Introduction

Breast cancer is the most frequently diagnosed malignancy, and the second commonest cause of cancer deaths amongst women in industrialized countries. Incidence rates have been increasing for decades. Breast cancer currently afflicts almost 40,000 women in the UK each year, with the lifetime risk for each woman in the UK estimated at 1:9.1 High penetrance susceptibility genes such as BRCA1 and BRCA2 account for only 5% of breast cancer cases; the factors responsible for the other 95% remain largely obscure. Age, family history, and various menstrual and reproductive factors are known to influence an individual's risk of developing breast cancer, but we are currently unable to ascribe a cause for the vast majority of cases of breast cancer. There are pointers to environmental factors: populations that migrate from low- to high-incidence countries often develop breast cancer rates that approximate those of the host country.2,3 One environmental factor that may be linked to the risk of developing breast cancer is diet.

There has been public interest in the possible role of diet in the development of cancers in general. Intake of dietary fibre, trace elements, rare metals, vitamins, retinoids, carotenoids and micronutrients have all been associated with protection against cancer risk. The first major scientific alarm calls to draw attention to the significance of diet as a cause for cancer were probably those published in the 1970s by the WHO in surveys of cancer incidence in five continents. Later in the 1970s, the relationship between dietary fat intake and cancer intensified these alarm calls, as the large international differences in rates of many cancers were noted to be strongly correlated with apparent per capita fat consumption.4,5 There was a particularly strong association with breast cancer. Can eating foods high in fat really cause breast cancer? Despite the potential for confounding (for example, countries that have higher per capita fat intake also tend to have lower age at menarche, later age at first birth, and lower parity, all risk factors for breast cancer), the media has been quick to jump on the 'fat causes breast cancer' bandwagon. This article addresses the available evidence as to whether an association exists between dietary fat and breast cancer. Are we in a position to advise women on how to lower their risk of developing breast cancer by manipulating their diet?

Pre-clinical studies

The first demonstration that a high-fat diet promoted mammary tumour growth in mice was over 50 years ago.6 Other animal models have subsequently supported this finding. Indeed, a meta-analysis of 100 animal studies supports a tumour-promoting effect of dietary fat.7 There is also evidence from rat and mouse models that there may be a threshold effect in the amount of fat required for tumorigenesis.8,9 One of the problems with many animal studies, however, is the difficulty in distinguishing the effects of fat intake from total caloric intake.
Some studies have looked at specific types of fat. For example, polyunsaturated fatty acids such as linoleic acid (which is found in vegetable oils and is a precursor of prostaglandins) may promote tumour growth. Monounsaturated fatty acids, olive oil and marine fatty acids may have the opposite effect. Long-chain omega-3 fatty acids and omega-9 fatty acids inhibit the growth of cancer cells, and omega-6 fatty acids may encourage cancer proliferation.

Epidemiological studies

International correlates between fat consumption and breast cancer mortality form the basis for the dietary fat hypothesis. This hypothesis was examined in a study of 65 Chinese counties, in which dietary assessment and mortality were measured using standardized methods. Per capita fat intake varied from 6% to 25%, but there was only a weak positive association between fat intake and breast cancer mortality. In the four counties where approximately 25% of energy intake was from fat, breast cancer rates were far below those of US women with similar fat intake.

Body mass index and risk

Recently, data from 73,542 pre-menopausal and 103,344 post-menopausal women from nine European countries taking part in the European Prospective Investigation into Cancer and Nutrition (EPIC) study were used to assess the association of weight, body mass index (BMI), and waist and hip circumferences with breast cancer risk. In post-menopausal women who had no history of hormone replacement therapy use, weight, BMI and hip circumference were positively correlated with breast cancer risk. Obese women (BMI >30) had a 31% excess risk, compared to women with BMI <25). Waist–hip ratio and waist circumference were not related to excess risk when adjusted for BMI. In pre-menopausal women, hip circumference was significantly positively correlated with breast cancer after accounting for BMI; weight and BMI itself showed non-significant inverse associations with risk.

Retrospective studies

A number of case-control studies have investigated the effect of dietary fat on breast cancer. In a pooled analysis of 12 studies that included 4312 cases and 5798 controls, there was a significant association between breast cancer risk and increasing total fat. The pooled relative risk was 1.35 for a 100 g increase in daily total fat intake, and the risk was greatest for postmenopausal women. This conclusion may be problematic because the analyses were retrospective, and could be criticized because of the problems associated with relying on memory to describe past diet. The largest case-control studies, which were of 2024 women with breast cancer and 2564 controls, also failed to demonstrate an association between fat intake and breast cancer risk. These two series were not included in the review.

Prospective studies

A substantial body of data from cohort studies is now available to assess the possible role of dietary fat in breast cancer. Because of the prospective design of these studies, most of the methodological biases of case-control studies are avoided. The US Nurses’ Health Study was among the first of these prospective studies to assess the fat and breast cancer hypothesis. The first publication on dietary fat and breast cancer from the Study in 1987 included 4 years of follow-up data and approximately 600 cases of breast cancer. No association was found, but rather the opposite: the women in the top quintile of fat intake had a relative risk of 0.85 vs. the lowest quintile. The study’s most recent analysis also failed to demonstrate an association between higher fat intake and increased risk of breast cancer. In fact, a weak and inverse trend was found, which was not statistically significant. The range of fat intake in this large study was broad and consisted of <20% to >55% of energy intake from fat. For women who reported <15% of their energy from fat, a slight but significant risk in breast cancer was found (RR 1.15). There were inverse associations of breast cancer risk with polyunsaturated and monounsaturated fats, and with linoleic acid and linolenic acid. Omega-3 fatty acid intake from fish was associated with increased risk.

A combined analysis of several large prospective studies was published in 1996, and included 5000 cases of breast cancer. This also failed to find an association between total dietary intake and breast cancer risk. A Swedish cohort study involving 61,471 women with 674 cases of breast cancer occurring during a mean follow-up of 4.2 years again found no overall relation between fat intake and breast cancer, although mono-unsaturated fat had a significant protective effect, and an increased risk was found with polyunsaturated fat. A protective role of mono-unsaturated fat was also suggested by three further cohort studies conducted in Greece, Spain and Italy, where women with high intakes of olive oil, which is rich in mono-unsaturated fatty acid, had reduced risks of breast cancer.
In the Data from the US Breast Cancer Detection Demonstration Project Follow-up Cohort Study involving over 40,000 post-menopausal women with approximately 1000 cases of breast cancer during a mean follow-up period of 5.3 years, demonstrated no association between total fat or any fat subtype and breast cancer. A further analysis found a significant positive association among women with no history of benign breast disease.

Boyd et al. in 2003 published a meta-analysis of all case-control and cohort studies previously conducted that examined the association of dietary fat, or fat-containing foods, with risk of breast cancer. A total of 45 risk estimates for total fat were obtained. The relative risk, comparing the highest and lowest levels of intake of total fat, was 1.13 with significantly increased risk for saturated fat and meat intake.

**Dietary fat and survival from breast cancer**

Patients frequently change their lifestyle after a diagnosis of cancer, hoping that this will improve their chance for survival. Lifestyle changes are most commonly centred around diet. There have been very few studies of dietary fat intake and breast cancer survival, and all have substantial limitations. Naturally, most were not specifically designed for this purpose, and refer to premorbid diet assessed either before or at about the time of diagnosis, and most studies have been small. The conclusions are not definitive. The most significant in terms of patient numbers was the Nurses’ Health Study, which examined the relation between dietary factors and survival. Approximately 2000 women with breast cancer were included. No significant survival difference was observed for women consuming a low-fat diet after a diagnosis of breast cancer, though a modest effect could not be excluded.

**Dietary fat and risk of breast cancer relapse**

The results of a large, prospective, randomized study investigating whether a low-fat diet could reduce breast cancer recurrence rates in post-menopausal women who had been treated for early-stage breast cancer were presented at ASCO 2005, amid much publicity. Between 1994 and 2001, the study enrolled 2437 women who in the previous year had had breast cancer surgery followed by therapy appropriate to their particular cancer. The women, whose average age was 62 years, were randomly assigned to one of two dietary groups. One group was asked to follow their standard diet. Women in this group met with a nutritional counsellor periodically, but were not urged to change their diet, which contained an average of about 51 g fat a day (about 40% of total calories from fat). Women in the second group were asked to modify their diet to reduce their consumption of dietary fat to 20% of total calories. Each woman received eight one-on-one dietary counselling sessions with a nutritionist (one every other week for 16 weeks). After that, they saw the nutritionist every 3 months for the duration of the study. The nutritionist offered support and advice about reducing dietary fat consumption by, for example, using less oil when cooking, increasing intake of fruit and vegetables, controlling portion sizes, and so on. The diet eaten by women in the low-fat group contained an average of 33 g fat a day. Women in both groups kept diaries in which they recorded their daily food consumption. In addition, trained interviewers periodically contacted all of the women by phone to question them about what they were eating.

After a median of 5 years follow-up, breast cancer had recurred in 9.8% of those on the low-fat diet and 12.4% of those on the standard diet: a 24% reduction in the risk of recurrence for the women on the low-fat diet. The largest risk reduction (42%) was seen among women on the low-fat diet whose tumours were oestrogen-receptor-negative. Although weight loss was not a goal of the study, women who followed the low-fat diet lost an average of four pounds.

The investigators admitted they could not be certain that the low-fat diet was responsible for the lower rate of recurrence in the women assigned to that group. Other factors, such as the modest weight loss seen in the low-fat group, or increased consumption of fruit and vegetables, may have contributed to the outcome.

**Diet and oestrogen levels**

Oestrogen levels in the blood are a factor for breast cancer risk, and thus the effects of fat and other dietary factors on oestrogen levels are of potential interest. Vegetarian women (who consume higher levels of fibre and lower amounts of fat) have lower blood levels and reduced urinary excretion of oestrogens. A meta-analysis has suggested that reduction in dietary fat may reduce plasma oestrogen levels, but the study design has been criticized because of its duration, control selection, and methodology. In a large randomized trial
among post-menopausal women with a previous diagnosis of breast cancer, reduction in dietary fat did not affect oestradiol levels when analysed appropriately.\(^{33}\)

**Adolescent diet and breast cancer risk**

There is growing interest in the possible role of dietary and nutritional influences earlier in life on breast carcinogenesis. This interest is indicated partly by evidence that adult height and weight are positively associated with risk of breast cancer.\(^{34,35}\) Among other factors, adult height may reflect the nutritional milieu and availability of food energy during growth up to the time of attainment of maximal height. The observation that women who had attained their maximal adult height at 18 years or over were at decreased risk of breast cancer compared with women who reached maximal height by age 13 years,\(^{36}\) strengthens the argument that nutritional factors during adolescence may influence risk later in life. Nutritional factors may also influence the age of menarche, another factor known to be associated with the risk of breast cancer. A German study found high fat intake to be linked to early onset of menarche,\(^{37}\) although no such association was found in US and Canadian cohorts.\(^{38,39}\)

**Conclusion**

There is a need to address the issue of the primary prevention of breast cancer, and the potential gains from this approach could be immense. We have seen the benefits of the approach of primary prevention in other malignancies, such as lung cancer. But is there sufficient data to allow us to conclude whether dietary modification for the reduction of breast cancer risk is appropriate, media hype clearly is not.

...studies of many thousands of cases of breast cancer have failed to find a strong relationship between dietary fat and breast cancer risk. In medical editorial writing, it has become clichéd to describe the literature and bemoan the lack of a clinical trial, but there is a real lack at this time of published randomized controlled data in this area. As well as the Women’s Intervention Nutrition Study, another large-scale randomized trial examining the effects of dietary fat on breast cancer relapse risk is also currently in progress (the Women’s Healthy Eating and Living Well Study), and we eagerly await the results. Many practical problems exist in conducting a randomized trial in this area, the most important being the need to maintain a difference in fat intake between the intervention and control groups for many years. This difficulty is supported by problems experienced in the Multiple Risk Factor Intervention Trial heart disease prevention study and the pilot studies for the Women’s Health Initiative.\(^{41,42}\) Moreover, the necessary duration for such a study is not known, as evidence suggests that factors acting from childhood can influence the risk of breast cancer.

Although we are not at a stage where we can justifiably advise well women to reduce their fat intake to reduce the chances of them developing breast cancer, we should not lose sight of what is known about the benefits of dietary manipulation. Practical and simple dietary changes should always be encouraged by health professionals, because they could improve the quality and overall longevity of patients’ lives. While controlled enthusiasm about the role of diets and their effect on specific diseases is appropriate, media hype clearly is not.

**References**

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