Title
Therapeutic prevention of colorectal carcinogenesis.

Permalink
https://escholarship.org/uc/item/5f52g48x

Journal
Journal of carcinogenesis, 10

ISSN
1477-3163

Author
Meyskens, FL

Publication Date
2011

DOI
10.4103/1477-3163.79682

License
CC BY 4.0

Peer reviewed
Therapeutic prevention of colorectal carcinogenesis

Frank L. Meyskens, Jr

Department of Medicine, Biological Chemistry, and Public Health, Chao Family Comprehensive Cancer Center, University of California, Irvine - 92868, California, USA
Frank L. Meyskens, Jr: flmeyske@uci.edu

Corresponding author

Received 2011 Mar 10; Accepted 2011 Mar 10.

Copyright © 2011 Meyskens Jr

This is an open-access article distributed under the terms of the Creative Commons Attribution-Noncommercial-Share Alike 3.0 Unported, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

An overwhelming amount of experimental and observational information about the basic processes underlying carcinogenesis obtained during the 1970s to 1990s, led to a series of translational and eventually definitive placebo-controlled, double blind randomized controlled trials (RCT), involving patients at increased risk for breast, prostate, non-melanoma skin, cervix, chronic myelogenous leukemia (CML), and colon cancer. Despite clear evidence of the favorable effects on the primary endpoints, regulatory approval has been low and usage of those compounds, which have been approved, has been minimal to non-existent. How come? And what can we do to improve this situation, as we move ahead to the next generation of clinical studies?

For cervical cancer and CML, respectively, we have the good news that a highly effective vaccine and a targeted therapy (Imatinib) supplanted retinoids as the intervention of choice.[1-2] However, it is probably still worth looking into the vitamin A status of patients who develop cervical cancer, who have received the vaccine, or CML patients who relapse on Imatinib.

For the remaining malignancies the issues are very similar. We have recently presented a comprehensive review of this topic, including for those interested, a discussion of regulatory and business challenges.[3] In this current perspective we will focus on the issues of particular concern to the audience being served at this symposium: Scientific, translational, and clinical issues related to colorectal cancer.

The major questions that need to be asked and addressed regardless of the organ site are contained in these five areas:

- What relevance do cellular, animal studies, and epidemiological observations have to the cancer in ‘at-risk individuals’?
- How can we better identify those at true risk, to develop a more favorable risk-benefit profile?
- How can we better assess toxicity, and thus a potential risk-benefit in our preclinical experiments?
- How can we better convey the risks and benefits to trial participants in prevention studies? to regulatory bodies (FDA, EMA, etc.) after a positive RCT? or to potential future patients after a drug is approved?
- How should we move forward?
PRE-CLINICAL STUDIES

From the viewpoint of a translational clinical scientist and clinical researcher, the results from pre-clinical studies need to be viewed skeptically, as successful translation of laboratory and epidemiological studies to a positive clinical trial has occurred infrequently. How might this situation be improved beyond the general tendency of emphasizing positive over negative results?

A major issue is of course the identification and validation of biomarkers, a topic on which I and others have discussed extensively.[4–8] There has been a hope that biomarkers equivalent to hypertension and lipids, for predicting cardiovascular risks, may be developed. The positive viewpoint may be that we are just 20 years or more behind the cardiovascular field,[3] while the negative viewpoint is that the process of cancer formation is too complex and organ-specific to develop general biomarkers. The truth is probably somewhere in between and the concerted attempts of the Early Detection Research Network (edrn.nci.nih.gov) to validate biomarkers as true intermediate surrogates for cancer is important. A related problem is of course the use of pre-neoplastic histological changes, such as adenomas, as risk markers.

IDENTIFYING HIGHER-RISK INDIVIDUALS

The initial trials of cardiovascular risk prevention utilized patients at the highest risk for an event: Very high diastolic blood pressures and later very high cholesterol levels. Although these have been some notable exceptions [e.g., retinoids for xerodermapigmentosis patients[9] and NSAIDs for individuals with familial adenomatosis polyposis (FAP)[10] ], the large RCTs involving major specific organ sites have involved individuals at relatively low risk, and therefore, the tolerance for toxicity has been low. Among others, these RCTs have included lung (CARET), prostate (PCPT, SELECT), breast (P1, P2, P3), and trials of NSAIDs in individuals at relatively low / moderate risk for adenomas and / or colon cancer. Moving forward, as outlined by Dr. Zell and Lance's Perspectives in this issue[11,12] we need to focus on individuals at higher risk for colorectal cancer: FAP patients, patients with advanced adenomas, and patients with prior treated low stage (I, II, III) colorectal cancer.

THE ISSUE OF TOXICITY

The ultimate result of toxicity is of course death, fortunately this is not an issue in RCTs for prevention, to date. Close behind, however, is the development of cancer, wherein excess cancers were detected and reported in the initial analysis of the major large trials of lung and prostate cancers cited earlier. However, for intervention trials in patients at high risk for colorectal cancers, this phenomenon has not yet been described. Nevertheless, the clear demonstration of serious cardiovascular events in patients on several cox-2 selective agents in chemo-prevention trials of colorectal cancer has cast a pall over the otherwise very positive outcomes in modulating primary endpoints of adenomas, including advanced adenomas and possibly cancers.[13–15] Could this issue have been avoided by a more judicious review of the mechanistic data regarding the effect of cox-2 and cox-1 on coagulation? Possibly, because, even in the late 1990s, when the RCTs were being planned it was suggested that knocking out cox-2 favored a pro-coagulant state.[16] These results were unfortunately confirmed in the RCTs, in which time (12 – 18 months), the dose and frequency of administration (qd vs. bid) all played a role.[17] As a similar phenomenon occurred in the CARET trial, in which mechanistic data suggested that high doses of β-carotenes produced carcinogenic epoxides,[18] one would need to pay very close attention to these ‘lessons learned’ in the development of future trials.

PARTICIPANTS, PATIENTS, REGULATORY BODIES

The assessment and perception of risk is a very complex topic.[19] Although Americans worry about nuclear power plants, the French use them for two-thirds of their energy generation. Actually, the most dangerous thing we do in ‘So Cal’ every day is drive to and from work at 80 miles per hour (yes I know the speed limit
is 65, but no-one pays attention to it) in crowded traffic. Yet, we worry more about being eaten by a shark (about one per year in the U.S.) when we go to the beach. So how do we rationally and quantitatively approach the conveyance of risk to participants and patients in a general population where less than 10% know what statistics (and risk) even means? There have been some recent attempts by the communication field to address this issue: [20] For example, “your chance of a serious medical event is equivalent to being in a serious accident while driving to work each day (for a week, a month, a year)”. Clearly as we move forward, better ways to convey risk are needed.

A PRESCRIPTION FOR THE FUTURE OF PREVENTION TRIALS

- Continue to develop animal models that are true surrogates, not pretty mannequins.
- Assess potential toxicity by paying close attention to mechanistic effects on pathways.
- Conduct dose-de-escalation phase Ib, Ila, and Iib translational trials to assess the relative effects on drug-related biological markers and toxicity.
- Identify truly high-risk individuals and determine an acceptable level of toxicity up front.
- Consider lower doses of combinations of two different compounds. At least in one such reported RCT, the efficacy was high in preventing advanced adenomas and the toxicity very low. [21]

AUTHOR’S PROFILE

Dr. Frank L. Meyskens Jr., University of California, Irvine Medical Center 101 The City Drive Building 56, Room 210 Orange, California 92868.

Acknowledgments

Dr Meyskens is co-founder of Cancer Prevention Pharmaceuticals and holds a major equity interest.

REFERENCES


