Nutritional factors associated with benign breast disease etiology: a case-control study¹–³

Flora Lubin, Yochanan Wax, Elaine Ron, Maurice Black, Angela Chetrit, Nechama Rosen, Esther Alfantary, and Baruch Modan

ABSTRACT  Between 1977 and 1980, 854 biopsied cases of benign breast disease (BBD) and 755 matched surgical and 723 matched neighborhood controls subjects were interviewed in Israel by using a detailed food frequency questionnaire. Cases were classified according to degree of ductal atypia (Black-Chablon grading system). Women with atypical lesions (grades ≥ 3) reported a higher intake of all types of foods compared with both control series. Further analyses indicated that the increased consumption was due primarily to foods containing ≥ 10% fat. Odds ratios associated with the highest fat consumption quartile were close to 3.0. There was a trend for increasing saturated fatty acid consumption with increasing ductal atypia. After adjusting for hormonal and demographic confounders, the association with fat intake was strengthened. Because atypical BBD has been reported to be a precursor of breast cancer, our findings lend support to the hypothesis that dietary fat is a risk factor for breast cancer.  


KEY WORDS  Benign breast disease, breast neoplasms, diet, ductal atypia

Introduction

Mammary carcinogenesis appears to be a stepwise process where the development of invasive breast cancer frequently proceeds from recognizable benign precursor breast lesions (1–5). Although the mechanism has not been clearly established, recent studies provide suggestive evidence that the risk of developing breast cancer is greatest among women with epithelial hyperplasia, particularly when accompanied by ductal atypia (1, 3, 4). Because this process may take several years (2, 4, 5) it is important to identify risk factors that may prevent the transformation from benign to malignant neoplastic cells. Thus by studying the epidemiology of specific histologic types of benign breast disease (BBD) we may be able to improve our understanding of the etiology of breast cancer.

Animal experimentation as well as epidemiologic studies have repeatedly provided evidence that nutrition plays an important role in tumorigenesis (6, 7). In animals high-fat diets enhance the yield of spontaneous and chemically induced mammary tumors (6–12) whereas in humans fat intake has been shown to be a risk factor for breast cancer in some studies (13–17) but not in others (18–20). A recent review of the subject was published by Rohan and Bain (21). To our knowledge nutrition has not yet been studied in humans in relation to BBD.

We hypothesized that high fat consumption may be a risk factor for benign breast lesions, in particular, those histopathological types with mild to severe proliferation and atypical changes designated by Black et al (3) as precancerous mastopathy or in situ carcinoma. To evaluate this hypothesis we conducted a dietary case-control study of 854 cases of BBD, 755 surgical control subjects (SCs), and 723 neighborhood control subjects (NCs).

Methods

Study population

Between 1977 and 1980 a specially trained nurse reviewed the records of the operating rooms and pathology departments of the eight major hospitals in the central area of Israel. She abstracted the names and identifying data of all potential BBD cases and SCs. After the histopathological diagnosis was confirmed, cases were selected for inclusion in the study according to a predetermined sampling frame by type of histology, degree of ductal atypia, age, and ethnic origin. Patients gave informed consent and the study was approved by the Institutional Review Board of the Chaim Sheba Medical Center.

The study included two matched control series: SCs NCs.

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SCs who had nonmalignant, nongastrointestinal, nongynecological diseases requiring short hospitalizations were selected to match the short hospitalization of BBD patients. The majority of control subjects were hospitalized for hernia (20%), varicose veins (18%), orthopedic surgery (17%), and appendicitis (16%). NCs were selected from national voting lists and matched to a case living in the same or adjacent voting tract. Voting tracts encompass a population of ~500 adults, generally with similar socioeconomic status. All control subjects were matched to cases by age (± 5 y), country of origin, and length of residence in Israel (± 5 y). If there was more than one potential NC subject, the control subject closest in age was chosen. Cases and control subjects having had past BBD were not excluded from the study.

At least four attempts were made, each at a different time of day, to interview study subjects at home. If > 6 mo elapsed between study enrollment and interview, the subject was excluded. The overall response rate was 73%; 75%, 78%, and 66% for cases, SCs, and NCs, respectively. Nonresponse was due to patient refusal (cases, 3%; both control groups, 2%), incorrect address (cases, 13%; SCs, 12%; NCs, 26%), or lack of an interview within 6 mo of entry (cases and SCs, 8%; NCs, 6%).

The final study population included 854 cases, 755 SCs, and 723 NCs. Because we were unable to match for so many characteristics, two control subjects to each case, the matched analyses presented in this paper refer to the 755 pairs of cases and SCs and 723 pairs of cases and NCs.

**Questionnaire**

Trained female interviewers conducted standardized home interviews lasting ~1.5 h. Data were collected on suspected risk factors for BBD, as well as on 250 food and beverage items eaten by the various ethnic groups in Israel. Subjects were asked about usual consumption frequency of each food item. Frequencies were classified as never, seldom (once a month or less), several times a month (twice monthly to once weekly), several times a week (two to five times a week), or daily (6 or 7 d/wk). For daily consumption, number of times a day was requested. Questions first referred to consumption 6 mo before the interview (present consumption). In addition, for each food item the interviewee was asked whether she had changed her consumption frequency in the last 10 y. If yes, the frequency before the change was also recorded (past consumption). Interview quality was periodically examined in the field as well as by conducting mock interviews in the presence of the study staff.

**Histologic methods**

Two or more pathology specimens cut from the same block and adjacent to those used for hospital diagnosis were independently classified by the study pathologists. Cases were classified according to conventional histologic categories (fibroadenoma, microcystic, proliferative, precancerous mastopathy, and in situ) and by the grading system proposed by Black et al (3, 22), which reflects the degree of atypia of extra- and intralobular mammary ducts (grade 1 = normotypic, normoplastic; grade 2 = normotypic, hyperplastic; grades 3 and 4 = mild to moderate atypia; and grade 5 = marked atypia, in situ carcinoma).

**Analysis**

Reported consumption frequencies for each food item were converted into average daily consumption scores. Based on the distribution of the scores for both case and control populations, quartiles of consumption levels were defined. Individual food items were grouped according to their principal food component (23, 24) into four major food groups: 1) foods containing ≥ 10% fat, 2) foods with ≥ 10% animal protein, 3) foods with ≥ 10% carbohydrates, and 4) food items containing dietary fiber. These groups are not mutually exclusive and certain foods are included in several groups. In addition, foods containing ≥ 10% fat were subclassified as those whose fatty acids were at least 40% saturated, ≥ 40% monounsaturated or polyunsaturated, or contained at least 50 mg cholestererl/100 g food. We also analyzed the role of carbohydrates, proteins, and dietary fiber, including and excluding foods containing ≥ 10% fat. It is difficult to evaluate energy intake by using a frequency questionnaire. As an alternative method, we therefore combined all food items from the carbohydrate, protein, and fat foods groups into what we defined as the energy food group.

Because a longer period of exposure to a nutritional factor would be expected to be of more importance biologically, data are presented for past consumption. To reduce possible disease misclassification associated with having some control subjects with previous BBD, we also analyzed the data excluding control subjects with a history of BBD (67 pairs).

Odds ratios (ORs) of BBD associated with the quartiles of daily consumption frequency of each food group were estimated from the number of discordant pairs of cases and control subjects by both the observed ORs and the maximum likelihood estimates under the consistency assumption as derived from the conditional logistic analysis (25). Corresponding approximate 95% confidence intervals were derived from the distribution of the log of the OR (25) and from the asymptotic normal distribution of maximum likelihood estimates (25).

Conditional logistic-regression analysis was used to adjust the risk associated with consumption of one food group to the risk associated with consumption of other food groups and to control for the following potential confounding variables: menopausal status (premenopausal, perimenopausal, or postmenopausal); oral contraceptive use (never; 1–2 y; > 2 y); number of livebirths (0 ≥ 1); previous BBD (yes; no); body mass index ([weight (kg)/height² (cm)], ≤ 24, > 25); and education (0–11 y, ≥ 12 y). The model indices were estimated by the conditional maximum likelihood method (25). Significance tests were derived from the asymptotic normal distribution of the conditional maximum likelihood estimates. The significance of the linear trend of the log of the ORs associated with the four consumption levels was assessed by the corresponding linear contrast. A log-linear analysis (26) was used to assess the differences in response rates between cases and control subjects.

Analyses were performed by using the atypia grading system of Black et al (3) and by conventional histopathologic diagnosis. There was, however, considerable overlap in the two systems because the majority of the fibroadenomas were classified as grade 1, proliferative disease as grades 2 or 3, and precancerous mastopathy as grades 3 or 4, and all in situ as grade 5. Part of the analysis was also performed excluding fibroadenoma cases from Black's grade 1 category, but there was virtually no difference in the results. In this paper results are presented by degree of atypia. Grades 3–5 were combined for analysis because they all included patients with ductal atypia and the number of cases was small (n = 70, 17, and 20 for grades 3, 4, and 5, respectively). The hypothesis that the risk associated with higher food intake increases with degree of ductal atypia was assessed by testing the linear trend in the log of the ORs of highest (high quartile) consumption frequency quartile vs the lowest (low quartile) consumption frequency quartile, with the three ductal grade categories.
TABLE 1
Crude odds ratios of benign breast disease associated with frequency of consumption of major dietary food groups by the ductal grading system of Black et al (3)*

<table>
<thead>
<tr>
<th>Degree of ductal atypia</th>
<th>Consumption quartile</th>
<th>Foods containing†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>≥ 10% Fats</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C-SC‡</td>
</tr>
<tr>
<td>Grade 1, normotypic</td>
<td>I (low)</td>
<td>1.0 [43]</td>
</tr>
<tr>
<td>normoplastic</td>
<td>II</td>
<td>1.0 [79]</td>
</tr>
<tr>
<td>(n = 627)</td>
<td>III</td>
<td>0.9 [53]</td>
</tr>
<tr>
<td></td>
<td>IV (high)</td>
<td>1.0 [61]</td>
</tr>
</tbody>
</table>

* Number of discordant pairs in brackets.
† Number of food items in each food group: ≥ 10% fats, 50; ≥ 10% carbohydrates, 67; ≥ 10% animal fats, 46; and food containing fiber, 82.
‡ Cases compared with surgical control subjects.
§ Cases compared with neighborhood control subjects.
|| Lower 95% confidence limit is above unity.

Results

The crude ORs presented in Table 1 indicate a weak association between grades 1 and 2 (normotypic) BBD and high frequency of consumption of some of the following food groups: foods containing ≥ 10% fats, ≥ 10% animal protein, ≥ 10% carbohydrates, as well as all foods containing fiber. The association, however, does not hold true for both SCs and NCs, does not suggest a dose-response relationship within each grading category, and risks do not increase from grade 1 to grade 2. An elevated risk in all food groups studied is observed for grade 3+ (mild to marked atypia). This association shows a dose-response relationship and is consistent with respect to both control groups.

The increased intake of all food groups among women with grade 3+ BBD as compared with both control groups suggests an association with higher energy intake. To evaluate this hypothesis food items were combined into an energy food group (see Methods). For grades 1 and 2 the logistic ORs for the highest level of consumption are barely above unity but for patients with grade 3+, a two-fold increased risk of BBD is seen among the highest eaters (Table 2). Because of these results we confined further analysis to the atypical grade 3+ BBD subgroup. Because many foods contain ≥ 10% fat, in addition to other components, an overlap of food items in the different food groups exists. To assess the specific effect of carbohydrates, proteins, and fiber, foods containing ≥ 10% fat were excluded from these food groups. Table 3 shows that the risks become substantially smaller, particularly for protein and carbohydrates. These findings suggest that the elevated risks seen in Tables 1 and 2 were in great part due to fat rather than the other food components. Analysis was repeated excluding the control subjects who had had previous BBD and the results remain essentially the same (not shown).

The estimated ORs associated with foods characterized by different types of fat indicate that each of the four types of fat are risk factors for grade 3+ BBD (Table 4). ORs for the highest consumption frequency are close to 3.0 for each of the fat components studied although saturated fatty acids exhibited a more stable trend for increasing risk with increasing levels of intake.

To take into account the correlation between intake of high-fat foods and low-fat foods, logistic analyses were done adjusting for the consumption effect of each food group on the others. In addition, analyses were also adjusted for selected hormonal and demographic factors because dietary habits may be related to life style (Table 5). Included in this analysis were the following food groups: 1) items containing ≥ 10% fat; 2) items containing saturated fatty acids; 3) items containing ≥ 10% fat, which were not included in the saturated fatty acid food group; 4) items containing carbohydrates and proteins, which were not included in the ≥ 10% fat food group; and 5) all food items containing fiber. The results suggest that saturated fatty acids, but not the other food groups, are associated with grade 3 BBD.

Discussion

Results from this study indicate an association between high food intake and grade 3+ BBD. This increased risk was due mostly to the consumption of high levels of fat, particularly saturated fatty acids, by the sub-
TABLE 2
Odds ratios for benign breast disease (BBD) associated with frequency of consumption of energy food group items by degree of ductal atypia*

<table>
<thead>
<tr>
<th>Consumption quartile</th>
<th>C-SC†</th>
<th>C-NC‡</th>
<th>C-SC</th>
<th>C-NC</th>
<th>C-SC</th>
<th>C-NC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grades 1 and 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I (low)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>II</td>
<td>1.6</td>
<td>1.0</td>
<td>1.5</td>
<td>1.0</td>
<td>1.7</td>
<td>1.2</td>
</tr>
<tr>
<td>III</td>
<td>1.4</td>
<td>1.1</td>
<td>1.4</td>
<td>1.1</td>
<td>1.3</td>
<td>0.8</td>
</tr>
<tr>
<td>IV (high)</td>
<td>1.3</td>
<td>1.3</td>
<td>1.2</td>
<td>1.2</td>
<td>2.1</td>
<td>2.2</td>
</tr>
<tr>
<td>Grades ≥ 3</td>
<td>(1.0–1.8)$</td>
<td>(0.9–1.7)</td>
<td>(0.9–1.7)</td>
<td>(0.9–4.6)</td>
<td>(1.0–4.9)</td>
<td></td>
</tr>
</tbody>
</table>

* Derived from the conditional logistic-regression analysis.
† Cases compared with surgical control subjects.
‡ Cases compared with neighborhood control subjects.
§ 95% confidence interval for the odds ratio of the highest vs the lowest level of consumption.

TABLE 3
Odds ratios for atypic grades 3+ benign breast disease associated with frequency of consumption of major dietary food groups excluding foods containing ≥ 10% fat*

<table>
<thead>
<tr>
<th>Foods containing</th>
<th>≥ 10% Protein</th>
<th>≥ 10% Carbohydrates</th>
<th>Fiber</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consumption quartile</td>
<td>C-SC†</td>
<td>C-NC‡</td>
<td>C-SC</td>
</tr>
<tr>
<td>I (low)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>II</td>
<td>0.7</td>
<td>1.1</td>
<td>0.9</td>
</tr>
<tr>
<td>III</td>
<td>0.4</td>
<td>0.5</td>
<td>2.6</td>
</tr>
<tr>
<td>IV (high)</td>
<td>1.1</td>
<td>1.2</td>
<td>1.1</td>
</tr>
<tr>
<td>(0.5–2.7)$</td>
<td>(0.5–2.7)</td>
<td>(0.5–2.4)</td>
<td>(0.8–4.3)</td>
</tr>
</tbody>
</table>

* Derived from the conditional logistic-regression analysis.
† Cases compared with surgical control subjects.
‡ Cases compared with neighborhood control subjects.
§ 95% Confidence interval for the odds ratio of the highest vs lowest level of consumption.
assessed by analyzing the intake of the energy food group excluding foods containing \( \geq 10\% \) fat, as well as foods containing \( \geq 10\% \) fat from sources other than saturated fatty acids. In a quantified dietary study of colon cancer, Howe et al. (28) used a similar approach to assess the risk of saturated fatty acids, as differentiated from that of total caloric intake.

As in all case-control studies there are undoubtedly problems with long-term dietary recall. However, studies of BBD are less susceptible to recall bias because the women are relatively young and the disease itself is not preceded by a change in diet. Furthermore, because patients did not know their ductal grading, there should be no substantial differences in recall bias among case subgroups. A very similar study instrument was used in previous studies (29) and a reliability appraisal showed that only 1% of the food items had a reliability of < 70%. Using this methodology, we have been able to detect dietary risk factors for other cancer sites (17, 29, 30) and our results were in accord with findings from other studies (13, 14, 21).

Although the response rate for NCs is a reason for concern, a high proportion of the nonresponse was due to nonlocation of NCs whose addresses were obtained solely from the Central Population Registry. In general, this is due to an individual recently moving and neglecting to notify the Central Population Registry. Nonlocation was less of a problem for cases and SCs because an address was available from their recent hospital admissions record. A log-linear model analysis (26) revealed a similar age and ethnic distribution \((p = 0.13)\) among cases and control subjects who had incorrect addresses, but when both incorrect address and refusals were considered, SCs aged \( > 50 \) y were overrepresented \((p < 0.05)\). However, because the study results were the same with either control group, it is unlikely that the nonresponse unduly influenced the findings.

Given the limitations discussed, our findings are

### TABLE 4
Odds ratios for atypic benign breast disease grade 3+ associated with frequency of consumption, by specific fat groups*

<table>
<thead>
<tr>
<th>Consumption quartile</th>
<th>Saturated†</th>
<th>Monounsaturated†</th>
<th>Polyunsaturated†</th>
<th>Cholesterol†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C-SC‡</td>
<td>C-NC§</td>
<td>C-SC</td>
<td>C-NC</td>
</tr>
<tr>
<td>I (low)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>II</td>
<td>1.9</td>
<td>1.4</td>
<td>1.6</td>
<td>1.5</td>
</tr>
<tr>
<td>III</td>
<td>2.0</td>
<td>1.5</td>
<td>0.8</td>
<td>1.1</td>
</tr>
<tr>
<td>IV (high)</td>
<td>3.6</td>
<td>3.8</td>
<td>2.2</td>
<td>3.1</td>
</tr>
</tbody>
</table>

\( (1.4-9.4)\) \( (1.3-10.7)\) \( (0.9-3.1)\) \( (1.2-7.9)\) \( (1.2-6.4)\) \( (1.1-6.5)\) \( (1.1-6.6)\) \( (1.4-7.6)\)

\( p \) value for linear trend

|                      | 0.01 | 0.01 | 0.08 | 0.18 | 0.02 | 0.04 | 0.05 | 0.10 |

* Derived from the conditional logistic-regression analysis.
† Foods containing > 40% saturated, monounsaturated, or polyunsaturated fatty acids. Number of food items in each fat group: saturated, 16; monounsaturated, 16; polyunsaturated, 9; and cholesterol, 57.
‡ Cases compared with surgical control subjects.
§ Cases compared with neighborhood control subjects.
|| 95% Confidence interval for odds ratio of highest vs lowest level of consumption.

### TABLE 5
Odds ratios for grade 3+ benign breast disease (BBD) associated with specific dietary food groups adjusted for nonnutritional factors*

<table>
<thead>
<tr>
<th>Consumption quartile</th>
<th>≥ 10% Fat</th>
<th>Saturated fatty acid</th>
<th>≥ 10% Fat (excluding saturated fatty acids)</th>
<th>Energy food group (excluding ≥ 10% fat)</th>
<th>Fiber</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (low)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>II</td>
<td>1.1</td>
<td>2.0</td>
<td>1.6</td>
<td>0.6</td>
<td>3.6</td>
</tr>
<tr>
<td>III</td>
<td>1.2</td>
<td>1.4</td>
<td>0.4</td>
<td>1.2</td>
<td>0.3</td>
</tr>
<tr>
<td>IV (high)</td>
<td>7.6</td>
<td>2.9</td>
<td>1.3</td>
<td>1.0</td>
<td>0.7</td>
</tr>
</tbody>
</table>

\( (1.4-40.2)\) \( (1.0-9.1)\) \( (0.5-3.5)\) \( (0.2-4.2)\) \( (0.1-4.0)\)

* Derived from the conditional logistic regression analysis adjusting for other food groups and menopausal status, oral contraceptive use, number of children, previous BBD, body mass index, and years of education. Odds ratios of cases compared with both control groups combined.
† 95% Confidence interval for the odds ratio of the highest vs lowest level of consumption.
stretched because 1) associations were similar when cases were compared with either of the matched control groups, reducing the possibility that they could occur by chance; 2) results were consistent when different analytical approaches were used; 3) the association with fat was seen among cases having grade 3+ BBD, which is the type of BBD most closely linked to breast cancer; 4) the analysis was also performed excluding control subjects who reported BBD in the past, to reduce effects of disease misclassification and 5) adjustment for potential nonnutritional confounding strengthened the findings.

BBD is a general term that includes a wide variety of degenerative and proliferative lesions with and without structural atypia (1, 2). Many studies have shown an association between invasive and noninvasive breast lesions but the biological relationships may have been obscured by the tendency to designate most noninvasive lesions (with the exception of fibroadenoma) as fibrocystic disease regardless of distinctive differences in proliferative and atypical features. Direct and inferential evidence indicates that the precursor to invasive progression is impeded by cell-mediated immunity to a particular immunogen that is characteristically expressed in the preinvasive phase of mammary carcinogenesis (31, 32).

Confirmation of our findings from other studies is needed. Nevertheless, our results suggest that fat consumption is implicated in breast tumorigenesis, particularly in what appears to be precursor breast cancer lesions.

We thank Dr. Howard Cuckle for providing some results from his quantified analyses. We also thank the interviewing staff for their dedication; the chiefs of the Surgery and Pathology Departments of Belinson, Sharon, Meir, Wolfson, Hadassah, Chaim Sheba, Rambam, and Ichilov Hospitals for their cooperation; and Elizabeth Anderson for her continuing support.

References