Overview

Animal models of breast cancer: experimental design and their use in nutrition and psychosocial research

Robert Clarke
Vincent T. Lombardi Cancer Center, Georgetown University Medical School, Washington DC, USA

Key words: animal models, breast cancer, cell lines, DMBA, NMU, AIN76, AIN93

Summary

This is the second Special Issue addressing the diversity and use of animal models of breast cancer. The previous issue (Breast Cancer Res Treat 39:1-135, 1996), dealt with a variety of topics such as the characteristics of chemically- and virally-induced rodent models, immunobiologies of immunedeficient mice, transgenic mouse models, and models of metastasis. In the first part of this second Special Issue, the articles address animal models for studying lifestyle factors, including psychosocial, exercise, and nutritional research in breast cancer. In the second section, there is emphasis on the controversial area of dietary fat, with other authors addressing caloric restriction and dietary isoflavonoids, retinoids, and monoterpenes in the third part. In the final section, a series of authors provide suggestions for approaching various issues involving experimental design, including nutritional studies, drug screening models, statistical considerations, quantitation of tumor growth kinetics, and animal husbandry. These articles, and some additional issues raised during the previous Special Issue, are briefly discussed in this overview. They include a further evaluation of the relative merits of 7,12-dimethylbenz(a)anthracene and N-nitroso-N-methylurea as carcinogens, and of the use of the AIN-76 and AIN-93 semipurified diets in studies of mammary carcinogenesis.

Introduction

This is the second Special Issue dedicated to animal models of breast cancer. It picks up several of the topics notable by their absence in the first issue, particularly in terms of the use of animal models and experimental design [1]. Articles are included describing the use of these models in areas of research that have been less well studied using animal models. A significant focus is given to nutritional studies. These are becoming more important as the search for natural compounds with chemopreventive activity increases, and as investigators attempt to identify the dietary and environmental factors that contribute to the significant differences in breast cancer risk apparent from international, migrant, and case-control studies [2,3]. In this latter regard, animal models provide one of the few means to address the potential role of specific dietary components in a controlled, cost and time efficient manner. These models can allow investigators to evaluate hypotheses generated from human studies and generate additional hypotheses.

Address for correspondence and offprints: Robert Clarke PhD, Vincent T. Lombardi Cancer Center and Department of Physiology & Biophysics, W405A The Research Building, Georgetown University Medical School, 3970 Reservoir Road NW, Washington, DC 20007, USA; Phone: (202) 687-3755; Fax: (202) 687-7505; email: clarker@gunet.georgetown.edu
that can subsequently be examined in human studies. These movements to and from human and animal studies are clearly evident from the discussion of the dietary fat and breast cancer hypothesis in several of the articles in this issue.

Animal models for the study of psychosocial factors and breast cancer risk

Psychosocial factors have long been associated with breast cancer risk. While the majority of studies have been performed in human populations, there are well established rodent models for assessing behavioral and other endpoints. These models have not been widely used in the field of breast cancer research [4], despite their validation and widespread use in the Behavioral Sciences. Indeed, several of these models of behavior have been as successfully used in the development and assessment of psychotropic drugs, as human tumor xenografts have been used in the development of antineoplastic drugs. Animal models of exercise also have been widely used outside the area of breast cancer research, e.g., in studies of exercise physiology and stress.

Several of the more applicable behavioral assays are described in detail by Hikakivi-Clarke [5], who provides sufficient information and/or citations to enable these to be established in other laboratories. These endpoints include those for assessing such behaviors as depressive and aggressive behavior and voluntary alcohol consumption. Comparisons of data from these endpoints in rodents with data from human populations are provided and discussed in some detail. Finally, the author presents a novel hypothesis, linking these behaviors and breast cancer risk through modifications in the activity of estrogens [5].

In a related article, Thompson describes the use of animal models to study the association among physical activity, exercise, and carcinogen-induced mammary carcinogenesis [6]. Like the models described for the behavioral endpoints, these rodent models also allow for the generation of novel hypotheses that can subsequently be addressed in human studies. In this review, Thompson describes the criteria for defining laboratory studies as investigating either exercise or physical activity [6]. A critical reinterpretation of the published literature is presented, reflecting these recategorizations. The study concludes with the observation that exercise ≥70% of maximal aerobic capacity is consistently associated with a substantial reduction in carcinogenicity and the suggestion that “future studies must define physical activity or physical fitness markers of the cancer protected state” [6].

Nutritional studies of breast cancer —
calories and micronutrients

The first of the articles in this section describes the well established role of caloric restriction in inhibiting experimental mammary carcinogenesis. This is an important issue for many reasons. In addition to those described within the text by Kritchevsky [7], many experimental agents can induce weight loss and reduced caloric intake. It is important in studies screening such compounds to ensure that apparent antineoplastic activity is not merely the result of a toxicity-induced caloric restriction. As described by Kritchevsky, caloric restriction reduces serum hormone levels, alters antioxidant enzyme activities, and can affect DNA repair [7]. Oncogene expression also is directly affected by caloric restriction. Perhaps it is not surprising that caloric restriction is one of the most consistent and potent of the dietary manipulations affecting chemically-induced mammary carcinogenesis in rodents.

The potential role of soy isoflavonoids is discussed by Barnes [8]. The primary active isoflavone from soy is genistein. Its potential as a therapeutic and/or chemopreventive has received particular attention in animal models of breast cancer. As described by Barnes, the timing of exposure is critical, with neonatal or prepubertal exposure reducing tumor number and increasing tumor latency [8]. However, the use of genistein