Diet, Anthropometry and Breast Cancer: Integration of Experimental and Epidemiologic Approaches

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ABSTRACT The interrelationships of dietary fat and energy, growth rates and anthropometry, and breast carcinogenesis have been examined by a diverse array of approaches throughout the last 50 y as new investigative tools have been developed by laboratory scientists and epidemiologists. A consensus among investigators has not emerged, however, and dietary recommendations for breast cancer prevention have not been clearly formulated or effectively communicated to the public. Indeed, the gap between those investigators utilizing laboratory-based approaches and those using epidemiologic models has expanded in recent years. Cancer epidemiologists have become increasingly skeptical that results derived from laboratory animal models of breast carcinogenesis and in vitro systems are directly applicable to human breast cancer risk. Concurrently, laboratory scientists have questioned the ability of epidemiological tools to accurately measure dietary intake and relevant biomarkers and to account for a diverse array of potentially confounding environmental and genetic factors characteristic of human populations under study. These polarized views are reinforced by a failure of investigators using diverse approaches to interact, integrate their skills and resources, develop novel hypotheses, and propose solutions using both laboratory and epidemiologic techniques. Therefore, the objectives of this symposium are to summarize experimental and epidemiologic knowledge, foster communication and collaboration, and attempt to identify appropriate studies to bridge the gaps in our knowledge concerning dietary lipid and energy, anthropometrics, and breast cancer risk. J. Nutr. 127: 916S–920S, 1997.

KEY WORDS: breast cancer nutrition anthropology dietary fat

Breast cancer remains the most frequently diagnosed malignancy in American women and the second most common cause of cancer death (Wingo et al. 1995). Although breast cancer is a common disease, the perception among many women is that their personal risk is even greater than the estimated 1 in 8 lifetime chance of being diagnosed with breast cancer or the 1 in 28 lifetime risk of dying from breast cancer. American women in increasing numbers participate in screening programs involving breast self-exam and mammography in the hope that early detection will prevent mortality. However, a significant portion of breast cancer cases elude early detection due to the expression of invasive and metastatic biological phenotypes prior to the development of a palpable tumor or radiographic changes on a mammogram. Many concerned women desire and seek information regarding diet and nutritional approaches for breast cancer prevention. The rapid growth of a multibillion dollar "health food" and supplement industry and the emergence of many "alternative" health care practitioners focusing upon nutrition in American communities is a direct result of a failure of the established medical and nutritional sciences profession to provide appropriate education and guidance to the public. The news media often compromises nutrition education by sensationalizing individual studies without consideration of the much larger body of data. The tabloid press frequently promotes stories of unsubstantiated and miraculous cures of human cancers by poorly characterized products and approaches related to diet and nutrition. Breast cancer patients, and the public in general, increasingly report that information in the media changes week to week and seems contradictory or confusing. Indeed, a similar perception by non-nutritional scientists and health care practitioners further weakens efforts to obtain funding for nutrition education, intervention and research in the area of breast cancer.

The importance of developing and implementing effective, nontoxic and health-promoting strategies for prevention of breast cancer depends upon a greater understanding of etiologic factors. This symposium is an effort by the American Society for Nutritional Sciences to provide an overview of a complex and often controversial area of nutritional and breast cancer. The goals are to provide a summary of current knowledge derived from laboratory and epidemiologic studies, discuss the strengths and limitations of current investigative tools, and foster collaborative multidisciplinary and integrative research.
approaches to test novel hypotheses. The following is a brief historical perspective on the development of major concepts in the area of dietary lipids and energy, anthropometry, genetics and breast carcinogenesis.

HISTORICAL PERSPECTIVES: EXPERIMENTAL NUTRITION AND BREAST CARCINOGENESIS

The investigation of nutrition and breast cancer greatly expanded during the latter half of this century due to the development and characterization of the tools necessary for laboratory and epidemiologic investigations. The first half of this century was the “golden age” of nutrition, when human nutrient deficiency syndromes were characterized and animal models developed, essential nutrients identified and chemical structures determined, biological and chemical assays for nutrients validated, nutrient composition of major foods tabulated, and public health interventions involving supplementation and nutrition education were instituted. These efforts culminated in the virtual elimination of nutritional deficiency syndromes for the majority of the American public.

In parallel to the progress in the nutritional sciences, many fundamental principles of carcinogenesis were also established during this period. The identification of pure chemical carcinogens from environmental substances associated with human cancer rapidly led to the characterization of many animal models of carcinogenesis. The concept that specific chemical substances act as tumor initiators, co-carcinogens or tumor-promoting agents by Berenblum (1941) provided the framework for many future studies of nutrition and carcinogenesis. The development in the 1930s and 1940s of genetically homogeneous inbred strains of mice that exhibited various susceptibilities to breast tumor development provided early clues into a role for genetic factors (Strong 1935). The possibility that viral infections contributed to mammary carcinogenesis was indicated in early studies showing the transmission of a tumor-promoting substance via the milk in mice (Bittner 1935). By 1940 the nutrient requirements of rodents were well defined, and purified components of foods were available for the preparation of carefully controlled experimental diets in studies using the new models of mammary carcinogenesis. The meticulous studies of Albert Tannenbaum and colleagues published (1940) confirmed tumor (odds of a tumor/probability of no tumor) induced by more recent studies describing increased growth rates of breast tumours in immune deficient mice fed high fat diets (Blank and Ceriani 1989, Borsoson et
TABLE 1
Effects of dietary fat concentration as corn oil on energy intake, body weight and tumor incidence in female Sprague-Dawley rats given 7,12-dimethylbenz(a)anthracene at 56 d of age

<table>
<thead>
<tr>
<th>Dietary fat (% energy)</th>
<th>No. rats</th>
<th>Intake kcal/d</th>
<th>Final body weight g</th>
<th>Palpable tumors %</th>
<th>No. lesions</th>
<th>Tumors at necropsy %</th>
<th>No. lesions</th>
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<tbody>
<tr>
<td>12</td>
<td>119</td>
<td>46</td>
<td>263</td>
<td>35</td>
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<td>54</td>
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<tr>
<td>48</td>
<td>117</td>
<td>47</td>
<td>260</td>
<td>74</td>
<td>222</td>
<td>70</td>
<td>182</td>
</tr>
</tbody>
</table>

1 Rats were assigned to dietary treatment at weaning (28 d of age) (Clinton et al. 1984).

al. 1989, Gabor et al. 1990, Gonzalez et al. 1991). The strength and overall consistency of results with regards to dietary fat and energy in the laboratory studies cannot be easily dismissed, particularly because these same models mimic many aspects of human breast cancer biology and have proven useful for the testing of anti-cancer therapies.

HISTORICAL PERSPECTIVES: NUTRITIONAL EPIDEMIOLOGY OF HUMAN BREAST CANCER

Nutritional epidemiology has emerged as a vigorous discipline in recent decades. Epidemiologic studies in the area of nutrition and cancer can be generally categorized as ecologic, case-control, prospective and intervention. The initial efforts in nutritional epidemiology were dependent upon the development of cancer incidence surveys in the nations around the world. It was soon evident that cancer rates varied dramatically in different countries (Wingo et al. 1995) and that migration from a low risk area to a high risk location was associated with the migrant population assuming the rates observed in the adopted country. These observations focused etiologic hypotheses upon environmental factors, foremost of which was diet. Breast cancer rates in Japanese immigrants to the United States approach the prevailing rate of Americans over two generations (Buell 1974). Perhaps there is a gradual acculturation and adoption of the affluent American diet. This hypothesis seems less likely with the data showing that colon cancer rates increase much more rapidly, even in the first generation migrants (Willett 1989). These data also suggest that risk may be related to dietary factors during adolescence, a period of maximal breast development. Indeed, rodent studies have shown a profound interdependence of age, breast development and time of carcinogen exposure on risk of breast carcinogenesis. The observations in human migrants and rodent models strongly suggest that additional efforts should be directed to understanding the combined effects of diet, nutrition, endocrine status and genetic factors during adolescence and how they may combine to modify breast development and susceptibility to cancer.

A second component of the puzzle was provided when food availability data and estimated nutrient contents of foods in nations around the globe were compiled. A report by Carroll and Kohr (1975) showed a strong and direct correlation between the per capita availability of dietary fat and national breast cancer rates, which supported the many published animal studies. The hypothesis that dietary fat played a critical role in human breast cancer became a predominant theory of breast cancer etiology for many years. Causal inference based upon ecologic studies alone is impossible because so many other characteristics differ between the populations that could be contributing to cancer risk and the intake of dietary fat. Although nonspecific, ecologic studies allow the evaluation of nutrition intake or a food component across a much wider range than can be conducted within a nation and provide a fertile source of new hypotheses.

Case control studies are based on comparisons of retrospective dietary data between paired groups with and without breast cancer. Many of the past studies were of such limited size that the ability to detect an effect of fat over the narrow range of intake observed was very limited. The major concern, however, is the issue of differential recall of diet by persons with breast cancer compared with controls (Giovannucci et al. 1993). Breast cancer has been the subject of many case control investigations, and recent meta-analyses of published studies suggest a modest increase in risk associated with high fat dietary patterns (Boyd et al. 1993, Howe et al. 1990).

Prospective or cohort studies define a population that is monitored for incidence of disease and exposure to potential risk factors over time. Large cohort studies in the area of nutrition became possible with the gradual evolution and refinement of the food-frequency questionnaire over the last three decades (Willett 1990). The studies avoid inaccuracies of estimating dietary intake retrospectively, and the prospective assessment of diet is unbiased by the cancer experience. The
main disadvantage is the enormous cost associated with large studies having long periods of follow-up. To the surprise of many, the prospective studies have not provided data supportive of the dietary fat and breast cancer relationship (Hunter et al. 1996). Indeed, these highly publicized studies are often quoted as proving that a relationship between fat concentration and breast cancer is extremely unlikely. The limitations of current assessment tools to accurately measure exposure and of statistical approaches to correctly dissect independent effects of dietary fat concentration, lipid source, energy balance or body size while adjusting for the other variables should be recognized and efforts directed towards improving our methodology.

Intervention studies offer obvious scientific advantages compared with observational epidemiology and would be most analogous to the laboratory studies in animal models. However, intervention studies will remain few in number due to costs associated with the very large sample population necessary to generate the statistical power needed to evaluate the effects of a dietary risk factor on outcomes that are infrequent in the average population. Furthermore, the inability to ensure or carefully document compliance, as well as ethical considerations that limit major interventions over long time periods, prevents implementation of studies.

HISTORICAL PERSPECTIVES: GENETICS AND BREAST CANCER

The contribution of genetics to the human breast cancer burden is poorly understood. However, progress in the field is rapid, and it is reasonable to postulate that genetic testing focusing upon a panel of relevant genes will be technically feasible within a decade. In contrast to the pace of development in the science and technology of genetic testing for breast cancer risk, many ethical, psychological, economic and social consequences of individual or population-based testing remain to be addressed. For example, the possibility that common genes of lower penetrance and those genes modifying host-environment interactions. Polymorphisms in genes controlling lipid and energy metabolism, carcinogen activation and detoxification, hormone synthesis and clearance, signal transduction pathways and immune function are beginning to be characterized, and these may potentially interact with diet, nutrition and other environmental variables to modulate breast cancer risk.

SUMMARY

It is clear that an improved understanding of the complex relationships of dietary fat, energy balance, anthropometrics, genetics and breast cancer risk can be accomplished only by multidisciplinary approaches. Definitive intervention studies designed to test dietary hypotheses are rarely practical in human populations, and it is unlikely that funding to support these efforts will become easier to obtain in the near future. Therefore, dietary and genetic interactions will be inferred from observational epidemiologic studies, short-term intervention trials examining biological markers of cancer risk, and investigations in laboratory models. A major obstacle in this field has been the failure to clearly define the sequence or pattern of events involved in the breast cancer cascade. In contrast, many studies of dietary intervention have been completed using blood cholesterol, triglycerides or lipoprotein profiles as surrogates for coronary artery disease. It is very important that intermediate markers of breast cancer risk be characterized because many short-term studies could be undertaken to provide data that will augment or refute the etiologic hypotheses that have been proposed. These and many other issues will be explored in this symposium, with the hope that readers will integrate information derived from a diverse array of investigations and formulate new approaches that will take us one step closer to effective breast cancer prevention programs.

LITERATURE CITED

Gabor, H., Blank, E. W. & Ceriani, R. L. (1990) Effects of dietary fat and mono-


