MALIGNANT TUMORIGENESIS OF MAMMARY GLAND

O. S. TAHIN and T. C. CAVALCANTI

RESUMO

O câncer mamário (CAM) é altamente afetado por fatores ambientais como os lipídios dietários. Há várias hipóteses para explicar a ação promocional dos lipídios, nutricionais e como precursores da síntese de compostos prostanóides, componentes de membranas biológicas, podem afetar produção de hormônios, etc. O estatuto hormonal como estrogênio e prolactina podem ser importantes para a maturação do tecido mamário que poderia ser relevante para a ação de carcinogênio e para a própria tumorigênese mamária.

ABSTRACT

The cancer of mammary gland (CAM) is highly affected by environmental factors like the dietary lipids. There are several hypotheses for explaining the promotional action of nutritional fats as precursor of the synthesis of prostanoid compounds, so biological membrane components, they may affect hormone production, and so on. The hormone status like estrogen and prolactin may be important for mammary tissue maturation that could be very relevant for the action of carcinogens and for the breast tumorigenesis itself.

In general, 80-90% of several types of human cancer are caused by environmental factors. Those factors include nutritional factors, food additives, earth pollution, natural components of food that may have carcinogen action like flavonoids, alkaloids, aflatoxins and chemical compounds (from industrial exposures, pharmaceutical and cigarette smoke). This fact may help to explain the high increase of the rate of mortality from cancer of mammary gland (CAM) in most of countries (1).

Epidemiological study showed that in 1975 American women had about 5 times higher rates of mortality from CAM than Japanese women, however, the later had about 7 times higher rates of mortality

(* I. B., CAISM, UNICAMP, C. P. 6151, 13081, Campinas, S. P., Brasil.)
from stomach cancer than American women (2). Those differences are probably more related to environmental factors than genetic factors. In fact, it has been observed that native women of Greenland had a very low rates of mortality from CAM in the beginning of this century but more recently these rates are highly increasing at the same time the population acquired western cultural habits, and the same is happening with Japanese women after the Second World War (3).

NUTRITIONAL FACTORS OF CAM

Several epidemiological studies have extensively demonstrated that the amount of animal protein intake (4) and mainly the daily fat intake (1) are associated to the rates of incidence and mortality from CAM. The correlation coefficient between the dietary fat consumption and the age-adjusted mortality from CAM in different countries is very high and positive, equal to + 0.935 (1).

Besides the daily total fat ingestion, it has been also described the importance of the type of dietary fatty acids (1-5). Fatty acids have to be classified in four series of family accord to their biochemical, metabolic, physiological and pathological characteristics: 1) saturated fatty acid (SFA), 2) n-9 unsaturated fatty acid (n-9 UFA) or oleic acid family, 3) n-6 polyunsaturated FA (n-6 PUFA) or linoleic acid family, and 4) n-3 polyunsaturated FA (n-3 PUFA) or linolenic acid family (5,6).

The main sources for n-6 PUFA are vegetable seed oils and for n-3 PUFA are sea fish oil. These two FA families show antagonist actions. With animals, better than with humans, it is well demonstrated that linoleic acid increases the incidence and malignity of breast tumors.

The mechanism of action of dietary fat is not yet well known. However, several hypotheses have been proposed for explaining the promotional action of nutritional fat on CAM: 1) n-6 and n-3 PUFAs are precursors of eicosanoids or prostanoid compounds that could mediate the tumorigenesis and or the immunological response system because prostaglandin synthesis inhibitor also inhibits breast carcinogenesis (7); 2) PUFAs are cell membrane components and the alterations of PUFA composition of membrane lipids caused by dietary fat manipulation may alter some important cellular membrane-dependent functions like cellular receptors, cell to cell interactions, or enzyme system (5,8); 3) although linoleic acid has a clear promotional action on CAM, this n-6 PUFA is required for mammary ducts maturation (9); 4) dietary FAs have direct or indirectly action on the production of certain hormones that would have special role on the development of CAM (8); and so on.
HORMONE STATUS AND CAM

The age at the first menarche, the number of pregnancies (nulliparous women show much more incidence of CAM than multiparous women), the age at the first conception and lactation may be risk factors of the incidence of CAM in humans. Estrogen hormone is associated to the development of CAM. With experimental animals it is well demonstrated that the age for the administration of chemical carcinogen is very important for the carcinogenic action. Female virgin rats or mice at the pre-sexual mature age are much more susceptible to the induction of CAM by chemical carcinogen than older (10) or post-pregnancy animals (11). It was already demonstrated that chemical carcinogen does not induce (CAM) in pregnant rats (11).

Estrogen hormone and prolactin may have a role on mammary gland tissue maturation that is important to CAM development, too (12).

Another very interesting point is that the dietary fats affect hypothalamus, then adrenals that produce estronogens, and also would affect prolactin production (8).

Those facts might suggest that hormones would favour or protect against the development of breast tumorigenesis. However, there are yet no direct evidences to prove this hypothesis.

BREAST TUMORIGENESIS INDUCED BY CHEMICAL CARCINOGEN

The experimental studies of mammary tumorigenesis is necessary for the knowledge of many unknown events of human CAM and for explaining the possible mechanism of the promotional action of dietary fat on CAM.

Breast tumorigenesis in experimental animals may be induced by administration of chemical carcinogen like 7,12-dimethylbenz(a)anthracene(DMBA) (10) or by transplantation of hyperplastic mammary cells (12).

The yield of number of tumors, malignity, time of tumor development and of the percentage of rats with mammary tumors induced by DMBA is a function of several factors like the best age of the animals for DMBA administration, number of doses and quantity of the carcinogen, sex of animal (only female rats) and dietary lipids (unpublished data).

The action of DMBA is observed after few days of the carcinogen administration causing hyperplasia (11,13). However, it was
already well demonstrated that DMBA has very small if any action on pregnant female rats or on multiparous rats (11). These evidences support the hypothesis that the maturation of mammary tissue, the rate of transformation of terminal end bud (TEBs) to alveolar and mainly to lobular structure of mammary gland is very important for the development of breast tumorigenesis (11). Young virgin female rats have much more TEBs than alveolar or lobular structure. There are evidences that TEBs structures are the target for DMBA action for inducing hyperplasias and eventually later pre and neoplasia lesions on mammary tissue (11).

Recent studies have demonstrate that the ATPase and FA composition of mammary mitochondria could be used as good molecular markers for the study of breast tumorigenesis (14, 15).

REFERENCES


