I. INTRODUCTION

In 1984, we first reported that n-3 polyunsaturated fatty acids (PUFA) present in fish oil, had an inhibitory effect on growth of a transplanted rat mammary tumor (1). The idea that some PUFA may actually have inhibitory effects on mammary tumorigenesis contradicted with published findings. The prevalent theory at that time was that PUFA in general, and n-6 PUFA in particular, promoted the development of chemically-induced mammary cancers and enhanced the growth and metastasis of mammary carcinomas (2-3).

II. ANIMAL TUMOR SYSTEMS

The evidence from animal studies supported a tumor-promoting role for linoleic acid (LA) in mammary and colon tumor models, especially when the essential fatty acid requirements were met. These effects of LA were counteracted by inhibiting arachidonic acid (AA) metabolism with cyclooxygenase inhibitors. Since n-3 PUFA, eicosapentaenoic (EPA) and docosahexaenoic (DHA) also inhibit AA metabolism, we examined their effects in experimental models of mammary and prostatic tumors. Published reports of these studies have been reviewed elsewhere (4-5).

A number of investigators have recently tested the effect of n-3 fatty acids and LA in carcinogen-induced tumor models. Compared to corn oil, inhibitory effects of fish oil were reported in the 7,12 dimethylbenz(a)anthracene (DMBA)- and nitrosomethylurea (NMU)-induced mammary tumor models, the L-azaserine-induced pancreatic preneoplastic lesions, and azoxymethane-induced colon tumor. Similar results with the n-3 PUFA were observed in transplanted tumors R3230AC, DU-145 and Yoshida sarcoma (5).

III. BIOCHEMICAL MECHANISMS OF n-3 FATTY ACIDS

1. Lipid and Arachidonic Acid Metabolism. In seeking an understanding of the influence of the various dietary fatty acids on different animal tumor systems, a number of biochemical systems have been studied. First, in fish oil-fed rats, the synthesis of dienoic prostaglandins (PG) and thromboxane (TX) was significantly inhibited in tumor tissues. Interestingly, there was no significant difference in four PGs in normal mammary fad pads taken from rats fed a 5% LA diet and a 4.7% EPA plus 0.3% LA diet (6). Second, in a number of studies, EPA plus DHA were incorporated into tumor
phospholipids at the expense of LA and AA (5-7). The amount and nature of the fatty acids present in the membranes are of the utmost importance for the regulation of cellular functions. Membrane fluidity, permeability, and stability, as well as the kinetic properties of a number of enzymes are regulated by lipids. These results suggest that the inhibition by n-3 PUFA of several tumor models may be mediated via the modulation of lipid and AA metabolism.

2. Ornithine Decarboxylase Activity (ODC). The n-3 PUFA significantly inhibited the azoxymethane-induced colon carcinogenesis as well as the activity of the colonic mucosal ODC. Ornithine decarboxylase is a rate-limiting enzyme in the polyamine biosynthesis and has been suggested to play a role in tumor promotion. It has been reported that the inhibition of AA metabolism depresses the 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced ODC activity as well as the tumor formation in the DMBA-induced skin carcinogenesis model (8). However, in mice fed fish oil, ultraviolet (UV)-induced ODC of the skin was reduced compared to the corn oil group (9). This disparity in ODC activity between UV and TPA models may be explained by the different mechanisms of induction and/or promotion. Research findings on the role of AA metabolites in the TPA model of promotion have been mixed and controversial, partly due to the number of metabolites involved and the complexity of their actions in the TPA model (10-11). More importantly, because many biochemical effects are elicited by TPA (10), TPA has proven to be a useful phorbol ester tumor promoter to study in animal models. However, in human skin cancer, UV radiation has been shown to be the most important contributory factor (12) and therefore the UV model of promotion may be more appropriate to study human skin cancer.

3. The Yoshida- Sarcoma Model. A structured lipid composed of fish oil and medium-chain triglycerides (Fish/MCTs) inhibited the growth and protein synthesis in the Yoshida-sarcoma model compared to the long-chain triglycerides (13). Additionally, the effects of Fish/MCTs on tumor growth were synergistic with those of the treatment with tumor necrosis factor.

4. Tumor metastasis. A number of investigators have tested the effect of n-3 PUFA on metastasis of tumor cells. The prevention of platelet aggregation is considered in part, to be the result of changes in blood platelet function induced by EPA and DHA. It has been suggested that the intravascular balance between TXA2 and PGI2 is disrupted in favor of platelet aggregation during tumor cell metastasis (14). Since EPA and DHA inhibit TXA2 synthesis, this selective inhibition of TXA2 may influence metastasis formation. n-3 PUFA inhibited metastasis formation in the CT-26 and 1376MAT:B models but not in the BN472 and the Lewis Lung carcinoma (5,15). When malignant murine melanoma and human fibrosarcoma cells were incubated in media supplemented with EPA, there was a dose and time dependent decrease in invasiveness, collagenase IV production and in the case of melanoma cells, a reduced ability to metastasize to
the lung after intravenous injection (16). These studies indicate that n-3 PUFA have a potential to reduce the metastasis of certain tumor cells.

IV. EPIDEMIOLOGICAL STUDIES

The relevance of experimental studies to human cancer risk and disease progression is unclear. Most epidemiological investigations that support an association between dietary fats and breast or colon cancer implicate saturated fat (17). However, recent reports suggest that the increasing breast cancer incidence in the United States may be related to the increase in vegetable oil consumption, and thus due to an increase in consumption of n-6 PUFA (18-19). Moreover, Kaizer et al (20) recently reported that the per capita percentage calories from fish in 32 countries had a significant inverse correlation with breast cancer incidence. Hursting et al (21) suggested that fish n-3 PUFA intake in 20 countries had a nonsignificant negative correlation with cancers of the breast, cervix, lung, colon and prostate during 1973-1977. In a case control study of 100 prostatic cancer patients, Mishina et al (22) reported that cases consumed seafood significantly less frequently than controls. The putative anticancer effect of n-3 PUFA is also indirectly supported by epidemiological data on Greenland Eskimos, who prior to westernization of their dietary habits, consumed large amounts of n-3 PUFA and had relatively low reported incidence rates of breast and prostate cancer (23-24).

SUMMARY

A number of reports indicate that fish n-3 PUFA inhibit the development, growth and progression of several experimental tumors. There emerges a pattern of complex and diverse biochemical actions of n-3 PUFA in different animal tumor models, from the studies undertaken to date to evaluate the underlying mechanisms. These findings, along with the recent epidemiological evidence of an inverse correlation between fish intake and incidence of some human cancers, makes it worthwhile to determine the role of n-3 PUFA in cancer.

REFERENCES


