Fat intake and breast cancer: a review

Eunyoung Cho, ScD

Channing Laboratory, Dept. of Medicine,
Harvard Medical School and Brigham and Women's Hospital

Abstract : The relationship between fat intake and breast cancer has been debated for a long period of time. Animal, ecological, and case-control studies have supported that dietary fat increases breast cancer risk. However, cohort studies have not support any strong association between dietary fat intake and breast cancer risk. It has not been clear whether fat *per se* or some specific type of fat is responsible for the increased risk. Recently, a few cohort studies have found some positive association between specific types of fat intake, but not overall fat intake and breast cancer risk. In this review, the findings from previous studies will be summarized with advantages and disadvantages of different types of study design and recent findings will be introduced.

Key Words : fat intake, breast cancer, cohort study, case-control study

I. Introduction

Breast cancer is the most common incidence cancer and cause of death from cancer and incidence rates have been increasing in women worldwide[1]. Incidence of breast cancer varies more than fivefold internationally, suggesting that lifestyle factors rather than genetic factors play a role in the variation of incidence. Diet, especially fat intake has been hypothesized to be one of the major factors contributing to the international variations. The relationship between fat intake and breast cancer has been debated for a long period of time since several animal studies have shown that dietary fat increase the occurrence of mammary tumors in early 1950[2]. Given that several risk factors for breast cancer including age at menarche, height, age at first birth, parity are hard to modify, it is very important to clarify the association between fat intake and breast cancer because fat intake is a modifiable life-style. Besides alcohol intake, not many dietary factors have been well-established to be linked to breast cancer risk.

It has not been also not clear whether fat *per se* is related to the disease or some specific type of fat is responsible for the disease risk. For specific types of fat relevant to breast cancer risk, the evidence is more complex. Case-control studies have supported a positive association between saturated fat intake and breast cancer[3], but animal studies are more supportive of a positive

Corresponding Author: Eunyoung Cho, ScD, Channing Laboratory, 181 Longwood Avenue, Boston, MA 02115
Tel: (617) 525-2091, Fax: (617) 525-2008, E-mail: eunyoung.cho@channing.harvard.edu

association for n-6 polyunsaturated fats[4]. A pooled analysis of prospective studies found no association with intake of total fat or specific types of fat except for a weak positive association with saturated fat intake[5].

II. Biological mechanism

Fat intake in general has been postulated to increase breast cancer risk by elevating levels of circulating estrogen. Although a meta-analysis of 13 intervention studies reported that reduction of fat intake decreased serum estradiol levels among both premenopausal and postmenopausal women (especially among postmenopausal women)[6], some of the studies had no control group and participants were often not in energy balance[7]. In one recent study among postmenopausal women, neither total fat nor animal fat was positively related to estrogen levels[8]. Animal studies have shown a weaker tumor-promoting effect of saturated fat than of polyunsaturated fat[4, 9].

Other biological possibilities relating fat intake to breast cancer risk include eicosanoid production, lipid peroxidation, and modulation of genes that are involved in mammary carcinogenesis[10].

III. Animal studies

After the report linking dietary fat to mammary tumor development in rodents in 1950[2], several animal studies with and without initiated by chemical carcinogens found that high fat diet promotes mammary tumorgenesis[9]. These studies have shown that polyunsaturated fat have stronger tumor-promoting effect than saturated fat. Findings from animal studies cannot be extrapolated to human directly. However, animal studies help understanding the carcinogenesis process in humans.

IV. Migrant studies

A study on Japanese migrants to the U.S. found that breast cancer rates do not increase in the 1st generation but reach similar rates to the U.S. population in the 2nd generation[11]. However, a study on Polish migrants to the U.S. showed that the 1st generation caught up the breast cancer rates of the U.S. population[12]. These studies suggest that the differences in breast cancer rates across countries are not attributable to genetic differences but some environmental differences. Acculturation process including dietary changes might have occurred faster for Polish migrants than Japanese migrants, which might explain the different patterns of change in breast cancer rates in two migrant populations.

V. Ecological studies

Studies have reported a strong correlation between national per capita fat intake and breast cancer rates[13]. An advantage of ecological studies is the large variability of fat intake across countries. It could contribute to generating hypotheses. However, ecological studies have been criticized because it cannot account for confounding by other

risk factors. For example, those countries with higher fat intake may be more westernized and have higher prevalence of other breast cancer risk factors such as earlier age at menarche, taller height, and later age at first birth.

VI. Case-control studies

There have been several case-control studies examining fat intake and breast cancer risk. A combined analyses of 12 case-control studies reported relative risks of 1.48 ($P<0.001$) for postmenopausal women and 1.13 ($P=0.21$) for premenopausal women for each 100 g/d increase of total fat intake[3]. This analysis included approximately twice more cases of postmenopausal breast cancer than premenopausal cancer, which may partly explain the significant association only among postmenopausal women. Case-control studies are susceptible to recall and selection biases. For example, breast cancer cases who are aware of fat intake and breast cancer hypothesis may not recall their fat intake the same way as controls. This possibility has been suggested in a meta-analysis which included both case-control studies and cohort studies[14]. The study found a positive association between higher fat intake and breast cancer only among case-control studies (RR=1.12) but not among cohort studies (RR=1.01) instead of RR please put relative risk.

VII. Prospective studies

In prospective cohort studies, fat intake is measured before diagnosis of breast cancer. Thus, disease status cannot affect reporting of diet, a major source of bias in case-control studies. Several cohort studies have not found any strong association between fat intake and breast cancer risk. These have been criticized by small sample sizes, homogeneous fat intake in the populations, and measurement errors in estimating fat intake. A pooled analysis of 7 prospective studies examined fat intake and breast cancer extensively and addressed the issues from the previous cohort studies. The study included cohort studies with validated dietary assessment method, corrected for measurement error assessing fat intake, and examined wide range of fat intake with very large sample size. However, the study did not find any positive associatin between either total fat or types of fat intake and breast cancer risk[5, 15]. When different types of fat were examined, there was a suggestive of positive association only between saturated fat intake and breast cancer risk[5].

VIII. Recent findings

There have been a few caveats from previous epidemiologic studies. First, preivious studies have included primarily postmenopausal women and also measured their diet after 40 years of age. Because the etiologies of pre- and postmenopausal breast cancer are different in many respects, the relation of dietary fat to breast cancer risk in premenopausal women could be different from that in postmenopausal women. It has been known that some of the breast cancer risk factors have different associations among pre- and postmenopausal

women. For example, adiposity is inversely related to breast cancer in premenopausal women and positively related to breast cancer in postmenopausal women[16]. Several known risk factors operate primarily before middle age. For example, reproductive factors act largely during the early adult years, and the breast becomes minimally sensitive to radiation-induced carcinogenesis after age 35[17]. It is also possible that diet in early adult life may have stronger impact than that in later in life as it has been hypothesized that the years before the first birth of a child may be most relevant to future risk of breast cancer[18].

These issues were addressed by a recent study among premenopausal women[19]. The study included over 90,000 premenopausal women aged 26 to 46 years and followed them for 8 years. A total of 714 incident cases of invasive breast cancer were documented during the follow-up. Total fat intake was not related to breast cancer risk. However, when total fat was divided into animal and vegetable sources, intake of animal fat, but not vegetable fat, was associated with up to 54% elevated risk of breast cancer. Intake of saturated fat and monounsaturated fat, major components of animal fat in the population, was related to increased risk of breast cancer also. When food sources of animal fat were examined, both red meat and high-fat dairy products were associated with increased risk.

It is not clear why animal fat intake, but not vegetable fat intake was related to breast cancer risk in these premenopausal women. Given that positive associations were observed for red meat and high-fat dairy food intakes, there is a possibility that some other components in these foods are responsible for the apparent positive association. Cooked red meat contains several carcinogenic compounds and has been related to other cancers including colorectal cancer[20, 21]. High-fat dairy foods contain fat-soluble hormones or growth factors, which may be related to breast cancer risk[22].

Interestingly, another recent prospective study found a positive association between saturated fat intake and breast cancer risk[23]. This study included women in their age of 45-74, followed them for 9 years, and documented 168 breast cancer cases. Given that saturated fat is an important part of animal fat, the findings from two cohorts are comparable.

A meta-analysis of the published literature on fat intake and breast cancer which included 31 case-control studies and 14 cohort studies published until year 2,003 reported a positive association between total fat and saturated fat while mono and polyunsaturated fat intake were not related to the risk[10]. Saturated fat intake was significantly related to breast cancer risk both in case-control and cohort studies although the association was little stronger in case-control studies.

IX. Conclusions

The relationship between fat intake and breast cancer risk has been an area of extensive debate. Although previous ecological and animal studies have supported a strong positive association, prospective studies have failed to find any strong association. However, based on recent data, it appears that total fat *per se* is not a causal factor for

breast cancer risk. The positive association between total fat and breast cancer is probably due to specific types of fat (e.g., animal fat or saturated fat), which has been consistently shown in recent studies. Further studies are warranted to identify the mechanism relating these types of fat to breast carcinogenesis. The findings from premenopausal women also need to be confirmed in other populations.

■ References

1) World Cancer Research Fund, American Institute for Cancer Research. Food, Nutrition and the Prevention of Cancer: A Global Perspective. Washington, DC: American Institutue for Cancer Research; 1997.

2) Tannenbaum A, Silverstone H. Nutrition in relation to cancer. Adv Cancer Res 1953;1:451-501.

3) Howe GR, Hirohata T, Hislop TG, Iscovich JM, Yuan JM, Katsouyanni K, et al. Dietary factors and risk of breast cancer: combined analysis of 12 case-control studies. J Natl Cancer Inst 1990;82:561-9.

4) Fay MP, Freedman LS, Clifford CK, Midthune DN. Effect of different types and amounts of fat on the development of mammary tumors in rodents: a review. Cancer Res 1997;57:3979-88.

5) Smith-Warner SA, Spiegelman D, Adami HO, Beeson WL, van den Brandt PA, Folsom AR, et al. Types of dietary fat and breast cancer: a pooled analysis of cohort studies. Int J Cancer 2001;92:767-74.

6) Wu AH, Pike MC, Stram DO. Meta-analysis: dietary fat intake, serum estrogen levels, and the risk of breast cancer. J Natl Cancer Inst 1999;91:529-34.

7) Holmes MD, Schisterman EF, Spiegelman D, Hunter DJ, Willett WC. Re: Meta-analysis: dietary fat intake, serum estrogen levels, and the risk of breast cancer. J Natl Cancer Inst 1999;91:1511-2.

8) Holmes MD, Spiegelman D, Willett WC, Manson JE, Hunter DJ, Barbieri RL, et al. Dietary fat intake and endogenous sex steroid hormone levels in postmenopausal women. J Clin Oncol 2000;18:3668-76.

9) Fay MP, Freedman LS. Meta-analyses of dietary fats and mammary neoplasms in rodent experiments. Breast Cancer Res Treat 1997;46:215-23.

10) Boyd NF, Stone J, Vogt KN, Connelly BS, Martin LJ, Minkin S. Dietary fat and breast cancer risk revisited: a meta-analysis of the published literature. Br J Cancer 2003;89:1672-85.

11) Buell P. Changing incidence of breast cancer in Japanese-American women. J Natl Cancer Inst 1973;51:1479-83.

12) Adelstein AM, Staszewski J, Muir CS. Cancer mortality in 1970-1972 among Polish-born migrants to England and Wales. Br J Cancer 1979;40:464-75.

13) Hems G. The contributions of diet and childbearing to breast cancer rates. Br J Cancer 1978;37:974-82.

14) Boyd NF, Martin LJ, Noffel M, Lockwood GA, Tritchler DL. A meta-analysis of studies of dietary fat and breast cancer risk. Br J Cancer 1993;68:627-36.

15) Hunter DJ, Spiegelman D, Adami HO, Beeson L, van den Brandt PA, Folsom AR, et al. Cohort studies of fat intake and the risk of breast cancer--a pooled analysis. N Engl J Med 1996;334:356-61.

16) Huang Z, Hankinson SE, Colditz GA, Stampfer MJ, Hunter DJ, Manson JE, et al. Dual effects of weight and weight gain on breast cancer risk. J Am Med Assoc 1997; 278:1407-11.

17) Miller AB, Howe GR, Sherman GJ, Lindsay JP, Yaffe MJ, Dinner PJ, et al. Mortality from breast cancer after irradiation during fluoroscopic examinations in patients being treated for tuberculosis. N Engl J Med 1989;321:1285-9.

18) Colditz G, Frazier A. Models of breast cancer show that risk is set by events of early life: prevention efforts must shift focus. Cancer Epidemiol Biomarkers Prev 1995;4:567-71.

19) Cho E, Spiegelman D, Hunter DJ, Chen WY, Stampfer MJ, Colditz GA, et al. Premenopausal fat intake and risk of breast cancer. J Natl Cancer Inst 2003;95:1079-85.

20) Willett WC, Stampfer MJ, Colditz GA, Rosner BA, Speizer FE. Relation of meat, fat, and fiber intake to the risk of colon cancer in a prospective study among women. N Engl J Med 1990;323:1664-72.

21) Giovannucci E, Rimm EB, Stampfer MJ, Colditz GA, Ascherio A, Willett WC. Intake of fat, meat, and fiber in relation to risk of colon cancer in men. Cancer Res 1994;54:2390-7.

22) Outwater JL, Nicholson A, Barnard N. Dairy products and breast cancer: the IGF-I, estrogen, and bGH hypothesis. Med Hypotheses 1997;48:453-61.

23) Bingham SA, Luben R, Welch A, Wareham N, Khaw KT, Day N. Are imprecise methods obscuring a relation between fat and breast cancer? Lancet 2003;362:212-4.

Received November 8, 2003
Accepted November 18, 2003