Title
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Permalink
https://escholarship.org/uc/item/07s0b75j

Journal

ISSN
0959-8049

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Publication Date
2000-06-01

Peer reviewed
Cancer population genetics and tumour prevention: an unfulfilled paradigm

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Received 24 March 2000; accepted 27 March 2000

Abstract

The molecular approach to cancer has identified specific abnormalities that contribute to malignant pathogenesis in an aetiological manner and define individuals who are at higher risk for specific malignancies. Studies of cancer distribution in families suggest that 15–20% of all malignancies may have a significant germ line hereditable mutation that directly or indirectly contributes to tumour development. Additionally, the identification of many genetically-determined polymorphisms that regulate carcinogen metabolism indicate that their assessment may contribute to selecting individuals for preventive surveillance or intervention as well. Locating individuals in the population who have moderate to high risk germ line mutations in critical oncogenic regulatory genes and assessing a panel of polymorphisms that underlie a significant attributable risk for cancer development may allow the recruitment of individuals at high risk for a particular malignancy and, therefore, represent good candidates for either directed organ surveillance and/or chemoprevention trials. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: Genetic; Chemoprevention; Prevention; Polymorphism; Tumour suppressor gene; Oncogene; Predisposition; Surrogate endpoint biomarkers

1. Some lessons learned from prior chemoprevention trials

Overall, despite the extensive epidemiological studies and experimental data that supports such an approach, the overall results from large chemoprevention trials in human cancers have been disappointing [1]. Although there have been a few quite positive trials in sporadic aerodigestive, cervical, hepatocellular, colon and breast cancer [2–6], only in breast cancer have the results been sufficiently impressive to lead to drug approval, although widespread usage has not yet occurred.

Several overall important lessons can be gleaned from these trials which should be important in the planning of future studies, including the participation of individuals at high familial or genetic risk. These observations include:

1. Epidemiology is not enough. The negative trials involving cervical intraepithelial neoplasia and folic acid or β-carotene [7–10] and antioxidants and colon cancer [11] and the adverse results (increased numbers of lung cancers and increases in overall mortality) with β-carotene in heavy smokers [12,13] should raise considerable concern, in particular, since the experimental data to support the implementation of the β-carotene studies was minimal.

2. Indirect markers are not enough. Despite the favourable effect of fibre supplementation on bile acids [14] the addition of wheat bran to the diet did not affect the appearance of new colonic polyps in a carefully done phase III randomised trial (D. Alberts, Arizona Cancer Center, USA). Additionally, none of the candidate surrogate endpoint biomarkers developed to date have been validated as predictive of cancer development, although expression of beta-retinoic acid receptor in aerodigestive malignancies may be an important predictor of response [15].

3. Toxicity may preclude general usage, even if the compound is effective. The best example of this principle by far has been the experience with 13-cis retinoic acid (Accutane, Isotretinoin). This retinoid has been shown to suppress oral leucoplakia [16] and second malignancies in patients with prior

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Received 24 March 2000; accepted 27 March 2000

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2. Types of endpoint markers and chemoprevention

A presumption in the identification and development of endpoint markers to assess chemoprevention efficacy is that carcinogenesis is the disease, not cancer, and that the markers are true surrogates for cancer occurrence. However, the correlation need not be precise, for example, the lowering of cholesterol, one of many factors that contribute to atherosclerosis, leads to a remarkable lowering of the appearance of cardiovascular-associated disease. Notwithstanding this caveat, two general principles have emerged from the attempt to develop biomarkers relevant for cancer chemoprevention. First, compounds need to affect the relevant biochemical pathway in the target tissue at doses that produce minimal or no toxicity. Second, compounds need to affect the relevant biomarker in the target tissue at doses that produce little or no toxicity.

Markers can be considered at five different levels of pathogenesis: (Table 1) hereditable susceptibility (pre-disposition), exposure, intermediate endpoint (both on non-causal and causal pathways), drug modulatable and tumour. Our main interest in markers vis-à-vis population cohorts and chemoprevention are predisposition and intermediate endpoints. It has been estimated that up to 15–20% of the population may have a familial tendency to cancer and that the influence of polymorphisms on the metabolic regulation of carcinogens may be even more pervasive. Predisposition alterations have, in general, not been considered as also serving simultaneously as surrogate endpoint biomarkers (SEBM), although in this writer’s opinion they should be and direct (e.g. oncogene or tumour suppressor gene) or indirect (e.g. enzyme polymorphisms) measurements of their expression at the RNA and protein level in relevant tissues are frequently possible.

An assignment of risk based on the presence of predisposition and intermediate markers can be developed. In general, high relative risks associated with germ line mutations in tumour suppressor or oncogenes are uncommon and, therefore, the attributable risk is low. In contrast, metabolic polymorphisms produce low relative risks but involve a substantial portion of the population and, therefore, the attributable risk may be high. It may be that simultaneous identification of a defined cohort with familial (in contrast to hereditary) risk and selected metabolic polymorphisms may be a particularly useful way to identify a large number of individuals appropriate for a chemoprevention trial. To date this approach has not been tried, but would be reasonable and timely to pursue.

3. Steps in the development of a surrogate endpoint biomarker

The study of SEBMs presents innumerable problems. Although most investigators accept intraepithelial neoplasia and other precancers (e.g. actinic keratoses, adenomatous polyps, bronchial metaplasia) as a SEBM with relatively high relative risk, earlier markers of risk, such as a molecular (e.g. particular RNA expression), biochemical (e.g. protein expression or enzymatic activity) or immunological (e.g. antigenic expression) changes have not yet been validated. The goal of validating a pre-histological marker has not been achieved as it is difficult to do so and takes a great deal of time and resources.

Formally, the steps to the successful development of a SEBM include identification of a candidate intermediate marker associated with carcinogenesis in the target organ of interest, demonstration that modulation of the marker occurs in response to the drug of interest, correlation of the marker with the development of cancer and demonstration that modulation of the marker by the drug of interest correlates with the incidence of the cancer under study. To date this schema has not been fulfilled although studies of retinoids and p53 and β-
retinoic acid receptor expression in aerodigestive malignancies and difluoromethylornithine and polyamine content in colon polyp patients are moving toward fulfilling these criteria [15]. A diagrammatic representation of some of the issues is presented in Fig. 1. In scenario A, a strong hereditable change leads directly to cancer. Such cases are rare (e.g. retinoblastoma). In scenario B, the predisposition alteration is also strong and a clear histologically-identifiable preneoplastic phase is traversed during the development of a frank malignancy. The familiar example of this situation would include familial adenomatous polyposis. Scenario C represents a situation in which either a hereditable and/or acquired change occurs but other genes are involved before a preneoplastic phase is encountered on the way to cancer. Scenario D is similar to C, except that multiple acquired genetic changes have occurred that are nevertheless the causal pathway. In scenario E, an acquired change (or it could be hereditable) occurs that produces downstream marker changes that are not on the causal pathway. This pathway is likely to be the most common one encountered but making that designation a priori may be impossible. Recently, there has been considerable interest in using modulation of intraepithelial neoplasia and other precancers with associated high risk as a SEBM. This is probably prudent as it should allow drug approvals in a shorter time frame and importantly should lead to a commitment of the pharmaceutical industry to chemoprevention drug development; the recent approval of Celebrex for familial adenomatous polyposis patients is a recent case in point and has led to re-energising the entire field.

4. The future of chemoprevention

The concurrent development and application of relative risk profiles in population cohorts and organ-specific SEBMs in these individuals should be an effective way to identify candidates for chemoprevention of sufficiently high risk so that sample sizes can be reduced and trials completed in less time with lower costs. Pre-disposition relative risk as assessed by germ line mutations, targeted polymorphic gene assessment and classical epidemiological profiling, linkage of molecular alterations that are on the causal pathway to carcinogenesis and the development of specific agents that modulate the carcinogenesis process should be a powerful paradigm from which to move the field of chemoprevention forward to an increasing role in overall cancer management.

Acknowledgement

Supported in part by the Chao Family Comprehensive Cancer Center and P50 CA62230.

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