Prevention and Epidemiology

A Randomized Trial of Dietary Intervention for Breast Cancer Prevention

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Abstract

Epidemiologic data and animal experiments suggest that dietary fat may influence risk of breast cancer. To determine whether intervention with a low-fat, high-carbohydrate diet would reduce breast cancer incidence in women at increased risk of the disease, we carried out a randomized controlled trial in Canada. We recruited 4,690 women with extensive mammographic density and randomized them to an intervention group or a comparison group. The intervention group received intensive dietary counseling to reduce fat intake to a target of 15% of calories and increase carbohydrate to 65% of calories. Dietary intakes were assessed throughout using food records. Subjects were followed for at least 7 years and for an average of 10 years. The main outcome was invasive breast cancer. Percentage of calories from fat in the intervention group decreased from 30% at baseline to 20% after randomization and remained 9% to 10% lower than the comparison group throughout. There were 118 invasive breast cancers in the intervention group and 102 in the comparison group \[\text{adjusted hazard ratio} = 1.19 \ (95\% \ CI: 0.91–1.55)\]. Analysis of food records showed that fat intake at baseline and after randomization was not associated with total breast cancer incidence. Greater weight and lower carbohydrate intake at baseline and after randomization were associated with an increased risk of estrogen receptor (ER)-positive breast cancer. Our findings suggest that a sustained reduction in dietary fat intake did not reduce risk of breast cancer in women with extensive mammographic density. Weight and carbohydrate intakes were associated with risk of ER-positive breast cancer. Cancer Res 71(1): 123–33. ©2011 AACR.

Introduction

The large variations in breast cancer incidence that exist among countries (1), and the changes in rates that occur in migrants from low-risk to high-risk countries (2–4), show that environmental factors influence the frequency of the disease. Differences in diet may contribute to these effects and international breast cancer incidence and mortality rates show a strong, positive correlation with estimates from food disappearance data of total fat intake and a negative correlation with cereal consumption (5, 6). There is also a strong association between estimated changes in dietary fat intake and changes in breast cancer rates in migrants (7). Case–control and cohort studies have however given mixed results, but in a meta-analysis of the published literature, we concluded that the combined estimates of risk for total and saturated fat intake, and for meat intake, all showed that higher intakes were associated with a modest increase in risk of breast cancer (8). However, the pooling project of cohort studies (9) and the AICR/WCRF review and meta-analysis (10) did not find evidence of an association between fat intake and breast cancer.

Published estimates of breast cancer risk associated with fat intake may underestimate the true effect because of error in the measurement of fat intake in epidemiologic studies that generally use food frequency questionnaires (FFQ; refs. 11, 12). These considerations led us to carry out a randomized trial of dietary intervention to determine whether a reduction in fat intake reduced risk of breast cancer in women at increased risk of the disease. Data on dietary intakes were collected throughout the trial by using food records. These quantitative diaries were used to record all food consumed on days selected by study dietitians and were used to facilitate dietary counseling, to assess dietary compliance, and to analyze the associations with breast cancer risk of the nutrients that the intervention sought to change.

Methods

General method

We have carried out a randomized controlled trial (13) to determine whether the incidence of breast cancer in a high-risk population of women could be reduced by intensive individual counseling to reduce dietary fat intake and increase carbohydrate intake. We selected highly motivated subjects at...
increased risk of breast cancer, provided those in the intervention group with a high level of assistance in making dietary alterations, ensured the complete identification of subjects who developed breast cancer, and have analyzed the results according to both intention to treat and intakes of the nutrients that the intervention sought to modify. Ethics approvals were obtained from the University Health Network, Toronto, McMaster University, Hamilton, the University of Western Ontario, and the University of British Columbia. We report here the primary outcome of the trial—risk of invasive breast cancer.

Recruitment, screening, and randomization of subjects

Recruitment, randomization, and outcomes in the trial are summarized in Figure 1. Recruitment began in Toronto in 1988 and other sites were added as additional funds were obtained. All sites were funded from 1993 until the end of the trial in December 2005. Details of the trial sites and their staff are given in the Appendix. Mammography units in the 8 trial sites in Ontario and British Columbia, Canada, routinely recorded percentage mammographic density on all women examined. Women aged 30 to 65 years, without breast cancer and with mammographic density in at least 50% of the breast, were approached by letter, followed by a phone call. Potentially eligible women were asked to attend 2 screening visits (see the following text). To avoid counseling modification of total caloric intake, we excluded subjects with a body mass index (BMI) of less than 19 or greater than 27. Other criteria for exclusion were a previous history of cancer (excluding nonmelanomatous skin cancer), pregnant (or planning to be), or breast-feeding, on a medically prescribed diet for any reason, or previous or present treatment to reduce blood lipids, habitually (i.e., 4 or more times per week) eating more than 1 meal a day in a restaurant (place and cafeterias were not counted as restaurants), and reduction or augmentation mammoplasty.

At the first screening visit, women who were eligible and wished to proceed were taught to keep food records. If records were of adequate quality when reviewed at the second screening visit, subjects were asked for consent to be randomized to an intervention or comparison group. Randomization was carried out by telephone contact with the Department of Biostatistics, Princess Margaret Hospital, Toronto, a department separate from the co-coordinating site of the trial. Random assignments were stratified by trial site and concealed from dietitians and subjects until the subject had been registered and the assignment made. Subjects were told their assignment at the visit following the completion of screening.

Dietary intervention

The dietary intervention was planned after randomization. The subject’s usual meal pattern and primary sources of dietary fat and food preferences were assessed, and subjects in the intervention group counseled were individually with the aim of reducing fat intake to 15% of calories and increasing carbohydrate intake to 65%. A diet was calculated using food exchange lists for fat, protein, grains, fruits, vegetables, and dairy products. Total caloric intake was maintained at the level consumed before intervention. Women in the comparison group were given general dietary advice based on Canada’s Food Guide but were not counseled to change their intake of fat.

Collection and analysis of food records

After randomization, subjects in the intervention and comparison groups were asked to provide at every visit food records on 3 nonconsecutive days selected by the diettian who reviewed records to ensure adequate detail and clarity. The nutrient analysis of food records is time consuming and we have analyzed samples of all available records. Samples of food records were analyzed at intervals throughout the trial to monitor dietary intakes, and to illustrate dietary intakes in a subset of 723 subjects (n = 358 for intervention and n = 365 for comparison groups), randomly selected from all subjects (n = 2,827) who had food records at each of 4 time points: baseline, years 1 or 2; years 4–6; and years 8–10. Further food records were analyzed to assess the associations of fat and carbohydrate with breast cancer risk in a case–control study nested in the trial cohort (described in section Statistical Methods).

Food records were analyzed using the Nutrition Data System from the Nutrition Coordinating Center, University of Minnesota, modified to include Canadian foods. Dietitians trained and certified in the use of the system were “blinded” to the identity and study group of the subjects whose food records they analyzed (14).

Because subjects may alter their food intakes on days when food records are kept, we obtained an additional assessment of dietary intakes, independent of that obtained from food records, between July 2004 and November 2005 (an average of 9 years after randomization); we further examined dietary fat intake by 3 random, unannounced 24-hour recalls collected by telephone interview in a cross-sectional substudy of 123 subjects in the intervention group and 155 subjects in the comparison group.

Total cholesterol (TC) and high-density lipoprotein cholesterol (HDL-C) were measured using standard Lipid Research Clinic methods in nonfasting serum samples from the 723 randomly selected subjects whose food records were analyzed. The sample size was selected to provide at least 80% power to detect a difference in change of approximately 5% in TC or HDL-C between randomized groups.

Follow-up and study end points

Women in the intervention group were seen every month for the first year, every 3 months in the second year, and every 6 months thereafter. Women in the comparison group were seen every 3 months for the first year, every 6 months for the second year, and then annually. Minimum follow-up was 7 years and average follow-up 10 years. Data on risk factors, anthropometric measures, and a blood sample were collected at baseline and annually thereafter. All subjects, including dropouts (see the following text), were asked annually about breast biopsies, other biopsies, and major illnesses. Pathology reports were obtained for all reported breast biopsies or any type of malignant disease.
Of all 4,690 subjects randomized, 571 (12%) dropped out, 327 from the intervention group and 244 from the comparison group. Between July 2005 and the end of the trial in December 2005, we contacted in person 4,610 (98.3%) of 4,690 randomized subjects, and the date of contact for each subject was the final date used in the analysis. The cancer registries of Ontario and British Columbia were searched for records of the remaining 80 (1.7%) subjects and none were found.

### Sample size

We calculated sample size using an adaptation of the procedure described by Self et al. (15), taking into account the age distribution of the subjects, allowance for dropouts, dietary compliance and risk of breast cancer, and assuming a linear decline in risk. We estimated the dropout rate to be 4% in the first year and 1% per year thereafter, and estimated that there would be a 12% difference between intervention and comparison group in percent calories from fat in the first 4 years and a difference of 8% thereafter. The sample size of 4,690 subjects followed for at least 7 years gave an 80% probability of detecting a relative risk of 0.3 at the end of the follow up period. We expect 94 cancers in the control group and 59 in the intervention group for a reduction in breast cancer incidence of 37%. (Dropouts were also followed for the development of cancer but are not included in these calculations.) This estimate of the effect of the intervention is smaller than the effect predicted from estimates of the effect of dietary fat on breast cancer risk from international epidemiologic data and also smaller than the 3.5-fold changes in breast cancer risk that have been observed in Japanese migrants to the United States.

### Statistical methods

Characteristics of subjects in the randomized groups were compared using the Student t test for continuous variables...
with approximately normal distributions, the Wilcoxon rank-sum test for continuous variables whose distributions were skewed, and the chi-square test for categorical variables. Nutrient intakes according to randomized group were compared at baseline, 1–2 years, 4–6 years, and 8–10 years by calculating standardized differences (the differences in means divided by the standard error of the difference) and values greater than 2 are statistically significant. The relationship between TC and HDL-C, randomization group and time of data collection, and the association between change in lipids and change in total fat intake were analyzed using repeated measurements.

All tests of statistical significance were 2-sided, and significance was declared at the 5% level.

Analyses of outcomes

The primary end point was invasive breast cancer, and all were confirmed by pathology report. Breast cancer incidence in the intervention and comparison groups was compared by the Cox proportional hazards model, with adjustment for age at randomization, baseline weight, and other risk factors for breast cancer (see Fig. 3, footnotes). All randomized subjects, including dropouts, were included in the analysis. Subjects who developed end points other than breast cancer (see Fig. 1) were censored at the time of their diagnosis or event. We have also carried out planned analyses to estimate the influence on results of dietary compliance by examining the associations of fat and carbohydrate intakes, the nutrients whose intakes the intervention sought to modify, and weight, with breast cancer risk without reference to randomization. These analyses were carried out with all invasive breast cancer as the outcome and also after stratification of cancers by estrogen receptor (ER) status (16).

The association of weight with breast cancer incidence was analyzed in the cohort of the trial by the Cox proportional hazards model, with annual measurements of weight (including baseline) treated as time-dependent continuous variables, adjusted for age, and the other risk factors shown in the footnotes to Figure 3.

The associations of fat and carbohydrate with breast cancer risk were analyzed in a case–control study nested within the trial cohort. Cases were all subjects who developed invasive breast cancer after randomization and before January 1, 2006. Each case was matched individually to 2 controls randomly selected from the entire trial population by using "risk-set" sampling and matched for age (within 1 year), date of randomization (within 1 year), center of randomization, and duration of follow-up after randomization (within 6 months; ref. 17).

We analyzed all available baseline and annual postrandomization food records of cases and their matched controls. The median number of daily food records was 3 at baseline for both cases and controls and after randomization was 15 (range, 2–61) for cases and 18 (range, 2–61) for controls. Average weight and intakes of fat and carbohydrate at baseline and after randomization were used as continuous variables in analysis by conditional logistic regression, with adjustment for the risk factors of breast cancer shown in the footnotes to Figure 3.

Nutrient residual models were used to calculate the interquartile range of energy-adjusted nutrients in the following way: residuals were obtained from general linear regression with nutrient as the response and total energy intake as the independent variable. The predicted nutrient intake at the mean total energy intake of 1,600 kcal per day was added to the quartiles of the residuals to calculate the 75% and 25% percentiles of energy adjusted nutrient. All odds ratios/hazard ratios were calculated by comparing the 75% percentile versus 25% percentile with weight, energy, and all nutrient variables treated as continuous variable, with adjustment for the following risk factors of breast cancer: age at randomization, parity, menopausal status, female hormone ever use, smoking history, first-degree relatives with a diagnosis of breast cancer, age at menarche, age at first birth, number of live births, and randomized group. In addition, baseline nutrients were adjusted for baseline weight and energy, and postrandomization nutrients for postrandomization weight and energy. All nutrient analyses were by logistic regression.

Results

Characteristics of subjects

As shown in Figure 1 and Table 1, 4,690 women were randomized and about 6% of those approached. Their mean age was 47 years, and most were Caucasian and premenopausal at entry. The randomized groups were similar except for small but statistically significant differences in age at menarche and age at first live birth. Many women invited by letter to participate could not be contacted by telephone. Of those who were contacted, some were excluded because of preexisting illnesses; others declined our invitation to attend for screening. The most common reasons given by potentially eligible women for not attending screening were lack of interest, lack of time, and unwillingness to change their current diet.

Changes in nutrient intakes and serum lipids

Table 2 shows that average nutrient intakes of the comparison and intervention groups from analysis of food records. One 3-day set of food records per subject, collected at baseline, 1–2 years, 4–6 years, and 8–10 years, and a blood sample for serum lipids were analyzed for each of these time periods.

Dietary intakes in the comparison and intervention groups were similar at baseline and similar to the populations of Ontario and British Columbia (18–20). In the intervention group, after randomization, the mean total energy intake decreased by an average of 48 kcal per day and the mean percentage of energy from fat decreased from 28.6% to 18.8%. Differences in the intake of total fat between groups persisted throughout, but the standardized difference was slightly smaller at 8–10 years than at 1–2 years. Intake of carbohydrate as a percentage of calories increased in the intervention group.

Despite substantial differences in mean fat intake between groups after randomization, there was substantial overlap between the groups. Fat intake in the intervention group was greater than 25% of calories in 14% of subjects at 1–2 years and in 32% of subjects at 8–10 years. Furthermore, in the comparison group 25% of subjects had a fat intake below 25%.
of calories at 1–2 years and 19% of subjects at 8–10 years (data not shown).

To assess dietary intakes using a second method that might better reflect usual intake, we collected 3 random 24-hour food recalls at a median of 9 years postrandomization (range, 5–17 years). Percentage of energy from fat from food recalls was 23.2% and 32.1%, respectively, in the intervention (n = 123) and comparison groups (n = 155) compared with 22.3% and 32.0% from food records in the same subjects.

As shown in Table 3, blood levels of TC and HDL-C, adjusted for age and weight, increased over time in the comparison group, and after an initial fall, also increased in the intervention group. Statistically significant differences in HDL-C between intervention and comparison groups persisted throughout the trial. Repeated measures analysis showed that there was a statistically significant interaction between randomized group and time period with levels of TC (P = 0.003) and HDL-C (P < 0.0001). Changes in both TC and HDL-C were significantly associated with changes in dietary fat intake.

Surveillance and breast cancer risk

Between randomization and the end of the trial in December 2005, women in the intervention and comparison groups had 16,695 and 17,020 mammograms and 349 and 404 surgical biopsies of the breast, respectively. Invasive breast cancer was detected in 118 women in the intervention group and 102 in the comparison group. Figure 2 shows breast cancer risk according to randomized group in a cohort analysis (left-hand column), and the case–control study nested in the cohort (right-hand column) in which we also examined associations of macronutrients with risk (see below).

**Table 1.** Selected baseline characteristics of subjects in intervention and comparison groups

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Mean (SD)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>2,341</td>
<td>2,349</td>
</tr>
<tr>
<td>Age, y</td>
<td>47.1 (6.4)</td>
<td>47.2 (6.4)</td>
</tr>
<tr>
<td>Ethnicity, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>90.0</td>
<td>91.3</td>
</tr>
<tr>
<td>Mixed race</td>
<td>2.3</td>
<td>2.1</td>
</tr>
<tr>
<td>Other</td>
<td>5.6</td>
<td>4.8</td>
</tr>
<tr>
<td>Unknown</td>
<td>2.1</td>
<td>1.8</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>62.2 (7.6)</td>
<td>62.3 (7.4)</td>
</tr>
<tr>
<td>Height, cm</td>
<td>163.2 (6.1)</td>
<td>163.4 (6.0)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>23.3 (2.3)</td>
<td>23.3 (2.3)</td>
</tr>
<tr>
<td>Age at menarche, y</td>
<td>12.8 (1.5)</td>
<td>12.9 (1.5)</td>
</tr>
<tr>
<td>Parity, % parous</td>
<td>73.8</td>
<td>74.5</td>
</tr>
<tr>
<td>Age at first live birth, y</td>
<td>25.8 (4.9)</td>
<td>26.3 (5.0)</td>
</tr>
<tr>
<td>Number of children for parous women</td>
<td>2.2 (0.9)</td>
<td>2.2 (0.8)</td>
</tr>
<tr>
<td>Marital status, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never married</td>
<td>9.6</td>
<td>9.5</td>
</tr>
<tr>
<td>Divorced or separated</td>
<td>11.8</td>
<td>11.9</td>
</tr>
<tr>
<td>Married now</td>
<td>76.5</td>
<td>76.7</td>
</tr>
<tr>
<td>Widowed</td>
<td>2.1</td>
<td>1.9</td>
</tr>
<tr>
<td>First-degree relatives with breast cancer, % yes</td>
<td>17.7</td>
<td>18.3</td>
</tr>
<tr>
<td>Menopausal status, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premenopausal</td>
<td>73.2</td>
<td>73.9</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>26.8</td>
<td>26.1</td>
</tr>
</tbody>
</table>

*a*Intervention group: data missing for height and BMI (n = 1), age at menarche (n = 6), age at first live birth (n = 3), and first-degree relatives with a diagnosis of breast cancer (n = 29).

*b*Comparison group: data missing for age at menarche (n = 3), age at first live birth (n = 1), and first-degree relatives with a diagnosis of breast cancer (n = 20).
## Table 2. Weight and selected nutrients according to group and time of data collection

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Group</th>
<th>Baseline</th>
<th>Years 1 or 2</th>
<th>Years 4 or 5 or 6</th>
<th>Years 8 or 9 or 10</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>STDiff</td>
<td>Mean</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>I</td>
<td>358.0</td>
<td>61.9</td>
<td>0.39</td>
<td>61.2</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>365.0</td>
<td>62.1</td>
<td>0.39</td>
<td>62.8</td>
</tr>
<tr>
<td>Energy, kcal</td>
<td>I</td>
<td>1,691.0</td>
<td>360</td>
<td>4.02</td>
<td>1,642</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>1,739.0</td>
<td>386</td>
<td>4.02</td>
<td>1,786</td>
</tr>
<tr>
<td>Total fat, %</td>
<td>I</td>
<td>28.60</td>
<td>6.35</td>
<td>2.20</td>
<td>18.81</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>29.67</td>
<td>6.69</td>
<td>2.20</td>
<td>20.54</td>
</tr>
<tr>
<td>Saturated fat, %</td>
<td>I</td>
<td>9.74</td>
<td>3.00</td>
<td>2.20</td>
<td>6.05</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>10.36</td>
<td>3.08</td>
<td>2.20</td>
<td>6.05</td>
</tr>
<tr>
<td>Polyunsaturated fat, %</td>
<td>I</td>
<td>5.70</td>
<td>1.83</td>
<td>0.88</td>
<td>5.70</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>5.58</td>
<td>1.84</td>
<td>0.88</td>
<td>5.68</td>
</tr>
<tr>
<td>Total carbohydrate, %</td>
<td>I</td>
<td>54.72</td>
<td>7.53</td>
<td>0.88</td>
<td>7.53</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>54.72</td>
<td>7.53</td>
<td>0.88</td>
<td>7.53</td>
</tr>
</tbody>
</table>

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**a** For intervention group and C for comparison group.

**b** Total number of subjects in randomized group who have food records at 4 time points.

**c** Standardized difference, which is the $t$ statistic from a 2-sample $t$ test with unequal variances.

**d** Intervention group: data missing for weight at baseline ($n = 1$), years 1 or 2 ($n = 1$), years 4 or 5 or 6 ($n = 2$), years 8 or 9 or 10 ($n = 1$). Comparison group: data missing for weight at years 8 or 9 or 10 ($n = 2$).
cancer (see footnote to Fig. 1) before December 2005 were censored on the date of diagnosis. As shown in Figure 2A (left-hand column), the adjusted hazard ratios comparing intervention and comparison groups were 1.19 (95% CI: 0.91–1.55) for all breast cancers, 1.06 (95% CI: 0.78–1.43). Results were similar for ER-positive cancers, and 1.44 (95% CI: 0.77–2.66) for ER-negative cancers (data not shown). Hazard ratios for all invasive cancers were 1.19 (95% CI: 0.87–1.63) for premenopausal and 1.17 (95% CI: 0.71–1.95) for postmenopausal women. Results were unchanged when dropouts were censored at the time of their leaving the trial (data not shown).

**Nested case–control analysis.** Figure 2B (right-hand column) shows adjusted odds ratios, comparing intervention and control groups, in a nested case–control study. Odds ratios were similar to the hazard ratios for the entire cohort and were 1.15 (95% CI: 0.83–1.60) for all cancers, 0.94 (95% CI: 0.64–1.36). Results were similar for ER-positive cancers, and 1.45 (95% CI: 0.63, 3.34) for ER-negative cancers (data not shown). Odds ratios for all invasive cancers were 1.19 (95% CI: 0.80–1.76) for premenopausal and 1.28 (95% CI: 0.68–2.42) for postmenopausal women (data not shown).

**Breast cancer risk according to intakes of weight, fat, and carbohydrate**

We examined in the nested case–control study the associations with breast cancer risk of weight, which the intervention sought to maintain, and fat and carbohydrate intakes, which the intervention sought to change. Intakes were determined using all available food records before diagnosis. Weight was known for all subjects throughout the trial and was examined in the entire the cohort. The associations of these variables with breast cancer risk were similar in intervention and comparison groups and the groups were combined in analysis. Results are shown in Figure 3.

Weight at baseline and after randomization was not associated with overall risk of breast cancer. However, a 10-kg difference in baseline weight was associated with a 25% difference in risk of ER-positive breast cancer, and after randomization, with an 18% difference in risk. Change in weight after randomization was not associated with breast cancer risk (data not shown). For BMI, the interquartile range was 25 to 22 and the associated odds ratios for ER-positive breast cancer were 1.24 (95% CI: 1.04–1.47) for baseline BMI and 1.18 (95% CI: 1.00–1.34) for postrandomization BMI. The interquartile odds ratio (IQOR) and 95% CIs for the associations of baseline weight with ER-positive breast cancer were 1.13 (0.9–1.42) for premenopausal women and 1.63 (1.14–2.34) for postmenopausal women.

After adjustment for weight, total fat intake after randomization was not significantly associated with risk of all invasive breast cancer, either in premenopausal (IQQR = 1.18; 95% CI: 0.81–1.71) or postmenopausal women (IQQR = 1.09; 95% CI: 0.58–2.06). However, after randomization, the interquartile difference of 18 g per day in total fat intake was not significantly associated with risk of ER-positive breast cancer but higher fat intake was inversely and significantly associated with a lower risk of ER-negative breast cancer.
(IQOR = 0.18; 95% CI: 0.05–0.60) that was seen with all subtypes of fat. Change in fat intake after randomization was not associated with risk of breast cancer (data not shown). Results were unchanged after adjustment for BMI rather than weight (data not shown).

Higher carbohydrate intake at baseline and after randomization was significantly associated with a lower risk of ER-positive cancers, but was not significantly associated with ER-negative breast cancer. Change in carbohydrate intake after randomization was not associated with risk of breast cancer (data not shown). Results were unchanged after adjustment for BMI rather than weight.

Discussion

In this randomized trial, we examined the effect on breast cancer risk of an intervention in which we provided motivated women at increased risk of breast cancer because of extensive mammographic density with long-term intensive individual dietary counseling to reduce intake of fat and to increase intake of carbohydrate. The nature and long duration of the trial, and the screening process before entry, resulted in only about 6% of eligible subjects being randomized.

Analysis of food records showed that baseline intakes were similar to those of women in the Canadian population. After randomization, there was a substantial reduction in intake of all types of fat in the intervention group, accompanied by changes in blood lipid levels. The food records of the comparison group showed no evidence of a reduction in fat intake and there was an average 9% to 10% difference in intake of percentage calories from fat between randomized groups throughout the trial. This difference in fat intake, the annual dropout rate, and the observed breast cancer risk were all close to those assumed in the sample size calculations. Surveillance for breast cancer was similar in both randomized groups, and active follow-up was complete for 98.3% of subjects randomized. However, the dietary intervention did not reduce breast cancer incidence over an average of 10 years. Rather, there was in the intervention group a trend to a higher risk of breast cancer (hazard ratio = 1.19) that was not statistically significant (95% CI: 0.91–1.55).

Limitations of the present study include lack of statistical power to detect any but large effects, a degree of dietary overlap between intervention and comparison groups, and limited generalizability. The statistical power is limited by the number of cancers observed, and we cannot exclude the smaller effects on breast cancer incidence suggested by the Women’s Health Initiative (WHI) trial (21). Despite average differences in fat intake between intervention and comparison groups that were close to those planned, the analysis of food records showed substantial overlap between the groups in intakes of both fat and carbohydrate that persisted throughout the trial and evidence of some increase in fat intake in the intervention group in the last years of the trial. We selected for
randomization, women at increased risk of breast cancer who had completed screening procedures and we provided individual dietary counseling. These features of the trial design were intended to increase the probability of finding an effect of dietary fat reduction on breast cancer risk if such exists. However, the highly selected nature of the cohort, which represented only 6% of the original group approached, means that inferences from these analyses should be made with caution. Furthermore, only adult women were enrolled and we cannot exclude the possibility that fat intake in early life may influence later risk of breast cancer.

The present trial differs from the much larger WHI randomized trial of dietary intervention in a number of ways. The WHI selected postmenopausal women from the general population rather than women at increased risk of breast cancer, screened for baseline fat intake, and used group rather than individual dietary counseling (21). The comparison of intervention and control groups gave a hazard ratio of 0.91 (95% CI: 0.83–1.01). Average body weight at baseline in the WHI trial was 77 kg compared with 62 kg in the present trial, in which women whose BMI was within a healthy range were selected. The goal of the dietary intervention in the present trial was to maintain baseline caloric intake, and at 1 year, there was a 1.6-kg difference in weight between intervention and comparison groups in the present trial compared with a 2.2-kg difference in the WHI. The greater difference in weight change between groups may, in part, contribute to the nonsignificant trend toward lower risk in the WHI intervention group.

Reduction in dietary fat intake reduces blood levels of HDL-C (22). In the present trial, HDL-C at years 1–2 was 4.3% (0.07 mmol/L) lower in the intervention group than at baseline and remained significantly lower than in the control group throughout the trial. HDL-C decreased only 0.7% (0.07 mmol/L) lower in the intervention group than at baseline and remained significantly lower than in the control group throughout the trial. HDL-C decreased only 0.7% (0.07 mmol/L) lower in the intervention group than at baseline and remained significantly lower than in the control group throughout the trial. HDL-C decreased only 0.7% (0.07 mmol/L) lower in the intervention group than at baseline and remained significantly lower than in the control group throughout the trial. HDL-C decreased only 0.7% (0.07 mmol/L) lower in the intervention group than at baseline and remained significantly lower than in the control group throughout the trial.

Figure 3. Associations of weight and selected nutrients with breast cancer risk; IQOR (95% confidence interval). *, the effect of baseline weight was analyzed in the cohort of the trial, calculated by hazard ratios from Cox proportional hazards model, adjusted for risk factors listed above and trial site (site was omitted for ER-negative cancers because of small numbers). Interquartile range obtained from baseline weight of all subjects in the cohort who did not have a diagnosis of breast cancer. **, the effect of postrandomization weight was analyzed similarly as in *, whereas that obtained with annual weight measurements (including baseline) was treated as a time-dependent variable. Interquartile range obtained from the average postrandomization weight of all subjects in the cohort who did not have a diagnosis of breast cancer. Data missing for ER status (n = 11), female hormone use (n = 1), first-degree relatives with a diagnosis of breast cancer (n = 5), age at menarche (n = 3), age at first live birth (1 parous, 205 nonparous), postrandomization weight (n = 29), and postrandomization macronutrients (n = 22).
25th percentiles of weight and BMI seen in the trial suggest that attainable long-term changes in weight or BMI may achieve reductions in risk of breast cancer, particularly of ER-positive cancers. However, our findings suggest that a sustained reduction in dietary fat intake did not reduce risk of breast cancer in women with extensive mammographic density.

Appendix: The Canadian Diet and Breast Cancer Prevention Study Group

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**References**


**Disclosure of Potential Conflicts of Interest**

No potential conflicts of interests were disclosed.

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