

# Symposium: Diet, Anthropometry and Breast Cancer: Integration of Experimental and Epidemiologic Approaches

## Fat, Energy and Breast Cancer<sup>1</sup>

Walter C. Willett

*Departments of Epidemiology and Nutrition, Harvard School of Public Health, and the Channing Laboratory, Department of Medicine, Harvard Medical School and Brigham and Women's Hospital, Boston, MA 02115*

**ABSTRACT** Rates of breast cancer vary approximately fivefold among countries and are strongly correlated with national per capita availability of dietary fat. However, this relation may be substantially confounded by many other factors associated with affluent lifestyles, such as reduced parity and physical activity. In large prospective epidemiologic studies, little evidence has been seen to support any major positive association between dietary fat and risk of breast cancer over the range of 15–45% or more of energy from fat. The observation that women in counties in China consuming approximately 25% of energy from fat have much lower rates of breast cancer than U.S. women with similar fat intakes provides additional evidence that factors other than dietary fat account for the large international differences. Some epidemiologic evidence suggests that monounsaturated fat and olive oil in particular may reduce risk of breast cancer when substituted for other types of fat. In contrast to findings for dietary total fat, most types of epidemiologic studies provide indirect support for a protective effect of energy restriction and reduced growth rates against breast cancer, which is consistently observed in animal studies of mammary carcinogenesis. *J. Nutr.* 127: 921S–923S, 1997.

**KEY WORDS:** • breast cancer • fat • energy • energy • diet

Dietary fat as a possible cause of cancer became of interest in the first half of the 20th century when studies by Tannenbaum and colleagues (Tannenbaum and Silverstone 1953) indicated that diets high in fat could promote tumor growth in animal models. In this early work, energy (caloric) restriction also profoundly reduced the incidence of tumors. Dietary fat has a clear effect on tumor incidence in many models (Birt 1986, Freedman et al. 1990, Welsch 1992), although not in all (Appleton and Landers 1986, Sonnenschein et al. 1991); however, a central issue has been whether this is independent of the effect of energy intake. An independent effect of fat has been seen in some animal models (Birt 1986, Freedman et al. 1990, Welsch 1992), but this effect has been either weak (Ip 1990) or nonexistent (Boissonneault et al. 1986) in some studies designed specifically to address this issue.

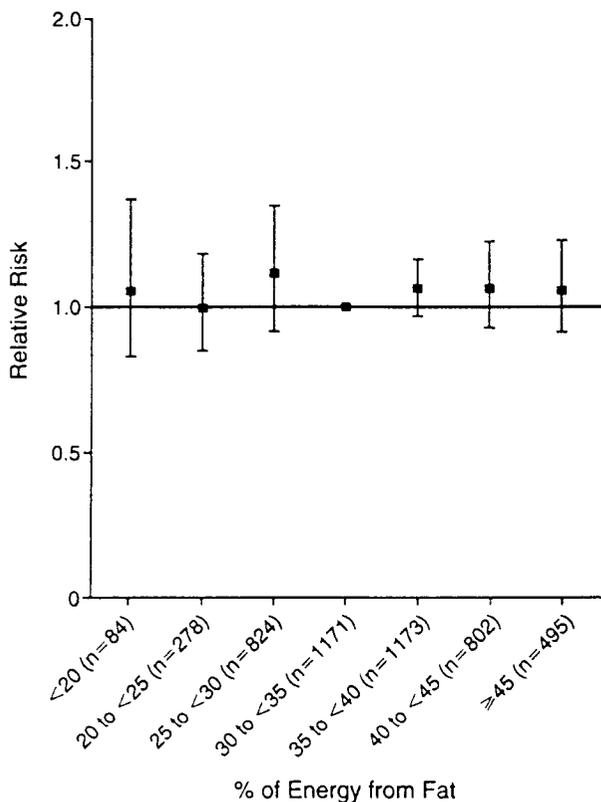
Breast cancer is the most frequent malignancy among women in Western countries, and the disease still continues to show a steady increase (Sondik 1994). Rates in most parts of Asia, South America and Africa have been only about one fifth as high as in the United States (Aoki et al. 1992), but in almost all these areas rates of breast cancer are also increasing. Populations that migrate from low to high incidence countries

develop breast cancer rates that approximate those in the new host country (Adelstein et al. 1979). However, among Japanese immigrants to the United States, not until the second or third generation do rates approach those of the general U.S. population (Buell 1973). This slower rate of change for Japanese immigrants may indicate delayed acculturation, although a similar delay in increase is not observed for colon cancer.

A major rationale for the dietary fat hypothesis has been the international correlation between fat consumption and national breast cancer mortality (Armstrong and Doll 1975). A principal limitation of both the international correlational and migrant studies is the potential for confounding; many other differences besides dietary fat exist between the low fat-consuming (less affluent) and high fat-consuming (more affluent) countries. Indeed, the correlations with gross national product are similar to those for fat intake (Armstrong and Doll 1975). Among the many factors that differ between low and high fat-consuming countries, reproductive behaviors, physical activity level and body fatness are particularly notable and are strongly associated with specific cancers. In a study of 65 Chinese counties (Marshall et al. 1992) in which both dietary assessment and mortality rates were measured using standardized methods and per capita fat intake varied from 6 to 25% of energy, only a weak positive association was seen between fat intake and breast cancer mortality. Notably, women in four counties consumed approximately 25% of energy from fat, yet experienced rates of breast cancer far below those of U.S. women with similar fat intake (Willett et al. 1992), thus providing strong evidence that factors other than fat intake account for the large international differences.

Breast cancer incidence rates have increased substantially

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**FIGURE 1** Pooled relative risks and 95% confidence intervals for various levels of energy from fat. A level of 30% to less than 35% of total energy from fat was designated as the reference category; *n* denotes the number of cases in each category. Reprinted from Hunter et al. (1996) by permission of The New England Journal of Medicine, copyright (1996), Massachusetts Medical Society. All rights reserved.

in the United States during this century, as have the estimates of per capita fat consumption based on food disappearance data. However, surveys based on reports of individual actual intake, rather than food disappearance, indicate that consumption of energy from fat, either as absolute intake or as a percentage of energy, has actually declined in the last several decades (Stephan and Wald 1990), a time during which breast cancer incidence has increased (Sondik 1994).

### CASE CONTROL STUDIES

In the largest case control study so far (Graham et al. 1982), dietary fat was unrelated to risk of breast cancer. The results from 12 smaller case control studies were summarized in a meta-analysis by Howe et al. (1990), which included 4312 cases and 5978 controls. The pooled relative risk was 1.35 ( $P < 0.0001$ ) for a 100 g increase in daily total fat intake, although the risk was somewhat stronger for postmenopausal women (relative risk = 1.48,  $P < 0.001$ ). This magnitude of association, however, could potentially be compatible with biases due to recall of diet or the selection of controls (Giovannucci et al. 1993).

### COHORT STUDIES

In a pooled analysis of the six prospective studies with more than 200 cases of breast cancer (Hunter et al. 1996), no association was seen for overall fat intake over the range of <20 to >45% of energy from fat (Fig. 1). A similar lack of association was seen among postmenopausal women only and

for specific types of fat. Only among the small number of women consuming less than 15% of energy from fat was a significant association seen; breast cancer risk was elevated more than twofold in this group. These cohort findings therefore do not support the results of the case control studies cited above.

### DIFFERENT TYPES OF FAT

In experimental animal mammary tumor models, the tumor-promoting effect of fat intake was observed primarily for polyunsaturated fats fed in high amounts (Welsch 1992). However, in a meta-analysis of case control studies (Howe et al. 1990), increased risk of breast cancer was somewhat greater for saturated (relative risk = 1.46) and monounsaturated fats (relative risk = 1.41) than for polyunsaturated fats (relative risk = 1.25).

In data based on the detailed food frequency questionnaire administered in 1984 in the Nurses' Health Study, an inverse association between monounsaturated fat and breast cancer was present (Willett et al. 1992). This is an intriguing observation given the relatively low rates of breast cancer in southern European countries, which have high average intakes of monounsaturated fats due to the use of olive oil as the primary fat. In two recent case control studies in Spain and Greece, women who used more olive oil had reduced risks of breast cancer (Martin-Moreno et al. 1994, Trichopoulos et al. 1995). Furthermore, olive oil has been shown to be protective relative to other sources of fats in some animal studies (Welsch 1992).

### FAT, ENERGY BALANCE AND AGE AT PUBERTY

An earlier age at menarche is an established risk factor for breast cancer. Although the relative risks associated with early menarche are generally modest, usually less than about 1.5 for the earliest compared with the latest age groups within a population, this is likely to be due to the limited range of age at menarche within a population. For example, in the United States, the average age is between 12 and 13 y (Wyshak and Frisch 1982), but in rural China the typical age is ~17–18 y (Chen et al. 1987). Further, the average age at menarche has been declining worldwide for the last 200 y (Wyshak and Frisch 1982), thus suggesting that increasing breast cancer rates that occur with increasing industrialization have been associated with decreasing average age at menarche.

For this reason, nutritional factors that influence age at menarche are of particular interest as they are likely to contribute to the risk of breast cancer and also to account, at least in part, for increases in breast cancer rates over time. Body mass index, height and weight have consistently been strong determinants of age at the onset of menstruation (Maclure et al. 1991, Merzenich et al. 1993, Moisan et al. 1990). In two cohorts (Maclure et al. 1991, Moisan et al. 1990), no association was found between the fat composition of the diet and occurrence of menarche, but a suggestion of earlier onset with higher fat intake was seen in one study (Merzenich et al. 1993). Collectively, these studies provide strong evidence that rapid growth rates prior to puberty play an important role in determining future risk of breast cancer, but that overall energy balance rather than the fat composition of the diet is most important.

### ENERGY INTAKE AND BREAST CANCER

As noted earlier, total energy intake is strongly associated with the development of mammary cancer in animal models.

It is thus tempting to evaluate this hypothesis by examining the association between energy intake and incidence of breast cancer. Such an approach is likely to be of little use and may be completely misleading, because in free living populations variation in energy intake is determined largely by energy expenditure as physical activity. Thus, for example, energy intake is inversely associated with risk of coronary heart disease, because of the protective effects of exercise against this disease (Willett 1990). The overall lack of association between energy intake and risk of breast cancer in prospective studies of breast cancer thus provides some evidence against an important protective effect of physical activity (Hunter et al. 1996) but does not exclude an effect of energy balance, because small differences between energy intake and expenditure that could not be detected epidemiologically could translate into important gains or losses of weight over a period of years. The most informative indication of energy balance in epidemiological studies will thus be anthropometric measurements: height as a reflection of childhood growth and weight and weight change in adults. These are discussed elsewhere (Hunter and Willett 1996, Ziegler 1997). In general, these studies do indicate positive associations between height and breast cancer incidence and associations between weight gain and risk of breast cancer in postmenopausal women, thus indicating adverse effects on breast cancer risk of positive energy balance and more rapid growth throughout life.

### SUMMARY

Based largely on the results of animal studies, international correlations and a few case control studies, great enthusiasm developed in the 1980s that modest reductions in fat intake would have a major effect on breast cancer incidence. However, as the findings from large prospective studies have become available, support for this relationship has weakened considerably. Despite the large body of data on dietary fat and cancer that has accumulated since 1985, any conclusions should be regarded as tentative because we are dealing with disease processes that are poorly understood but likely to take many decades to develop. Because almost all of the reported literature from prospective studies is based on less than 10 y of follow-up, further evaluation of the effects of diet earlier in life and at longer intervals of observation will be needed to fully understand these complex relationships. Even though there may be little effect on breast cancer incidence, persons interested in reducing their risk of cancer could be advised, as a prudent measure, to minimize their intake of foods high in animal fat, particularly red meat, because this is likely to decrease the risk of prostate and colon cancers (Kolonel 1996, Potter 1996). Such a dietary pattern is also likely to be beneficial from the standpoint of cardiovascular disease. On the other hand, unsaturated fats (with the exception of *trans* fatty acids) are likely to be beneficial with regard to cardiovascular disease, and little evidence suggests that they adversely affect cancer risk; thus, efforts to reduce their intake do not seem to be warranted at this time. Because excess adiposity adversely affects risks of several cancers and cardiovascular disease, balancing energy from any source with adequate physical activity is extremely important.

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