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Hereditary cancer syndromes as model systems for chemopreventive agent development

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ABSTRACT

Research in chemoprevention has undergone a shift in emphasis for pragmatic reasons from large, phase III randomized studies to earlier phase studies focused on safety, mechanisms, and utilization of surrogate endpoints such as biomarkers instead of cancer incidence. This transition permits trials to be conducted in smaller populations and at substantially reduced costs while still yielding valuable information. This article will summarize some of the current chemoprevention challenges and the justification for the use of animal models to facilitate identification and testing of chemopreventive agents as illustrated though four inherited cancer syndromes. Preclinical models of inherited cancer syndromes serve as prototypical systems in which chemopreventive agents can be developed for ultimate application to both the sporadic and inherited cancer settings.

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1. Introduction

The search for the ideal natural, synthetic, or biologic agents to reverse, suppress, or prevent cancer has been the aim of cancer chemoprevention research, beginning in 1976 with Dr Michael Sporn's [1] creation of the term "chemoprevention". The approvals of tamoxifen and raloxifene by the FDA (1999 and 2007, respectively) for breast cancer chemoprevention, or more precisely risk reduction, were successes that have yet to be achieved by other agents such as aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) for colorectal cancer and finasteride for prostate cancer prevention.

Disappointing results from large trials and budgetary constraints have led to a shift in focus from funding large, phase III randomized trials to smaller earlier phase studies focused on safety, mechanistic elucidation, and biomarker development. Biomarkers of drug effect may serve as surrogate endpoints for cancer incidence and drug toxicity.

Another approach to overcoming the burden of large trials is to study very high-risk populations with germline mutations. Among individuals with such inherited genetic changes the rate of cancer development is much higher, allowing the use of smaller sample sizes than do trials involving moderately increased risk populations. Another advantage of the inherited syndrome approach is the well-defined genetic cancer predisposition of the cohort, which contrasts with the use of populations at moderately increased risk that may be considerably more heterogeneous at the molecular level. The use of genetic syndromes also facilitates the development of agents that target the relevant mutations. The value of testing chemopreventive agents in these high penetrance syndromes extends beyond the syndromes themselves to possible relevance for prevention of equivalent cancers in the sporadic setting.

In addition, representative animal models of human hereditary cancers driven by germline mutations in a single gene or family of genes can be very useful. Inserting the relevant mutation into the genome of an animal, results in an imperfect but valuable model of human disease. Despite routine use, animal models of cancer have certain limitations, especially the fact that the physiology of a rodent is in many ways dissimilar to that of a human. Rodents have a much shorter life span, and in general tumors that arise in rodents are not as genetically complex at the chromosomal level as

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Table 1
Mouse models of hereditary cancer syndromes.

Animal model	Description	Outcome
APC mutant mice (Min, *APC* codon 1638 mutation)	Have mutation in *APC* gene relevant for Gardner syndrome (FAP) as well as most sporadic colon cancers.	• Mice develop multiple adenomas but most are in small intestine • Mice respond to multiple agents that are effective in humans (NSAIDs, DFMO) • Results in mice supported celecoxib trial in FAP that gave a positive result
MSH or *MLH* knockout mice Lynch/HNPCC	Have knockout of *MSH* or *MLH* while humans (Lynch/HNPCC) have mutations or methylation (sporadic colon cancer).	• Mouse tumors like the humans exhibit MSI phenotype • Mouse tumors do not show mutations in *TGFβRII* or *BAX*, which are mutated in humans, due to lack of nucleotide repeats in coding region of mice. • Mice appear to be responsive to NSAIDs as are humans.
p53 knockout mice (LFS)	Typically knockout *p53* mutations. Partially overlapping tumor spectra between human and mouse (osteosarcomas and lymphomas but not carcinomas and no metastasis). Tumor spectrum is dependent on strain of mouse.	• Mice with *p53* mutations or knockouts respond to agents which are effective in the organ in which they occur.
p53 R270H or R172H knockin mice (Li-Fraumeni)	LFS mouse model with specific *p53* arginine to histidine missense mutation at codon 172 or 270 corresponding to human hotspot mutation at codon 175 or 273, respectively.	• Mice develop osteosarcomas, lymphomas, and carcinomas (similar to human LFS), with metastasis occurring to lymph nodes, lung, liver, and brain.
BRCA1/2 mice	Often knockout or partial deletion of *BRCA1/2* in mice versus typically nonsense mutations in humans	• In *BRCA1*-deficient mice, a *p53* alteration must also be present in order to get a reasonable number of tumors. Most human *BRCA1* tumors have P53 mutations • Resulting mammary tumors have multiple genomic changes in mice and humans. • PARP inhibitors are relatively effective in both mice and humans.

Abbreviations: APC, adenomatous polyposis coli; DFMO, difluoromethylornithine; FAP, familial adenomatous polyposis; HNPCC, hereditary nonpolyposis colon cancer; LFS, Li- Fraumeni syndrome; MSI, microsatellite instability; NSAIDs, nonsteroidal anti-inflammatory drugs.

human tumors. Cancers in animals typically exhibit less systematic amplification or deletion of specific chromosomal regions that are affected in human cancers.

A key difference between the species is evident in the nature of the mutation. In man most hereditary syndromes are driven by one mutated allele in the germline and a second mutation in or loss of the intact allele in the tumor tissue. Interestingly, in animals, mutation or loss of a single allele (eg, *BRCA1/2*, *MSH* or *MLH*) in the germline does not routinely yield an animal with a tumor phenotype. Yet, mutations or knockouts of both copies of the gene in the germline can result in developmental changes or even embryonic toxicity, as in the case of *BRCA1/2* [2]. This has prompted the development of models (Table 1) where the mutation or knockout of these genes is accomplished selectively in the target tissue.

Herein we will address the current challenges of chemoprevention and the rationale for using inherited cancer syndromes as model systems for identifying and testing chemopreventive agents. While more than 50 hereditary cancer predisposition syndromes have been identified [3], four major inherited cancer syndromes that have accepted clinical genetic testing, established animal models, and ongoing chemoprevention efforts will be discussed: hereditary breast and ovarian cancer syndrome, Li-Fraumeni syndrome, familial adenomatous polyposis, and Lynch syndrome.

2. Hereditary breast and ovarian cancer syndrome, *BRCA1* and *BRCA2*

Having a family history of breast and/or ovarian cancer has long been recognized as a risk factor for these malignancies [4–5]. Of the dominant, high-penetrance susceptibility alleles identified to date, mutations in *BRCA1* and *BRCA2* associated with hereditary breast and ovarian cancer syndrome (HBOC) are the most prevalent affecting approximately 1/400–800 in the general population [6]. The prevalence is higher in populations such as Ashkenazi Jewish and Icelandic populations due to founder mutations [7–9].

2.1. Mutation spectrum

Both *BRCA1* and *BRCA2* are large genes: 24 exons encoding 1,863 amino acids for *BRCA1* [10]; and 27 exons encoding 3,418 amino acids for *BRCA2* [11]. Hundreds of different mutations span each gene, with more than 1,700 different *BRCA1* and 2,000 different *BRCA2* mutations, polymorphisms, and variants reported in the Breast Cancer Information Core, an online *BRCA1/2* mutation database [12].

2.2. Penetrance data

Since the identification of *BRCA1* in 1994 [10] and *BRCA2* in 1995 [13], several studies have described the cancer penetrance of these mutations. The breast and ovarian cancer risks vastly exceed the risks found in the general population. Two separate meta-analyses have been conducted that help clarify the risks for breast and ovarian cancer by age 70, which are summarized in Table 2. These risks are lower in these population-based studies than in the original Breast Cancer Linkage Consortium data where risks for *BRCA1*or *BRCA2* mutation-associated breast cancers approached 85%. Of note, the latter data were subject to family ascertainment bias [14,15]. Individual risks do vary based on personal, environmental, and genetic modifiers. Additionally, mutations in the 3′ and 5′ end of the *BRCA1* and *BRCA2* genes confer higher risks for breast cancer while mutations in the central portion of the *BRCA1* and *BRCA2* confer higher risks for ovarian cancer but lower overall breast cancer risks [15].

2.3. Mechanistic data

Both *BRCA1* and *BRCA2* are tumor suppressor genes and critical to chromosome structure preservation and numeric control during