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Journal
Recent results in cancer research. Fortschritte der Krebsforschung. Progrès dans les recherches sur le cancer, 166

ISSN
0080-0015

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Publication Date
2005

Peer reviewed

RRCR (2005) 166:113–124

How Should We Move the Field of Chemopreventive Agent Development Forward in a Productive Manner?

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Abstract Epidemiologic observations and preclinical experimental investigations suggest that the prevention or reversal of precancers should be an effective strategy in humans to control cancer. Although "proof of principle" has been established in humans, the results of randomized trials have not been confirmatory in most cases. Toxicity in normal or near-normal populations has also been greater than anticipated. We examine the problems associated with testing chemoprevention agents in humans and offer a process and guidelines that may better inform the logical development of this relatively young clinical field.

1 Introduction

The word "chemoprevention," with reference to cancer, was coined in 1976 and has evolved to encompass the suppression or reversal of cancer using natural or synthetic compounds (Sporn et al. 1976; Meyskens 1992a,b). Both prior to 1976 and subsequently, a considerable amount of epidemiologic and preclinical experimental evidence has accumulated suggesting that human cancer should either be preventable or else reversible or suppressible in its early stages. However, definitive large randomized trials in humans based on epidemiologic observations have generally yielded disappointing results (review cervix, Follen et al. 2001; colorectal, Viner et al. 2002), with adverse results (more lung cancers) produced by β-carotene supplementation in smokers (Omenn et al. 1996) and no effect of fiber supplementation on ade-

nomatous polyp recurrence in patients with one or more prior adenoma (Alberts et al. 2000; Schatzkin et al. 2000).

Randomized trials based on experimental data have yielded somewhat more encouraging results, with retinoids being demonstrated to clearly suppress the development of second cancers in head and neck cancer patients (Hong et al. 1990), and tamoxifen given at standard doses being effective in substantially decreasing the incidence of breast cancers in women at high risk for this event (Fisher et al. 1998). However, both studies demonstrated a sufficiently high level of toxicity (for putatively healthy individuals) such that neither compound has entered widespread usage, despite FDA approval for the latter indication. Attempts to use a lower non-toxic dose of retinoid were unsuccessful and ineffective in preventing secondary lung cancers in a well-defined cohort (Lippman et al. 2001). Similarly, the attempt to prevent prostate cancer with finasteride, a specific inhibitor of the conversion of testosterone to its active form dihydrotestosterone, has produced mixed results. The total incidence of prostate cancer was significantly decreased in a large randomized placebo-controlled trial; however, the number of advanced ($\geq$Gleason 7) tumors was significantly increased and a slightly increased incidence of urogenital side effects was noted (Thompson et al. 2003). Whether or not finasteride is approved by the FDA, these findings suggest that this agent may not be widely adopted.

One of us (F.M.) has posed a number of questions in this series of conferences (Meyskens 1998; Meyskens 2000a,b,c). The two broad questions we must now ask ourselves are: (1) Why have we been so unsuccessful in translating positive epidemiologic and experimental findings to clinical benefit? (2) How should we move the field of chemopreventive agent development forward in a manner that is more productive?

2 Through the Retrospectroscope

Based on the results of randomized studies done to date, a series of questions that need to be addressed, discussed, and debated has emerged:

1. *Are the results of epidemiologic observations alone ever enough to embark on a phase III trial?*

   Studies of non-oncological diseases have suggested that a very substantial effect must be evident in epidemiologic observations if a significant result is to be demonstrated in a randomized clinical trial (Ioannidis et al. 2001). In general, the effect demonstrated in a randomized trial is 40%–50% less than would be anticipated from observation studies. This caveat therefore

indicates that relative risks or odds ratios that are much greater than 0.5 or 0.6 will require a very large sample size in a randomized trial to demonstrate the 25%–30% reduction that might occur with a highly effective agent. In general, the effects of dietary compounds as measured by observation trials has been modest, so it is entirely likely that most cancer clinical chemoprevention trials involving dietary compounds have been underpowered to demonstrate a clinical effect, notwithstanding the possibility that the negative trials could also reflect assessment of the incorrect nutrient or dietary compound as well as incorrect doses of such compounds.
Our answer to this first question is:

No, epidemiologic observations alone are rarely, if ever, enough.

2. *What level of toxicity precludes further development of preventive agents?*

From the experience to date, it is clear that the presence of efficacy and excessive toxicity have about equal weight in determining whether an agent is developed or adopted, with potential effectiveness driving development and toxicity inhibiting both development and adoption. Several aspects about the assessment of toxicity in a chemoprevention setting are worth reviewing. Given that cancer prevention aims to prevent an event (cancer) that has not yet occurred and may never occur in a significant portion of the at-risk population, the toxicity of chemopreventive compounds must be considerably lower than the toxicity of agents used in cancer treatment trials, and the risk–benefit ratio must be considerably lower as well.
As an example (with the clarity provided by hindsight), first generation retinoids were used beyond the point at which it should have been evident that they were too toxic for most preventive indications; also, there was failure to recognize that effectiveness and toxicity were too closely linked to allow separation of these two features by simple dose reduction. Retinoid drug development would have been better served by the conduct of careful phase II dose–response preliminary efficacy studies before proceeding to large randomized trials. In contradistinction, tamoxifen had been used in the treatment setting for over 20 years by the time that the P-1 breast cancer prevention trial was begun and the side-effect profile was well known. However, tamoxifen had not been studied systematically in a randomized trial of the size of the P-1 trial, with the same attention to long-term toxicity monitoring as was provided by the P-1 trial. Hence, it should not have been a surprise that side effects were seen; what was surprising was that despite a very efficacious result, tamoxifen has not been widely adopted for risk reduction of breast cancer due to the perception by both patients and physicians alike that the drug is "too toxic."
On the other hand, toxicity of agents that have been used for other indications may be exaggerated and a potentially effective compound may be dismissed. An instructive case in point has been our experience in developing the polyamine synthesis inhibitor difluoromethylornithine (review,

Meyskens and Gerner 1999). Originally developed to treat leukemia using massive doses, the uncommon side effect of ototoxicity was uncovered. Once preclinical and mechanistic studies suggested that difluoromethylornithine may be a potent chemopreventive agent, its development was markedly hampered by the perception of ototoxicity. However, careful and systematic placebo-controlled studies have subsequently shown that polyamine-lowering in tissues can be achieved using doses that are 1/100th of those used for treatment, and that at these doses hearing loss in placebo and treated patients is equivalent (Croghan et al. 1991; Meyskens et al. 1994, 1998, 2001).

Our answer to the second question is:

Toxicity of chemoprevention agents in humans has, in general, not been well-delineated in the phase II setting, and careful placebo-controlled trials should be mandatory before proceeding to definitive phase III randomized studies. Toxicity has been both underestimated and overestimated from failure to critically assess this parameter in relation to the modulation of the relevant biologic/biochemical/molecular endpoint.

3. *How much can animal models tell us?*

In general, animal models have not adequately simulated the human disease being studied. The use of high single (or a few) doses of carcinogen in most animal models does not represent the manner in which humans are exposed to carcinogens. Transgenic animals that are highly engineered to produce a certain result have similar limitations. Nevertheless, demonstration that a particular compound reduces the incidence of tumors across a spectrum of animal models may suggest efficacy and provide important insights into mechanisms of carcinogenesis and cancer prevention. One must keep in mind, however, that the dose of the chemopreventive compound employed in animal studies may be unrealistically high for human use, thereby producing a toxic effect that cannot be detected in animal studies; however, this explanation has been rarely invoked for failure of a compound active in the preclinical setting that was ineffective clinically.

Of greater importance is the failure of animal models to develop the field of intermediate markers (Meyskens 1992, 2001). Although the measured endpoint is almost always tumor (adenoma and/or carcinoma) incidence or multiplicity in animal models, the relationship of the true endpoint of cancer to the intermediate markers has not been systematically assessed. However, in the human setting, where the development of cancer as an endpoint requires lengthy studies in very large numbers of participants, large numbers of potential markers are being advocated without the possibility of correlation with the true endpoint, which is rarely measured. A critical set of information that animal models could contribute to the database would be systematic studies of intermediate markers and their correlation to the true endpoint in models that represent the disease process in humans as closely as possible.

Our answer to the third question is:

Animal studies can provide valuable information aiding the decision-making process for chemopreventive agent development, both in agent identification and in validation of intermediate endpoints. However, the value of such studies in agent identification is frequently overestimated, while the value in validating intermediate endpoints has been underutilized.

4. The final and most critical question in chemopreventive agent development is:

   What level of evidence will lead to adoption of a chemopreventive compound for general usage?

   On the one hand, several compounds have been approved for chemoprevention (Table 1, broadly defined) and are in general use, including topical BCG for bladder carcinoma in situ and topical 5-fluorouracil and diclofenac (a COX-1 inhibitor) for actinic keratoses. Both aspirin and calcium have been shown to reduce adenomatous polyps in large randomized trials (Baron et al. 2003; Sandler et al. 2003), but their usage has thus far not been widely adopted—perhaps because the risk reduction was relatively small (about 20%). However, tamoxifen produced a substantial (50%) reduction in the P-1 breast cancer prevention study, but has not been widely adopted because "toxicity" in this cancer-free group of women has been deemed excessive (despite FDA approval). More surprising is the fact that tamoxifen does not seem to be widely used even in high-risk women who show a genetic predisposition to breast cancer. In contrast, the photosensitizer Photofrin has demonstrated a modest effect in Barrett's esophagus in a non-randomized trial, but its usage, at least in the U.S., appears to be substantial (review, Wang and Kim 2003). Although, these usages and approvals seem to undermine a call for the systematic development of chemoprevention

Table 1. How much/how often are chemopreventive agents used for approved indications

Condition	Agent	Use
Bladder CIS	BCG/topical	High
	Chemotherapy (several)	High
AK	5FU	High
	Diclofenac	?
Adenomas (FAP)	Celebrex	?
Adenoma (sporadic)	Aspirin	?
	Calcium	?
Barrett's esophagus	Photofrin	Often
Breast	Tamoxifen	Low (sporadic)
		? BRCA
Stomach	Antioxidants	?

AK, adenylate kinase; BCG, bacillus Calmette-Guérin; CIS, carcinoma in situ; FAP, familial adenomatous polyposis.

agents (Kelloff et al. 1995, 2000), the high cost, risk–benefit considerations, and potentially broad impact of chemopreventive agents mandate that agents be developed carefully. A proposed algorithm for the process by which candidate chemopreventive compounds enter definitive randomized trials (phase III and potentially phase IIb) is discussed below.
Our answer to the fourth question is:

Chemopreventive agent usage is dictated by risk–benefit assessments, both real and perceived. High efficacy and low toxicity are required. To ensure that both criteria are met, agent development guidelines, incorporating an assessment of all existing information and calling for ascertainment of missing information, are proposed.

3 Some Further Caveats

Other critical issues which are discussed in more detail elsewhere (Baker 2000; Armstrong et al. 2003) and in this volume (see the chapter by Armstrong et al.) include:

1. The multiple pathways to cancer and the limiting effect this may have on the development of biomarkers as surrogates for the true endpoint.
2. The common assumption is that modulation of a biomarker equates to a change in the incidence of the true endpoint and therefore is predictive; hence the biomarker is a surrogate. But this assumption is incorrect. This is a particularly common mistake when a marker seems to have good prognostic ability; that is, the presence of the marker is a good estimator of the disease endpoint. Simply put: prognostic is not predictive (also see Fleming and DeMets 1996 and Herrington and Howard 2003).
3. The term "surrogate endpoint biomarker" (SEBM) has been used in a rather cavalier fashion, and imprecision in language has resulted in much confu-

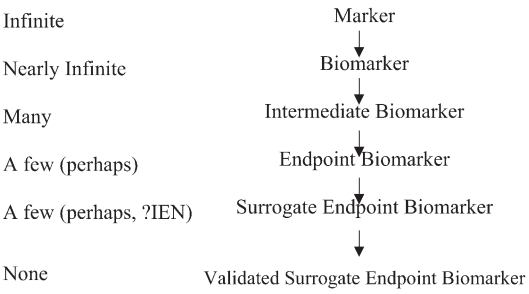

Fig. 1. The terminology of markers. In assessing the carcinogenesis process, representation ranges from a nearly infinite number of markers to the rare (currently none) validated surrogate endpoint

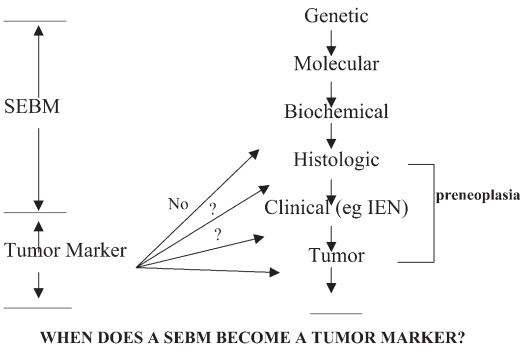

Fig. 2. A tumor marker is not a surrogate endpoint biomarker. The carcinogenesis process is a continuum, but once a marker has evolved from a potential surrogate (*SEBM*) to an actual tumor marker, the process of assessment and the implications changes

sion. A hierarchy of marker terminology is shown in Fig. 1. Accurate use of these terms is critical to avoid over- or underestimating progress.

4. Another serious mistake in cataloging is the equating of biomarker, especially SEBM, with tumor marker (Fig. 2). Notwithstanding the difficult issue of knowing when a cell becomes cancer, a tumor marker implies (and represents) something entirely different than an intermediate marker, and the two should not be confused if we are going to be successful in moving the field of chemoprevention ahead intelligently.

4 Guidelines

A major challenge facing those dedicated to bringing promising preclinical agents to clinical fruition is their systematic development. Although the process by which agents are advanced from preclinical to clinical studies and the systematic development of early clinical activity (pilot, phase Ia/Ib, IIa) is extremely important—a topic which we and others have discussed at length (Goodman 1992; Meyskens 1992b, 2001; Kelloff et al. 2000)—the critical juncture in chemopreventive agent development (and in the development of most drugs) is the decision to proceed to a definitive randomized phase IIb or phase III trial. The process by which this occurs in medicine in general has not always been systematic, and this is even more true for chemoprevention.

We propose a set of guidelines by which decision-making can be better informed (Table 2). The overall goal is to require the decision-maker to evaluate all available evidence that can be informative and to identify missing information before embarking on phase III trials, so that the final decision to proceed with lengthy and costly definitive studies will take place after full

Table 2. Level of evidence and relative merit in moving a chemopreventive agent to large randomized trials

1. Experimental evidence	Maximum points	Low
Mechanism	Low	↓
In vitro	↓	↓
Animal	High	↓
2. Epidemiologic		↓
Case-control	Low	↓
Cohort/ecologic	↓	↓
Secondary analysis	High	↓
3. Clinical		↓
Biomarker	Low	↓
Preneoplasia	↓	↓
Neoplasia	High	↓
4. Trials		↓
Phase Ia/Ib	Low	↓
Phase IIa biomarker/dose-response	↓	↓
Phase IIb biomarker/dose-response	High	High

Other beneficial effects on health (e.g., prevention of CAD, osteoporosis, etc.): additional positive points. Toxicity: negative points.

consideration of all information. The guidelines identify various types of evidence (experimental, epidemiologic, clinical, and trials) that should be considered and assign point values for each category. Within each category we have established a hierarchy of evidence, with increasing value given to those elements that are regarded as more likely to translate to or be correlated with clinical outcome. An important feature of this algorithm is that a maximal number of points will be allowed for each subcategory and for each criterion within a subcategory, regardless of the number of observations, or studies. For example, within the category of experimental evidence, the maximal assignable value for mechanistic data might be 25 points and for animal studies the total value might be 75 points. For epidemiologic evidence, the maximum value assignable to case-control studies might be 25 points while a positive secondary analysis of a randomized trial might be worth 150 points. The result of having a maximal point value for each subcategory is that the evidence from multiple weak studies would not be able to overcome the evidence from one stronger and more informative study in providing the rationale for further chemopreventive agent development.

Using such an approach, we have scored several completed trials using the information available in the original protocol. Not surprisingly, the evidence for the CARET Carotene And Retinol Efficacy Trial) study was weak, and the trial probably would not have been started without new non-epidemiologic data, were the proposed guidelines in force at that time. As is well-known, this trial produced more lung cancers in the treatment arm (Omenn et al. 1996), a result that could not have been anticipated at the time

the study was begun. In contrast, the evidence underlying the basis for the use of tamoxifen in the P-1 breast cancer trial was strong, consistent across all categories of evidence, and produced a high score. Therefore, it is not surprising that a favorable reduction in the number of breast cancers in the treatment arm was demonstrated (Fisher et al. 1998). An important consideration in the design of future chemoprevention trials will include a more complete evaluation of toxicity and assignment of negative values based on the known side-effects profile, as well as a more careful evaluation of dose–response effects and toxicity in the run-up to the randomized trial. Similarly, if an agent has been shown to have other beneficial effects on health (e.g., aspirin and cardiovascular health), this needs to be considered during the decision-making process, and positive points up to a preset maximum will also be assigned.

The development of these guidelines involves an interactive iterative process based on evaluation of prior studies whose outcomes are known. We anticipate that this process will also allow us to score ongoing trials for which results are not currently known and trials which are being considered. With time, a database will emerge that may allow us to prospectively recommend whether the evidence is sufficient from a scientific viewpoint to proceed to definitive randomized trials, all of which are lengthy and expensive. However, we recognize that the implementation of large trials is also influenced by non-scientific considerations, including public pressure, competing priorities, importance of the question, and a likelihood that the result of a definitive trial will lead to a change in clinical practice or public usage. The guidelines that we propose are meant to offer a framework for informed decision-making based on evaluation of all known evidence and recognition of "missing pieces".

5 Conclusions

Before the next generation of clinical chemoprevention trials begins, the following four key issues should be taken into consideration.

1. Generation of data in animal models that links/correlates biomarkers and cancer should be a high priority.
2. Non-validated biomarkers should be used as guides to developing drugs rather than as surrogates to estimate reduction of the true endpoint.
3. Assessments of efficacy and safety are equally important in determining whether a drug should be evaluated in a phase III randomized trial. While demonstration of the former (efficacy) is an absolute requirement for definitive phase III testing, demonstration of the latter (safety) is merely a prerequisite and is insufficient alone to merit further drug development. The

balance of efficacy and safety shifts, based on the clinical situation, with higher-risk clinical scenarios tolerating greater toxicity from potential interventions.

4. The systematic development of chemopreventive agents is a long process. Shortcuts have not led to much progress as reflected by a change in medical practice. Prior studies have established the "proof of principle" that several different epithelial cancers can be prevented, or at least delayed. The next step is the development of studies that will identify safe efficacious drugs that can be integrated into routine medical care of individuals identified to be at high risk for specific cancers. As a research community, we need guidelines to inform that process in a useful way.

Acknowledgements Supported in part by CA 62203 (FLM).

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