Macronutrient Intake and Change in Mammographic Density at Menopause: Results from a Randomized Trial[1]

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Abstract

To examine the effects of dietary fat intake on breast cancer risk, we are conducting a randomized trial of dietary intervention in women with extensive areas of radiologically dense breast tissue on mammography, a risk factor for breast cancer. Early results show that after 2 years on a low-fat, high-carbohydrate diet there is a significant reduction in area of density, particularly in women going through menopause. In women who went through menopause during the 2-year follow-up, the mean decreases in area of density and percentage of density in the intervention group were 11.0 cm^2 and 11.0%, respectively, whereas the control group decreased 4.5 cm^2 and 5.2%. The purpose of this analysis was to determine whether changes in intake of specific macronutrients could account for the observed reduction in breast density in these women.

Differences between 2-year and baseline values of macronutrients (averaged over 3 nonconsecutive days of food intake) were calculated. We examined the effect of dietary variables, adjusted for changes in total calorie intake and weight and for family history of breast cancer, on changes in area of density and percentage of density using linear regression. Reduction in total or saturated fat intake or cholesterol intake was significantly associated with decreased dense area ($p \leq .004$). The most significant dietary variable associated with reduction in percentage of density was reduction in dietary cholesterol intake ($P = 0.001$), although reducing saturated fat intake was of borderline significance ($P = 0.05$). The effect of the membership in the intervention and control groups on change in area of density or percentage of density was reduced by models that included changes in intake of any fat, or cholesterol, or carbohydrates.

The observation of an effect of diet at menopause on breast density, a marker of increased risk of breast cancer, may be an indication that exposures at this time have an enhanced effect on subsequent risk.

Introduction

The role of dietary fat in the development of breast cancer is controversial. Ecological studies (1), and many case control studies (2), have found a link between fat intake and breast cancer risk, but cohort studies have, in general, failed to find that higher intake of fat is associated with a greater risk of breast cancer (3). However, studies within a population are limited by a lack of variation in fat consumption.

To examine the effects of a wider range of dietary fat intake on breast cancer risk we are conducting a randomized controlled trial of dietary intervention in women identified to be at increased risk of breast cancer due to the presence in the mammogram of extensive areas of radiologically dense breast tissue, a risk factor for breast cancer (4–6).

In our trial, women with extensive mammographic densities are randomized to either a control group that continues usual diet, or to an intervention group that receives intensive counseling to adopt a low-fat, high-carbohydrate diet. Both groups in the trial are monitored by collecting food records at specified intervals, and are asked to have mammograms every 2 years that are compared with mammograms taken at baseline.

Initial results of the trial in 817 participants showed that after 2 years women in the intervention group experienced a reduction in total area of breast density significantly greater than that seen in controls (7). This effect was strongly influenced by menopausal status. No effect was seen in women who were postmenopausal at entry. An effect was seen only in those who were premenopausal at entry to the trial. This effect was greatest among women who became postmenopausal at 2 years. We expect any differences between control and intervention groups in this randomized trial to be largely due to differences in diet, and that the effect of dietary variables should be most easy to identify in the group in whom the effect was greatest. Therefore, the purpose of the analyses presented here was to determine which macronutrient(s) could account for the observed change in breast density in women in whom the change was largest (*i.e.*, in women who became postmenopausal after entry) and to determine how much of the variation in change in breast density could be accounted for by dietary and other variables. Results for women who remained premenopausal or who were postmenopausal at baseline will be discussed in a separate publication, because results differed among the three menopausal groups.

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Materials and Methods

The subjects included in the present study are participants in a multicenter randomized controlled trial of intervention with a low-fat, high-carbohydrate diet. Mammograms were taken at baseline and ~2 years after randomization, the area of dense tissue and total area were measured using quantitative methods, and percentage of density was calculated. In the present study, we examine the relationship between change in area of dense tissue and percentage of density in relation to change in nutrient intake over the previous 2 years. We have limited the analysis here to women who were premenopausal at entry to the trial and who became postmenopausal within 2 years of entry, because it was in this group that the effect of dietary intervention on mammographic density was greatest. Subjects were classified as premenopausal if they had a menstrual period in the previous 6 months, were on HRT[3] and <50 years of age, or had a hysterectomy without oophorectomy and were <50 years of age. Menopause was defined as 6 consecutive months without menstruating, being on HRT and ≥50 years of age, having a hysterectomy without oophorectomy and being ≥50 years, or having a hysterectomy with oophorectomy while still menstruating.

Dietary Intervention Trial. A detailed description of the dietary intervention trial is presented elsewhere (7), and we give only a brief summary here. Subjects with mammographic densities occupying >50% of the breast area were enrolled in the study and randomized either to a dietary intervention arm or a control arm. The intervention involved intensive individual dietary counseling aimed at reducing total fat intake to a target of 15% of calories while maintaining caloric intake by increasing consumption of carbohydrate. Controls received general advice about nutrition but were not counseled to change their intake of fat.

Subjects in the intervention group were seen every month for the 1st year and every 3 months in the 2nd year. Controls were seen every 4 months in the 1st year and every 3 months in the 2nd year. At each visit, subjects were asked to provide 3 nonconsecutive days of food records, which were reviewed with each subject by a dietitian to ensure completeness. Nutrient analysis of food records was performed using the Minnesota Nutrient Data System software developed by the Nutrition Coordinating Center, University of Minneapolis (Minneapolis, MN). Information on nondietary variables, including menstrual history, was collected at baseline and updated 1 and 2 years after randomization.

Mammographic Measurements. Mammographic measurements were made using a randomly selected, craniocaudal (viewing from above, down) mammographic view of one breast from each subject at baseline and 2 years later. Mammograms were digitized and presented for analysis as an array of 675 × 925 pixels (6.76×10^{-4} cm^2/pixel). The observer first selected a gray value as a threshold to separate the image of the breast from the background and determined the breast size. A second threshold was then selected to identify the edge of region(s) representative of radiographically dense tissue in the image, the sum of which gives the area of density in the breast. The proportion of the total area occupied by the radiographically dense tissue was calculated as the percentage of the entire projected area of the breast, expressed as "percent density." All thresholds were selected by one observer (N. F. B.), blinded to the membership of subjects in the intervention or control groups. Digitized images were presented in pairs, but randomly ordered so the operator did not know the sequence in which they had been taken.

Further details of this method, including inter- and intraobserver reliability (intraclass coefficients of about 0.9) and the relationship of the measurements to cancer risk (relative risks of 4–6 between the highest and lowest categories of density), are described elsewhere (8–10).

Ethics. This study was approved by the institutional review board of each participating center, and all of the participants provided written informed consent.

Statistical Analysis. Values for each nutrient were transformed by natural logarithm or by square root, averaged over the 3 days of food intake at baseline and 2 years, and differences between 2-year and baseline values were calculated. We used linear regression to examine the effect of a number of nondietary and dietary variables on change in area of density and on change in percent density. A negative β coefficient indicates an association between increasing intake and decreasing density, and a positive β coefficient indicates an association between increasing intake and increasing density.

The following nondietary variables at baseline were examined for an effect on change in area of density and percent density: age, family history of breast cancer (defined as reporting any relative with breast cancer), being a smoker, ever having been pregnant, ever having breast-fed, ever having used oral contraceptives, age at menarche, age at first birth, and level of physical activity (on a 7-point scale). In addition, physical activity at 2 years and change in physical activity (using four categories) were also examined. Users of HRT were defined for analysis as those who were using HRT at either baseline or at 2 years. As women could be using HRT at either or both time points, the number of women within each of these subcategories was insufficient for a more detailed analysis.

Dietary variables tested in the models consisted of change in intake of the following macronutrients: total fat, type of fat (saturated, monounsaturated, and polyunsaturated), cholesterol, total carbohydrates, total fiber, type of fiber (insoluble and soluble), and protein. The intakes of all dietary components were measured in grams except cholesterol, which was measured in milligrams. Change in total calorie intake (in kilocalories) and weight change were included as potential confounders in all models testing the effect of changes in macronutrient intake.

Finally, the effect of the addition of each dietary variable on the *P* of the group variable was also considered to determine which dietary variables best "explained" the observed group effect, defined by the value of R^2, indicating the proportion of variance explained (11). The values of R^2 shown are adjusted for the number of variables in the model.

Change in area and percentage of mammographic density were approximately normally distributed and were not transformed.

Results

There were 91 women in the dietary trial who were premenopausal at entry into the trial and postmenopausal 2 years after entry. Two of these women were extreme outliers in change in area of density and were excluded, leaving 89 women, of whom 78 had complete dietary and weight information, and on whom all subsequent analyses were based. Of these 78 subjects classified as postmenopausal: (*a*) thirty [17 interventions (Is); 13 controls (Cs)] were classified at 2 years because of 6 consecutive months without menstruating; (*b*) thirteen (10 Is; 3 Cs)

[3] The abbreviations used is: HRT, hormone replacement therapy.

were classified because of a hysterectomy without oophorectomy at baseline and ages ≥50 years at 2 years; (*c*) four (1 I; 3 Cs) were classified because of hysterectomy with oophorectomy while still menstruating; and (*d*) thirty-one (16 Is; 15 Cs) were classified because they were on HRT and ≥50 years of age at 2 years. The mean change in area of density and mean change in percent density were similar in these 78 subjects and the whole group of 89 (change in area of density, -8.2 cm^2 and -8.1 cm^2, respectively; change in percent density, -8.5% and -8.5%, respectively). Over 2 years, the intervention group experienced a mean decrease in dense area (-11.0 cm^2 *versus* -4.5 cm^2; $P = 0.004$) and in percent density (-11.0% *versus* -5.2%; $P = 0.025$) that was more than twice as great as that experienced by the control group. These changes were much greater than those observed in 453 women premenopausal at baseline and at 2 years with complete information, and excluding extreme outliers. Among these women, the intervention group had a marginally significant greater decrease in dense area (-3.0 cm^2 *versus* -1.0 cm^2; $P = 0.08$) and no difference in change in percent density (-1.1% *versus* -1.6%; $P = 0.55$). Postmenopausal women with complete information ($n = 181$) experienced little change in either the intervention or the control group in either dense area (-1.6 cm^2 *versus* -0.9 cm^2; $P = 0.68$) or percent density (+1.2% *versus* +0.4%; $P = 0.57$).

Baseline Characteristics. Table 1 shows baseline characteristics of subjects by study group (intervention and control). There were no significant differences between the groups in any of these variables, except for baseline weight ($P = 0.02$) and the greater proportion of the intervention group who were using HRT at baseline ($P = 0.025$). Baseline weight and HRT were not associated with density change. Among women in the intervention group taking hormones at baseline ($n = 11$), the mean reduction in dense area at 2 years was 13.0 cm^2, and percent density was reduced by 12.5%. In those not taking hormones at baseline ($n = 33$), dense area was reduced by 10.4 cm^2, and percent density was reduced by 10.5%. The same comparison cannot be made among controls because only two were taking hormones at baseline.

The average weight and median intake of the major macronutrients at baseline and at 2 years by group is shown in Table 2. The differences between the groups in changes in intake (after transformation) were significant (Wilcoxon, $P = 0.005$) for fat and cholesterol. The difference in weight change between the groups was not significant.

Nondietary Variables: Influence on Change in Density. Of the nondietary variables of which the influence on change in mammographic features was examined, only family history was significantly associated with the magnitude of the change at menopause in both area of density and percent density ($P = 0.01$ and 0.03, respectively). The mean reduction in area of density was 14.5 cm^2 in subjects in the intervention group without a family history of breast cancer ($n = 26$), and 6.0 cm^2 in those with a family history ($n = 18$). For control subjects without a family history of breast cancer ($n = 21$), the reduction in area of density was 5.9 cm^2, and for those with a family history ($n = 13$) it was 2.2 cm^2. Mean percent density was reduced at menopause by 13.7% in subjects in the intervention group without a family history, and by 7.1% in those with a family history. For control subjects without a family history, mean percent density was reduced at menopause by 7.0%, and by 2.3% in those with a family history. Family history had an R^2 value of 0.08 for area of density and 0.06 for percent density, and was included in the multivariate models described below.

Table 1 Baseline characteristics of 78 women enrolled in dietary intervention trial who went through menopause and who have complete information

Baseline characteristic	Intervention ($n = 44$)	Control ($n = 34$)
Age[a] (years)	49.5 (2.4)	49.2 (2.6)
Dense breast area[a] (cm^2)	64.3 (27.2)	55.3 (28.5)
% breast density[a]	65.6 (14.1)	60 (17.4)
% ever pregnant	79.6	76.5
% with any relative with breast cancer	40.9	38.2
% using hormone replacement	25	5.9[b]
Weight[a] (kg)	62.7 (6.5)	66.4 (7.4)[c]

[a] Values shown are mean and (SD).
[b] p = 0.025.
[c] p = 0.02.

Macronutrient Variables: Influence on Change in Density. Table 3 shows the results of models of the effect of change in intake of each macronutrient on change in area of density and change in percent density, adjusted for change in total calories, weight change, and family history. Decreasing intake in all types of fat was significantly associated with a greater decrease in area of density. Saturated fat was the most significant of the subtypes of fat, but change in cholesterol intake was the most significant dietary variable. Change in cholesterol intake was also the variable most strongly associated with change in percent density, and saturated fat achieved borderline significance ($P = 0.05$). Change in protein intake was not related to change in dense area, but was directly related to change in percent density (defined as dense area divided by total area) because of an inverse relationship between protein and change in total breast area ($P = 0.02$; adjusted for change in total calories, weight change, and family history).

We have estimated the size of the effect on breast density of selected nutrient changes observed in the intervention group using the regression equations: change in dense area in $cm^2 = \beta$ [Tr(group median nutrient intake at 2 years) - Tr(group median nutrient intake at baseline)]; where Tr is the log or square root transformation applied to the nutrient; β is taken from Table 3; and the median nutrient intake changes for the intervention group are taken from Table 2. The equations used to estimate change in percent density had the same form.

The median change in dietary fat intake in the intervention group was from 57–31 g/day, giving an estimated average reduction of 5.61 cm^2 in the area of dense breast tissue. Intake of saturated fat, which was the most significant subtype of fat, was reduced from a median of 21 g/day to 11 g/day, resulting in an estimated average reduction of 5.54 cm^2 in the area of dense breast tissue and a reduction of 3.93 in the percentage of breast density. Intake of dietary cholesterol, which was the most significant nutrient for both area and percent density, was reduced from a median of 229 mg/day to 150 mg/day, resulting in an estimated average 3.27 cm^2 reduction in the area of dense tissue and a reduction of 3.52 in percent density.

On the basis of the R^2 values in Table 3, change in cholesterol intake accounted for more of the variation in density change than any other variable. A model including changes in cholesterol intake, family history, weight change and change in total calories resulted in an adjusted R^2 of 0.18 for both area of density and percent density.

We next sought to "explain" the effect of group membership (intervention or control) on the reduction in breast density by examining the effects on the statistical significance of group membership on change in breast density by including dietary

Table 2 Mean weight and median macronutrient intakes/day at baseline and 2 years for the 78 women who went through menopause and by group (intervention and control)

	Intervention (n = 44)		Control (n = 34)	
	Baseline	2 yr	Baseline	2 yr
Weight (kg)[a]	62.7 (6.5)	62.8 (6.9)	66.4 (7.4)	67.3 (8.4)
Total calories (kcal)[b]	1626 (560)	1466 (506)	1617 (647)	1423 (582)
Fat (g)[b]	57 (28)	31 (20)	60 (43)	50 (26)
Saturated fat (g)[b]	21 (10)	11 (8)	22 (17)	18 (11)
Carbohydrates (g)[b]	206 (68)	209 (98)	193 (69)	184 (93)
Protein (g)[b]	58 (19)	62 (22)	66 (21)	67 (22)
Fibre (g)[b]	19 (9)	19 (8)	16 (8)	18 (6)
Cholesterol (mg)[b]	229 (103)	130 (67)	225 (154)	197 (131)

[a] Values shown are means and (SD).
[b] Values shown are medians and (interquartile range).

Table 3 Linear regression results for change in macronutrient intake and change in area of density and percent density among women who went through menopause in the first 2 years (n = 78 with complete information), adjusted for change in total calorie intake, weight change, and family history of breast cancer

	Dense area (cnn^2)			% density		
	β[a]	P	Adjusted model R^2	Nutrient β[a]	P	Adjusted model R^2
Total calories + weight + family history			0.06			0.06
Total fat[b] (g)	9.21	0.004	0.15	5.32	0.13	0.08
Saturated fat[b] (g)	8.57	0.002	0.17	6.07	0.05	0.10
Monounsaturated fat[b] (g)	6.23	0.02	0.12	3.77	0.19	0.07
Polyunsaturated fat[b] (g)	4.83	0.05	0.10	1.22	0.65	0.05
Cholesterol[b] (mg)	5.77	0.001	0.18	6.21	.001	0.18
Carbohydrates[c] (g)	−1.25	0.15	0.08	−1.54	0.10	0.09
Total fibre[c] (g)	0.71	0.66	0.05	−0.75	0.67	0.05
Insoluble fibre[c] (g)	0.45	0.81	0.05	−1.12	0.57	0.06
Soluble fibre[c]	1.98	0.49	0.06	−0.74	0.81	0.05
Protein[c] (g)	0.36	0.79	0.05	3.19	0.02	0.12

[a] Positive values indicate a direct association with change in area of density while negative values indicate an inverse association.
[b] Log transformation.
[c] Square root transformation.

and nondietary variables in a series of models whose results are shown in Table 4. With change in dense area as the dependent variable, models that included change in total calorie intake, change in weight, family history, and either change in intake of any fat, or cholesterol, or carbohydrates, all reduced the statistical significance of the group effect. Change in intake of total fat, saturated fat, or cholesterol had the largest influence on the group variable.

Similarly, in models where change in percent density was the dependent variable, the statistical significance of the group variable was reduced by including change in intake of any fat (except polyunsaturates), cholesterol, or carbohydrates. Change in saturated fat or cholesterol had the greatest effect.

Discussion

The radiological appearance of the female breast varies between individuals because of variations in the amounts of fat, stromal and epithelial tissue (12, 13). These tissues attenuate X-rays to different degrees and, as a result, fat is radiologically lucent, and appears dark in a mammogram. Stromal and epithelial tissues are radiologically dense, and appear light in a mammogram. It is known that the prevalence of mammographically dense breast tissue in the population declines with increasing age (14, 15), and that dense breast tissue is more common before than after menopause (15, 16). These changes indicate that there is a reduction in the proportion of epithelial and stromal tissue and an increase in fat in the breast at menopause. The present results provide direct evidence of a large reduction in the area and percentage of dense breast tissue at menopause, and suggest that the magnitude of this change is strongly influenced by diet and by at least one nondietary variable, a family history of breast cancer.

Family history, defined as any relative with breast cancer, was significantly associated with a smaller decrease in area of breast density and percent density at menopause. Thus, failure to decrease density as much as other women at menopause may contribute to the continuing greater risk of breast cancer experienced by women with a family history of breast cancer.

As expected, women in the intervention group had lower intakes of all of the types of fat and cholesterol than controls, and all of these dietary differences were related to the decrease in area of dense tissue in the breast. Only changes in saturated fat and dietary cholesterol intake were related to the magnitude of the decrease in percent density. Changes in carbohydrates, fiber, and protein intake were not significantly related to density change (although change in protein intake was related to change in total area, which affects percent density). The variables associated with the largest R^2 for the observed change in dense area were changes in total fat, saturated fat, and dietary cholesterol. Changes in dietary cholesterol and saturated fat best explained the observed change in percent density. About 18% of the observed variation in change in area of density in

Table 4 Effect of macronutrient variables on the *P* of the difference in density change between intervention and control groups among 78 women going through menopause

	Dense area			% density		
	Nutrient *P*	Group *P*	R^2	Nutrient *P*	Group *P*	R^2
Group only		0.006	0.08		0.03	0.05
Group + total calories + family history + weight		0.004	0.15		0.01	0.13
Total fat[a]	0.07	0.07	0.18	0.69	0.04	0.12
Saturated fat[a]	0.06	0.11	0.18	0.41	0.07	0.13
Monounsaturated fat[a]	0.13	0.03	0.17	0.63	0.03	0.12
Polyunsaturated fat[a]	0.22	0.02	0.16	0.76	0.01	0.12
Cholesterol[a]	0.02	0.06	0.21	0.01	0.12	0.19
Carbohydrates[b]	0.6	0.01	0.15	0.39	0.03	0.13
Total fibre[b]	0.37	0.003	0.15	0.96	0.01	0.12
Insoluble fibre[b]	0.51	0.004	0.15	0.81	0.01	0.12
Soluble fibre[b]	0.22	0.002	0.16	0.85	0.01	0.12
Protein[b]	0.76	0.004	0.14	0.02	0.008	0.19

[a] Log transformation and adjusted for study group, family history, change in weight, and change in total calorie intake.
[b] Square root transformation and adjusted for study group, family history, change in weight, and change in total calorie intake.

women becoming postmenopausal was accounted for by change in cholesterol intake, change in total calorie intake, weight change, and family history, although much variation is still unaccounted for.

All of the models presented here include only one dietary variable (other than change in total calories) for two reasons. One reason is the high correlation between some of the dietary variables. The other reason is concern that, if measurement error varies among the dietary variables, the relative importance of each variable could be obscured when they are combined. Measurement error in individual dietary intake variables and in breast density may have led to some underestimation of the observed R^2. Some of the unexplained variation may be due to complex interactions between variables, which cannot be fully explored with the sample size available to us here and without further consideration of measurement error. In an exploratory analysis, a significant interaction was observed between changes in soluble fiber and saturated fat intake.

Ecological analysis (1), pooled analysis of case control studies (2), meta-analysis of cohort and case control studies (17), and animal experimental evidence (18) all suggest a positive association between intake of fat and breast cancer incidence. However, cohort studies have shown mostly null or weakly positive associations, and a combined analysis of cohort studies showed no relationship between fat intake and breast cancer risk (3). All observational epidemiological studies are, however, likely to be affected by the limited range of fat intake found within most populations and by error in the measurement of intake (4). For example, an analysis of cohort studies (3) contained 4980 cases of breast cancer of whom only 84 (1.7%) reported consuming <20% of calories from fat. In the present trial, as a result of intervention with intensive dietary counseling, the range of dietary fat intake is much greater, and the mean intake of the intervention group is 20% of calories.

The strong association found here between change in dietary cholesterol and density change is in keeping with evidence in the literature of a relationship between dietary cholesterol and breast cancer risk. A review of the evidence relating cholesterol and cancer concluded that there was evidence for a small or moderate increase in risk of breast cancer associated with dietary cholesterol (19). Dietary cholesterol intake was significantly related to increased risk of breast cancer in two combined case-control studies carried out in France and Italy (20), in premenopausal women in an Australian case-control study (21), marginally in a Finnish cohort study (22), and in the Nurses' Health Study cohort (1984 data), although in premenopausal women only (23). In the recent pooled analysis of dietary fat and cholesterol data from cohort studies, only cholesterol achieved marginal significance (3). Dietary cholesterol has also been considered as a marker for proportion of monounsaturated fat derived from olive oil *versus* animal sources (24). A possible role of dietary cholesterol in the development of breast cancer needs further investigation.

It has been suggested that adolescence, when the breasts are undergoing rapid development, may be an important period for exposures to factors that may subsequently influence breast cancer risk (25, 26). Menopause also seems to play a key role in influencing breast cancer risk. The age-specific incidence of breast cancer increases rapidly until about age 50 after which the rate of increase slows (27). Further, the difference in age-specific incidence seen between countries occurs after about age 50 (28). It may be that at menopause, another period in a woman's life when the breasts undergo rapid change, breast tissue is also more vulnerable to external risk factors with respect to subsequent risk. That is, if this is a time when the breasts are in the process of shifting to a lower risk state, exposure to risk factors at this time of change may affect the degree of shift. Preliminary evidence presented here from a dietary intervention trial supports this hypothesis in the sense that dietary change at menopause affected the magnitude of decrease in breast density, which has been shown to be associated with the risk of breast cancer. Further research will be necessary to determine whether diet at menopause, specifically cholesterol, total fat, and saturated fat intake, alter breast cancer risk, although disentangling the relative roles of these dietary components may be difficult.

References

1. Prentice, R., and Sheppard, L. Dietary fat and cancer: consistency of the epidemiologic data, and disease prevention that may follow from a practical reduction in fat consumption. Cancer Causes Contol, *1:* 81–97, 1990.

2. Howe, G. R., Hirohata, T., Hislop, T. G., Iscovich, J. M., Yuan, J. M., Katsouyanni, K., Lubin, F., Marubini, E., Modan, B., Rohan, T., Toniolo, P., and Shunzhang, Y. Dietary factors and risk of breast cancer: combined analysis of 12 case-control studies. J. Natl. Cancer Inst., *82:* 561–569, 1990.

3. Hunter, D. J., Spiegelman, D., Adami, H. O., Beeson, L., van den Brandt, P. A., Folsom, A. R., Fraser, G. E., Goldbohm, A., Graham, S., Howe, G. R., Kushi, L. H., Marshall, J. R., McDermott, A., Miller, A. B., Speizer, F. E., Wolk,

A., Yaun, S. S., and Willett, W. Cohort studies of fat intake and the risk of breast cancer – a pooled analysis. N. Engl. J. Med., *334:* 356–361, 1996.

4. Goodwin, P., and Boyd, N. F. Critical appraisal of the evidence that dietary fat intake is related to breast cancer risk in humans. J. Natl. Cancer Inst., *79:* 473–485, 1987.

5. Saftlas, A. F., and Szklo, M. Mammographic parenchymal patterns and breast cancer risk. Epidemiol. Rev., *9:* 146–174, 1987.

6. Oza, A. M., and Boyd, N. F. Mammographic parenchymal patterns: a marker of breast cancer risk. Epidemiol. Rev., *15:* 196–208, 1993.

7. Boyd, N. F., Greenberg, C., Lockwood, G., Little, L., Martin, L., Byng, J., Yaffe, M., and Tritchler, D. Effects at two years of a low-fat, high-carbohydrate diet on radiologic features of the breast: results from a randomized trial. J. Natl. Cancer Inst., *89:* 488–496, 1997.

8. Byng, J. W., Boyd, N. F., Fishell, E., Jong, R. A., and Yaffe, M. J. The quantitative analysis of mammographic densities. Phys. Med. Biol., *39:* 1629–1638, 1994.

9. Boyd, N. F., Byng, J. W., Jong, R. A., Fishell, E. K., Little, L. E., Miller, A. B., Lockwood, G. A., Tritchler, D. L., and Yaffe, M. J. Quantitative classification of mammographic densities and breast cancer risk: results from the Canadian National Breast Screening Study. J. Natl. Cancer Inst., *87:* 670–675, 1995.

10. Boyd, N. F., Lockwood, G. A., Byng, J. W., Little, L. E., Yaffe, M. J., and Tritchler, D. The relationship of anthropometric measures to radiological features of the breast in premenopausal women. Br. J. Cancer, *78:* 1233–1238, 1998.

11. Tritchler, D. Explanatory analyses of randomized studies. Biometrics, *52:* 1450–1456, 1996.

12. Ingleby, H., and Gerson-Cohen, J. Comparative Anatomy, Pathology and Roentgenology of the Breast. Philadelphia: University of Philadelphia Press, 1960.

13. Ryan, J. M., Ostrow, D. G., Breakefield, X. O., Gershon, E. S., and Upchurch, L. A comparison of the proliferative and replicative life span kinetics of cell cultures derived from monozugotic twins. In Vitro (Rockville), *17:* 20–27, 1981.

14. Grove, J. S., Goodman, M. J., and Gilbert, F. Factors associated with mammographic pattern. Br. J. Radiol., *58:* 21–25, 1985.

15. Grove, J. S., Goodman, M. J., Gilbert, F. I., and Clyde, D. Factors associated with breast structures in breast cancer patients. Cancer (Phila.), *43:* 1895–1899, 1979.

16. Wolfe, J. N. Breast parenchymal patterns and their changes with age. Radiology, *121:* 545–552, 1976.

17. Boyd, N. F., Martin, L. J., Noffel, M., Lockwood, G. A., and Tritchler, D. L. A meta-analysis of studies of dietary fat and breast cancer risk. Br. J. Cancer, *68:* 627–636, 1993.

18. Freedman, L. S., Clifford, C., and Messina, M. Analysis of dietary fat, calories, body weight and the development of mammary tumors in rats and mice: a review. Cancer Res., *50:* 5710–5719, 1990.

19. McMichael, A. J., Jensen, O. M., Parkin, D. M., and Zaridze, D. G. Dietary and endogenous cholesterol and human cancer. Epidemiol. Rev., *6:* 192–216, 1984.

20. Gerber, M., Richardson, S., Cavallo, F., Marubini, E., Crastes De Paulet, P., Crastes De Paulet, A., and Pujol, H. The role of diet history and biologic assays in the study of diet and breast cancer. Tumori, *76:* 321–330, 1990.

21. Rohan, T. E., McMichael, A. J., and Baghurst, P. A. A population-based case-control study of diet and breast cancer in Australia. Am. J. Epidemiol., *128:* 478–489, 1988.

22. Knekt, P., Albanes, D., Seppanen, R., Aromaa, A., Jarvinen, R., Hyvonen, L., Teppo, L., and Pukkala, E. Dietary fat and risk of breast cancer. Am. J. Clin. Nutr., *52:* 903–908, 1990.

23. Willett, W., Hunter, D., Stampfer, M., Colditz, G., Manson, J., Spiegelman, D., Rosner, B., Hennekens, C., and Speizer, F. Dietary fat and fiber in relation to risk of breast cancer. J. Am. Med. Assoc.., *268:* 2037–2044, 1992.

24. Gerber, M. Olive oil, monounsaturated fatty acids and cancer. Cancer Lett., *114:* 91–92, 1997.

25. Hunter, D. J., and Willett, W. C. Diet, body size, and breast cancer. Epidemiol. Rev., *15:* 110–132, 1993.

26. Kaaks, R. Nutrition, hormones, and breast cancer: is insulin the missing link? Cancer Causes Contol, *7:* 605–625, 1996.

27. Pike, M. C., Spicer, D. V., Dahmoush, L., and Press, M. F. Estrogens, progestogens, normal breast cell proliferation, and breast cancer risk. Epidemiol. Rev., *15:* 17–35, 1993.

28. Muir, C., Waterhouse, T., Mack, J., Powell, S., and Whelan, S. Cancer Incidence in Five Continents, Vol. VI. Lyon, France: IARC Scientific Publications, 1992.

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