and breast cancer in cohort studies may be due to error in measuring dietary fat intake. However, the Nurses' Health Study specifically addressed this possibility, using the relationship between fat intake measured by the study questionnaire and by four weeks of weighed dietary records collected from a subset of the cohort to correct the observed relative risk and its CI for measurement error (99, 127). For an increase of 24 g/day of fat (from 32% of calories from fat to 44%), the original RR was 1.01 (95% CI 0.92–1.10). After adjustment for measurement error, this estimate was 1.00 (95% CI 0.79–1.27). Even the upper bound of this deattenuated CI is still substantially less than the RRs of 1.4–1.5 predicted by the international

Table 3 Prospective studies of the association between total fat intake and risk of breast cancer

Study (Reference)	Population	Total cohort	Follow-up (years)	Cases	Range of total fat intake (as % of calories from fat)	RR (high vs low intake)#	95% CI
Jones et al, 1987 (53)	US	5485	10	99	< 30–≥ 42	0.62	0.33–1.19
NHS 4 years, 1987 (130)	US	89,538	4	601	32–44	0.82	0.64–1.05
Mills et al, 1989 (80)	California	20,341	6	193	NA@	1.21@@	0.81–1.81
Knekt et al., 1990 (60)	Finland	3988	20	54	NA	1.72	0.61–4.82
Howe et al, 1991 (40)	Canada	56,837	5	519	31–47	1.30	0.90–1.88
Kushi et al, 1992 (63)	US	32,080	4	408	27–41	1.13	0.84–1.51
NHS 8 years, 1992 (127)	US	89,494	8	1,439	29–>49	0.86	0.67–1.08
Graham et al, 1992 (31)	New York State	17,401	7	344	< 26–>37	1.00	0.59–1.70
Byrne et al, 1992 (8)	US	6122	4	53	NA	1.1	0.5–2.4
Van den Brandt, 1993 (115)	Netherlands	62,573	3	471	NA	1.08	0.73–1.59

#For most studies, categories are quintiles of the intake distribution; in some, quartiles or tertiles are used.
@NA, Not available.
@@Estimate for animal fat intake only.

correlation between fat intake and breast cancer risk (93) as well as the estimate from the pooled analysis of case-control studies (41).

Thus, the data from the prospective studies provide solid evidence that no major relationship exists between dietary fat intake and breast cancer incidence among women in developed countries during up to 10 years of follow-up. Available data do not permit exclusion of two important modifications of the dietary fat and breast cancer hypothesis. Dietary fat intake during childhood and adolescence may affect breast cancer risk decades later, although, as summarized above, an association with energy intake rather than fat intake alone is a more plausible explanation. The other possible modification of the dietary fat hypothesis is that a much greater decrease in fat intake (e.g. to <20% of calories from fat) may reduce risk. As can be seen from Table 3, the lowest categories of fat intake (usually quintiles) in the available studies are less than ~ 27% of calories from fat. However, among women in the Nurses' Health Study who responded to a second food-frequency questionnaire in 1984, the median intake for the lowest decile of intake was 23% of calories from fat (127). Even at this low level, no evidence of a reduction in risk was apparent; indeed, the relative risk for the lowest decile (<25% calories from fat) compared with the highest decile (>40% calories from fat) was 1.20. In order for a reduction in total fat intake to <20% of calories from fat to substantially reduce risk of breast cancer, the association would have to be highly nonlinear, with a threshold at ~ 20% of calories from fat. The ecologic comparisons of per capita fat consumption and breast cancer incidence do not suggest that such a threshold exists.

To resolve the uncertainty about the association between dietary fat and breast cancer, randomized trials of fat reduction have been proposed, and the Women's Health Initiative (sponsored by the US National Institutes of Health) has the goal of enrolling and randomizing several tens of thousands of women, half of whom will be trained to reduce their total fat intake to 20% of calories from fat. However, such a trial will definitely not address the most promising modification of the dietary fat hypothesis—that dietary fat reduction at an early age may reduce breast cancer risk decades later. Problems such as the difficulty of maintaining compliance with a diet incompatible with prevailing food consumption habits and the gradual secular decline in total fat consumption already underway, which may reduce the size of the comparison in fat intake between intervention groups and controls, may severely compromise the ability of any trial to address the effect of reducing percent of fat from calories to 20% (79). Moreover, intake of vitamin A and fiber is increased simultaneously with a reduction in fat in the intervention; thus, even if an effect of the test diet were observed, it could not be attributed specifically to fat consumption.

Type of Fat

In animal mammary tumor models, the adverse effect of fat intake has been noted for increases in both saturated and polyunsaturated fat intake (9). The meta-analysis of case-control studies (41) reported increased risk of breast cancer for increased saturated and monounsaturated fat intake, whereas polyunsaturated fat intake was modestly protective. In the largest prospective investigation, the Nurses' Health Study, the association for all three types of fat was similar during eight years of follow-up, from 1980 to 1988. However, in data based on the second food-frequency questionnaire in 1984, when monounsaturated fat was included simultaneously in a multivariate model with saturated and polyunsaturated fat and other breast cancer risk factors, a significant protective effect of monounsaturated fat was present (127). This observation is intriguing given the low rates of breast cancer in southern European countries, which have high average intakes of monounsaturated fats due to the use of olive oil. Furthermore, some animal studies have shown olive oil to be protective relative to other sources of fats (124). Further examination of the hypothesis that monounsaturated fats may protect against breast cancer is clearly justified.

DIETARY FIBER AND BREAST CANCER

Diets high in fiber may protect against breast cancer, perhaps because fiber may reduce the intestinal reabsorption of estrogens excreted via the biliary system (28). In one animal study (13), a high-fiber diet was associated with reduced incidence of mammary cancer. Assessment of fiber intake in epidemiologic studies has been problematic because of a paucity of data on the fiber content of individual foods and disagreement about the most appropriate methods of biochemical analysis to determine different types of fiber. These difficulties may explain why relatively few epidemiologic studies have reported on the association of fiber with breast cancer. In their meta-analysis of 10 case-control studies, which included data on dietary fiber intake, Howe et al (41) reported a statistically significant 15% reduction in risk for a 20 g/day increase in dietary fiber. In a case-control study of 519 cases nested in a prospective cohort, Rohan et al (96) observed a marginally significant inverse association between dietary fiber and breast cancer risk, but this finding was no longer significant after controlling for vitamin A intake. Graham et al (31) observed no suggestion of a protective association in another prospective cohort with 344 cases. The relationship between total dietary fiber intake and subsequent breast cancer incidence in the largest prospective investigation (1439 cases) was very close to null (127), which suggests that any protective effect of dietary fiber is likely to be small. However, some subfractions of fiber intake may still be relevant in breast cancer etiology.

MICRONUTRIENTS

Vitamin A

Vitamin A is an important regulator of cell differentiation and may prevent the emergence of cells with a malignant phenotype (104). Many carotenoids, including those without provitamin A activity, are also potent antioxidants and thus may provide a cellular defense against reactive oxygen species that damage DNA (89). Retinol inhibits the growth of human breast carcinoma cells in vitro (22), and retinyl acetate reduces breast cancer incidence in some rodent models (75, 83, 84).

Human studies of vitamin A intake and breast cancer have been mainly case-control investigations (Table 4). Of the four studies that have reported data for total vitamin A intake (retinol plus carotenoids with vitamin A activity), all have documented a protective association. In a meta-analysis of nine case-control studies with data on vitamin A intake, Howe et al (41) also reported a significant protective association between total vitamin A and breast cancer.

Of nine case-control studies that presented data for preformed vitamin A, four reported relative risks between the highest and lowest category of intake of 1.0 or above, and five reported risks of 0.9 or less. Relative risks of ≥1.0 were observed in 4 of 14 studies with data for carotenoid vitamin A, whereas 10 of the studies found relative risks of 0.8 or less. In their meta-analysis of case-control studies, Howe et al (41) reported a significant protective effect of β-carotene from the eight studies with available data; no significant association was observed among eight studies with data for preformed vitamin A. Thus, the data from case-control studies are more supportive of a protective association for carotenoid vitamin A than for preformed vitamin A.

Fewer prospective data are available. Studies from California (87) and New York (54) observed inverse but nonsignificant associations for both preformed vitamin A and carotenoids, and a Canadian study (96) found a marginally significant inverse association. In the Nurses' Health Study, a modest (RR = 0.8) but significant protective association was found for total vitamin A (44). This association was somewhat stronger for preformed vitamin A than for carotenoid vitamin A, and associations of a similar magnitude were reported based on four years of follow-up of a second food-frequency questionnaire administered in 1984. Thus, the available prospective data support a modest inverse association between vitamin A and breast cancer and, in contrast to data for most other cancers, inverse associations are not limited primarily to carotenoid sources of vitamin A.

Measurement of vitamin A compounds in blood represents an alternative to dietary assessment of vitamin A intake. Unfortunately, most studies have

Table 4 Studies of vitamin A intake and breast cancer

Study (Reference)	Population	Number of cases	Comparison	Relative risk for high vs low intake		
				Total vitamin A (RR)	Preformed vitamin A (RR)	Carotenoid vitamin A (RR)
Case-control studies						
Graham et al,	New York State	1803	highest vs lowest quartile[%]	0.8	—	1982 (30)
La Vecchia et al,	Italy	1108	highest vs lowest tertile[%]	—	0.9	1987 (64)
Katsouyanni et al,	Greece	118	highest vs lowest decile	0.5	0.6	1986 (55)
Marubini et al,	Italy	214	highest vs lowest quintile	—	0.7	1988 (72)
Rohan et al,	Australia	451	highest vs lowest quintile	—	1.2	1988 (97)
Toniolo et al,	Italy	250	highest vs lowest quartile	—	1.2	1989 (110)
Ewertz et al,	Denmark	1267	highest vs lowest quartile	—	—	1990 (192)
Potischman et al, 1990 (91)	New York State	83	highest vs lowest quartile	0.7	—	0.8
Van't Veer et al, 1990 (117)	Holland	133	highest vs lowest quartile	—	—	0.6
Graham et al,	New York State	439	highest vs lowest quartile	—	—	1991 (296)
Ingram et al,	Australia	99	above vs below median	—	1.0	1991 (49)
Lee et al,	Singapore	109	highest vs lowest tertile	—	—	* 1991 (67)

Table 4 (*Continued*)

Study (Reference)	Population	Number of cases	Comparison	Relative risk for high vs low intake		
				Total vitamin A (RR)	Preformed vitamin A (RR)	Carotenoid vitamin A (RR)
Richardson et al, 1991 (95)	France	409	highest vs lowest tertile	—	1.5	1.0
Zaridze et al, 1991** (133)	Moscow	81	highest vs lowest quartile	0.2	0.5	0.2
London et al, 1992 (70)	Boston	313	highest vs lowest quintile	—	0.7	0.6
Prospective studies						
Paganini-Hill et al, 1987 (87)	California	123	highest vs lowest tertile	0.8	—	0.8
Graham et al, 1992 (31)	New York State	344	highest vs lowest quintile	1.0	0.9	0.9
Rohan et al, 1993 (96)	Canada	519	highest vs lowest quintile	0.8	0.9	0.9
Hunter et al, 1993 (44)	US	1439	highest vs lowest quintile	0.8	0.8	0.9

[%]These are evenly spaced categories rather than quantiles.
*Results for premenopausal women.
**Results for postmenopausal women.

assessed blood retinol, which is unresponsive to vitamin A intake in well-nourished populations (131). Studies of blood retinol and breast cancer are therefore uninformative with respect to vitamin A intake. Although blood levels of β-carotene reflect β-carotene intake, there is little consistency among studies. Marubini et al (74) and London et al (70) did not observe protective associations in case-control studies in Italy and Boston. In a case-control study in New York State, Potischman et al (91) observed a significant protective association. Of 3 prospective studies (14, 62, 122), only 1 study with 39 cases reported a protective association (122), but the largest study had only 52 incident cases (62). A potential limitation in these studies is that blood β-carotene levels are unstable at usual freezer temperatures (134). Future studies of blood carotenoid levels and breast cancer should use storage conditions of −70° C or less, with identical treatment of case and control specimens.

In summary, available data suggest a protective association between vitamin A intake and breast cancer, but this information is not conclusive. The effect of vitamin A supplements, either in the form of preformed vitamin A or carotenoids, should ideally be evaluated in randomized trials; however, the required duration is uncertain. A randomized trial of the synthetic retinoid fenretinide in the prevention of contralateral breast cancer in women diagnosed with a first cancer in one breast is underway in Italy (21), and the recently commenced Women's Health Study will test the effect of β-carotene on more than 44,000 postmenopausal women in the US.

Vitamin E

Vitamin E is also an antioxidant and has inhibited mammary tumors in rodents in some (33, 66) but not all (57) experiments. Relatively few studies have examined the association between dietary vitamin E intake and breast cancer. Three case-control studies reported a protective association (RR = 0.6 in two studies and RR = 0.7 in the third, comparing the highest category of intake with the lowest) (29, 67, 70); two other studies reported relative risks of 1.0 and 1.3 (95, 111). None of the three published prospective studies documented a significant inverse association (31, 44, 96). The largest of these, the Nurses' Health Study (44), reported almost as many cases as the five case-control studies combined. This study yielded no evidence of a protective association when vitamin A was controlled for, and no such association was observed with either high dose or long-term supplementation with vitamin E.

Blood levels of vitamin E reflect vitamin E intake, especially once blood lipid levels are controlled for (132). Two case-control studies comparing blood vitamin E in cases and controls have been conducted; in the first, blood vitamin E was actually significantly higher in cases than in controls (26), whereas the second reported a weak protective association (70). An initial report from a cohort in Guernsey of lower serum vitamin E values among 39 women who

subsequently developed breast cancer compared with controls (122) may have been based on differential degradation of vitamin E between cases and controls (123) and was not confirmed in further follow-up of this cohort. The two other prospective studies offer little support for the hypothesis that vitamin E is protective (14, 59).

Vitamin C

Vitamin C (ascorbic acid) is also an antioxidant and can block the formation of carcinogenic nitrosoamines (16). Few animal studies appear to have been conducted to assess the effect of vitamin C on mammary cancer; in a study in rats, no effect of ascorbic acid on the growth of either transplanted or dimethylbenzanthracene-induced mammary tumors was observed (1).

In the largest case-control study reported, Graham et al (30) found no protective association for vitamin C; however, a subsequent study (29) by the same group reported a significant protective association (RR = 0.6 for highest vs lowest quartile). In their meta-analysis, Howe et al (41) observed a significantly inverse association (RR = 0.69 for each 300 mg/day increase in vitamin C). Three prospective studies reported on the relation of vitamin C and breast cancer (31, 44, 96); only in one (31) was an (nonsignificant) inverse association observed. In the other two studies, the trend actually tended toward a positive association when vitamin C supplements were included and intake of vitamin A controlled for. Thus, existing data on intake of vitamin C and breast cancer risk generally do not support an inverse association; however, more prospective data with longer follow-up periods are needed. Because intake of the antioxidant micronutrients is often internally correlated, each with the others, careful attention should be given to controlling each separately.

Selenium

Selenium is an important component of the antioxidant enzyme glutathione peroxidase and also inhibits cell proliferation (77). Animal studies have shown that selenium (usually at high levels of intake) protects against a variety of cancers, including mammary tumors, with remarkable consistency (51). Countries and (within the US) counties with low selenium intake tend to have higher rates of breast cancer (11, 101, 102). However, these studies should be interpreted with caution; in the US, for example, high-selenium regions tend to be sparsely populated rural areas, which differ in many respects from low-selenium areas. Selenium intake cannot be measured accurately by means of dietary assessment in geographically dispersed populations because the selenium content of individual foods may vary up to 100-fold depending on the geographic area where the foods were grown (68). Fortunately, selenium levels in tissues such as blood and toenails reflect selenium intake (43, 46).

Case-control and prospective studies of tissue selenium and breast cancer

have quite consistently provided no evidence of a protective effect (12, 47, 78, 85, 116, 118). Only the study from Finland by Knekt et al (61) shows any suggestion of increased risk for the lowest category of selenium. Because Finland has unusually low dietary selenium levels, this observation is consistent with the possibility of a threshold below which low selenium intake increases breast cancer risk. However, selenium intake is not likely associated with breast cancer in countries with moderate or high levels of selenium intake.

OTHER DIETARY CONSTITUENTS

Alcohol

Whether alcohol and breast cancer are related has been a controversial topic, but substantial evidence has accumulated to strongly support a modest positive association. In a 1988 meta-analysis of 12 case-control studies, Longnecker et al (71) estimated a relative risk of 1.4 (95% CI 1.0–1.8) for each 24 grams of alcohol/day (about 2 drinks of an alcoholic beverage). From the 4 cohort studies, Longnecker et al (71) calculated a pooled relative risk of 1.4 (95% CI 1.1–1.7) for women drinking 12 g/day and a relative risk of 1.7 (95% CI 1.3–2.2) for women consuming 24 g/day of alcohol. Data from five more prospective studies were published subsequent to this meta-analysis. In the two smallest studies, little association was evident. However, in the three largest studies, all controlled for major breast cancer risk factors, relative risks for the highest category of alcohol consumption compared with zero consumption were 3.3 (95% CI 1.2–9.3) (36), 1.6 (95% CI 1.0–2.6) (25), and 1.5 (95% CI 1.0–2.0) (24), respectively. Thus, increased risk among women consuming alcohol makes alcohol the best-supported dietary risk factor for breast cancer. Positive associations have been noted for beer, wine, and liquor, which suggests that alcohol per se is the risk factor rather than some beverage-specific compound. Recently, Reichman et al (94) provided evidence that consuming approximately two alcoholic drinks per day increases both total and bioavailable estrogen levels, thereby suggesting a mechanism by which alcohol may increase breast cancer risk.

Caffeine

A report (81) that women with benign breast disease experience relief from symptoms after eliminating caffeine from their diet led to considerable speculation that caffeine may be a risk factor for breast cancer. However, the majority of case-control studies have not reported evidence of a positive association. A number of prospective studies have also examined this association. Snowden & Phillips observed no increase in breast cancer risk among

Seventh-Day Adventist women who consumed coffee (103), and Hunter et al (45) actually found a weak but significant inverse association between caffeine consumption and breast cancer risk. Thus, the epidemiologic evidence is not compatible with any substantial increase in breast cancer risk associated with caffeine consumption.

Anticarcinogenic Phytochemicals

As reviewed in detail elsewhere, fruits and vegetables contain several compounds that have potential anticarcinogenic activity (106), including the micronutrients already discussed, e.g. carotenoids with provitamin A activity and other antioxidants. Other compounds, e.g. some isoflavonoids, may act as antiestrogens and thereby reduce risk of breast cancer (2). Components of cruciferous vegetables appear to alter the balance of estrogen metabolism toward less active forms, which might also decrease risk. Still other components of fruits and vegetables can block formation of carcinogens and induce detoxifying enzymes. Higher intakes of vegetables appear to be associated with lower rates of breast cancer; evidence indicates that this finding may be explained at least in part by consumption of carotenoids with provitamin A activity (44). Whether other phytochemicals contribute to reduced risk of human breast cancer in a quantitatively important way remains uncertain because relevant data are limited. In one case-control study from southeast Asia (67), intake of soy products, a major source of isoflavonoids with antiestrogenic activity, was associated with lower risk of breast cancer. Despite the limited information related to specific phytochemicals, the evidence that higher intakes of vegetables in general can reduce breast cancer risk is reasonably strong.

CONCLUSIONS

The considerable international differences in breast cancer rates, together with the increasing incidence rates over time in many countries and the results of studies of migrants, suggest that environmental factors are responsible for a major portion of breast cancer incidence in the US and other affluent countries. Among environmental factors, aspects of diet remain likely causes of breast cancer. A modest association between alcohol consumption and breast cancer is the best-supported dietary relationship at this time. Prospective studies suggest that the relationship between dietary fat intake in middle life and breast cancer development is insignificant, although the hypothesis that very low fat intakes may be protective has not been fully tested. Energy intake and growth restriction during growth may explain much of the international variation in breast cancer rates but does not immediately suggest a feasible intervention. Substantial evidence indicates that vitamin A from animal or vegetable sources

may reduce risk, but this hypothesis requires further investigation. The influence of adult diet on breast cancer should become clearer in the next five years as a number of large ongoing prospective studies report more data. Hypotheses relating diet early in life to breast cancer will remain difficult to test unless histologic, radiographic, or other intermediate markers of breast cancer risk are found and validated or unless novel data sources or methods of measuring childhood diet are developed.

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