Mechanisms by which high maternal fat intake during pregnancy increases breast cancer risk in female rodent offspring

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Summary

Emerging evidence indicates that a high in utero estrogenic environment increases breast cancer risk in women. We have proposed that a maternal intake of a high fat diet is a source for high pregnancy estrogen levels and increases breast cancer risk among female offspring. In this review, the role of dietary fat in breast cancer, particularly during fetal life, is discussed. In addition, we provide possible mechanisms of action of the effects of a high-fat diet on the breast. These mechanisms include protein kinase C, estrogens and estrogen receptor, and alterations in mammary parenchymal structures.

Dietary fat in breast cancer

There is a substantial amount of evidence implicating environmental factors, particularly diet, as risk factors for developing breast cancer. The fat per capita intake in a given country correlates with the national breast cancer incidence [1-4], suggesting that a high-fat diet increases breast cancer risk. Case-control studies also have demonstrated a relationship between total fat and/or meat consumption and breast cancer [5-7]. In addition, survival from breast cancer appears to be shortened, and breast cancer mortality to be increased, in women consuming a high-fat diet [8-10]. Animal studies indicate a strong association between a high-fat diet and promotion of spontaneous and carcinogen-induced mammary tumorigenesis [11,12]. While these studies support a role for fat consumption in post-menopausal breast cancer, evidence linking pre-menopausal breast cancer to fat intake has not been forthcoming [13,14]. Recent cohort studies performed in North America also have generally failed to link dietary fat intake and breast cancer (pre- and postmenopausal) [15,16].

Although no consensus exists as to whether a high-fat consumption affects breast cancer risk, the potential benefits of successful dietary intervention regimens are highly significant. Boyd et al. estimated that appropriate dietary modifications could produce an overall reduction of 35% in breast cancer incidence [17]. Even a 10% reduction in risk could produce an annual reduction of 18,000 in the number of new breast cancer cases in the U.S. alone [18]. Therefore, it is critical to determine whether a dietary fat intake, at any given time during a woman's life-span, alters breast cancer risk. It is equally important to determine the mechanisms mediating the effects of fat on breast tissues.

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Type of dietary fat

The type of dietary fat appears critical for the promotional effects on breast tumorigenesis. Among humans, total fat intake and intake of saturated and unsaturated fats are believed to be more strongly associated with increased breast cancer risk than intake of polyunsaturated fatty acids (PUFAs) [5]. However, some evidence suggests that n-6 PUFA, present in high levels for example in corn oil, safflower-seed oil, and sunflower-seed oil, may accelerate mammary tumor growth and metastasis in humans [19]. In animal models, saturated fats of animal (e.g., lard and beef tallow) and plant origin (e.g., coconut oil and palm oil) have no effect or inhibit carcinogen-induced mammary tumor promotion in rats [12]. However, if the exposure to high levels of saturated fats occurs between puberty and adulthood, these fats stimulate the subsequent development of mammary tumors [20]. The n-6 PUFA has been strongly implicated as a promotional agent in the carcinogen-induced rat mammary tumor model [21,22], and in tumor metastasis in nude mice [23]. n-6 PUFAs are relatively ineffective before tumor initiation. Since we do not know when the initiation of breast cancer occurs in humans, we cannot adequately assess the role of dietary fats in the initiation and promotion of human breast cancer.

In marked contrast to n-6 PUFAs, the n-3 PUFAs present in fish and other marine oils inhibit both breast tumor growth [24,26] and metastasis [23] in humans and animal studies. Clinical studies suggest that consumption of a diet high in n-3 PUFA also prevents colon cancer [27]. A high dietary intake of n-6 linoleic acid reduces the n-3 α-linolenic acid content in cellular membranes [28]. Linoleic acid can suppress the incorporation of α-linolenic acid into phospholipids [29], because these fatty acids compete for the same elongase and desaturase metabolizing enzyme systems [28]. Thus, the effect of a diet high in n-6 PUFA on tumorigenesis may also be caused by a deficit in n-3 fatty acids. This possibility has not been addressed adequately in either human or animal studies.

Dietary fat in utero and breast cancer risk

Exposure to a high-fat diet during early life may increase breast cancer risk. This has become evident in studies investigating the changes in the incidence of breast cancer among women immigrating from Asia to the United States. The breast cancer incidence is 2.5 to four times higher for women living in the U.S. than women living in Asian countries [30]. Many studies have shown that breast cancer rates increase over two to three generations in women migrating from Asia to the U.S., and reach that in U.S. Whites (for example [31-34]). It was recently noted that breast cancer risk among Asians is already 80% higher after a decade of living in the U.S., compared with the risk of Asian women living in Asia [35]. However, the most dramatic increase in risk occurs between Asian-Americans born in the West and those born in the East [35]. If a grandmother also is born in the West, an Asian-American woman's risk is even higher than in Whites living in the same communities [35]. A higher dietary fat intake, also during pregnancy, in the West compared with the East may be responsible for the transition towards higher breast cancer risk between Asian generations living in the West.

Experimental evidence directly indicates that a high maternal fat intake during pregnancy increases mammary tumorigenesis in the offspring in animal models [36,37], and possibly in humans [38]. In our studies, pregnant female Sprague-Dawley rats were fed with diets containing either 12% calories from fat or 40% calories from fat [37]. The fat source was corn oil that contains high levels of n-6 PUFAs. Female offspring of high-fat fed mothers, kept on a laboratory chow from birth onwards, developed a significantly higher incidence of carcinogen-induced mammary tumors than female offspring of low-fat fed